EAU - ESTRO - ESUR - SIOG Guidelines on

Prostate Cancer

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1. INTRODUCTION

1.1 Aims and scope

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

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

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

1.2 Panel composition

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

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

Section 6.3: Treatment - Definitive Radiotherapy, has been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. A.M. Henry, Prof.Dr. M.D. Mason and Prof.Dr. T. Wiegel.

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

1.2.1 Acknowledgement

The PCa Guidelines Panel are most grateful for the support and considerable expertise provided by Prof.Dr. J-P. Droz, Emeritus Professor of Medical Oncology (Lyon, France) on the topic of 'Evaluating health status and life expectancy'. 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 as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the PCa Guidelines. All documents can be accessed on the EAU website: http://uroweb.org/guideline/prostate-cancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU PCa Guidelines were first published in 2001. This 2018 document presents a full update of the 2017 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 2018 EAU PCa Guidelines.

Key changes for the 2018 print:

The literature for the complete document has been assessed and updated, where relevant. The treatment sections have been completely restructured and evidence summaries and recommendations have been amended throughout the current document.

Several new sections have been added:

- Section 5.3.3.2 - Fluoride PET and PET/CT, choline PET/CT and MRI
- Section 5.3.3.3 - Prostate-specific membrane antigen-based PET/CT
- Section 5.3.3.4 - Summary of evidence and practical consideration regarding initial N/M staging

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

- Section 5.2.4.2 - Multiparametric magnetic resonance imaging (mpMRI) and Section 6.2.1.1.3 – Imaging for treatment selection [3].
- Section - 6.1.2.1.1 Pelvic lymph node dissection and Section 6.1.2.3.1 - Early complications of extended lymph node dissection [4].

2. METHODS

2.1 Data identification

For the 2018 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive literature search, covering all sections of the PCa Guidelines was performed. The search was limited to studies representing only high levels of evidence (i.e. SRs with meta-analysis, randomised controlled trials (RCTs), and prospective comparative studies) published in the English language. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 23rd 2016 and May 10th 2017. After deduplication, a total of 1,753 unique records were identified, retrieved and screened for relevance. A total of 97 new papers were added to the 2018 PCa Guidelines.

A detailed search strategy is available online:
http://uroweb.org/guideline/prostatecancer/?type=appendices-publications.

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [5, 6]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

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

2.2 Review

Publications ensuing from SRs have all been peer-reviewed.

2.3 Future goals

The results of ongoing and new SRs will be included in the 2019 update of the PCa Guidelines.

Ongoing SRs:

- How does biochemical recurrence following curative treatment for prostate cancer impact on overall survival, cancer-specific survival and development of metastatic disease? [9].
- What evidence-based supportive interventions improve disease-specific quality of life in men with prostate cancer?
- A SR of oncological effectiveness and harms of primary local interventions for high-risk localised and locally advanced prostate cancer [10].
- Systematic review of deferred treatment with curative intent for localised prostate cancer to explore heterogeneity of definitions, thresholds and criteria and clinical effectiveness [11].
- The findings of the 'SR of deferred treatment with curative intent for localised prostate cancer to explore heterogeneity of definitions, thresholds and criteria and clinical effectiveness' will be integrated in a formal consensus-finding project, the findings of which will be published in the 2019 edition of the EAU - ESTRO - ESUR - SIOG Prostate Cancer Guidelines.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [12]. The frequency of autopsy-detected PCa is roughly the same worldwide [13]. A SR of autopsy studies reported a prevalence of PCa at age < 30 years of 5% (95% CI: 3-8%), increasing by an odds ratio (OR) of 1.7 (1.6-1.8) per decade, to a prevalence of 59% (48-71%) by age > 79 years [14].

The incidence of PCa diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs 94.9 and 85, respectively), largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-Central Asia (ASRs 10.5 and 4.5, respectively), whilst rates in Eastern and Southern Europe, which were low, have showed a steady increase [12, 13].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (Caribbean: ASR 29 and Sub-Saharan Africa: ASRs 19-24), intermediate in the USA and very low in Asia (South-Central Asia: ASR 2.9) [12].

3.2 Aetiology

*3.2.1 **Family history/genetics***

Family history and racial/ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [15, 16]. However, only a small subpopulation of men with PCa (~9%) have true hereditary disease. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset PCa (< 55 years) [16]. It is associated with disease onset six-seven years earlier than average, but the disease aggressiveness and clinical course does not seem to differ in other ways [16, 17]. Men of African descent show a higher incidence of PCa and generally have a more aggressive course of disease [18].

Of the underlying determinants of genomic diversity and mechanisms between genetic and environmental factors, much remains unknown. Genome-wide association studies have identified 100 common susceptibility loci contributing to the risk for PCa, explaining ~38.9% of the familial risk for this disease [19, 20]. Furthermore, among men with metastatic PCa, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes [21]. Germline mutations in genes such as *BRCA1/2* and *HOXB13* have been associated with an increased risk of PCa and targeted genomic analysis of these genes could offer options to identify families at high risk [22, 23]. Prostate cancer screening trials targeting *BRCA* mutation carriers are ongoing [24].

*3.2.2 **Risk factors***

A wide variety of exogenous/environmental factors have been discussed as being associated with the risk of developing PCa or as being aetiologically important for the progression from latent to clinical PCa [25]. Japanese men have a lower PCa risk compared to men from the Western world. However, as Japanese men move from Japan to California, their risk of PCa increases, approaching that of American men, implying a

role of environmental or dietary factors [26]. However, currently there are no effective preventative dietary or pharmacological interventions.

3.2.2.1 Metabolic syndrome (MetS)

The single components of MetS hypertension (p = 0.035) and waist circumference > 102 cm (p = 0.007) have been associated with a significantly greater risk of PCa, but in contrast, having ≥ 3 components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60-0.82) [27, 28].

3.2.2.1.1 Diabetes/metformin

On a population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never-users (adjusted OR: 0.84; 95% CI: 0.74-0.96) [29]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with PCa (OR: 1.19; p = 0.50) [30].

3.2.2.1.2 Cholesterol/statins

A meta-analysis of fourteen large prospective studies did not show an association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of either overall PCa or high-grade PCa [31]. Results of the REDUCE study also did not show a preventive effect of statins on PCa risk [30].

3.2.2.1.3 Obesity

Within the REDUCE study, obesity was associated with lower risk of low-grade PCa in multivariable analyses (OR: 0.79; p = 0.01), but increased risk of high-grade PCa (OR: 1.28; p = 0.042) [32]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [33].

3.2.2.2 Dietary factors

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

Table 3.1: Dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [34]. A meta-analysis shows a dose-response relationship with PCa [35].
Dairy	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [36].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [37]. A relation between intake of fried foods and risk of PCa may exist [38].
Lycopenes (carotenes)	A trend towards a favourable effect of lycopene on PCa incidence has been identified in meta-analyses [39]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [40].
Meat	A meta-analysis did not show an association between red meat or processed meat consumption and PCa [41].
Phytoestrogens	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [42].
Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [43, 44].
Vitamin E/Selenium	An inverse association of blood, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [45, 46]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [47].

3.2.2.3 Hormonally active medication

3.2.2.3.1 5-alpha-reductase inhibitors (5-ARIs)

Although it seems that 5-ARIs have the potential of preventing or delaying the development of PCa (~25%, for Gleason 6 cancer only), this must be weighed against treatment-related side-effects as well as the potential

small increased risk of high-grade PCa [48-50]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

3.2.2.3.2 Testosterone

Hypogonadal men receiving testosterone supplements do not have an increased risk of PCa [51].

3.2.2.4 Other potential risk factors

Balding was associated with a higher risk of PCa death [52]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31; 95% CI: 1.14-1.52) [53]. Occupational exposure may also play a role, based on a meta-analysis which revealed that night-shift work is associated with an increased risk (2.8%; p = 0.030) of PCa [54]. Current cigarette smoking was associated with an increased risk of PCa death (relative risk [RR] 1.24; 95% CI: 1.18-1.31) [55]. A meta-analysis on Cadmium (Cd) found a positive association (magnitude of risk unknown due to heterogeneity) between high Cd exposure and risk of PCa for occupational exposure, but not for non-occupational exposure, potentially due to higher Cd levels during occupational exposure [56].

A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [57] and self-reported acne [58]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa [59, 60].

Ultraviolet radiation exposure decreased the risk of PCa (hazard ratio [HR]: 0.91; 95% CI: 0.88-0.95) [61]. A protective effect for PCa of circumcision was found [62]. Higher ejaculation frequency (≥ 21 times a month vs. four to seven times) has been associated with a 20% lower risk of PCa [63].

3.2.3 Summary of evidence and guidelines for epidemiology and aetiology

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

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

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the formulation of recommendations for the treatment of these patient populations. Throughout these Guidelines the 2017 Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [64] and the EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, are used (Table 4.3) [65]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT).

Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [64]

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

**Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.*
[1]Metastasis no larger than 0.2 cm can be designated pNmi.
[2]When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCas after RP are pathological stage T2 and the current Union for International Cancer Control (UICC) no longer recognises pT2 substages [64].

4.2 Gleason score and International Society of Urological Pathology 2014 grade

The 2005 International Society of Urological Pathology (ISUP) modified Gleason score (GS) of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern, if two are present. If one pattern is present, it needs to be doubled to yield the GS. For three grades, the GS comprises the most common grade plus the highest grade, irrespective of its extent. When a carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the GS. A GS ≤ 4 should not be given based on prostate biopsies [66]. In addition to reporting of the carcinoma features for each biopsy, an overall (or global) GS based on the carcinoma-positive biopsies can be provided. The global GS takes into account the extent of each grade from all prostate biopsies. The 2014 ISUP Gleason Grading Conference of Prostatic Carcinoma [67, 68] limits the number of PCa grades, ranging them from 1 to 5 (see Table 4.2), in order to:

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

Table 4.2: International Society of Urological Pathology 2014 grades

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

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

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

4.3 Prognostic relevance of stratification

A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management. The adoption of the current ISUP grading system, defining the split-up of GS 7 cancers into ISUP grade 2 (primary Gleason grade 3) and ISUP grade 3 (primary Gleason grade 4) because of their distinct prognostic impact [68] strengthens such a separation of the intermediate-risk group into a low-intermediate (ISUP grade 2) and high intermediate-risk (ISUP grade 3) group.

Emerging clinical data support this distinction between favourable- and unfavourable-risk patient categories within the intermediate-risk group [69].

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 finding, 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;
- a maintained quality of life (QoL) as expressed by QoL-adjusted gain in life years (QALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world [70]. Mortality due to PCa has decreased in most Western nations 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 [71].

Currently, screening for PCa is one of the most controversial topics in the urological literature [72]. Three large prospective RCTs published data on screening in 2009 [73-75] resulting in conflicting positions and policy papers. Some authors argue that following the current American Urological Association (AUA) guidelines [76] or the US Preventive Services Task Force (USPSTF) recommendations for screening [77-79] may lead to a substantial number of men with aggressive disease being missed [80, 81]. In 2017 the USPSTF issued an updated statement suggesting that men aged 55-69 should be informed about the benefits and harms of PSA-based screening as this might be associated with a small survival benefit. The USPSTF upgraded this recommendation to a grade C, whilst it was previously graded as 'D' [79, 82]. The grade D recommendation remains in place for men over 70 years old. This represents a major switch from discouraging PSA-based screening (grade D) to offering screening to selected patients depending on individual circumstances but a final statement is still pending. 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 [83]. 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 [84], which has since been updated [85], presents the main overview to date. The findings of the updated publication (based on a literature search until April 3, 2013) are almost identical to the 2009 review:

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

Moreover, screening was associated with minor and major harms such as over-diagnosis and over-treatment. Surprisingly, the diagnostic tool (i.e. biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [49, 50].

The impact on the patient's overall QoL is still unclear [86-88], although screening has never been shown to be detrimental at population level. Nevertheless, 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 thirteen years of follow up (see Table 5.1) [89]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen and to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials [90].

Table 5.1: Follow-up data from the ERSPC study [89]

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

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

Men at elevated risk of having PCa are those > 50 years, or at age > 45 years with a family history of PCa (either paternal or maternal [91]), or African-Americans [92]. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [93, 94] are also at increased risk of PCa metastasis or death from PCa several decades later. The long-term survival and QoL benefits of such an approach remain to be proven at a population level. In 2014, as for breast cancer, a genetic abnormality associated with an increased risk has been shown prospectively i.e. *BRCA2* [24, 69]. Several new biological markers such as *TMPRSS2-ERG* fusion, PCA3 [95, 96] or kallikreins as incorporated in the Phi or 4Kscore tests [97, 98] have been shown to add sensitivity and specificity on top of PSA, potentially avoiding unnecessary biopsies and lowering over-diagnosis. At this time there is too limited data to implement these markers into routine screening programmes.

Risk calculators may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available including:

- the PCPT cohort: PCPTRC 2.0 http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp;
- the ERSPC cohort: http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-riskcalculators; An updated version was presented in 2017 including prediction of low and high risk now also based on the ISUP grading system and presence of cribriform growth in histology [99].
- a local Canadian cohort: http://sunnybrook.ca/content/?page=occ-prostatecalc (among others).

Since none of these risk calculators has clearly shown superiority, it remains a personal decision as to which one to use [100].

Informed men requesting an early diagnosis should be given a PSA test and undergo a digital rectal examination (DRE) [101]. The optimal intervals for PSA testing and DRE follow-up are unknown, as they varied between several prospective trials. A risk-adapted strategy might be considered based on the initial PSA level. This could be every two years for those initially at risk, or postponed up to eight to ten years in those not at risk [102]. Data from the Goteborg arm of the ERSPC trial suggest that the age at which early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a fifteen-year life expectancy are unlikely to benefit, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy, comorbidity is at least as important as age. A detailed review can be found in Section 5.4 'Evaluating health status and life expectancy' and in the SIOG Guidelines [103].

Based on the tools currently available, an individualised strategy will diagnose many insignificant lesions (> 50% in some trials), most of which will not require any form of active treatment (see Section 6.1.1 – Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

5.1.1 Guidelines for screening and early detection

Recommendations	LE	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	3	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status (PS) and a life-expectancy of at least ten to fifteen years.	3	Strong
Offer early PSA testing in well-informed men at elevated risk of having PCa: • men > 50 years of age; • men > 45 years of age and a family history of PCa; • African-Americans > 45 years of age.	2b	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to eight years in those not at risk.	3	Weak
Stop early diagnosis of PCa based on life expectancy and PS; men who have a life-expectancy of < fifteen years are unlikely to benefit.	3	Strong

5.2 Clinical diagnosis

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores 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 [104]. A suspect DRE in patients with a PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [105]. An abnormal DRE is associated with an increased risk of higher GS and is an indication for biopsy [106, 107].

5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [108]. 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) [109].

There are no agreed standards defined for measuring PSA [110]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [111]. Table 5.2.1 demonstrates the occurrence of GS ≥ 7 (or ISUP grade 2) PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant PCa. The use of nomograms may help in predicting indolent PCa [112].

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

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥ 7 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

5.2.2.1 PSA density

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

5.2.2.2 PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [113];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [114].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treating PCa [115], 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 [116-119].

5.2.2.3 Free/total PSA ratio

Free/total (f/t) PSA must be used cautiously because it may be adversely affected by several pre-analytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [120]. However, it continues to have value in stratifying 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 [121]. Free/total PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow up of known PCa.

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 U.S. Food and Drug Administration (FDA) approved Prostate Health Index (PHI) test, (combining free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2]). 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 [98, 122, 123]. In a head to head comparison both tests performed equally [124].

5.2.2.5 PCA3 marker/SelectMDX

Prostate cancer gene 3 (PCA3) is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available Progensa urine test for PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies [125-128].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts the GS, and its use for monitoring in active surveillance (AS) is, as yet, not confirmed [129]. Currently, the main indication for the Progensa test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain [130].

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of *HOXC6* and *DLX1* mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer [131]. Based of the available evidence, some biomarkers could help in discriminating between aggressive and non-aggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians [132].

5.2.2.6 Guidelines for risk-assessment of asymptomatic men

Recommendation	LE	Strength rating
In order to avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level 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. Prostate Health Index test [PHI], four kallikrein [4K]score, Prostate cancer gene 3 [PCA3], *HOXC6*/*DLX1*) or; • imaging.	3	Strong

*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 and/or imaging (see Section 5.2.4.2). Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [133]. Risk stratification is a potential tool for reducing unnecessary biopsies [133].

Limited PSA elevation alone should not prompt immediate biopsy. Prostate specific antigen level should be verified after a few weeks, in the same laboratory, using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections [UTIs]) [134, 135]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [136].

Ultrasound (US)-guided biopsy is now the standard of care. Prostate biopsy is performed by either the transrectal or transperineal approach. Cancer detection rates, when performed without prior imaging with magnetic resonance imaging (MRI), are comparable between the two approaches [137], however some evidence suggests reduced infection risk with the transperineal route (see Section 5.2.3.11). Rectal disinfection with povidone-iodine may be considered [138].

5.2.3.2 Repeat biopsy after previously negative biopsy

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2.1 for risk estimates);
- suspicious DRE, 5-30% cancer risk [104, 105];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 31-40% risk [139, 140];
- extensive (multiple biopsy sites, i.e., ≥ 3) high-grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [140, 141];
- a few atypical glands immediately adjacent to high-grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [142];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade PCa [143];
- positive multiparametric MRI (mpMRI) findings (see Section 5.2.4).

Additional information may be gained by the Progensa-PCA3 and SelectMDX DRE urine tests, the serum 4Kscore and PHI tests or a tissue-based epigenetic test (ConfirmMDx). The role of PHI, Progensa PCA3, and SelectMDX in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective [130]. The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. If the PCa is missed at biopsy, demonstration of epigenetic changes in the benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes in benign prostatic tissue. A multicentre study found a negative predictive value (NPV) of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men [144]. Given the limited available data, no recommendation can be made regarding its routine application.

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

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

**Isolated high-grade prostatic intraepithelial neoplasia (PIN) in one or two biopsy sites is no longer an indication for repeat biopsy [145].*

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 [146]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention (10%) is a drawback [147].

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. At least eight systematic biopsies are recommended in prostates with a size of about 30 cc [148]. Ten to twelve core biopsies are recommended in larger prostates, with > twelve cores not being significantly more conclusive [149, 150].

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 [151].

5.2.3.6 Seminal vesicle biopsy

Indications for seminal vesicle (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20-25% [152]. A seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent radiotherapy (RT). Its added value compared with mpMRI is questionable.

5.2.3.7 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to repeat biopsies [153].

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 [154]. Increased quinolone resistance is associated with a rise in severe post-biopsy infection [155, 156]. Regional and local antibiotic resistance patterns should be taken into account when deciding on the choice of antibiotic.

5.2.3.9 Local anaesthesia prior to biopsy

Ultrasound-guided periprostatic block is recommended [157]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [158].

5.2.3.10 Fine-needle aspiration biopsy

Fine-needle aspiration biopsy is no longer recommended.

5.2.3.11 Complications

Biopsy complications are listed in Table 5.2.3 [159]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [160]. Low-dose aspirin is no longer an absolute contraindication [161]. A SR found favourable infections rates for transperineal compared to transrectal biopsies with similar rates of haematuria, haematospermia and urinary retention [162] but a meta-analysis of 4,280 men randomised between transperineal vs. transrectal biopsies in thirteen studies found no significant differences in complication rates although the transperineal approach required more (local)anaesthesia [137].

Table 5.2.3: Percentage of complications per biopsy session, irrespective of the number of cores

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

5.2.4 The role of imaging in clinical diagnosis

5.2.4.1 Transrectal ultrasound (TRUS) and ultrasound-based techniques

Grey-scale TRUS is not reliable at detecting PCa [163]. Thus, there is no evidence that US-targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography and contrast-enhanced US are still under investigation and not ready for routine use.

5.2.4.2 Multiparametric magnetic resonance imaging (mpMRI)

Correlation with RP shows that mpMRI, associating T2-weighted imaging with at least one functional imaging technique (DWI, DCE, H1-spectroscopy) has good sensitivity for the detection and localisation of GS ≥ 7 cancers (see Table 5.2.4) [164-168].

Table 5.2.4: PCa detection rates (%) by mpMRI for tumour volume and Gleason score in radical prostatectomy specimen [166]

Gleason score	Tumour volume (mL)		
	< 0.5	0.5-2	> 2
GS 6	21-29%	43-54%	67-75%
GS 7	63%	82-88%	97%
GS >7	80%	93%	100%

As a result, mpMRI is increasingly performed before prostate biopsy. Theoretically, pre-biopsy mpMRI could be used in two different ways. Strategy 1 uses mpMRI to improve the detection of clinically significant PCa (csPCa). In this diagnostic pathway, magnetic resonance imaging-targeted biopsies (MRI-TBx) would be added to systematic biopsies in case of a positive mpMRI, and systematic biopsies would be performed in all patients with a negative mpMRI. Strategy 2 consists in using mpMRI as a triage test before biopsy. In this diagnostic pathway, only MRI-TBx would be performed in case of a positive mpMRI. Patients with a negative mpMRI would not undergo prostate biopsy at all.

Strategy 1: A large body of evidence suggests that MRI-TBx have a higher detection rate of csPCa compared to systematic biopsy [169-173]. However, sub-group analysis showed that MRI-TBx significantly improved the detection of csPCa in the repeat-biopsy setting, but not in biopsy-naïve men [169, 170]. Single-centre RCTs performed in biopsy-naïve men provided contradictory findings as to whether or not the combination of systematic biopsies and MRI-TBx had a higher detection rate for PCa and csPCa as compared to systematic biopsies alone [174-176]. The Prostate MRI Imaging Study (PROMIS) evaluated mpMRI and TRUS-guided systematic biopsy against template prostate mapping (TPM) biopsy in 576 biopsy-naïve men [177]. For detection of csPCa (GS ≥ 4+3 or cancer core length (CCL) ≥ 6 mm), mpMRI showed a significantly higher sensitivity than TRUS (93% [95% CI: 88-96] vs. 48% [95% CI: 42-55], p < 0.0001). This result must, however, be interpreted with care, since no MRI-TBx were performed in this study design. Since the analysis was made at the patient level, no spatial concordance was required between the location of mpMRI lesions and the location of the positive TPM cores. Some patients, considered as true positives for mpMRI in the PROMIS study, may in fact have had a TPM-detected csPCa at any distance from the MR lesion, resulting in both a MR false positive and false negative. This is likely since mpMRI showed poor specificity in the PROMIS population (41% [95% CI: 36-46]). Thus, the results of the PROMIS study cannot be extrapolated to evaluate the diagnostic yield of targeted biopsy in biopsy-naïve patients [178]. As a result, there is insufficient evidence to recommend routine use of mpMRI in biopsy-naïve men. Several multicentre controlled trials are currently ongoing and should clarify this matter in the near future.

Magnetic resonance imaging-targeted biopsies can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature does not show a clear superiority of one technique over the others [172, 179-181].

Strategy 2: Whether systematic biopsies can be omitted in patients (or prostate lobes) with negative mpMRI depends on the NPV of mpMRI. A single-centre RCT recently randomised 212 biopsy-naïve men in two arms. Patients in arm A underwent pre-biopsy mpMRI and TBx only when mpMRI was positive (arm A+) and systematic biopsy when mpMRI was negative (arm A-). Patients in arm B underwent systematic biopsy without any mpMRI. The detection rates for csPCa (GS ≥ 3+4 or CCL ≥ 5 mm) were 56.8%, 3.8%, and 18.1% in arms A+, A- and B, respectively ($p < 0.001$) [182].

If the PROMIS study would not allow for the assessment of the role of mpMRI in strategy 1 (see above), its design is perfect to evaluate the mpMRI NPV. In this study, mpMRI showed a significantly higher NPV than systematic biopsy (89% [95% CI: 83-94] vs. 74% [95% CI: 69-78], $p < 0.0001$) [177]. Negative predictive value (NPV), however, depends not only on the sensitivity of the test, but also on the disease prevalence (40% in the PROMIS population). A SR performed under the auspices of the EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel showed a highly variable prevalence of overall PCa (13.0-74.7%) and csPCa (13.7-50.9%) in patients undergoing pre-biopsy mpMRI [3]. As the population of patients referred to pre-biopsy mpMRI varies so much from one institution to another, it is necessary to risk-stratify patients before defining the patients that could safely omit biopsy in case of a negative mpMRI. Prostate-specific antigen density [183] or risk calculators [100] can be used to identify groups of patients with low risk of PCa in whom mpMRI would have a high NPV. The impact of these risk-stratification tools on the NPV of pre-biopsy mpMRI needs to be carefully evaluated, both in the biopsy-naïve and in the repeat-biopsy setting.

Despite the use of the new PIRADS v2 scoring system [184], mpMRI inter-reader reproducibility remains moderate at best [185-188], which currently limits its broad use outside expert centres. It is of note that the good results of the PROMIS study were obtained after intensive training of the radiologists involved. This remains a major unresolved issue that may lead to substantial patient mismanagement if the results obtained with mpMRI in expert hospitals cannot be reproduced in less-experienced centres. It is currently too early to define if quantitative approaches and computer-aided diagnosis systems will improve the characterisation of lesions seen at mpMRI in the future [189-191].

5.2.4.3 Guidelines for imaging

Recommendations	LE	Strength rating
Perform multiparametric magnetic resonance imaging (mpMRI) before repeat biopsy when clinical suspicion of PCa persists in spite of negative biopsies.	1a	Strong
Include systematic biopsies and targeting of any mpMRI lesions seen during repeat biopsy.	2a	Strong

*5.2.5 **Pathology of prostate needle biopsies***

5.2.5.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [192]. 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 [193, 194]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [153] and intervening unstained sections 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 [195-197]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [195]. Table 5.2.5 lists the recommended terminology for reporting prostate biopsies [193].

Table 5.2.5: Recommended terminology for reporting prostate biopsies [193]

Recommended terminology	LE	Strength rating
Benign/negative for malignancy; if appropriate, include a description	3	Strong
Active inflammation		
Granulomatous inflammation		
High-grade prostatic intraepithelial neoplasia (PIN)		
High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)		
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer		
Adenocarcinoma		
Intraductal carcinoma		

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2014 Gleason grading system [67]. A global GS comprising all biopsies is also reported according to the ISUP grade system (see Section 4.2). The global ISUP grade takes into account all biopsies positive for carcinoma, by estimating the total extent of each grade present. For instance, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site of Gleason grade 4 only, the global GS would be 7(3+4), i.e. ISUP grade 2 or 7(4+3), i.e. ISUP grade 3, dependent on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the worse grade would be GS 8(4+4), i.e. ISUP grade 4. Recent publications demonstrated that global ISUP grade is somewhat superior in predicting prostatectomy GS [198] and BCR [199].

Intraductal carcinoma, lymphovascular invasion (LVI) and extraprostatic extension (EPE) must each be reported, if identified. More recently, expansile cribriform pattern of PCa as well as intraductal carcinoma in biopsies were identified as independent prognosticators of metastatic disease [200] and PCa-specific survival [201].

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the GS, tumour volume, surgical margins and pathologic stage in RP specimens and predict BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [202-204]. 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 [205]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [206] triggering immediate treatment vs. AS in patients with GS 6.

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

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

5.2.5.3 Tissue-based prognostic biomarker testing

The Prolaris test (Myriad Genetics) measures the expression of 31 cell-cycle associated genes in biopsy-derived PCa tissue and may be of clinical use to determine whether a patient needs curative treatment or may have his treatment deferred [207]. A SR on the topic concluded that cell-cycle-associated gene expression can be helpful in predicting BCR risk after local treatment and may alter clinical decision-making but the economic impact on healthcare systems remains to be determined [208].

Similarly, Oncotype Dx® is a RNA-based test based on twelve carcinoma-associated genes and five 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 GS 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 GS ≥ 7 with accurate staging in 96% of cases [209].

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 [210]. 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 [66]. 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

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

5.2.6.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.6). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.7). Synoptic reporting results in more transparent and complete pathology reporting [211].

Table 5.2.6: Mandatory elements provided by the pathology report

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

Table 5.2.7: Example checklist: reporting of prostatectomy specimens

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

5.2.6.2.1 Gleason score in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system [67] is the strongest prognostic factor for clinical behaviour and treatment response. The GS is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [212].

The GS 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 GS (5% rule). The primary and secondary grades are reported in addition to the GS. A global GS is given for multiple tumours, but a separate tumour focus with a higher GS 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 [213] in addition to the global GS as well as the ISUP 2014 grade group (see Section 4.2).

5.2.6.2.2 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE because the latter is related to recurrence risk [214].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [215] or extension as < 1 per high-power field (HPF) [216], whereas others measure the depth of extent in millimetres [217].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e., not as

pT4, because it does not carry independent prognostic significance for PCa recurrence [218, 219] and should be recorded as EPE (pT3a). A positive margin at the bladder neck should be reported as EPE (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [220].

5.2.6.3 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [216, 221-224]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [221]. 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 [225].

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 [222] 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 [226].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [227]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [216]. 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 [228], or number of blocks with positive margin involvement.

*5.2.7 **Guidelines for the clinical diagnosis of prostate cancer***

Recommendations	LE	Strength rating
Do not use transurethral resection of the prostate as a tool for cancer detection.	2a	Strong
Use the International Society of Urological Pathology (ISUP) 2014 Gleason grading system for grading of PCa.	2a	Strong
In symptomatic men, base the initial decision to perform a biopsy on prostate-specific antigen testing and digital rectal examination.	2b	Strong
Do not initially offer transition zone biopsies due to low detection rates.	2b	Weak
For initial diagnosis, perform a core biopsy of ten to twelve systematic transrectal or transperineal peripheral zone biopsies under ultrasound guidance.	2a	Strong
Perform transrectal prostate needle biopsies under antibiotic protection.	1b	Strong
Use a local anaesthetic by periprostatic infiltration for transrectal prostate needle biopsies.	1a	Strong
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	3	Strong
Adhere to the 2010 ISUP Consensus Meeting Guidelines for processing and reporting of prostatectomy specimens.	3	Strong

5.3 Diagnosis: Clinical staging

The extent of PCa is evaluated by DRE and PSA, and may be supplemented with mpMRI, bone scanning and computed tomography (CT) 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 5.2.5 for details).

5.3.1.2 DRE, PSA level and biopsy findings

The first level of assessment is local tumour stage as the distinction between organ-confined (T1/T2) and extraprostatic (T3/T4) disease affects treatment decisions. Digital rectal examination is positively correlated

with tumour stage in < 50% of cases [229], 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 [230]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [231]. An increase in tumour-positive biopsies is an independent predictor of EPE, margin involvement, and lymph node (LN) invasion [232]. Serum PSA, GS, and T-stage are more useful together than alone in predicting final pathological stage [212, 233]. Models may help to select candidates for nerve-sparing surgery and lymphadenectomy (LND) (see Section 6.1.2.1.1).

Seminal vesicle invasion is predictive of local relapse and distant metastatic failure. Seminal vesicle biopsies can improve pre-operative staging accuracy [234]. This is not recommended for first-line examination, but should be reserved for patients with high risk of SVI in whom a positive biopsy would modify treatment. Patients with T-stage > 2a and serum PSA > 10 ng/mL are candidates for seminal vesicle biopsy [235, 236]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [237].

Transperineal 3D prostate mapping biopsy is an alternative to transrectal biopsies because it provides more accurate tumour localisation, extent and Gleason grading [238], and has acceptable morbidity [162].

5.3.1.3 TRUS

Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [239]. Transrectal ultrasound derived techniques (e.g. 3D-TRUS, colour Doppler) [240, 241] cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for staging.

5.3.1.4 mpMRI

T2-weighted imaging remains the most useful method for local staging on mpMRI. At 1.5 Tesla, mpMRI has good specificity but low sensitivity for detecting T3 stages. Pooled data from a meta-analysis for EPE, SVI, and overall stage T3 showed a sensitivity and specificity of 0.57 (95% CI: 0.49-0.64) and 0.91 (95% CI: 0.88-0.93) and 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 [242]. Multiparametric MRI cannot detect microscopic EPE. Its sensitivity increases with the radius of extension within periprostatic fat. In one study, the EPE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [243]. In another study, mpMRI sensitivity, specificity and accuracy for detecting pT3 stage were 40%, 95% and 76%, respectively, for focal (i.e. microscopic) EPE, and 62%, 95% and 88% for extensive EPE [244].

The use of high field (3 Tesla) or functional imaging in addition to T2-weighted imaging improves sensitivity for EPE or SVI detection [242], but the experience of the reader remains of paramount importance [245] and the inter-reader agreement remains moderate with kappa values ranging from 0.41 to 0.68 [246]. Multiparametric magnetic resonance imaging, although not perfect for local staging, may improve prediction of the pathological stage when combined with clinical data [247, 248]. Other MRI-derived parameters such as the tumour volume or the contact length of the tumour with the capsule [249-251], or the GS obtained through MRI-TBx [252] could further improve the local staging.

Given its low sensitivity for focal (microscopic) EPE, mpMRI is not recommended for local staging in low-risk patients [247, 253, 254]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [255].

*5.3.2 **N-staging***

5.3.2.1 Computed tomography (CT) and magnetic resonance imaging

Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of non-metastatic LNs varies widely and may overlap the size of LN metastases, since microscopic invasion does not enlarge LNs. The normal range for non-metastatic LNs also varies with different anatomical regions. Usually, LNs with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are considered malignant. Decreasing these thresholds improves sensitivity but decreases specificity. As a result, the ideal size threshold remains unclear [256, 257]. Computed tomography and MRI sensitivity is less than 40% [258, 259]. Among 4,264 patients, 654 (15.3%) of whom had positive LNs at LND, CT was positive in only 105 patients (2.5%) [256]. In a multicentre database of 1,091 patients who underwent pelvic LN dissection, CT sensitivity and specificity were 8.8% and 98% respectively [260]. Detection of microscopic LN invasion by CT is < 1% in patients with a GS < 8, PSA < 20 ng/mL, or localised disease [261-263].

Diffusion-weighted MRI may detect metastases in normal-sized nodes, but a negative diffusion-weighted MRI cannot rule out the presence of LN metastases [257, 264].

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

5.3.2.2 Choline PET/CT

^{11}C- or ^{18}F-choline positron emission tomography (PET)/CT have good specificity for LN metastases, but their reported sensitivity falls in a wide range of 10-73% [265, 266].

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51-66%) and 92% (95% CI: 89-94%), respectively [267]. 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 value [268].

In intermediate/high-risk patients, comparisons between choline PET/CT and diffusion-weighted MRI yielded contradictory results, with PET/CT sensitivity found to be superior [269], similar [270, 271] or inferior [268] than that of diffusion-weighted MRI.

Due of its low sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases, or to rule out a nodal dissection based on risk factors or nomograms (see Section 6.1.2.1.1).

5.3.2.3 Prostate-specific membrane antigen-based PET/CT

^{68}Ga- or ^{18}F-labelled prostate-specific membrane antigen PET/CT (PSMA PET/CT) is increasingly used, because it provides excellent contrast-to-noise ratio, thereby improving the detectability of lesions. Prostate-specific membrane antigen is also an attractive target because of its specificity for prostate tissue, even if non-prostatic expression of PSMA in other malignancies, sarcoidosis or Paget disease may cause incidental false-positive findings [272, 273, 274]. Preliminary assessment showed promising sensitivity for LN involvement.

A meta-analysis of five retrospective studies performed in an initial staging and/or recurrence setting reported combined sensitivities and specificities of 86% (95% CI: 37-98%) and 86% (95% CI: 3-100%) at patient level, and 80% (95% CI: 66-89%) and 97% (95% CI: 92-99%) at lesion level [275]. A multicentre prospective study has recently compared PSMA PET/CT and LN dissection in 51 high-risk patients with negative ^{99}mTc bone scan. At patient level, PSMA PET/CT sensitivity and specificity were 53% and 86%, respectively. The mean maximal length of metastases within LNs detected and missed by PSMA PET/CT was 13.1 ± 7.7 mm and 3.9 ± 2.7 mm respectively [276]. Another prospective single-centre study also found that metastatic LNs missed by PSMA PET/CT were on average < 5 mm [277]. The tracer uptake is also influenced by the GS and the PSA level. In a series of 90 patients with primary PCa, tumours with a GS of 6, 7(3+4) and 7(4+3) showed significantly lower tracer uptake than tumours with a GS of ≥ 8. Similarly patients with PSA levels ≥ 10 ng/mL showed significantly higher uptake than those with PSA levels < 10 ng/mL [278].

5.3.3 ***M-staging***

5.3.3.1 Bone scan

^{99}mTc-Bone scan has been the most widely used method for evaluating bone metastases of PCa. A recent meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73-83%) and 82% (95% CI: 78-85%) at patient level and 59% (95% CI: 55-63%) and 75% (95% CI: 71-79%) at lesion level [279]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour GS and these three factors were the only independent predictors of bone scan positivity in a study of 853 patients [280]. The mean bone scan positivity rate in 23 different series was 2.3% in patients with PSA levels < 10 ng/mL, 5.3% in patients with PSA levels between 10.1 and 19.9 ng/mL and 16.2% in patients with PSA levels of 20.0-49.9 ng/mL. It was 6.4% in men with organ-confined cancer and 49.5% in men with locally advanced cancers. Detection rates were 5.6% and 29.9% for GS of 7 and ≥ 8, respectively [256]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive bone scan [281, 282].

Bone scanning should be performed in symptomatic patients, independent of PSA level, GS or clinical stage [256].

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

^{18}F-sodium fluoride (^{18}F-NaF) PET or PET/CT shows similar specificity and superior sensitivity to bone scan [283, 284]. However, unlike choline PET/CT, it does not detect LN metastases, and it is less cost-effective compared to bone scan [283].

It remains unclear whether choline PET/CT is more sensitive than conventional bone scan, but it has higher specificity, with fewer indeterminate bone lesions [265, 267, 285].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa [286, 287]. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [288]. A meta-analysis found that MRI is more sensitive than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity [279].

It is of note that choline PET/CT and diffusion-weighted MRI can also detect visceral metastases. Bone scan and ^{18}F-NaF PET/CT only assess the presence of bone metastases.

5.3.3.3 Prostate-specific membrane antigen-based PET/CT

Only limited evidence is available on the performance of ^{68}Ga-PSMA PET/CT in initial staging. In one retrospective study of 37 patients, PSMA PET/CT significantly outperformed bone scan at patient-based and region-based analysis. At region-based analysis, PSMA PET/CT sensitivity and specificity were 100% and 99.3-100% respectively, depending whether equivocal lesions were considered positive or not. Bone scan sensitivity and specificity were 46.2-61.5% and 92.1-97.9%, respectively.

One prospective multicentre study evaluated changes in planned management before and after PSMA PET/CT in 108 intermediate- and high-risk patients referred for primary staging. As compared to conventional staging, additional LNs and bone/visceral metastases were detected in 25% and 6% of patients respectively. Management changes occurred in 21% of patients. The main changes resulted in 7 patients undergoing prostatectomy and regional LN dissection rather than prostatectomy alone and 5 patients undergoing unplanned chemotherapy. Clearly, this study could not assess whether this changes in management induced better outcome [289].

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

The field of non-invasive nodal and metastatic staging of PCa is evolving very rapidly. Evidence shows that choline PET/CT, MRI and PSMA PET/CT provide a more sensitive detection of LN and bone metastases than the classical work-up associating bone scan and abdominopelvic CT. It could then be tempting to conclude that bone scan and abdominopelvic CT must be replaced by more sensitive tests in all patients undergoing initial PCa staging. Yet, the clinical benefit of detecting metastases at an earlier time-point remains unclear [290].

The prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. It is unclear whether these patients should be contraindicated to local treatments and managed using systemic therapies, or whether they should be submitted to aggressive local and metastases-directed therapies. It needs to be kept in mind that generally oligometastatic PCa should be considered a systemic disease, which cannot be detected due to the insensitivity of the current diagnostic tests [291].

Well-designed controlled trials evaluating the management and outcome of patients with (and without) metastases detected by choline PET/CT, MRI and PSMA PET/CT are needed before the decision can be made to treat patients or not based on the results of these tests.

*5.3.4 **Guidelines for staging of prostate cancer***

Any risk group staging	**LE**	**Strength rating**
Do not use computed tomography and transrectal ultrasound for local staging.	2a	Strong

Low-risk localised PCa	**LE**	**Strength rating**
Do not use additional imaging for staging purposes.	2a	Strong

Intermediate-risk PCa	**LE**	**Strength rating**
In predominantly Gleason pattern 4 (≥ ISUP 3), use prostate multiparametric magnetic resonance imaging (mpMRI) for local staging.	2b	Weak
In predominantly Gleason pattern 4, include at least a cross-sectional abdominopelvic imaging and bone-scan for metastatic screening.	2a	Weak

High-risk localised PCa/locally advanced PCa	**LE**	**Strength rating**
Use prostate mpMRI for local staging.	2b	Strong
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong

5.4 Evaluating health status and life expectancy

*5.4.1 **Introduction***

Evaluation of health status and life expectancy is important in clinical decision-making on screening, diagnosis, and treatment of PCa. Prostate cancer is common in older men (median age 68) and diagnoses in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the USA [292, 293].

Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over ten years life expectancy is considered mandatory for any benefit from local treatment. Older age and worse baseline health status have been associated with a smaller benefit in PCa-specific mortality (PCSM) and life expectancy of surgery vs. AS [294]. Although in a RCT the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR: 0.45), RP was associated with a reduced risk of metastases and use of androgen deprivation therapy (ADT) among older men (RR: 0.68 and 0.60, respectively) [295]. External beam radiotherapy shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [296].

Older men with a high incidence of PCa may be under-treated despite the high overall mortality rates [297, 298]. Of all PCa-related deaths 71% occur in men aged ≥ 75 years [299], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [300-302]. 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 [303].

*5.4.2 **Health status screening***

The International SIOG PCa Working Group recommends that treatment for senior adults should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (Table 5.4.1) [304]. Healthy patients with a G8 score > 14 or frail patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Disabled patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (Figure 1) [304]. Patients with a G8 score ≤ 14 should undergo a full geriatric evaluation as this score is associated with 3-year mortality, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [305].

5.4.2.1 Comorbidity

Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [306, 307]. Ten years after not receiving active treatment for PCa, most men with a high comorbidity score had died from competing causes, irrespective of age or tumour aggressiveness [306] Measures for comorbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [308, 309] (Table 5.4.2) and Charlson Comorbidity Index (CCI) [310].

5.4.2.2 Nutritional status

Malnutrition can be estimated from body weight during the previous three months (good nutritional status < 5% weight loss; risk of malnutrition: 5-10% weight loss; severe malnutrition: > 10% weight loss) [311].

5.4.2.3 Cognitive function

Cognitive impairment can be measured using the mini-COG (mini-cog.com), assessing the patient's ability to make an informed decision and is deemed increasingly important in health status assessment) [312-314].

5.4.2.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [315]. Measures for dependence in daily activities include: Activities of Daily Living (ADL; basic activities) and Instrumental Activities of Daily Living (IADL; activities requiring higher cognition and judgement) [316-318].

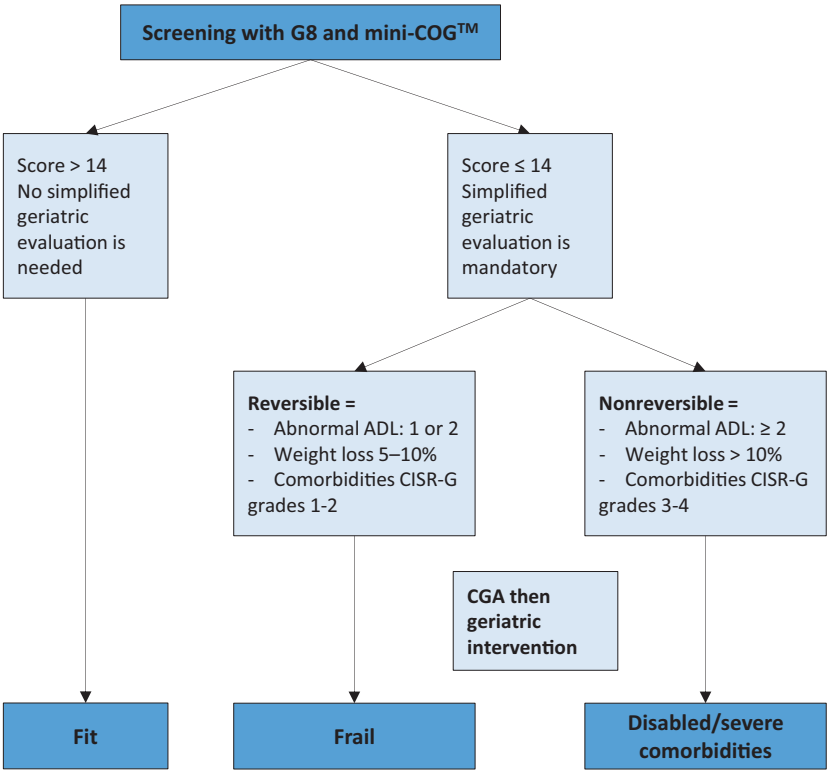
*5.4.3 **Conclusion***

Individual health status and comorbidity, not only age, should be leading in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of 10 years is most commonly used as a threshold for benefit of local treatment. Older men may be undertreated. Resolution of impairments in frail men allows a similar urological approach as in fit patients.

Table 5.4.1: G8 screening tool (adapted from [305]**)**

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
	Age	0: > 85
		1: 80-85
		2: < 80
	Total score	0-17

Figure 5.4.1: Decision tree for health status screening (men > 70 years)* [304]



**Reproduced with permission of Elsevier, from Droz J-P, et al. Eur Urol 2017:72(4); 521 [304].*
Mini-COG™ = cognitive test; ADL = activities of daily living; CIRS-G = cumulative illness rating score-geriatrics; CGA = comprehensive geriatric assessment.

Table 5.4.2: Cumulative Illness Score Rating-Geriatrics (CISR-G)

1	Cardiac (heart only)
2	Hypertension (rating is based on severity; affected systems are rated separately)
3	Vascular (blood, blood vessels and cells, marrow, spleen. lymphatics)
4	Respiratory (lungs, bronchi, trachea below the larynx)
5	ENT (eye, ear, nose, throat, larynx)
6	Upper GI (esophagus, stomach, duodenum. Biliar and parcreatic trees; do not include diabetes)
7	Lower GI (intestines, hernias)
8	Hepatic (liver only)
9	Renal (kidneys only)
10	Other GU (ureters, bladder, urethra, prostate, genitals)
11	Musculo-Skeletal-Integumentary (muscles, bone, skin)
12	Neurological (brain, spinal cord, nerves; do not include dementia)
13	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)
14	Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation, psychosis)
All body systems are scores on a 0 - 4 scale. - 0: No problem affecting that system. - 1: Current mild problem or past significant problem. - 2: Moderate disability or morbidity and/or requires first line therapy. - 3: Severe problem and/or constant and significant disability and/or hard to control chronic problems. - 4: Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.	
	Total score 0-52

5.4.4 *Guidelines for evaluating health status and life expectancy*

Recommendations	Strength rating
Systematically screen the health status of older men (> 70 years) diagnosed with PCa.	Strong
Use the Geriatric-8 and mini-COG tools for health status screening.	Weak
Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.	Strong
Consider standard treatment in frail patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak
Offer adapted treatment in patients with irreversible impairment.	
Offer palliation in patients with poor health status.	

6. TREATMENT

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

6.1 Treatment modalities

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

In localised disease a life expectancy of at least 10 years is considered mandatory for any benefit from local treatment. Comorbidity is more important than age in predicting life expectancy in men with PCa. However, for those men with a short life expectancy, watchful waiting (WW) with symptom-guided treatment is appropriate in order to maintain QoL.

Many men with screening-detected localised PCa will not benefit from curative treatment [319] and 45% of them are suitable for AS. Mortality from untreated screen-detected PCa in patients with GS 5-7 might be as low as 7% at fifteen years follow-up [319].

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

6.1.1.1 *Definitions*

Active surveillance aims to achieve correct timing for curative treatment in patients with clinically localised PCa, rather than delay palliative treatment [320]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, still potentially curable, while considering individual life expectancy.

Watchful waiting 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 [319]

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

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

6.1.1.2 Active surveillance

No formal RCT is available comparing this modality to standard treatment. The ProtecT trial [321] is discussed later as it is not a formal AS strategy, but rather Active Monitoring (AM), which would represent a 'very light' AS strategy.

One of the largest published cohorts with the longest follow up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [322]. These men presented with stage T1c or T2a and PSA ≤ 10 ng/mL, age ≤ 70 years and a GS ≤ 6 or age > 70 years with a GS of ≤ 7. After a median follow-up of 6.4 years the ten- and fifteen-year OS were 80% and 62%, respectively, and DSS rates were 98.1% and 94.3%, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years (43.5%), a GS progression on repeat biopsies (35%) and patient preference (6%). Thirty men (3%) developed metastases during follow up; 2% of those initially classified as Gleason 6 compared to 9.7% as initially Gleason 7, and fifteen men died [323].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a SR including > 3,900 patients [324] (Table 6.1.2). There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated. They have been summarised and will be discussed in Section 6.2.1 [320].

Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	n	Median FU (mo)	pT3 in RP patients	OS (%)	CSS (%)
Van As, *et al.* 2008 [325]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [326]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [327]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [328]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [329]	278	41	-	89	100
Khatami, *et al.* 2007 [330]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [322]	993	77	-	85	98.1
Total	**2,130-3,000**	**43**		**90**	**99.7**

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

6.1.1.3 Watchful Waiting

6.1.1.3.1 Introduction

Studies on WW have included patients with up to 25 years of follow-up, with endpoints of OS and CSS. Several series have shown a consistent CSS rate of 82-87% at ten years [331-336], and 80-95% for T1/T2 and GS ≤ 7 [337]. In three studies with data beyond fifteen years, the DSS was 80%, 79% and 58% [333, 335, 336], and two reported twenty-year CSS rates of 57% and 32%, respectively [333, 335]. Many patients classified as GS 6 would now be classified as Gleason 7 based on the revised Gleason classification, suggesting that the above-mentioned results should be considered as minimal. Patients with well-, moderately- and poorly-differentiated tumours had ten-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [337]. Observation was most effective in men aged 65-75 years with low-risk PCa [338].

In an analysis at ten years follow up in 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI score ≥ 2 died from competing causes at ten years whatever their initial age. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at ten years, especially for well- or moderately-differentiated lesions [306]. This highlights the importance of checking the CCI before considering a biopsy.

6.1.1.3.2 Outcome of watchful waiting compared with active treatment

The SPCG-4 study randomised patients to either WW or RP (Table 6.1.3) [295] before the PSA era and found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 13.4 years (range 3 weeks - 23.2 years). The PIVOT trial made a similar comparison in 731 randomised men (50% with non-palpable disease) [339] and found no benefit of treatment within a median follow-up period of 12.7 years (interquartile range, 7.3 to 15.5 years). Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a RR reduction in mortality of 33% and 31%, respectively. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%). Overall, no major perturbation of HRQoL and psychological well-being was apparent in the first years [340].

Table 6.1.3: Outcome of SPCG-4 at fifteen years follow-up [295]

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

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

6.1.1.4 The ProtecT study

The ProtecT trial randomised 1,643 patients, three-ways, between active treatment (RP or EBRT) and AM [321]. In this AM schedule, patients with a PSA rise of more than 50% in twelve months underwent a repeat biopsy, but none had systematic repeat biopsies (which presents an intermediary approach, between AS and WW). Most patients had low-risk disease with 90% PSA < 10 ng/mL, 77% Gleason 6 (20% Gleason 7), 76% T1c. After ten years of follow up, the CSS was the same between those actively treated and those on AM (99% and 98.8% respectively), as was the OS. Only metastatic progression differed (6% in the AM group as compared to 2.6% in the treated group).

The key finding is that AM is as effective as active treatment at ten years, at a cost of increased progression and a double metastatic risk. Metastases remained quite rare (6%), but more frequent compared to results from AS protocols based on patient selection. It is important to note that the AM arm in the study differs from contemporary AS protocols in terms of a monitoring strategy based almost entirely on PSA measurements alone; there was no use of mpMRI scan either at recruitment nor during the monitoring period, nor was there any protocol-mandated repeat prostate biopsies at regular intervals.

Nevertheless, in spite of these caveats, the ProtecT study has reinforced the role of deferred active treatment (i.e. either AS or some form of initial AM) as a feasible alternative to active curative interventions for patients with low-grade and low-stage disease. Beyond ten years, no data is available yet and AS is possibly safer, especially in younger men, based on initial patient selection. Individual life expectancy must be evaluated before considering any active treatment in low-risk situations, and for those with up to ten years individual life expectancy, AM or WW are probably very good options.

6.1.2 ***Radical prostatectomy***

The goal of RP by any approach must be eradication of disease, while, whenever possible, preserving continence and potency [341]. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [326]. An estimation of life expectancy is paramount in counselling a patient about surgery [331] (see also Section 5.4 – Evaluating health status and life expectancy). The main results from multicentre RCTs involving RP are summarised in Table 6.1.4.

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

Study	Acronym	Population	Year of treatment	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2014 [295]	SPCG-4	Pre-PSA era	1989-1999	160	Low risk Intermediate risk	89.8 84.9 (at 18 yr)
Wilt, *et al.* 2017 [339]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk Intermediate risk	95.9 91.5 (at 19.5 yr)
Hamdy, *et al.* 2016 [321]	ProtecT	Screened population	1999-2009	120	Mainly low- and intermediate risk	99 (at 10 yr)

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

6.1.2.1 Surgical techniques

Prostatectomy can be performed by open, laparoscopic or robot-assisted (RARP) approaches. In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss but not early (twelve weeks) functional or oncological outcomes [342]. Increased surgical experience has lowered the complication rates of RP and improved cancer cure [335-338]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, can improve cancer control with RP [343-345].

There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [295, 306, 333, 334, 339, 340, 346]. A first SR and meta-analysis of non-RCTs demonstrated that RARP had lower peri-operative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy (LRP), although there was considerable methodological uncertainty [333]. There was no evidence of differences in urinary incontinence at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes. Another SR and meta-analysis [347] included two small RCTs comparing RARP vs. LRP. The results suggested higher rates of return of erectile function (RR 1.51; 95% CI: 1.19-1.92) and return to continence function (RR 1.14; 95% CI: 1.04-1.24) in the RARP group. Consequently, there is emerging data to suggest some benefits of the robotic approach over the laparoscopic and open approaches, in terms of peri-operative, recovery and short term functional outcomes; however, uncertainty remains over oncological outcomes, longer term functional and QoL outcomes [348]. Therefore, no surgical approach can be recommended over another.

6.1.2.1.1 Pelvic lymph node dissection

A recent SR demonstrated that performing pelvic lymph node dissection (PLND) during RP failed to improve oncological outcomes, including survival [4]. However, it is generally accepted that extended pelvic LN dissection (eLND) provides important information for staging and prognosis which cannot be matched by any other currently available procedure [4]. The individual risk of finding positive LNs can be estimated using preoperative tools. Only a few of these tools are based on eLND templates. A risk of nodal metastases over 5% (Briganti nomogram [349, 350] or Roach formula [351] which has been shown to be almost as good as the nomogram) is an indication to perform nodal sampling by an extended nodal dissection [352-354].

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. With this template, 94% of patients are correctly staged [355].

6.1.2.1.2 Sentinel node biopsy analysis

The rationale for a sentinel node biopsy (SNB) is based on the concept that a sentinel node is the first to be involved by migrating tumour cells. Therefore, when this node is negative, it is possible to avoid an ePLND. A multi-disciplinary collaborative endeavour attempted to standardise definitions, thresholds and strategies in relation to techniques of SNB [356]. Indeed SNB has been shown to have a sensitivity of 95.2% for detecting men with metastases at eLND in a SR [357]. However, there is still insufficient quality evidence supporting oncological effectiveness of SNB for nodal staging. Sentinel node biopsy is therefore still considered as an experimental nodal staging procedure.

6.1.2.1.3 Nerve-sparing surgery

Nerve-sparing RP can be performed safely in most men with localised PCa [358, 359]. 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 [360, 361]. 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 [362].

6.1.2.1.4 Neoadjuvant ADT

Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of them using a 3 month period. The main findings were summarised in a Cochrane review [363]. It is associated with a decreased rate of pT3 (downstaging); decreased positive margins, and a lower incidence of positive LNs. These benefits are greater with increased treatment duration (up to 8 months). However, since neither the PSA relapse-free survival nor the specific survival were shown to improve, neoadjuvant ADT should not be considered in clinical practice.

6.1.2.2 Comparing effectiveness of radical prostatectomy vs. other interventions for localised disease

6.1.2.2.1 Radical prostatectomy vs. deferred treatment

Currently, three large prospective RCTs have compared RP over deferred treatment (see Section 6.1.2). In summary, there was conflicting evidence regarding the benefit of RP over deferred treatment. The only study to find a benefit of RP over WW (SPCG-4) [295] was conducted in the pre-PSA era. When comparing RP against WW [339], or against AM [321] no statistically significant benefit in OS at 10 years' of follow-up was observed. These findings highlight the importance of risk classification before discussing any form of surgery.

6.1.2.2.2 Radical prostatectomy vs. radiotherapy

ProtecT compared RP vs. AM vs. EBRT (combined with 6 months of ADT) [321]. At a median follow-up of ten years, there were no differences between surgery vs. EBRT in all oncological outcomes.

6.1.2.3 Acute complications of surgery

Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as robotic-assisted laparoscopic prostatectomy (RALP). Recent SRs have documented complication rates after RALP [364-368], and can be compared with contemporaneous reports after radical retropubic prostatectomy (RRP) [369]. From these reports, the mean continence rates at twelve months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP. There is, as yet, no evidence from retrospective studies on differences in urinary incontinence at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or ED outcomes. The major limitations of the included studies were the retrospective study design and the use of different assessment tools preventing comparison between techniques and series. Recently, a prospective, controlled, non-RCT of patients undergoing RP in fourteen centres using RALP or RRP was published. At twelve months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [370]. A recent RCT comparing RALP and RRP, has reported outcomes at twelve weeks in 326 patients [342]. Functional outcomes were similar in the two groups, but longer follow up is needed to report on longer term effects. The intra-and peri-operative complications of retropubic RP and RALP are listed in Table 6.1.5. The early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation remains controversial resulting in a lack of clear recommendations (see Section 8.3.2).

Table 6.1.5: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [364]**)**

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

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

6.1.2.3.1 Early complications of extended lymph node dissection

Pelvic eLND increases morbidity in the treatment of PCa [4]. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event. Other authors have reported more acceptable complication rates [371]. Similar rates of lymphoceles have been observed in RALP series; however, in one subgroup analysis lymphoceles were more common with the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [372, 373]. Briganti *et al.* [374] also showed more complications after extended compared to limited LND. Twenty percent of men suffer a complication of some sort after eLND. Thromboembolic events occur in less than 1% of cases.

6.1.3 ***Radiotherapy***

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

6.1.3.1 External Beam Radiation Therapy:

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

Intensity-modulated external-beam radiotherapy and VMAT employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes. Both techniques allow for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves, which are particularly useful as a means of sparing the rectum. Radiotherapy treatment planning for IMRT and VMAT differs from that used in conventional EBRT, requiring a computer system capable of 'inverse planning', and the appropriate physics expertise. Treatment plans must conform to pre-specified dose constraints to critical organs at risk of normal tissue damage, and a formal quality assurance process should be routine.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of image-guided radiotherapy (IGRT), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [375]. Tomotherapy is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

6.1.3.1.2 Dose escalation

Several RCTs have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year biochemical relapse [376-385]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant hormone therapy (HT) has varied (see Table 6.1.6). The best evidence of an OS benefit for patients with intermediate- or high-risk PCa, but not with low-risk PCa, comes from a non-randomised but well conducted propensity matched retrospective analysis of the U.S. National Cancer Database covering a total of 42,481 patients [386]. In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT plus HT, with no different recommendations according to the patient's risk group. If IMRT and IGRT are used for dose escalation, rates of severe late side-effects (≥ grade III) for the rectum are 2-3% and for the GU tract 2-5% [378, 385, 387-400].

Table 6.1.6: Randomised trials of dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
MD Anderson study 2011 [376]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs.78 Gy	9 yr	DSM vs. other cause of death	High risk/PSA > 10 16% DSM at 70 Gy 4% DSM at 78 Gy (p = 0.05) Higher risk 15% DSM at 70 Gy 2% DSM at 78 Gy (p = 0.03)
PROG 95-09 [377]	393	T1b-T2b PSA 15 ng/mL 75% GS < 6	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	8.9 yr	10-year ASTRO BCF	All patients: 32% BF at 70.2 Gy 17% BF at 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF at 70.2 Gy 7% BF at 79.2 Gy (p < 0.0001)
MRC RT01 [401]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	10 yr	BFS; OS	43% BFS at 64 Gy 55% BFS at 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)

Dutch randomised phase III trial [385]	664	T1b-T4 143 pts. with (neo) adjuvant HT	68 vs. 78 Gy	110 mo.	Freedom biochemical (Phoenix) and/or clinical failure at 10 yr	43% FFF at 68 Gy 49% FFF at 78 Gy (p = 0.045)
GETUG 06 [380]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	61 mo.	BCF (ASTRO)	39% BF at 70 Gy 28% BF at 80 Gy

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

6.1.3.1.3 Hypofractionation (HFX)

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue, and slowly proliferating cells are very sensitive to an increased dose per fraction [383]. A meta-analysis of 25 studies including > 14,000 patients concludes that because PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8-2 Gy [384]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient and cheaper for the health care system.

Several studies report on HFX applied in various techniques and, in part, also including HT [97, 402-410]. A SR concludes that studies on moderate HFX (2.5-4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking [411]. Moderate HFX should only be done by experienced teams using high quality EBRT using IGRT and IMRT in carefully selected patients and adhere to published phase 3 protocols (see Table 6.1.7 below).

Table 6.1.7: Major phase 3 randomised trials of moderate hypofractionation for primary treatment

Study/ Author	n	Risk, GS, or NCCN	ADT	RT Regimen	BED, Gy	Median FU, mo	Outcome
Lee, *et al.* [412]	550 542	low risk	None	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	5 yr DFS 86.3% (n.s.) 5 yr DFS 85.3%
Dearnaley, *et al.* [402, 413] CHHiP	1077/19 fx 1074/20 fx 1065/37 fx	15% low 73% intermediate 12% high	3-6 mo. before and during EBRT	57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx	73.3 77.1 74	62	5 yr BCDF 85.9% (19 fx) 90.6% (20 fx) 88.3% (37 fx)
Aluwini, *et al.* [405, 414, 415]	403 392	30% GS < 6 45% GS > 7, 25% GS 8-10	None	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	60	5 yr RFS 80.5% (n.s.) 5 yr RFS 77.1%
Catton, *et al.* [416]	608	intermediate risk 53% T1c 46% T2a-c	None	60 Gy/20 fx	77.1	72	5 yr BCDF both arms 85% HR: 0.96 (n.s)
	598	9% GS 6 63% GS 7a 28% GS 7b		78 Gy/39 fx	78		

ADT = androgen deprivation therapy; BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/β of 1.5 Gy; DFS = disease-free survival; EBRT = external beam radiotherapy; FU = follow-up; fx = fractions; GS = Gleason score; HR = hazard ratio; n = number of patients; NCCN = National Comprehensive Cancer Network; n.s. = not significant; y = year.

Extreme HFX has been defined as radiotherapy with > 3.4 Gy per fraction [417]. It requires IGRT and stereotactic body radiotherapy (SBRT). Table 6.1.8 gives an overview of selected studies. Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade GU and rectal toxicity, and long-term side-effects may not all be known yet [411, 418, 419]. Therefore it seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.1.8: Selected trial on extreme hypofractionation for intact localised PCa

Reference	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Freeman, *et al.* [420]	1743	-	41% low 42% intermediate 10% high 7% data missing	35-40 Gy/4-5 fx (8% SBRT-boost 19.5-21.8 Gy/3 fx after 45-50 Gy EBRT)	FFBF 92% at 2 yr 99% low risk 97-85% intermediate 87% high risk
Katz, *et al.* [421]	515	72	63% low 30% intermediate 7% high	35-36.25 Gy/5 fx	FFBF at 7 yr 96% low risk 89% intermediate 69% high risk

EBRT = external beam radiotherapy in standard fractionation; FFBF = freedom from biochemical failure; FU = follow-up; fx = number fractions; mo = months; n = number of patients; TD = total dose; SBRT = stereotactic body radiotherapy; y = year.

6.1.3.1.4 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with luteinising-hormone-releasing hormone (LHRH) ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [422-426] (Table 6.1.9). The main message is that for intermediate risk a short duration of around 6 months is optimal, while a longer one, around 3 years, is needed for high-risk patients.

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

Trial	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 [423]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65-70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with GS 7-10
RTOG 94-13 [427]	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10 [424]	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65-70 Gy RT	No significant difference at 10 yr
D'Amico AV, et al (2008) [425]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit (HR: 0·55, 95% CI: 0.34-0.90, p = 0.01) that may pertain only to men with no or minimal comorbidity
RTOG 92-02 [428]	T2c-4 N0-1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr as adjuvant after 4 mo. as neoadjuvant	65-70 Gy RT	p = 0.73, p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with GS 8-10

EORTC 22961 [382]	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr	70 Gy 3D-CRT	Better result with 3 yr treatment than with 6 mo. (3.8% improvement in survival at 5 yr)
EORTC 22863 [422]	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist For 3 yr (adjuvant)	70 Gy RT	Significant benefit at 10 yr for combined treatment (HR: 0.60, 95% CI: 0.45-0.80, p = 0.0004).
TROG 96-01 [426]	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in OS reported; benefit in PCa-specific survival (HR: 0.56, 95% CI: 0.32-0.98, p = 0.04) (10 yr: HR: 0.84, 0.65-1.08; p = 0.18)
RTOG 99-10 [429]	intermediate risk (94% T1-T2, 6% T3-4)	1579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk	70.2 Gy 2D/3D	67 vs. 68% p = 0.62, confirms 8 + 8 wk LHRH as a standard

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

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

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

Trial	Year	TNM stage	n	Trial	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 [430]	2014	T1b-2 Grade 2-3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. plus continuous flutamide	70 Gy 3D-CRT vs. no RT	18.9% (30.7%) vs. 8.3% (12.4%) CSM at 10 (15) yr favouring combined treatment (HR: 0.35; p < 0.0001 for 15-yr results) NCIC CTG PR.3/MRC
PRO7/SWOG [431, 432]	2015	T3-4 (88%), PSA > 20 ng/mL (64%), GS 8-10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRH agonist	65-70 Gy 3D-CRT vs. no RT	10-yr OS = 49% vs. 55% favouring combined treatment HR: 0.7, p < 0.001)
Mottet 2012 [433]	2012	T3-4 N0 M0	273	ADT ± EBRT	LHRH agonist for 3 yr	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr OS 71.4% vs. 71.5%
			264				

ADT = androgen deprivation therapy; CSM = cancer-spefic mortality; EBRT = external beam radiotherapy; GS = Gleason score; HR = hazard ratio; LHRH = luteinizing hormone-releasing hormone; mo = months; n = number of patients; OS = overall survival; RT = radiotherapy.

6.1.3.1.5 Combined dose-escalated radiotherapy and androgen-deprivation therapy

Zelefsky *et al.* [434] reported a retrospective analysis comprising 571 patients with low-risk PCa, 1,074 with intermediate-risk PCa, and 906 with high-risk PCa. 3D-conformal RT or IMRT were administered. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last ten years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was 3 months for low-risk patients and six months for intermediate-risk and high-risk patients, starting at three months before RT. The ten-year biochemical disease-free rate (BDFR) was significantly improved by dose escalation: above 75.6 Gy in low risk, and above 81 Gy for the intermediate- and high-risk groups. It was also improved by adding six months of ADT in intermediate- and high-risk patients. In the multivariate analysis, neither the dose > 81 Gy, nor adding ADT influenced OS. Published results from a RCT are awaited, but adding ADT does not seem to compensate for the dose increase.

6.1.3.2 Proton beam therapy

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

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose, but it cannot be used as evidence for the superiority of proton therapy per se [377]. Thus, unequivocal information that shows an advantage of protons over IMRT photon therapy is still not available. Studies from the SEER database, and from Harvard [435, 436], 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 [436].

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

6.1.3.3 Brachytherapy

6.1.3.3.1 Low-dose rate (LDR) brachytherapy

Low-dose rate brachytherapy uses radioactive seeds permanently implanted into the prostate. There is a consensus on the following eligibility criteria for LDR monotherapy [437]: Stage cT1b-T2a N0, M0; GS 6 (ISUP grade 1) with ≤ 50% of biopsy cores involved with cancer or GS 7(3+4), ISUP grade 2) with ≤ 33% of biopsy cores involved with cancer; An initial PSA level of ≤ 10 ng/mL; a prostate volume of < 50 cm^3; and an International Prostatic Symptom Score (IPSS) ≤ 12 and maximal flow rate > 15 mL/min on urinary flow tests [438].

The only available RCT comparing RP and brachytherapy as monotherapy was closed due to poor accrual [439]. Outcome data are available from a number of large population cohorts with mature follow-up [440-447]. The BDFS for Gleason 6 patients after five and ten years has been reported to range from 71% to 93% and 65% to 85%, respectively [440-447]. A significant correlation has been shown between the implanted dose and biochemical control [448]. A D90 (dose covering 90% of the prostate volume) of > 140 Gy leads to a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after four years (92 vs. 68%). There is no benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [440].

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

6.1.3.3.2 High-dose rate (HDR) brachytherapy

High-dose-rate brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in Table 6.1.11. The use of published guidelines is strongly recommended [449]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [450]. A single RCT of EBRT (55 Gy in 20 fractions) vs. EBRT (35.75 Gy in 13 fractions), followed by HDR brachytherapy (17 Gy in two fractions over 24 hours) has been reported [451]. In 218 patients with organ-confined PCa the combination of EBRT and HDR brachytherapy showed a significant improvement in the BDFR ($p = 0.04$) at five and ten year (75% and 46% compared to 61% and 39%). There were no differences in the rates of late bowel, urinary or sexual patient QoL over a ten-year follow-up period. However, a very high, uncommon, rate of early recurrences was observed in the EBRT arm alone,

even after two years, possibly due to a dose lower than the current standard used [451]. A SR of non-RCTs has suggested outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective, randomised trial [452].

Fractionated HDR brachytherapy as monotherapy can be offered to patients with low- and intermediate-risk PCa, informed that results are only available from limited series in very experienced centres [408, 453]. Five year PSA control rates over 90% are reported, with late Grade 3+ GU toxicity rates < 5% and no or very minimal Grade 3+ GI toxicity rates [408, 453].

Table 6.1.11: Difference between LDR and HDR brachytherapy

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

6.1.3.4 Side-effects of external beam radiotherapy and brachytherapy

Gastrointestinal and urinary side-effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of Grade I, 20% of Grade 2, and 2% Grade 3. In the same trial, approximately 30% of patients reported acute Grade I GI toxicity, 10% Grade 2, and less than 1% Grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [391]. In addition, general side-effects such as fatigue are common. It should be noted that the incidence of acute side-effects is greater than that of late effects (see Section 8.2.2.1), implying that most acute effects resolve. In a randomised trial of conventional dose EBRT vs. EBRT plus LDR brachytherapy, the incidence of acute proctitis was reduced in the brachytherapy arm, but other acute toxicities were equivalent [454]. Acute toxicity of HDR brachytherapy has not been documented in a RCT, but retrospective reports confirm lower rates of GI toxicity compared with EBRT alone and Grade 3 GU toxicity in 10% or fewer patients, but a higher incidence of urinary retention [455]. Similar findings are reported using HFX. For example, in a pooled analysis of 864 patients treated using extreme HFX and stereotactic radiotherapy, declines in urinary and bowel domains were noted at three months, which returned to baseline or better by six months [456].

6.1.4 ***Hormonal therapy***

6.1.4.1 Introduction

6.1.4.1.1 Different types of hormonal therapy

Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor. These two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB) [457].

6.1.4.1.1.1 Testosterone-lowering therapy (castration)

6.1.4.1.1.1.1 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 castration 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 [458]. Therefore, a more appropriate level is defined as < 20 ng/dL (1 nmol/L). This new definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [459-461]. 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).

6.1.4.1.1.1.2 Bilateral orchiectomy

Bilateral orchiectomy, or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [462] and it is the quickest way to achieve a castration level, which is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment.

6.1.4.1.1.2 Oestrogens

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [463]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side-effects, especially thromboembolic complications, even at lower doses [464-466] these drugs are not considered as standard first-line treatment.

6.1.4.1.1.3 Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon, which starts two to three days after administration and lasts for about one week. This may lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [467]. Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely remove the risk.

Anti-androgen therapy is usually continued for four weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare-up' is unknown [468].

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within two to four weeks [469]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [470] and at least comparable to orchiectomy [471].

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

6.1.4.1.1.4 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available.

Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [472]. An extended follow-up has been published, suggesting a better PSA PFS compared to monthly leuprorelin [471]. A SR did not show major difference between agonists and Degarelix and highlighted the paucity of on-treatment data beyond twelve months as well as the lack of survival data [473]. Its definitive superiority over the LHRH analogues remains to be proven.

6.1.4.1.1.5 Anti-androgens

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

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

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

6.1.4.1.1.5.1 Steroidal anti-androgens

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

6.1.4.1.1.5.1.1 Cyproterone acetate

Cyproterone acetate was the first licensed anti-androgen, but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31-41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT, CPA showed a poorer OS when compared with LHRH analogues [474]. 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 [475]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.1.4.1.1.5.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [476]. Non-androgen-related pharmacological side-effects differ between agents. Bicalutamide shows a more favourable safety and tolerability profile than flutamide and nilutamide [477]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.1.4.1.1.5.2.1 Nilutamide

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

6.1.4.1.1.5.2.2 Flutamide

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

6.1.4.1.1.5.2.3 Bicalutamide

The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [476, 478].

6.1.4.1.1.6 New compounds

Once on castration, the development of castration-resistance (CRPC) is imminent. It is considered to be mediated through two main overlapping mechanisms: androgen-receptor (AR)-independent and AR-dependent mechanisms (see Section 6.5 - Castrate-resistant PCa). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells, and an over-expression of the AR has been observed, suggesting an adaptive mechanism [479]. This has led to the development of several new compounds targeting the androgen axis: the two licenced drugs are abiraterone acetate (AA) and enzalutamide, both approved for mCRPC. Abiraterone acetate has also been approved for hormone-sensitive PCa, combined with ADT.

6.1.4.1.1.6.1 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-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 to prevent drug-induced hyperaldosteronism.

6.1.4.1.1.6.2 Enzalutamide

Enzalutamide is a novel anti-androgen with a higher affinity for the AR receptor than bicalutamide. 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.

*6.1.5 **Investigational therapies***

6.1.5.1 Background

Besides RP, EBRT and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa [480-483]. In this section, both whole gland and focal treatment will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy, as sufficient data are available to form the basis of some initial judgements. Other options - such as radiofrequency ablation and electroporation, among others - are considered to be in the early phases of evaluation [484]. All these modalities 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 [484, 485], whereby lesion-targeted ablation is undertaken in a precise, organ-sparing manner.

6.1.5.2 Cryotherapy

Cryotherapy uses freezing techniques to induce cell death by dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals and vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [480-483].

Freezing of the prostate is ensured by the placement of 17 gauge cryoneedles under TRUS guidance, placement of thermosensors at the level of the external sphincter and rectal wall, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryotherapy devices are mainly used. Since its inception, cryotherapy has been used for whole-gland treatment in PCa either as a primary or salvage treatment option.

The main adverse effects of cryosurgery are erectile dysfunction (ED) (18%), urinary incontinence (2-20%), urethral sloughing (0-38%), rectal pain and bleeding (3%) and recto-urethral fistula formation (0-6%) [486]. There is a lack of prospective comparative data regarding oncological outcomes of whole-gland cryosurgery as a curative treatment option for men with localised PCa, with most studies being non-comparative single-arm case series with short follow-up periods [486].

6.1.5.3 High-intensity focused ultrasound

High-intensity focused ultrasound consists of focused US waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation [487]. The goal of HIFU is to heat malignant tissues above 65°C so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anaesthesia, with the patient lying in the lateral or supine position. High-intensity focused US has previously been widely used for whole-gland therapy. The major adverse effects of HIFU include acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), recto-urethral fistula (0-5%) and urinary incontinence 10%) [486]. Disadvantages of HIFU include difficulty in achieving complete ablation of the prostate, especially in glands larger than 40 mL, and in targeting cancers in the anterior zone of the prostate. Similar to cryosurgery, the lack of any long-term prospective comparative data on oncological outcomes prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [486].

6.1.5.4 Focal therapy

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [488-490]. 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 [491-493].

A previous SR and network meta-analysis [486] on ablative therapy in men with localised PCa performed a sub-group analysis of focal therapy vs. RP and EBRT. Nine case series reporting on focal therapy were identified (five studies reporting on focal cryosurgical ablation of the prostate (CSAP), three studies on focal HIFU, and one study reported on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at three years. For focal HIFU vs. RP or EBRT, there were no comparable data on oncological, continence nor potency outcomes at one year, or more. More recently, Valerio *et al.* [485] performed a SR to summarise the evidence regarding the effectiveness of focal therapy in localised PCa. Data from 3,230 patients across 37 studies were included, covering different energy sources including HIFU, CSAP, photodynamic therapy, laser interstitial thermotherapy, focal brachytherapy, irreversible electroporation and radiofrequency ablation. The overall quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and retrospective in design, heterogeneity of definitions, approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review suggests that focal therapy has a favourable toxicity profile in the short to medium-term, its oncological effectiveness remains unproven due to lack of reliable comparative data against standard interventions such as RP and EBRT.

Another RCT compared focal therapy using padeliporfin-based vascular-targeted photodynamic therapy (PDT) vs. AS in men with low-risk PCa [494]. The study found at a median follow-up of 24 months, less patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24–0.46). In addition, more men in the PDT arm had a negative prostate biopsy at two years than men in the AS

arm (adjusted RR: 3.67, 95% CI: 2.53–5.33). Nevertheless, limitations of the study include inappropriately comparing an intervention designed to destroy cancer tissue in men with low-risk PCa against an intervention primarily aimed at avoiding unnecessary treatment in men with low-risk PCa, and an unusually high observed rate of disease progression in the AS arm (58% in two years). Given the lack of robust comparative data on medium to long-term oncological outcomes for focal therapy against curative interventions (i.e. RP or EBRT), focal therapy should remain experimental for the time being; robust prospective trials reporting standardised outcomes [495] are needed before recommendations in support of focal therapy for routine clinical practice can be made.

6.1.5.5 General guidelines for active treatment

Recommendations	Strength rating
Inform patients that no active treatment modality has shown superiority over any other active management options in terms of survival.	Strong
Inform patients that all active treatments have side-effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Strong
Perform an extended lymph node dissection (LND), when a LND is deemed necessary.	Strong
Do not perform nerve sparing surgery when there is a risk of extracapsular extension (based on cT stage, Gleason score, nomogram, multiparametric magnetic resonance imaging).	Strong
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Only offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	Strong
Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	Strong
Only offer focal therapy within a clinical trial setting.	Strong

*6.1.6 **Discussing treatment options***

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 appropriate therapy modalities has been considered together with the patient. In the following paragraphs we will only discuss active modalities where the aim is to try to be “curative” in patients were that is appropriate.

6.2 Treatment by disease stages

*6.2.1 **Treatment of low-risk disease***

6.2.1.1 Selection criteria for active surveillance

The main risk for men with low-risk disease is over-treatment. The ProtecT trial randomised 1,643 patients with PSA detected PCa between active treatment (RP or EBRT) and AM (a less intense form of AS) [321]. Although this included men with both low- and intermediate-risk disease, AM was as effective as active treatment at ten years, at a cost of an increased progression and a doubling of metastatic risk. However, metastases remain quite rare (6%), but more frequent when compared to results from AS protocols based on stricter patient selection [323]. This confirms that especially for low-risk patients, some form of initial AM is safe.

6.2.1.1.1 Clinical and pathological variables

Selection criteria for AS are limited by a lack of prospective RCTs, or findings from a formal consensus meeting. The criteria most often published include: Gleason 6, when specified < 2-3 positive cores with < 50% cancer involvement in every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc [324, 496]. The latter threshold remains controversial [496, 497]. A pathology consensus group suggested

excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [498] and perineal invasion [499].

A Canadian consensus group consider that AS is the treatment of choice for low-risk disease, without stratifying for biopsy results, although they clearly recommend that men < 55 years should be closely scrutinised for high-volume Gleason 6 cancer. In this setting, re-biopsy within six to twelve months to exclude sampling error is mandatory [496, 500] even if this could be modified in the future [501]. A SR and meta-analysis [502] found three clinico-pathological variables which were significantly associated with reclassification, which were; PSA-density, ≥ 2 positive cores, and African-American race.

6.2.1.1.2 Biological markers

Biological markers, including urine PCA3, transmembrane protease, serine 2-*TMPRSS2-ERG* fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself [503-505]. However, further data will be needed before such markers can be used in standard clinical practice [132].

6.2.1.1.3 Imaging for treatment selection

Imaging with mpMRI is of particular interest due to its high NPV value for lesion upgrading in low-risk patients [3] and for staging anterior prostate lesions [506, 507] and is summarised in a recent review of the literature [508]. The added value of mpMRI and targeted biopsies could be promising in reducing misclassifications at initial diagnosis and follow-up, reducing unnecessary (targeted or systematic) biopsies at follow-up, and aiding in monitoring patients on AS. It may differ at different time points in an AS setting. At confirmatory biopsy in men who did not have a mpMRI before, the reclassification rate due to targeted biopsies can be estimated to be 2-22% (absolute numbers) [507, 509-512]. The added value of mpMRI for surveillance/repeat biopsies (hence more than one year following the confirmatory biopsy) has not been evaluated yet. However, combined data of confirmatory and surveillance repeat biopsies show a reclassification rate due to targeted biopsies of 2-14% (absolute numbers) [513-515]. These numbers are directly related to the eligibility criteria for AS, and the reclassification criteria used within these populations.

The concordance of systematic and targeted biopsies at confirmatory biopsies is approximately 80%. However omitting systematic biopsies may induce a misclassification rate of 3-13% [507, 509-511, 513-515], therefore systematic biopsy should be systematically performed, even facing a normal mpMRI.

Targeted biopsies of suspicious lesions on mpMRI are mainly performed for Likert/PIRADS (Prostate Image Reporting and Data System) ≥ 3 lesions. Although increased rates of reclassification occur in PIRADS 4 and 5 lesions, a substantial proportion of PIRADS 3 lesions show reclassification following targeted biopsies [509, 510], thereby confirming the significance to biopsy Likert/PIRADS ≥ 3 lesions within AS management.

6.2.1.1.4 Follow up

The follow up strategy is based on serial DRE (at least once yearly), PSA (at least once, every six months) and repeated biopsy (at a minimum interval of three to five years). Based on two small single centre studies [516, 517], not all patients with progression/reclassification at biopsy had radiological progression and vice versa. Therefore, mpMRI cannot be used as a stand-alone tool to trigger follow-up biopsies, but efforts are being made to define and standardise radiological progression during AS [518].

Risk prediction in men on AS is under investigation to further reduce unnecessary biopsies and misclassification [501]. In an AS cohort of 259 men with Gleason 6 and Gleason 7(3+4) cancers detected by MRI-targeted and systematic biopsies, independent predictors of upgrading at 3 years were Gleason 7(3+4), PSA density ≥ 0.15 ng/mL/cm^3 and a score 5 lesion on MRI [519]. Thus, the role of mpMRI in risk prediction should be further investigated.

6.2.1.1.5 Switching to active treatment

The decision to start active treatment should be based on a change in the biopsy results (GS, number of positive cores, core length involvement), or T-stage progression. These criteria are recognised in all published cohorts but are limited by the heterogeneity of inclusion criteria for AS. A PSA change (especially a PSA-DT < three years) is a less powerful indicator to change management based on its weak link with grade progression [520, 521]. Active treatment may also be instigated upon a patient's request. This occurs in around 10% of patients on AS [522].

6.2.1.2 Active treatment

Patients not meeting criteria listed for AS or showing progression during surveillance or unwilling AS should be discussed for active treatment.

6.2.1.2.1 Radical prostatectomy

At 10 years' follow-up in the ProtecT study, where the majority of men had early localised disease (i.e. > 75%

had either clinical T1 or Gleason sum score 6 disease), a benefit for metastases-free and PFS, but neither cancer-specific nor OS, for RP compared to AM and RT was seen [321]. In the SPCG-4 study [332], death from any cause and distant metastases were significantly reduced in low-risk PCa at eighteen years for RP compared with WW. However, death from PCa was not reduced. In the PIVOT trial, a pre-planned subgroup analysis of men with low-risk PCa showed that RP did not significantly reduce all-cause mortality or death from PCa at ten years compared with WW [339].

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 [523]. Individual patient preferences should always be considered in shared decision-making. If RP is performed in low-risk PCa, pelvic LN dissection is not necessary (pN+ risk ≤ 5%) [524].

6.2.1.2.2 Radiation therapy treatment policy

The ProtecT study also confirmed that RT combined with six months of ADT failed to improve cancer-specific or OS in this PSA-screened population, but did improve PFS, as per RP [321]. As with RP, the decision to offer treatment should be based upon the probabilities of clinical progression, side-effects and potential benefit to survival [523]. Individual patient preferences should always be considered in shared decision-making. If RT is performed in this group, intensity-modulated RT with escalated dose (74-80 Gy) and without ADT, or moderate HFX (see Section 6.1.3.1.3) should be used. Low-dose rate brachytherapy is a valid alternative provided the patient fulfils the criteria (see Section 6.1.3.3.1).

6.2.1.3 Other treatments

All other treatment modalities should be considered as investigational. Neither whole gland treatment nor focal treatment can be considered as standard (see 6.1.4). Ideally, they should only be performed in a clinical trial setting.

6.2.1.4 Guidelines for the treatment of low-risk disease

Recommendations	Strength rating
Watchful waiting (WW)	
Offer a WW policy to asymptomatic patients with a life expectancy < ten years (based on comorbidities).	Strong
Active surveillance (AS)	
Offer AS to patients suitable for curative treatment but with low-risk PCa.	Strong
Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.	Strong
During confirmatory biopsy include systematic and targeted biopsies.	Strong
Base follow up on digital rectal examination, prostate-specific antigen and repeated biopsies.	Strong
Counsel patients about the possibility of needing further treatment in the future.	Strong
Active treatment	
Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	
Do not perform a PLND (estimated risk for pN+ < 5%).	Strong
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate and with a good International Prostatic Symptom Score and a prostate volume < 50 mL.	Strong
Use intensity-modulated radiation therapy with a total dose of 74-80 Gy, without androgen deprivation therapy.	Strong
Offer moderate hypofractionation (60 Gy/20 fx in four weeks or 70 Gy/28 fx in six weeks) as an alternative treatment option.	Strong
Other therapeutic options	
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting.	Strong

6.2.2 ***Treatment of Intermediate-risk disease***

When managed with non-curative intent, intermediate-risk PCa is associated with ten-year and fifteen-year PCSM rates of 13 and 19.6%, respectively [525].

6.2.2.1 Active Surveillance

In the ProtecT trial, up to 22% of the randomised patients in the AM arm had a GS > 6 and 10% a PSA > 10 ng/mL [321]. No data stratified by risk group have so far been reported. A Canadian consensus group proposes that low volume Gleason 7(3+4) (< 10% pattern 4) may also be considered for AS. These recommendations have also been endorsed by the American Society of Clinical Oncology ASCO [526] However, recent findings suggest that any grade 4 pattern is associated with a three-fold increased risk of metastases compared to Gleason 6, while a PSA up to 20 ng/mL might be an acceptable threshold [500, 527, 528]. Including mpMRI and a systematic rebiopsy (eventually targeted) might improve the accuracy of staging. However clear evidence to support AS in the intermediate-risk group is not available and therefore care must be taken if advocating this treatment strategy especially in patients with the longest life expectancy.

6.2.2.2 Surgery

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71; 95% CI: 0.53-0.95), death from PCa (RR: 0.38; 95% CI: 0.23-0.62) and distant metastases (RR: 0.49; 95% CI: 0.32-0.74) were significantly reduced in intermediate-risk PCa at eighteen years. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69 [95% CI: 0.49-0.98]), but not death from PCa (0.50; 95% CI: 0.21-1.21) at ten years.

The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [524]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [524]. In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes.

6.2.2.3 Radiation therapy

6.2.2.3.1 Recommended external beam radiation therapy for intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months) [381, 529, 530]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT or VMAT at an escalated dose (76-80 Gy) or a combination of IMRT or VMAT and brachytherapy (see Section 6.2.3.2.3).

6.2.2.3.2 Brachytherapy monotherapy

Low-dose rate brachytherapy can be offered to very selected patients (ISUP grade 2 with ≤ 33% of biopsy cores involved with cancer), provided they fulfil all the other criteria. Fractionated HDR brachytherapy as monotherapy can be offered to selected patients with intermediate-risk PCa although they should be informed that results are only available from small series in very experienced centres. Five-year PSA control rates over 90% are reported, with late Grade 3+ GU toxicity rates < 5% and no, or very minimal, Grade 3+ GI toxicity rates [408, 453]. There are no direct data to inform on the use of ADT in this setting.

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

All other treatment modalities should be considered as investigational. Neither whole gland treatment nor focal treatment can be considered as standard (see Section 6.1.5). Ideally they should only be offered in clinical trials [484].

6.2.2.5 Guidelines for the treatment of intermediate-risk disease

Recommendations	Strength rating
Active surveillance (AS)	
Offer AS to highly selected patients (< 10% pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with intermediate-risk disease and a life expectancy > ten years.	Strong
Offer nerve-sparing surgery to patients with a low risk of extracapsular disease (refer to nomograms).	Strong
Pelvic lymph node dissection (ePLND)	
Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to selected patients (see Section 6.2.3.2.3); patients without a previous transurethral resection of the prostate and with a good International Prostatic Symptom Score and a prostate volume < 50 mL.	Strong
For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy, in combination with short-term neoadjuvant plus concomitant androgen deprivation therapy (ADT) (four to six months).	Strong
In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
Other therapeutic options	
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting.	Strong

*6.2.3 **Treatment of high-risk localised disease***

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP [531]. When managed with non-curative intent, high-risk PCa is associated with ten-year and fifteen-year PCSM rates of 28.8 and 35.5%, respectively [525]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

6.2.3.1 Radical prostatectomy

Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable option in selected patients with a low tumour volume. Extended PLND should be performed in all high-risk PCa cases undergoing RP, as the estimated risk for positive LNs is 15-40% [524]. Patients should be aware pre-operatively that surgery may be part of multi-modality treatment

6.2.3.1.1 Gleason score 8-10 (ISUP grade 4-5)

The incidence of organ-confined disease is 26-31% in men with a GS 8-10 on systematic biopsy. A high rate of downgrading exists between the biopsy GS and the GS of the resected specimen [532]. Several retrospective case series have demonstrated CSS rates over 60% at fifteen years after RP in the context of a multimodal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy GS > 8 [295, 342, 533, 534].

6.2.3.1.2 Prostate-specific antigen > 20 ng/mL

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a CSS at fifteen years of over 70% [295, 342, 347, 535-537].

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

cN0 patients who undergo RP but who were found to have pN1 were reported to have an overall CSS and OS of 45% and 42% respectively at fifteen years [538-544]. However, this is a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Section 6.2.4.5).

6.2.3.2 External beam radiation therapy

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

For high-risk localised PCa, use a combined modality approach, consisting of dose-escalated IMRT or VMAT, plus long-term ADT. The duration of ADT has to take into account PS, comorbidities, and the number of poor prognostic factors. It is important to recognise that in several studies EBRT plus short-term ADT did not improve OS in high-risk localised PCa [424, 425, 427], and long-term ADT (at least two to three years) is currently recommended for these patients.

6.2.3.2.2 Lymph node irradiation in cN0

There is no level 1 evidence for prophylactic whole-pelvic irradiation, since RCTs have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic LNs in high-risk cases [545-547]. In the RTOG 94-13 study [427], 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. Furthermore, in most trials dealing with high-risk PCa, a whole pelvis field was considered standard of care. The benefits of pelvic nodal irradiation using IMRT or VMAT merit further investigation in RCTs as conducted by the RTOG or the UK NCRI group. Performing an ePLND in order to decide whether or not pelvic RT is required (in addition to combined prostate EBRT plus long-term ADT) remains purely experimental in the absence of level 1 evidence.

6.2.3.2.3 Low-dose rate brachytherapy boost

In men with intermediate- or high-risk PCa, LDR brachytherapy boost with supplemental EBRT and hormonal treatment [548] may be considered. Dose-escalated EBRT (total dose of 78 Gy) has been compared with EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy) in intermediate-risk and high-risk patients in a randomised trial, with twelve months of ADT in both arms [549]. The LDR boost resulted in five- and seven-year PSA PFS increase (89% and 86% respectively compared to 84% and 75%). This improvement came with an increase in late Grade 3+ urinary toxicity (18% compared to 8%). Toxicity was mainly due to urethral strictures and incontinence and great care should be taken during treatment planning.

6.2.3.3 Options other than surgery and radiotherapy for the primary treatment of localised prostate cancer.

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

6.2.3.4 Guidelines for radical treatment of high-risk localised disease

Recommendation	Strength rating
Radical Prostatectomy (RP)	
Offer RP to patients with high-risk localised PCa and a life expectancy of > ten years only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk disease.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatments	
In patients with high-risk localised disease, use external-beam radiation therapy (EBRT) with 76-78 Gy in combination with long-term androgen deprivation therapy (ADT) (two to three years).	Strong
In patients with high-risk localised disease, use EBRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (two to three years).	Weak
Other therapeutic options outside surgery and radiotherapy	
Do not offer either whole gland or focal treatment to high-risk patients.	Strong
Do not use ADT monotherapy in asymptomatic patients.	Strong

6.2.4 ***Treatment of locally advanced prostate cancer***

No standard treatment can be defined in the absence of level 1 evidence. But a local treatment combined with a systemic one provides the best outcome, provided the patient is ready and fit enough to receive both. The optimal local treatment is still a matter of debate. Randomised controlled trials are only available for EBRT.

6.2.4.1 *Surgery*

Surgery for locally advanced disease as part of a multimodal therapy has been reported [532, 550, 551]. Retrospective case series demonstrated over 60% CSS at fifteen years and over 75% OS at ten years [532, 550-556]. For cT3b-T4 disease, PCa cohort studies showed 10 year CSS of over 87% and OS of 65% [557-559].

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Although no RCT is available, data from prospective cohorts comparing the survival of pN+ patients (as defined following pathological examination after RP) is another argument for omitting frozen sections if a RP is planned as well as the continuation of the procedure in case of suspected nodes [560]. Only limited evidence exists supporting RP for cN+ patients. Hsu *et al.* compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at pre-operative staging. cN+ was not a significant predictor of CSS [561]. An ePLND is considered standard if a RP is planned.

6.2.4.2 *Radiotherapy for locally advanced PCa*

In locally advanced disease, RCTs have clearly established that the additional use of long-term ADT combined with RT produces better OS than ADT or RT alone (see Section 6.1.3.1.4 and Tables 6.1.9 and 6.1.10). In clinical, or pathological node-positive disease, RT monotherapy is associated with poor outcomes [382], and these patients should receive RT plus long-term ADT. A subgroup analysis from the RTOG 85-31 with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic RT with immediate HT had better five-year (54%) and nine-year (10%) PFS rates vs. 33% and 4%, respectively, for radiation alone ($p < 0.0001$). Multivariate analysis showed that this combination had a statistically significant impact on the OS [562]. These findings are also confirmed from the control arm of the STAMPEDE trial (HR: 0.48 [95% CI: 0.29-0.79]) in a non-randomised comparison [563].

6.2.4.3 *Options other than surgery and radiotherapy for primary treatment*

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

The deferred use of ADT as single treatment modality has been answered by the EORTC 30891trial [524]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa received ADT alone, either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS HR was 1.21 (95% CI: 1.05-1.39), favouring immediate treatment. Surprisingly, no different disease-free or symptom-free survival were observed, raising the question of survival benefit. In locally advanced T3-T4 M0 disease unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50 ng/mL and a PSA-DT < 12 months [524, 564], or those that are symptomatic. The median time to start deferred treatment was seven years. In the deferred treatment arm, 25.6% died without needing treatment.

6.2.4.4 *Guidelines for radical treatment of locally-advanced disease*

Recommendations	Strength rating
Radical Prostatectomy (RP)	
Offer RP to highly selected patients with (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection (eLND)	
Perform an eLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatments	
In patients with locally advanced cN0 disease, offer radiotherapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer long-term ADT for two to three years.	Weak
Other therapeutic options outside surgery and radiotherapy	
Do not offer whole gland treatment or focal treatment to high-risk patients.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment and who are either symptomatic or asymptomatic, but with a prostate-specific antigen (PSA)-doubling time < 12 months or a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

6.2.4.5 Adjuvant treatment after radical prostatectomy

Adjuvant treatment is by definition added to the primary or initial therapy; to decrease the risk of relapse. With EBRT, short- or long-term ADT is selected based on the initial risk classification (see Section 6.1.3.1.4). Regarding RP, the key factor is that the PSA must be below 0.1 ng/mL to be considered undetectable. All information listed below, refers to patients with a post-operative undetectable PSA. A post-operative PSA of above 0.1 ng/mL is an indication of persistent PCa cells. In such a case, further treatment will be salvage treatment.

6.2.4.5.1 Risk factors for relapse

Gleason score ≥ 7 or patients classified as pT3 pN0 after RP due to positive margins (highest impact), capsule rupture and/or invasion of the seminal vesicles are at high risk of relapse which can be as high as 50% after five years [565]. Irrespective of the pT stage, the number of removed nodes [358, 566-572], tumour volume within the LN and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [359]. A LN density (defined as the percentage of positive LNs in relation to the total number of analysed/removed LNs) over 20% was found to be associated with poor prognosis [360]. Finally the number of involved nodes [567, 568, 573] seems to be a major factor for predicting relapse, the threshold being considered to be less than three positive nodes from an ePLND [4, 567, 573]. However, prospective data are needed before defining a definitive threshold value.

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

Three prospective randomised trials have assessed the role of immediate post-operative RT (adjuvant RT [ART]) (Table 6.2.1). It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial, representing a major limitation in interpretation, as patients with a detectable PSA would now be considered for salvage therapy rather than adjuvant radiotherapy. Thus, for patients at increased risk of local relapse, who present with a PSA level of < 0.1 ng/mL, two options can be offered in the framework of informed consent. These are:

- Immediate ART to the surgical bed [574-576] after recovery of urinary function, during the first six months post-surgery;
  or
- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [577, 578] (see Section 6.3.5.1 on Salvage EBRT).

Table 6.2.1: Overview of all three randomised trials for adjuvant surgical bed radiation therapy after RP*

Reference	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical progression-free survival	Overall survival
SWOG 8794 [576]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr: 53% vs. 30% (p < 0.05)	10 yr: 74% vs. 66% Median time: 15.2 vs. 13.3 yr p = 0.023
EORTC 22911 [574]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr: 60.6% vs. 41% (p < 0.001)	81% vs. 77% n.s.
ARO 96-02 [575]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr: 56% vs. 35% (p = 0.0001)	10 yr: 82% vs. 86% n.s.

**See Section 6.3.5.2.3 for delayed (salvage) post-radical prostatectomy external irradiation.*
BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; n.s. = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

6.2.4.5.3 Adjuvant androgen ablation

6.2.4.5.3.1 Adjuvant androgen ablation in men with N0 disease

Adjuvant androgen ablation with bicalutamide 150 mg daily did not improve PFS in localised disease while it did for locally advanced disease after RT. However this never translated to an OS benefit [361] A SR showed a possible benefit for PFS, but not OS for adjuvant androgen ablation [363].

6.2.4.5.3.2 Adjuvant androgen ablation in men with pN1 disease

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a ten-year CSS rate of 80% [579, 580]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective RCT [580]. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and the findings may not apply to men with less extensive nodal metastases.

6.2.4.5.3.3 Adjuvant radiotherapy combined with ADT in men with pN1 disease

In a retrospective multicentre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated adjuvantly with continuous ADT [581]. The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), GS 7-10 and pT3-4 or R1 as well as men with three to four positive nodes were more likely to benefit from RT after surgery, while the other subgroups were not [282]. 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 [280]. No recommendations can be made on the extent of adjuvant RT in pN1 disease (prostatic fossa only or whole pelvis) 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 [282]. No data is available regarding adjuvant EBRT without ADT.

6.2.4.5.3.4 Adjuvant chemotherapy

The TAX3501 trial comparing the role of leuprolide (eighteen months) with and without docetaxel (six cycles) ended prematurely due to poor accrual. Adjuvant chemotherapy after RP should only be considered in a clinical trial [582].

6.2.4.5.4 Guidelines for adjuvant treatment options after radical prostatectomy

Recommendations	Strength rating
Only discuss adjuvant treatment in men with a post-operative prostate-specific antigen (PSA) < 0.1 ng/mL.	Strong
Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients.	Strong
Offer adjuvant external-beam radiation therapy to the surgical field to patients at increased risk of local relapse: pT3 pN0 with positive margins (highest impact), and/or invasion of the seminal vesicles.	Strong
Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT for node-positive (pN+). 2. Offer adjuvant ADT with additional radiotherapy. 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

6.2.4.5.5 Guidelines for non-curative or palliative treatments in prostate cancer

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

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

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

*6.3.1 **Background***

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

*6.3.2 **Definitions of clinically relevant PSA relapse***

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

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [583-585] However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients. After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is any PSA increase ≥ 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [586].

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

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

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

6.3.3.1 Post-radical prostatectomy biochemical recurrence

Not all patients with BCR after RP will develop clinical recurrences. In two studies of 1,997 and 2,400 men treated by RP, only 23-34% of those with BCR developed a clinical recurrence and 6% subsequently died of PCa [569, 587].

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. A PSA-DT < three months, SVI (pT3b), specimen GS 8-10, or time to PSA recurrence < 3 years indicate a high risk of metastases and PCSM. Conversely, a PSA-recurrence > three years following surgery, specimen GS < 7, pathologic organ-confined disease or limited extracapsular extension (pT3a), and PSA-DT > twelve months indicates a low risk of metastases and PCSM [588-591]. A rising PSA-DT,

≤ 0.2 ng/mL, has been associated with an increased risk of metastases and death [592]. Patients in the low-risk subgroup typically respond very well to SRT with a high probability of PSA being undetectable [593]. 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 [594]. Trock *et al.* demonstrated that SRT was associated with a significant three-fold increase in PCa-specific survival relative to those who received no salvage treatment. The increase in PCa-specific survival associated with SRT was limited to men with a PSA-DT of < six months and remained after adjustment for pathological stage and other established prognostic factors. Salvage RT initiated > two years after recurrence provided no significant increase in PCa-specific survival [594].

6.3.3.2 Post-radiotherapy biochemical recurrence

In patients experiencing PSA-recurrence after RT, PSA-DT < three months, time to biochemical progression < three years, biopsy GS 8-10 or clinical stage cT3b-T4 also indicate a high risk of metastases and PCSM. Conversely, PSADT > fifteen months, biopsy GS < 7, clinical stage < cT3a and time to BCR > three years indicate a low risk of metastases and PCSM [590, 595, 596].

Zumsteg *et al.* have designed a risk score to further subdivide patients who develop PSA recurrence following RT. Those with > two high-risk factors (PSA-DT < three months, time to BCR < three years, biopsy GS 8-10 and clinical stage cT3b-T4) have an increased risk of developing metastases and PCSM as compared to those with 0 or 1 risk factor [596].

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

6.3.4.1 Assessment of metastases

6.3.4.1.1 Bone scan and abdominopelvic CT

Because BCR after RP or RT precedes clinical metastases by seven to eight years, on average [569, 597], the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [598]. 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 [599, 600].

Only 11-14% of patients with BCR after RP have a positive CT [599]. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [601].

6.3.4.1.2 Choline PET/CT

In two different meta-analyses, the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86-89% and 89-93%, respectively [602, 603].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [604] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [605]. The specificity of choline PET/CT is also higher than bone scan with fewer false-positive and indeterminate findings [279]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.2).

Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [265, 606-608]. In patients with BCR after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL, but rises to 67-100% when the PSA level is > 5 ng/mL. In a recent meta-analysis, choline PET/CT detection rates were 65% (95% CI: 58%-71%) when the PSA-DT was < six 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 [606].

Despite its limitations, choline PET/CT may change medical management in 18-48% of patients with BCR after primary treatment [609-611]. 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) [611].

Choline PET/CT cannot be recommended in all patients, but should be limited to patients who are fit enough for curative loco-regional salvage treatment.

After RP, the optimal PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL [607, 608]. 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 [607]. 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 [612]. In another study of 140 patients the choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [613].

6.3.4.1.3 Fluoride PET and PET/CT

^{18}F-Fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases [614]. However, ^{18}F-Fluoride is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [615].

6.3.4.1.4 Prostate-specific membrane antigen-based PET/CT

Prostate-specific membrane antigen-based PET/CT has shown promising potential in patients with BCR, although most studies are limited by their retrospective design. Detection rates of 15-58%, 25-73% and 69-100%, 71-100% have been reported for PSA ranges of 0.2-0.5 ng/mL, 0.5-1 ng/mL, 1-2 ng/mL and > 2 ng/mL respectively [290, 616-620]. In these PSA ranges, the relative proportion of positive findings corresponding to purely local recurrences or to distant metastases remains unclear. Nonetheless, PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL. Two head-to-head comparisons confirmed this finding [617, 621]. PSMA PET/CT identified the site of recurrence in 14 of 32 patients with negative choline PET/CT (44%; prostatic bed, n = 8; LNs, n = 6) [622]. Higher PSA velocity or lower PSA doubling time seem associated with higher PSMA PET/CT positivity rates [275, 290, 616, 623], even if some authors found no correlation between PSA kinetics and positivity rates [617].

In a prospective multicentre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [289].

A single-centre study assessed 164 men who underwent PSMA PET/CT for rising PSA after RP, with PSA levels < 1 ng/mL. In men with a negative PSMA PET/CT who received salvage RT, 85% (n = 23/27) demonstrated a treatment response, compared to further PSA increase in 65% (22/34) in those not treated. In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (n = 29/36) responded to salvage RT [624]. Thus, PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to prostate) and poor response (positive nodes or distant disease) to salvage RT. However, these results based on small numbers and short follow-up should be confirmed in other studies.

6.3.4.1.5 Whole-body and axial MRI

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT [625]. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

6.3.4.2 Assessment of local recurrences

6.3.4.2.1 Local recurrence after radical prostatectomy

Because the sensitivity of anastomotic biopsies is low, especially for PSA levels < 1 ng/mL [598], salvage RT is usually decided on the basis of the BCR, without histological proof of the local recurrence, preferably when the PSA level is below 0.5 ng/mL. The dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Thus, most patients undergo salvage RT without local imaging.

Multiparametric magnetic resonance imaging can detect local recurrences in the prostatic bed, but its sensitivity in patients with PSA level < 0.5 ng/mL remains controversial [626, 627]. Choline PET/CT is less sensitive than mpMRI when the PSA level is < 1 ng/mL [628]. Prostate-specific membrane antigen-based PET/CT is positive in 15-58% of patients with BCR and PSA levels < 0.5 ng/mL [617, 618, 620], but published series are difficult to interpret since they usually mix patients with history of RP and RT and do not specify the proportion of local recurrences and distant metastases diagnosed at PSA levels < 0.5 ng/mL.

Precise detection and location of local recurrences after RP will be needed only if it is proven that stereotaxic boost to the recurrence site during salvage RT improves the patient outcome.

6.3.4.2.2 Local recurrence after radiation therapy

In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [598].

Transrectal US is not reliable in depicting local recurrences after RT. In contrast, mpMRI has yielded excellent results [598, 629-631] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with choline PET/CT [613], but choline PET/CT has not been

compared to mpMRI yet. It is also too soon to know if PSMA PET/CT can play a role in the detection of local recurrences after RT [275].

6.3.4.3 Summary of evidence on imaging in case of biochemical recurrence

Detection and localisation of the local recurrence site after RP is not necessary since it has not been proven that stereotaxic boost to the recurrence site during salvage RT improves the outcome.

It is necessary to confirm the local recurrence after RT by biopsy and to localise it as precisely as possible before salvage treatment. Multiparametric MRI is so far the best technique to localise the recurrence and guide the biopsy.

Many recent studies suggest that PSMA PET/CT is substantially more sensitive than abdominopelvic CT, bone scan and choline PET/CT in the detection of distant metastases in patients with BCR. Although most studies are retrospective and/or monocentric, they all came to the same conclusion. Early detection of metastases in a BCR setting is clinically highly relevant. This is particularly true in the post-RT setting. Salvage therapies for local recurrences after RT induce a substantial morbidity and it is necessary to detect metastatic patients with the highest possible sensitivity, to avoid the morbidity of useless salvage therapies in these patients. After RP, unlike choline PET/CT, PSMA PET/CT showed high positivity rates, even for PSA levels < 1 ng/mL. Because the localisation of the local recurrence is not useful, the indication of a sensitive test like PSMA PET/CT in patients with PSA levels < 1 ng/mL will depend on their risk of having metastatic disease. Prostate-specific antigen kinetics might be useful, but this needs to be proven.

6.3.4.4 Guidelines for imaging in patients with biochemical recurrence

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	**LE**	**Strength rating**
Perform imaging only if the outcome will influence subsequent treatment decisions.		Strong
If the PSA level is ≥ 1 ng/mL, perform a prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT), if available, or a choline PET/CT imaging otherwise.	2b	Weak
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients who are considered candidates for local salvage therapy.	3	Strong
Perform PSMA PET/CT (if available) or choline PET/CT imaging to rule out positive lymph nodes or distant metastases in patients fit for curative salvage treatment.	2b	Strong

6.3.5 ***Treatment of PSA-only recurrences***

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

6.3.5.1 Salvage radiotherapy [SRT] for PSA-only recurrence after radical prostatectomy

Early SRT provides the 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 [632-635], corresponding to a ~80% chance of being progression-free five years later [578]. 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 two years of BCR, showed that salvage RT was associated with a three-fold increase in PCa-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage RT has also been effective in patients with a short PSA-DT [594]. Despite the indication for salvage RT, a “wait and see” strategy remains an option in patients with a long PSA-DT of > twelve months [587]. For an overview, see Table 6.3.1.

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

Reference	Year	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr results
Bartkowiak, *et al.* [636]	2017	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Tendulkar, *et al.* [637]	2016	2460	60	0.5	66 Gy 16% ADT	56% (5)	SRT; PSA ≤ 0.2 ng/mL 71% 0.21-0.5 ng/mL 63% 0.51-1.0 ng/mL 54% 1.01-2.0 ng/mL 43% > 2 ng/mL 37% p < 0.001
Stish, *et al.* [632]	2016	1106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Soto, *et al.* [638]	2012	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16

**Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival'. Therefore, data sets without ADT are highlighted. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.*
ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up; mo = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen; SRT = salvage radiotherapy; yr = year.

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence, metastatic disease, disease specific and OS are more clinically meaningful endpoints which are used to support clinical decision making. However, low event rates and the necessity for long-term follow-up limit the volume of available evidence, in terms both of statistics and of the effects of RT technical developments over time. Table 6.3.2 summarises results for recent studies on clinical endpoints after SRT.

Two studies report significantly better outcomes (DM, DSM and OS) in patients who re-achieve a PSA nadir < 0.1 ng/mL after SRT without ADT [636, 639]. A recent, international, multi-institutional analysis of pooled data from RCTs has suggested that metastasis-free survival is the surrogate endpoint of most validity, in respect of its impact on OS [640].

Table 6.3.2: Recent studies reporting clinical endpoints after SRT

Reference	Year	n	Median FU (mo)	Regimen	Outcome
Tendulkar, *et al.* [637]	2016	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10 yr DM SRT; PSA 0.01-0.2 ng/mL 9% SRT; PSA 0.21-0.50 ng/mL 15% SRT; PSA 0.51-1.0 ng/mL 19% SRT; PSA 1.01-2.0 ng/mL 20% SRT; PSA > 2 ng/mL 37%, p < 0.001

Stish, *et al.* [632]	2016	1106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr DM SRT; PSA ≤ 0.5 ng/mL 7% and 12% SRT; PSA > 0.5 ng/mL 14% and 23% p < 0.001 5 and 8.9 yr DSM SRT; PSA ≤ 0.5 ng/mL < 1% and 6% SRT; PSA > 0.5 ng/mL 5% and 10% p = 0.02 5 and 8.9 yr OS SRT; PSA ≤ 0.5 ng/mL 94% and 86% SRT; PSA > 0.5 ng/mL 91% and 78% p = 0.14
Jackson, *et al.* [639]	2014	448	64	68.4 Gy no ADT	5 yr DM post-SRT PSA < 0.1 ng/mL 5% post-SRT PSA ≥ 0.1 ng/mL 29% p < 0.0001 5 yr DSM post-SRT PSA < 0.1 ng/mL 2% post-SRT PSA ≥ 0.1 ng/mL 7% p < 0.0001 OS post-SRT PSA < 0.1 ng/mL 97% post-SRT PSA ≥ 0.1 ng/mL 90% p < 0.0001
Bartkowiak, *et al.* [636]	2017	464	71	66.6 (59.4- 72) Gy no ADT	5.9 yr OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p = 0.005

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

Recent data from RTOG 9601 [641] suggested both CSS and OS benefits for adding two years of bicalutamide to SRT. According to GETUG-AFU 16, also six months treatment with gonadotropin-releasing hormone (GnRH) analogue can improve five-year PFS significantly, but a longer follow-up is required [642]. Both trials used outdated radiation dosages and technique. Table 6.3.3 gives an overview of these two RCTs. A recent literature review recommends risk stratification based on the pre-SRT PSA (> 0.7 ng/mL), margin status (positive), and high GS, to personalise the use of hormone therapy with SRT [643].

Table 6.3.3: RCTs comparing salvage radiotherapy alone and salvage radiotherapy combined with androgen deprivation therapy

Reference	Year	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 Carrie, *et al.* [642]	2016	369 RT + ADT 374 RT	GS ≤ 7 89%, GS ≥ 8 11% cN0	63	66 Gy + GnRH analogue 6 mo 66 Gy	5 yr PFS 80% p < 0.0001 5 yr PFS 62%
RTOG 9601 Shipley, *et al.* [641]	2017	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy + bicalutamide 24 mo 64.8 Gy + placebo	12 yr DM 14% p = 0.005 12 yr DM 23% 12 yr OS 76% p = 0.04 12 yr OS 71% 12 yr DSM 5.8% p < 0.001 12 yr DSM 13.4%

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

6.3.5.1.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for “clinical target volumes” of PCa [644-647] and for organs at risk of normal tissue complications [648]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved

The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the base of the seminal vesicles, depending on the pathological stage after RP) [633, 649]. A USA Guideline Panel regarded 64-65 Gy as the minimum dose that should be delivered post RP [650]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at three to five years [651]. In a SR, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level [652]. The combination of pT stage, margin status and GS and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [653-655]. The updated Stephenson nomograms incorporate the SRT-dose and ADT as predictive factors for biochemical failure and distant metastasis [637]. In a study on 894 node-negative PCa patients, sufficient doses ranging from 64 to ≥ 74 Gy were assigned to twelve risk groups, defined by the pre-SRT PSA classes < 0.1, 0.1-0.2, 0.2-0.4, and > 0.4 ng/mL and the GS, ≤ 6 vs. 7 vs. ≥ 8 [656].

In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute Grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late Grade 3 reactions of the GI tract. Severe GU tract toxicity was not observed. Late Grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [636]. 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 [657].

In a RCT on dose escalation for SRT involving 350 patients, acute Grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastrointestinal tract toxicity of Grades 2 and 3 occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy. Late effects are yet to be reported [658].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side-effects, especially GU, clearly increases, even with newer planning and treatment techniques [659, 660]. Of note, when compared with 3D-CRT, IMRT was associated with a reduction in Grade 2 GI toxicity from 10.2 to 1.9% ($p = 0.02$), but had no differential effect on the relatively high level of GU toxicity (5-yr: 3D-CRT 15.8% vs. IMRT 16.8%) [659]. After a median salvage IMRT dose of 76 Gy, the five-year risk of Grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [660].

6.3.5.1.2 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 (ADT was excluded), in which 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 over-treatment, which is a major issue in both ART and in SRT [661].

The results were confirmed for metastasis-free and OS [654]. However, these retrospective studies are underpowered for high-risk cases such as pT3b/R1/GS 8-10.

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

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 event of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before RP that adjuvant RT may be of benefit 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, will best inform the discussion between the physician and the patient.

6.3.5.2 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or local procedures such as salvage RP (SRP), cryotherapy, interstitial brachytherapy and HIFU [662-671]. Strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of low quality. The following is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

6.3.5.2.1 Salvage radical prostatectomy

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.

6.3.5.2.1.1 Oncological outcomes

In a recent SR of the literature, Chade, *et al.* showed that SRP gave five- and ten-year BCR-free survival estimates ranging from 47-82% and from 28-53%, respectively. The ten-year CSS and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy GS were the strongest predictors of the presence of organ-confined disease, progression, and CSS [672].

In most contemporary series, organ-confined disease, negative surgical margins, and the absence of seminal vesicle and/or LN metastases were favourable prognostic indicators associated with a better DFS of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [671].

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

Reference	n	Median FU (mo)	Pathologic organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability (yr)
Sanderson, *et al.* 2006 [673]	51	-	25	36	28	47	-	5
Leonardo, *et al.* 2009 [674]	32	35	53	34	0	75	-	3
Heidenreich, *et al.* 2010 [670]	55	23 (2-56)	73	11	20	87	-	2
Chade, *et al.* 2011 [675]	404	55	55	25	16	37	83	10
Mandel, *et al.* 2016 [676]	55	36	50	27	22	49	89	5

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

6.3.5.2.1.2 Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [677]. In more recent series, these complications appear to be less common [669, 672]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [672].

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

Reference	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5 (%)	Blood loss, mL, mean, range
Stephenson, *et al.* 2004 [669]	100	15 vs. 2*	30	33 vs. 13*	-
Ward, *et al.* 2005 [678]	138	5	22	-	-
Sanderson, *et al.* 2006 [673]	51	2	41	6	-
Gotto, *et al.* 2010 [677]	98	9	41	25	-
Heidenreich, *et al.* 2010 [670]	55	2	11	3.6	360 (150-1450)

** SRP performed before vs. after 1993.*
n = number of patients.

6.3.5.2.1.3 Summary of salvage radical prostatectomy
In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL and biopsy GS ≤ 7, no LN involvement or evidence of distant metastatic disease pre-SRP, and who's initial clinical staging was T1 or T2 [672]. A meta-regression analysis suggested that SRP may be associated with worse continence outcomes than non-surgical approaches [679].

6.3.5.2.2 Salvage cryoablation of the prostate
6.3.5.2.2.1 Oncological outcomes
Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the five-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [680]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the five-year BCR-free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [681].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The five-year BCR-free survival was 61% following SRP, significantly better than the 21% detected after SCAP. The five-year OS was also significantly higher in the SRP group (95% vs. 85%) [682].

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

Reference	n	Median FU (mo)	BCR-free probability (%)	Time probability (yr)	Definition of failure
Pisters, *et al.* 1997 [682]	150	17	44	-	Nadir + 0.2
Bahn, *et al.* 2003 [683]	59	82	59	7	PSA > 0.5
Ismail, *et al.* 2007 [680]	100	33	73 (low risk)	5	ASTRO
Pisters, *et al.* 2008 [681]	279	22	58	5	ASTRO and Phoenix
Williams, *et al.* 2011 [684]	187	7.46 yr	39	10	Nadir +2
Spiess, *et al.* 2010 [685]	450	40.8	34	-	PSA > 0.5

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

6.3.5.2.2.2 Morbidity
According to Cespedes, *et al.* [686], the risks of urinary incontinence and ED at at least twelve months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In a recent study by Pisters, *et al.*, the urinary incontinence rate was 4.4%. The rectal fistulae rate was 1.2% and 3.2% of patients required a TURP for removal of sloughed tissue [681]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.3.5) [687].

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

Reference	n	Incontinence (%)	Obstruction/ Retention (%)	Rectourethral fistula (%)	ED (%)
Pisters, *et al.* 1997 [688]	150	73	67	1	72
Bahn, *et al.* 2003 [683]	59	8	-	3.4	-
Ismail, *et al.* 2007 [680]	100	13	4	1	-
Pisters, *et al.* 2008 [681]	279	4.4	3.2	1.2	-
Ahmad, *et al.* 2013 [689]	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

6.3.5.2.2.3 Summary of salvage cryoablation of the prostate

In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, an initial organ-confined PCa cT1c to cT2, initial GS ≤ 7, a pre-salvage PSA-DT ≥ sixteen months and a pre-salvage PSA < 10 ng/mL.

6.3.5.2.3 Salvage brachytherapy for radiotherapy failure

Although there is no role for salvage EBRT following local recurrence after previous definitive RT, for carefully selected patients with primary localised PCa and histologically proven local recurrence, HDR- or LDR brachytherapy remain effective treatment options with an acceptable toxicity profile [690-692]. However, the published series are relatively small and consequently this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR brachytherapy over a period of nine years [690]. With a median follow-up of 60 months the five-year biochemical control was 51% and only 2% Grade 3 GU toxicities were reported. Comparable with these data, 42 patients were treated in a phase-II-trial at MSKCC in New York [693]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after five years was 69% (median follow-up 36 months). Grade 2 late side-effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side-effects have been reported [694].

Using LDR brachytherapy with ^{103}palladium, long-term outcome was reported in 37 patients with a median follow-up of 86 months [691]. The biochemical control rate after ten years was 54%. However, the crude rate of ≥ Grade 2 toxicity was 46% and ≥ Grade 3 toxicity was 11%. These side-effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side-effects seem to be lower with HDR brachytherapy [695]. In conclusion, freedom from BCR after salvage HDR- and LDR brachytherapy is promising and the rate of severe side-effects in experienced centres seem to be acceptable. Salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.3.5.2.4 Salvage high-intensity focused ultrasound

6.3.5.2.4.1 Oncological outcomes

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

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

Reference	n	Median FU (mo)	BCR-free probability (%)	Negative biopsy rate
Colombel, *et al.* 2006 [696]	224	15-18	-	80
Gelet, *et al.* 2000 [697]	-	-	-	-
Gelet, *et al.* 2004 [698]	-	-	-	-
Uchida, *et al.* 2011 [699]	22	24	59 (Phoenix) (24 mo.)	92 (only 12 biopsied)
Berge, *et al.* 2011 [700]	46	9	60.9 (9 mo)	-
Crouzet, *et al*, 2017 [701]	418	42	49% (5 y); 82% CSS (7 yr)	-

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

6.3.5.2.4.2 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.

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

*6.3.6 **Salvage lymph node dissection***

Novel imaging modalities improve the early detection of nodal metastases [702]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [410, 702, 703]. The majority of treated patients showed BCR but clinical recurrence-free and CSS ten-year survival over 70% has been reported [410, 704]. Neither the template nor the real value of nodal salvage dissection is available. It must, however, be remembered that the imaging modalities under-evaluate the real nodal involvement. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [705]. Addition of RT to the lymphatic template after salvage LND may improve the BCR rate [706]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival [707].

*6.3.7 **Hormonal therapy***

The Guidelines Panel conducted a SR including studies published from 2000 onwards [708]. The key findings are summarised below:

Conflicting results on the clinical effectiveness of HT after previous curative therapy of the primary tumour were found. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [709]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [710]. 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 GS, high PSA, increased age and comorbidities. In some studies, such as the Boorjian, *et al.* study [587], high-risk patients, mainly defined by a high GS and a short PSA-DT (most often less than six 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 [594]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [711]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors.

Based on the lack of definitive efficacy and the undoubtedly associated significant side-effects, patients with recurrence after primary curative therapy should not receive standard HT. Only a minority of them will progress to metastases or PCa-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 [712, 713]. Early HT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA-DT at relapse (less than six to twelve months) or a high initial GS (> 7), and a long life expectancy.

*6.3.8 **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 less than ten years and/or are unwilling to undergo salvage treatment. In unselected relapsing patients, the median actuarial time to the development of metastasis will be eight years and the median time from metastasis to death will be a further five years [569].

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

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence after radical prostatectomy	
Offer active surveillance and possibly delayed salvage radiotherapy (SRT) to patients with biochemical recurrence and favourable prognostic factors (≤ pT3a, time to biochemical recurrence > three year, prostate-specific antigen doubling-time (PSA-DT) > twelve months, Gleason score ≤ 7), who may not benefit from intervention.	Strong
Treat patients with a PSA rise from the undetectable range with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	Strong
Recommendations for biochemical recurrence after radiotherapy	
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	Weak
Salvage RP should only be performed in experienced centres.	Strong
Do not offer high intensity focused ultrasound, cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence since it is still experimental.	Strong
Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-DT > twelve months.	Strong

6.4 Treatment: Metastatic prostate cancer

6.4.1 *Introduction*

A SR of ADT in PCa has been published [457].

6.4.2 *Prognostic factors*

Median survival of patients with newly diagnosed metastases is about 42 months [714]. However, the M1 population is heterogeneous. Several prognostic factors for survival have been suggested including the number and location of bone metastases, visceral metastases, GS, PS status and initial PSA [715], alkaline phosphatase [716], but none of these have been directly compared and only few have been validated [717]. In most clinical trials, the number and location of bone metastases and the presence of visceral lesions were used [718]. Visceral metastases, more than five bone metastases on bone scan, appendicular locations, and ISUP groups > 3 are all independently associated with a decreased survival.

Based on a large SWOG 9346 cohort, the PSA level after seven months of ADT was used to create three prognostic groups (see Table 6.4.1) [719]. This grouping, however, still requires independent confirmation.

Table 6.4.1: Prognostic factors based on the SWOG 9346 study

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

6.4.3 *First-line hormonal treatment*

Primary ADT has been the standard of care for over 50 years [457]. There is no level 1 evidence in favour of a specific type of ADT, neither for orchiectomy nor for an LHRH analogue or antagonist. The exception are patients with impending spinal cord compression for whom either a bilateral orchidectomy, or LHRH antagonists are the preferred options.

6.4.4 *Combination therapies*

6.4.4.1 *Complete androgen blockade*

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [720]. However, results with other anti-androgens or castration modalities have differed and SRs have shown that CAB using a non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [721, 722] beyond five years of survival [723] but this minimal advantage in a small subset of patients must be balanced against the increased side-effects associated with long-term use of NSAAs.

6.4.4.2 Non-steroidal anti-androgen monotherapy

Based on a Cochrane SR [724] 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.

6.4.4.3 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [725-727] and two meta-analyses [728, 729], looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included eight RCTs of which only three were conducted in patients with exclusively M1 disease. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 [730] is the largest trial addressing IAD in M1b patients. Out of 3,040 screened patients, only 1,535 patients finally met the inclusion criteria. This highlights that, at best, only 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1; CI: 0.99-1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out.

Other trials did not show any survival difference with an overall HR for OS of 1.02 (0.94-1.11) [725]. These reviews and the meta-analyses came to the conclusion that a difference in OS or CSS between IAD and continuous ADT is unlikely. A recent review of the available phase III trials highlighted the limitations of most trials and suggested a cautious interpretation of the non-inferiority results [731]. None of the trials that addressed IAD vs. continuous ADT in M1 only patients showed a survival benefit in favour of the latter, but there was a trend towards better OS and PFS with continuous ADT. Most of these trials, however, were non-inferiority trials. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side-effects, such as hot flushes. In some cohorts the negative impact on sexual function was less pronounced with IAD. Two prospective trials came to the same conclusions [732, 733].

Other possible long-term benefits of IAD from non-RCT include a protective effect against bone loss, metabolic syndrome and cardiovascular problems [734]. This possible protective effect was recently challenged by the results from a detailed analysis of the SWOG 9346 trial [735]. These results showed an increased risk for thrombotic and ischaemic events, while there was no benefit concerning endocrine, psychiatric, sexual and neurological side-effects with IAD. Testosterone recovery was observed in most studies [736] leading to only intermittent castration. These outcomes, as well as the lack of any survival benefit in M1 patients, suggest that this treatment modality should only be considered as an option in a well-informed patient bothered by significant side-effects.

The PSA threshold at which ADT must be stopped or resumed for IAD still needs to be defined in prospective studies [726, 736]. Nevertheless, there is consensus amongst many authors on the following statements:

- IAD is based on intermittent castration; therefore, only drugs leading to castration are suitable.
- Luteinising-hormone releasing hormone antagonist might be a valid alternative to an agonist.
- The induction cycle should not be longer than nine months, otherwise testosterone recovery is unlikely.
- Androgen deprivation therapy should be stopped only if all of the following criteria have been met:
  - well-informed and compliant patient;
  - no clinical progression;
  - a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.
- Strict follow-up is mandatory which should include a clinical examination every three to six months. The more advanced the disease, the closer the follow-up should be.
- PSA should always be measured by the same laboratory.
- Treatment is resumed when the patient progresses clinically, or has a PSA rising above a pre-determined (empirically set) threshold: usually 10-20 ng/mL in metastatic patients.
- The same treatment is used for at least three to six months.
- Subsequent cycles of treatment are based on the same principles until the first sign of castration resistance becomes apparent.
- The group of patients who will benefit most from IAD still has to be defined but the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response [726].

6.4.4.4 Immediate versus deferred androgen deprivation therapy

In symptomatic patients, immediate treatment is mandatory. However, controversy still exists for asymptomatic

metastatic patients due to the lack of quality studies. A Cochrane review extracted four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [724]. All of these studies were conducted in the pre-PSA era and included patients with advanced PCa, who had received early vs. deferred ADT, either as primary therapy or as adjuvant therapy after RP [737]. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications.

*6.4.5 **Androgen deprivation combined with other agents***

6.4.5.1 Combination with abiraterone acetate

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus Prednisone (5 mg daily) (AA plus P) to ADT in men with hormone-sensitive metastatic prostate cancer (mHSPC) was studied [738, 739]. The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit of 38% at three years [HR: 0.62 (0.53-0.71) [740]. The inclusion criteria in the two trials differed with respect to risk definition, but both trials were positive for OS. This suggests that the treatment with ADT plus AA plus P should be a standard for all patients and not be restricted to a specific high-risk group e.g. as defined in LATITUDE [738].

All secondary objectives such as progression-free survival, time to radiographic progression, time to pain, or time to chemotherapy were positive and in favour of the combination. The key findings are summarised in Table 6.4.2. No difference in treatment related deaths was observed with the combination of ADT plus AA plus P compared to ADT monotherapy [HR: 1.37 (0.82-2.29]. However, twice as many patients discontinued treatment due to for toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%). Based on these data, upfront docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [741].

M0 and M1 relapsing patients were included in the STAMPEDE study, but not in LATITUDE [738, 739]. In the subgroup of M0 patients, there was no improvement in OS. This lack of benefit might be related to the relatively short follow-up period and very few events. Therefore, combination treatment should not be considered as standard in patients with M0 HSPC. As to patients relapsing after a local treatment [20] there is also some uncertainty since only a small group of such patients was included in STAMPEDE [740]. Therefore, combination treatment in such patients should be based on an individual discussion with the patient but cannot be regarded as the standard of care.

Table 6.4.2: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [James] [739]		**LATITUDE [Fizazi] [738]**	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
n	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, GS ≥ 8, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. OR PSA > 20 ng/mL, OR nodal OR metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: GS ≥ 8, ≥ 3 bone lesions, measurable visceral metastasis	
Primary objective	Overall survival		Overall survival Radiographic progression-free survival	
Median follow up (mo)	40		30.4	
3 years overall survival	83% (ADT + AA + P)		66% (ADT + AA + P)	
	76% (ADT)		49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52 - 0.76)		0.62 (0.51-0.76)	

M1 only		
n =	1002	1199
3 years overall survival	NA	66% (ADT + AA + P) 49% (ADT + placebo)
HR (95% CI)	0.61 (0.49-0.75)	0.62 (0.51-0.76)
HR	Failure-free survival (biological, radiological, clinical or death): 0.29 (0.25-0.34)	Radiographic progression-free survival: 0.49 (0.39-0.53)

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; GS = Gleason score; HR = hazard ratio; mo = month; n = number of patients; NA = not available; P = prednisone.

6.4.5.2 ADT combined with chemotherapy

Three large RCTs were conducted [718, 742, 743]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every three weeks) (within three months of ADT initiation). The primary objective in all three studies was OS. The key findings are summarised in Table 6.4.3.

Table 6.4.3: Key findings - Hormonal treatment combined with chemotherapy

Study	Population	n	Med FU (mo)	Median OS (mo)		HR	p-value
				ADT + D	ADT		
Gravis, *et al.* [743]	M1	385	50	58.9	54.2	1.01 (0.75-1.36)	0.955
ASCO GU 2015 [744]	HV : 47%		82.9	60.9	46.5	0.9 (0.7-1.2)	0.44
Sweeney, *et al.* [718]	M1 HV: 65%	790	28.9	57.6	44	0.61 (0.47-0.8)	< 0.001
STAMPEDE [742]	M1 [61%]/N+ [15%]/relapse	1,184 /593 (D) 593 (D + ZA)		81 76	71 n.r.	0.78 (0.66-0.93) 0.82 (0.69-0.97)	0.006 0.022
	M1 only	725 + 362 (D)		60	45	0.76 (0.62-0.92)	0.005

D = docetaxel; FU = follow-up; HR = hazard ratio; HV = high volume: either visceral metastases or more than four bone metastases, with at least one outside the spine and pelvis; n = number of patients; n.r. = not reported; ZA = zoledronic acid.

In the GETUG 15 trial, all patients had newly diagnosed M1 PCa, either *de novo* or after a primary treatment [743]. They were stratified based on previous treatment, and Glass risk factors [715]. In the Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial, the same inclusion criteria applied and patients were stratified according to disease volume; high volume being defined as either presence of visceral metastases or four, or more, bone metastases, with at least one outside the spine and pelvis [718].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1, or N1, or having two of the following three criteria: T3/4, PSA ≥ 40 ng/mL or Gleason 8-10. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < 6 months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [742].

In all three trials toxicity was mainly haematological with around 12-15% Grade 3-4 neutropenia, and 6-12% Grade 3-4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [741, 745].

Based on these data, upfront docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [741]. Docetaxel is used at the standard dose of 75 mg/sqm combined with steroids as premedication. Prolonged corticosteroid therapy is not mandatory.

6.4.5.3 Treatment selection and patient selection

The choice between six cycles of docetaxel and the long-term use of AA + P in newly diagnosed mHSPC

remains open. Both modalities have different and agent-specific side-effects. Mainly febrile neutropenia with docetaxel and cardiovascular events potentially related to mineralocorticoid-associated side-effects as well as hepatic disorders with AA plus P. Both treatments require a strict follow-up policy. Therefore, the choice will most likely be driven by patient preference, the specific side-effects, availability and cost.

6.4.6 Deferred treatment for metastatic PCa (stage M1)

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. However, since the median survival is 42 months only, 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 [525, 531]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.4.7 Treatment of the primary tumour in newly diagnosed metastatic disease

Several cohort studies suggest an OS and CSS benefit when RP or brachytherapy are added to ADT in newly diagnosed M1 patients [746]. The lack of clear treatment selection criteria is a major limitation of these findings. Prospective trials are ongoing addressing this important question and until they report, such interventions should still be considered experimental.

6.4.8 Metastasis-directed therapy

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. A recent SR clearly highlighted that at this time this approach must, as yet, be considered as experimental [705].

6.4.9 Guidelines for the first-line treatment of metastatic disease

Recommendations	Strength rating
In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	Strong
Offer luteinizing hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
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.	Weak
In M1 patients treated with a LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer anti-androgen monotherapy for M1 disease.	Strong
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.	Strong
Offer castration combined with abiraterone acetate plus prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone.	Strong
Intermittent treatment	
In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major prostate-specific antigen (PSA) response after the induction period.	Strong
• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. • Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL).	Weak
Do not use castration combined with any local treatment (radiotherapy/surgery) outside an investigational setting except for symptom control.	Strong

6.5 Treatment: Castration-resistant PCa (CRPC)

6.5.1 Definition of Castration-resistant PCa

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;

a. Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,
b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [747]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

6.5.2 Non-metastatic castration-resistant PCa

Frequent PSA testing for men on treatment with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases detectable on bone scan within two years [748], however, there are no available studies suggesting a benefit for immediate treatment. In the STRIVE trial (a) Enzalutamide was compared to bicalutamide including a sub group of men with no apparent evidence of metastatic disease and showed a decrease in rPFS but OS was not assessed and currently there is insufficient evidence to allow a recommendation to be provided [749].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free and OS [748, 750]. 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 [751] suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level.

6.5.3 Metastatic castration-resistant PCa

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

6.5.3.1 Conventional androgen deprivation in castration-resistant PCa

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [752, 753]. 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 in these patients.

Table 6.5.1: Randomised phase III controlled trials - first-line treatment of metastatic castration-resistant PCa*

Author	Intervention	Comparison	Selection Criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 Petrylak, DP, *et al.* 2004 [754]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		OS: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) PFS: 6.3 vs. 3.2 mo. (p < 0.001)
TAX 327 2008 [755, 756]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID Or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, Prednisone 5 mg BID		OS: 19.2 for 3 weekly vs. 17.8 mo. four weekly and 16.3 in the control group. (p = 0.004, HR: 0.79 95% CI: 0.67-0.93)

ABIRATERONE				
COU-AA-302 Ryan CJ, *et al.* 2013 [757-759]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	OS: 34.7 vs. 30.3 mo. (HR: 0.81 p = 0.0033). FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo. p < 0.0001)
ENZALUTAMIDE				
PREVAIL Beer TM, *et al.*2014 [760]	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)
SIPULEUCEL-T				
Kantoff PW, *et al.* 2010 [761]	sipuleucel-T [762]	placebo [762]	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	OS: 25.8 vs. 21.7 mo. (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo. (no difference)
Small EJ, *et al.* 2006 [763]	sipuleucel-T [763]	Placebo [763]	- ECOG 0-1. - No visceral metastases. - No bone or cancer pain. - No corticosteroids.	OS: 25.9 vs. 21.4 mo. (p. 01). FU: 36 mo. PFS: 11.7 vs. 10.0 wk.

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

*6.5.4 **First-line treatment of metastatic castration-resistant PCa***

6.5.4.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients in the phase III trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [757]. Patients with visceral metastases were excluded. 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) [759]. Adverse events (AEs) related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly Grade 1-2. Sub-set analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [764].

6.5.4.2 Enzalutamide

A randomised phase III trial (PREVAIL) [760] included a similar patient population and compared enzalutamide and placebo. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naïve mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186; CI: 0.15-0.23,

p < 0.0001), and OS (HR: 0.706; CI: 0.6-0.84, p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men > 75 years [765] as well as in those with or without visceral metastases [766]. However, for men with liver metastases, there seems to be no discernible benefit [766, 767]. Enzalutamide has also been compared with bicalutamide in a phase II study [768] revealing a significant improvement in PFS (15.7 months vs. 5.8 months, HR 0.44, p < 0.0001).

6.5.4.3 Docetaxel

A significant improvement in median survival of 2-2.9 months occurred with docetaxel-based chemotherapy compared to mitoxantrone plus prednisone therapy [756, 769]. The standard first-line chemotherapy is docetaxel 75 mg/m^2 three-weekly doses combined with prednisone 5 mg BID, up to ten cycles. Prednisone can be omitted if there are contraindications or no major symptoms. The following independent prognostic factors: visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help to stratify response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), showing three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [770].

Age by itself is not a contraindication to docetaxel [771] but attention must be paid to careful monitoring and comorbidities as discussed in Section 5.4 [772]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m^2 every two weeks seems to be well tolerated with less Grade 3-4 AEs and a prolonged time to treatment failure [773].

6.5.4.4 Sipuleucel-T

In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [750]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related AEs Grade 1-2 in the sipuleucel-T group, but the same Grade 3-4 AEs in both arms. Sipuleucel-T is not available in Europe.

Table 6.5.2: Randomised controlled phase III - second-line trials in metastatic castration-resistant PCa*

Author	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
Fizazi, *et al.* 2012 [774]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	OS: 15.8 vs. 11.2 mo (p < 0.0001). FU: 20.2 mo. Radiologic PFS: no change
de Bono, *et al.* 2011 [775]				OS: 14.8 vs. 10.9 mo. (p < 0.001 HR: 0.65; 95% CI: 0.54-0.77). FU: 12.8 mo. Radiologic PFS: 5.6 vs. 3.6 mo.
Radium-223				
Parker, *et al.* 2013 [776]	radium-223	Placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	OS: 14.9 vs. 11.3 mo. (p = 0.002, HR: 0.61; 95% CI: 0.46-0.81). All secondary endpoints show a benefit over best standard of care

CABAZITAXEL				
Bahl, *et al.* 2013 [777]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	OS: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI: 1.33-3.33). FU: 25.5 months OS ≥ 2y 27% vs. 16% PFS: -
deBono, *et al.* 2010 [778]				OS: 15.1 vs. 12.7 mo. ($p < 0.0001$, HR: 0.70; 95% CI: 0.59-0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. ($p < 0.0001$, HR: 0.74; 95% CI: 0.64-0.86)
ENZALUTAMIDE				
Scher, *et al.* 2012 [779]	enzalutamide	Placebo	Previous docetaxel. ECOG 0-2.	OS: 18.4 vs. 13.6 mo. ($p < 0.001$ HR: 0.63; 95% CI: 0.53-0.75). FU: 14.4 mo. Radiologic PFS: 8.3 vs. 2.9 mo. HR: 0.40; 95% CI: 0.35-0.47 $p < 0.0001$)

**Only studies reporting survival outcomes as primary endpoints have been included.*
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; HR = hazard ratio; mo = months OS = overall survival; PFS = progression-free survival.

*6.5.5 **Second-line treatment for mCRPC***

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.2.

6.5.5.1 Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [778]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) 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 [780]. In two post-marketing randomised phase 3 trials, firstly, cabazitaxel was shown not to be superior to docetaxel in the first-line setting and, secondly, 20 mg/m^2 cabazitaxel is not inferior to 25 mg/m^2 in the second-line setting in terms of OS, but it is less toxic. Therefore, the lower dose should be preferred [781, 782]. In any case, cabazitaxel should preferably be given with prophylactic granulocyte colony-stimulating factor and should be administered by physicians with expertise in handling neutropenia and sepsis [783].

6.5.5.2 Abiraterone acetate after prior docetaxel

Positive results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [775] and confirmed by the final analysis [774]. 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 AEs did not differ significantly between arms, but mineralocorticoid-related side-effects were more frequent in the abiraterone group, mainly Grade 1-2 (fluid retention, oedema and hypokalaemia).

6.5.5.3 *Enzalutamide after docetaxel*

The planned interim analysis of the AFFIRM study was published in 2012 [779]. 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 Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$). This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post progression therapies [784].

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side-effects was observed in the two groups, with a lower incidence of Grade 3-4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.5.5.4 *Radium-223*

The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA), 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo, plus standard of care. The primary end-point was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70; $p < 0.001$) [776]. It was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, it did not differ significantly from that in the placebo arm [776]. Radium-223 was effective and safe no matter if the patients were docetaxel pre-treated, or not [785].

6.5.6 ***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 [786]. Either Radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [787, 788] and there is evidence of cross-resistance between enzalutamide and abiraterone [789]. Poly(ADP-ribose) polymerase (PARP) inhibitors have shown high rates of response in men with somatic homologous recombination deficiency (HRD) in initial studies. Men previously treated with both docetaxel and at least one novel hormonal agent and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate [790]. Patients without HRD did not show a clear benefit from olaparib. Although not yet available, PARP inhibitors offer an exciting new opportunity to tailor therapy based on the mutation profile contained within a tumour.

6.5.7 ***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 [791]. Prostate-specific antigen alone is not reliable enough [792] for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA [793]. Instead, PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [769]. A majority of experts at a recent consensus meeting suggested regular review and repeat blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [791]. This reflects that the agents with a proven OS survival benefit all have potential toxicity and considerable cost, and patients with no objective benefit should have treatment modified. This panel stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of “no longer clinically benefiting” to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [794]. These recommendations also seem valid for clinical practice outside trials.

6.5.8 ***When to change treatment***

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Although, the number of effective treatments is increasing, head to head comparisons are still lacking, as are data assessing the sequencing of available agents. Therefore it is not clear how to choose the appropriate “second-

line" treatment. In the absence of other data, the inclusion criteria from licensing trials have been used to prioritise treatment sequencing.

The Eastern Cooperative Oncology group PS has been used to stratify patients. Generally men with a PS of 0-1 are likely to tolerate treatments and those with PS of 2 or more are less likely to benefit. However, it is important that treatment decisions are individualised. This applies particularly where symptoms related to disease progression are determining PS. In such cases it may be appropriate to trial active life-prolonging agents to establish if treatment would improve PS. Sequencing is discussed in a summery paper published following the St. Gallen Advanced Prostate Cancer Consensus Conference 2017 [791, 795].

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

Castration-resistant PCa is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [796]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

6.5.9.1 Common complications due to bone metastases

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [797], even as a single fraction [798]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [799]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [800]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [801, 802]. Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT [803]. Otherwise, EBRT, with or without systemic therapy, is the treatment of choice.

*6.5.10 **Preventing skeletal-related events***

6.5.10.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anticancer treatments but docetaxel were available. 643 patients who had CRPC [804] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for fifteen consecutive months, or placebo. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at fifteen and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44 vs. 33%, $p = 0.021$) and in particular fewer pathological fractures (13.1 vs. 22.1%, $p = 0.015$). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.5.10.2 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, $p = 0.028$) [803]. 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 [805].

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 [806].

The potential toxicity (e.g., osteonecrosis of the jaw) of these drugs must always be kept in mind [797, 803]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection [807].

6.5.11 *Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease*

Summary of evidence	LE
First-line treatment for metastatic castrate-resistant PCa (mCRPC) will be influenced by which treatments were used when metastatic cancer was first discovered.	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist.	3

Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
Do not treat patients for non-metastatic CRPC outside of a clinical trial.	Strong
Counsel, manage and treat patients with metastatic CRPC in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong

6.5.12 *Guidelines for cytotoxic treatment of castrate-resistant disease*

Recommendations	Strength rating
Counsel, manage and treat patients with metastatic castration-resistant PCa (mCRPC) in a multidisciplinary team.	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every three weeks.	Strong
In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
Base second-line treatment decisions of mCRPC on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease.	Strong

6.5.13 *Guidelines for supportive care of castrate-resistant disease*

These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.	Strong
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

6.6 Summary of guidelines for the treatment of prostate cancer

Table 6.6.1: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

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

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

6.6.1 General guidelines recommendations for active treatment

Recommendations	**Strength rating**
Inform patients that no active treatment modality has shown superiority over any other active management options in terms of survival.	Strong
Inform patients that all active treatment have side-effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Strong
Perform an extended pelvic lymph node dissection (ePLND), when a LND is deemed necessary.	Strong
Do not perform nerve-sparing surgery when there is a risk of extracapsular extension (based on cT stage, Gleason score, nomogram, multiparametric magnetic resonance imaging).	Strong
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Only offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy (IGRT) to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in six weeks.	Strong
Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	Strong
Only offer focal therapy within a clinical trial setting.	Strong

6.6.2 Guidelines recommendations for the various disease stages – first line treatment

Recommendations		**Strength rating**
Low-risk disease		
Watchful waiting (WW)	Offer a WW policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Active surveillance (AS)	Offer AS to patients suitable for curative treatment but with low-risk PCa.	Strong
	Perform mpMRI before a confirmatory biopsy.	Strong
	During confirmatory biopsy include systematic and targeted biopsies.	Strong
	Base follow up on DRE, PSA and repeated biopsies.	Strong
	Counsel patients about the possibility of needing further treatment in the future.	Strong
Active treatment	Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak

Pelvic lymph node dissection (PLND)	Do not perform a PLND (estimated risk for pN+ < 5%).	Strong
Radiotherapy	Offer LDR brachytherapy to patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL.	Strong
	Use IMRT with a total dose of 74-80 Gy, without ADT.	Strong
	Offer moderate HFX (68 Gy/20 fx in four weeks or 70Gy/28 fx in six weeks) as an alternative treatment option.	Strong
Other options	Only offer whole gland treatment (such as cryotherapy, HIFU, etc.) or focal treatment within a clinical trial setting.	Strong
Intermediate-risk disease		
Active surveillance (AS)	Offer AS to highly selected patients (< 10% pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease (refer to nomograms).	Strong
ePLND	Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Radiotherapy	Offer LDR brachytherapy to selected patients; patients without a previous TURP and with a good IPSS and a prostate volume < 50 mL.	Strong
	For EBRT, use a total dose of 76-78 Gy, in combination with short-term neoadjuvant plus concomitant ADT (four to six months).	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
Other options	Only offer whole gland treatment (such as cryotherapy, HIFU, etc.) or focal treatment within a clinical trial setting.	Strong
High-risk localised disease		
Radical prostatectomy (RP)	Offer RP to patients with high-risk localised PCa and a life expectancy of > 10 years only as part of multi-modal therapy.	Strong
ePLND	Perform an ePLND in high-risk disease.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapy	In patients with high-risk localised disease, use EBRT with 76-78 Gy in combination with long-term ADT (two to three years).	Strong
	In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (two to three years).	Weak
Other options	Do not offer either whole gland or focal treatment to high-risk patients.	Strong
	Do not use ADT monotherapy in asymptomatic patients.	Strong
Locally-advanced disease		
Radical prostatectomy (RP)	Offer RP to highly selected patients with (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	Strong
ePLND	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapy	In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT.	Strong
	Offer long-term ADT for two to three years.	Weak
Other options	Do not offer whole gland treatment or focal treatment to high-risk patients.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment and who are either symptomatic or asymptomatic, but with a PSA-DT < 12 months or a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

Adjuvant treatment after radical prostatectomy		
	Only discuss adjuvant treatment in men with a post-operative PSA < 0.1 ng/mL.	Strong
	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Offer adjuvant EBRT to the surgical field to patients at increased risk of local relapse: pT3 pN0 with positive margins (highest impact), and/or invasion of the seminal vesicles.	Strong
	Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT for node-positive (pN+). 2. Offer adjuvant ADT with additional radiotherapy. 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak
Non-curative or palliative treatments		
Localised disease		
WW	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
	While on WW, base the decision to start non-curative treatment on symptoms and disease progression.	Strong
Locally-advanced disease		
WW	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA doubling time > twelve months, a PSA < 50 ng/mL and well differentiated tumour, who are unwilling or unable to receive any form of local treatment.	Strong
Metastatic disease - first-line treatment		
Symptomatic patients	In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	Strong
Asymptomatic patients	In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
	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.	Weak
All M1 patients	Offer LHRH antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
	In M1 patients treated with a LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer anti-androgen monotherapy for M1 disease.	Strong
	Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.	Strong
	Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
	Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate + prednisone.	Strong

M1 patients receiving intermittent treatment	In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.	Strong
	• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. • Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL).	Weak
	Do not use castration combined with any local treatment (radiotherapy/surgery) outside an investigational setting except for symptom control.	Strong

6.6.3 *Guidelines for second-line and palliative treatments*

Biochemical recurrence after treatment with curative intent		
Biochemical recurrence after radical prostatectomy (RP)	Offer AS and possibly delayed SRT to patients with a biochemical recurrence (BCR) and favourable prognostic factors (≤ pT3a, time to BCR > three years, PSA-DT > twelve months, GS ≤ 7), who may not benefit from intervention.	Strong
	Treat patients with a PSA rise from the undetectable range with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	Strong
Biochemical recurrence after radiotherapy (RT)	Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	Weak
	Salvage RP should only be performed in experienced centres.	Strong
	Do not offer HIFU, cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence since it is still experimental.	Strong
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > twelve months.	Strong
Life-prolonging treatments of castrate-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Do not treat patients for non-metastatic CRPC outside of a clinical trial.	Strong
	Counsel, manage and treat patients with metastatic CRPC in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the PS, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive PCa (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong
Cytotoxic treatment of castrate-resistant disease		
	Counsel, manage and treat patients with metastatic castration-resistant PCa (mCRPC) in a multidisciplinary team.	Strong
	Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every three weeks.	Strong
	In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
	Base second-line treatment decisions of mCRPC on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease.	Strong

Supportive care of castrate-resistant disease		
	Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.	Strong
	Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

ADT = androgen deprivation therapy; AS = active surveillance; BCR = biochemical recurrence; CPRC = castration-resistant prostate cancer; EBRT = external-beam radiation therapy; GS = Gleason score; HDR = high-dose rate; HFX = hypofractionation; HIFU = high-intensity focused ultrasound; IGRT = image-guided radiation therapy; IMRT = intensity-modulated radiation therapy; IPSS = International Prostatic Symptom Score; LDR = low-dose rate; LHRH = luteinizing hormone-releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; (e) PLND = (extended) pelvic lymph node dissection; PS = performance score; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SRP = salvage radical prostatectomy; TURP = transurethral resection of the prostate; VMAT = volumetric arc external-beam radiotherapy; WW = watchful waiting.

7. FOLLOW-UP

The rationale for following up patients is to assess immediate- and long-term oncological results, side-effects or complications of therapy, functional outcomes and to provide psychological support to PCa survivors. Only the oncological aspects are covered below; the functional outcomes and side-effects are covered in Chapter 8.

7.1 Follow-up: After local treatment

*7.1.1 **Definition***

Local treatment is defined as RP or RT, either by EBRT or LDR- or HDR-brachytherapy, or any combination of these. Unestablished alternative treatments, such as HIFU and cryosurgery do not have a well-defined, validated PSA cut-off to define BCF, but 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.

Patients who receive curative therapy are followed up to discuss the need and possibility of second-line treatment either with curative or palliative intent. It will be based on initial treatment, patient age, comorbidity and the patient's own wishes

*7.1.3 **How to follow-up?***

The procedures indicated at follow-up visits vary according to clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. Prostate specific antigen level and DRE are the only tests that should be performed routinely. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications must be individualised, which is beyond the scope of these Guidelines. The examinations used 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 [585, 808]. 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. No formal consensus exists regarding the best definition of PSA relapse after RP. Recurrent cancer after RP is usually defined by two

consecutive PSA rises ≥ 0.2 ng/mL [809]. However, others have argued for a higher cut-off of 0.4 ng/mL to best represent the risk of subsequent metastases (see Section 6.3.2) [585].

Ultrasensitive PSA assay remains controversial for routine follow-up after RP. Men with an ultrasensitive PSA nadir < 0.01 ng/mL have a 4% likelihood of early biochemical relapse [810]. Detectable post-operative ultrasensitive PSA does not predict BCR in all cases, although it adds prognostic value. In men with ultrasensitive PSA > 0.05 ng/mL, 66.8% remained free of biochemical disease at five years [811]. If survival is improved by early adjuvant treatment after RP (before PSA reaches > 0.2 ng/mL), lower PSA nadir levels may help identify suitable candidates, as well as low PSADT calculated using the first detectable PSA up to 0.2 ng/mL [592].

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 [586]. It applies to patients with or without HT.

After HIFU or cryotherapy, no endpoints have been validated to indicate clinical progression or survival; therefore, it is not possible to give a firm recommendation of BCF after these alternative local treatments.

7.1.3.3 Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within six weeks after successful RP [812]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease.

A rapidly increasing PSA level suggests distant metastases, whereas a later, slowly increasing, level most likely suggests local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [813]. Local treatment failure and distant metastases can occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [814]. Thus, in patients with favourable pathology (< pT3, pN0, GS < 8), PSA measurement and disease-specific history could be a single test in follow-up after RP.

7.1.3.4 Prostate-specific antigen 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 [815], although the optimal value is controversial. The interval before reaching the nadir can be up to three years or more. After RT, PSA-DT is correlated with site of recurrence; patients with local recurrence have a PSA-DT of thirteen months compared to three months for those with distant failure [816].

7.1.3.5 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [814]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Prostate-specific antigen measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT or RP, but PSA measurement may be the only test needed in cases with favourable pathology (< pT3, pN0, Gleason < 8) after RP [817].

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

Imaging techniques have no place in routine follow-up of localised PCa. They are only justified in patients for whom the findings affect treatment decisions, either with BCF or in patients with symptoms. (See Section 6.3.4.2.1 for a more detailed discussion).

7.1.3.6.1 Transrectal ultrasonography/magnetic resonance imaging guided biopsy.

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

7.1.4 ***When to follow-up?***

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

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

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

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

Recommendations	Strength rating
Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at three, six and twelve months after treatment, then every six months until three years, and then annually.	Strong
During follow up, perform a systematic DRE after surgery if unfavourable pathology (> pT3, pN1, Gleason ≥ 8).	Weak
During follow up, perform a systematic DRE after radiotherapy.	Strong
At recurrence, only image to detect local recurrence if it affects treatment planning.	Strong
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 possible progression, restaging should be considered irrespective of serum PSA level.	Strong

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

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. Follow-up for mCRPC is addressed in treatment Section 6.10.4, as fist-line management of mCRPC and follow-up are closely linked.

7.2.2 *Purpose of follow-up*

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

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

7.2.3 *Methods of follow-up*

7.2.3.1 *Clinical follow-up*

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

7.2.3.1.1 Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive PCa. Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa [719].

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), but rarely disease progression. A decline in Hb after three months of ADT is independently associated with shorter progression-free and OS rates [818] and might explain significant fatigue. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [819]. 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 [820]. New symptomatic bone lesions require a bone scan, as well as a PSA progression suggesting CRPC status if a treatment modification is considered. The PCWG has clarified the definition of bone scan progression as the appearance of at least two new lesions [769], 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. Many men receiving medical castration will achieve a castrate testosterone level (< 20 ng/dL), and most a testosterone level < 50 ng/dL. However, approximately 13-38% of patients fail to achieve this goal and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [459], known as the 'acute on-chronic effect' or 'breakthrough response'.

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

7.2.3.1.5 Monitoring of metabolic complications

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

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and regularly), as for blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. A cardiology consultation should be considered in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. Monitoring serum levels of vitamin D and calcium is important. It is suggested that routine bone monitoring should be performed every two years during castration [821], or yearly if there are other risk factors [822, 823]. However, there is no evidence that this favourably impacts on bone complications due to ADT. 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 existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [818, 819]. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

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

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

7.2.4.1 Stage M0 - M1 patients

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

*7.2.5 **Imaging as a marker of response in metastatic prostate cancer***

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods (CT or MRI) using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [824, 825].

Quantitative estimation of tracer uptake at BS can be obtained through automated methods such as the Bone Scan Index [826]. Nonetheless, BS is limited by the so-called flare phenomenon that is defined by the development of new images induced by treatment on a first follow-up scan that actually represent a favourable response on longer observation. Flare is observed within eight to twelve weeks of treatment initiation and can lead to false-positive diagnosis of disease progression. As a result, the PCWG suggested that all patients with at least two new lesions on the first follow-up BS require a confirmatory BS at least six weeks later while the treatment is continued [769]. This means that management change for primary therapy resistance cannot occur until after at least 14 weeks of treatment. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. The ability of choline PET/CT to assess response has been assessed in a few studies that showed changes in disease extent

and specific uptake values. So far it has no place. It is of note that the flare phenomenon can also be observed with choline PET/CT. Magnetic resonance imaging can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available and might help using these image modalities [827].

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

7.2.6 Guidelines for follow-up during hormonal treatment

Recommendations	Strength rating
Evaluate patients at three to six months after the initiation of treatment.	Strong
The follow up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up every six months. As a minimum requirement, include a disease-specific history, DRE and serum PSA determination in the diagnostic work-up.	Strong
In patients with stage M1 disease, schedule follow-up every three to six months. As a minimum requirement, include a disease-specific history, DRE, serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, adapt/individualise follow up.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration resistant PCa (CRPC) requires a testosterone level < 50 ng/dL (< 1 mL/L).	Strong
Do not offer routine imaging to otherwise stable asymptomatic patients.	Strong

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (8.2) will summarise long-term consequences (≥ 12 months) of therapies for PCa. Based on two SRs, the second (8.3) will make evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and also supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1 Introduction

Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of QoL [828]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others. Attention to the psychosocial concerns of men with PCa is integral to quality clinical care, and this can include the needs of carers and partners [783]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side-effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed.

8.2 Adverse effects of prostate cancer therapies

8.2.1 Surgery

The absence of standardisation in reporting surgical complications for RP and the introduction of different techniques has resulted in a wide variation in the types of complications reported as well as variation in the overall incidence of complications [829-832]. The most common post-operative issue is ED but other related

issues to consider include dry ejaculation which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [833].

The second most commonly occurring complication is long-term incontinence [829-832] but voiding difficulties may also occur associated with bladder neck contracture (e.g. 1.1% after RALP) [834].

For those men undergoing minimally invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar [835] and can occur more rarely with 8 mm and 5 mm trocars [836]. A key consideration for men is whether long-term consequences of surgery are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [364-368], and can be compared with contemporaneous reports after RRP [369]. From these reports, the mean continence rates at twelve months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP. There is, as yet, no evidence from retrospective studies of differences in urinary incontinence at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or ED outcomes. The major limitations of the included studies were the retrospective study design and the use of different assessment tools preventing comparison between techniques and series. More recently, a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen centres using RALP or RRP was published. At twelve months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [370].

*8.2.2 **Radiotherapy***

8.2.2.1 Side-effects of external beam radiotherapy

The introduction of IMRT to deliver radiotherapy has resulted in less long-term toxicity. The Memorial Sloan-Kettering Cancer Center group have reported data on late toxicity from their experience in 1,571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of ten years [837]. Both acute GI and GU toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) Grade 2 or more GI 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 GI toxicity and 3% for GU toxicity. These data suggest that IMRT might offer better late GI toxicity outcomes. Owing to the single centre and observational nature of these data, these results must be interpreted with caution, however. Interestingly, with dose escalation, GU toxicity may become the predominant type of morbidity [837].

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients [838]. A meta-analysis has shown that the 1-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy plus 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 [839].

The Memorial Sloan-Kettering Cancer Center group have reported 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 [837]. Both acute GI and GU toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) Grade 2 or more, GI 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 GI toxicity and 3% for GU toxicity. These data suggest that IMRT can successfully protect against late GI toxicity. Interestingly, with dose escalation, GU toxicity may become the predominant type of morbidity [837].

A SR and meta-analysis of observational studies comparing patients exposed or unexposed to radiotherapy in the course of treatment for PCa demonstrate an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62) with similar risks over lag times of five and ten years. Absolute risks over ten years are small (1-4%) but should be discussed with younger men in particular [840].

8.2.2.2 Side-effects from brachytherapy

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0-19%) [841]. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for BPH increases the risk of post-implantation incontinence and urinary morbidity. Prevention of morbidity depends on careful patient selection, and expert assessment of IPSS score, backed up by urodynamic studies.

*8.2.3 **Local primary whole-gland treatments other than surgery or radiotherapy***

8.2.3.1 Cryosurgery

In Ramsay *et al.*'s SR and meta-analysis [486], there was evidence that the rate of urinary incontinence at one year was lower for CSAP than for RP, but the size of the difference decreased with longer follow-up. There was no significant difference between CSAP vs. EBRT in terms of urinary incontinence at one year (< 1%); CSAP had a similar ED rate (range 0-40%) to RP at one year. There was insufficient data to compare CSAP vs. EBRT in terms of ED.

8.2.3.2 High-intensity focused ultrasound

In terms of toxicity, there are insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at one year HIFU had lower incontinence rates than RP (OR: 0.06, 95% CI: 0.01-0.48) [486].

*8.2.4 **Hormonal therapy***

A summary of impacts on psychological factors due to the use of ADT such as sexual function, mood, depression, cognitive function and impact on men's partners can be found in two clinical reviews [842, 843]. A small RCT evaluated the QoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. ADT patients reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue and irritability during treatment [844]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [845]. 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 [846].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at twelve months [847]. 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 [848], preserved libido and erectile function [849]. Intermittent androgen deprivation has been discussed elsewhere (see Section 6.4.4.3).

8.2.4.1 Sexual function

Cessation of sexual activity is very common on men undergoing ADT, affecting up to 93% of men [850]. The management of acquired ED is mostly non-specific [851].

8.2.4.2 Hot flushes

Hot flushes are a common side-effect of ADT (prevalence estimated between 44-80% of men on ADT) [850]. They appear three months after starting ADT, usually persist long-term and have a significant impact on QoL.

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications [852].

Serotonin re-uptake inhibitors (e.g. venlafaxine or sertraline) appear to be effective in men, but less than hormone therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [853]. After six months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, Venlafaxine was inferior -47.2% (IQR -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group.

With a placebo effect influencing up to 30% of patients [854], the efficacy of clonidine, veralipride, gabapentine [855] and acupuncture [856] need to be compared in prospective RCTs.

8.2.4.3 Non-metastatic bone fractures

Due to increased bone turnover and decreased bone mineral density (BMD) in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% RR with long-term ADT) [857]. Hip fractures in men are associated with a significant risk of death [858]. 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 [859]. Both changes increase the fracture risk.

8.2.4.3.1 Hormonal treatment modalities

Bicalutamide monotherapy could be a relative bone-protective treatment [860, 861], but is limited by its suboptimal efficacy (see Section 6.1.4.1.1.5.2.3 - Metastatic PCa - Hormonal Therapy). The intermittent LHRH-agonist modality might be associated with less bone impact [862].

8.2.4.3.2 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 [863] or yearly [864] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [865]. A quarterly regimen could be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [866].

8.2.4.3.3 Denosumab

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after two years, using a 60 mg subcutaneous regimen every six months [867]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, p = 0.006). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every four weeks), a delay in bone metastases of 4.2 months has been shown [806] without any impact on OS, but with an increase in side-effects. Therefore, this later regimen cannot be recommended.

8.2.4.4 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [859]. ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [868], 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 [869]:

- 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 [870].

Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [871]. Androgen deprivation therapy induced hypogonadism results in negative effects on skeletal muscle health. A prospective longitudinal study involving 252 men on ADT for a median of 20.4 months reported lean body mass decreases progressively over 3 years; 1.0% at one year, 2.1% at two years, and 2.4% at three years which appears more pronounced in men at ≥ 70 years of age [872].

8.2.4.5 Cardiovascular morbidity

Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [713, 873, 874]. Several studies showed that ADT, after only six months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [875]. The RTOG 92-02 [876] and 94-08 [381] 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 [877]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [878, 879]. Meta-analysis of observational data reports consistent links between ADT and the risk of CVD in men treated for PCa e.g. the associations between GnRH agonists and nonfatal or fatal myocardial infarction or stroke RR: 1.57 (95% CI, 1.26-1.94) and RR: 1.51 (95% CI, 1.24-1.84), respectively [880]. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [881] or presenting with a metabolic syndrome [882].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [883]. However, the methodology used in these studies does not provide convincing evidence to show a clear superiority of these compounds.

These concerns resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [712]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, improved nutrition and smoking cessation [884].

8.2.4.6 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure. Anaemia may be a cause of fatigue [850, 885]. 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 [886].

8.2.4.7 Neurological side-effects

Castration seems also to be associated with an increased risk of stroke [887], and is suspect to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [888].

8.3 Overall quality of life in men with prostate cancer

Living longer with PCa, does not necessarily equate to living well [783, 828]. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa [889]. Radical treatment for PCa can negatively impact long-term QoL (e.g. sexual, urinary and bowel dysfunction), as can ADT used in short or long-term treatment e.g. sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae increased cardiovascular and bone fracture risk [842, 890]. Direct symptoms from advanced or metastatic cancer e.g. pain, hypercalcaemia, spinal cord compression, pathological fractures, also adversely affect health [891, 892]. Men's QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [893, 894].

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

Table 8.3.1: PROMs assessing cancer specific quality of life

Questionnaire	Domains / items
Functional Assessment of Cancer Therapy-General (FACT-G) [895]	Physical well-being, Social/family well-being, Emotional well-being, and Functional well-being
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [896]	12 cancer site specific items to assess for prostate related symptoms. Can be combined with FACT-G or reported separately.
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [897]	Five functional scales (physical, role, cognitive, emotional, and social); Three symptom scales (fatigue, pain, and nausea and vomiting); Global health status/QoL scale; and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [898]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Expanded prostate cancer index composite (EPIC) [899]	Urinary, bowel, sexual, and hormonal symptoms.

Expanded prostate cancer index composite short form 26 (EPIC 26) [900]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [901]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [902]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [903]	Urinary, bowel, and sexual domains.

*8.3.1 **Long-term (≥ 12 months) quality of life outcomes in men with localised disease.***

8.3.1.1 Men undergoing local treatments

The results of the Prostate Testing for Cancer and Treatment (ProtecT) trial (n = 1,643 men) [904] reported no difference in EORTC QLQ-C30 assessed global QoL, up to five years of follow-up in men aged 50-69 years with T1-T2 disease randomised for treatment with AM, RP or RT [904]. However, EPIC urinary summary scores (at 6 years) were worse in men treated with RP compared to AM or RT (88.7 vs. 89.0 vs. 91.4, respectively) as were urinary incontinence (80.9 vs. 85.8 vs. 89.4, respectively) and sexual summary, function and bother scores (32.3 vs. 40.6 vs. 41.3 for sexual summary, 23.7 vs. 32.5 vs. 32.7 for sexual function and 51.4 vs. 57.9 vs. 60.1 for sexual bother, respectively) at six years of follow-up. Minimal clinically important differences for the 50 item EPIC questionnaire are not available. For men receiving RT, EPIC bowel scores were poorer compared to AM and RP in all domains: function (90.8 vs. 92.3 vs. 92.3, respectively), bother (91.7 vs. 94.2 vs. 93.7, respectively) and summary (91.2 vs. 93.2 vs. 93.0, respectively) at six years of follow-up in the ProtecT trial.

The findings regarding RP and RT are supported by other observational studies, the most important being The Prostate Cancer Outcomes Study (PCOS) [832] that studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT. The study reported that at five years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However, despite these differences detected at five years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at fifteen years. More recently, investigators reported that although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance 12 months after treatment [905]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side-effects in contemporary treatments may be slightly less.

With respect to brachytherapy cancer-specific QoL outcomes, the best available evidence come from one small RCT (n = 200) evaluating bilateral nerve sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsening of physical functioning as well as irritative urinary symptomatology in 20% of brachytherapy patients at one year of follow-up. However, there were no significant differences in EORTC QLQ-C30/PR-25 scores at five years of follow-up when comparing to pre-treatment values [906]. It should be noted of this trial within group tests only were reported. These data and a synthesis of 18 randomised and non-randomised studies in a SR involving 13,604 patients, are the foundation of the following recommendations [907].

8.3.1.2 Guidelines for quality of life in men undergoing local treatments

Recommendations	Strength rating
Advise eligible patients for active surveillance, that global quality of life is equivalent for up to five years compared to radical prostatectomy or external beam radiotherapy.	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.	Strong
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.	Weak

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

Men undergoing local treatments

In men with localised disease, nurse led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, dyadic adjustment, depression, managing bowel and urinary function problems) provided positive short-term effects (four months) on sexual function (effect size 0.45) and long-term (twelve months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [908].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single centre, double blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [909]. However, a multi-centre double blind RCT (n = 423) in men aged

< 68 years, with normal pre-treatment erectile function undergoing either open, conventional or robot assisted laparoscopic nerve-sparing RP, Tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6: 95% CI: 3.1-16.0) when compared to 20 mg 'on demand' or placebo at nine months of follow-up [401]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation. A detailed discussion can be found in the EAU Male Sexual Dysfunction Guidelines [910].

Men undergoing systemic treatments

Similar to men treated with a radical approach (see above) men with T1-T3 disease undergoing RT and ADT a combined nurse led psychological support and physiotherapist led multi-disciplinary rehabilitation has reported improvements in QoL. Specifically this intervention involved action planning around patients' needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5: 95% CI: 0.6-8.4), irritative (adjusted mean 5.8: 95% CI: 1.4-10.3) and hormonal (adjusted mean 4.8: 95% CI: 0.8-8.8) EPIC domains were found up to 22 weeks of follow-up [911].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8: 95% CI: 6.6-24.9) and cognitive domain outcomes (adjusted mean 11.4: 95% CI: 3.3-19.6) as well as symptom scales for fatigue (adjusted mean –11.0: 95% CI: –20.2,–1.7), nausea (adjusted mean –4.0: 95% CI: –7.4,–0.25), and dyspnoea (adjusted mean –12.4: 95% CI: –22.5,–2.3) up to three months in men treated with ADT [912]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9: 95% CI: 3.7-14.2) in men on long-term ADT [913, 914]. These findings are supported by a SR which reported improvements up to twelve weeks in cancer-specific QoL in a meta-analysis of high quality trials (SMD 0.33: 95%, CI: 0.08-0.58) [885].

8.3.2.1 Guidelines for quality of life in men undergoing systemic treatments

Recommendations	Strength rating
Offer men on androgen deprivation therapy, twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Offer men with T1-T3 disease specialist nurse led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	Strong

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10. CONFLICT OF INTEREST

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

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11. CITATION INFORMATION

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