

# Guidelines on Prostate Cancer

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# 1. INTRODUCTION

## 1.1 Introduction

The European Association of Urology (EAU) Guidelines Group for Prostate Cancer have prepared this guidelines document to assist medical professionals assess the evidence-based management of prostate cancer (PCa). The multidisciplinary guidelines panel includes urologists, radiation oncologists, a medical oncologist, a radiologist and a pathologist.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, also taking individual circumstances and patient preferences into account.

## 1.2 Data identification and evidence sources

The recommendations provided in the current guidelines are based on literature searches performed by the panel members. A systemic literature search was performed to assess the evidence for the medical management of men with CRPC (Chapter 20 - Castration-resistant PCa). Key findings are presented in the text. For this review, Embase, Medline on the Ovid platform and the Cochrane Central Register of Controlled Trials were searched without time limitations. Search cut-off date was October 2013. A total of 1158 records were identified and after deduplication and a structured data selection, nine studies were included in the review.

Standard procedure for EAU publications includes an annual assessment of newly published literature in this field, guiding future updates.

## 1.3 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (Table 1.1), and guideline recommendations have been graded (Table 1.2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). Grading aims to provide transparency between the underlying evidence and the recommendation given.

**Table 1.1: Level of evidence\***

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

\*Modified from (1).

When recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not translate into a grade A recommendation when there are methodological limitations or disparity in published results.

Absence of high-level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptions where corroborating studies cannot be performed, perhaps for ethical or other reasons, and unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as “upgraded based on panel consensus”. The quality of the underlying scientific evidence must be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can it address local/national preferences systematically. The expert panels include this information whenever it is available.

**Table 1.2: Grade of recommendation\***

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

\*Modified from (1).

## 1.4 Publication history

The Prostate Cancer Guidelines were first published in 2001, with partial updates achieved in 2003 and 2007, followed by a full text update in 2009. Also in 2011, 2012 and 2013 a considerable number of sections of the PCa guidelines were revised. For this 2014 publication all chapters have been re-assessed, as detailed below.

A quick reference document presenting the main findings of the PCa guidelines is also available, alongside several scientific publications in European Urology (5,6).

All documents are available with free access through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

For the 2015 PCa Guidelines publication a complete restructuring of the document is envisaged as well as inclusion of data from additional systematic reviews.

## 1.5 Summary of updated information

### 1.5.1 Acknowledgement

The EAU Prostate Cancer 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) for the topic of 'Management of PCa in senior adults' (Chapter 14). As a leading expert in this field, and prominent member of the International Society of Geriatric Oncology, his contribution has been invaluable.

**For this 2014 update, the following changes should be noted:**

Chapter 2: Background The literature has been revised.
Chapter 3: Classification The literature has been updated and the text has been expanded (definitions and d'Amico classification).
Chapter 4: Risk factors and chemoprevention The literature has been revised and additional information included on 5-alpha-reductase inhibitors (5-ARIs).
Chapter 5: Screening and early detection The literature has been revised.
Chapter 6: Diagnosis The literature has been revised and information on the role of imaging as a diagnostic tool has been added. A number of recommendations have been included.
Chapter 7: Staging This chapter has been restructured, and additional information on the use the use of MRI as a diagnostic tool has been added.
Chapter 8: Treatment: deferred treatment (active surveillance/watchful waiting) The literature has been revised and the text has been restructured.
Chapter 9: Treatment Radical Prostatectomy New information has been included, in particular in sections 9.4.1 - 9.4.3.
Chapter 10: Treatment: definitive radiotherapy The literature has been revised and an overview table listing the three randomized trials for adjuvant radiation therapy after radical prostatectomy has been added.
Chapter 11: Options other than surgery and radiotherapy for the primary treatment of localised PCa The literature has been revisited and the text was restructured. A number of new recommendations were added.
Chapter 12: Hormonal therapy; rationale and available drugs The literature has been revised.
Chapter 13: Metastatic PCa - Hormonal therapy The literature has been revised.

Chapter 14: Management of PCa in senior adults This section was completely revised.
Chapter 15: Quality of life of patients with localised PCa The literature has been revised and the text has been condensed. A number of new recommendations were added.
Chapter 17: Follow-up after treatment with curative intent The literature has been revised and the text was condensed.
Chapter 18: Follow-up after hormonal treatment The literature has been revised and the text was condensed.
Chapter 19: Treatment of biochemical failure after curative intent The literature has been revised and the text has been restructured. A number of new recommendations were added.
Chapter 20: Castration-resistant PCa (CRPC) The literature has been updated and the text has been completely restructured. Table 20.3 presents an overview of the review done to assess the medical management of men with CRPC. A treatment flowchart is provided and a number of new recommendations were added.

## 1.6 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

## 1.7 References

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## 2. BACKGROUND

Prostate cancer is the most common cancer in elderly males in Europe. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population. The incidence is highest in Northern and Western Europe (> 200 per 100,000), while rates in Eastern and Southern Europe have showed a continuous increase (1). There is still a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe (2). Overall, during the last decade, the 5-year relative survival percentages for prostate cancer steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 (2).

With the expected increases in the life expectancy of men and in the incidence of prostate cancer, the disease's economic burden in Europe is also expected to increase substantially. It is estimated that the total economic costs of prostate cancer in Europe exceed € 8.43 billion (3), with a high proportion of the costs of prostate cancer care occurring in the first year after diagnosis. In European countries with available data (UK, Germany, France, Italy, Spain, the Netherlands), this amounted to € 106.7-179.0 million for all prostate cancer patients diagnosed in 2006.

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## 3. CLASSIFICATION

The 2009 TNM (Tumour Node Metastasis) classification for PCa is shown in Table 3.1 (1).

**Table 3.1: Tumour Node Metastasis (TNM) classification of PCa**

<b>T - Primary tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
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] level)
T2	Tumour confined within the prostate <sup>1</sup>
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 <sup>2</sup>
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
<b>N - Regional lymph nodes<sup>3</sup></b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
<b>M - Distant metastasis<sup>4</sup></b>	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis

M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

<sup>1</sup> Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.

<sup>2</sup> Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

<sup>3</sup> Metastasis no larger than 0.2 cm can be designated pN1 mi.

<sup>4</sup> When more than one site of metastasis is present, the most advanced category should be used.

**Table 3.2: Defined risk groups of localized prostate cancer**

	Very low-risk	Low-risk	Intermediate-risk	High-risk	Locally advanced
D'Amico (2)		PSA ≤ 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/mL or GS ≤ 7, or cT2b	PSA > 20 ng/mL, or GS > 7, or cT2c-3a	
NCCN (3)	cT1c, GS < 7, PSA < 10 ng/mL, PSAD < 0.15, < 3 positive biopsies	PSA < 10 ng/mL, GS < 7, cT1-2a	PSA 10-20 ng/mL, or GS 7, or cT2b-2c	PSA > 20 ng/mL, or GS > 7, or cT3a	cT3b-4
CAPRA score (4)		< 3	3-5	6-10	
EAU (5)		PSA < 10 ng/mL, GS < 7, cT1c	PSA 10-20 ng/mL, or GS 7, or cT2b-2c	PSA < 20 ng/mL, GS 8-10 or = > cT3a	

In these guidelines, the D'Amico risk-group classification is used to define high-risk PCa (high-risk or locally advanced PCa comprise stages T3 and T4). Low-risk, versus high-risk PCa is based on PSA findings only, or on Gleason score only.

### 3.1 References

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## 4. RISK FACTORS AND CHEMOPREVENTION

The factors that determine the risk of developing clinical prostate cancer (PCa) are not well known, although a few have been identified. There are three well-established risk factors for PCa:

- increasing age;
- ethnic origin;
- heredity.

If one first-line relative has PCa, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases by 5-11-fold (1,2). A small subpopulation of individuals with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before age 55 (2). Patients with hereditary PCa usually have an onset six to seven years earlier than spontaneous cases, but do not differ in other ways (2).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (3). This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the USA and northern Europe and low in South-East Asia. However, if Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men (4) (LE: 2).

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as the foods consumed, the pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation (5,6) and occupational exposure have all been discussed as being aetiologically important (6). PCa may be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, because of some specific features:

- high prevalence
- long latency
- endocrine dependency
- availability of serum markers (prostate-specific antigen)
- the histological precursor lesion prostatic intraepithelial neoplasia (5).

Nevertheless, there is currently no evidence to suggest that dietary interventions would reduce the risk of PCa. The outcome of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was negative, and therefore vitamin E and selenium are not recommended for the prevention of PCa (7) (LE: 1b). Similarly, a meta-analysis of eight randomized controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa (8).

Metabolic syndrome is weakly and non-significantly associated with the risk of PCa, but associations vary with geography. Among single components of the syndrome (body mass index, dysglycaemia or dyslipidaemia, high triglycerides, low HDL cholesterol) only hypertension and waist circumference >102 cm were associated with a significantly greater risk of PCa, increasing it by 15% ( $p = 0.035$ ) and 56% ( $p = 0.007$ ), respectively (9). Currently, there are no data to suggest that medical intervention would effectively reduce progression of PCa. Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing risk of developing PCa. Although it seems that 5-ARIs have a potential benefit in preventing or delaying the development of PCa (~25%, only of Gleason 6 cancer), this must be weighed against treatment-related side-effects as well as the potential increased risk of high-grade PCa (10-12). None of the available 5-ARIs have been approved for this indication.

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on this risk. There is as yet insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk (13) (LE: 2-3).

### 4.1 Recommendation for preventative measures

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

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## 5. 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 screening consists of individual case findings, which are initiated by the person being screened (patient) and/or his physician. The primary endpoint of both types of screening has two main aspects:

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

Prostate cancer mortality trends range widely from country to country in the industrialized world (1). Decreased mortality rates due to PCa have occurred in most Western countries but the magnitude of the reduction varies between countries. The reduced mortality seen recently in the USA is considered to be partly due to a widely adopted aggressive PCa screening policy (2). However, there is still no level 1 evidence that prostate-specific



antigen (PSA) screening reduces mortality due to PCa (3) (LE: 2).

Prostate cancer screening is one of the most controversial topics in urological literature. A huge number of passionate papers, discussions and debates have been produced, as well as at least three large prospective RCTs initially published in 2009 (4-6). The great importance of this subject requires the highest-quality evidence, which can only be obtained by a systematic literature search of published trials or cohorts summarized in a structured meta-analysis. The subgroup analysis of cohorts that are part of a large trial, or mathematical projections, can never provide level 1 evidence and are only useful for generating hypotheses.

The main summary of findings from literature published on PCa screening is the Cochrane review published in 2013 (3). This review was based on an up-to-date systematic literature search during November 2012 and is an update of a 2010 paper with the same methodology. Its findings are as follows:

- Screening was associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).
- Screening was associated with more localized 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, representing more than 341,000 randomized men, no PCa-specific survival benefit was observed (RR: 1.00; 95% CI: 0.86-1.17). This was the main objective of all the large trials.
- From the results of four available RCTs, no overall survival benefit was observed (RR: 1.00; 95% CI: 0.96-1.03).

Moreover, screening was associated with minor and major harms such as overdiagnosis and overtreatment. Surprisingly, the diagnostic tool (i.e. the biopsy) was not associated with any mortality in the selected papers, which is in contrast with some other known data (7,8).

The impact on the patient's overall QoL is still unclear. It appears to be minimal in some subgroup analysis (9), but significant in others (10). This has led to strong advice against population-based systematic screening in all countries, including Europe (LE: 1a; GR: A).

Nevertheless, at 11 years of median follow-up, the ERSPC has shown a 21% reduction in PCa-specific mortality and a 29% reduction after adjustment for non-compliance. However, there is still no overall survival benefit (11).

Thus, an individualized risk-adapted strategy for early detection might be offered to a well-informed man with a least 10-15 years of individual life expectancy (LE: 3; GR: B). However, this approach may still be associated with a substantial risk of overdiagnosis. It is therefore important to identify carefully those 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 aged above 50 years, or with a family history of PCa and aged more than 45 years, or African-Americans (12) (LE: 2b; GR: A). In addition, men with PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years (13) are also at increased risk of PCa-related mortality or a diagnosis of advanced or metastatic disease.

Early PSA testing could be used to detect these cohorts of men at risk and in need of further follow-up (LE: 2b; GR: B). However, the long-term benefit for survival and QoL of such an approach remains to be proven at a population level (LE: 3; GR: A).

Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE (14). The optimal intervals for PSA testing and DRE follow up are unknown, and it has varied between several prospective trials. A risk-adapted strategy might be considered based on the initial PSA level. This could be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk (LE: 3; GR: C).

The age at which attempts to make an early diagnosis of PCa should be stopped remains controversial but is influenced by an individual's life expectancy. Men who have less than a 15-year life expectancy are unlikely to benefit based on the PIVOT and the ERSPC trials (LE: 3; GR: A). Furthermore, although there is not a simple tool to evaluate individual life expectancy, co-morbidity is at least as important as age. A detailed review can be found in the chapter on senior adults and in the recently updated SIOG guidelines (15).

Based on the tools currently available, an individualized strategy will diagnose many insignificant lesions (above 50% in some trials), most of which will not require any form of active treatment (Chapter 8, Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only way to decrease overtreatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it (LE: 2b; GR: A).



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

## 5.1 Recommendations for screening and early detection

	LE	GR
An individualized risk-adapted strategy for early detection might be offered to a well-informed man with a good performance status and at least 10-15 years of life expectancy.	3	B
Early PSA testing in men at elevated risk of having PCa: <ul style="list-style-type: none"> <li>• men over 50 years of age</li> <li>• men over 45 years of age and a family history of PCa</li> <li>• African-Americans</li> <li>• men with a PSA level of &gt; 1 ng/mL at 40 years of age</li> <li>• men with a PSA level of &gt; 2 ng/mL at 60 years of age</li> </ul>	2b	A
A risk-adapted strategy might be considered (based on initial PSA level), which may be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk.	3	C
The age at which early diagnosis of PCa should be stopped is influenced by life expectancy and performance status; men who have < 15-year life expectancy are unlikely to benefit based on the PIVOT and the ERSPC trials.	3	A

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## 6. DIAGNOSIS

Prostate cancer (PCa) is usually suspected on the basis of digital rectal examination (DRE) and prostate-specific antigen (PSA) levels. Definitive diagnosis depends on the histopathological verification of adenocarcinoma in prostate biopsy cores or operative specimens.

### 6.1 Digital rectal examination

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level (1) (LE: 2a). A suspect DRE in patients with a PSA level up to 2 ng/mL has a positive predictive value of 5-30% (2) (LE: 2a). An abnormal DRE is associated with an increased risk of a higher Gleason score and should therefore be considered an indication for prostate biopsy (3,4).

### 6.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionized the diagnosis of PCa (5). PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate, which is organ- but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or transrectal ultrasound (TRUS) (6).

There are many different commercial test kits for measuring PSA, but no commonly agreed international standard exists (7). The level of PSA is a continuous parameter: the higher the value, the more likely the existence of PCa. The finding that many men may harbour PCa despite having low serum PSA has been underscored by results from a US prevention study (8) (LE: 2a). Table 6.1 gives the rate of PCa in relation to serum PSA for 2,950 men with PSA values  $\leq$  4 ng/mL in the placebo-arm of the study.

**Table 6.1: Risk of PCa in relation to low PSA values**

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason $\geq$ 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

The data in Table 6.1 clearly demonstrate the occurrence of Gleason  $\geq$  7 PCa even at very low PSA levels, precluding an optimal PSA threshold value for detecting non-palpable but clinically significant PCa (LE: 3). The use of nomograms may help to reduce the number of unnecessary prostate biopsies (9).

Several modifications of serum PSA value that may improve the specificity of PSA in the early detection of PCa have been described. They include:

- PSA density;

- PSA density of the transition zone;
- age-specific reference ranges;
- PSA molecular forms.

However, these derivatives and PSA isoforms - complex PSA (cPSA), precursor isoforms of PSA (proPSA), benign PSA (BPSA) and intact PSA (iPSA) - are of limited use in the routine clinical setting and have therefore not been considered for inclusion in these guidelines.

### 6.2.1 **Free/total PSA ratio**

The free/total PSA ratio (f/t PSA) is the concept most extensively investigated and most widely used in clinical practice to differentiate BPH from PCa. The ratio is used to stratify the risk of PCa for men who have total PSA levels of between 4 ng/mL and 10 ng/mL and a negative DRE. In a prospective multicentre trial, PCa was found on biopsy in 56% of men with f/t PSA < 0.10, but in only 8% of men with f/t PSA > 0.25 (10) (LE: 2a).

Nevertheless, the concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA, e.g. the instability of free PSA (unstable at 4°C and room temperature), variable assay characteristics, and concomitant BPH in large prostates, which may result in a dilution effect (11). Furthermore, f/t PSA is of no clinical use if total serum PSA values are > 10 ng/mL or during follow-up of patients with known PCa.

### 6.2.2 **PSA velocity and PSA doubling time**

There are two methods of measuring PSA over time:

- the PSA velocity (PSAV), which is defined as an absolute annual increase in serum PSA (ng/mL/year) (12) (LE: 1b);
- the PSA doubling time (PSADT), which measures the exponential increase in serum PSA over time, reflecting a relative change (13).

These two concepts may have a prognostic role in patients with treated PCa (14), but have limited use in the diagnosis of PCa because of background noise (total volume of prostate, BPH), the variations in interval between PSA determinations, and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have shown that these measurements do not provide additional information compared with PSA alone (15-18).

### 6.2.3 **PCA3 marker**

PCA3 is an increasingly studied new biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The costly ProgenSA urine test for PCA3 is now commercially available. The amount of the prostate-specific non-coding mRNA marker PCA3 normalized against PSA mRNA (urine sediment) gives a PCA3 score. This is superior to total PSA and percent-free PSA in the detection of PCa in men with elevated PSA levels as it shows slight but significant increases in the area under the receiver-operator characteristics curve (AUC) for positive biopsies (19-22).

The PCA3 score increases with PCa volume, but there is conflicting data about whether the PCA3 score independently predicts the Gleason score, and its use as a monitoring tool in active surveillance has not been confirmed (23). The main current indication for the PCA3 urine test may be to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome, but its cost-effectiveness remains to be shown.

## 6.3 **Prostate biopsy**

### 6.3.1 **Baseline biopsy**

The need for a prostate biopsy should be determined on the basis of the PSA level and/or a suspicious DRE. The patient's age, potential co-morbidities (American Society of Anesthesiologists' physical status classification index [ASA] and Charlson co-morbidity index), and the therapeutic consequences should all also be considered (25). Risk stratification is becoming an important tool for reducing unnecessary prostate biopsies (25).

The first elevated PSA level should not prompt an immediate biopsy. The PSA level should be verified after a few weeks by the same assay under standardized conditions (i.e. no ejaculation, no manipulations such as catheterisation, cystoscopy or transurethral resection, and no urinary tract infections) in the same diagnostic laboratory, using the same methods (26,27) (LE: 2a).

It is now considered the standard of care to perform prostate biopsies guided by ultrasound. Although a transrectal approach is used for most prostate biopsies, some urologists prefer to use a perineal approach. The cancer detection rates from perineal prostate biopsies are comparable to those obtained from transrectal biopsies (28,29) (LE: 1b).

The ultrasound-guided perineal approach is a useful alternative in special situations, e.g. after rectal amputation.

### 6.3.2 **Repeat biopsy**

The indications for a repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 6.1 for risk estimates);
- suspicious DRE, 5-30% risk of cancer (1,2);
- atypical small acinar proliferation (ASAP), 40% risk of cancer (30);
- extensive (multiple biopsy sites) prostatic intra-epithelial neoplasia (PIN), 20-30% risk of cancer (30,31).

High-grade PIN as an isolated finding is no longer considered an indication for repeat biopsy (32) (LE: 2a). A repeat biopsy should therefore be prompted by other clinical features, such as the DRE findings and the PSA level. Extensive PIN (i.e. in multiple biopsy sites) could be a reason for an early repeat biopsy because the risk of subsequent PCa is slightly increased. If clinical suspicion for PCa persists despite negative prostate biopsies, magnetic resonance imaging (MRI) may be used to investigate the possibility of an anterior-located PCa, followed by TRUS or MRI-guided biopsies of the suspicious area (33).

### 6.3.3 **Saturation biopsy**

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is between 30% and 43% and depends on the number of cores sampled during earlier biopsies (34) (LE: 2a). In special situations, saturation biopsy may be performed with the transperineal technique. This will detect an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback (35) (LE: 2b).

### 6.3.4 **Sampling sites and number of cores**

On baseline biopsies, the sample sites should be as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS. These should be chosen on an individual basis.

Sextant biopsy is no longer considered adequate. At a glandular volume of 30-40 mL, at least eight cores should be sampled. The British Prostate Testing for Cancer and Treatment Study recommended 10 core biopsies (36) (LE: 2a), with > 12 cores being not significantly more conclusive (37) (LE: 1a).

### 6.3.5 **Diagnostic transurethral resection of the prostate**

The use of diagnostic transurethral resection of the prostate (TURP) instead of repeat biopsies is a poor tool for cancer detection (38) (LE: 2a).

### 6.3.6 **Seminal vesicle biopsy**

Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA levels > 15 ng/mL, the odds of tumour involvement are 20-25% (39) (LE: 2a), but a biopsy is useful only if the outcome will have a decisive impact on treatment, i.e. if the biopsy result rules out radical removal for tumour involvement or radiotherapy with intent to cure. Its added value compared with multiparametric MRI is questionable.

### 6.3.7 **Transition zone biopsy**

Transition zone sampling during baseline biopsies gives a very low detection rate and should therefore be confined to repeat biopsies (40) (LE: 1b).

### 6.3.8 **Antibiotics prior to biopsy**

Oral or intravenous antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin (41) (LE: 1b), but increased resistance to quinolones (42) associated with a rise in severe infectious complications after biopsy (43) has been reported in the past few years.

### 6.3.9 **Local anaesthesia prior to biopsy**

Ultrasound-guided periprostatic block is state-of-the-art (44) (LE: 1b). It does not make any difference whether the depot is apical or basal. Intrarectal instillation of a local anaesthetic is clearly inferior to periprostatic infiltration (45) (LE: 1b).

### 6.3.10 **Fine-needle aspiration biopsy**

Fine-needle aspiration biopsy is no longer state-of-the-art.

### 6.3.11 **Complications**

Complications include visible (macro) haematuria and haemospermia (Table 6.2) (46). Severe post-

procedural infections were initially reported in < 1% of cases, but this rate has increased over the past few years as a consequence of the evolution of antibiotic resistant strains, and there have been more post-biopsy hospitalisations for infectious complications while the rate of non-infectious complications has remained stable (47).

Low-dose aspirin is no longer an absolute contraindication (48) (LE: 1b).

**Table 6.2: Percentage of complications per biopsy session, irrespective of the number of cores**

Complications	Percentage of biopsies affected
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C (101.3°F)	0.8
Epididymitis	0.7
Rectal bleeding > 2 days ± requiring surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

## 6.4 The role of imaging

### 6.4.1 TRUS

The classic picture of a hypo-echoic area in the peripheral zone of the prostate will not always be seen. Grey-scale TRUS is not adequately reliable at detecting areas of PCa (24). It is therefore not useful to replace systematic biopsies of suspect areas with targeted ones, although additional biopsies of suspect areas may be useful.

### 6.4.2 Multiparametric MRI

Correlation with radical prostatectomy specimens have shown that multiparametric MRI (mMRI), associating T2-weighted imaging with functional sequences such as diffusion-weighted imaging, dynamic contrast-enhanced imaging or H1-spectroscopy, has excellent sensitivity for detecting aggressive Gleason ≥ 7 cancers (49-52). In a series of 175 patients treated by prostatectomy, detection rates for tumours of < 0.5 cc, 0.5-2.0 cc and > 2.0 cc were 21-29%, 43-54% and 67-75% for Gleason ≤ 6, 63%, 82-88% and 97% for Gleason 7, and 80%, 93% and 100% for Gleason ≥ 8 cancers, respectively (52).

mMRI is particularly good at accurately detecting anterior tumours that are usually missed by systematic biopsy (53,54) and therefore trigger a (targeted) repeat biopsy (55-57). In a recent series of 265 patients undergoing repeat biopsy, MR-guided samples were positive in 41% of the patients; 87% of the detected cancers were clinically significant as judged by the Epstein criteria (55). These positive results have prompted some authors to propose mMRI as a triage test for candidates for biopsy, in an attempt both to increase detection of aggressive cancers and reduce over-detection of non-significant foci (58,59).

A recent multicentre study comparing systematic and targeted biopsy (performed by two different operators in 95 patients referred for a first prostate biopsy) showed targeted biopsies yielded a significantly higher rate of positivity for all cancers (69% vs 59%,  $p = 0.033$ ) and for clinically significant cancers (67% vs 52%,  $p < 0.0011$ ) (60).

However, these promising results need further confirmation, and the cost-effectiveness of mMRI as a triage test before the first biopsy has not been assessed. Inter-reader variability is also a current concern, especially outside reference centres. Recent publication of a standardized scoring system (61) may improve inter-reader agreement, but this remains to be confirmed (62).

### 6.4.3 Recommendation for imaging

	LE	GR
When available, mMRI of the prostate can be used to trigger a (targeted) repeat prostate biopsy.	2b	B

*mMRI = multiparametric magnetic resonance imaging*

## 6.5 Pathology of prostate needle biopsies

### 6.5.1 Grossing and processing

Prostate core biopsies taken from different sites are usually sent to the pathology laboratory in separate vials and should be processed in separate cassettes. Before processing, the number of cores per vial and the length of each core should be recorded. There is a significant correlation between the length of prostate biopsy tissue on the histological slide and the detection rate of PCa (63). To achieve optimal flattening and alignment of individual cores, a maximum of three cores should be embedded per cassette, and sponges or paper should be used to keep the cores stretched and flat (64,65). To optimize the detection of small lesions, blocks should be cut at three levels (40). It is helpful routinely to mount intervening tissue sections in case additional immunostaining is needed.

### 6.5.2 Microscopy and reporting

Diagnosis of PCa is based on histological examination. Ancillary staining techniques (e.g. basal cell staining) and additional (deeper) sections should be considered if a suspect lesion is identified (66-68). Diagnostic uncertainty in biopsies may often be resolved by intradepartmental consultation or a second opinion from an external institution (66). Table 6.3 lists the recommended concise terminology for the reporting of prostate biopsies (64).

**Table 6.3: Recommended diagnostic terms for the reporting of prostate biopsy findings\***

Benign/negative for malignancy. If appropriate, include a description (e.g. atrophy)
Active inflammation, negative for malignancy
Atypical adenomatous hyperplasia/adenosis, no evidence of malignancy
Granulomatous inflammation, negative for malignancy
High-grade PIN, negative for adenocarcinoma
High-grade PIN with atypical glands, suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
Adenocarcinoma

\*From Van der Kwast et al. 2013 (64); PIN = prostatic intra-epithelial neoplasia

For each biopsy site, the proportion of biopsies that are positive for carcinoma and the International Society of Urological Pathology (ISUP) 2005 Gleason score should be reported (69).

A recent study has demonstrated the improved concordance of pattern and change of prognostic groups for the modified Gleason grading (70). According to current international convention, the (modified) Gleason score of cancers detected in prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component, plus the second most common lower grade if two grades are present. If three grades are present, the Gleason score consists of the most common grade plus the highest grade, irrespective of its extent (no 5% rule). When the carcinoma largely consists of grade 4/5 carcinoma, identification of a small portion (< 5% of the carcinoma) of Gleason grade 2 or 3 glands should be ignored. A diagnosis of Gleason score 4, or lower, should not be given on prostate biopsies (69). The presence of intraductal carcinoma, lymphovascular invasion and extraprostatic extension should be reported. In addition to a report of the carcinoma features for each biopsy site, an overall Gleason score based on findings in the individual biopsies is commonly provided.

The proportion (percentage) or length (in millimetres) of tumour involvement per biopsy core correlates with tumour volume, extraprostatic extension, and prognosis after prostatectomy (71-73), and an extent of > 5 mm or > 50% of adenocarcinoma in a single core is used as a cut-off, triggering immediate treatment versus active surveillance in patients with Gleason score 6 carcinoma. For these reasons, a measure of the extent of cancer involvement (in millimetres or as a percentage) should be provided for each core. The length of the carcinoma, and the percentage of carcinoma involvement in the biopsy, have equal prognostic impact (74).

The extent of a single, small focus of adenocarcinoma, located in only one of the biopsies, should be clearly stated (e.g. < 1 mm or < 1%), as this might be an indication for further diagnostic work-up before the selection of therapy, as this finding is associated with an increased risk of vanishing cancer (75-77). A prostate biopsy that does not contain glandular prostate tissue should be reported as inadequate for diagnostic purposes.



## 6.6 Pathohistology of radical prostatectomy specimens

### 6.6.1 Processing of radical prostatectomy specimens

The histopathological examination of radical prostatectomy (RP) specimens aims to provide information about the actual pathological stage, grade and surgical margin status of the PCa. The weight and dimensions of the specimen are recorded before embedding for histological processing. It is generally recommended that RP specimens are totally embedded so as to enable the best assessment of location, multifocality and heterogeneity of the cancer.

However, for cost-effectiveness, partial embedding using a standard method may also be considered, particularly for large prostates (> 60 g). The most acceptable method includes the complete embedding of the posterior (dorsal) part of the prostate in addition to a single mid-anterior left and right section. In comparison with total embedding, partial embedding detected 98% of PCa with a Gleason score  $\geq 7$  and accurate staging in 96% of cases (78).

Upon receipt in the histopathology laboratory, the entire RP specimen is inked in order to appreciate the surgical margin status. The specimen is fixed by immersion in buffered formalin for a few days, preferably prior to incision of the sample, as incision causes distortion of the tissue. Fixation can be enhanced by injecting formalin using 21-gauge syringes, which provides a more homogeneous fixation and sectioning after 24 hours (79). After fixation, the apex is removed and cut with (para)sagittal or radial sections; the shave method is not recommended (80). Separate removal and sagittal sectioning of the bladder neck is optional. The remainder of the RP specimen is generally cut in transverse sections at 3-4 mm steps, perpendicularly to the posterior surface. The resultant tissue slices can be embedded and processed either as whole-mounts or after quadrant sectioning. Whole-mount processing provides better topographic visualisation of the carcinoma and faster histopathological examination. However, it is a more time-consuming and expensive technique that requires specialist equipment and personnel. Although whole-mount sectioning may be necessary for research, its advantages do not outweigh its disadvantages for routine sectioning.

#### 6.6.1.1 Recommendations for processing a prostatectomy specimen

	LE	GR
Total embedding of a prostatectomy specimen is preferred, by either conventional (quadrant sectioning) or whole-mount sectioning.	3	C
The entire surface of RP specimens should be inked before cutting in order to evaluate the surgical margin status.	3	C
The apex should be examined separately using the cone method with sagittal or radial sectioning.	3	C

RP = radical prostatectomy.

#### 6.6.2 RP specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 6.4). As a result of the complex information provided on each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 6.5). Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (81).

**Table 6.4: Information provided by the pathology report**

Typing: > 95% of PCa represents conventional (acinar) adenocarcinoma.
Grading according to the Gleason score.
(Sub)staging and surgical margin status of the tumour.
If appropriate, presence of intraductal carcinoma, location and extent of extraprostatic extension, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion, location and extent of positive surgical margins.
Additional information may be provided on multifocality, diameter of the dominant tumour and zonal location (transition zone, peripheral zone, anterior horn) of the dominant tumour.

**Table 6.5: Example checklist: reporting of prostatectomy specimens**

<b>Histological type</b> <ul style="list-style-type: none"> <li>• Type of carcinoma, e.g. conventional acinar, ductal, etc.</li> </ul>
<b>Histological grade</b> <ul style="list-style-type: none"> <li>• Primary (predominant) grade</li> <li>• Secondary grade</li> <li>• Tertiary grade (if applicable)</li> <li>• Total/global Gleason score</li> <li>• Approximate percentage of Gleason grade 4 or 5 (optional)</li> </ul>
<b>Tumour quantitation (optional)</b> <ul style="list-style-type: none"> <li>• Percentage of prostatic gland involved</li> <li>• Tumour size of dominant nodule (if identified), greatest dimension in millimetres</li> </ul>
<b>Pathological staging (pTNM)</b> <ul style="list-style-type: none"> <li>• If extraprostatic extension is present: <ul style="list-style-type: none"> <li>o indicate whether it is focal or extensive</li> <li>o specify site(s)</li> <li>o Indicate whether there is seminal vesicle invasion</li> </ul> </li> <li>• If applicable, regional lymph nodes: <ul style="list-style-type: none"> <li>o location</li> <li>o number of lymph nodes retrieved</li> <li>o number of lymph nodes involved</li> </ul> </li> </ul>
<b>Surgical margins</b> <ul style="list-style-type: none"> <li>• If carcinoma is present at the margin: <ul style="list-style-type: none"> <li>o specify sites and extra- or intraprostatic involvement</li> </ul> </li> </ul>
<b>Other</b> <ul style="list-style-type: none"> <li>• If identified, presence of angio-invasion and/or intraductal carcinoma</li> <li>• Location (site, zone) of dominant tumour (optional)</li> <li>• Perineural invasion (optional): <ul style="list-style-type: none"> <li>o if present, specify extra- or intraprostatic location</li> </ul> </li> </ul>

#### 6.6.2.1 Gleason score

Grading of conventional prostatic adenocarcinoma using the (modified) Gleason score system (69) is the single strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is therefore one of the parameters incorporated in nomograms that predict the risk of recurrence after prostatectomy (82).

#### 6.6.2.2 Interpreting the Gleason score

The Gleason score is the sum of the most and second most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises  $\leq 5\%$  of the cancer volume, this grade is not incorporated in the Gleason score (5% rule). Both the primary and the secondary grade are reported in addition to the Gleason score, e.g. Gleason score 7 (4 + 3). A global Gleason score is given when there are multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. A tertiary Gleason grade 4 or 5, particularly if exceeding 5% of the PCa volume, is an unfavourable prognostic indicator for biochemical recurrence. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported (83) in addition to the Gleason score.

#### 6.6.2.3 Definition of extraprostatic extension

The TNM staging system of the International Union Against Cancer is recommended for pathological staging of prostate carcinoma (80,84). Pathologic substaging of pT2 PCa is optional as it does not correlate with clinical T2 substage and lacks prognostic significance (85).

Extraprostatic extension is the recommended term for the presence of tumour beyond the confines of the prostate. Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that is bulging out beyond the contours of the prostate gland, e.g. at the neurovascular bundle or the anterior prostate. Bladder neck invasion is also considered to be an extraprostatic extension. It is useful to report not only the location, but also the extent of extraprostatic extension because extension is related to the risk of recurrence.

There are no well-established and internationally accepted definitions of the terms 'focal' and 'non-focal' or 'extensive extraprostatic extension'. Some authors describe focal as 'a few glands' (86) or extension



< 1 high-power field (87), whereas others measure the depth of extent in millimetres (88). It is currently considered clinically useful to report the extent of extraprostatic extension, e.g. less or more than 1 high-power field or 1 mm (89).

At the apex of the prostate gland, tumour mixed with skeletal muscle does not constitute extraprostatic extension. In the bladder neck, microscopic invasion of small fibres of smooth muscle is not equated to (gross) bladder wall invasion because it does not carry independent prognostic significance for PSA recurrence (90,91) and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as an extraprostatic extension (pT3a) with positive margin, and not as pT4 disease. Stage pT4 can only be assigned when the tumour invades the muscle wall of the bladder as determined by the urologist (92).

### 6.6.3 Prostate cancer volume

The independent prognostic value of the volume of PCa in RP specimens has not been established (87,93-96). Nevertheless, a PCa volume cut-off of 0.5 mL continues to be an important parameter to distinguish insignificant from clinically relevant cancer (93). Continued improvement in radio-imaging of the prostate gland has allowed more accurate measurement of cancer volume before surgery. It can therefore be recommended that the greatest dimension of the dominant tumour nodule be assessed (if identified), or that a rough estimate of the percentage of cancer tissue in the prostate be provided.

### 6.6.4 Surgical margin status

Surgical margin status is an independent risk factor for biochemical recurrence. Margin status is positive if tumour cells are in touch with the ink on the surface of the specimen. Margin status is negative if tumour cells are very close to the inked surface of the margin (94) or when they are at the surface of the tissue lacking any ink.

In tissues that have severe crush artefacts (usually at the apex), it may not be possible to assign a surgical margin status (97). Surgical margin status is independent of the pathological stage, and a positive margin is not evidence of extraprostatic extension (98). There is insufficient evidence to prove a relationship between the extent of positive margin and the risk of recurrence (87). However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in millimetres, or the number of blocks with positive margin involvement.

### 6.6.5 Other factors

According to the College of American Pathologists' consensus statement (99), additional potential biomarkers have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting (category III), including perineural invasion, neuro-endocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, PSA derivatives, and other factors (e.g. oncogenes, tumour suppressor genes, or apoptosis genes).

## 6.7 Recommendations for the diagnosis of prostate cancer

	LE	GR
Prostate cancer should be graded according to the ISUP 2005 modified Gleason grading system.	2a	A
The decision to biopsy should be based on PSA testing and DRE.	2b	A
For initial diagnosis, a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies should be performed under ultrasound imaging guidance.	2a	B
Transrectal prostate needle biopsies should be taken under antibiotic protection.	1b	A
Local anaesthetic by periprostatic infiltration is recommended for prostate needle biopsies.	1a	A
Prostate core biopsies from different prostatic sites should be submitted separately for processing and pathology reporting.	3	A
Processing and reporting of prostatectomy specimens by pathology should follow the guidelines provided by the 2010 ISUP consensus meeting.	3	A

*DRE = digital rectal examination; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen.*

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## 7. CLINICAL STAGING

The assessment of prostate cancer (PCa) extent is usually made by DRE and PSA measurement, and supplemented with bone scan and computed tomography (CT) or MRI in specific situations.

### 7.1 T-staging

#### 7.1.1 DRE, PSA level and biopsy findings

The first level of assessment is local tumour stage because the distinction between organ-confined (T1-T2) and extraprostatic (T3-T4) disease has the most profound impact on treatment decisions. DRE often underestimates tumour extension; a positive correlation between DRE and pathological tumour stage was found in < 50% of cases (1). However, more extensive examinations for adequate T-staging are only recommended in selected cases when more precise staging directly affects the treatment decision, i.e. when curative treatment is an option.

Serum PSA levels increase with advancing stage. However, PSA levels measured in an individual patient appear to have a limited ability to predict the final pathological stage accurately. As PSA is produced by both benign and malignant prostatic tissue, there is no direct relationship between serum PSA concentration and clinical and pathological tumour stages (2). Of the prostate needle biopsy parameters examined, the percentage of tissue with cancer is the strongest predictor for positive surgical margins, seminal vesicle invasion (SVI) and non-organ-confined disease (3). An increased number of tumour biopsies is an independent predictor of extraprostatic extension, margin involvement and lymph node invasion (4). A combination of serum PSA level, Gleason score on prostate biopsy and clinical T-stage (e.g. the Partin tables) is more useful in predicting the final pathological stage than the individual parameters themselves (5,6). These models may help to select candidates for a nerve-sparing operation and to decide whether to perform a lymphadenectomy (see Section 7.2 N-Staging). The ability of the molecular forms of PSA to predict T-stage is controversial and their routine measurement is not indicated (7,8).

Seminal vesicle invasion is predictive of local relapse and distant failure. Seminal vesicle biopsies may be used to increase the accuracy of pre-operative staging (9). This is not recommended as a first-line examination, but should be reserved for patients with a substantial risk of SVI in whom a positive SV biopsy would modify treatment decisions. Patients with a clinical stage greater than T2a and a serum PSA level of more than 10 ng/mL could be candidates for SV biopsies (10,11). Patients with any of the basal biopsies positive for cancer are more likely to have positive SV biopsies (12).

Transperineal three-dimensional prostate mapping biopsy (3D-PMB) may be a viable alternative compared to transrectal biopsies as 3D-PMB provides more accurate tumour localization, extent and Gleason grading (13). Unlike transrectal saturation biopsy, 3D-PMB has acceptable morbidity. The question of bacterial resistance might further increase the appeal of this approach.

#### 7.1.2 TRUS

The most commonly used method for viewing the prostate is TRUS. However, only 60% of tumours are visible with TRUS, and the remainder are undetectable due to their isoechogenicity. In a large multi-institutional study, TRUS was no more accurate at predicting organ-confined disease than DRE (14). These findings were supported by another large study, which showed that there was no meaningful superiority of TRUS over DRE (15). A combination of DRE and TRUS can detect T3a PCa more accurately than either method alone (16) (LE: 3).

Three-dimensional TRUS (3D-TRUS) is claimed to have a better staging accuracy than 2-D techniques (17). Several adjuncts to 3D-greyscale TRUS have been investigated. A greater sensitivity for cancer detection has been achieved with the addition of power colour Doppler and contrast agents (18-20). Unfortunately, all TRUS techniques remain largely operator-dependent and are not able to differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine use in staging.

#### 7.1.3 Multiparametric MRI

The most useful pulse sequence for local staging on MRI remains T2-weighted imaging. At 1.5T, MRI has a low sensitivity for detecting extracapsular extension of carcinoma (EEC) (22-82%) or SVI (0-71%), but higher specificity (61-100% and 62-100% respectively) (Tables 7.1 and 7.2). Overall, MRI accuracy for distinguishing T1-T2 stages from  $\geq$  T3 stages falls within the 50-85% range in most studies (Table 7.3). These disappointing results are explained by the fact that MRI cannot detect microscopic EEC. Its sensitivity increases with the radial length of extension within periprostatic fat. In one series, the EEC detection rate was 14% when the



radial length of extension was < 1 mm and 100% when it was > 3 mm (23). In another study using the Epstein criteria to distinguish focal from non-focal (extensive) extraprostatic extension (41), MR sensitivity, specificity and accuracy for detecting pT3 stages were, respectively, 40%, 95% and 76% for focal (i.e. microscopic) invasions and 62%, 95% and 88% for extensive extra-prostatic extension (31).

The use of the endorectal coil improves staging accuracy at 1.5T, as shown by two studies that found accuracies of 77-83% for combined endorectal and external coils versus 59-68% for external coils alone (34,42). Dynamic contrast-enhanced imaging used in combination with T2-weighted imaging may also improve local staging, at least for less-experienced readers (32,35). The high-field strength allows high-resolution T2-weighted imaging (43) and results obtained at 3T seem better than those obtained at 1.5T (33,40) (Table 7.3). Even if MRI performances in local staging are not perfect, it may improve the prediction of the pathological stage when combined with clinical data (44,45).

Given its low sensitivity to microscopic invasion, MRI is not recommended in the local staging of low-risk patients, but MRI may be useful in selected patients with intermediate- to high-risk cancers (44,46,47).

**Table 7.1: MRI performance in detecting extracapsular extension**

	Field strength	Pulse sequence	n	Se (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)
Outwater, 1994 (21)	1.5T	T2	30	68	72	32	-	71
Harris, 1995 (22)	1.5T	T2	50	57/20 <sup>(1)</sup>	61/100 <sup>(1)</sup>	36/100 <sup>(1)</sup>	79/65 <sup>(1)</sup>	64/68 <sup>(1)</sup>
Jager, 1996 (23)	1.5T	T2	34	36	89	36	88	79
Chefchaouni, 1996 (24)	1.5T	T2	47	52	100	100	72	79
Presti, 1996 (25)	1.5T	T2	56	91	49	51	90	-
Yu, 1997 (26)	1.5T	T2	77	82/47/59 <sup>(2)</sup>	72/74/67 <sup>(2)</sup>	70/59/59 <sup>(2)</sup>	84/64/67 <sup>(2)</sup>	77/62/64 <sup>(2)</sup>
Rorvik, 1999 (27)	1.5T	T2	31	71	47	53	67	-
Yu, 1999 (28)	1.5T	T2	53	54/17 <sup>(3)</sup>	95/94 <sup>(3)</sup>	76/44 <sup>(3)</sup>	88/79 <sup>(3)</sup>	85/76 <sup>(3)</sup>
Ikonen, 2001 (29)	1.5T	T2	44	22	99	-	-	95
May, 2001 (30)	1.5T	T2	56	80/67 <sup>(4)</sup>	97/50 <sup>(4)</sup>	-	-	93/53 <sup>(4)</sup>
Cornud, 2002 (31)	1.5T	T2	336	38	94	-	-	77
Futterer, 2005 (32)	1.5 T	T2	124	59/50 <sup>(5)</sup>	96/93 <sup>(5)</sup>	87/77 <sup>(5)</sup>	83/79 <sup>(5)</sup>	83/79 <sup>(5)</sup>
Futterer, 2005 (32)	1.5 T	T2+DCE	124	65/74 <sup>(5)</sup>	s95/94 <sup>(5)</sup>	88/86 <sup>(5)</sup>	84/87 <sup>(5)</sup>	85/87 <sup>(5)</sup>
Heijmink, 2007 (33)	3T	T2	46	0-8/8-77 <sup>(6)</sup>	91-100/94-97 <sup>(6)</sup>	ND	ND	67-74/70-89 <sup>(6)</sup>
Futterer, 2007 (34)	1.5T	T2	88	43-60/47-63 <sup>(7)</sup>	70-72/96 <sup>(7)</sup>	50-56/88-90 <sup>(7)</sup>	66-73/73-80 <sup>(7)</sup>	61-66/76-83 <sup>(7)</sup>
Bloch, 2007 (35)	1.5T	T2	159	64/54 <sup>(8)</sup>	86/91 <sup>(8)</sup>	70/75v	82/79 <sup>(8)</sup>	ND
Bloch, 2007 (35)	1.5T	T2 + DCE	159	91-82 <sup>(8)</sup>	95 <sup>(8)</sup>	91-90 <sup>(8)</sup>	95-91 <sup>(8)</sup>	ND <sup>(8)</sup>

DCE = dynamic contrast enhanced; n = number of patients; ND = no data; Se = sensitivity; Spe = specificity; PPV = positive predictive value; NPV = negative-predictive value.

<sup>(1)</sup> Results in 25 first cases / 25 last cases.

<sup>(2)</sup> Results obtained by readers with 3 years / 1 year / 6 months of experience.

<sup>(3)</sup> Results obtained by readers with 5 years / 2 years of experience.

<sup>(4)</sup> Results obtained by two experienced readers.

<sup>(5)</sup> Results obtained by one experienced reader and two less-experienced readers working in consensus.

<sup>(6)</sup> Results obtained by four readers on images obtained with a body coil / with an endorectal coil.

<sup>(7)</sup> Results obtained by five readers on images obtained with a pelvic phased-array coil / with combined pelvic phased-array and endorectal coils.

<sup>(8)</sup> Results obtained by readers with 4 and 15 years of experience.

**Table 7.2: MRI performance in detecting seminal vesicle invasion**

	Field strength	Pulse sequence	n	Se (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)
Chelsky, 1993 (36)	1.5T	T2	47	63	97	83	93	91
Harris, 1995 (22)	1.5T	T2	50	50/67 <sup>(1)</sup>	62/89 <sup>(1)</sup>	20/67 <sup>(1)</sup>	87/89 <sup>(1)</sup>	60/84 <sup>(1)</sup>
Jager, 1996 (23)	1.5T	T2	34	55	85	60	79	74
Chefchaoui, 1996 (24)	1.5T	T2	47	25	97	66	86	85
Presti, 1996 (25)	1.5T	T2	56	50	94	40	96	-
Rorvik, 1999 (27)	1.5T	T2	31	71	83	56	91	-
Ikonen, 2001 (29)	1.5T	T2	44	50	90	-	-	88
May, 2001 (30)	1.5T	T2	54	58/0 <sup>(2)</sup>	95/81 <sup>(2)</sup>	-	-	87/73 <sup>(2)</sup>
Cornud, 2002 (31)	1.5T	T2	336	34	99	-	-	89
Futterer, 2005 (32)	1.5T	T2	124	71/43 <sup>(3)</sup>	99/99 <sup>(3)</sup>	83/75 <sup>(3)</sup>	98/96 <sup>(3)</sup>	97/95 <sup>(3)</sup>
Futterer, 2005 (32)	1.5T	T2+DCE	124	71/71 <sup>(3)</sup>	100/100 <sup>(3)</sup>	100/100 <sup>(3)</sup>	98/98 <sup>(3)</sup>	98/98 <sup>(3)</sup>
Heijmink, 2007 (33)	3T	T2	46	0-20/0-40 <sup>(4)</sup>	88-100/100 <sup>(4)</sup>	ND	ND	ND
Futterer, 2007 (34)	1.5T	T2	88	30-50/40-90 <sup>(5)</sup>	80-94/92-99 <sup>(5)</sup>	26-43/57-91 <sup>(5)</sup>	91-93/92-99 <sup>(5)</sup>	76-86/90-98 <sup>(5)</sup>

DCE = dynamic contrast enhanced; n = number of patients; ND = no data; Se = sensitivity; Spe = specificity; PPV = positive predictive value; NPV = negative-predictive value.

<sup>(1)</sup> Results in 25 first cases / 25 last cases.

<sup>(2)</sup> Results obtained by two experienced readers.

<sup>(3)</sup> Results obtained by one experienced reader and two less-experienced readers working in consensus.

<sup>(4)</sup> Results obtained by four readers on images obtained with a body coil / with an endorectal coil.

<sup>(5)</sup> Results obtained by five readers on images obtained with a pelvic phased-array coil / with combined pelvic phased-array and endorectal coils.

**Table 7.3: MRI performance in predicting stage  $\geq$  pT3 disease**

	Field strength	Pulse sequence	n	Se (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)
Chelsky, 1993 (36)	1.5 T	T2	47	58	78	73	64	68
Tempany, 1994 (37)	1.5 T	T2	183	60	42	-	-	52
Quinn, 1994 (38)	1.5 T	T2	70	-	-	-	-	51/67 <sup>(1)</sup>
Harkaway, 1995 (39)	1.5 T	T2		26	77	50	54	51
Jager, 1996 (23)	1.5 T	T2	34	67	68	53	79	68
Chefchaoui, 1996 (24)	1.5 T	T2	47	53	94	94	58	70
Presti, 1996 (25)	1.5 T	T2	56	47	86	51	84	62.5
Cornud, 2002 (31)	1.5 T	T2	336	40	95	-	-	76
Futterer, 2005 (32)	1.5 T	T2	124	60/51 <sup>(2)</sup>	97/93 <sup>(2)</sup>	91/78 <sup>(2)</sup>	83/79 <sup>(2)</sup>	84/79 <sup>(2)</sup>
Futterer, 2005 (32)	1.5 T	T2+DCE	124	69/71 <sup>(2)</sup>	97/95 <sup>(2)</sup>	92/ND <sup>(2)</sup>	85/ND <sup>(2)</sup>	87/87 <sup>(2)</sup>
Futterer, 2006 (40)	3 T	T2	32	55-85 <sup>(3)</sup>	94-99 <sup>(3)</sup>	29-79 <sup>(3)</sup>	98-99 <sup>(3)</sup>	91-98 <sup>(3)</sup>
Heijmink, 2007 (33)	3T	T2	46	7-13/13-80 <sup>(4)</sup>	81-100/94-100 <sup>(4)</sup>	25-100/50-100 <sup>(4)</sup>	66-69/69-91 <sup>(4)</sup>	59-70/67-93 <sup>(4)</sup>
Futterer, 2007 (34)	1.5T	T2	88	47-61/56-64 <sup>(5)</sup>	62-69/96-98 <sup>(5)</sup>	54-61/91-96 <sup>(5)</sup>	64-69/73-77 <sup>(5)</sup>	59-65/78-83 <sup>(5)</sup>

DCE = dynamic contrast enhanced; n = number of patients; ND = no data; Se = sensitivity; Spe = specificity; PPV = positive predictive value; NPV = negative-predictive value.

(1) Prospective / retrospective accuracy.

(2) Results obtained by one experienced reader and two less-experienced readers working in consensus.

(3) Results obtained by three independent readers.

(4) Results obtained by four readers on images obtained with a body coil / with an endorectal coil.

(5) Results obtained by five readers on images obtained with a pelvic phased-array coil / with combined pelvic phased-array and endorectal coils.

## 7.2 N-staging

### 7.2.1 PSA level and biopsy findings

N-staging should be performed only when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatments are planned. High PSA values, stages T2b-T3 disease, poor tumour differentiation and perineural tumour invasion have been associated with a higher risk of the presence of nodal metastases (5,48,49). The measurement of PSA level alone is unhelpful in predicting the presence of lymph node metastases for an individual patient.

Nomograms or Partin tables could be used to define a group of patients with a low risk of nodal metastasis, i.e. < 10% (6,50). The simple Roach formula could also be used (51). In such cases, patients with a serum PSA level of < 20 ng/mL, stage T2a or less, and a Gleason score of < 6 may be spared N-staging procedures before potentially curative treatment (5).

The extent of the Gleason 4 pattern in sextant biopsies has also been used to define the risk of N1 disease. If any core had a predominant Gleason 4 pattern, or > three cores any Gleason 4 pattern, the risk of nodal metastases was found to be 20-45%. For the remaining patients, the risk was 2.5%, supporting the idea that nodal staging is unnecessary in selected patients (52).

### 7.2.2 Nodal staging using CT and MRI

Abdominal CT and MRI have similar performances in PCa nodal staging. They indirectly assess nodal invasion

by measuring lymph node diameter. As a consequence, their sensitivity is low and microscopic invasions cannot be detected. Using a 10 mm threshold, CT or MR sensitivity is < 40% (53-65). In a meta-analysis of 4,264 patients who underwent CT and lymphadenectomy, 654 (15.3%) patients had positive lymph nodes at lymphadenectomy. Only 105 (2.5%) had positive CT. Median estimations of CT sensitivity, specificity, NPV and PPV were 7%, 100%, 85% and 100%, respectively (64).

A fine-needle aspiration biopsy (FNAB) may provide a decisive answer in cases of positive imaging results. However, the lymph node can be difficult to reach because of its anatomical position. In addition, FNAB is not a highly sensitive staging procedure and a false-negative rate of 40% has been reported (66).

Since CT or MRI cannot detect microscopic lymph node invasion, detection rates are typically < 1% in patients with a Gleason score < 8 cancer, PSA < 20 ng/mL or clinically localized disease (61,67,68). They should therefore not be performed in low-risk patients and reserved for patients with high-risk cancers.

### 7.2.3 **Lymphadenectomy**

The gold standard for N-staging is operative lymphadenectomy, either by open or laparoscopic techniques. It is worth pointing out that recent studies with more extensive lymphadenectomy have shown that the obturator fossa is not always the primary site for metastatic deposits in the lymph nodes and that pelvic lymph node dissection limited to the obturator fossa will therefore miss about 50% of lymph node metastases (69,70). When deciding on pelvic lymph node dissection, extended lymphadenectomy should be considered (see Section 9.6 Indication and extent of eLND).

The primary removal of the so-called sentinel lymph node (SLN), defined as the first lymph node that receives lymphatic drainage from PCa, has the main aim of reducing the eventual morbidity associated with an extended pelvic node dissection, while preserving maximal sensitivity for the diagnosis of metastatic disease (71) (LE: 3). It remains experimental in 2014 (see Section 9.7).

## 7.3 **M-staging**

### 7.3.1 **Alkaline phosphatase**

The axial skeleton is involved in 85% of patients who die from PCa (72). The presence and extent of bone metastases accurately reflect the prognosis for an individual patient. Elevated skeletal alkaline phosphatase levels may indicate the presence of bony metastasis in 70% of affected patients (73). Furthermore, the measurement of skeletal alkaline phosphatase and PSA at the same time increases clinical effectiveness to approximately 98% (74). In a prospective study, multiple regression analysis showed the extent of bone disease to be the only variable influencing the serum levels of skeletal alkaline phosphatase and PSA. However, in contrast to serum PSA, skeletal alkaline phosphatase demonstrated a statistical correlation with the extent of bone disease (75).

### 7.3.2 **Bone scan**

The bone scan negative predictive value is estimated between 87% and 100% in the literature (66,76-84). However, its diagnostic yield is highly dependent on the PSA level (Table 7.4). In the meta-analysis by Abuzallouf et al. the bone scan positivity rate was 2.3%, 5.3%, 16.2%, 39.2% and 73.4% for PSA levels of 0-9.9, 10-19.9, 20-49.9, 50-99.9 and > 100 ng/mL, respectively (64).

Bone scan diagnostic yield is also influenced by the clinical stage (Table 7.5) and the Gleason score of the tumour (Table 7.6). A recent prospective study of 635 consecutive patients showed that no bone scan was positive in the 212 patients with a PSA level < 10 ng/mL (independently of the clinical stage and Gleason score of the tumour) and in 97 patients with a PSA level < 20 ng/mL and a stage < T3 and a Gleason score < 8 (89).

As a result, most authors do not recommend systematic bone scan in asymptomatic patients unless the PSA level is > 10 ng/mL (77,79,80,82,83,85) or even > 20 ng/mL (87,88), or in case of Gleason score ≥ 8 or clinical stage ≥ T3 (64). Of course, a bone scan should also be obtained in symptomatic patients, independently of the PSA level, Gleason score or clinical stage (64).

**Table 7.4: Bone scan positivity rate as a function of the PSA level**

	n	Bone scan positivity rate (%)	PSA < 10 ng/mL	PSA 10-19.9 ng/mL	PSA 20-49.9 ng/mL	PSA 50-99.9 ng/mL	PSA > 100 ng/mL
Chybowski, 1991 (76)	521	71	0/207 (0%)	1/99 (1%)	7/106 (6.6%)	23/83 (27.7%)	40/56 (71.4%)
Miller, 1992 (66)	146	34	5/57 (8.7%)	5/26 (19.2%)	-	-	-
Oesterling, 1993 (77)	852	7	3/561 (0.5%)	4/291 (1.4%)	-	-	-
Levrán, 1995 (78)	861	8	0	0	0		
Rudoni, 1995 (79)	118	54	0/23	7/21 (33.3%)	7/35 (20%)	8/26 (30.7%)	32/35 (91.4%)
Gleave, 1996 (80)	490	28	0/290 (0%)	4/84 (4.7%)	5/59 (8.5%)	-	-
Rydh, 1999 (81)	446	138	4/77 (5.2%)	3/93 (3.2%)	37/96 (38.5%)	28/55 (51%)	64/81 (79%)
Ataus, 1999 (82)	160	51	3/50 (6%)	8/44 (18.2%)	11/35 (31.4%)	9/11 (81.8%)	20/20 (100%)
Bruwer, 1999 (83)	404	206	5/60 (8.3%)	7/33 (21.2%)	-	-	131/164 (79.9%)
Jacobson, 2000 (84)	432	38	-	-	3/74 (4%)	7/40 (17.5%)	25/43 (58.1%)
Wymenga, 2001 (85)	363	111	14/89 (15.7%)	5/56 (9)	11/74 (14.9%)	-	-
Kosuda, 2002 (86)	1294	287	4/300 (1.3%)	-	-	-	-

*n* = number of patients; PSA = prostate-specific antigen.

**Table 7.5: Bone scan positivity rate as a function of the clinical stage**

	n	Bone scan positivity rate (%)	Clinically localized cancer	Locally advanced cancer
Chybowski, 1991 (76)	521	71	26/405 (6.4%)	45/116 (38.7%)
Gleave, 1996 (80)	490	28	5/369 (1.3%)	23/121 (19%)
Ataus, 1999 (82)	160	51	13/95 (13.6%)	59/65 (90.7%)
Bruwer, 1999 (83)	404	206	17/148 (11.4%)	188/352 (53.4%)
Wymenga, 2001 (85)	363	111	13/143 (9%)	92/208 (44.2%)

*n* = number of patients.

**Table 7.6: Bone scan positivity rate as a function of the Gleason score of the tumour**

	n	Bone scan positivity rate (%)	Gleason score ≤ 7	Gleason score ≥ 8
Lin, 1999 (87)	270	24	12/243 (4.9%)	12/51 (23.5%)
Lee, 2000 (88)	631	88	24/411 (5.8%)	46/155 (29.6%)

*n* = number of patients.

### 7.3.3 New imaging modalities

Ultra-small particles of iron oxide (USPIO) can dramatically improve the detection of microscopic lymph node metastases on MRI. In a series of 80 patients who underwent lymph node resection or biopsy, MR sensitivity

improved from 35.4% to 90.5% with the use of USPIO (63). In another series of 75 patients with clinically localized bladder or PCa, combined USPIO and diffusion-weighted MRI had a per-patient sensitivity and specificity for detecting lymph node invasion of 65-75% and 93-96%, respectively (90). This approach may be cost-effective (91), but is limited by the lack of availability of USPIO in Europe.

<sup>11</sup>C- or <sup>18</sup>F-choline PET/CT have a good specificity for detecting lymph node metastases, only with a low-to-moderate sensitivity, ranging from 10-73% (92,93). <sup>18</sup>F-fluoride PET or PET/CT shows superior sensitivity to bone scan, at least on a lesion basis (92,94-97). <sup>11</sup>C-choline PET/CT seems slightly less sensitive than conventional bone scanning, but its specificity is higher and it yields less indeterminate lesions (92,98). In a series of 90 patients with high-risk cancer who underwent both <sup>18</sup>F-choline and <sup>18</sup>F-fluoride PET, choline PET was positive in 35 patients and fluoride PET in 37 patients. Both investigations together were positive in 50 patients (56%) and changed patient management in 18 patients (96). However, the cost-effectiveness of replacing conventional bone scan by <sup>18</sup>F-fluoride and/or choline PET remains to be assessed.

Diffusion-weighted whole-body MRI and axial MRI (MRI evaluation of the spine and the pelvifemoral area only) are more sensitive than bone scan and targeted radiographs (99-101) and equally as effective as <sup>11</sup>C-choline PET/CT (102) in detecting bone metastases in patients with high-risk PCa. However, their sensitivity is low for lymph node metastases in high-risk patients and similar to that of <sup>11</sup>C-choline PET/CT (103,104). Recently, whole-body MRI was shown to be more sensitive and specific than the combination of bone scan, targeted radiographs and abdominopelvic CT (105). However, as with PET/CT, the cost-effectiveness of these new MR-based approaches remains to be assessed (106).

#### 7.4 Guidelines for the diagnosis and staging of PCa

<b>Recommendations for the diagnosis of PCa</b>	<b>LE</b>	<b>GR</b>
Biopsy and further staging investigations are only indicated if they affect the management of the patient.	3	A
Transrectal ultrasound (TRUS)-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 10-12 systemic, laterally directed, cores are recommended, with more cores in larger volume prostates.	1	A
Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates.	2b	B
One set of repeat biopsies is warranted in cases with persistent indication for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy).	2a	B
Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	3	C
Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies.	1	A
<b>Recommendations for the staging of PCa</b>		
Imaging is not indicated for staging in low-risk tumours.	3	A
For local staging (T-staging) of PCa, the most relevant information will be provided by the number and sites of positive prostate biopsies, the tumour grade, and the level of serum PSA.	2	A
For local staging, CT and TRUS should not be used.	3	A
Prostate multiparametric MRI should be used in local staging only if its results change patient management.	2b	A
Prostate multiparametric MRI is not recommended for staging purposes in patients with low-risk PCa.	2b	B
Lymph node status (clinical N-staging) needs only to be assessed when potentially curative treatment is planned.	3	B
Lymph node imaging (using CT or MRI) is recommended in asymptomatic patients only if the PSA level > 10 ng/mL or Gleason score ≥ 8 or clinical stage ≥ T3 (i.e. intermediate-/high-risk situations).	2b	A
Bone scan is recommended in asymptomatic patients only if the PSA level > 10 ng/mL or Gleason score ≥ 8 or clinical stage ≥ T3 (i.e. intermediate-/high-risk situations).	2b	A
Bone scan is indicated in patients with symptoms evocative of bone metastases.	3	A

CT = computed tomography; DRE = digital rectal examination; MRI = magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.



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## 8. TREATMENT: DEFERRED TREATMENT (ACTIVE SURVEILLANCE/ WATCHFUL WAITING)

### 8.1 Introduction

There is a great difference between the incidence of prostate cancer (PCa) and the death rate from it. Data from the European Cancer Observatory (EUREG) database, which comprises the cancer registries of 26 countries, show a continuous increase in the incidence of PCa between 1998 and 2007 (1,2). Several autopsy studies have demonstrated that 60-70% of older men who die from other causes harbour a histological PCa (3), while a recent autopsy study on Japanese and Russian men showed the prevalence of prostate cancers with a Gleason score  $\geq 7$  to be 10-15% (4). PCa is currently diagnosed in 15-20% of men during their lifetime, but the lifetime risk of death from PCa is only 3% (5).

The incidence of small, localized, well-differentiated PCa is increasing, mainly as a result of prostate-specific antigen (PSA) screening (6) and 'multicore' schemes of prostate biopsy. These data suggest that many men with localized PCa will not actually benefit from definitive treatment (7), and it is estimated that 45% of men with a PSA-detected PCa are candidates for conservative management (8). Furthermore, in men with co-morbidities and a limited life-expectancy, treatment of a more advanced localized PCa may be deferred in order to avoid loss of quality of life from the PCa treatment. With the aim of reducing overtreatment (which is defined as treatment of a disease that causes no threat to the man's well-being during his lifetime) in both subsets of patients, two distinct strategies for conservative management have been proposed: 'active surveillance' and 'watchful waiting' (see Table 8.1).

#### 8.1.1 Definition

##### 8.1.1.1 Active surveillance

Active surveillance is also known as 'active monitoring'. As opposed to watchful waiting, active surveillance aims at the proper timing of curative treatment rather than the delayed application of palliative treatment options. Introduced during the past decade, it includes an active decision not to treat the patient immediately. Instead, the patient remains under close surveillance, and treatment is prompted by predefined thresholds indicative of the presence of a potentially life-threatening disease, while taking the patient's life-expectancy into consideration. The treatment options are intended to be curative.



### 8.1.1.2 Watchful waiting

Watchful waiting is also known as 'deferred treatment' or 'symptom-guided treatment'. This term was coined in the pre-PSA screening era (before 1990) and referred to the conservative management of PCa until the development of local or systemic progression with (imminent) disease-related complaints. At this point, the patient would then be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction, and hormonal therapy or radiotherapy for the palliation of metastatic lesions. No standardized follow-up scheme is recommended.

**Table 8.1: Definitions of active surveillance and watchful waiting (9-11)**

	<b>Active surveillance</b>	<b>Watchful waiting</b>
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, rebiopsy, optional MRI	Not predefined
Life-expectancy	> 10 y	< 10 y
Aim	Minimize treatment-related toxicity without compromising survival	Minimize treatment-related toxicity
Comments	Only for low-risk patients	Can apply to patients with all stages

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

## 8.2 Deferred treatment of localized PCa (stage T1-T2, Nx-N0, M0)

Clinical stage T1c currently represents 40-50% of new cases of PCa (12). The incidence of small, localized, well-differentiated PCa is increasing, mainly as a result of PSA screening and 'multicore' schemes of prostate biopsy (8). The Prostate Cancer Intervention Versus Observation Trial (PIVOT) (13) did not show any survival difference at 10 years between watchful waiting and radical prostatectomy for screen-detected men with a PSA of < 10 ng/mL.

The lead-time in PSA screening is about 10 years (9,10). It is therefore possible that cancer-related mortality from untreated, non-screen-detected PCa in patients with contemporary Gleason scores of 6 might be as low as 10% at 20-year follow-up (11).

### 8.2.1 Active surveillance

Active surveillance was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined very low-risk PCa, without giving up the option of curative treatment, as happens with watchful waiting. Currently, the only data available is data from non-mature randomized clinical trials of active surveillance, with a follow-up of less than 10 years. Active surveillance can therefore only be proposed for highly selected low-risk patients. This conclusion is also supported by other studies, which have shown that patients with a life-expectancy of > 10 years have a higher mortality rate from PCa in the absence of curative treatment. These studies include the Johansson series, which showed that there is a higher risk of dying from PCa in patients surviving more than 15 years with well- and moderately differentiated tumours at diagnosis (14) (LE: 3). In the light of these findings, it is essential to improve the selection criteria of candidates for active surveillance.

A multicentre clinical trial of active surveillance versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025. Choo and co-workers were the first to report on a prospective active surveillance protocol (15,16). A series with a long follow-up was reported by Klotz (17). A total of 452 patients with clinical stage T1c or T2a and a PSA of  $\leq 10$  ng/mL were enrolled. Patients aged 70 years or younger had a Gleason score of  $\leq 6$ ; patients that were > 70 years had a Gleason score of  $\leq 7$  (3+4). Initially, six biopsies were performed, but in recent years the usual extended 12-core protocol was introduced. At a median follow-up of 6.8 years, the 10-year overall survival was 68%. At 10 years, the disease-specific survival was 97.2%, with 62% of men still alive on active surveillance. A total of 30% of patients had, in the end, undergone a radical treatment for the following reasons:

- 48% for a PSA doubling time of < 3 years;
- 27% for Gleason score progression on repeat biopsies;
- 10% because of patient preference.

A variety of additional studies have now been published on active surveillance in clinically organ-confined disease (Table 8.2 and Table 8.3). Disease-specific survival in low-grade disease in the pre-PSA era was 87% at 10 years with delayed non-curative treatment. However, longer follow-ups are necessary to obtain definitive results.

Active surveillance might mean no treatment at all for patients older than 70 years, while in younger patients it might mean delaying treatment by possibly as long as years. The repeated biopsies that are part of active surveillance might then become important for their potential side-effect on nerve preservation if surgery is subsequently considered. Repeat biopsies may result in an increase in erectile dysfunction observed during active surveillance (18), and infectious complications increased after repetitive biopsies with a factor of 1.3 for each set of earlier biopsies in an active surveillance programme (19).

Quality of life analyses conducted during active surveillance programmes have shown improved functional outcome for active surveillance compared with active treatment (20-22). Overall QoL showed minimal changes over time during active surveillance (20), and up to 18% of men on active surveillance chose active treatment for reasons of anxiety (23).

**Table 8.2: Clinical trials of active surveillance for organ-confined PCa: inclusion criteria**

Study	n	Median age	Criteria
Dall'Era, et al. (24)	321	64	Gleason $\leq$ 3+3, PSAD $\leq$ 0.15 ng/mL, T1-T2a, $\leq$ 33% biopsies +, $\leq$ 50% cores
van As, et al. (25)	326	67	Gleason $\leq$ 3+4, PSA $<$ 15 ng/mL, T1-T2a, N0-Nx, M0-Mx $\leq$ T2a, $\leq$ 50% biopsies +
Soloway, et al. (26)	230	64	Gleason $\leq$ 6, PSA $\leq$ 10 ng/dL, T1a-T2, $\leq$ 2 biopsies +, $\leq$ 20% cores +
Klotz, et al. (17)	453	70	Gleason $\leq$ 6, PSA $\leq$ 10 ng/mL (up to 1999: Gleason $\leq$ 3+4, PSA $\leq$ 15 ng/mL), $<$ 3 biopsies +, $<$ 50% each core
Tosoain, et al. (27)	769	66	Gleason $\leq$ 3+3, PSAD $\leq$ 0.15 ng/mL, T1, $\leq$ 2 biopsies +, $\leq$ 50% cores
Adamy, et al. (28)	238	64	Gleason $\leq$ 3+3, PSA $\leq$ 10 ng/mL, T1-T2a, $\leq$ 3 biopsies +, $\leq$ 50% cores
Bul, et al. (29)	2492	66	Gleason $\leq$ 6, PSA $\leq$ 10 ng/mL, PSAD $<$ 0.2 ng/mL/cc, T1-T2, $\leq$ 2 biopsies +

**Table 8.3: Clinical trials of active surveillance for organ-confined PCa: main results**

Study	Median follow-up (months)	Progression		RP (%)	Survival (%)		
		Biopsy (%)	PSA/PSADT	Patient's request	OS	CSS	Remaining on active surveillance* (PFS)
Dall'Era, et al. (24)	47	35	5	8	97	100	54
van As, et al. (25)	22	13	18	2	98	100	73
Soloway, et al. (26)	32	10	-	-	100	100	86
Klotz et al. (17)	82	9	14	3	78.6	97.2	70
Tosoain, et al. (27)	32	14	-	9	98	100	54
Adamy, et al. (28)	22	13	14	11	-	-	-
Bul, et al. (29)	19	27	21	10	97	100	76 (2 y)

\*active treatment-free survival

CSS = cancer-specific survival; OS = overall survival; PFS = progression-free survival; PSADT = PSA doubling time; RP = radical prostatectomy.

The various series have applied several eligibility criteria for enrolment in active surveillance programmes (30):

- clinically confined PCa (T1-T2);
- Gleason score  $<$  7 for most studies;
- PSA  $<$  10-15 ng/mL;
- prostate cancer volume criteria on biopsies, e.g. number of positive biopsies, maximum cancer involvement of biopsy.

Limited tumour volume is defined by a low number of involved cores and a low tumour length on each involved



core. The role of other tools such as multiparametric magnetic resonance imaging (mMRI) in better defining acceptable lesions is under investigation (31), but this latter might be particularly useful for the better staging of lesions that are anterior in the prostate (32). When mMRI is applied, a standardized scoring system, such as PI-RADS (33), or START (34,35) is highly recommended.

Active surveillance is based on repeated digital rectal examination (DRE), PSA and, most importantly, repeat biopsies. Early repeated confirmatory biopsies have become an important part of the selection process, and are based on the risk of underdetection of grade 4 at the initial biopsy (24,28,36,37).

The criteria for active treatment are less well defined (6), but most groups have used the following.

- A PSA doubling time (PSADT) with a cut-off value ranging between  $\leq 2$  and  $\leq 4$  years. This criterion is becoming questionable, however, because of a weak link between the PSADT and grade progression on repeated biopsy (38).
- Gleason score progression to  $\geq 7$  during systematic follow-up biopsies, at intervals ranging from one to four years.
- SPCG-4 data suggest that surgery does not seem justified in men with a Gleason score of 6, cT1 disease or those over 70 years of age with respect to overall survival (39).
- Patients' requests for treatment are based mainly on anxiety. This is a significant factor (40) and might affect 10-18% of treated patients. Self-administered questionnaires answered by 87% of the patients enrolled in the SPCG-4 trial, showed that the treatment group always reported inferior well-being, depression and psychological status, but the difference between this group and men treated by prostatectomy was not significant (41).

Several patient and tumour characteristics were found to be predictive of later biopsy progression and deferred treatment. Men with positive confirmatory biopsies (42), a higher PSA density (29,42), and a higher number of positive cores (29) were at increased risk of progression. Active surveillance follow-up schemes may therefore be tailored to initial findings at entry (43).

### 8.2.2 **Watchful waiting**

The rationale behind watchful waiting is the observation that PCa often progresses slowly, and is predominantly diagnosed in older men in whom there is a high incidence of co-morbidity and related high competitive mortality (44). Watchful waiting can be considered as an option for treating patients with localized PCa and a limited life-expectancy, or for older patients with less aggressive cancers.

There have been several attempts to summarize the key papers dealing with deferred treatment in patients with presumed localized PCa (45-47). Most have presented the same results, as they analyse roughly the same series, but using somewhat different methodologies. The outcome studies in watchful waiting usually included patients whose PSA readings were not always available and who had predominantly palpable lesions that would currently be defined as intermediate-risk tumours (48). The most recent study used data from the PSA era of the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute in the USA (49). These studies included patients with a follow-up of up to 25 years, for whom the endpoints are overall survival (OS) and disease-specific survival (DSS). Several watchful waiting series show a very consistent DSS ratio at 10 years, ranging from 82-87% (45,50-54), and up to 80-95% if the tumours were graded T1-T2 Gleason  $\leq 7$  (49). In three studies with data beyond 15 years, the DSS was 80%, 79% and 58%, respectively (51,53,54). Two studies reported a 20-year DSS of 57% and 32%, respectively (51,53).

Chodak et al. reported a pooled analysis of the original data from 828 patients treated by watchful waiting (45). The paper was based on patients from six non-randomized studies and described cancer-specific survival and metastasis-free survival after five and 10 years of follow-up (45) (LE: 2b).

Tumour grade is clearly significant, with very low survival rates for grade 3 tumours. Although the 10-year cancer-specific rate is equally good (87%) for grade 1 and 2 tumours, the latter have a significantly higher progression rate, with 42% of patients with these tumours developing metastases (Table 8.4). Patients with grade 1, 2 and 3 tumours had 10-year cancer-specific survival rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis (49) (LE: 3).

A cost-effectiveness analysis revealed observation as most effective in men aged between 65 and 75 years and with low-risk PCa (7).

**Table 8.4: Outcome of deferred treatment in localized PCa in relation to tumour grade: percentage of patients (95% confidence interval) surviving at five and 10 years (46)**

	Grade	5 years (%)	10 years (%)
Disease-specific survival	Grade 1	98 (96-99)	87 (81-91)
	Grade 2	97 (93-98)	87 (80-92)
	Grade 3	67 (51-79)	34 (19-50)
Metastasis-free survival	Grade 1	93 (90-95)	81 (75-86)
	Grade 2	84 (79-89)	58 (49-66)
	Grade 3	51 (36-64)	26 (13-41)

The paper by Chodak et al. also specifically described the outcome for stage cT1a patients (45), with cancer-specific 10-year survival rates of 96% and 94%, respectively, for grade 1 and 2 tumours. The metastasis-free survival rate was 92% for patients with grade 1 tumours, but 78% for those with grade 2 tumours, indicating a higher risk of progression in individuals with moderately differentiated tumours. This difference in progression rate correlates with other studies on stage cT1a disease (55,56).

The impact of grade on the risk of tumour progression and ultimately death from PCa was also described in a paper by Albertsen et al. in the pre-PSA era (57). This paper also showed that Gleason 6-10 tumours carry a continuously increasing risk of ending the patient's life for up to 15 years of follow-up after conservative management. The study re-evaluated all biopsy specimens using the more widely accepted Gleason score, and showed that the risk of PCa death was very high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 cancers (Table 8.5) (58,59) (LE: 3).

**Table 8.5: The 15-year risk of dying from PCa in relation to Gleason score at diagnosis in patients with localized disease aged 55-74 years (58-60)**

Gleason score	Risk of cancer death* (%)	Cancer-specific mortality† (%)
2-4	4-7	8
5	6-11	14
6	18-30	44
7	42-70	76
8-10	60-87	93

\*The figures on the risk of cancer death differ for different age groups and represent the true risk in the studied population (taking actual competing mortality from other causes into consideration)

†The cancer-specific mortality figures compensate for differences in competing mortality and indicate the outcome if the patient actually lived for 15 years

Three randomized clinical trials have reported long-term follow-up of patients randomized to watchful waiting or radical prostatectomy: the first was in the pre-PSA screening era (59); the second was at the beginning of PSA screening (60) and the third was a recent study, the results of which were published in 2012 (13).

Between 1989 and 1999, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomized 695 patients with clinical stage T1-T2 to watchful waiting (n = 348) or radical prostatectomy (n = 347) (Table 8.6) (60). This study began after PSA screening was introduced into clinical practice, but only 5% of men were diagnosed by screening. After a median follow-up of 12.8 years, this study showed a significant decrease in cancer-specific mortality, overall mortality, metastatic-risk progression and local progression in patients treated with radical prostatectomy versus watchful waiting (LE: 1b).

**Table 8.6: Outcome of Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) at 15 years of follow-up (median of 12.8 years) (60)**

	RP (n = 347) (%)	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)	

CI = confidence interval; n = number of patients; RP = radical prostatectomy.

Subgroup analysis showed that the overall difference was not modified by PSA level (below or above 10 ng/

mL) or by the Gleason score (below or above 7) at the time of diagnosis. However, age at that the time of randomization had a profound impact, the benefit on overall survival and metastasis-free survival being seen only in those younger than 65 years of age.

The PIVOT: VA/NCI/AHRQ Cooperative Studies Program #407 study recruited 731 men with clinically organ-confined PCa to the randomly-assigned arms of radical prostatectomy or watchful waiting (13). Inclusion criteria were clinically organ-confined PCa (cT1-2cN0cM0) with a PSA of < 50 ng/mL, patient age < 75 years, and a life-expectancy of > 10 years. It must be considered that 50% of the men had a non-palpable PCa, which was the case in only 12% of the patients in the SPCG-4 trial (60). It is of note that despite the fact that a 10-year life-expectancy was an inclusion criteria for the PIVOT study, more than one-third of the men died within 10 years of being accepted, suggesting that the population may have been less fit than expected, reducing the ability to assess a survival benefit for active treatment (13).

After a mean follow-up of 10 years, no statistically significant difference between the two treatment arms could be demonstrated with regard to overall mortality (47% versus 49.9%,  $p = 0.22$ ) and PCa-specific survival (5.8% versus 8.4%,  $p = 0.09$ ). There were also no statistically significant differences concerning overall survival between the two treatment groups when considering patient age, Gleason score, performance status, and Charlson co-morbidity score. Only patients exhibiting a pretreatment PSA serum concentration > 10 ng/mL or high-risk PCa experienced a statistically significant benefit from prostatectomy with regard to overall survival, with a relative-risk reduction in mortality of 33% ( $p = 0.02$ ) and 31% ( $p < 0.01$ ), respectively. In the pooled analysis, a relative-risk reduction and an absolute-risk reduction of 31% and 10.5%, respectively, was identified for patients with intermediate/high-risk PCa ( $p < 0.01$ ). Patients who underwent radical prostatectomy also experienced a statistically significant reduction concerning the development of bone metastases (4.7% versus 10.6%,  $p < 0.01$ ).

No data are available comparing watchful waiting with radiotherapy. Some data are available for hormonal treatment. For patients who choose deferred treatment, there appears to be a modest risk of disease progression, although shorter cancer-specific survival has been reported after deferred therapy compared with immediate hormone therapy in presumed localized PCa (not using PSA for staging) after 15 years of follow-up (61). In contrast to the Lundgren et al. study (61), the report of the Casodex Early Prostate Cancer Trialists' Group programme showed a higher mortality in a group of men with localized PCa treated with bicalutamide, 150 mg/day, than in those who received placebo (62).

The data on deferred and conservative management of low-risk disease contrast with the observation that the incidence of local treatment in the USA recently increased from 25% to 34% in men with a life-expectancy of < 10 years (63). Data from Sweden show a higher prevalence of deferred treatment in low-risk disease of 46% (64).

It appears that many small, localized well-differentiated tumours will not progress, and radical therapy may lead to substantial overtreatment, affecting patients' QoL and treatments costs. This has been further confirmed by a recent analysis at five and 10 years of 19,639 patients aged > 65 years on the SEER database who were not given curative treatment. Based on co-morbidities (Charlson score), most men with a Charlson score of  $\geq 2$  died from competing causes at 10 years whatever their initial age (below or above 65 years). However, men with no or just one co-morbidity had a low risk of death at 10 years, especially for well- or moderately differentiated lesions (Table 8.7) (65). In men with a Charlson score of  $\geq 2$ , tumour aggressiveness had little impact on overall survival, suggesting that perhaps these patients could have been spared the biopsies and diagnosis of cancer. This demonstrates the importance of performing an initial co-morbidity evaluation leading to an individual survival probability before proposing that an individual embark on any form of medical intervention such as biopsies or treatment (66).

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

The literature reporting on deferred treatment for locally advanced PCa is sparse. There are no randomized studies that compare treatments with curative intent, such as radiotherapy or surgery, with or without hormones.

Most patients whose disease progresses after deferred treatment of locally advanced PCa will be candidates for hormone therapy. There are reports from non-randomized studies showing that hormone treatment may safely be delayed until metastatic progression occurs, as no survival advantage was noted between patients treated with immediate orchiectomy compared with delayed treatment (67,68).

In a prospective randomized clinical phase III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0 PCa were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic

disease progression or occurrence of serious complications (69,70). After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% confidence interval [CI]: 1.05-1.48; non-inferiority  $p > 0.1$ ) favouring immediate treatment, seemingly due to fewer deaths of non-prostatic cancer causes ( $p = 0.06$ ). The time from randomization to progression of hormone-refractory disease did not differ significantly, nor did PCa-specific survival. The median time to the start of deferred treatment after study entry was seven years. In this group, 126 patients (25.6%) died without ever needing treatment (44% of deaths in this arm). The conclusion drawn from this study is that immediate ADT resulted in a modest but statistically significant increase in overall survival, but no significant difference in PCa mortality or symptom-free survival. This raises the question of the usefulness of such a small statistical benefit.

Furthermore, the authors identified significant risk factors associated with a worse outcome: in both arms, patients with a baseline PSA  $> 50$  ng/mL were at a  $> 3.5$ -fold higher risk of dying of PCa than patients with a baseline PSA  $\leq 8$  ng/mL. If the baseline PSA was between 8 ng/mL and 50 ng/mL, the risk of PCa death was approximately 7.5-fold higher in patients with a PSADT of  $< 12$  months than in patients with a PSADT of  $> 12$  months. The time to PSA relapse following a response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA may also reflect disease aggressiveness.

When early and delayed treatments were compared in a large randomized trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormone therapy was demonstrated (71), comparable with the results of the Lundgren et al. study mentioned above (61) (LE: 1b). In addition, a comparison of bicalutamide, 150 mg/day, with placebo showed that progression-free survival was better with early treatment in patients with locally advanced PCa (62) (LE: 1b).

In a study by Adolfsson and co-workers, 50 selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 PCa were followed up for 169 months (72). The five- and 10-year cancer-specific survival rates were 90% and 74%, respectively, and the likelihood of being without treatment at five and 10 years was 40% and 30%, respectively. The authors concluded that watchful waiting might be a treatment option for selected patients with non-poorly differentiated T3 tumours and a life-expectancy of less than 10 years (LE: 3).

**Table 8.7: Active surveillance in screening-detected PCa**

Author	n	Median follow-up (mo)	pT3 in RP patients	OS	CSS
van As, et al. (25)	326	22	8/18 (44%)	98	100
Carter, et al. (73)	407	41	10/49 (20%)	98	100
Bul, et al. (28)	533-1,000	48	4/24 (17%)	90	99
Soloway, et al. (26)	99	45	0/2	100	100
Roemeling, et al. (74)	278	41		89	100
Khatami, et al. (75)	270	63		Not stated	100
Klotz, et al. (17)	452	73	14/* (58%)	82	97 at 10 y
<b>Total</b>	<b>2,130-3,000</b>	<b>43</b>		<b>90</b>	<b>99.7</b>

CSS = cancer-specific survival; OS = overall survival; RP = radical prostatectomy.

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

There are only very sparse data on this subject. The only candidates for such treatment should be asymptomatic patients with a strong wish to avoid treatment-related side-effects (LE: 4). As the median survival time is about two years, the time without any treatment (before symptoms occur) is very short in most cases. The MRC trial highlighted the risk of developing symptoms (pathological fractures, spinal cord compression), and even death from PCa, without receiving the possible benefit from hormone treatment (71,76) (LE: 1b). If a deferred treatment policy is chosen for a patient with advanced PCa, close follow-up must be possible.

## 8.5 Recommendations on active surveillance and watchful waiting

Recommendations - active surveillance	LE	GR
Active surveillance is an option in patients with the lowest risk of cancer progression: over 10 years of life-expectancy, cT1-2, PSA $\leq$ 10 ng/mL, biopsy Gleason score $\leq$ 6 (at least 10 scores), $\leq$ 2 positive biopsies, minimal biopsy core involvement ( $\leq$ 50% cancer per biopsy).	2a	A
Follow-up should be based on DRE, PSA and repeated biopsies. The optimal timing for follow-up is still unclear.	2a	A
Patients with biopsy progressions should be recommended to undergo active treatment.	2a	A

Recommendations - watchful waiting	LE	GR
Watchful waiting may be offered to all patients not willing to accept the side-effects of active treatment, particularly patients with a short life-expectancy.	1b	A
When on watchful waiting, the decision to start any non-curative treatment should be based on symptoms and disease progression (see Chapter 12).	1a	B

DRE = digital rectal examination

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## 9. TREATMENT: RADICAL PROSTATECTOMY

### 9.1 Introduction

The surgical treatment of prostate cancer (PCa) consists of radical prostatectomy (RP). This involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. In men with localized PCa and a life expectancy  $\geq 10$  years, the goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency (1). There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone (2). Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes (3). An estimation of life expectancy is paramount in counselling a patient about surgery (4).

Currently, RP is the only treatment for localized PCa to show a benefit for OS and cancer-specific survival (CSS), compared with conservative management, as shown in one prospective randomized trial (5). After a follow-up of 15 years, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality: relative risk (RR) = 0.75 (0.61-0.92). According to a post-hoc statistical subgroup analysis, the number needed to treat (NNT) to avert one death was 15 for all men and 7 for men < 65 years of age. Radical prostatectomy was also associated with a reduction in PCa-specific mortality (RR = 0.62 [0.44-0.87]). The benefit in OS and CSS was not reproduced in the overall study population of another prospective randomized trial. After a median follow-up of 10 years, the PIVOT trial showed that RP did not significantly reduce all-cause mortality (hazard ratio [HR] = 0.88 [0.71-1.08];  $p = 0.22$ ) or significantly reduce PCa mortality (HR = 0.63 [0.36-1.09];  $p = 0.09$ ). According to a preplanned subgroup analysis among men with low-risk tumours ( $n = 296$ ), RP non-significantly increased all-cause mortality (HR = 1.15 [0.80-1.66]). Among men with intermediate-risk tumours ( $n = 249$ ), RP significantly reduced all-cause mortality (HR = 0.69 [0.49-0.98]). Among men with high-risk tumours ( $n = 157$ ), RP non-significantly reduced all-cause mortality (HR = 0.40 [0.16-1.00]). Among men with PSA > 10, RP significantly reduced all cause mortality (HR = 0.67 [0.48-0.94]).

Surgical expertise has decreased the complication rates of RP and improved cancer cure (6-10). If performed by an experienced surgeon, the patient's subsequent QoL should be satisfactory. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can decrease positive surgical margin rates and improve cancer control with RP (11,12).

Radical retropubic prostatectomy (RRP) and perineal prostatectomy are performed through open incisions. More recently, minimally invasive laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic prostatectomy (RALP) have been developed. RALP is displacing RRP as the gold standard surgical approach for clinically localized PCa in the USA and is being increasingly used in Europe and other parts of the world. This trend has occurred despite the paucity of high-quality evidence to support the superiority of RALP over more-established treatment modalities.

Recent in-depth systematic reviews of the literature have compared the results of RRP versus LRP/RALP. Robot-assisted laparoscopic prostatectomy is associated with less blood loss and transfusion rates compared with RRP. There appears to be minimal differences between the two surgical approaches in terms of overall post-operative complications. Positive surgical margin rates are at least equivalent to RRP, but firm conclusions about biochemical recurrence and other oncological endpoints are difficult to make due to the relatively short follow-up in the published literature and the limited overall experience with RALP in locally advanced PCa. It remains unclear whether RALP is beneficial for urinary continence and erectile function because most published studies addressing these outcomes suffer from methodological limitations. There is a need for well-controlled comparative outcomes studies of PCa surgery following best-practice guidelines (13-17).

### 9.2 Low-risk prostate cancer: cT1-T2a, Gleason score $\leq 6$ and prostate-specific antigen < 10 ng/mL

Patients with low-risk PCa should be informed about the results of two randomized trials comparing retropubic RP versus watchful waiting (WW) in localized PCa. In the SPCG-4 study, the survival benefit associated with RP was similar before and after 9 years of follow-up and was also observed in men with low-risk PCa, and was confined to men < 65 years of age. In the PIVOT trial, a preplanned subgroup analysis of men with low-risk tumours showed that RP did not significantly reduce all-cause mortality.

#### 9.2.1 Stage T1a-T1b prostate cancer

Stage T1a PCa is defined as an incidental histological finding of cancer in  $\leq 5\%$  of resected prostatic tissue (transurethral resection of the prostate [TURP] or open adenomectomy). Stage T1b PCa is defined as > 5% cancer. Published series have shown a pT0 stage in 4-21% and an organ-confined stage in 47-85% of patients at subsequent RP (18). T1a-T1b PCa is found incidentally in 4-16% of patients surgically treated for benign prostatic obstruction without any clinical suspicion of PCa.

In a recent analysis of T1a/b PCa (18):

- The only significant predictors of the presence of residual cancer at RRP were PSA measured before and after surgery for benign prostatic hyperplasia (BPH) and Gleason score at surgery for BPH.
- The only independent predictors of biochemical recurrence after RRP were PSA measured after surgery for BPH and Gleason score at surgery for BPH.
- The stage (cT1a or cT1b) lost its significance in predicting the above-mentioned outcomes.

The decision to offer RP in cases of incidental cancer should be based upon the estimated probability of clinical progression compared to the relative risk of therapy and potential benefit to survival. In patients with a longer life expectancy, especially for poorly differentiated tumours, RP should be considered. Levels of PSA before and after TURP increase the accuracy in estimating the need for active management (18).

Systematic prostate biopsies of the remnant prostate may be useful in detecting residual cancer or concomitant peripheral zone cancer, or to ascertain a more correct tumour grade. Radical prostatectomy may be difficult after thorough TURP, when almost no residual prostate is left behind (19).

### 9.2.2 **Stage T1c and T2a prostate cancer**

Clinically unapparent tumour identified by needle biopsy because of an elevated PSA (cT1c) has become the most prevalent type of PCa. In an individual patient, it is difficult to differentiate between clinically insignificant and potentially life-threatening PCa. However, most reports stress that cT1c tumours are often significant with up to 30% of cT1c tumours being locally advanced at final histopathological analysis (20). The major challenge is how to recognize those tumours that need RP.

Partin tables may help to improve the selection of patients for surgical treatment as they provide an estimation of the final pathological stage (21). Others have suggested the inclusion of biopsy information, such as the number of cores or the percentage of cores invaded (22). If only one or a few cores are invaded and the percentage of invasion in one core is limited, the PCa is more likely to be an insignificant cancer, particularly if the lesion has a low Gleason score (23). It might therefore be reasonable to propose active monitoring to selected patients whose tumours are most likely to be insignificant.

In stage T2a patients with a 10-year life expectancy, RP is one of the recommended standard treatments, as 35-55% of these patients will show disease progression after 5 years if not treated. If active monitoring is proposed for low-grade T2 cancer, it should be remembered that pre-operative assessment of tumour grade by needle biopsy is often unreliable (24).

Extended pelvic lymph node dissection (eLND) is not necessary in low-risk PCa because the risk for positive lymph nodes does not exceed 5% (25).

## 9.3 **Intermediate-risk, localized prostate cancer: cT2b-T2c or Gleason score = 7 or prostate-specific antigen 10-20 ng/mL**

Patients with intermediate-risk PCa should be informed about the results of two randomized trials comparing RRP versus WW in localized PCa. In the SPCG-4 study, the survival benefit associated with RP was similar before and after 9 years of follow-up and was confined to men < 65 years of age. The NNT to avert one death was 15 overall and seven for men < 65 years of age. In the PIVOT trial, a preplanned subgroup analysis of men with intermediate-risk tumours showed that RP significantly reduced all-cause mortality.

Radical prostatectomy is one of the recommended standard treatments for patients with intermediate-risk PCa and a life expectancy of > 10 years (26). The prognosis is excellent when the tumour is confined to the prostate, based on pathological examination (27,28). A policy of active monitoring has been proposed for some selected patients with intermediate-risk localized tumours (29). However, when the tumour is palpable or visible on imaging and clinically confined to the prostate, disease progression can be expected in most long-term survivors. Stage T2b cancer will progress in > 70% of patients within 5 years (30). These data have been confirmed by a large RCT, which included mostly T2 PCa patients and compared RP and WW. The results showed a significant reduction in disease-specific mortality in favour of RP (5). Another large RCT corroborated these results (6).

An eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5% (25). In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes. Limited LND should no longer be performed because this misses at least half of the nodes involved.

### 9.3.1 **Oncological results of radical prostatectomy in low- and intermediate-risk prostate cancer**

The results achieved in a number of studies involving RP are shown in Table 9.1.

**Table 9.1: Oncological results of radical prostatectomy in organ-confined disease**

Reference	Prospective/ retrospective	n	Year of RP	Median follow-up (months)	10-year PSA-free survival (%)	10-year CCS (%)	15-year CCS (%)	25-year CCS (%)
Bill-Axelsson et al. (2011) (5)	Prospective	347 randomized to RP	1989-99	153			85	
Wilt et al. (2012) (6)	Prospective	364 randomized to RP	1994- 2002	120		95.6 (12- year)		
Porter et al. (2006) (31)	Retrospective	752	1954-94	137	71	96	91	82
Isbarn et al. (2009) (32)	Retrospective	436	1992-97	122	60	94		
Han et al. (2001) (33)	Retrospective	2404	1982-99	75	74	96	90	
Roehl et al. (2004) (34)	Retrospective	3478	1983- 2003	65	68	97		
Hull et al. (2002) (35)	Retrospective	1000	1983-98	53	75	98		
Stephenson et al. (36)	Retrospective	6398	1987- 2005	48			88	

CCS = cancer-specific survival; n = number of patients; PSA = prostate-specific antigen; RP = radical prostatectomy.

The first externally validated nomogram predicting PCa-specific mortality after RP for patients treated in the PSA era was published in 2009. The nomogram predicts that few patients die from PCa within 15 years of RP, despite the presence of adverse clinical features. This nomogram can be used in patient counselling and clinical trial design (36).

#### **9.4 High-risk localized and locally advanced prostate cancer: cT3a or Gleason score 8-10 or prostate-specific antigen > 20 ng/mL**

The widespread use of PSA testing has led to a significant migration in stage and grade of PCa with > 90% of men in the current era diagnosed with clinically localized disease (21). Despite the trends towards lower-risk PCa, 20-35% of patients with newly diagnosed PCa are still classified as high-risk based on either PSA > 20 ng/mL, GS ≥ 8, or an advanced clinical stage (37). Patients classified with high-risk PCa are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP (38).

There is no consensus regarding the optimal treatment of men with high-risk PCa. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patient with regard to their own individual circumstances.

Extended LND should be performed in all high-risk PCa cases, because the estimated risk for positive lymph nodes is 15-40% (25). Limited LND should no longer be performed, because it misses at least half the nodes involved.

##### **9.4.1 Locally advanced prostate cancer: cT3a**

Stage T3a cancer is defined as cancer that has perforated the prostate capsule. In the past, locally advanced PCa was seen in about 40% of all clinically diagnosed tumours. This figure is lower today; nevertheless its management remains controversial. The surgical treatment of clinical stage T3 PCa has traditionally been discouraged (39), mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse (40,41). Several randomized studies of radiotherapy combined with ADT versus radiotherapy alone have shown a clear advantage for combination treatment, but no trial has ever proven combined treatment to be superior to RP (42). Another problem is 'contamination' by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal therapy (HT) in most series reporting



the outcomes of RP for clinical T3 PCa. In recent years, there has been renewed interest in surgery for locally advanced PCa and several retrospective case series have been published. Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease (43-45).

Overstaging of cT3 PCa is relatively frequent and occurs in 13-27% of cases. Patients with pT2 disease and those with specimen-confined pT3 disease have similarly good biochemical and clinical PFS (44,45). In 33.5-66% of patients, positive section margins are present, and 7.9-49% have positive lymph nodes (46). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or HT (44,45).

The problem remains the selection of patients before surgery. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease (21,46). In addition, nodal imaging with CT or MRI, and seminal vesicle imaging with MRI, or directed specific biopsies of the nodes or seminal vesicles can help to identify those patients unlikely to benefit from a surgical approach (47). Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. Increased overall surgical experience must contribute to decreased operative morbidity and to improved functional results after RP for clinical T3 cancer (44,48). It has been shown that continence can be preserved in most cases, and in selected cases, potency can also be preserved (49).

Recent studies demonstrate 5-, 10- and 15-year biochemical progression-free survival (BPFS) to range between 45-62%, 43-51% and 38-49%, respectively. RP may provide excellent tumour control in selected patients with cT3 disease, with 5-, 10- and 15-year CSS ranging between 90-99%, 85-92% and 62-84%, respectively. Even though more than half of the patients received adjuvant HT and/or RT in most of the presented studies, the high CSS suggests that local cancer control remains especially important in men with locally advanced disease. Five- and 10-year OS ranged from 90-96% and 76-77%, respectively (Table 9.2). These survival rates surpass radiotherapy alone and similar to radiotherapy combined with adjuvant HT (42).

#### 9.4.2 **High-grade prostate cancer: Gleason score 8-10**

Although most poorly differentiated tumours extend outside the prostate, the incidence of organ-confined disease is 26-31%. Patients with high-grade tumours confined to the prostate at histopathological examination have a good prognosis after RP. One of the reasons to opt for surgery is the high rate of downgrading between the biopsy Gleason score and the Gleason score of the resected specimen. Indeed, Donohue et al. reported a 45% downgrading to  $GS \leq 7$  in the RP specimen in men with biopsy GS 8-10. Downgraded patients had an improved BPFS probability (56% vs 27%). Moreover, patients with a biopsy GS 8 and a cT1c were more likely to be downgraded and thus had a better BPFS probability. Of these patients, 64% were free of biochemical or clinical recurrence during further follow-up (50). Several other studies corroborated these observations and concluded that one-third of patients with a biopsy GS 8 are downgraded (29,51,52). These men in particular may benefit most from potentially curative resection.

Several studies have demonstrated good outcomes after RP in the context of a multimodal approach for patients with a biopsy  $GS \geq 8$ . The BPFS at 5- and 10-years' follow-up ranged between 35-51% and 24-39%, respectively, while the CSS at 5-, 10- and 15-years' follow-up was 96%, 84-88% and 66%, respectively (Table 9.2).

#### 9.4.3 **Prostate cancer with prostate-specific antigen > 20 ng/mL**

Yossepowitch et al. have reported the results of RP as monotherapy in men with PSA > 20 ng/mL in a cohort with mostly clinically organ-confined tumours and found a PSA failure rate of 44% and 53% at 5 and 10 years, respectively (38). D'Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP (53). Spahn et al. published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years' follow-up, respectively (54). In the same analysis, they demonstrated that the combination of PSA > 20 ng/mL with cT3 stage and/or biopsy GS 8-10 significantly lowered CSS. More recently, Gontero et al. described a subanalysis of the same patient cohort. Ten-year CSS was 80%, 85% and 91% in patients with PSA > 100 ng/mL, 50.1-100 ng/mL and 20.1-50 ng/mL, respectively. These results argue for aggressive management with RP as the initial step (55).

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach, demonstrated a BPFS at 5-, 10- and 15-years' follow-up, ranging between 40-63%, 25-48% and 25%, respectively. The CSS at 5, 10 and 15 years ranged between 93-97%, 83-91% and 71-78%, respectively (Table 9.2).

**Table 9.2: Overall survival (OS) and cancer-specific survival (CSS) rates for high-risk localized and locally advanced PCa treated with RP as first treatment in a multimodal approach**

Reference	n	Time span	OS			CSS			PSA-free survival		
			5-yr	10-yr	15-yr	5-yr	10-yr	15-yr	5-yr	10-yr	15-yr
<b>GS 8-10 at biopsy</b>											
Donohue et al. (2006) (50)	246	1983-2004	-	-	-	-	-	-	51	39	-
Bastian et al. (2006) (56)	220	1982-2004	-	-	-	-	-	-	40	27	-
Yossepowitch et al. (2008) (57)	401	1985-2005	-	-	-	96	88	-	-	-	-
Stephenson et al. (2009) (36)	702	1987-2005	-	-	-	-	84	66	-	-	-
Walz et al. (2010) (58)	269	1987-2005	-	-	-	-	-	-	35	24	-
<b>PSA &gt; 20 ng/mL</b>											
Zwergel et al. (2007) (59)	275	1986-2005	87	70	58	93	83	71	53	25	25
Magheli et al. (2007) (60)	265	1984-2005	-	-	-	-	-	-	47	33	-
Yossepowitch et al. (2008) (57)	441	1985-2005	-	-	-	97	91	-	-	-	-
Stephenson et al. (2009) (36)	726	1987-2005	-	-	-	-	90	78	-	-	-
Walz et al. (2010) (58)	370	1987-2005	-	-	-	-	-	-	40	26	-
Gontero et al. (2011) (55)	712	1987-2005	90	73	-	95	89	-	63	48	-
<b>cT3a</b>											
Ward et al. (2005) (44)	841	1987-1997	90	76	53	95	90	79	58	43	38
Carver et al. (2006) (61)	176	1983-2003	-	-	-	94	85	76	48	44	-
Hsu et al. (2007) (45)	200	1987-2004	96	77	-	99	92	-	60	51	-
Freedland et al. (2007) (62)	62	1987-2003	-	-	-	98	91	84	62	49	49
Yossepowitch et al. (2008) (57)	243	1985-2005	-	-	-	96	89	-	-	-	-
Xylinas et al. (2009) (63)	100	1995-2005	-	-	-	90	-	-	45	-	-
Stephenson et al. (2009) (36)	254	1987-2005	-	-	-	-	85	62	-	-	-
Walz et al. (2010) (58)	293	1987-2005	-	-	-	-	-	-	52	44	-

CSS = cancer-specific survival; n = number of patients; PSA = prostate-specific antigen; RP = radical prostatectomy.

### 9.5 Very-high-risk prostate cancer: cT3b-T4 N0 or any T, N1

Men with very-high-risk PCa generally have a significant risk of disease progression and cancer-related death if left untreated. Very-high-risk PCa presents two specific challenges. There is a need for local control as well as treatment of any microscopic metastases that are likely to be present but undetectable until disease progression. The optimal treatment approach therefore often necessitates multiple modalities. The exact combinations, timing and intensity of treatment continue to be strongly debated.

There is no consensus regarding the optimal treatment of men with very-high-risk PCa. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a



reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.

Extended LND should be performed in all very-high-risk cases, because the estimated risk for positive lymph nodes is 21-49% (64,65). Limited LND should no longer be performed, because it misses at least half the nodes involved.

#### 9.5.1 **cT3b-T4 N0**

A recent US study has shown that 72 patients who underwent RP for cT4 disease had better survival than those who received HT or radiotherapy alone, and showed comparable survival to men who received radiotherapy plus HT (66). Another study has compared the outcomes of RP in very-high-risk PCa (T3-T4 N0-N1, N1, M1a) with those in localized PCa. The two groups did not differ significantly in surgical morbidity except for blood transfusion, operative time, and lymphoceles, which showed a higher rate in patients with advanced disease. The OS and CSS at 7 years were 76.69% and 90.2% in the advanced disease group and 88.4% and 99.3% in the organ-confined disease group, respectively (65). Another recent study assessed the outcomes of RP in 51 patients presenting with cT3b or cT4 PCa. Intriguingly, overstaging in this group was still substantial, with approximately one-third of patients having either organ-confined disease (7.8%) or capsular perforation only (29.4%). Overstaged patients were often cured by surgery alone: 35.3% of the whole group did not receive any form of (neo)adjuvant treatment and 21.6% remained free of additional therapies at a median follow-up of 108 months (64).

In the above mentioned studies, the CSS was 88-92% at 5 years and 92% at 10 years, while the OS was 73-88% at 5 years and 71% at 10 years (Table 9.3).

#### 9.5.2 **Any T, N1**

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Clinical lymph node-positive (N+) disease will mostly be followed by systemic disease progression, and all patients with significant N+ disease ultimately fail treatment.

Nevertheless, the combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% (67,68). Most urologists are reluctant to perform RP for clinical N+ disease or they will cancel surgery if a frozen section shows lymph node invasion. However, a retrospective observational study has shown a dramatic improvement in CSS and OS in favour of completed RP versus abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and the abandonment of RP in N+ cases may not be justified (69). These findings have been corroborated in a contemporary retrospective analysis (70). This highlights the fact that frozen section is probably useless and should no longer be considered. Radical prostatectomy resulted in superior survival of patients with N+ PCa after controlling for lymph node tumour burden. The findings from these studies support the role of RP as an important component of multimodal strategies of N+ PCa.

The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only (71,72). In patients who prove to be pN+ after RP, early adjuvant HT has been shown to improve CSS and OS significantly in a prospective randomized trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more frequently performed extended LND. The benefits should be judged against the side effects of long-term HT. Follow-up of PSA and delaying the initiation of HT until rising PSA level is therefore an acceptable option in selected cases with  $\leq 2$  microscopically involved lymph nodes in an extended nodal dissection. Interestingly, in a retrospective cohort study, maximal local control with radiotherapy of the prostatic fossa appeared to be beneficial in PCa patients with pN+ after RP, treated adjuvantly with continuous ADT (73).

Recent studies described excellent survival outcomes after surgery, with 5-, 10- and 15-year CSS ranging from 84-95%, 51-86% and 45%, respectively. The overall survival at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively (Table 9.3).

**Table 9.3: Overall survival (OS), cancer-specific survival (CSS) rates for very-high-risk PCa treated with RP as first treatment in a multimodal approach**

Reference	n	Time span	OS			CSS			PSA-free survival		
			5-yr	10-yr	15-yr	5-yr	10-yr	15-yr	5-yr	10-yr	15-yr
<b>cT3b-T4</b>											
Johnstone et al. (2006) (66)	72	1995-2001	73	-	-	88	-	-	-	-	-
Joniau et al. (2012) (64)	51	1989-2004	88	71	-	92	92	-	53	46	-
<b>Any T and N1</b>											
Messing et al. (2006) (68) (*with vs without ADT)	98	1988-1993		55* 36 (11.5 yr)			85* 51 (11.5 yr)			53* 14 (11.5 yr)	
Schumacher et al. (2008) (72)	122	1989-2007	83	52	42	85	60	45	14	3	-
Da Pozzo et al. (2009) (74)	250	1988-2002	-	-	-	89	80	-	72	53	-
Engel et al. (2010) (69)	688	1988-2007	84	64	-	95	86	-	-	-	-
Steuber et al. (2011) (70)	108	1992-2004	79	69	-	84	81	-	-	-	-
Briganti et al. (2011) (73)	364	1988-2003	85	60	-	90	75	-	-	-	-

CSS = cancer-specific survival; n = number of patients; PSA = prostate-specific antigen; RP = radical prostatectomy.

## 9.6 Indication and extent of extended pelvic lymph node dissection

It is generally accepted that extended pelvic lymph node dissection (eLND) provides important information for prognosis (number of nodes involved, tumour volume within the lymph node, and capsular perforation of the node), which cannot be matched by any other current procedure. However, consensus has not been reached about when eLND is indicated and to what extent it should be performed. Instead, when making such decisions, many physicians rely on nomograms based on pre-operative biochemical markers and biopsies (21).

According to these nomograms, patients with PSA < 10 ng/mL and biopsy GS < 7 have a low risk of lymph node metastasis and therefore eLND might not be beneficial. However, the fact that most nomograms are based on a limited eLND (obturator fossa and external iliac vein) probably results in underestimation of the incidence of patients with positive nodes (25). Lymphography studies have shown that the prostate drains not only to the obturator and external iliac lymph nodes but also to the internal iliac and presacral nodes. Performing eLND results in removal of all lymph nodes in these particular anatomical regions, producing a higher yield of excised lymph nodes compared with a limited LND. Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (75,76). Clearly, the removal of a greater number of nodes results in improved staging. In the largest study of its kind, a cut-off  $\leq 2$  versus  $> 2$  affected nodes was shown to be an independent predictor of CSS (71).

### 9.6.1 Extent of extended lymph node dissection

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. Some lymph node mapping studies have advocated extending the template to include the common iliac lymph nodes up to the ureteric crossing. With this template, 75% of all anatomical landing sites are cleared (77). A recent prospective mapping study confirmed that a template including the external iliac, obturator and internal iliac areas was able to stage correctly 94% of patients. Nevertheless, in pN+ patients, this template was associated with a 24% incomplete clearance from positive nodes (78). Adding the common iliac area and the presacral area decreased this risk to only 3%. It is recommended that the nodes should be sent in separate containers for each region for histopathological analysis, because this will usually be associated with a higher diagnostic gain by the uropathologist.

### 9.6.2 Therapeutic role of extended lymph node dissection

Besides being a staging procedure, pelvic eLND can be curative, or at least beneficial, in a subset of patients with limited lymph node metastases (79-81). In some series, the number of nodes removed during

lymphadenectomy has been significantly correlated with time to disease progression (82). In one population-based study with a 10-year follow-up, patients undergoing excision of at least 10 nodes (node-negative patients) had a lower risk of PCa-specific death at 10 years than those who did not undergo lymphadenectomy (83). A recent prospective study randomized 360 consecutive patients to receive extended LND versus standard LND. After a median follow-up of 74 months, this study confirmed that an extended LND positively affected BDFS in intermediate and high-risk PCa (84).

### 9.6.3 Morbidity

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended versus limited LND, three-fold higher complication rates have been reported by some authors (85). Complications consist of lymphocele, lymphoedema, deep venous thrombosis and pulmonary embolism. However, other authors have reported more acceptable complication rates (86,87).

### 9.6.4 Conclusions for extended lymph node dissection

Extended LND may play a role in the treatment of a subset of intermediate-risk cases with > 5% nomogram predicted risk of positive lymph nodes, and in all high-risk cases.
Extended LND increases staging accuracy and influences the decision to use adjuvant therapy. The number of lymph nodes removed correlates with time to disease progression.
Surgical morbidity must be balanced against the therapeutic effects, and decisions are made on an individual basis.

## 9.7 Recommendations for radical prostatectomy and eLND in low-, intermediate- and high-risk prostate cancer

	LE	GR
RP is a reasonable treatment option in selected patients with cT3a PCa, GS 8-10 or PSA > 20.	2b	B
Furthermore, RP is optional in highly selected patients with cT3b-4 N0 or any cT N1 PCa in the context of a multimodality approach.	3	C
Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.	1b	A
If RP is performed, pelvic eLND must be performed, because the estimated risk for positive lymph nodes is 15-40%.	2a	A
The patient must be informed about the likelihood of a multimodal approach.	1a	A
When nodal involvement is detected after surgery:		
• Adjuvant ADT is recommended when > 2 nodes are involved;	1b	A
• Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement.	2b	B
eLND is not necessary in low-risk PCa, because the risk for positive lymph nodes does not exceed 5%.	2b	A
eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%, as well as in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15-40%.	2b	A
Limited LND should no longer be performed, because it misses at least half the nodes involved.	2a	A

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

## 9.8 Neoadjuvant hormonal therapy and radical prostatectomy

Neoadjuvant or up-front hormonal therapy (NHT) is defined as therapy given before definitive local curative treatment (e.g. surgery or radiotherapy). Since PCa is an androgen-dependent tumour, NHT is an appealing concept. Attempts to decrease the size of the prostate before RP were first reported by Vallett as early as 1944 (88). A recent review and meta-analysis studied the role of NHT and prostatectomy (89). NHT before prostatectomy did not improve OS or disease-free survival (DFS), but did significantly reduce positive margin rates (RR = 0.49; 95% confidence interval [95%CI]: 0.42-0.56; p < 0.00001), organ confinement (RR = 1.63; 95% CI: 1.37-1.95; p < 0.0001) and lymph node invasion (RR = 0.49; 95% CI: 0.42-0.56; p < 0.02). Thus, the absence of improvement in clinically important outcomes (OS, DFS or biochemical DFS) was demonstrated

despite improvements in putative pathological surrogate outcomes, such as margin-free positive status. This calls into question the use of these pathological markers of treatment outcomes as valid surrogates for clinically relevant outcomes.

Further studies are needed to investigate the application of HT as both neoadjuvant treatment and with chemotherapy in early disease. More information is also needed to evaluate these agents in terms of side effects and QoL, which was lacking in most studies presented in this review. Further cost analyses should be undertaken to update the data. A recent Cochrane review and meta-analysis have studied the role of adjuvant HT following RP: the pooled data for 5-year OS showed an odds ratio (OR) of 1.50 (95% CI: 0.79-2.84). This finding was not statistically significant, although there was a trend favouring adjuvant HT. Similarly, there was no survival advantage at 10 years. The pooled data for DFS gave an overall OR of 3.73 (95% CI: 2.3-6.03). The overall effect estimate was highly significant ( $p < 0.00001$ ) in favour of the HT arm.

It is noteworthy that the Early Prostate Cancer Trialists' Group (EPC) trial was not included in the Cochrane review. The third update from this large randomized trial of bicalutamide, 150 mg once daily, in addition to standard care in localized and locally advanced, non-metastatic PCa was published in November 2005 (90). Median follow-up was 7.2 years. There was a significant improvement in objective PFS in the RP group. This improvement was only significant in the locally advanced disease group (HR: 0.75; 95% CI: 0.61-0.91). There was no significant improvement in OS in the RP-treated groups (localized and locally advanced disease). In the WW group, there was an OS trend in favour of WW alone in the localized disease group (HR: 1.16; 95% CI: 0.99-1.37).

### 9.8.1 Recommendations for neoadjuvant and adjuvant hormonal treatment and radical prostatectomy

	LE	GR
NHT before RP does not provide a significant OS advantage over prostatectomy alone.	1a	A
NHT before RP does not provide a significant advantage in DFS over prostatectomy alone.	1a	A
Adjuvant HT following RP shows no survival advantage at 10 years.	1a	A

DFS = disease-free survival; NHT = neoadjuvant hormonal therapy; OS = overall survival; RP = radical prostatectomy

## 9.9 Complications and functional outcome

The intra- and peri-operative complications of retropubic RP and RALP are listed in Table 9.4 (91) and see Section 15.3 Radical prostatectomy also.

**Table 9.4: Intra- and peri-operative complications of retropubic RP and RALP**

Complication, mean %	Retropubic RP	RALP
Peri-operative death	0.1	0.04
Readmission	3.0	3.5
Reoperation	2.3	0.9
Vessel injury	0.04	0.08
Nerve injury	0.4	0.4
Ureteral injury	1.5	0.1
Bladder injury	0.05	0.07
Rectal injury	0.5	0.3
Bowel injury	0	0.09
Ileus	0.8	0.8
Deep vein thrombosis	1.0	0.3
Pulmonary embolism	0.5	0.3
Pneumonia	0.5	0.05
Myocardial infarction	0.2	0.2
Haematoma	1.6	0.7
Lymphocele	3.2	0.8
Anastomotic leakage	10.0	3.5
Fistula	0.07	0.03
Bladder neck/anastomotic stricture	2.2	0.9
Sepsis	0.2	0.1
Wound infection	2.8	0.7

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

Post-operative incontinence and erectile dysfunction are common problems following surgery for PCa. A recent systematic review found that the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with retropubic RP (92). A similar study reported mean potency recovery rates at 12 months of 55-81% for patients treated with RALP and 26-63% for patients treated with retropubic RP (93). The major limitations of the included studies were the frequent retrospective study design and the use of different assessment tools preventing a proper comparison between techniques and series.

### 9.10 Summary of indications for nerve-sparing surgery\* (100-104)

Selection criteria	References				
	Sofer (94)	Walsh & Thompson (95)	Alsikafi & Brendler (96)	Graefen (97)	Bianco et al (98)
<b>Pre-operative criteria</b>					
Stage > T2	+	+	+	+	+
PSA > 10	+				
Biopsy Gleason score 7			+		
Biopsy Gleason score 8-10	+			+	
Partin tables		+			+
Side with > 50% tumour in biopsy			+		
Side with perineural invasion		+/-	+		
<b>Intra-operative criteria</b>					
Side of palpable tumour			+		
Side of positive biopsy				+	
Induration of lateral pelvic fascia		+			+
Adherence to neurovascular bundles		+			+
<b>Positive section margins</b>	<b>24%</b>	<b>5%</b>	<b>11%</b>	<b>15.9%</b>	<b>5%</b>

\*Clinical criteria used by different authors when NOT to perform a nerve-sparing RP.

Nerve-sparing RP can be performed safely in most men with localized PCa undergoing RP (99,100). In the past decade, a dramatic shift towards lower-stage tumours has become evident. More importantly, men are younger at the time of diagnosis and more interested in preserving sexual function. Nevertheless, 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, or more than one biopsy > 6 at the ipsilateral side. Partin tables help to guide decision making (21). Multiparametric MRI is increasingly being used in the decision-making process to select a nerve-sparing approach (101-103).

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. This is especially helpful in patients with a palpable lesion close to the capsule during nerve-sparing RP. A wedge of the prostate can then be resected and inked differently. When there is carcinoma adherent to the capsule on frozen-section analysis, the NVB is resected; otherwise, the NVB remains in situ. In patients with intra-operatively detected tumoural lesions during nerve-sparing RP, frozen-section analysis objectively supports the decision of secondary NVB resection, as well as preservation (104).

The patient must be informed before surgery about the potency rates achieved. The patient must be aware that, to ensure adequate cancer control, the nerves may be sacrificed despite any pre-operative optimism suggesting their salvage might be possible.

The early administration of intracavernous injection therapy could improve the definitive potency rates (105,106). Finally, the early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. Placebo-controlled prospective studies have shown no benefit from daily early administration of vardenafil or sildenafil versus on-demand vardenafil or sildenafil in the post-operative period (107,108). Conversely, another placebo-controlled prospective study has shown that sildenafil has a significant benefit on the return of normal spontaneous erections (109).

## 9.11 Conclusions and recommendations for radical prostatectomy

Indications	LE	GR
In patients with low and intermediate risk localized PCa (cT1a-T2b and GS 2-7 and PSA < 20 ng/mL) and life-expectancy > 10 years.	1b	A
<i>Optional</i>		
Selected patients with low-volume, high-risk, localized PCa (cT3a or GS 8-10 or PSA > 20 ng/mL), often in a multimodality setting.	2b	B
Highly selected patients with very-high-risk, localized PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.	3	C
Short-term (3 months) or long-term (9 months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is NOT recommended for the treatment of stage T1-T2 disease.	1a	A
Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	2b	B
Multiparametric MRI can help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	2b	B

GS = Gleason-score; MRI = magnetic resonance imaging; PCa = prostate cancer.

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## 10. TREATMENT: DEFINITIVE RADIOTHERAPY

### 10.1 Introduction

There have been no randomized studies comparing radical prostatectomy (RP) with either external-beam radiotherapy (EBRT) or brachytherapy for localized prostate cancer (PCa). The National Institutes of Health (NIH) consensus statement in 1988 (1) stated that external irradiation offers the same long-term survival results as surgery. In addition, EBRT provides a QoL at least as good as that following surgery (2). A recent systematic review has provided a more sophisticated overview of outcomes from trials that meet the criteria for stratifying patients by risk group, standard outcome measures, numbers of patients, and minimum median follow-up period (3). Radiotherapy continues to be an important and valid alternative to surgery alone for curative therapy.

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT. All centres that do not yet offer IMRT should plan to introduce it as a routine method for the definitive treatment of PCa.

In addition to external irradiation, transperineal low-dose or high-dose rate brachytherapy are widely used. In localized and locally advanced PCa, several randomized phase III trials conducted by the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) have established the indications for the combination of external irradiation and androgen deprivation therapy (ADT).



Regardless of the technique used, the choice of treatment is multidisciplinary. After the extent of the tumour has been properly assessed, the following are taken into account:

- 2009 TNM classification;
- Gleason score, defined using an adequate number of core biopsies (at least 12);
- Baseline prostate-specific antigen (PSA);
- Age of the patient;
- Patient's comorbidity, life expectancy, and QoL;
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings;
- National Comprehensive Cancer Network (NCCN) and/or D'Amico prognostic factor classification (4).

Additional information on the various aspects of radiotherapy in the treatment of PCa is available in an extensive overview (5).

## **10.2 Technical aspects: three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated external-beam radiotherapy (IMRT)**

Anatomical data is acquired by scanning the patient in a treatment position. The data are transferred to the three-dimensional (3D) treatment planning system, which visualizes the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field using portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. Three-dimensional CRT improves local control through dose escalation, without significantly increasing the risk of morbidity.

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

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualized and corrected for in real time, although the optimum means of achieving this is still unclear (6). Tomotherapy is another evolving technique for the delivery of IMRT, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning. Preliminary data suggest that this technique is feasible in PCa treatment (7).

Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists and computer scientists.

## **10.3 Radiotherapy for localized PCa**

### **10.3.1 Dose escalation**

Before the advent of 3D-CRT, radiotherapy dosages to the prostate were usually about 64 Gy in 2-Gy fractions, or equivalent. With 3D-CRT, and more recently IMRT, dose escalation above this limit has been possible. Several randomized studies (see below) have shown that dose escalation (range 76-80 Gy) has a significant impact on 5-year survival without biochemical relapse (8-14). These trials have generally included patients from several risk groups, and the use of neoadjuvant /adjuvant hormone therapy (see below) has varied. To date, no trials have shown that dose escalation results in an OS benefit. However, the trials have been remarkably consistent in reporting improvements in freedom from biochemical progression in patients treated with dose-escalated radiotherapy.

#### *10.3.1.1 MD Anderson study*

The MD Anderson study compared 78 Gy with 70 Gy conventional radiotherapy in 305 patients with stage T1-3, pre-treatment PSA level > 10 ng/mL and a median follow-up period of 9 years. At 10 years' follow-up, 16% of the high-risk patients treated with 70 Gy had died of disease compared with 4% of patients treated with 78 Gy ( $p = 0.05$ ). These were similar percentages to those observed in patients with higher PSA values, 15% versus 2% ( $p = 0.03$ ) (8).

#### *10.3.1.2 Prog 95-09 study*

The PROG 95-09 study evaluated different radiotherapy dosages in 393 patients with T1b-T2b, 75% of whom had a Gleason score  $\leq 6$  and a PSA level < 15 ng/mL. The patients were randomly assigned to receive an initial

boost to the prostate alone, using conformal protons, of either 19.8 Gy or 28.8 Gy, and then 50.4 Gy to a larger volume. With a median follow-up period of 8.9 years, there was a significant difference in the 10-year American Society for Therapeutic Radiology and Oncology (ASTRO) biochemical failure rate, at 32.4% for conventional-dose treatment (70.2 Gy) and 16.7% for high-dose treatment (79.2 Gy) ( $p < 0.0001$ ). The difference persisted when only low-risk patients (58% of the total) were examined, when it was found to be 28.2% for conventional and 7.1% for high-dose treatment ( $p < 0.0001$ ) (9).

#### 10.3.1.3 MRC RT01 study

The MRC RT01 study compared dosages of 64 Gy with 74 Gy, both with neoadjuvant hormonal therapy, in 843 men with T1b-T3b disease. The study showed an 11% difference in the 5-year biochemical disease-free survival (BDFS) in favour of dose-escalated radiotherapy ( $p = 0.0007$ ) (15).

#### 10.3.1.4 Dutch randomized phase III trial

In a Dutch randomized phase III trial, a dosage of 68 Gy was compared with 78 Gy. The study found a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose ( $p = 0.02$ ) (11).

#### 10.3.1.5 Phase III trial of the French Federation of Cancer Centres

The Phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in 306 men with localized PCa, with a pelvic lymph node involvement risk of  $< 10\%$  (Partin) or pN0, with no hormonal therapy allowed before, during, or after radiotherapy. With a median follow-up period of 61 months, better 5-year biological outcomes were seen in favour of dose-escalated radiotherapy ( $p = 0.036$ ) (12).

#### 10.3.1.6 Conclusion

In everyday practice, it is the expert opinion of the EAU Guidelines Working Panel that a minimum dose of  $\geq 74$  Gy is recommended for EBRT + hormone therapy. Currently, it is not possible to make different recommendations according to the patient's risk group. There is evidence from these randomized trials for an impact of dose-escalation in low-risk, medium-risk, and high-risk patients, although probably of different magnitudes (10).

### 10.3.2 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

Several randomized trials have shown clearly that in at least some patients with non-metastatic PCa, radiotherapy alone is inferior to the combination of radiotherapy plus ADT.

#### 10.3.2.1 EORTC 22863 study

The EORTC 22863 study recruited 415 patients, with either T1-2 grade 3 World Health Organization (WHO) or T3-4 N0 M0 and any histological grade, and compared radiotherapy plus adjuvant ADT with radiotherapy alone. Androgen deprivation treatment was allowed in cases of relapse. A total of 82% of patients were diagnosed as T3, 10% as T4, and 89% as N0. Hormonal treatment consisted of oral cyproterone acetate (CPA) 50 mg three times daily for 1 month, beginning 1 week before the start of radiotherapy, and goserelin acetate (Zoladex), 3.6 mg subcutaneously every 4 weeks for 3 years, starting on the first day of radiotherapy. The pelvic target volume received was 50 Gy and the prostatic target volume was 20 Gy. With a median follow-up period of 66 months, the combination therapy compared with radiotherapy alone yielded significantly better survival (78% vs 62%;  $p = 0.001$ ) (16). At a median follow-up of 9.1 years, the 10-year OS remained significantly higher at 58.1% versus 39.8% ( $p < 0.0001$ ), as did the clinical PFS at 47.7% versus 22.7% ( $p < 0.0001$ ). The 10-year cumulative incidences of PCa mortality were 11.1% versus 31.0% ( $p < 0.0001$ ), and the 10-year cumulative incidences of cardiovascular mortality were 11.1% versus 8.2% ( $p = 0.75$ ) (17).

#### 10.3.2.2 RTOG 85-31 study

The RTOG 85-31 study recruited 977 patients who had been diagnosed with T3-4 N0-1 M0, or pT3, after RP. Androgen deprivation therapy was begun in the last week of irradiation and continued up to relapse (Group I) or was started at recurrence (Group II). A total of 15% of patients in Group I and 29% in Group II had undergone RP, and 14% of patients in Group I and 26% in Group II were pN1. Goserelin acetate, 3.6 mg subcutaneously, was administered every 4 weeks. The pelvis was irradiated with 45 Gy, while the prostatic bed received 20-25 Gy. Patients diagnosed with stage pT3 received 60-65 Gy. With a median follow-up time of 7.6 years for all patients, the 10-year OS was significantly greater for the adjuvant arm at 49% versus 39% ( $p = 0.002$ ) (18).

#### 10.3.2.3 RTOG 86-10 study

The RTOG 86-10 study recruited 471 patients with bulky (5x5 cm) tumours T2-4 N0-X M0. Androgen deprivation therapy was administered at 2 months before irradiation and during irradiation, or in the case

of relapse in the control arm. Patients were diagnosed as having T2 (32%), T3-4 (70%), and N0 (91%). The hormone treatment consisted of oral flutamide (Eulexin), 250 mg three times daily, and goserelin acetate (Zoladex), 3.6 mg every 4 weeks by subcutaneous injection. The pelvic target volume received 45 Gy and the prostatic target volume received 20-25 Gy. The 10-year OS estimates were 43% for ADT + irradiation versus 34% for hormonal treatment, although the difference was not significant ( $p = 0.12$ ). There was a significant improvement in the 10-year disease-specific mortality (23% vs 36%;  $p = 0.01$ ), disease-free survival (11% vs 3%;  $p < 0.0001$ ) and in the BDFR (65% vs 80%;  $p < 0.0001$ ), with the addition of ADT having no statistical impact on the risk of fatal cardiac events (19).

#### 10.3.2.4 Boston trial

In the Boston trial, 206 patients, with a PSA level of 10-40 ng/mL, a Gleason score of 7-10, or radiographic evidence of extraprostatic disease, were randomized to either 3D-CRT alone or 3D-CRT + 6 months of ADT. After a median follow-up period of 7.6 years, intermediate- or high-risk patients (without moderate or severe comorbidity), who were randomly assigned to receive 3D-CRT + ADT, showed a 13% improvement in the OS rate ( $p < 0.001$ ) (20).

#### 10.3.2.5 RTOG 94-08 study

The RTOG study 94-08 of 1979 patients with T1b-T2b and PSA < 20 ng/mL showed that adding complete androgen blockade for 2 months before and 2 months during conventional lower-dose radiotherapy (66 Gy) significantly improved the 10-year OS rate (62% vs 57%;  $p = 0.03$ ) (13).

#### 10.3.2.6 EORTC 22991 study

The EORTC 22991 study compared 3D-CRT, with or without IMRT, with a choice of three levels of dosage (70 Gy, 74 Gy, or 78 Gy), with or without 6 months of neoadjuvant and concomitant hormonal therapy, was closed in April 2008 after recruiting 800 patients; the results are awaited.

#### 10.3.2.7 Conclusion

These trials included patients with a wide range of clinical risk factors, most of whom were thought to be at high-risk of disease progression, usually by virtue of their clinical stage, but in some instances because of their PSA level or Gleason grade. The most powerful conclusion from these studies comes from the EORTC 22863 study, which is the basis for the combination of radiotherapy and ADT in patients with locally advanced (T3-T4) non-metastatic PCa. Whether these results should be applied to patients at all stages of PCa is unclear.

### 10.3.3 Duration of adjuvant or neoadjuvant ADT in combination with radiotherapy

Several phase III trials have attempted to define the optimum timing and/or duration of ADT in combination with radiotherapy.

#### 10.3.3.1 EORTC-22961 study

The EORTC-22961 randomized phase III trial compared 36 months versus 6 months of ADT + radiotherapy in 970 patients. It showed that an increased duration of ADT improved OS in patients with high-risk PCa after 5 years (14). The 5-year overall mortality rates for short-term and long-term suppression were 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79;  $p = 0.65$  for non-inferiority).

#### 10.3.3.2 Trans-Tasman Oncology Group (TROG) trial

The Trans-Tasman Oncology Group (TROG) randomized trial recruited 818 patients with T2b-T4 N0 M0 PCa. It compared no neoadjuvant ADT with 3 months or 6 months of neoadjuvant ADT, with goserelin and flutamide starting 2 months before radiotherapy, or 6 months of ADT with the same regimen starting 5 months before radiotherapy. Although 3 months of ADT improved the biochemical PFS compared to radiotherapy alone, 6 months of ADT was shown to further improve the PCa-specific survival and OS (21).

#### 10.3.3.3 RTOG 94-13 study

The RTOG 94-13 randomized trial used a 2x2 design comparing whole-pelvic with prostate-only radiotherapy (see below) and neoadjuvant with adjuvant ADT in 1323 patients, with stages T1c-T4 N0 M0 PCa, and found no differences in the PFS. However, the report describes possible interactions between the timing of ADT and the radiotherapy volume in subgroup analyses (22).

#### 10.3.3.4 RTOG 92-02 study

The RTOG 92-02 study compared 4 months of neoadjuvant ADT (2 months before and during radiotherapy) with the same plus an additional 24 months of adjuvant ADT in 1554 patients with T2c-T4 PCa and reported

improvements in local progression, disease-free survival, biochemical survival, and metastasis-free survival in patients treated with additional adjuvant ADT. However, an OS benefit was restricted to men with a Gleason score of 8-10 in the subgroup analysis (23).

#### **10.3.4 Combined dose-escalated RT and ADT**

Zelevsky et al. (24) reported a retrospective analysis of 2251 patients with T1-3 N0-X M0 PCa, comprising 571 patients with low-risk PCa (22.4%), 1074 patients with intermediate-risk PCa (42.1%), and 906 patients with high-risk PCa (35.5%), according to the NCCN classification. 3D-conformal radiotherapy or IMRT were administered to the prostate and seminal vesicles only. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years of the study using image-guided IMRT. Androgen deprivation therapy by complete androgen blockade with a luteinizing hormone-releasing hormone (LHRH) agonist + oral antiandrogen was administered, at the discretion of the treating physician, to 1249 patients (49% of the study group) of whom 623 had high-risk PCa (69%), 456 had intermediate-risk PCa (42%) and 170 had low-risk PCa (30%). The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before radiotherapy and continuing during radiotherapy. With an 8-year median follow-up period, the 10-year BDFR in each risk group was significantly improved by dose escalation: 84% (> 75.6 Gy) versus 70% for low-risk PCa ( $p = 0.04$ ), 76% (> 81 Gy) versus 57% for intermediate-risk PCa ( $p = 0.0001$ ), and 55% (> 81 Gy) versus 41% for high-risk patients ( $p = 0.0001$ ). The 6-month ADT also influenced the BDFR in intermediate- and high-risk patients, with 55% for intermediate-risk versus 36% for high-risk patients ( $p < 0.0001$ ). In the multivariate analysis, a dosage > 81 Gy ( $p = 0.027$ ) and ADT ( $p = 0.052$ ) were found to be significant predictive factors for distant metastasis-free survival. However, none of these parameters influenced PCa mortality or OS. There were very low rates of grade 3-4 acute or late toxicity (25).

#### **10.3.5 Proposed EBRT treatment policy for localized PCa**

##### **10.3.5.1 Low-risk PCa**

Intensity-modulated radiotherapy with escalated dose and without ADT is an alternative to brachytherapy (see below).

##### **10.3.5.2 Intermediate-risk PCa**

Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months) (26,27). For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT at an escalated dose (80 Gy) or a combination of IMRT and brachytherapy.

##### **10.3.5.3 High-risk PCa**

EBRT + short-term ADT did not show any impact on OS in high-risk PCa, using the definition for high-risk PCa suggested by results from the Boston and 04-08 RTOG trials, i.e. T1-2 N0-X M0, with either a baseline PSA value > 20 ng/mL and/or a Gleason score of 8-10. The high risk of relapse outside the irradiated volume makes it compulsory to use a combined modality approach, consisting of dose-escalated IMRT, including the pelvic lymph nodes + long-term ADT. The duration of ADT has to take into account WHO performance status, comorbidities, and the number of poor prognostic factors, including cT stage (> T2c), Gleason score 8-10, and PSA > 20 ng/mL.

#### **10.3.6 The role of radiotherapy in locally advanced PCa: T3-4 N0, M0**

The results of radiotherapy alone are very poor (28). The randomized trials discussed above have clearly established that the use of ADT produces better outcomes in patients with locally advanced disease who are treated with radiotherapy. Some clinicians have considered that the better outcomes were due to the earlier use of ADT, and questioned the benefits of radiotherapy itself in this context. However, three trials have established that, in locally advanced disease, radiotherapy is effective and that combined radiotherapy + ADT is clearly superior to ADT alone.

##### **10.3.6.1 MRC PR3/PR07 study - The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study**

This study comprised 1205 patients, consisting of T3-4 ( $n = 1057$ ), or T2, PSA > 40 ng/mL ( $n = 119$ ), or T2, PSA > 20 ng/mL and Gleason score > 8 ( $n = 25$ ) and T-category unknown ( $n = 4$ ), who were randomly assigned to lifelong ADT (bilateral orchiectomy or LHRH agonist), with or without radiotherapy (65-70 Gy to the prostate, with or without 45 Gy to the pelvic lymph nodes). After a median follow-up period of 6 years, the addition of radiotherapy to ADT reduced the risk of death from any cause by 23% ( $p = 0.03$ ) and the risk of death due to PCa by 46% ( $p = 0.0001$ ) (29,30).

### 10.3.6.2 The Groupe d'Etude des Tumeurs Uro-Génitales (GETUG) trial

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to lifelong ADT using an LHRH agonist (leuprorelin), with or without radiotherapy (70 Gy to the prostate plus  $48 \pm 2$  Gy to the pelvic lymph nodes). After a median follow-up period of 67 months, there was a significant improvement in the 5-year disease free survival ( $p < 0.001$ ), metastatic disease-free survival ( $p < 0.018$ ), and locoregional PFS ( $p < 0.0002$ ), but the effect on OS was not reported (31).

### 10.3.6.3 The SPCG-7/SFUO-3 randomized study (32)

The study compared hormonal treatment alone (i.e. 3 months of continuous androgen blockade followed by continuous flutamide treatment ( $n = 439$ ) with the same treatment combined with radiotherapy ( $n = 436$ ). After a median follow-up period of 7.6 years, the 10-year cumulative incidences for PCa specific mortality were 23.9% and 11.9%, respectively (95% confidence interval (CI): 4.9-19.1%), and the 10-year cumulative incidences for overall mortality were 39.4% in the hormonal treatment-only group and 29.6% in the hormonal treatment + radiotherapy group (95% CI: 0.8-18%).

## 10.3.7 Benefits of lymph node irradiation in PCa

### 10.3.7.1 Prophylactic irradiation of pelvic lymph nodes in high-risk localized PCa

Invasion of the pelvic lymph nodes is a poor prognostic factor and makes systemic medical treatment mandatory, since radiotherapy alone is insufficient (14). There is no firm evidence for prophylactic whole-pelvic irradiation, since randomized trials have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77 06 study ( $n = 484$  with T1b-T2) (33), the Stanford study ( $n = 91$ ) (34), and the GETUG 01 trial ( $n = 444$  with T1b-T3 N0 pNx M0) (35). In the RTOG 94-13 study (22), there were no differences in the PFS in patients treated with whole-pelvic or prostate-only radiotherapy, but interactions between whole-pelvic radiotherapy and the duration of ADT were reported following the subgroup analysis.

Pelvic lymphadenectomy may be needed to improve the selection of patients who may be able to benefit from pelvic lymph node irradiation and to supplement the use of Partin's tables (36) and/or the Roach formula (37). The results of pelvic lymphadenectomy, especially in young patients, allows radiation oncologists to tailor both the planning target volume and the duration of ADT, particularly ensuring that there is no pelvic irradiation for pN0 patients, while providing pelvic irradiation for pN1 patients with long-term ADT. The benefits of pelvic nodal irradiation at a high dosage using IMRT merit further investigation in a phase II trial. One such trial is currently recruiting through the RTOG, while a second is in randomized phase II in the UK.

### 10.3.7.2 Very high-risk PCa: c or pN1, M0

Patients with pelvic lymph node involvement lower than the iliac regional nodes,  $< 80$  years old, with a WHO performance status 0-1 and no severe comorbidity, may be candidates for EBRT + immediate long-term hormonal treatment. The RTOG 85-31 randomized phase III trial, with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better 5-year (54%) and 9-year (10%) PFS rates (PSA  $< 1.5$  ng/mL) versus 33% and 4%, respectively, with radiation alone and hormonal manipulation instituted at the time of relapse ( $p < 0.0001$ ). The multivariate analysis showed that this combination had a statistically significant impact on the OS, disease-specific failure, metastatic failure and biochemical control rates (38). The GETUG 12 trial investigated the impact of neoadjuvant chemotherapy with docetaxel on the PFS in a cohort of 413 high-risk patients, defined as having one or more of the following criteria: T3-4, Gleason score  $\geq 8$ , PSA  $\geq 20$  ng/mL, pN+. Patients were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years, + four cycles of docetaxel, 70 mg/m<sup>2</sup> every 3 weeks, + estramustine 10 mg/kg/dL on days 1-5 (arm 1) or to goserelin alone (arm 2). Local therapy was administered at 3 months and consisted of radiotherapy in 358 patients (87%). Toxicity included grade 3-4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death and no secondary leukaemia. With a median follow-up period of 4.6 years, the 4-year PFS was 85% in arm 1 versus 81% in arm 2 ( $p = 0.26$ ), but the data need to mature (39).

## 10.4 Proton beam and carbon ion beam therapy

In theory, proton beams are an attractive alternative to photon-beam radiotherapy 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.

However, in practice, this has the disadvantage that dose distributions from protons are highly sensitive to changes in internal anatomy, such as may occur with bladder or rectal filling. Prostate proton therapy is usually delivered with lateral beams. It is also possible that high linear energy transfer (LET)



radiotherapy using protons or carbon ions might offer inherent biological advantages over photons, which have a greater capacity for DNA damage dose for dose.

Only one randomized trial has incorporated proton therapy in one arm: the Loma Linda/Massachusetts General Hospital trial compared standard-dose CRT with dose-escalated radiotherapy using protons for the boost dose (9). This trial cannot be used as evidence for the superiority of proton therapy per se, as its use in this trial could be viewed simply as a sophisticated method of dose escalation. A randomized trial comparing equivalent doses of proton-beam therapy with IMRT is needed to compare the efficacy of protons versus photons; a study of this type is under consideration by the RTOG.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing (40); the other study suggested a clearer advantage for protons (41). Further studies are clearly needed. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy. Theoretically, proton therapy may be associated with a lower risk of secondary cancers compared with IMRT because of the lower integral dose of radiation, but there are no data from patients treated for PCa to support this.

Carbon ions offer similar theoretical advantages to those of protons as an alternative to photon-beam therapy. In a phase II study, 175 patients with T1-3 N0-1 M0 PCa were treated with carbon ions at a dosage equivalent to 66 Gy in 20 fractions over 5 weeks (42). The treatment appeared to be well tolerated, with no RTOG grade 3 or 4 bowel or genitourinary toxicity, and an overall 4-year BDFR of 88% (41). As with protons, a randomized trial comparing carbon ions with IMRT and using equivalent doses is required.

### 10.5 Transperineal brachytherapy

Transperineal brachytherapy is a safe and effective technique. There is a consensus on the following eligibility criteria:

- Stage cT1b-T2a N0, M0;
- A Gleason score  $\leq 6$  assessed on an adequate number of random biopsies;
- An initial PSA level of  $\leq 10$  ng/mL;
- $\leq 50\%$  of biopsy cores involved with cancer;
- A prostate volume of  $< 50$  cm<sup>3</sup>;
- An International Prostatic Symptom Score (IPSS)  $\leq 12$  (43).

Patients with low-risk PCa are the most suitable candidates for low-dose-rate (LDR) brachytherapy. Further guidelines on the technical aspects of brachytherapy have been published recently and are strongly recommended (44).

In 1983, Holm et al. described the transperineal method with endorectal sonography, in which the patient is positioned in a dorsal decubitus gynaecological position (45). Implantation is undertaken with the patient under general anaesthesia or spinal block, and involves a learning curve for the whole team: the surgeon for delineation of the prostate and needle placement, the physicist for real-time dosimetry, and the radiation oncologist for source loading. The sonography probe introduced into the rectum is fixed in a stable position.

There have been no randomized trials comparing brachytherapy with other curative treatment modalities. Outcomes are based on non-randomized case series. The results of permanent implants have been reported from different institutions, with a median follow-up ranging from 36 to 120 months (46). The recurrence-free survival after 5 and 10 years has been reported to range from 71% to 93% and from 65% to 85%, respectively (47-54). A significant correlation has been shown between the implanted dose and recurrence rates (55). Patients receiving a D90 (dose covering 90% of the prostate volume) of  $> 140$  Gy had a significantly higher biochemical control rate (PSA  $< 1.0$  ng/mL) after 4 years than patients who received less than 140 Gy (92% vs 68%). There is no benefit from adding neoadjuvant or adjuvant ADT to LDR brachytherapy (46).

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implantation transurethral resection of the prostate (TURP), which is required in up to 8.7% of cases, and incontinence (0-19%) (56). A small randomized trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity (57). This observation requires further study in a larger number of patients. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for benign prostatic hyperplasia increases the risk of post-implantation incontinence and urinary morbidity.

The incidence of grade III toxicity is less than 5%. Erectile dysfunction develops in about 40% of the patients after 3-5 years. In a recent retrospective analysis of 5,621 men who had undergone LDR



brachytherapy (58), the urinary, bowel, and erectile morbidity rates were 33.8%, 21%, and 16.7%, respectively, with invasive procedure rates of 10.3%, 0.8%, and 4%, respectively.

In patients with permanent implants, iodine-125 in granular form is the radioactive element of reference, while palladium-103 may be used for less differentiated tumours with a high doubling time. The doses delivered to the planning target volume are 144 Gy for iodine-125 and 125 Gy for palladium-103. A Gleason score of 7 is still a 'grey area', but patients with a Gleason score of 4 + 3 showed no difference in outcome (59).

A small randomized trial has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice (60). In cases of intermediate- or high-risk localized PCa, brachytherapy + supplemental external irradiation (61) or neoadjuvant hormonal treatment (62) may be considered. The optimum dose of supplemental EBRT is unclear. A randomized trial comparing 44 Gy versus 20 Gy of EBRT + palladium-103 brachytherapy closed early, showing no difference in the biochemical outcomes (63).

Non-permanent transperineal interstitial prostate brachytherapy using a high-dose-rate iridium-192 stepping source and a remote afterloading technique can be applied with a total dose of 12-20 Gy in two to four fractions, combined with fractionated external radiotherapy of 45 Gy (64). Higher doses of supplemental EBRT than this may best be delivered with IMRT, as supported by a report from the Memorial Sloan-Kettering Cancer Center indicating that this approach is safe and feasible (65).

Recent data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) (66). In a retrospective analysis of modern series (67,68), BDFS rates of 85.8%, 80.3% and 67.8% in men with low-risk, intermediate-risk, and high-risk PCa, respectively, were reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar with high-dose EBRT and high-dose-rate (HDR) brachytherapy in terms of diarrhoea and insomnia (69). However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs 34%). A single randomized trial of EBRT versus EBRT + HDR brachytherapy has been reported (70). A total of 220 patients with organ-confined PCa were randomized to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the BDFR ( $p = 0.03$ ). There were no differences in the rates of late toxicity. Patients randomly assigned to EBRT + brachytherapy had a significantly better QoL as measured by their Functional Assessment of Cancer Therapy-Prostate (FACT-P) score at 12 weeks. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to the uncommon fractionation used (70). There is still a need to compare dose-escalated EBRT + hormone therapy with the same followed by a brachytherapy boost in intermediate-risk and high-risk patients.

For T1-2 N0 M0 disease, the 5-year BDFR are similar for permanent seed implantation, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and radical prostatectomy, according to a study of 2991 patients diagnosed with T1-2 consecutive localized PCa treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Center, with a minimum follow-up period of 1 year (66).

## 10.6 Late toxicity

Patients must be informed about the potential for late genitourinary or gastrointestinal toxicity and the impact of irradiation on erectile function. Late toxicity was analyzed using a dose of 70 Gy in a prospective EORTC randomized trial 22863 (1987-1995) (71), in which 90% of patients had stage T3-4. A total of 377 patients (91%) out of 415 enrolled were evaluable for long-term toxicity, which was graded according to a modified RTOG scale. Eighty-six patients (22.8%) had grade  $\geq 2$  urinary or intestinal complications or leg oedema, 72 of whom had grade 2 (moderate) toxicity, while 10 had grade 3 (severe) toxicity and four died due to grade 4 (fatal) toxicity. Although four (1%) late treatment-related deaths occurred, the long-term toxicity was limited, with a grade 3 or 4 late complication rate of less than 5% being reported (Table 10.1). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT and IMRT.

**Table 10.1: Incidence of late toxicity by Radiation Therapy Oncology Group (RTOG) grade (from EORTC trial 22863)**

Toxicity	Grade 2		Grade 3		Grade 4		Any significant toxicity ( $\geq$ grade 2)	
	n	%	n	%	n	%	n	%
Cystitis	18	4.7	2	0.5	0	0	20	5.3
Haematuria	18	4.7	0	0	0	0	18	4.7
Urinary stricture	18	4.7	5	1.3	4	1	27	7.1
Urinary incontinence	18	4.7	2	0.5	0	0	20	5.3
<b>Overall GU toxicity</b>	<b>47</b>	<b>12.4</b>	<b>9</b>	<b>2.3</b>	<b>4<sup>†</sup></b>	<b>1<sup>†</sup></b>	<b>60</b>	<b>15.9</b>
Proctitis	31	8.2	0	0	0	0	31	8.2
Chronic diarrhoea	14	3.7	0	0	0	0	14	3.7
Small bowel obstruction	1	0.2	1	0.2	0	0	2	0.5
<b>Overall GI toxicity</b>	<b>36</b>	<b>9.5</b>	<b>1</b>	<b>0.2</b>	<b>0</b>	<b>0</b>	<b>37</b>	<b>9.8</b>
<b>Leg oedema</b>	<b>6</b>	<b>1.5</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>6</b>	<b>1.5</b>
<b>Overall toxicity*</b>	<b>72</b>	<b>19.0</b>	<b>10</b>	<b>2.7</b>	<b>4</b>	<b>1</b>	<b>86</b>	<b>22.8</b>

GI = gastrointestinal; GU = genitourinary.

\* Overall toxicity included GU and GI toxicity and leg oedema. As most patients had more than one type of toxicity, the overall toxicity does not result from simple addition.

<sup>†</sup> Two of the grade 4 patients were irradiated with cobalt-60.

Note: there was no other significant ( $\geq$  grade 2) toxicity among patients irradiated with cobalt-60 ( $n = 15$ ), except for two patients with grade 4 GU (stated above) and only one patient with grade 2 GI toxicity.

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients (2). A recent meta-analysis has shown that the 1-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing radical prostatectomy, 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 (72).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (73,74). In a retrospective evaluation of 30,552 and 55,263 men, who had undergone either EBRT or RP, the risk of being diagnosed with rectal cancer increased by 1.7-fold in comparison with the surgery group (73). Another analysis (74) showed that the relative risk of developing bladder cancer increased by 2.34-fold in comparison with a healthy control population. On the other hand, a re-analysis of SEER data including more than 100,000 patients, demonstrated a risk of about 0.16% (i.e. 160 cases per 100,000 patients) of radiation-induced malignant tumours (75). The Memorial Sloan-Kettering Cancer Center group have also reported corresponding data on late toxicity from their experience in 1571 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 (76). Both acute gastrointestinal and genitourinary toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) grade 2 or more gastrointestinal toxicity was 5% with IMRT versus 13% with 3D-CRT. The incidence of grade 2 or higher late genitourinary toxicity was 20% in patients treated with 81 Gy versus 12% in patients treated with lower doses. The overall incidences of grade 3 toxicity were 1% for gastrointestinal toxicity and 3% for genitourinary toxicity. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity. However, interestingly, with dose escalation, genitourinary toxicity may become the predominant type of morbidity (76).

#### 10.6.1 Immediate (adjuvant) post-operative external irradiation after RP (Table 10.2)

Extracapsular invasion (pT3), Gleason score  $\geq 7$  and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after 5 years (77,78). Three prospective randomized trials have assessed the role of immediate post-operative radiotherapy (adjuvant radiotherapy, ART), as follows.

##### 10.6.1.1 EORTC 22911

EORTC 22911 (79), with a target sample size of 1005 patients, compared immediate post-operative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after retropubic RP. Immediate post-operative radiotherapy was well tolerated. Grade 4 toxicity was not observed. The rate of grade 3 genitourinary toxicity was 5.3% versus 2.5% in the observation group after 10 years. For patients younger than 70 years, the study concluded that immediate

post-operative radiotherapy after surgery significantly improved the 10-year biological PFS to 60.6% versus 41.1% in the observation group. A difference was observed in the clinical progression rates for the entire cohort that favoured ART after 5 years, but this trend was not sustained after 10 years. Locoregional control was better in the long-term follow-up at 10 years after immediate irradiation (hazard ratio [HR] = 0.45;  $p < 0.0001$ ). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after 10 years (HR = 0.69;  $p = 0.008$ ). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of ART was on the biochemical progression (HR reduced to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors (80,81).

#### 10.6.1.2 ARO trial

The most suitable candidates for immediate radiotherapy may be those with multifocal positive surgical margins and a Gleason score  $> 7$ . The conclusions of ARO trial 96-02 ( $n = 385$ ) appear to support those of the EORTC study. After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in BDFR of 72% versus 54%, respectively ( $p = 0.0015$ ). However, unlike other studies, and of major interest, the randomization of patients was carried out after they had achieved an undetectable PSA level following RP ( $< 0.1$  ng/mL) and only pT3 tumours were included. This result indicates that ART is effective, even in the setting of an undetectable PSA after RP and additional risk factors (81).

#### 10.6.1.3 SWOG 8794 trial

Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% versus 61% (median prolongation of 1.8 years,  $p = 0.016$ ) and a 10-year OS of 74% versus 66% (median: 1.9 years prolongation;  $p = 0.023$ ) (82).

#### 10.6.1.4 Conclusion

Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of  $< 0.1$  ng/mL, two options can be offered in the framework of informed consent. These are:

- Immediate ART to the surgical bed (79,81-83,86) after recovery of urinary function;
- or
- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL (84,85).

**Table 10.2: Overview of all three randomized trials for adjuvant radiation therapy after RP**

Reference	n	Inclusion criteria	Randomization	Definition of biochemical recurrence PSA (ng/mL)	Median follow-up (mo)	Biochemical progression-free survival (bNED)	Overall survival
<b>SWOG 8794</b> (83)	431	pT3 cN0 ± involved SM	60-64 Gy vs 'wait and see'	$> 0.4$	152	10 years: 53% vs 30% ( $p < 0.05$ )	10 years: 74% vs 66% Median time: 15.2 vs 13.3 years $p = 0.023$
<b>EORTC 22911</b> (79)	1005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs 'wait and see'	$> 0.2$	127	10 years: 60.6% vs 41% ( $p < 0.001$ )	81% vs 77% NS
<b>ARO 96-02</b> (81)	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs 'wait and see'	$> 0.05 +$ confirmation	54	5 years: 72% vs 54% ( $p = 0.015$ )	Not provided

NS = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

For delayed (salvage) post-operative external irradiation after radical prostatectomy see Chapter 19 - Treatment of PSA-only recurrence after treatment with curative intent.

## 10.7 Guidelines for definitive radiotherapy

	LE	GR
In localized prostate cancer, T1c-T2c N0 M0, 3D-CRT with or without IMRT, is recommended, even for young patients who decline surgical intervention.	1b	B
For high-risk patients, long-term ADT before and during radiotherapy is recommended, as it results in increased overall survival.	2a	B
In patients with locally advanced PCa (T3-4 N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.	1b	A
In patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.	2a	B
In patients with pathological tumour stage T3 N0 M0, immediate post-operative external irradiation after RP may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.	1b	A
In patients with locally advanced PCa T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.	1b	A
In a subset of patients with T2c-T3 N0-X and a Gleason score of 2-6, short-term ADT before and during radiotherapy can be recommended, as it may favourably influence the overall survival.	1b	A
In patients with very high-risk PCa c-pN1 M0, with no severe comorbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended, as it may improve the overall survival, disease-specific failure rate, metastatic failure rate, and biochemical control.	2b	B

ADT = androgen deprivation therapy; CRT = conformal radiotherapy; EBRT = external-beam radiation therapy; IMRT = intensity-modulated radiotherapy; PCa = prostate cancer; PSA = prostate-specific antigen; TURP = transurethral resection of prostate; WHO = World Health Organization.

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# 11. OPTIONS OTHER THAN SURGERY AND RADIOTHERAPY FOR THE PRIMARY TREATMENT OF LOCALIZED PROSTATE CANCER

## 11.1 Background

Besides radical prostatectomy (RP), external-beam radiation and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localized prostate cancer (PCa) (1-4). In this chapter, we will consider both whole gland and focal treatment, looking particularly at high-intensity focused ultrasound (HIFU) and cryosurgery (CSAP) as sufficient data are available to form the basis of some initial judgements on these latest additions to the management of PCa.

Other options - such as photodynamic therapy, radiofrequency ablation and electroporation, among others - are considered to be in the early phases of evaluation and will therefore not be discussed in this edition of the guidelines.

Both HIFU and CSAP have been developed as minimally invasive procedures with the aim of equivalent oncological safety with reduced toxicity.

## 11.2 CSAP

Cryosurgery uses freezing techniques to induce cell death by:

- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemia apoptosis (1-4).

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

### 11.2.1 Indication for CSAP

Patients who are potential candidates for CSAP are those who have organ-confined PCa and those identified as having minimal tumour extension beyond the prostate (1-3). The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobes under the pubic arch. Prostate-specific antigen (PSA) serum levels should be < 20 ng/mL, and the biopsy Gleason score should be ≤ 7. Potential candidates for CSAP are:

- patients with low-risk PCa (PSA < 10 ng/mL, < T2a, Gleason score ≤ 6) or intermediate-risk PCa (PSA > 10 ng/mL, or Gleason score ≤ 7, or stage > 2b) whose condition prohibits radiotherapy or surgery
- at the time of therapy, the size of the prostate should be < 40 mL; volume reduction may be achieved by androgen ablation.

It is important that patients with a life expectancy > 10 years should be fully informed that there are limited data on the long-term outcome for cancer control at 10 and 15 years.

### 11.2.2 Results of modern cryosurgery for PCa

The therapeutic results of cryotherapy have improved over time with the introduction of enhanced techniques such as gas-driven probes and transperineal probe placement, as used in third-generation cryosurgery (5-10).

An objective assessment of PSA outcome is not easily performed because some institutions use PSA values < 0.1 ng/mL as an indicator of therapeutic success, whereas others use the American Society of Therapeutic Radiology and Oncology (ASTRO) criteria, which require three consecutive increases in PSA level.

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, biochemical disease-free survival (BDFS) at five years is 60% and 36% for low-risk and high-risk patients, respectively (5,6).

Long et al. (5) have performed a retrospective analysis of the multicentre, pooled, CSAP results of 975 patients stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL at a mean follow-up of 24 months, the five-year actuarial BDFS rate was:

- 76% and 60%, respectively, for the low-risk group
- 71% and 45%, respectively, for the intermediate-risk group
- 61% and 36%, respectively, for the high-risk group.

According to a recent meta-analysis of 566 cryosurgery-related publications, there were no controlled trials, survival data or validated biochemical surrogate end-points available for analysis (11).

Cryosurgery showed progression-free survival (PFS) of 36-92% (projected one- to seven-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72-87% of cases, but no biopsy data were available for the currently used third-generation cryotherapy machines.

With regard to third-generation cryosurgery, clinical follow-up is short, with a 12-month PSA follow-up carried out in only 110/176 (63%) patients (5-10). Eighty of these (73%) patients still had a PSA nadir < 0.4 ng/mL, whereas 42/65 (64.6%) low-risk patients remained free from biochemical progression using the 0.4 ng/mL cut-off.

Longer follow-up has been reported by Bahn et al. (8), who have analysed the therapeutic results of 590 patients undergoing CSAP for clinically localized and locally advanced PCa. At a PSA cut-off level of < 0.5 ng/mL, the seven-year BDFS for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively. PSA nadir levels in 2,427 patients registered in the Cryo On-Line Data (COLD) Registry showed that a PSA nadir of 0.6 ng/mL or above was associated with significant risks of biochemical failure (29.5%, 46% and 54% in low-, intermediate- and high-risk groups, respectively) within the first two years (12).

In a randomized comparison between whole-gland cryotherapy and external-beam radiotherapy, no difference in 36 months of disease progression was observed at 100 months follow-up (13). Men in both arms of the study received three to six months of neoadjuvant androgen ablation therapy.

### 11.2.3 Complications of CSAP for primary treatment of PCa

Erectile dysfunction occurs in about 80% of patients and this remains a consistent complication of the CSAP procedure, independent of the generation of the system used (14). The complication rates described in third-generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% (5-10). The development of fistula is usually rare, being < 0.2% in modern series. About 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.

Quality of life and sexuality following CSAP were investigated in a clinical phase II trial that recruited 75 men (15). Quality-of-life analysis by the prostate-specific FACT-P questionnaire showed that most subscales return to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes were seen when comparing data at 36 months with those at 12 months. With regard to sexuality, 37% of men were able to have intercourse three years after CSAP.

In a recent, prospective, randomized clinical trial, 244 men with newly diagnosed organ-confined PCa were randomized to receive either external-beam radiation therapy (EBRT) or to undergo CSAP (16). After a follow-up of three years, sexual function was significantly less impaired in the EBRT group.

## 11.3 HIFU of the prostate

HIFU consists of focused ultrasound waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation (17). The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis.

HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position.

The procedure is time-consuming, with about 10 g prostate tissue treated per hour. In a 2006 review, 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters (11). No controlled trial was available for analysis, and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy. Potential candidates are patients with low to moderate risk in investigational settings. The patient should be informed about the lack of long-term outcome data at > 10 years (see 11.4.2).

### 11.3.1 Results of HIFU in PCa

As with CSAP, various PSA thresholds are defined for biochemical cure, and no international consensus exists on objective response criteria. The Stuttgart criteria (> PSA nadir + 1.2 ng/mL) have been proposed to define biochemical recurrence after HIFU treatment (18). As a consequence of the lower PSA cut-off for recurrence than in the Phoenix criteria (PSA nadir + 2 ng/mL), the outcome may be approximately 10% lower using the Stuttgart criteria than the Phoenix criteria (19). According to the review mentioned above (11), HIFU showed PFS (based on PSA ± biopsy data) of 63-87% (projected three- to five-year data), but median follow-up in the studies ranged from 12-24 months only.



In one of the largest single-centre studies, 227 patients with clinically organ-confined PCa were treated with HIFU, and their outcome data were analysed after a mean follow-up of 27 months (range: 12-121 months) (20) (see Table 9.1). The projected five-year BDFS was 66%, or only 57% if patients had exhibited a pre-therapeutic PSA value of 4-10 ng/mL. Incontinence and bladder neck stricture decreased over time from 28% and 31%, respectively, to 9% and 6%, respectively. In another study (21), a significant decrease in pre-treatment PSA serum levels from 12 ng/mL to 2.4 ng/mL was observed. However, 50% of the 14 patients demonstrated positive prostate biopsies during follow-up. In a third study (22), a complete response rate (i.e. PSA < 4 ng/mL) and six negative biopsies were achieved in 56% of the patients.

From a single centre, the eight-year BDFS rates (Phoenix definition) were 76%, 63%, and 57% for low-, intermediate-, and high-risk patients, respectively ( $p < 0.001$ ) after whole-gland treatment. At 10 years, the PCa-specific survival rate and metastasis-free survival rate (MFSR) were 97% and 94%, respectively (23).

Thüroff et al. (22) have summarized the efficacy results of a European multicentre study comprising the data of 559 patients with mainly low- and intermediate-risk PCa, and have reported a negative biopsy rate of 87.2% in 288 men with a follow-up of at least six months. A PSA nadir after six months' follow-up could be determined in 212 patients, and was 1.8 ng/mL. However, following the initial procedure, it could be demonstrated that the PSA nadir might be reached in 12-18 months.

Blana et al. have reported the results of 146 patients undergoing HIFU with a mean follow-up of 22.5 months (24). The mean PSA level before treatment was 7.6 ng/mL; the PSA nadir achieved after three months was 0.07 ng/mL. However, after 22 months, the median PSA level was 0.15 ng/mL. Of the 137 men available for analysis, 93.4% demonstrated a negative control biopsy. The PSA nadir appeared to be strongly associated with treatment failure (25) ( $p < 0.001$ ). Patients with a PSA nadir of 0.0-0.2 ng/mL had a treatment failure rate of only 11% compared with 46% in patients with a PSA nadir of 0.21-1.00 ng/mL, and 48% with a PSA nadir of >1.0 ng/mL. Recently, the group has updated its results, with a total of 163 men treated for clinically organ-confined PCa. Within the  $4.8 \pm 1.2$  years of follow-up, the actuarial DFS rate at five years was 66%, with salvage treatment initiated in 12% of patients (26).

In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU (27). Biochemical failure was defined as the PSA nadir + 2 ng/mL, according to the Phoenix guidelines with regard to radiotherapy. After a median follow-up of 24 months, the BDFS was 72% for the entire cohort. The BDFS in patients with stage T1c, T2a, T2b, T2c and T3 groups at five years was 74%, 79%, 72%, 24% and 33%, respectively ( $p < 0.0001$ ). The BDFS in patients in the low-, intermediate- and high-risk groups at five years was 84%, 64% and 45%, respectively ( $p < 0.0001$ ). The BDFS in patients treated with or without neoadjuvant hormonal therapy at seven years was 73% and 53% ( $p < 0.0001$ ), respectively. Post-operative erectile dysfunction was noted in 33 out of 114 (28.9%) patients who were pre-operatively potent.

In a retrospective study, 137 patients with PCa underwent HIFU (28). After a median follow-up of 36 months, 22% of the patients relapsed according to the Phoenix criteria. The five-year DFS rate was 78% based on these criteria, and 91%, 81% and 62% in the low-, intermediate- and high-risk groups, respectively. Urge incontinence (16 cases) and dysuria (33 cases) occurred after removal of the urethral catheter in 11.8% and 24.1%, respectively.

To evaluate whether the location (apex/mid-gland/base) of PCa influences the risk of incomplete transrectal HIFU ablation, Boutier et al. (29) analysed 99 patients who underwent PCa HIFU ablation (Ablatherm; EDAP, Vaulx-en-Velin, France) with a 6 mm safety margin at the apex, and had systematic biopsies at three to six months after treatment. After treatment, residual cancer was found in 36 patients (36.4%) and 50 sextants (8.4%); 30 (60%) positive sextants were in the apex, 12 (24%) in the mid-gland, and eight (16%) in the base. Statistical analysis showed that the mean (95% CI) probability for a sextant to remain positive after HIFU ablation was 8.8% (3.5-20.3%) in the base, 12.7% (5.8-25.9%) in the mid-gland, and 41.7% (27.2-57.89%) in the apex. When a 6 mm apical safety margin was used, treatment-associated side-effects, especially incontinence and erectile dysfunction, were fewer but residual cancer after HIFU ablation was significantly more frequent in the apex.

Komura et al. (30) have analysed the oncological outcome in 144 patients with T1/T2 PCa and a median follow-up of 47 (2-70) months. Thirty-nine percent of patients relapsed and approximately 40% developed a clinical or subclinical urethral stricture post-operatively. Most interestingly, the five-year DFS was significantly better in those with a stricture than in those without (78.2% vs 47.8%,  $p < 0.001$ ), indicating the need for more aggressive treatment, especially at the apex of the prostate. Crouzet et al. (23) published the results of 1,002 men treated with whole-gland HIFU with a median follow up of 6.4 years. PCa-specific survival and metastasis-free survival at 10 years were 97% and 94%, respectively. Overall, 37.1% of men received any form of salvage treatment.



**Table 9.1: Summary of studies examining the use of HIFU in PCa**

Study (reference no.)	n	Median follow-up	Outcome measure
Blana et al. 2004 (24)	137	22.5 mo	87% PSA < 1 at follow-up
Poissonnier et al. 2007 (20)	227	27 mo	66% biochemical recurrence-free at 5 y
Crouzet et al. 2013 (23)	1,002	6.4 y	76%, 63% and 57% biochemical recurrence-free (Phoenix) for low-, intermediate- and high-risk disease, respectively DFS at 10 y: 97%; metastasis-free: 94%
Thüroff et al. 2003 (22)	559	6 mo	87% biopsy negative at 6 mo
Uchida et al. 2009 (27)	517	24 mo	72% biochemical recurrence-free (Phoenix)
Inoue et al. 2011 (28)	137	36 mo	78% biochemical recurrence-free (Phoenix)
Boutier et al. 2011 (29)	99	6 mo	64% biopsy tumour-free
Komura et al. 2011 (30)	144	47 mo	61% biochemical recurrence-free (Phoenix)
Thüroff and Chaussy 2013 (31)	704	5.3 y	60%, biochemical recurrence-free (Phoenix) at 10 y 99% DFS at 10 y; 95% metastasis-free at 10 y
Pfeiffer et al. 2012 (32)	191	53 mo	85%, 65% and 55% biochemical-free survival rate (Stuttgart) for low-, intermediate- and high-risk disease, respectively
Pinthus et al. 2012 (33)	402	24 mo	68% biochemical recurrence-free (Stuttgart) at 4 y

DFS = disease-free survival; n = number of patients; PSA = prostate-specific antigen.

### 11.3.2 Complications of HIFU

Urinary retention appears to be one of the most common side-effects of HIFU, developing in almost all patients, with the mean interval of catheterization via a suprapubic tube varying from between 12 and 35 days (17,20,21). Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common, and is sometimes even performed at the time of HIFU. Post-operative impotence occurs in 55-70% of patients.

Elterman et al. (34) have treated 95 patients with clinically organ-confined PCa using the Sonablate 500 device (SonaCare Medical, Charlotte, NC, USA) and have evaluated the type and frequency of treatment-associated complications. With a minimum follow-up of six months, 17% (7/41) of the men had significant incontinence, and 2% developed significant erectile dysfunction. Early and late subvesical obstruction necessitating surgical treatment occurred in 17 (17.9%) and 20 (21.1%) patients, respectively.

Moderate to severe stress urinary incontinence was rare, occurring in fewer than 6.4% of men, and decreased in more recent treatment to 3.1% (23). Acute urinary retention was seen in 7.6% of men. Even in more recent treatment, the rate of urethral-rectal fistula was 0.7%.

## 11.4 Focal therapy of PCa

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease (35-37).

Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU or photodynamic therapy, electroporation, focal radiotherapy by brachytherapy, or CyberKnife Robotic Radiosurgery System technology (Accuray Inc., Sunnyvale, CA, USA). The main purpose of focal therapy is to limit treatment toxicity in patients that could benefit from local disease control (38-40).

### 11.4.1 Pre-therapeutic assessment of patients

The high number of random and systematic errors associated with TRUS-guided random biopsy regimens means that this procedure is not sufficiently accurate for selecting candidates for focal therapy. Perineal biopsy or magnetic resonance imaging (MRI) may be useful tools. For characterizing men considering focal therapy, transperineal prostate biopsy using a template-guided approach is recommended (41-43). When used with a 5 mm sampling frame, this approach can rule in or out PCa foci with volumes of 0.5 mL and 0.2 mL with 90% certainty (44). Thus, the exact anatomical localization of the index lesion - defined as the biologically most aggressive - can be accurately determined.

#### 11.4.2 Patient selection for focal therapy

The primary objective of treatment must be the eradication of measurable and biologically aggressive disease with minimal toxicity. However, although treatment is usually intended to be a single session, patients should know that further treatment might be necessary in the future. Standardized follow-up schedules and retreatment indications are currently non-existent.

Based on published data, the following criteria identify possible candidates for currently ongoing trials of focal treatment:

- candidates for focal therapy should ideally undergo transperineal template mapping biopsies; multifunctional MRI with or without TRUS biopsy may be an option in the hands of experts;
- focal therapy should be limited to patients with a low to moderate risk in investigational settings; retrospective data have shown the presence of grade I-III toxicity in 13% of cases (45);
- patients should be counselled with caution because no data on functional and oncological outcomes are available;
- patients must be informed that:
  1. the therapy is investigational;
  2. the long-term consequences are unknown;
  3. the optimal method for follow-up and the criteria for salvage therapy are not clear;
  4. focal therapy is not without toxicity.

Early reports suggest the feasibility of MRI-guided focal salvage cryotherapy after local radiotherapy (46) and focal electroporation (47).

### 11.5 Conclusions and recommendations for experimental therapeutic options to treat clinically localized PCa

Conclusions	LE
HIFU has been shown to have a therapeutic effect in low-stage PCa, but prospective randomized comparison studies are not available.	3
Cryotherapy for PCa compares unfavourably with external-beam radiation for the preservation of sexual function.	2
PSA nadir values after ablative therapies may have prognostic value.	3
Focal therapy of any sort is investigational, and the follow-up and retreatment criteria are unclear.	3
HIFU treatment for localized PCa results in mild to moderate urine incontinence in less than 20% of men.	

Recommendations	GR
In patients who are unfit for surgery or radiotherapy, CSAP can be an alternative treatment for PCa.	C
If HIFU is offered, the lack of long-term comparative outcome data (> 10 y) should be discussed with the patient.	C
Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A

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## 12. HORMONAL THERAPY; RATIONALE AND AVAILABLE DRUGS

### 12.1 Introduction

Since Huggins and Hodges (1), androgen-suppressing strategies have become the mainstay of management of advanced PCa (2). More recently, there has been a move towards the increasing use of hormonal treatment in earlier disease (i.e. non-metastatic) or recurrent disease after definitive treatment, either as single-agent therapy or as a part of a multimodal approach.

#### 12.1.1 Basics of hormonal control of the prostate

Prostate cells are physiologically dependent on androgens to stimulate growth, function and proliferation. Testosterone, although not tumorigenic, is essential for the growth and perpetuation of tumour cells (3). The testes are the source of most androgens, with adrenal biosynthesis providing only 5-10% of androgens (i.e. androstenedione, dihydroepiandrosterone and dihydroepiandrosterone sulphate).

Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. Hypothalamic luteinizing hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Luteinizing hormone stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cell, testosterone is converted to 5- $\alpha$ -dihydrotestosterone (DHT) by the enzyme 5- $\alpha$ -reductase; DHT is an androgenic stimulant about 10 times more powerful than testosterone. Meanwhile, circulating testosterone is peripherally aromatized and converted to oestrogens, which together with circulating androgens, exert a negative feedback control on hypothalamic LH secretion.

If prostate cells are deprived of androgenic stimulation, they undergo apoptosis (programmed cell death). Any treatment that results ultimately in suppression of androgen activity is referred to as androgen deprivation therapy (ADT).

#### 12.1.2 Different types of hormonal therapy

ADT can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor using competing compounds known as anti-androgens. In addition, these two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB).

### 12.2 Testosterone-lowering therapy (castration)

#### 12.2.1 Castration level

Surgical castration is still considered the 'gold standard' for ADT, against which all other treatments are rated. It leads to a considerable decline in testosterone levels and induces a hypogonadal status, known as the 'castration level'.

The standard castrate level is < 50 ng/dL. It was defined more than 40 years ago, when testosterone level testing was limited. Current testing methods using chemiluminescence have found that the mean value of testosterone after surgical castration is 15 ng/dL (4) (LE: 2). This has led to a revisiting of the current definition of castration, with a more appropriate level defined as below 20 ng/dL (1 nmol/L).



### 12.2.2 **Bilateral orchiectomy**

Bilateral orchiectomy, which is either total or subcapsular pulpectomy is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia (5) and is the quickest way to achieve a castration level, usually within less than 12 hours.

Its main drawback is its negative psychological effect: some men consider it to be an unacceptable assault on their manhood. In addition, it is irreversible and does not allow for intermittent treatment.

## 12.3 **Oestrogens**

Oestrogens have several mechanisms of action such as:

- down-regulation of LHRH secretion;
- androgen inactivation;
- direct suppression of Leydig cell function.

There is still a special interest in using oestrogens to treat PCa because the resultant testosterone suppression is not associated with bone loss and cognitive decline (6) (LE: 3). Furthermore, their use in castrate-refractory PCa is associated with a PSA response as high as 86% of patients.

### 12.3.1 **Diethylstilboesterol (DES)**

Diethylstilboesterol (DES) was the most commonly used oral oestrogen in PCa. Early studies by the Veterans Administration (VACURG) tested DES at 5 mg/day. This dosage was associated with high cardiovascular morbidity and mortality, which was secondary to first-pass hepatic metabolism and the formation of thrombogenic metabolites. Lower doses of 1 mg/day and 3 mg/day were therefore tested. Both were found to be as effective as bilateral orchiectomy (7) (LE: 1a). However the side-effects were still significantly greater than with castration.

### 12.3.2 **Strategies to counteract the cardiotoxicity of oestrogen therapy**

Two strategies have been attempted to neutralize the oestrogen cardiotoxicity. However, the results were ineffective and have therefore precluded oestrogen as a standard first-line treatment. The strategies attempted were:

- parenteral route. The aim was to avoid first-pass hepatic metabolism: The Scandinavian Prostatic Cancer Group Study 5 compared a parenteral oestrogen (polyoestradiol phosphate) with CAB. No difference was observed in survival. However a significantly higher incidence of non-fatal cardiovascular events was observed in the oestrogen-treated group (8).
- concomitant use of cardiovascular-protective agents. The use of either warfarin sodium, 1 mg/day, or aspirin, 75-100 mg/day in combination with DES, 1 mg/day or 3 mg/day, did not suppress the thromboembolic complications associated with DES (9,10).

## 12.4 **LHRH agonists**

Long-acting LHRH agonists are currently the main forms of ADT. They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH leading to the 'testosterone surge' or 'flare-up' phenomenon, which begins 2-3 days later and lasts for about 1 week. The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection. It is important to follow the directions carefully for using a particular drug to avoid any misuse.

### 12.4.1 **Achievement of castration levels**

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. The castration level is usually obtained within 2-4 weeks (11). However, about 10% of treated patients fail to achieve castration levels (12), which rise to 15% if the castration threshold is defined as 20 ng/dL.

When 2-year survival is the target outcome, LHRH agonists have a similar efficacy compared to orchiectomy or DES (8) (LE: 1a). This finding raises the question about the clinical impact of changing the definition of the castrate testosterone level from 50 ng/dL to 20 ng/dL. In addition, although only based on indirect comparison, the LHRH agonists seemed equally effective whatever their formulation (7) (LE: 3).

### 12.4.2 **Flare-up phenomenon**

The 'flare phenomenon' might lead to detrimental effects such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and fatal cardiovascular events due to hypercoagulation status.



Clinical flare needs to be distinguished from the biochemical flare and even from asymptomatic radiographic evidence of progression (13). Patients at risk are usually those with high-volume, symptomatic, bony disease, which account for only 4-10% of M1 patients. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely suppress the risk.

Some testosterone mini-flares have also been observed with the LHRH agonists. The clinical impact might be associated with a negative impact on overall survival (see Chapter 19).

## 12.5 LHRH antagonists

LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. This seems to be a more desirable mechanism of action and has made LHRH antagonists very attractive to use. However, the practical shortcoming of these compounds is the lack of a long-acting depot formulation.

### 12.5.1 *Abarelix*

Abarelix was as effective as LHRH agonists in achieving and maintaining castration levels of testosterone and in reducing serum PSA, without any biochemical 'flare up' phenomenon in the abarelix arm (14,15). However, based on prolonged analysis, the FDA has issued a warning about allergic reactions with the long-term use of abarelix, which has resulted in suspension of its further development. It is however licensed in metastatic and symptomatic PCa, for which no other treatment option is available, or as a short-term induction modality.

### 12.5.2 *Degarelix*

Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. The standard dosage of degarelix is 240 mg in the first month, followed by 80 mg monthly injections. More than 95% of patients have achieved a castrate level at day 3, associated with a rapid decline in PSA (as early as day 14). No allergic reaction was observed. Its main specific side-effect is a somewhat painful injection (moderate or mild) reported by 40% of patients, mainly after the first injection. An extended follow-up has been published (median 27.5 months), suggesting that degarelix might result in better progression-free survival compared to monthly leuporelin (16). Overall, this new family of LHRH antagonists seems appealing, but its definitive superiority over the LHRH analogues remains to be proven. Their use is limited by a monthly formulation.

## 12.6 Anti-androgens

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

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

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

### 12.6.1 *Steroidal anti-androgens*

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side-effects are loss of libido and erectile dysfunction, while gynaecomastia is quite rare. The non-pharmacological side-effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

#### 12.6.1.1 *Cyproterone acetate (CPA)*

Cyproterone acetate was the first anti-androgen to be licensed. However, it is the least studied. Its most effective dose in 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. There has been only one randomized trial (17) comparing CPA with standard medical castration, suggesting a poorer OS compared to LHRH analogues. Although there are other studies in CPA monotherapy, methodological limitations prevent firm conclusions.

The EORTC reported a monotherapy comparison with flutamide in metastatic PCa. No difference in cancer-specific survival and OS at a median follow-up of 8.6 years was observed, although the study was underpowered (18) (LE: 1b).

#### 12.6.1.2 *Megestrol acetate and medroxyprogesterone acetate*

Very limited information is available on these two compounds. But the overall poor efficacy (22) has prevented them from being recommended for either primary- or second-line hormonal therapy.

### 12.6.2 **Non-steroidal anti-androgens**

The use of non-steroidal anti-androgens as monotherapy has been promoted on the basis of improved quality of life (QoL) and compliance compared to castration. They do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are preserved (23). Although they have not been directly compared, the severity of androgen pharmacological side-effects, namely gynaecomastia, breast pain and hot flashes, appears similar for the three available non-steroidal anti-androgens. However, there are differences in non-androgen pharmacological side-effects, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide (19). All three agents share a common liver toxicity (occasionally fatal) and liver enzymes must be monitored regularly.

#### 12.6.2.1 *Nilutamide*

There are no comparative trials of nilutamide monotherapy with castration. Non-androgen pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, and specifically interstitial pneumonitis. Even if exceptional, interstitial pneumonitis is potentially life-threatening. Nilutamide is not licensed for monotherapy.

#### 12.6.2.2 *Flutamide*

Flutamide was the first non-steroidal anti-androgen available for clinical use. Although it has been studied as monotherapy for more than 20 years, there are no dose-finding studies against a currently accepted end-point (e.g. PSA response). Flutamide is a pro-drug, and the half-life of the active metabolite is 5-6 hours, so it must be administered three times daily. The recommended daily dosage is 750 mg. The non-androgen pharmacological side-effect of flutamide is diarrhoea.

#### 12.6.2.3 *Bicalutamide*

It is the most studied and used non-steroidal antiandrogen. The dosage licensed for use in CAB is 50 mg/day, and 150 mg dosage for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens (20,21), prophylactic radiotherapy (22), or surgical mastectomy. However, bicalutamide clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists (23,24).

## 12.7 **New compounds**

During castration, the occurrence of castration-resistant status (CRPC) is systematic. It is thought that it is mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see Chapter 20). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells, and an over-expression of the AR has been observed in CRPC, suggesting an adaptative mechanism (25). This has led to the development of two new major compounds targeting the androgen axis: abiraterone acetate and enzalutamide.

### 12.7.1 **Abiraterone acetate**

Abiraterone acetate (AA) is a CYP17 inhibitor (a combination of 17 hydrolase and a 17-20 lyase inhibition). It represents an improvement over ketokonazole, which is no longer available. By blocking CYP 17, AA significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level as inside the cancer cells (intracrine mechanism). Another compound targeting the 17-20 lyase is under development (orteronel).

### 12.7.2 **Enzalutamide**

Enzalutamide (previously known as MDV 3100) is a novel anti-androgen with a higher affinity than bicalutamide for the AR receptor. While non-steroidal anti-androgens still allow transfer of ARs to the nucleus, enzalutamide blocks AR transfer and therefore suppresses any possible agonist-like activity.

Both drugs have been first developed for use in CRPC after docetaxel. Both drugs have resulted in a significant overall improvement in survival (26,27). Detailed results are presented in Chapter 20.

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## 12.9 Side-effects, QoL and cost of hormonal therapy

The many deleterious side-effects of long-term ADT have been well known for years. As the use of ADT increases, it is increasingly important to consider these side-effects. A systematic review of the side-effects of long-term ADT has been recently published (1).

### 12.9.1 Sexual function

Loss of libido and erectile dysfunction are well-known side-effects of ADT. The management of acquired erectile dysfunction is mostly non-specific (2).

### 12.9.2 Hot flashes

Hot flashes are probably the most common side-effect of ADT. They appear 3 months after starting ADT, usually persist long term and have a significant impact on QoL. Treatments include hormonal therapy and antidepressants.

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flashes. Both treatments carry a risk of cardiovascular complications. Soya phytoestrogens have shown an efficacy in breast cancer patients, but have not been evaluated in men. Progesterone-based treatments have demonstrated efficacy with 80% of patients showing an improvement (3).

Antidepressants such as serotonin reuptake inhibitors (e.g. venlafaxine or sertraline) appear to be effective for hot flashes in men, but are not as effective as hormonal therapies. A randomized trial compared an antidepressant, venlafaxine, 75 mg daily, with the hormonal therapies, medroxyprogesterone, 20 mg daily, and CPA, 100 mg daily (4). After 6 months of LHRH (n=919), 311 men had significant hot flushes and were randomized to one of the treatments. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

Other treatments have been tested, including clonidine, vernalipride, gabapentine 900 mg daily (5), and acupuncture (6). With a placebo effect influencing up to 30% of patients (7), only the results from large, prospective, randomized, controlled trials should be considered, but these trials are still lacking.

### 12.9.3 Other systemic side-effects of ADT

Other systemic side-effects have been described and require increased attention, including bone problems, obesity and sarcopenia, lipid alterations and insulin resistance, metabolic syndrome, diabetes and cardiovascular disease.

### 12.9.3.1 Non-metastatic bone fractures

ADT increases the risk of non-metastatic bone fracture due to increased bone turnover and decreased BMD in a time-dependent manner, leading to an increased risk of fracture (up to 45% relative risk with long-term ADT [8]). Hip fractures in men are associated with a significant risk of death (9). Increased exercise, calcium and vitamin D supplementation are bone protective.

Bicalutamide monotherapy could be a bone-protective treatment based on two, small, prospective trials (10,11) (LE: 1b). The main drawback of this type of treatment is its limited efficacy (see Chapter 13 - Metastatic Prostate Cancer - Hormonal Therapy).

#### Bisphosphonates

Bisphosphonates, such as pamidronate, alendronate or zoledronic acid, have been shown to increase BMD in the hip and spine by up to 7% in 1 year. It is unclear whether an injection given every 3 months (12) or annually (13) is the optimal regimen for zoledronic acid. The optimal regimen is important because of the risk of jaw necrosis, which may be both dose- and time-related (14). The patient's initial BMD can be used to guide the choice of regimen (15). Thus, 3-month injections might be given to osteoporotic patients for whom a yearly injection is unlikely to provide sufficient protection.

In contrast to breast cancer, a significant benefit in OS has only been demonstrated in PCa for the oral first-generation clodronate versus placebo. In a post-hoc analysis, an absolute 8% increase in OS after 8 years of follow-up (16) was found only in M1 patients, but not in M0 patients. This result was surprising because clodronate has no bone-protective effect in PCa. This benefit has never been observed with more recent bisphosphonates.

#### Denosumab

In 2009, a major advance in bone protection was made with the introduction of denosumab, a fully human monoclonal antibody against RANKL. A total of 1468 men with non-metastatic PCa receiving ADT were randomized to denosumab, 60 mg subcutaneous every 6 months, or placebo (17). The primary end-point was the percentage change in lumbar spine BMD at 2 years. Denosumab was associated with 5.6% increase in the lumbar BMD versus 1% decrease in the placebo arm and a decrease in the vertebral fracture rate compared to the placebo-treated group (1.5% vs 3.9%,  $p = 0.006$ ). The bone-protective 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. Denosumab may therefore represent a major advance in bone protection.

Denosumab was shown to postpone bone metastases by 4.2 months in non-metastatic patients in a large RCT of 1432 patients at a higher dosage of 120 mg every 4 weeks (18). There was no impact on OS and side-effects were significant. These results highlight the importance of targeting the bone microenvironment. However, the daily use of a high-dosage regimen is questionable because of the significant side-effects and higher economic cost.

#### Bone-targeted lifestyle changes before starting long-term ADT

Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption, and to normalize their body mass index (BMI). Calcium and vitamin D supplements should be considered if low values of calcium and vitamin D are detected. (Normal values are calcium, 2.2-2.6 nmol/L, and vitamin D, 100-160 nmol/L). A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry 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>) can be used to evaluate individual risk.

#### Obesity and sarcopenia

Obesity and sarcopenia are common and often occur early during the first year of ADT. There is an expected increase in body fat mass by up to 10% and a decrease in lean tissue mass by up to 3% (19). Both changes are linked to an increased risk of fracture.

### 12.9.3.2 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment (19). ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. Once again, exercise is strongly recommended for its protective effect. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects (20), 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 (21):

- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure > 130/80 mmHg or use of medication for hypertension;
- 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 (22).

#### 12.9.3.3 Cardiovascular disease

Several studies showed that ADT, even after only 6 months or less duration, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction (23). Analysis of results from the RTOG 92-02 study confirmed an increase in cardiovascular risk, unrelated to the duration of ADT. However, this finding was not accompanied by an overall increased cardiovascular mortality (24). Similar results were observed in the RTOG 94-08 trial (25). No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 (26). However, an increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis (27).

These data resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations (28). However, to date, the data on cardiovascular mortality remain inconsistent. Preventive advice includes non-specific measures: loss of weight, increased exercise, improved nutrition and smoking cessation.

#### 12.9.3.4 Fatigue

Fatigue often develops as a side-effect of ADT. Exercise appears to be the best protective measure against fatigue (29,30). It should be noted that regular exercise also has other significant positive effects, including on bone health, cognition and possibly metabolic syndrome.

Anaemia may be a cause of fatigue, even if the anaemia is asymptomatic. Anaemia can be treated with erythropoiesis-stimulating agents taking into account the possible increased risk of thrombovascular events (1). Regular blood transfusion is required if severe anaemia is present.

## 12.10 Quality of life (QoL)

There is a lack of data on the effects of hormonal treatment on QoL, with only a single, large, prospective, RCT available. The study compared orchiectomy + flutamide versus orchiectomy + placebo in 739 patients with M1 PCa. Combined therapy resulted in a lower QoL in the first 6 months, with statistically significant differences in two QoL parameters, namely more frequent diarrhoea and worse emotional functioning, compared with castration alone (31).

In addition, there has been a small RCT, which evaluated the health-related quality of life (HRQoL) at 1-year follow-up in patients with non-localized PCa, who had been randomized to leuporelin, goserelin, CPA, or no treatment. Both sexual and cognitive function significantly declined in men on all forms of androgen suppression, while emotional distress significantly increased in those assigned to CPA or no treatment (32).

A prospective, non-randomized, observational study, which included 144 patients with non-metastatic PCa, found that immediate ADT (using bilateral orchiectomy, LHRH agonist or CAB) was associated with a lower overall QoL (increased fatigue, emotional distress, and decreased physical functioning) compared to deferred treatment (33). Another retrospective, non-randomized study with 431 patients assessed HRQoL outcomes at 12-months' follow-up after either orchiectomy or LHRH agonists as their primary therapy. 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 did orchiectomized patients. The stage at diagnosis had no significant independent effect on health outcome. However, the study was underpowered (34).

QoL has been evaluated with bicalutamide monotherapy using a specific non-validated questionnaire. At 12 months, bicalutamide showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) (35). A further post-hoc analysis, including only patients with sexual interest at study entry, found that bicalutamide was associated with better sexual preservation compared to castration, including maintained sexual interest, feeling sexually attractive (36), preserved libido and erectile function (37). Intermittent androgen deprivation has been discussed elsewhere (see Chapter 13 - Metastatic Prostate Cancer - Hormonal therapy).



The most common side-effects during non-steroidal anti-androgen monotherapy are gynaecomastia and breast pain, which are caused by an imbalance in the androgen-to-oestrogen ratio within breast tissue. In bicalutamide studies, these events were reported by up to 66% and 73% of patients, respectively, and may lead to treatment cessation in 16.4% of patients.

### 12.11 Cost-effectiveness of hormonal therapy options

A formal meta-analysis and literature review evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa (e.g. bilateral orchiectomy, DES, LHRH-agonist, non-steroidal anti-androgen monotherapy, and CAB using non-steroidal anti-androgens). For the analysis, a sophisticated statistical model was generated. This model assumed that the base case at entry was a 65-year-old man with clinically evident local recurrence of PCa and no distant metastases, who was then followed up for 20 years. The study concluded that, for men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT, providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits for a high relative cost. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred (38). Finally, once ADT is started, if a major response is obtained (see Chapter 13 - Metastatic Prostate Cancer), then IAD might be a useful way to lower treatment costs.

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## 13. METASTATIC PROSTATE CANCER

### 13.1 Introduction

A systematic review of ADT in prostate cancer (PCa) has been recently published (1). In this chapter, we will only review patients with metastatic disease, the use of IAD, and ADT monotherapy in the locally advanced situation. The combination of ADT with radiotherapy will be discussed in Chapter 10 and salvage ADT after surgery or at relapse in Chapter 19.

### 13.2 Prognostic factors

The M1 population is heterogeneous, with the most convincing data on prognosis produced by the large SWOG 8894 trial.

Previously, patients with nodal metastases or pelvic and axial bone metastases were classified as having minimal disease with a median survival of 58 months. Patients with visceral metastases or appendicular

bone metastases had more serious disease with median survival of 30 months (2). An updated more accurate classification (3) discriminates patients into three groups (Table 13.1).

It has been suggested that the PSA response to treatment is a prognostic factor. A short PSA-half time (< 1 month) is considered as a poor prognostic factor, although this requires further evaluation (4). In contrast, it is considered that the PSA level after 7 months of ADT may be an effective prognostic factor for survival. Thus, after 7 months of ADT, the median survival is 75 months if the PSA level < 0.2 ng/mL, 44 months if the PSA < 4 ng/mL and only 13 months if the PSA is > 4 ng/mL (5). Although these predictions are based on data from the large SWOG 9346 cohort, the prognostic use of PSA at 7 months of ADT still requires independent confirmation.

**Table 13.1: Prognostic factors for the heterogeneous M1 population for patients with advanced prostate cancer (3)**

Prognostic factors	Good	Intermediate	Poor
Axial bone metastasis and/or nodes	X		
Appendicular bone or visceral metastasis		X	X
Performance status < 1		X	
Performance status ≥ 1			X
Gleason score < 8	X		
Gleason score ≥ 8		X	
PSA < 65			X
PSA ≥ 65			X
Median survival (months)	54	30	21

PSA = prostate specific antigen.

### 13.3 First-line hormonal treatment

Primary ADT is the standard of care (1). There is no level 1 evidence to choose between an LHRH analogue or antagonist, except in patients with an impending spinal cord compression. In these patients, the choice for first-line treatment is between bilateral orchidectomy and an LHRH antagonist.

#### 13.3.1 Prevention of flare-up

Starting treatment with an LHRH analogue is likely to result in an initial testosterone flare, which can usually be prevented by starting an anti-androgen at the same time (6). Prevention of flare-up is important in symptomatic patients or when a clinical flare might lead to severe complications. The anti-androgen is usually continued for 4 weeks, though this duration is not based on evidence since there are no trials of the best regimen for preventing flare-up. In addition, the long-term impact of preventing flare-up is unknown (7).

### 13.4 Combination therapies

#### 13.4.1 Complete androgen blockade (CAB)

There are conflicting results from the many studies comparing CAB with monotherapy (6). The largest RCT in 1,286 M1b patients found no difference between surgical castration + flutamide compared to surgical castration without flutamide (2). Systematic reviews have shown that CAB using non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) versus monotherapy (surgical castration or LHRH agonists) (8, 9) beyond 5 years (10) (LE: 1a). However, some of the larger trials included in these reviews were methodologically flawed and it is unlikely that this small advantage, if any, is useful in daily clinical practice. LHRH analogues and NSAA have the highest estimated quality-adjusted survival. However, the use of CAB increases side effects and the economic cost. There is an incremental cost of more than US\$1 million per quality-adjusted life-year versus orchiectomy alone.

#### 13.4.2 Non-steroidal anti-androgen (NSAA) monotherapy

##### 13.4.2.1 Nilutamide

No comparative trial of nilutamide monotherapy is available. Nilutamide is not licensed for monotherapy.

##### 13.4.2.2 Flutamide

Apart from efficacy the main suggested advantage has been the preservation of sexual function. This was not confirmed in the EORTC trial 30892 (11); as few as 20% of men maintained sexual activity for up to 7 years. In the only published (underpowered) RCT, there was no significant difference in OS for flutamide monotherapy compared to castration in M1b patients with a PSA < 100 ng/mL (12). At a higher PSA level, flutamide was inferior to castration.

### 13.4.2.3 Bicalutamide

Bicalutamide, 150 mg once daily, has been compared to castration in two large prospective RCTs with similar designs, including a total of 1435 patients with locally advanced or M1 PCa (13). A pooled analysis showed:

- In M1 patients, OS was significantly better with castration, although the difference in median survival was only 6 weeks (13).
- In M0 patients (n = 480), no significant difference was observed in OS (14). Median survival was 63.5 months in the bicalutamide arm versus 69.9 months in the castration arm.

High-dose bicalutamide may be an alternative to castration for highly selected, well-informed patients with M1 PCa with a low PSA level (15) (LE: 1b). However, the expected benefit for QoL versus castration is far from proven.

### 13.4.3 Intermittent versus continuous ADT (IAD)

Long-term castration stimulates prostate cell apoptosis. After an average period of 24 months, the tumour relapses, characterized by a castrate-independent state of growth. Experimental data indicate that castrate-independent progression may begin early after castration, coinciding with the cessation of androgen-induced differentiation of stem cells (16). It has been suggested that stopping castration prior to progression would mean any subsequent tumour growth would be solely sustained by the proliferation of androgen-dependent stem cells. The stem cells should therefore be susceptible once again to androgen withdrawal. Thus IAD could delay the emergence of the androgen-independent clone. This rationale has been developed mainly through models (e.g. the Shionogi breast model), which may be significantly different to tumour behaviour in men. Other possible benefits of IAD include the preservation of QoL in off-treatment periods and a reduction in treatment cost.

An initial systematic review (17) concluded that IAD was feasible and accepted by patients. A similar conclusion has recently been made by two independent systematic reviews (18,19). The reviews were based on seven RCTs. Of the seven trials, only three trials were in patients with M1 disease. One trial was in patients with relapse after radiotherapy. The three remaining trials were combinations of different relapse situations, mainly locally advanced and metastatic cases.

The design of the seven trials is summarized in Table 13.2, while the main results for survival are summarized in Table 13.3. The most important survival finding was the lack of a significant difference in OS between continuous and intermittent ADT. Table 13.4 summarizes the expected treatment benefits of IAD. The most important finding was that the benefit in overall QoL was at best minimal. However, some treatment side effects were decreased using IAD.

**Table 13.2: Patient population and treatment cycles in seven phase III trials on IAD**

Parameter	SEUG9401 (20)	FINN VII (21)	SWOG9346 (22)	NCT3657 (23)	TULP (24)	TAP22 (25)	De Leval (26)
n	766	554	1535	1386	193	173	68
Tumour stage	Locally advanced/ metastatic	Locally advanced/ metastatic	Metastatic	After RT	Metastatic	Metastatic	Locally advanced/ metastatic/ biochemical recurrence
PSA (ng/mL) at inclusion	4-100	Any value	> 5	> 3	Any value	> 20	Any value
Therapy	CAD	CAD	CAD	CAD	CAD	CAD	CAD
Induction period (mo)	3	6	7	8	6	6	6
PSA (ng/mL) level to stop on-phase	< 4	< 10	< 4	< 4	< 4	< 4	< 4
PSA (ng/mL) level to restart on-phase	> 10 for symptomatic and > 20 for asymptomatic	> 20	> 20	> 10	> 10 no metastatic and > 20 metastatic	> 10	> 10
Time off therapy	50% at least 52 weeks; 29% for 36 mo	10.9-33.5 weeks	> 40% of time	20-59.6 mo	0.7-4.9 mo	1.0- 48.9 mo	3.3-8.3 mo
Follow-up (mo) median	50	65	108	84	31	44	31

CAD = complete androgen deprivation; n = number of patients; PSA = prostate specific antigen.

**Table 13.3: Oncological results in the 7 phase III trials on IAD**

Parameter	SEUG9401 (20)	FINN VII (21)	SWOG9346 (22)	NCT3657 (23)	TULP (24)	TAP22 (25)	De Leval (26)
End points considered	Time to progression/ survival	Time to progression/ survival	Time to progression/ survival	Time to progression/ survival	Time to progression	Time to progression/ survival	Time to progression
Time to progression	HR 0.81 in favour continuous arm. p = 0.11	IAD 34.5 mo Continuous 30.2 mo HR 1.08; p = 0.43	IAD 16.6 mo Continuous 11.5 mo p = 0.17	-	IAD 18.0 mo Continuous 24.1 mo	IAD 20.7 mo Continuous 15.1 mo p = 0.74	IAD 28 mo Continuous 21 mo
PCa-specific survival	IAD 23.6% dead. Continuous 20.8% dead. HR 0.88	IAD 43% dead; 45.2 mo Continuous 47% dead; 44.3 mo HR 1.17; p = 0.29	IAD 64% dead. Continuous 56% dead	IAD 17.4% dead. Continuous 13.5% dead. HR 1.23; p = 0.13	-	-	-
Overall survival	IAD 54.1% dead. Continuous 54.2% dead. HR 0.99; p = 0.84	IAD 45.2 mo Continuous 45.7 mo HR 1.15; p = 0.17	IAD 5.1 years. Continuous 5.8 yr. HR 1.09	IAD 38.8% dead; 8.8 yr. Continuous 36.8% dead; 9.1 yr. HR 1.02	-	IAD 56.9% dead; 42.2 mo Continuous 54.2% dead; 52.0 mo p = 0.75	-

HR = hazard ratio; IAD = intermittent androgen deprivation.



**Table 13.4: QoL and safety in the 7 phase III trials on IAD**

Parameter	SEUG9401 (20)	FINN VII (21)	SWOG9346 (22)	NCT3657 (23)	TULP (24)	TAP22 (25)
Hot flashes	IAD 19% Continuous 30%	IAD 47.1% Continuous 50.4%	-	-	IAD 50% Continuous 59%	IAD 60.4% Continuous 63.8%
Sexual dysfunction	At 15 mo sexually active: IAD 28% Continuous 10%	IAD 15.7% Continuous 7.9%	-	-	IAD 9% Continuous 10%	-
Long-term consequences	Cardiovascular deaths: IAD 13.1% Continuous 16.7%	Cardiovascular deaths: IAD 12.8% Continuous 15.4%	-	-	-	-
QoL	Overall no clinically relevant differences. Favour for IAD in sexual function domains	Favour for IAD in activity limitation, physical capacity and sexual functioning domains	-	No clinically relevant difference	No clinically relevant difference	No clinically relevant difference

IAD = intermittent androgen deprivation; QoL = quality of life.

- The SWOG 9346 (22) is the largest-ever conducted trial in M1b patients. Out of 3,040 selected patients, only 1,535 were randomized based on the inclusion criteria. This highlights again that at best only 50% of M1b patients might be candidates for IAD, i.e. the best PSA responders (patients with a PSA < 4 ng/mL after 6 months of ADT and remaining below 4 ng/mL at 7 months).
- The NCT3653 (23) is also the largest trial conducted on ADT at relapse after radiotherapy. The trial's major limitation of this trial is the lack of proven survival benefit when using salvage ADT at relapse. The survival benefit is only suggested and requires confirmation with a properly designed RCT. This is discussed further in the Chapter 19.
- Both trials were non-inferiority trials. The non-inferiority result of the NCT 3653 trial showed less than an 8% survival difference (HR: 1.03; CI: 0.87-1.22), with the pre-specified 90% upper limit being 1.25. The SWOG 9346 produced an inconclusive result (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2.

#### Potential other benefits of IAD

Other possible long-term benefits, include bone protection (28) and/or a protective effect against the metabolic syndrome. Testosterone recovery is seen in most studies (17), leading to an intermittent castration. Finally, IAD is associated with a very significant decrease in the treatment cost.

#### Practical aspects for IAD

The optimal thresholds at which ADT must be stopped or resumed are empirical (17,19). Nevertheless, several points are clear.

- Because IAD is based on intermittent castration, only drugs leading to castration are suitable for use in IAD.
- All published experiences are based on CAB, which is considered as standard treatment. An LHRH antagonist might be a valid alternative, but results from ongoing RCTs with antagonists are awaited.
- The induction cycle must last between 6 to 9 months, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
  - well-informed and compliant patient
  - no clinical progression
  - clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease, or < 0.5 ng/mL in relapsing disease.
- Strict follow-up is mandatory, with clinical examination every 3-6 months. The more advanced the disease, the closer the follow-up. The same laboratory should be used to measure the PSA level.

- Treatment is resumed when the patient reaches either a clinical progression, or a PSA above a predetermined, empirically fixed, threshold: usually 4-10 ng/mL in non-metastatic or 10-20 ng/mL in metastatic cases.
- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same rules until the first sign is seen of a castrate-resistant status.
- The best population to consider for IAD has still to be fully characterized. However, the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response (19).

In conclusion, IAD should be widely offered to patients with PCa in various clinical settings after a standardized induction period. IAD should be the standard of care for those relapsing after radiotherapy (if some form of ADT is required). It might be an option in metastatic situations, even if the benefits are fewer compared to those with less advanced PCa (LE: 1b).

#### 13.4.4 **Immediate versus deferred ADT**

There is no discussion regarding the introduction of IAD in symptomatic patients. However, there is still controversy concerning the best time to introduce hormonal therapy in asymptomatic metastatic patients due to the lack of properly conducted RCTs. These are underpowered trials with heterogeneous patient enrolment (i.e. locally advanced, M1a, M1b status) and a variation in ADT modalities and follow-up schedules.

A report by the Agency for Health Care Policy and Research (AHCPR) indicated a possible survival advantage for early ADT when ADT was the primary therapy (29). Furthermore, ADT was shown to be the most cost-effective therapy if started at the time the patient developed symptomatic metastases (30).

The Cochrane Library review extracted four good-quality RCTs: VACURG I and II trials, the MRC trial, and the ECOG 7887 study. These studies were all conducted in the pre-PSA era and included patients with advanced PCa, who had received early versus deferred ADT, either as primary therapy or adjuvant to radical prostatectomy (31). The Cochrane review found that M1a/b patients showed no improvement in OS, although early ADT significantly reduced disease progression and complication rates due to progression. However, locally advanced PCa showed a relatively small benefit in OS. There was an absolute risk reduction of 5.5% after 10 years (31), while another review reported an OS benefit (+10%) and SS (+20%) (40), especially in combination with a local treatment.

In M0 situations and in the PSA era, the EORTC 30891 study has clarified the results for patients unable to receive or unwilling to undergo a local treatment. The final analysis after a median follow-up of 12.8 years (32) showed that immediate treatment was better than IAD for time-to-first clinical progression and 10 years' progression rate. However, there was no difference in the time-to-objective-castration resistance or in the PCa-specific survival time, except for the most aggressive situations resulting in death within 3-5 years, i.e. PSA > 50 ng/mL and PSADT < 12 months. The OS was in favour of immediate treatment (HR: 1.21; CI: 1.05-1.39;  $p = 0.0085$  for difference). With deferred treatment, up to 30% of patients died without needing or receiving any form of ADT. A further 55.8% of patients received deferred treatment for symptomatic progression (pain, symptomatic metastases, ureteric obstruction, WHO deterioration).

Based on a systematic review of the literature, the ASCO guidelines on initial hormonal treatment for androgen-sensitive, metastatic, recurrent or progressive PCa concluded it was not possible to make a recommendation about when to start hormonal therapy in advanced asymptomatic PCa (15). The ESMO guidelines do not make any statement (33).

Immediate or deferred ADT for failure after surgery or radiation therapy is discussed in Section 8.3.

### 13.5 Recommendations for hormonal therapy

<b>Castration</b>	<b>Benefits</b>	<b>LE</b>	<b>GR</b>
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskelatal metastasis).	1b	A
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b	A
	An active clinical surveillance protocol is an acceptable option in clearly informed patients if survival is the main objective.	3	B
Locally advanced (as single treatment for patients unwilling or unable to receive any form of associated local treatment)	Immediate castration should be considered in the most aggressive situations (PSA > 50 ng/mL, PSADT < 12 months).	2a*	A
	Otherwise a wait-and-see policy with deferred treatment at clinical progression is a reasonable option.	1b	A
* Post-hoc analysis from an RCT.			
<b>Anti-androgens</b>			
Short-term administration	To reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist (91,92).	2a	A
	It may be sufficient to give an anti-androgen for some weeks of concomitant use, starting treatment on the same day as an LHRH analogue is started, or for up to 7 days before the first LHRH analogue injection.	4	B
Long-term administration as monotherapy	This is an option in highly selected and motivated patients with a low PSA.	3	B
<b>Intermittent treatment</b>			
Threshold to start and stop ADT	The threshold is empirically chosen. However, it should reproduce what has been used in clinical trials. In trials, treatment is usually stopped when the PSA level is < 4 ng/mL (M1) and < 0.5-4 ng/mL (relapsing). Treatment is usually re-started when the PSA is > 4-10 (relapsing) and > 10-20 ng/mL (M1).	4	C
Drug	Combined treatment with LHRH agonists and NSAA. Antagonists might be an option.	1b 4	A B
Population:	Metastatic patients: asymptomatic, very motivated, with a major PSA response after the induction period.	1b	B
	Relapsing after radiotherapy: patients with a clear response after the induction period.	1b	A

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

### 13.6 Contraindications for various therapies

<b>Therapy</b>	<b>Contraindications</b>	<b>LE</b>	<b>GR</b>
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration.	3	A
Oestrogens	Known cardiovascular disease.	2b	B
LHRH agonists monotherapy	Patients with metastatic disease at high risk for clinical 'flare-up' phenomenon.	2b	A
ADT, anti-androgen	Localized PCa as primary monotherapy (except in some high-risk localized situations in patients unwilling or unable to receive any form of local treatment).	1b	A

ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone.

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## 14. MANAGEMENT OF PROSTATE CANCER IN OLDER MEN

### 14.1 Introduction

Prostate cancer (PCa) is generally a disease of the senior adult (defined as > 70 years), with a median age at diagnosis of 68 years. Due to demographic changes there has been a worldwide increase in the number of men aged > 65 years. In the USA, this will result in an estimated 70% increase by 2030 in the annual diagnosis of PCa in patients aged > 65 years (1). A similar increase in incidence is expected in Europe (2).

Moreover, results from the Surveillance Epidemiology and End Results database (SEER) have shown that 71% of PCa-related deaths occur in men aged  $\geq$  75 years (3). This is probably due to the higher incidence of very advanced/metastatic disease in this age group (4-6).

However, despite high incidence and mortality rates in senior adults, the evidence suggests that senior adults are undertreated in both the USA (7) and Europe (8). In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease will receive curative treatment compared to 88% of patients aged between 65 and 74 years (9). In addition, two large studies (10,11) were carried out to assess the long-term outcomes of PCa treated with non-curative intent. The results showed that PCa-specific mortality rates were low in men with localized low- and intermediate-risk PCa, irrespective of age. In contrast, cancer-related mortality rates of up to 64% were described in patients with high-risk PCa (10,11).

### 14.2 Evaluation of life expectancy, comorbidities and health status

In localized disease, a life expectancy of > 10 years is usually considered mandatory for the patient to benefit from local treatment. Although life expectancy is a major determinant of potential benefit from therapy, it varies greatly between individuals within the same age groups. This variation can be predominantly explained by the presence of comorbidities, which is more important than biological age in predicting death in men with localized PCa (12).

The International Society of Geriatric Oncology (SIOG) Prostate Cancer Working Group therefore recommends that the decision-making process for treating older men with PCa should be based on a systematic evaluation of health status (13). Initially, senior adults with PCa should therefore undergo health status screening to distinguish healthy patients from those with impairments (14).

Research has demonstrated that the G8 (Geriatric 8) health status screening tool is a discriminant tool (see Table 14.1), and compared to VES-13 (Vulnerable Elders Survey), it was more discriminating. Other tools exist but have not yet been compared e.g. Groningen Frailty Index (GFI), abbreviated comprehensive geriatric assessment (aCGA), Fried frailty criteria and Barber (15,16).



**Table 14.1: The Geriatric 8 (G8) frailty screening method**

	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 <sup>2</sup> )	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

*BMI = body mass index*

Above 14, using the G8 score, patients are considered fit and should receive the same treatment as younger patients. Patients with impairments (G8 score ≤ 14), should undergo a full geriatric evaluation, assessing comorbidities, nutritional status, cognitive and physical functions (17). The purpose is to determine if the ‘impairment’ is reversible or not. Patients with a reversible impairment (‘vulnerable patients’) should be treated according to the EAU Guidelines. Patients with irreversible impairment (‘frail patients’) should receive adapted treatment (13).

#### 14.2.1 Comorbidities

Comorbidity is a major predictor of mortality. Using the Charlson index, Tewari et al. have demonstrated that comorbidity is the strongest predictor of non-cancer-specific death in men with localized PCa treated with RP (18). This finding was confirmed in a cohort of patients from the SEER database, all of whom had treatment-resistant PCa. At 10 years, most men with a Charlson score > 2 had died from competing causes, irrespective of age or tumour aggressiveness (12).

Currently, the Cumulative Illness Score Rating-Geriatrics (CISR-G) (19) is the best available tool for assessing the risk for death unrelated to PCa (20). Whereas the Charlson index rates only potentially lethal comorbid conditions, the CISR-G also rates non-lethal conditions, according to their severity and level of control (21). See Table 14.2.

**Table 14.2: Cumulative Illness Score Rating-Geriatrics (CISR-G)**

CUMULATIVE ILLNESS RATING SCALE			
Patient		Age	
Rater		Date	
Instructions: Please refer to the CISR-G manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use reverse side for more writing space).			
<b>Rating strategy</b>			
0	None		
1	Mild (or past significant problem)		
2	Moderate (moderate disability or morbidity, requires first-line therapy)		
3	Severe (constant significant disability/ uncontrollable chronic problems)		
4	Extremely severe (immediate treatment required/ end organ failure / severe impairment in function)		
			<b>Score</b>
Heart			
Vascular			
Respiratory			
Eyes, ears, nose, throat and larynx			
Upper GI			
Lower GI			
Hepatic			
Renal			
Genitourinary			
Musculoskeletal/integument			
Neurological			
Endocrine/metabolic			
Psychiatric illness			
<b>Total score</b>			

*A patient is considered fit if he has no Grade 3 score*

*Vulnerable: one, or two, Grade 3 score(s)*

*Frail: more than two Grade 3, or any Grade 4 score(s)*

*Too sick: multiple Grade 4*

#### 14.2.2 Independent daily activities

The level of dependence in daily activities is another factor influencing survival in senior adults (22-24).

Dependence can be evaluated using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales. The ADL scale rates an ability to accomplish basic activities of daily living, while the IADL scale rates activities that require a higher level of cognition and judgement (e.g. the ability to manage money or medication, to use transportation or the telephone).

#### 14.2.3 Malnutrition

Malnutrition has also been associated with an increased mortality rate in senior patients (25). A patient's nutritional status can be estimated from the patient's variation in weight during the previous 3 months:

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

#### 14.2.4 Cognitive impairment

Research has shown that mild and moderate-to-severe cognitive impairment are associated with an increased risk of mortality in senior adults (26). In patients undergoing major elective surgery, e.g. RP, an association has been shown between a patient's baseline cognitive impairment and post-operative complications and mortality in the long term (27). However, intervention is unlikely to reverse cognitive impairment, except in the case of depression for which there is successful medical treatment (13).

### 14.2.5 **Conclusions**

Systematic screening, using the G8 tool, is recommended by The SIOG Prostate Cancer Working Group (13). A patient who is impaired (G8 score < 14) should undergo a complete geriatric assessment to evaluate the possible reversibility of any impairments (13).

Senior adults can be classified into one of four groups regarding health status based on the G8 screening tool: when the score is above 14, the patient is considered fit. If the G8 score is below 14, based on the CISR-G score, he will be classified as vulnerable or frail. The treatment policy could then be:

1. 'Fit' or 'healthy' older men should receive standard treatment;
2. 'Vulnerable' patients (i.e. reversible impairment) may receive standard treatment after resolution of any geriatric problems through geriatric interventions;
3. 'Frail' patients (i.e. irreversible impairment) should receive adapted treatment;
4. Patients who are 'too sick' with 'terminal illness' should receive only symptomatic palliative treatment (13).

Once any reversible impairments have been resolved, a similar urological approach should be carried out in fit or vulnerable patients, based on existing recommendations (28,29). Older men with PCa should be managed according to their individual health status, which will be directed mainly by the needs of any associated comorbidities and not according to chronological age.

## 14.3 **Treatment**

### 14.3.1 **Localized PCa**

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

This section has already been elaborated in another chapter (see Chapter 8). Recent evidence suggests that active treatments are of most benefit to patients with intermediate- or high-risk disease and the longest expected survival.

#### 14.3.1.2 *Radical prostatectomy*

In senior adults with few comorbidities, RP has shown to improve life expectancy in intermediate- and especially high-risk disease (4,30).

The risk of short-term postoperative complications appears to be related more to the severity of comorbidities than chronological age. Conversely, the risk of long-term incontinence after RP is more influenced by increasing age than comorbidity (31,32).

#### 14.3.1.3 *External beam radiation therapy*

EBRT and RP have similar outcomes in terms of cancer control and treatment-related comorbidities in both older and younger patients, assuming a dose of > 72 Gy when using intensity modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT) (33).

The drawback of associating ADT to EBRT in older patients was discussed earlier (see Chapter 12). It is particularly important to evaluate the patient's cardiac status as the use of ADT in patients with pre-existing heart conditions can be associated with increased morbidity and mortality. Comorbidity alone can also be a discriminating factor, as suggested recently in high-risk patients with localized disease (34).

#### 14.3.1.4 *Minimally invasive therapies*

Minimally invasive therapies are being developed rapidly, but there is still a lack of evidence to support its role.

#### 14.3.1.5 *Androgen deprivation therapy*

In patients with non-metastatic localized PCa not suitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation. In the case of locally advanced T3-T4 disease, immediate ADT may benefit patients with PSA > 50 ng/mL and PSADT of < 12 months (35,36).

### 14.3.2 **Advanced PCa**

#### 14.3.2.1 *Hormone-naïve PCa*

ADT is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG Prostate Cancer Working Group recommends evaluation of baseline bone mineral status and prevention of osteoporosis by calcium and vitamin D supplements (13).

The routine use of bisphosphonates or denosumab to prevent skeletal complications in patients undergoing ADT is not recommended unless there is a documented risk for fracture or castration-resistant PCa with skeletal metastasis (37).

#### 14.3.2.2 Metastatic CRPC

In metastatic castration-resistant prostate cancer (CRPC), chemotherapy with docetaxel (75 mg/m<sup>2</sup> every 3 weeks) is the standard regimen in fit and vulnerable older men (38), with response and tolerance rates comparable to those observed in younger patients (39). However, the tolerability of the 3-weekly docetaxel regimen has not been specifically studied in frail older men. In elderly and frail patients, the use of G-CSF prophylaxis should be a consideration.

Several new drugs (cabazitaxel, abiraterone acetate, enzalutamide, sipuleucel-T) have been proven to increase survival in both chemotherapy-treated and chemotherapy-naïve metastatic CRPC in senior adults (40-45).

Palliative treatments in CRPC include palliative surgery, radiopharmaceuticals, EBRT, and medical treatments for pain and symptoms.

### 14.4 Conclusions and recommendations

	LE	GR
<b>Evaluation of health status</b>		
Senior adults with localized PCa should systematically undergo health status screening.	1b	A
Health status screening should be performed using the G8 screening tool.	2a	A
Patients with a G8 score ≤ 14 should undergo a full geriatric evaluation, preferably by a medical team specialized in geriatric medicine.	2a	A
Based on this evaluation, senior adults can be classified into one of four groups: 1. <b>'Fit'</b> or <b>'healthy'</b> older men, should receive standard treatment; 2. <b>'Vulnerable'</b> patients (i.e. reversible impairment), may be given standard treatment after resolution of any geriatric problems through geriatric interventions; 3. <b>'Frail'</b> patients (i.e. irreversible impairment), should receive an adapted treatment; 4. Patients who are <b>'too sick'</b> with have a <b>'terminal illness'</b> should receive only symptomatic palliative treatment.	3	B
<b>Treatment</b>		
<i>Localized disease</i>		
'Fit' and 'vulnerable' senior adults with a life expectancy of > 10 years, diagnosed with high-risk disease, should be offered standard treatment.	2b	A
In 'frail' patients or patients who are 'too sick', immediate ADT should only be used for symptom palliation.	1b	A
Minimally invasive therapies should not be applied routinely in senior adults. These therapies have a role only in highly selected fit and vulnerable senior adults with intermediate-risk disease.	3	B
<i>Advanced disease</i>		
Evaluation of bone mineral status and prevention of osteoporotic fracture are recommended in patients at high-risk of fractures.	2b	A
New chemotherapeutic and hormonal agents can be used successfully in fit and vulnerable adults.	1b	B

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## 15. QUALITY OF LIFE IN PATIENTS WITH LOCALIZED PROSTATE CANCER

### 15.1 Introduction

The increase in life expectancy of patients with localized PCa has made the quality of life (QoL) after treatment a key issue for PCa survivors. The term 'health-related quality of life' (HRQoL) is typically used to refer to the impact that disease and treatment have on a person's well-being and physical, emotional and social functioning, including daily functioning (1). HRQoL is a patient-centred outcome, which is rated by the patient himself; it is important because physicians often underestimate the impact of disease and treatment on their patients' lives (2).

In PCa, HRQoL is usually divided into PCa-specific and general issues. PCa-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel and sexual functioning. general HRQoL refers to the generic issues of well-being, including physical, social, emotional, and cognitive functioning, vitality/fatigue, pain, general health status, global QoL and life satisfaction (3).

HRQoL is measured using standardized questionnaires, which collect patient-centric data and provide an objective assessment and perception of both generic and disease-specific domains (4,5).

Various forms of therapy have different impacts on HRQoL. A comparison of the most common contemporary therapies for localized PCa is necessary to inform patients about treatment options and to address individual patient preferences for the various possible outcomes. There is still very little objective data about HRQoL for PCa treatment, mainly because of a lack of prospective trials.

### 15.2 Active surveillance

Although active surveillance avoids treatment-related side effects, it carries an increased risk of psychological distress, which can have significant effects on the patient's HRQoL. There are certain risk factors for patients who may not do well on active surveillance. These factors include the patient's perception that the physician is making most of the decision-making, poor physical health score, high neuroticism (anxiety) score, high PSA value, lack of a partner, impaired mental health, recent diagnosis and lower number of core samples taken at diagnostic biopsy. All these factors were found to have significant positive associations with lower HRQoL scores in multivariate analysis (6,7). Anxiety and distress did not increase and remained low during the first 9 months of surveillance in men enrolled in the active surveillance PRIAS study (8) (LE: 1b).

Long-term data from an RCT comparing WW and RP (9) found that depression, well-being and psychological status were not significantly different between treatment groups over an 8-year period, but the course of physical symptoms differed. Men in the RP group reported more symptoms throughout the follow-up period related to leakage, erection, and libido compared to baseline (LE: 1b).

Apart from psychological distress, men left without anticancer treatment may have a higher level of irritative-obstructive urinary symptoms compared to patients treated with RP or RT at 12-36 months of follow-up (10) (LE: 2b).

### 15.3 Radical prostatectomy

Several trials have shown that RP has a significant negative effect on multiple QoL domains, including a lower sexual function score, lower urinary function and incontinence scores, and a lower physical HRQoL (11-13).

In the Prostate Cancer Outcomes Study (PCOS), 8.7% of men at 24 months were bothered by a lack of urinary control and 41.9% reported that sexual function was a moderate-to-big problem in their daily lives (14). Sexual function and interest are the two prostate-specific domains that decline most after surgery and remain most affected after 1 year. The recovery of sexual dysfunction and urinary incontinence occurs over 2 to 3 years (15,16), with urinary incontinence being at its worst by 2 months after surgery (11) (LE: 2a).

Although certain advances have been made that help diminish these side effects, such as nerve-sparing RP or robotic-assisted radical prostatectomy (Sex Med), their impact on HRQoL remains controversial. Preserving the neurovascular bundles reduces the incidence of erectile dysfunction (11,17) and can also help to improve urinary function (18). Both Sex Med and open RP have demonstrated comparable functional outcomes and should therefore theoretically have similar HRQoL scores (19). In addition, Sex Med did not result in an improvement in the functional outcome of laparoscopic RP, with no difference regarding urological function/bother score or sexual function/bother score at 36-months' follow-up in a prospective non-randomized comparison (17). In two small prospective randomized comparative studies, however, Sex Med showed improved continence and erectile function outcome when compared to laparoscopic prostatectomy (20,21). Furthermore, the systematic review published by Novara (22) showed that, based on the quality of the available data, it was not possible to conclude that any approach was superior in terms of survival. General HRQoL domains that may be affected after surgery include pain and energy (14). Several studies have shown that pain and energy worsen immediately post-RP, but usually improve by 12 months (15,23).

A new methodology for reporting outcomes after RP was proposed recently: the so-called trifecta (24) and pentafecta (25). The new method combines major outcomes, including continence, potency and cancer control (trifecta) and peri-operative complications and positive surgical margins rates (pentafecta). Pentafecta rates reflect post-operative patient expectations and satisfaction more accurately and can be used in counselling patients with clinically localized PCa. The use of trifecta and pentafecta outcomes in post-operative HRQoL assessment needs further validation.

### 15.4 External-beam radiation therapy (EBRT) and low-dose rate (LDR) brachytherapy

Patients undergoing EBRT and iodine-125 LDR brachytherapy may have urinary, sexual and bowel dysfunction following treatment. Both methods can result in irritative voiding symptoms, such as urgency, frequency, and urge incontinence, that negatively affect overall urinary function and HRQoL (11).

A prospective multicentre study showed that the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months (11). In the same study, patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence compared with baseline. Incontinence after LDR brachytherapy was reported by 4-6% of patients at 1-2 years after treatment. Eighteen percent of patients in the LDR brachytherapy group and 11% of those in the EBRT group reported moderate or worse distress from overall urinary symptoms at 1 year (11) (LE: 3).

It has been shown that both EBRT and LDR brachytherapy have a significant impact on the bowel and rectal HRQoL domains (11). Bowel/rectal problems appeared to have an overall impact almost as important as that of the urinary domain (26,27). The onset of symptoms occurred during or early after treatment, and sometimes persisted into follow-up. Rectal urgency, frequency, pain, faecal incontinence, or haematochezia-caused distress related to bowel function were reported in 9% of patients at 1 year after EBRT or LDR brachytherapy (11). After contemporary dose-escalated EBRT up to 11% of patients had moderate/big problems with bowel HRQoL 2 years after treatment. Bowel HRQoL was related to baseline function, a volume of rectum  $\leq 25\%$  treated to 70 Gy (V70), and aspirin use (28). A multivariable analysis suggested that bowel and rectal symptoms were less profound after LDR brachytherapy than after EBRT (4) (LE: 2a).

A statistically significant deterioration in HRQoL in patients treated with iodine-125 LDR brachytherapy at 6 years was demonstrated for urinary symptoms, bowel symptoms, pain, physical functioning, and sexual activity (29). However, most of these changes were not clinically relevant. HRQoL scores returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. The only clinically relevant changes occurred in emotional functioning and sexual activity. Dietary intervention had no statistically significant positive impact on gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT (30) (LE: 1b).

Adjuvant androgen suppression may exacerbate the adverse effects of EBRT or LDR on sexuality, vitality (11) and long-term bowel function (31).

Among general domains, fatigue was commonly reported following EBRT. Fatigue increased over time, with the highest level seen at the end of EBRT. Severe fatigue was reported by 4% 5-year post-treatment adversely affecting QoL (32).

Men treated with interstitial LDR brachytherapy appeared to show only slight declines in general

HRQoL. Physical and functional status declines have been reported in the first few months after implant, but pretreatment levels of function are regained by most men at 1 year after implant (29).

### 15.5 Comparison of HRQoL between treatment modalities

The limitations of all published studies assessing QoL include the lack of randomization to treatment and therefore the presence of selection bias, which may influence outcomes. Thus, information regarding comparative outcome relies largely on results from non-randomized observational cohorts. Treatment comparison requires a long follow-up, as measures of QoL may change with time. There are very few trials that directly compare different treatment modalities.

Studies addressing general HRQoL issues have found very few differences across treatments for clinically localized disease (3,33). In longitudinal studies, both surgery- and radiotherapy-treated men have reported some declines in role functioning and vitality/energy shortly after treatment, with surgically treated men reporting the most dysfunction (23). However most men recovered function by one year after treatment.

The PCOS was the first reported prospective study presenting treatment-specific QoL outcomes for PCa patients at 5 years after initial diagnosis (14). The cohort consisted of men with newly diagnosed localized PCa treated with RP (n = 901) or EBRT (n = 286). At 5 years after diagnosis, overall sexual function declined in both groups to approximately the same level, mostly because of a continuing decline in erectile function among EBRT patients between years 2 and 5. However, erectile dysfunction was more prevalent in the RP group (79.3% vs 63.5%, respectively). Approximately 14-16% of RP and 4% of EBRT patients were incontinent at 5 years. Bowel urgency and painful haemorrhoids were more common in the EBRT group (LE: 2a). However, at 15 years no significant disease specific differences were observed between men treated with RP or EBRT (34). Side effects of RP and EBRT were evaluated in 278 patients from the ERSPC study at 6 and 12 months following treatment (26). RP patients reported significantly higher incidences of urinary incontinence (39-49%) and erectile dysfunction (80-91%) compared with radiotherapy patients (6-7% and 41-55%, respectively). Bowel problems (urgency) affected 30-35% of the EBRT group versus 6-7% of the RP group (LE: 2a).

Downs et al. measured the impact of LDR brachytherapy alone on general HRQoL and disease-specific HRQoL compared to patients treated with RP (35). Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0-6 months after treatment (84.5%) than patients treated with RP (63.3%). Urinary bother scores were not significantly different (67.7% vs 67.4%, respectively). Both treatment groups showed decreases in sexual function that did not return to pretreatment levels (LE: 2a).

A multicentre longitudinal prospective study compared urinary, bowel and sexual function prior to RP, EBRT, and LDR brachytherapy to 24 months afterwards. Urinary incontinence increased sharply after RP, while bowel problems and urinary irritation-obstruction occurred after EBRT and LDR brachytherapy. Sexual function severely worsened immediately after surgery and then improved, while sexual function continued to decline after both radiation treatments. There was no change in urinary function and little change in overall bowel function after 12 months. The data showed that a patient with bowel dysfunction at 12 months after EBRT may expect modest improvement, with diverging trends for individual symptoms. Although diarrhoea will continue to subside, there will be little change in tenesmus and rectal urgency, while episodes of rectal bleeding will become more prevalent (4) (LE: 2a).

A prospective, multicentre study of 435 patients with a longer follow-up of 36 months (36) confirmed that there was a long-term change in adverse effects, e.g. an increase in urinary-related adverse effects after EBRT or in sexual adverse effects with LDR brachytherapy, which tended to reduce any differences between treatments over time. However, these changes were only slight. In accordance with other reports, the RP-treated group showed greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive results compared with the LDR brachytherapy group. Relevant differences between treatment groups persisted for up to 3 years of follow-up (36) (LE: 2a).

The American College of Surgeons Oncology Group phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial compared RP and LDR brachytherapy, but was closed after 2 years due to poor accrual at a mean of 5.3 years for 168 trial-eligible men, who either chose or were randomly assigned to RP or brachytherapy (37). There were no differences in bowel or hormonal domains. However, men treated with LDR brachytherapy scored slightly better in the urinary QoL domain (91.8 vs 88.1;  $p = 0.02$ ) and sexual (52.5 vs 39.2;  $p = 0.001$ ) domain, and in patient satisfaction (93.6 vs 76.9%;  $p < 0.001$ ). It should be noted that treatment allocation was random in only 19% of cases (LE: 2a).

A population-based study investigated the relationship between the presence of urinary, bowel or sexual dysfunction and global QoL in PCa survivors in Norway including men who did not have any active treatment. Men who had undergone RP reported more urinary incontinence (24%) than other treatment groups, but had the lowest level of moderate or severe urinary irritative-obstructive symptoms. Men from the 'no treatment' group had the highest level of moderate or severe irritative-obstructive urinary symptoms. Men who had undergone RT reported higher levels of irritative intestinal symptoms and faecal leakage compared with

the RP group and the no-treatment group. In all treatment groups, poor sexual drive and poor erectile function were common, with men treated with RP reporting the highest prevalence of poor erectile function (89%). The presence of irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global QoL in multivariate analyses (10) (LE: 2b).

In a single-institution study comparing the outcomes of surgery (RP, RALP), LDR brachytherapy and cryosurgical ablation of the prostate (CSAP) (38), the HRQoL of patients treated with LDR brachytherapy and CSAP was associated with higher urinary function and higher bother score compared to open RP and RALP. LDR brachytherapy was associated with a higher sexual function and higher bother score compared to all other treatment modalities. Unfortunately, the study used the UCLA-PCI questionnaire, which lacks items for evaluating irritative urinary symptoms, which are often observed in patients after LDR brachytherapy (35). This may have significantly compromised the results of the HRQoL assessment (LE: 3).

In conclusion, many men treated for clinically localized PCa will experience some post-treatment problems that may impact their daily lives. Each patient has therefore to decide which side effect profile is most acceptable to him when making a decision about treatment.

## 15.6 Recommendations on QoL in PCa management

	LE	GR
Patients with low risk prostate cancer should be informed on the fact that functional outcome of AS is better than for local active treatment.	2	B
Patients should be informed that functional outcome after Sex Med and open prostatectomy will be similar.	2	B
Patients should be informed that the long-term (15 year) QoL outcomes EBRT and RP will be similar.	2	B

AS = active surveillance; EBRT = external beam radiation therapy; QoL = quality of life; RP = radical prostatectomy.

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## 16. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF PCA

Stage	Treatment	Comment	GR
T1a	Watchful waiting	In patients with < 10-year life expectancy standard treatment for Gleason score ≤ 6 and 7 adenocarcinomas.	B
	Active surveillance	In patients with > 10-year life expectancy, re-staging with TRUS and biopsy is recommended.	B
	Radical prostatectomy	Optional in younger patients with a long life expectancy, especially for Gleason score ≥ 7 adenocarcinomas.	B
	Radiotherapy	Optional in younger patients with a long life expectancy, in particular in poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.	B
	Hormonal	Not an option.	A
	Combination	Not an option.	B
T1b-T2b	Watchful waiting	Patients with a life expectancy < 10 years.	B
	Active surveillance	Treatment option in patients with cT1c-cT2a, PSA < 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 biopsies positive, ≤ 50% cancer involvement of each biopsy.	B
		Patients with a life expectancy > 10 years once they are informed about the lack of survival data beyond 10 years. Patients who do not accept treatment-related complications.	
T1a-T2c	Watchful waiting	Patients with life expectancy < 10 years and Gleason score < 7.	A
		Patients with life expectancy < 10 years and Gleason score = 7.	B
	Radical prostatectomy	Optional in patients with pT1a PCa.	A
		Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.	
		Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery.	
	Radiotherapy	Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below).	B
		Low-dose rate brachytherapy can be considered for low risk PCa patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.	
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.	C
Anti-androgens are associated with a poorer outcome compared to 'watchful waiting' and are not recommended.		A	
Combination	For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A	

T3-T4	Watchful waiting	Option in asymptomatic patients with T3, Gleason score $\leq 7$ , and a life expectancy $< 10$ years who are unfit for local treatment.	C
	Radical prostatectomy	Optional for selected patients with T3a, PSA $< 20$ ng/mL, biopsy Gleason score $\leq 8$ and a life expectancy $> 10$ years.	C
		Patients have to be informed that RP is associated with an increased risk of positive surgical margins, unfavourable histology and positive lymph nodes and that, therefore, adjuvant or salvage therapy such as radiation therapy or androgen deprivation might be indicated.	
	Radiotherapy	T3 with $> 5-10$ years of life expectancy. Dose escalation of $> 74$ Gy seems to be of benefit. A combination with hormonal therapy can be recommended.	A
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level ( $> 25-50$ ng/mL), PSADT (DT) $< 1$ year.	A
		Patient-driven, unfit patients. Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.	
Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation.	A	
	NHT plus radical prostatectomy: no indication.	B	
N+, M0	Watchful waiting	Asymptomatic patients. Patient-driven (PSA $< 20-50$ ng/mL), PSADT $> 12$ months. Requires very close follow-up.	B
	Radical prostatectomy	Optional for highly selected patients with a life expectancy of $> 10$ years as part of a multimodal treatment approach.	C
	Radiotherapy	Optional in highly selected patients with a life expectancy of $> 10$ years, combination therapy with adjuvant androgen deprivation for 3 years is mandatory.	C
	Hormonal	Standard treatment after extended node dissection if $> 2$ positive nodes (irrespective of the local treatment: surgery or radiotherapy). Hormonal therapy should only be used as monotherapy in patients who are unfit for any type of local therapy.	A
	Combination	No standard option. Patient-driven.	B
M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.	B
	Radical prostatectomy	Not a standard option.	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.	C
	Hormonal	Standard option. Mandatory in symptomatic patients.	A

DT = doubling time; NHT = neoadjuvant hormonal treatment; IPSS = International Prostatic Symptom Score; PSA = prostate specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate

# 17. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

## 17.1 Definition

Curative treatment is defined as radical prostatectomy (RP) or radiotherapy, either by external beam radiotherapy or low- or high-dose brachytherapy, or any combination of these. Alternative treatment options that are not fully established, such as HIFU, do not have a well-defined, validated PSA cut-off point to define biochemical failure, but do generally follow the outlines given below.

## 17.2 Why follow-up?

Recurrence will occur at various time points after the primary therapy in a substantial number of patients who have previously received treatment with the intent to cure.

Reasons for follow-up may vary depending on the treatment given, patient age, co-morbidity and the patient's own wishes. In general, patients who receive curative therapy are followed up to diagnose a relapse or a complication and to assess:

- the possibility of second-line treatment with curative intent;
- the possibility of early hormonal therapy after failure.

## 17.3 How to follow-up?

The procedures indicated at follow-up visits vary depending on the clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. The PSA level, and eventually DRE, are the only tests that need to be carried out routinely. A disease-specific history should be mandatory at every follow-up visit and should include psychological aspects, signs of disease progression, and treatment-related complications. The examinations used to evaluate treatment-related complications must be individualized and are beyond the scope of these guidelines. The examinations used most often for cancer-related follow-up after curative surgery or radiation treatment are discussed below.

### 17.3.1 PSA monitoring

The measurement of PSA level is a cornerstone in follow-up after curative treatment. There is a difference in what can be expected after RP and radiotherapy, but PSA recurrence nearly always precedes clinical recurrence after either treatment, in some cases by many years (1,2). It is recommended that the finding of a single, elevated, serum PSA level should be re-confirmed before starting second-line therapy based solely on PSA elevation.

### 17.3.2 Definition of PSA progression

The level of PSA at which to define treatment failure differs between RP cases and radiation-treated cases. Following RP, there appears to be an international consensus that recurrent cancer can be defined by two consecutive PSA values of 0.2 ng/mL or more (3). However, other authors have argued for an even higher cut-off PSA level of 0.4 ng/mL as a better definition of patients with a high-risk for clinical progression (2).

The use of an ultra-sensitive PSA (US PSA) assay remains controversial for routine follow-up after RP. It was shown that men who achieve a US PSA nadir of less than 0.01 ng/mL have a low (4%) likelihood of early biochemical relapse (4). Although it adds prognostic value, a detectable post-operative US PSA does not 100% predict ultimate biochemical recurrence. In another study, it was found that 66.8% of men with a detectable level of US PSA (> 0.05 ng/mL) remained free of biochemical disease at 5 yr (5). If ongoing randomized trials show that survival is improved by early adjuvant treatment after RP (given before PSA reaches > 0.2 ng/mL), higher US PSA nadir levels may help to identify suitable candidates.

At the 2006 RTOG-ASTRO Consensus conference, a new definition of radiation failure was proposed with the aim of establishing a better correlation between the definition and clinical outcome. The new definition of radiation failure is a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value) (6). It applies to patients treated with or without hormonal therapy.

After HIFU or cryotherapy, a variety of definitions for PSA-relapse have been used (7). Most of these are based on a cut-off PSA level of around 1 ng/mL, eventually combined with a negative post-treatment biopsy. As yet, none of these end-points have been validated against clinical progression or survival, and it is therefore not possible to give a firm recommendation on the definition of biochemical failure.

### 17.3.3 PSA monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within 6 weeks after a successful RP (8). A persistently elevated PSA level in patients treated with PS is generally thought to be due to residual cancer, either micrometastases or residual disease in the pelvis.

A rapidly increasing PSA level (high PSA velocity, short PSADT) indicates distant metastases, while a later and slowly increasing concentration of PSA is most likely to indicate local disease recurrence. The time to PSA recurrence and tumour differentiation are also important predictive factors distinguishing between local and systemic recurrence (9). Both local treatment failure and distant metastases have been shown to occur with undetectable PSA levels. This is very rare and occurs almost only in patients with undifferentiated tumours (10).

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

#### 17.3.4 **PSA monitoring after radiation therapy**

The PSA level falls slowly after radiotherapy compared with RP. The optimal cut-off value for a favourable PSA nadir after radiotherapy is somewhat controversial. Achieving a PSA nadir of less than 0.5 ng/mL seems to be associated with a favourable outcome (11). The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. A PSA rising more than 2 ng/mL above the nadir PSA is the current definition of biochemical failure after radiotherapy (6). In addition, after radiotherapy, the PSADT has been correlated with the site of recurrence: patients with local recurrence had a DT of 13 months compared to 3 months for those with distant failure (12).

#### 17.3.5 **Digital rectal examination (DRE)**

As mentioned previously, a local disease recurrence after curative treatment is possible without a concomitant rise in PSA level (10). However, this has only been proven in patients with unfavourable pathology, i.e. those with undifferentiated tumours. Thus, PSA measurement and DRE comprise the most useful combination of tests as first-line examination in follow-up after radiotherapy or RP, but PSA measurement may well be the only test in cases with favourable pathology (13).

#### 17.3.6 **Transrectal ultrasonography (TRUS), bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), <sup>11</sup>C-choline PET/CT**

Imaging techniques have no place in routine follow-up of localized PCa. They are only justified in individuals with biochemical failure or in patients with symptoms for whom the findings will affect the treatment decision. (See Chapter 19 for a more detailed discussion).

#### **TRUS/MRI biopsy**

Biopsy of the prostate bed and urethrovesical anastomosis are only indicated if the finding of a local recurrence affects the treatment decision.

### 17.4 **When to follow-up?**

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. The patient should therefore be followed-up more closely during the first years after treatment when the risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at the following intervals: 3, 6 and 12 months post-operatively, every 6 months thereafter until 3 years, and then annually. The purpose of the first clinic visit is mainly to detect treatment-related complications and to assist patients in coping with the new situation. Tumour or patient characteristics may allow alterations to this schedule. For example, 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.

Obviously, advanced age or associated co-morbidity may make further follow-up in asymptomatic patients superfluous.

### 17.5 **Guidelines for follow-up after treatment with curative intent**

<b>Recommendations</b>	<b>GR</b>
In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	B
After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.	B
After radiation therapy, a rising PSA level over 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of recurrent disease.	B
Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.	B
Detection of local recurrence by imaging studies is only recommended if it will affect the treatment plan. In most cases, a biopsy is not necessary before second-line therapy.	B

Routine bone scans and other imaging studies are not recommended in asymptomatic patients with no signs of biochemical relapse. If a patient has bone pain or other symptoms of disease progression, re-staging should be considered irrespective of the serum PSA level.

B

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

## 17.6 References

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# 18. FOLLOW-UP DURING HORMONAL TREATMENT

## 18.1 Introduction

A large proportion of patients treated with hormonal therapy have either metastatic or locally advanced tumours at diagnosis. This will affect the scheme of follow-up because biochemical failure is often associated with rapid symptomatic progression.

## 18.2 Purpose of follow-up

The main objectives of following-up these patients are to:

- monitor the response to treatment;
- ensure compliance with treatment;
- detect potential complications of endocrine therapy;
- guide the modalities of palliative symptomatic treatment at the time of CRPC.

It is important to be clear about which complementary investigations are helpful at different stages of the disease to avoid unnecessary patient examinations and excessive economic cost. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up procedures following hormonal therapy.

## 18.3 Methods of follow-up

### 18.3.1 Prostate-specific antigen monitoring

Prostate-specific antigen (PSA) is a good marker for following the course of metastatic PCa. The initial PSA level can be a reflection of the extent of metastatic disease, although some poorly differentiated tumours do not secrete PSA.

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 after hormonal treatment has been initiated. Patients with the lowest absolute value of serum PSA (< 0.2 ng/mL) after 7 months of treatment have been shown to have the best survival compared to patients with a value of 0.2-4.0 ng/mL or > 4.0 ng/mL (1). Similar results have been seen in other studies of locally advanced and metastatic PCa (2,3). The PSA response has been shown to be equally important in patients treated with hormonal therapy, following a rising PSA after treatments with curative intent. Patients with the best response also had the best survival (4).

After the initial phase of response to endocrine treatment, patients should be regularly monitored to detect and treat any complications of endocrine escape. Clinical disease progression occurs after a median interval of about 12-18 months of treatment in patients with stage M1 disease. It is well established that regular PSA control in asymptomatic patients allows the earlier detection of biochemical escape because a rise in PSA level usually precedes the onset of clinical symptoms by several months. However, it must be stressed that the PSA level is not the absolute marker of escape and it should not be used alone as a follow-up test. Clinical disease progression (usually bone pain) with normal PSA levels has been reported.

### 18.3.2 Creatinine, haemoglobin and liver function monitoring

Creatinine monitoring has some value because it can detect upper urinary tract obstruction in cases of advanced cancer, which might need to be relieved by, for example, percutaneous nephrostomy or a JJ-stent. Haemoglobin and liver function tests may suggest disease progression and/or toxicity of hormonal treatment, which can lead to interruption of hormonal treatment (i.e. liver toxicity from non-steroidal antiandrogens). A decline in haemoglobin after 3 months of ADT is associated independently with a shorter progression-free and overall survival (5).

Alkaline phosphatase and its bone-specific isoenzymes have the advantage of not being directly influenced by hormonal therapy compared with PSA. These markers may be used to monitor patients with stage M1b disease. It should be remembered that increases in serum alkaline phosphatase might be due to androgen-induced osteoporosis (6). In this context, it may be helpful to determine the level of bone-specific alkaline phosphatase.

### 18.3.3 Bone scan, ultrasound and chest X-ray

In routine practice, asymptomatic patients with a stable PSA level should not undergo a bone scan at regular intervals because disease progression is more reliably detected by PSA monitoring, which also has a lower cost (7).

Moreover, it is also sometimes difficult to interpret bone scans. Thus, in an asymptomatic patient, the therapeutic approach is not modified by the appearance of a new site of uptake or deterioration of pre-existing



lesions. Recently, the Prostate Cancer Clinical Trials Working Group 2 has clarified the definition of bone scan progression as the appearance of at least two new lesions (8).

Clinical or laboratory suspicion of disease progression indicates the need for a chest X-ray or renal and hepatic ultrasound. Imaging modalities must also be guided by symptoms. However, these examinations are not recommended for a routine use in asymptomatic patients. In CRPC disease, follow-up examinations should be individualized with the aim of maintaining the patient's QoL.

During long-term ADT, it may be necessary to introduce regular measurement of bone mineral density (LE: 3), based on the initial T-score (9). Bone mineral density should be measured every 2 years if the initial T-score < 1.0, or every year if the T-score is between 1.0 and 2.5, in the absence of associated risk factors (LE: 4). Otherwise, active protective bone treatment should have started at the initiation of ADT (see Chapter 12).

#### **18.4 Testosterone monitoring**

Most PCa patients receiving LHRH analogues will achieve serum testosterone values at or below the castration level (< 20 ng/dL). However, about 13-38% of patients fail to achieve this therapeutic goal, while 2-17% of patients do not achieve a serum testosterone level below 50 ng/dL (10,11). Furthermore, up to 24% of men treated with LHRH analogues may experience testosterone surges (testosterone > 50 ng/dL) during long-term treatment upon re-administration of the agonist drug, which is described as the 'acute on-chronic effect' or 'breakthrough response' (10).

In view of these findings, the measurement of serum testosterone levels, as well as serum PSA levels, should be considered as part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. The first evaluation of testosterone level can be recommended at 1 month after initiating LHRH therapy to check the nadir testosterone level achieved before re-administration of the agonist drug. A 6-month testosterone level assessment may be performed to evaluate the effectiveness of treatment and to ensure the castration level is being maintained. If it is not being maintained, switching to another LHRH agent or surgical orchiectomy can be attempted. In patients with a rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

#### **18.5 Monitoring of metabolic complications**

Androgen deprivation therapy is beneficial in patients with prostate cancer, but has a greater range of complications than might be expected (see Chapter 12). The most common side effects of low testosterone levels include hot flashes, lack of libido, erectile dysfunction, gynaecomastia and loss of bone mineral density. In addition, recent studies have suggested that men with low testosterone levels have a higher prevalence of metabolic complications (12), including insulin resistance, arterial stiffness, diabetes and metabolic syndrome. Research has shown that the metabolic syndrome is present in more than 50% of men undergoing long-term ADT, predisposing them to a higher cardiovascular risk (13). Men with metabolic syndrome are almost three times more likely to die of coronary heart disease and other cardiovascular diseases (14), which have now become the most common cause of death in prostate cancer patients, even exceeding prostate cancer mortality (15).

In view of these findings, a cardiology consultation may be beneficial in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months [LE: 3]). In selected cases, glucose tolerance testing may be required. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension (16,17). The patient's GP or family physician should probably be more involved in those patients at risk of cardiovascular disease, including monitoring of fasting glucose, lipids profile and blood pressure, which is recommended in all patients receiving long-term ADT. 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 (12).

Monitoring bone health is also important, particularly serum levels of vitamin D and calcium. If necessary, supplements should be given to ensure the patient receives a daily intake of at least 1200 mg/day of calcium and 1000 UI of vitamin D. Preventive therapy with biphosphonates or denosumab using specific doses (which differ from those used in the CRPC stage) should be considered in patients who have an initial T-score of less than -2.5 on dual-energy X-ray absorptiometry (DEXA), which is the definition of osteoporosis. The FRAX score [<http://www.shef.ac.uk/FRAX/tool.aspx>] is of interest to assess the fracture risk in individual patients. However, optimal bone monitoring using DEXA is still controversial and should be prospectively evaluated. It is currently suggested that bone monitoring should be performed every 2 years after initiation of castration, provided there are no other risk factors (18), and every year if there are risk factors (9,19).

## 18.6 When to follow-up

After initiation of hormonal treatment, it is recommended that patients are followed up at 3 and 6 months. These guidelines must be individualized and each patient should be told to contact his physician in the event of troublesome symptoms.

### 18.6.1 Stage M0 patients

If there is a good treatment response, i.e. symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up visits are scheduled every 6 months.

### 18.6.2 Stage M1 patients

If there is a good treatment response, i.e. good symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up is scheduled every 3 to 6 months.

### 18.6.3 Castration-refractory PCa

Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualized follow-up scheme.

## 18.7 Guidelines for follow-up after hormonal treatment

Recommendations	GR
Patients should be evaluated at 3 and 6 months after the initiation of treatment.	A
As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and side effects.	A
In patients undergoing intermittent androgen deprivation, PSA and testosterone should be monitored at set intervals during the treatment pause (one or three months).	A
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.	A
In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and as a minimum should include a disease-specific history, DRE and serum PSA determination.	A
In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements. The testosterone level should be checked, especially during the first year.	A
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
When disease progression occurs, or if the patient does not respond to the treatment given, follow-up needs to be individualized.	A
In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient has a testosterone level of at least < 50 ng/mL.	B
Routine imaging of stable patients is not recommended.	B

CRPC = castrate-resistant prostate cancer; DRE = digital rectal examination; PSA = prostate-specific antigen.

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# 19. TREATMENT OF PSA-ONLY RECURRENCE AFTER TREATMENT WITH CURATIVE INTENT

## 19.1 Background

Primary curative procedures such as RP, BT and RT are well-established therapeutic options in the management of localised PCa. Despite technical improvements, there is still a significant risk of cancer recurrence after therapy. Between 27-53% of all patients undergoing RP or RT develop PSA-recurrence, and second-line treatment is required in 16-35% of cases (see Chapters 9 and 10). It has to be emphasized that the treatment recommendations for these patients should be given after discussion with a multidisciplinary team.

## 19.2 Definitions

### 19.2.1 Definition of biochemical failure

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. Following RP, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of  $> 0.2$  ng/mL (1). A retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa (2) was used to determine the best PSA cut-off point for defining biochemical recurrence (BCR). Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively (2).

After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of  $> 80\%$ ) is any PSA increase  $> 2$  ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir (3).

## 19.3 Natural history of biochemical failure

Once a PSA relapse has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites.

### 19.3.1 Post-RP biochemical recurrence

According to Pound et al. (4), not all patients with BCF after RP develop clinical recurrence. The authors evaluated the follow-up data for 1,997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data have been confirmed by Boorjian et al. in a study including approximately 2,400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only a few died of PCa (5.8%) (5).

Several important parameters have been suggested in order to differentiate between local and distant relapse:

- Timing of the PSA increase after surgery. PSA increases developing within the first 2 years following surgery are more often associated with distant recurrences (3-4).
- PSADT. It has been shown that a median PSADT of 4.3 months may be more associated with distant relapse, whereas a median PSADT of 11.7 months is a better predictor of local failure (6).
- Histopathological stage, with pT2-3a N0 being more associated with local recurrence, especially when margins are negative (specimen-confined disease). Conversely, pT3b-4 and/or pN1 are more predictive of systemic recurrence and PCa-related death (7).
- Gleason score in the prostatectomy specimen, with specimen Gleason score  $< 8$  being associated more with local recurrence and specimen Gleason score  $\geq 8$  more with systemic recurrence and PCa-related death (1,5).

### 19.3.2 Post-RT biochemical recurrence

In patients who have undergone RT, a rising PSA level of 2 ng/ml over the post-treatment nadir has been defined as biochemical progression by the ASTRO consensus (3). A late and slowly rising PSA level may be a sign of local failure only.

## 19.4 Assessment of metastases

### 19.4.1 Bone scan and abdominopelvic CT

The standard work-up to detect PCa metastases usually includes bone scan (to detect bone metastases) and abdominopelvic CT (to detect lymph node disease). However, because biochemical failure after RP or RT precedes clinical metastases by 7-8 years on average, the diagnostic yield of usual imaging techniques is poor in asymptomatic patients (8). In men with PSA-only recurrence after RP, the probability of a positive bone scan is  $< 5\%$ , when the PSA level is  $< 7$  ng/mL (9,10). A PSADT  $< 6$  months or a PSA velocity  $> 0.5$  ng/mL/month are predictors of positive bone scan (9,11).

CT sensitivity for detecting local recurrences or lymph node metastases is low. Only 11-14% of patients with biochemical failure after RP have a positive CT (9). In a series of 132 men with biochemical failure 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 (11). Therefore, bone scan and abdominopelvic CT should only be considered in patients with biochemical failure after RP who have a high baseline PSA (> 10 ng/mL) or a high PSA velocity (> 0.5 ng/mL/month) or in patients with symptoms of bone disease (9). In case of biochemical failure after RT, the rate of positive bone scan and positive CT also depends on the PSA level and kinetics (9). Detection of occult metastases in asymptomatic patients is useful only if a salvage local treatment is considered.

#### 19.4.2 **Choline and Acetate PET/CT**

The conventional tracer used in oncology (<sup>18</sup>F-fluorodeoxyglucose (FDG)) is of limited value because of its low uptake by PCa. In contrast, <sup>11</sup>C- or <sup>18</sup>F-choline and <sup>11</sup>C-acetate have shown promising results (12). PET/CT accuracy in detecting PCa local and distant recurrences remains difficult to assess because most published studies are retrospective, evaluate heterogeneous populations (often mixing recurrences after various types of primary treatments), use no or non-standardized definitions of biochemical failure and are limited by the lack of a reliable histological gold standard. Furthermore, results may be reported on a per-patient or a per-lesion basis and may combine the detection of local recurrences and distant metastases (12).

Recent studies report overall sensitivities and specificities of 55-96% and 57-100% (12), but these results are likely to be highly influenced by the composition of the study populations. Indeed, choline or acetate PET/CT sensitivity is strongly dependent on the PSA level and velocity (13-21) (Table 19.1). In patients with biochemical failure after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL. This notably limits its clinical usefulness since it is recommended to perform salvage RT before the PSA level reaches 0.5 ng/mL (see below). PET/CT sensitivity is excellent at higher PSA levels, with detection rates of 67-100% when the PSA level is > 5 ng/mL. Similarly, PET/CT sensitivity seems much higher when the PSA velocity is > 2 ng/mL/year or the PSADT is < 3 months (19,20,22) (Table 19.1).

Three studies evaluated <sup>11</sup>C-choline PET/CT in lymph node staging in patients with biochemical failure after primary treatment, using lymph node dissection as gold standard. Scattoni et al. found a sensitivity of 64%, a specificity of 90%, a positive predictive value of 86% and a negative predictive value of 72% (23). The main explanation for the low sensitivity of PET/CT was the lack of detection of micrometastases in lymph nodes. Rinnab et al. found a 100% sensitivity for <sup>11</sup>C-choline PET/CT. However, its positive predictive value was only 53% (24). Another study also found a worrying false positive rate with three of ten patients with pelvic nodal metastases on PET/CT having no tumour confirmed on pathology (25).

<sup>11</sup>C-choline PET/CT may detect multiple bone metastases in patients showing a single metastasis at bone scintigraphy (26) and may be positive for bone metastases in up to 15% of patients with biochemical failure after RP and negative bone scan (15). Other works suggested <sup>11</sup>C-choline PET/CT sensitivity was similar or slightly lower than that of bone scan or <sup>18</sup>F-fluoride PET, especially for sclerotic lesions. However, most studies agree that its specificity is higher with less false positive and indeterminate findings (27,28).

In total, choline- or acetate-PET/CT change medical management in 28-48% of patients with biochemical failure after primary treatment (16,17,21) (Table 19.1).

#### 19.4.3 **Other radionuclide techniques**

<sup>111</sup>In-capromab pendetide scan (ProstaScint™) yielded disappointing results in patients with biochemical failure after RP or RT (8,9). Its use is therefore not recommended.

<sup>18</sup>F-fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases (27).

However, <sup>18</sup>F-fluoride is not tumour-specific and accumulates in benign bone abnormalities. In a study of 38 patients with PCa (including 21 with progression after treatment), <sup>18</sup>F-fluoride PET/CT was more sensitive (81% vs 74%, p=0.12) but significantly less specific (93% vs 99%, p=0.01) than <sup>18</sup>F-choline PET/CT for detecting bone metastases (28). It must also be stressed that <sup>18</sup>F-fluoride imaging is limited by the fact that it does not assess soft-tissue metastases.

#### 19.4.4 **Whole-body and axial MRI**

Diffusion-weighted whole-body MRI and the so-called axial MRI (evaluation of the spine and the pelvi-femoral area only) are more sensitive than bone scan and targeted radiographs (29-31) and seem equally as effective as <sup>11</sup>C-choline PET/CT (32) in detecting bone metastases in patients with high-risk PCa. Their sensitivity for lymph node metastases remains low, even if it is slightly higher than that of <sup>11</sup>C-choline PET/CT in high-risk patients (33).

However, little is known regarding the accuracy of whole-body or axial MRI in the population of patients with biochemical failure after RP or RT (34). Therefore, the role of these techniques in detecting occult

bone or lymph node metastases in case of biochemical failure remains to be assessed.

## **19.5 Assessment of local recurrences**

### **19.5.1 Local recurrence after RP**

A precise localization of the local recurrence by imaging techniques is needed only if histological proof of the recurrence is mandatory before salvage treatment and/or if this localization could change treatment planning (for example total dose and/or target volume of RT).

Transrectal US is neither sensitive nor specific in detecting local recurrences after RP. Even with TRUS guidance, the sensitivity of anastomotic biopsies remains low: 40-71% for PSA levels >1 ng/mL, 14-45% for PSA levels < 1 ng/mL (8). As a consequence, because a negative biopsy does not rule out the presence of a local recurrence and a positive biopsy does not rule out the presence of metastases, salvage RT is usually decided on the basis of the biochemical recurrence, without any histological proof of the local recurrence. The dose delivered to the prostatic bed also tends to be uniform since it has not been demonstrated so far that a focal dose escalation on the site of the recurrence could improve the outcome. Thus, most patients undergo salvage RT without local imaging.

Nonetheless, several studies have reported promising results in detecting local recurrences using MRI, and particularly dynamic contrast-enhanced MRI, with sensitivities and specificities of 84-88% and 89-100% respectively (35-37). However, the mean PSA level in these studies was 0.8-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Recently, a study using multiparametric MRI in 88 patients showed a local recurrence detection rate of 37% in men with a PSA level > 0.3 ng/mL versus only 13% in men with a PSA level < 0.3 ng/mL (38). Thus, it remains to be defined whether MRI will be able to correctly detect local recurrences in patients with a PSA level < 0.5 ng/mL in order to allow a stereotactic boost on the recurrence site during salvage RT. Choline or acetate PET/CT can also detect local recurrences but seems less sensitive than MRI when the PSA level is < 1 ng/mL (39).

### **19.5.2 Local recurrence after radiation therapy**

In patients with biochemical failure 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 salvage options, it is thus necessary to obtain a histological proof of the local recurrence before treating the patient (8).

TRUS is not reliable in defining local recurrences after RT. In contrast, multiparametric MRI has yielded excellent results (8,40-42) (Table 19.2) and can be used for biopsy targeting and guidance of salvage treatment. Detection of recurrent cancer is also feasible with choline and acetate PET/CT, but PET/CT suffers from a poorer spatial resolution than MRI (16,17,19).



**Table 19.1: Detection rates of local and metastatic prostate cancer recurrences in patients with biochemical failure after primary treatment\***

Reference	Tracer	Population	n	PSA range	Detection rate <sup>(1)</sup>	Detection rate as a function of PSA and Gleason
Castellucci, et al. 2009 (20)	<sup>11</sup> C Choline	RP	190	4.2 (0.2-25.4)	38.9%	PSA ≤ 1 ng/mL: 19% ; 1-2: 25% ; 2-5: 41% ; > 5: 67% PSA velocity < 1 ng/mL/yr: 12% ; 1-2: 34% ; 2-5: 42% ; > 5: 70% PSADT ≥ 6 mo: 20% ; 4-6: 40% ; 2-4: 48% ; < 2: 60%
Giovacchini, et al. 2010 (13)	<sup>11</sup> C Choline	RP	109	0.81 <sup>(2)</sup> (0.22-16.8)	11%	PSA 0.2-1 ng/mL: 5% ; 1-2: 15% ; > 2: 28% Gleason ≤ 7: 10.9% ; Gleason > 7: 11.8%
Giovacchini, et al. 2010 (14)	<sup>11</sup> C Choline	RP	358	3.77 (0.23-45.2)	45%	PSA 0.2-0.4 ng/mL: 8% ; 0.4-0.6: 21% ; 0.6-0.8: 30% ; 0.8-1: 26% ; 1-2: 46% ; 2-3: 47% ; 3-5: 80% ; > 5: 83%
Fuccio, et al. 2012 (15)	<sup>11</sup> C Choline	RP	123	3.3 (0.2-25.5)	34%	
Soyka, et al. 2012 (17)	<sup>18</sup> F Choline	RP / RT	156	9.5	79%	
Mitchell, et al. 2013 (16)	<sup>11</sup> C Choline	RP / RT / HT / Cryotherapy	176	9.7 (0-189)	75%	PSA ≤ 1 ng/mL: 44% ; 1-2: 68% ; > 2: 86%
Ceci, et al. 2013 (18)	<sup>11</sup> C Choline	PR	157	8.3	66%	PSA < 2 ng/mL: 31%
Rybalov, et al. 2013 (19)	<sup>11</sup> C Choline	RP / RT	185	-	65%	PSA 0-1 ng/mL: 24% ; 1-2: 33% ; 2-3: 75% ; 3-4: 78% ; > 4: 78% PSA velocity < 1 ng/mL/yr: 40% ; 1-2 : 71 ; 2-4: 84% ; > 4 : 83% PSADT 0-3 mo: 79% ; 3-6: 69% ; 6-9: 70% ; 9-12: 61% ; 12-24: 68% ; > 24: 60%

\*Only series with more than 100 pts have been included.

HIFU = high-intensity focused ultrasound; HT = hormone therapy; mo = months; n = Number of patients; PSADT = PSA doubling time; RP = radical prostatectomy; RT= radiation therapy.

<sup>(1)</sup> Patient-based; <sup>(2)</sup> Median value

**Table 19.2: Performance of prostate multiparametric MRI (T2-weighted, diffusion-weighted and dynamic contrast-enhanced MRI) in detecting and localising local recurrences after radiation therapy**

Reference	n	Mean PSA at imaging	Gold Standard	Analysis	Se (%)	Spe (%)	PPV (%)	NPV (%)	AUC
Arumainayagam, et al. 2010 (40)	13	7.1 (0.83-27.9)	Template biopsy	Per quadrant	78-83 <sup>(1)</sup>	62-86 <sup>(1)</sup>	-	-	0.77-0.89
Akin, et al. 2011 (41)	24	1.63 <sup>(2)</sup> (0.43-6.3)	Biopsy (12-16 samples)	Per patient	81-94 <sup>(1)</sup>	75 <sup>(1)</sup>	-	-	0.86-0.95
				Per lobe	64-82 <sup>(1)</sup>	88 <sup>(1)</sup>	-	-	0.79-0.90
Donati, et al. 2013 (42)	53	2.5 (0.4-33.3)	Biopsy (12-20 samples)	Per patient	49-71 <sup>(3)</sup>	94 <sup>(3)</sup>	94-96 <sup>(3)</sup>	49-63 <sup>(3)</sup>	0.72-0.88
				Per sextant	27-45 <sup>(3)</sup>	94-96 <sup>(3)</sup>	75-77 <sup>(3)</sup>	78-82 <sup>(3)</sup>	0.67-0.75

NPV = negative predictive value; n = number of patients; Se = sensitivity; Spe = specificity; PPV = positive predictive value.

<sup>(1)</sup> For a suspicion score  $\geq 3/5$ ; <sup>(2)</sup> Median value; <sup>(3)</sup> For a suspicion score  $\geq 4/5$

## 19.6 Treatment of PSA-only recurrences

The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial.

After RP, the therapeutic options are:

- Radiotherapy at least to the prostatic bed.
- (Complete) androgen deprivation (CAD, AD).
- Intermittent androgen deprivation (IAD).
- "wait-and-see".

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

### 19.6.1 Radiotherapy (Salvage Radiotherapy -SRT) without and with androgen deprivation therapy for PSA-only recurrence after RP

Early SRT provides 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 again (43-46), providing patients with an ~ 80% chance of being progression-free 5 years later (47). A retrospective analysis based on 635 patients who underwent RP in 1982-2004, followed up through December 2007, who experienced biochemical and/or local recurrence and received no salvage treatment (n = 397) or salvage radiotherapy alone (n = 160) within 2 years of biochemical recurrence, showed that SRT was associated with a threefold increase in the PCa-specific survival relative to those who received no salvage treatment (p < 0.001). Salvage radiotherapy has also been effective in patients with a rapid PSADT (48). Despite the indication of SRT also a "wait and see"-strategy is an option in patients with a long PSADT of more than 12 months (5). For an overview see table 19.3.

**Table 19.3: Selected studies on post-prostatectomy salvage radiotherapy (SRT), sorted by pre-SRT PSA level.** Hormone suppression treatment (HT) can influence the outcome ‘biochemically no evidence of disease (bNED)’ or ‘progression free survival’ (PFS). Therefore, data sets without HT are highlighted. To facilitate comparisons, 5-year bNED/PFS read outs from Kaplan-Meier plots are included.

Reference	Yr	n	HT %	pre-SRT PSA (ng/ml) median	Median Dose (Gy)	bNED / PFS	5-Yr results
Siegmann, et al. (49)	2011	301	0	0.28	66.6 / 70.2	74% (2 y)	55% vs.88% @ 66.6 vs. 70.2 Gy
Wiegel, et al. (47)	2009	162	0	0.33	66.6	54% (3.5y)	60% vs. 33% @ PSA ≤ 0.5 vs. > 0.5
Goenka, et al. (50)	2011	285	31	0.4	> 70 (72%)	37% (7y)	39%
Cremers, et al. (51)	2010	197	0	0.59	63 /2.25 frct. (88%)	59% (5y)	
Bernard, et al. (52)	2010	364	0	0.6	64.8	50% (5y)	
Buskirk, et al. (53)	2006	368	15	0.7	64.8	46% (5y)	63% vs. 51% @ PSA < 0.5 vs. 0.5-1.0
Pazona, et al. (54)	2005	223	4.5	0.8	63	40/25% (5/10y)	42% vs. 30% @ < 1.3 vs. ≥ 1.3
Pisansky, et al. (55)	2000	166	4	0.9	64	46% (5y)	61% vs. 36% @ PSA ≤ 1 vs. > 1
Soto, et al. (56)	2012	441	24	< 1 (58%)	68	63/55% (3y) HT / no HT	44/40% HT / no HT
Stephenson, et al. (43)	2007	1540	14	1.1	64.8	32% (6y)	37%

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

The addition of HT to SRT (n = 78) was not associated with any additional increase in the CSS compared with SRT alone (48). So far, adding ADT to SRT has shown only some benefit in terms of biochemical progression free survival after 5 years in retrospective series (50,57) and for progression-free-survival for “high-risk”-tumours (56), but data from prospective randomised trials are missing. Results are awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting. To date there is no recommendation for patients with primary pN0-stage at RP for a combination of SRT plus additional ADT.

#### 19.6.1.1 Dose, target volume, toxicity

So far, the optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the bed of the seminal vesicles according to the pathological stage after RP) (44). Similarly, a US guideline panel regarded 64-65 Gy as the minimum dose that should be delivered post RP (58). However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at 3-5 years (52). In a systematic review, the pre-SRT PSA level and SRT dose were correlated with biochemical recurrence, showing that the relapse free survival decreased by 2.6% per 0.1 ng/mL PSA and improved by 2% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA (44,59,60).

There have been various attempts to define common outlines for “clinical target volumes” of PCa (61-63) and also for organs at risk of normal tissue complications (64). However, depending on the applied techniques and accepted constraints, a satisfactory consensus has not yet been achieved. The RTOG consensus was achieved considering two PCa cases, one T2c with positive margins at both sides of the apex and one T3b with extracapsular extension at the right base and right seminal vesicle but with negative margins (61).

In one report on SRT with 66.6-70.2 Gy in 1.8 Gy fractions, only 2.7% of the patients had moderate proctitis or cystitis grade II. Four patients (1.3%) had grade III cystitis. Six out of 301 patients (2%) developed urethral stricture which was not solely attributable to SRT but also results from RP alone (45). A retrospective cohort of 285 men receiving 3D-CRT (38%) or IMRT (62%) with 66 Gy in 95% of the cases, the high dose

subgroup did not show a significant increase in toxicity (50). In an analysis with 30 participating centres, a quality assurance program assessing target volumes, RT techniques (3D-CRT, IMRT, VMAT) and RT doses (64 vs. 70 Gy) found that 3D-CRT was applied in nearly half of the centres and was not associated with significantly worse rectum and bladder DVH parameters, for salvage RT using 70 Gy, when compared with IMRT (65).

However, with dose escalation (72 Gy) or up to a median of 76 Gy, the rate of severe side effects especially for the GU-system clearly increases, even with newer planning and treatment techniques (66,67). Of note, compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% ( $p=0.02$ ), while RT technique had no differential effect on the relatively high level of GU toxicity (5-yr: 3D-CRT 15.8% vs. IMRT 16.8%) (66). After a median salvage IMRT dose of 76 Gy, the 5-year risk of grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively (67).

#### 19.6.1.2 Comparison of ART and SRT

In a case-control analysis, 361 ART patients were compared with 722 non-ART patients, who were selected to match the cases by treatment period, age, pre-RP PSA, tumour stage, Gleason score and surgical margin status. While 10-year bNED after ART was significantly improved over non-ART (63 vs. 45%), there was no difference in overall survival. In the same study, an SRT cohort of 856 patients who were treated after biochemical relapse (median PSA 0.8 ng/ml) was followed up over median 5.9 years. Sixty-three percent of the SRT patients achieved an undetectable PSA after SRT and the hazard ratio for local recurrence after SRT was 0.13. However, same as after ART, no improved overall survival could be shown after SRT (68).

The largest retrospective case-matching study to evaluate ART versus early SRT included pT3N0 R0/R1 patients only (HT was excluded), 390 out of 500 observation-plus-early-SRT patients (median pre-SRT PSA was 0.2 ng/ml) were propensity matched with 390 ART patients. Two and five years after surgery, bNED rates were 91 and 78% for ART vs. 93 and 82% after SRT. Subgroup analyses did not yield significant differences for the two approaches, either. It was concluded that early SRT does not impair PCa control but clearly helps to reduce overtreatment which is a major issue in ART (69).

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

Decision-making on whether to proceed with adjuvant RT for high risk PCa - pT3-4 pN0 M0 with undetectable PSA - after radical prostatectomy, or to postpone RT as an early salvage procedure in case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before radical prostatectomy that adjuvant radiotherapy may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of radiotherapy when it is used and provides justification when it is not, and this will help the discussion between the physician and the patient.

#### 19.6.2 Hormonal therapy

##### 19.6.2.1 Postoperative hormonal therapy for PSA-only recurrence

Androgen deprivation therapy

Although patients with postoperative PSA recurrences often undergo ADT before there is any evidence of metastatic disease, the benefit of this approach is uncertain. A retrospective study including 1,352 patients with post-operative PSA recurrence showed no significant difference in the time to clinical metastases with early ADT (after PSA recurrence, but before clinical metastases) vs. delayed ADT (at the time of clinical metastases). However, after risk stratification, it was found that early ADT was able to delay the time to clinical metastases in high-risk patients with a Gleason score  $> 7$  and/or a PSADT  $< 12$  months. ADT had no overall impact on the PCa-specific mortality (70).

It has been shown (71) that adjuvant ADT (within 90 days of surgery) slightly improved the CSS and systemic PFS after RP in a large group of high-risk PCa patients. The survival advantage was lost when ADT was administered later in the disease process, at the time of PSA recurrence or systemic progression. It should be emphasised that there was no advantage with regard to OS (83% in both groups) and that the differences in the CSS and systemic PFS were only 3% and 5%, respectively. In a retrospective study including 422 patients with postoperative PSA recurrences, 123 developed distant metastasis, of whom 91 patients with complete data received deferred ADT at the time of documented metastasis after RP. It was concluded that when closely followed up after PSA recurrence, patients may have an excellent response to deferred ADT and a long survival

period, with a median failure time of 169 months from RP to death (72). These three studies are limited by their retrospective design and in assessing the side effects of long-term ADT. They do not allow any definitive conclusions to be drawn on the use of early HT in clinical practice.

In the setting of PSA-only recurrences, there are no prospective randomised trials and no clinical studies with sufficient data on long-term efficacy to justify the routine clinical application of IAD, despite its potential benefits. In the series in which PSA-only recurrences were treated with IAD (73-76), PSA threshold levels at study entry varied significantly, as did the PSA level at discontinuation of HT. Crook et al. randomly assigned 690 patients to IAD and 696 to CAD. There were no significant between-group differences with regard to adverse events; in the IAD group, full testosterone recovery occurred in 35% of patients, and testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent androgen deprivation provided potential benefits with respect to physical function, fatigue, urinary problems, hot flushes, libido, and erectile function (77).

### 19.6.3 “Wait-and-see”

Observation until the development of clinically evident metastatic disease may represent a viable option for unfit patients with a life expectancy < 10 years and/or are unwilling to undergo salvage treatment. In these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years (4).

## 19.7 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or local procedures such as SRP, cryotherapy, interstitial brachytherapy and high-intensity focused US (78-87). As a general rule, strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of (very) low quality. What follows is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

### 19.7.1 Salvage radical prostatectomy (SRP)

Salvage radical prostatectomy 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.

#### 19.7.1.1 Oncological outcomes

In a recent systematic review of the literature, Chade et al. showed that SRP gave 5- and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The 10-year cancer-specific and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS (88).

In most contemporary series, organ-confined disease, negative SMs, and an absence of seminal vesicle and/or lymph node metastases were favorable prognostic indicators associated with a better disease-free survival of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa (87).

**Table 19.4: Oncological results of selected SRP case series, including at least 30 patients**

Reference	Yr	n	Median FU (months)	Pathologic organ confined, %	PSM, %	Lymph node involvement, %	BCR-free probability, %	CSS, %	Time probability, yr
Sanderson, et al. (89)	2006	51	-	25	36	28	47	-	5
Leonardo, et al. (90)	2009	32	35	53	34	0	75	-	3
Heidenreich, et al. (86)	2010	55	23 (2-56)	73	11	20	87	-	2
Chade, et al. (91)	2011	404	55	55	25	16	37	83	10

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

### 19.7.1.2 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%) (92). In more recent series, these complications appear to be less common (85,88). Functional outcomes are also worse compared to primary surgery, with urinary continence (UI) ranging from 21% to 90% and erectile dysfunction in nearly all patients (88).

**Table 19.5: Perioperative morbidity in selected SRP case series, including at least 30 patients**

Reference	Yr	n	Rectal injury, (%)	Anastomotic Stricture (%)	Clavien 3-5, %	Blood loss, mL, mean, range
Stephenson, et al. (85)	2004	100	15 vs 2*	30	33 vs 13*	-
Ward, et al. (93)	2005	138	5	22	-	-
Sanderson, et al. (89)	2006	51	2	41	6	-
Gotto, et al. (92)	2010	98	9	41	25	-
Heidenreich, et al. (86)	2010	55	2	11	3.6	360 (150-1450)

\* SRP performed before vs after 1993.

*n* = number of patients; SRP = salvage radical prostatectomy.

### 19.7.1.3 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, an organ-confined PCa  $\leq$  T2b, Gleason score  $\leq$  7 and a preoperative PSA  $<$ 10 ng/mL.

### 19.7.2 Salvage cryoablation of the prostate

#### 19.7.2.1 Oncological outcomes

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA  $<$ 10 ng/mL (94). In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year BCR-FS estimate according to the Phoenix criteria was  $54.5 \pm 4.9\%$ . Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP (95).

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The 5-year BCR-FS was 61% following SRP, significantly better than the 21% detected after SCAP. The 5-year OS was also significantly higher in the SRP group (95% vs. 85%) (96).

**Table 19.6: Oncological results of selected SCAP case series, including at least 50 patients**

Reference	Yr	n	Median FU (months)	BCR-free probability, %	Time probability, yr	Definition of failure
Pisters, et al. (97)	1997	150	17	44	-	Nadir +0.2
Bahn, et al. (98)	2003	59	82	59	7 yr	PSA $>$ 0.5
Ismail, et al. (94)	2007	100	33	73 (low risk)	5 yr	ASTRO
Pisters, et al. (95)	2008	279	22	58	5 yr	ASTRO and Phoenix
Williams, et al. (99)	2011	187	7.46 yr	39	10 yr	Nadir +2
Spiess, et al. (100)	2010	450	40.8	34	-	PSA $>$ 0.5

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

#### 19.7.2.2 Morbidity

According to Cespedes et al. (101), the risks of UI and erectile dysfunction at least 12 months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of the patients underwent surgical procedures for the management of treatment-associated complications. The UI rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients had to undergo transurethral resection of the prostate (TURP) for removal of sloughed tissue (95). With the use of third-generation technology, severe complications such as rectourethral fistulae have been significantly less common over the last decade than in the past (102).



**Table 19.7: Perioperative morbidity, erectile function and urinary incontinence in selected SCAP case series, including at least 50 patients**

Reference	Yr	n	Incontinence, %	Obstruction/Retention, %	Rectourethral fistula, %	ED, %
Pisters (97)	1997	150	73	67	1	72
Bahn (98)	2003	59	8	-	3.4	-
Ismail (94)	2007	100	13	4	1	-
Pisters (95)	2008	279	4.4	3.2	1.2	-
Ahmad (103)	2013	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

#### 19.7.2.3 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 10 years, an organ-confined PCA cT1c to cT2, Gleason score  $\leq 7$ , a presalvage PSADT  $\geq 16$  months and a presalvage PSA  $< 10$  ng/mL.

#### 19.7.3 Salvage brachytherapy for radiotherapy failure

Following local recurrence after previous definitive RT there is no indication for external beam salvage RT because the total dose is limited and therefore the chance of cure is low. For carefully selected patients with primary localised PCA and histologically proven local recurrence high- or low-dose rate (H/LDR) brachytherapy remain effective treatment options with an acceptable toxicity profile (104-106). However, the published series are relative small and this treatment therefore should be offered in experienced centers only.

Fifty-two patients were treated at the Scripps Clinic with HDR-brachytherapy over a period of nine years (104). With a median follow-up of 60 months the 5-year biochemical control was 51% and only 2% grade 3 GU toxicity were reported. Comparable with these data, 42 patients were treated in a phase-II-trial at MCCC in New York (107). Of note, the median pretreatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse free survival after 5 years was 69% (median follow up 36 months). Grade 2 late side effects were seen in 15% and one patient developed grade 3 incontinence. However, older data with higher rates of side effects have been reported (108).

Using LDR-brachytherapy with (103)-Pd (palladium) long-term outcome was reported in 37 patients with a median follow-up of 86 months (105). The biochemical control rate after 10 years was 54%. However, the crude rate of  $\geq$  grade 2 toxicity was 46% and  $\geq$  grade 3 toxicity 11%. These rates of side effects were comparable with a series of 31 patients treated with salvage (125)-I brachytherapy in the Netherlands. Therefore, in these small series, late side effects seem to be lower with HDR-brachytherapy (109).

In conclusion, freedom from BCR after salvage HDR- and LDR-brachytherapy is promising and the rate of severe side effects in experienced centers seem to be acceptable. Therefore it remains a treatment option for selected patients with histologically proven local recurrence after RT.

#### 19.7.4 Salvage High-intensity focused ultrasound (HIFU)

##### 19.7.4.1 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 is very short, and outcome measures are non-standardized.

**Table 19.8: Oncological results of selected salvage HIFU case series, including at least 20 patients**

Reference	Yr	n	Median FU (months)	BCR-free probability, %	Negative biopsy rate
Colombel, et al. (110)	2006	224	15-18	-	80
Gelet, et al. (111)	2000				
Gelet, et al. (112)	2004				
Uchida, et al. (113)	2011	22	24	59 (Phoenix) (24 mo)	92 (only 12 biopsied)
Berge, et al. (114)	2011	46	9	60.9 (9 mo)	

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

#### 19.7.4.2 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.

#### 19.7.4.3 Summary of salvage HIFU

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

#### 19.7.5. Observation

Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. watchful waiting in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSADT of > 12 months after RT. The 5-year metastasis-free survival rate was 88% with hormone therapy versus 92% with watchful waiting (P = 0.74) (115).

### 19.8 Guidelines for imaging and second-line therapy after treatment with curative intent

Recommendations	LE	GR
<b>Biochemical failure (BCF) after RP</b>		
In case of BCF, bone scan and abdominopelvic CT should be performed only in patients with a PSA level > 10 ng/mL, or with high PSA kinetics (PSADT < 6 months or a PSA velocity > 0.5 ng/mL/month) or in patients with symptoms of bone disease.	3	A
A choline PET/CT is not recommended in patients with BCF and a PSA-level < 1 ng/mL.	3	A
For patients with a PSA rising out of the undetectable range and favourable prognostic factors (Gleason score < 7) surveillance and possibly delayed salvage RT (SRT) can be offered.	3	B
Patients with a PSA rising out of the undetectable range should be treated with SRT to the prostatic bed at least. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Patients with persistent PSA should be treated with SRT to the prostatic bed at least. The total dose of SRT should be at least 66 Gy and has to be given early (PSA < 0.5 ng/mL).	3	C

Recommendations	LE	GR
<b>Biochemical failure after RT</b>		
In patients with BCF who are candidates for local salvage therapy, prostate multiparametric MRI can guide biopsy.	3	C
Selected patients with localized PCa at primary treatment and histologically proven recurrence without evidence of metastatic disease should be treated with salvage RP (SRP).	3	B
Due to the increased rate of treatment-related complications and side effects, SRP and salvage brachytherapy should only be performed in experienced centres.	3	A
Permanent seed implantation, high-intensity focused ultrasound (HIFU) and cryosurgical ablation are treatment options in carefully selected patients without evidence of metastasis and with histologically proven local recurrence.	3	B

#### 19.9 References

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## 20. CASTRATION-RESISTANT PCA (CRPC)

### 20.1 Background

Our knowledge of the mechanisms involved in the development of castration-resistant prostate cancer (CRPC), remains incomplete, but is starting to become clearer (1,2). An alteration in normal androgen signaling is thought to be central to the pathogenesis of CRPC (3). It is mediated through two main, overlapping, mechanisms, which are androgen-receptor (AR)-independent and AR-dependent.

#### 20.1.1 *Androgen-receptor-independent mechanisms*

Androgen-receptor-independent mechanisms may be associated with the deregulation of apoptosis through the deregulation of oncogenes. High levels of bcl-2 expression are seen with greater frequency as PCA progresses. The regulation of microtubule integrity may be a mechanism through which bcl-2 induces its anti-apoptotic effect (4,5). Indeed, most drugs that are active in CRPC work by inhibiting microtubule formation. The tumour suppressor gene p53 is more frequently mutated in CRPC. Overexpression of bcl-2 and p53 in prostatectomy specimens has been shown to predict an aggressive clinical course (6,7). Clinical trials have been conducted and are underway to target the bcl-2 pathway (8), and the MDM2 (mouse double minute 2) oncogene (9). The PTEN (phosphatase and tensin homolog) suppressor gene may also be involved (10).

### 20.1.2 **Androgen-receptor-dependent mechanisms**

Direct AR-dependent mechanisms comprise the main pathway. Ligand-independent androgen receptor (AR) activation has been suspected, such as the tyrosine-kinase-activated pathway [insulin-like growth factor-1, keratinocyte growth factor, and epidermal growth factor (EGF)]. Epidermal growth factor is a potent mitogen of prostate stromal and epithelial cells. It is produced in high levels locally and acts as a paracrine stimulator. In AR-independent tumours, autocrine stimulation may become more important, which could allow unregulated growth.

Androgen receptor amplification and overexpression are observed in one-third of CRPC tissues (11,12) and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in receptor function (13). At the same time, there is an intracellular increase in androgens from in-situ conversion (14,15). This increase may be secondary to an increase in the enzymes involved in intracellular androgen synthesis (16). Androgen receptor mutations are found in only a subpopulation of tumour cells, therefore, they are unlikely to be responsible for the entire spectrum of the AR-independent state (17). The AR mutations might be related to the selective pressure of anti-androgens (17) and have been involved in the resistance to the new antiandrogens (18). The recent discovery of gene fusion between the androgen-driven TMPRSS2 and the EGR-ETS oncogene family (19) raises the question of oncogene regulation through androgen regulation pathways. In gene fusion, an androgen-responsive element from an androgen-regulated gene becomes associated with genes that are usually not androgen-regulated, so that they too become subject to androgen regulation. Currently, their implication in CRPC is hypothetical. Even in castrated patients, metastatic tissues have repeatedly shown high levels of androgens, suggesting a high level of intracrine synthesis (16,20). It is possible that a high intraprostatic cholesterol level can activate specific androgen pathways (21).

## 20.2 **Definition of relapsing prostate cancer after castration**

The precise definition of recurrent or relapsed PCa remains controversial and several groups have published practical recommendations for defining CRPC (20,21). Table 20.1 lists the key defining factors of CRPC.

**Table 20.1: Definition of CRPC**

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either: Biochemical progression: Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL.
or
Radiological progression: The appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours) (22).

## 20.3 **Assessing treatment outcome in CRPC**

Precise quantification of the effect of treatments on metastatic disease is difficult to quantify and rarely used in clinical practice. Improvements in QoL, progression free survival and prostate cancer specific survival are all used but the gold standard remains overall survival (23).

### 20.3.1 **PSA level as marker of response**

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a surrogate marker. Trials of the vaccines sipuleucel-T (Provenge) (24) and TRICOM (PROSTVAC) (25) have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs (26).

In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effect of drugs on PSA expression should be considered when interpreting PSA response data, which should be viewed together with other clinical data (27-34).

Nevertheless, it has been shown reproducibly that > 50% PSA decline following therapy carries a significant survival advantage (35,36). An improved PSA response was also associated with prolonged survival in the TAX 327 study, with a median survival of 33 months when the PSA was normalized (< 4 ng/mL) vs. 15.8 months for an abnormal PSA. According to the most recent evaluation of the TAX 327 and SWOG 99-16 studies, a PSA decline of > 30% is associated with a significant survival benefit (37,38), although this has not been observed in other studies.

### 20.3.2 Other parameters

The circulating tumour cell (CTC) count was related to survival in several trials (39-41) and might become a surrogate marker for survival if prospective trials confirm its value. The Food and Drug Administration (FDA) has recently approved an assay for CTCs.

In patients with symptomatic bone lesions, pain reduction or complete pain relief may be used as parameters to assess palliative therapeutic response (42). In a landmark analysis of TAX 327, PSA response and pain response, but not QoL response, were independently associated with survival (43).

## 20.4 Androgen deprivation in castration-resistant PCa

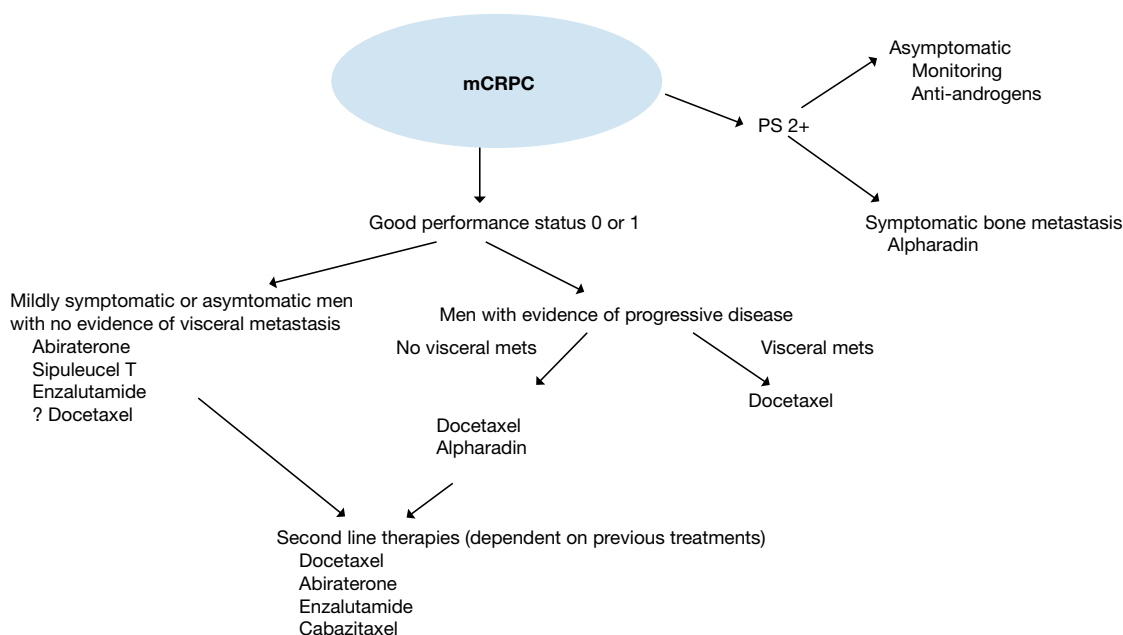
Eventually men with PCa show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in CRPC is debatable, as suggested by Manni et al. (44).

These data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies (45,46). However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition nearly all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients.

## 20.5 Secondary hormonal therapy

For the patient with progressive disease after ADT, there are many therapeutic options. They include addition of anti-androgens, anti-androgen withdrawal, oestrogenic compounds, adrenolytic agents, and novel approaches (47). Figure 20.1 summarises the treatment modalities and expected responses.

**Figure 20.1: Flowchart of the potential therapeutic options after PSA progression following initial hormonal therapy**



## 20.6 Classical hormonal treatment alternatives after CRPC occurrence

A number of second and third line hormonal manipulations remain in use despite the fact that no associated survival benefit has ever been reported.

### 20.6.1 Bicalutamide

Bicalutamide has a dose response, with higher doses producing a greater reduction in PSA level (48). The largest cohort so far is based on 52 CRPC patients treated with 150 mg bicalutamide (49). A palliative effect was clear and a 20% PSA response (at least 50% decrease) was observed, without any link to the palliative effect. The addition of a non-steroidal anti-androgen to gonadal suppression at the time of PSA failure appears to result in declining PSA in only a few patients (50,51).

### 20.6.2 Anti-androgen withdrawal

Approximately one-third of patients who had shown a PSA response to maximum androgen blockade will respond to anti-androgen withdrawal, as indicated by a > 50% PSA decrease, for a median duration of



approximately 4 months. Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (52-57). In the SWOG 9426 trial, PSA progression despite CAB was reported in a subgroup of 210 patients with an M0 or M1 stage tumour (58). A response was observed in 21% of patients, even though there was no radiographic response. Median PFS was 3 months, with 19% (all M0) having PFS > 12 months. Increased PFS and OS were associated with longer use of non-steroidal drugs, lower PSA at baseline and M0-stage. These results were obtained with patients on CAB following androgen withdrawal. No data were available on the withdrawal effect following second-line anti-androgen treatment.

### 20.6.3 Oestrogens

Prostate cancer usually expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. Diethylstilboestrol (DES) (59-61) achieved a positive PSA response in 24% and 80% of patients, with an overall estimated survival of 63% at 2 years. However, even at low doses of DES, about one-third (31%) of patients developed deep venous thrombosis and 7% experienced myocardial infarction.

## 20.7 Novel hormonal drugs targeting the endocrine pathways

In the past 3 years, following early phase I/II trials in patients with CRPC, new compounds appeared for treating CRPC (Section 19.4). Most have been developed post docetaxel, but abiraterone acetate and Enzalutamide have been used before chemotherapy. The initial results of abiraterone use in the pre docetaxel setting have been recently published from the large phase III trial COU-AA-302, in which 1,088 chemo-naïve CRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone (62). Patients were diagnosed with CRPC according to the PCWG2 criteria, and were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and asymptomatic or mildly symptomatic. The study had two joint primary end-points: OS and radiographic PFS. The results reported are from the second preplanned interim analysis. After a median follow-up of 22 months, there was significant radiological PFS (median 16.5 vs. 8.3 months, HR: 0.53,  $p < 0.001$ ). Regarding OS, there was a trend (median not reached vs. 27.2 months, HR: 0.75,  $P = 0.01$ ). However, this value was above the prespecified P value for the second interim analysis ( $p < 0.001$ ), leading to a non-significant difference. All the subgroup analyses and secondary end-points consistently favoured the abiraterone arm. Side effects related to mineralocorticoids and liver function were more frequent with abiraterone, but mostly grade 1/2. These positive results have led to European Medicines Agency (EMA) drug approval.

The Enzalutamide, phase III trial (PREVAIL) has also been unblinded early and presented as ASCO-GU 2014. In a similar chemo-naïve population this also showed a significant improvement in time to radiological progression (HR 0.186 [CI 0.15-0.23]  $p < 0.0001$ ) and statistical improvement in overall survival (HR 0.706 [CI 0.6-0.84]  $p < 0.001$ ). These results have not yet been published and complete results are awaited.

## 20.8 Non-hormonal therapy

Several chemotherapeutic options have been reported from phase III trials in CRPC (Table 20.2). A detailed review is far beyond the scope of these guidelines (1). Docetaxel is currently the standard of care.

### 20.8.1 Docetaxel regimen

A significant improvement in median survival of 2-2.5 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy (63,64). In the SWOG 99-16 trial, pain relief was similar in both groups, although side effects occurred significantly more often with docetaxel than with mitoxantrone, mainly due to the concomitant use of estramustine.

The standard for first-line cytotoxic chemotherapy is docetaxel using the same regimen as in the TAX 327 trial, that is, 75 mg/m<sup>2</sup> 3 weekly combined with prednisone 5 mg BID, up to 10 cycles of survival, and palliation is the main target. The patients considered for docetaxel represent a heterogeneous population. Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, PSADT < 55 days, or the presence of visceral metastases (65). A better risk group definition has been recently presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorized into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), leading to three different lengths of median OS: 25.7, 18.7 and 12.8 months, respectively (38). In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (HR, 2.96) (66,67,72). Age by itself is not a contraindication to docetaxel (68).



**Table 20.2: PSA response rates, mean survival, time to progression, and pain reduction in the large, prospective, randomized phase III trials of chemotherapy in patients with CRPC**

Study	PSA decrease > 50%	Decrease in pain	Survival (mo)	Time to progression
<b>TAX 327 (64)</b>				
Mitoxantrone, every 3 weeks, 12 mg/m <sup>2</sup> , Prednisone 5 mg BID	32%	22%	16.5	
Docetaxel, every 3 weeks, 75 mg/ m <sup>2</sup> prednisone 5 mg BID	45%	35%	18.91	
Docetaxel, weekly, 30 mg/m <sup>2</sup> prednisone 5 mg BID	48%	31%	17.4	
<b>SWOG 99-16 (63)</b>				
Mitoxantrone, every 3 weeks, 12 mg/m <sup>2</sup> prednisone 5 mg BID	50%		15.6	3.2 months
Docetaxel/EMP, every 3 weeks, 60 mg/m <sup>2</sup> , EMP 3 x 280mg/day	27%		17.52	6.3 months
<b>CALGB 9182 (69)</b>				
Hydrocortisone	38%		12.3	2.3 months
Mitoxantrone/HC, every 3 weeks, 12 mg/m <sup>2</sup>	22%		12.6	3.7 months
<b>Tannock et al (70)</b>				
Prednisone	22%	12%		18 weeks
Mitoxantrone, every 3 weeks, 12 mg/m <sup>2</sup> /Pred	33%	29%		43 weeks

EMP = estramustine; HC = hydrocortisone; 1p < 0.000 compared to mitoxantrone; 2p = 0.001 compared to mitoxantrone.

## 20.8.2 Other classical regimen

### 20.8.2.1 Mitoxantrone combined with corticosteroids

Mitoxantrone combined with corticosteroids (69,70) has been extensively studied; primarily in patients with symptomatic bone lesions due to CRPC. Palliation is effective with a clear PSA response and increased PFS, leading to a significant improvement in QoL, no survival benefit has been observed.

### 20.8.2.2 Other chemotherapy regimen

The synergy observed for estramustine combined with other drugs that target microtubule action has generated promising results in prospective clinical trials. Combination with vinblastine is the most frequently studied combination. Significant PSA and measurable responses have been reported, without any survival benefit (71). A recent meta-analysis (72) concluded that addition of estramustine to chemotherapy increased the time to PSA progression and OS. However, there was a significant increased risk (up to 7%) of thromboembolic events, (73), requiring systematic prevention with coumadin.

### 20.8.3 Vaccine

In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients (74). This was the first time that a PCa vaccine had shown a benefit and led to FDA and EMEA approval. Sipuleucel T is an active cellular immunotherapy agent consisting of autologous peripheral blood mononuclear cells, activated in vitro by a recombinant fusion protein comprising prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor, which is an immune-cell activator. In the above trial, patients with metastatic CRPC, with PSA > 5 ng/mL, castrate testosterone level, and no visceral metastases, were randomised to three infusions 2 weeks apart with Sipuleucel T or placebo. Up to two previous chemotherapy regimens were allowed (effective in 19.6% Sipuleucel T treated patients and in 15.2% respectively). The main objective was OS. After a median follow-up of 34 months, the median survival was 25.8 months in the Sipuleucel T group compared to 21.7 months in the placebo group, leading to a significant HR of 0.78 (P = 0.03). Surprisingly, no PSA decline was observed and PFS was equivalent in both arms (14 weeks). The overall tolerance was acceptable, with more cytokine-related adverse events in the Sipuleucel T group but the same grade 3-4 in both arms. Apart from its availability, the major question related to Sipuleucel T is its cost.

## 20.9 How to choose the first “second-line” treatment in CRPC

The timing of second-line treatment remains unclear in metastatic CRPC although it is clearly advisable to start immediately in men with symptomatic metastatic disease. As the number of effective treatments available increases and without head to head trials or data assessing the effectiveness of different sequencing options it is not clear how to choose the first “second-line” treatment although it appears certain that the role of adding anti-androgens will diminish.

## 20.10 Salvage treatment after first-line docetaxel

All patients who receive docetaxel-based chemotherapy for CRPC will progress, thus, there have been many clinical trials investigating the role of salvage chemotherapy. Several groups have used second-line intermittent docetaxel re-treatment in patients who had clearly responded to first-line docetaxel. In general, a PSA response can be achieved in about 60% of patients with a median time to progression of about 6 months, while treatment-associated toxicity is minimal and similar to that of first-line docetaxel (80-82). Structured literature searches were performed to assess LE1 data for the medical management of CRPC. Key findings are presented in Table 20.3.

**Table 20.3: Randomised controlled trials - drug treatment of CRPC\***

Author	Year	Intervention (N)	Comparison (N)	Selection criteria	Main outcomes
<b>ABIRATERONE</b>					
Ryan (62)	2013	Abiraterone + Prednisone (546)	Placebo + Prednisone (542)	No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms. No visceral metastases.	<u>Overall survival</u> : Median not reached vs 27.2 months (p.01). FU: 22.2 months. <u>Progression-free survival</u> : 16.5 vs 8.3 months. <u>Main side effects outcomes</u> : 48% vs 42% grade 3-4.
Fizazi (78)	2012	Abiraterone + Prednisone (797)	Placebo + Prednisone (398)	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	<u>Overall survival</u> : 15.8 vs 11.2 months (p < .0001). FU: 20.2 months. <u>Progression-free survival</u> : 5.6 vs 3.6 months. <u>Main side effects outcomes</u> : Similar.
de Bono (79)	2011				<u>Overall survival</u> : 14.8 vs 10.9 months (p < .001). FU: 12.8 months. <u>Progression-free survival</u> : 5.6 vs 3.6 months. <u>Main side effects outcomes</u> : More mineralocorticoid adverse events with abiraterone.
<b>ALPHARADIN</b>					
Parker (80)	2013	Alpharadin (614)	Placebo (307)	Previous or no previous docetaxel. ECOG 0-2. Two or more bone metastases. No visceral metastases.	<u>Overall survival</u> : 14.9 vs 11.3 months (p.002). FU: Interim analysis. <u>Progression-free survival</u> : 3.6 vs 3.4 months (PSA-progression). <u>Main side effects outcomes</u> : 56% vs 62% grade 3-4.

<b>CABAZITAXEL</b>					
Bahl (81)	2013	Cabazitaxel + Prednisone (378)	Mitoxantrone + Prednisone (377)	Previous docetaxel. ECOG 0-2.	<u>Overall survival:</u> 318/378 vs 346/377 events (odds ratio 2.11; 95% CI 1.33-3.33). FU: 2 years. <u>Progression-free survival:</u> - <u>Main side effects outcomes:</u> Similar.
deBono (82)	2010				<u>Overall survival:</u> 15.1 vs 12.7 months (p < .0001). FU: 12.8 months. <u>Progression-free survival:</u> 2.8 vs 1.4 months. <u>Main side effects outcomes:</u> 82% vs 58% neutropenia.
<b>ENZALUTAMIDE</b>					
Scher (83)	2012	Enzalutamide (800)	Placebo (399)	Previous docetaxel. ECOG 0-2.	<u>Overall survival:</u> 18.4 vs 13.6 months (p<.001). FU: 14.4 months. <u>Progression-free survival:</u> 8.3 vs 2.9 months. <u>Main side effects outcomes:</u> 45.3% vs 53.1% grade 3-4.
<b>SIPULEUCEL-T</b>					
Kantoff (74)	2010	Sipuleucel-T (341)	Placebo (171)	Some with previous docetaxel. ECOG 0-1. Asymptomatic or minimally symptomatic.	<u>Overall survival:</u> 25.8 vs 21.7 months (p.03). FU: 34.1 months. <u>Progression-free survival:</u> 3.7 vs 3.6 months. <u>Main side effects outcomes:</u> 31.7% vs 35.1%.
Small (24)	2006	Sipuleucel-T (82)	Placebo (45)	ECOG 0-1. No visceral metastases. No bone or cancer pain. No corticosteroids.	<u>Overall survival:</u> 25.9 vs 21.4 months (p.01). FU: 36 months. <u>Progression-free survival:</u> 11.7 vs 10.0 weeks. <u>Main side effects outcomes:</u> 31.1% vs 29.3% grade 3, 24.45% both groups grade 4.

\*Only studies reporting survival outcomes have been included.

### 20.10.1 Cabazitaxel

Cabazitaxel is a taxane derivative with some significant differences compared to docetaxel. Positive results have been published from a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with CRPC, who had progressed after or during docetaxel-based chemotherapy (82). Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m<sup>2</sup>) or mitoxantrone (12 mg/m<sup>2</sup>) plus prednisone (10 mg/day), respectively. Overall survival was the primary end-point and PFS, treatment response and safety were secondary end-points. An OS benefit (15.1 vs. 12.7 months, p < 0.0001) was observed in the cabazitaxel arm. There was also a significant improvement in PFS (2.8 vs. 1.4 months, p < 0.0001), objective response rate according to RECIST criteria (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 side effects developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) and non-haematological (57.4% vs. 39.8%, p < 0.0002) toxicity (82). This drug should be administered by physicians with expertise in handling neutropenia and sepsis, with granulocyte colony-stimulating factor in high-risk patient population.

### 20.10.2 Enzalutamide

Enzalutamide is a novel anti-androgen that blocks AR binding, nuclear translocation and transcription. Enzalutamide is used as a once-daily oral treatment. The planned preliminary analysis of the AFFIRM study was published in 2012 (83). This trial randomized 1,199 patients with metastatic CRPC in a 2/1 fashion between enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory but could be prescribed, and therefore received by 30% of the population. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months

compared to 13.6 months in the placebo arm (HR: 0.63,  $p < 0.001$ ). This led to the recommendation that the study be halted and unblinded. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects were observed in the 2 groups, with a lower incidence of grade 3-4 side effects in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm mainly seen in patients with predisposing conditions.

### 20.10.3 *Abiraterone acetate*

Abiraterone acetate is a CYP17 inhibitor. It is used once daily combined with prednisone twice daily (10 mg/day). Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months (79) and the final results have been reported more recently (78). A total of 1,195 patients with metastatic CRPC were randomised in a 1/1 fashion between abiraterone acetate or placebo. 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,  $p < 0.001$ ). The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). With regard to previous docetaxel therapy, no benefit was observed in the abiraterone arm when docetaxel had been used for  $< 3$  months, but the benefit remained independent of the delay since the last dose of docetaxel (less or more than 3 months). The incidence of the most common grade 3/4 side effects did not differ significantly between both arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly grade 1/2 (fluid retention, oedema or hypokalaemia). The longer follow-up did not lead to an unexpected increased in toxicity compared to the preliminary analysis.

As of today, the choice between third-line hormonal treatment (using enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) remains unclear with no clear decision-making findings published. Clinical/biological factors guiding treatment decision are urgently awaited. The optimal sequencing of drugs is not currently known. The cost of each drug will be a major challenge to public health.

## 20.11 Conclusion and recommendations for salvage treatment after docetaxel

Conclusion	LE
No definitive strategy regarding treatment choice (which drug/drug family first) can be devised.	4

Recommendations	LE	GR
Cabazitaxel, abiraterone and enzalutamide are effective in the management of progressive CRPC following docetaxel therapy.	1b	A
Ra 223 improves survival in men with bone predominant disease without visceral metastasis.	1b	A

## 20.12 Bone targeted therapies in mCRPC

CRPC is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is often required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers (84).

### 20.12.1 *Common complications due to bone metastases*

Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation is an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL (85). However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases (86,87). Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression, followed by external beam irradiation (88). Otherwise, external beam radiotherapy, with or without systemic therapy, is the treatment of choice.

### 20.12.2 **Painful bone metastases**

#### 20.12.2.1 *Ra 223 and other radiopharmaceuticals*

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective (89), even as single fraction (90). The two radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients, but should not be given too late when pain is intractable. Early use can give rise to myelosuppression, making subsequent chemotherapy more difficult (91), even though a recent phase I trial has demonstrated manageable haematological toxicity with repeated administration of docetaxel and samarium-153.

The only bone-specific drug that is associated with a survival benefit is alfaradin, a radium 223  $\alpha$ -emitter. In a large phase III trial (ALSYMPCA), 921 patients with symptomatic CRPC, who failed or were unfit for docetaxel therapy, were randomized to six injections of 50 kBq/kg alfaradin or placebo. The primary end-point was OS. Alfaradin significantly improved OS by 3.6 months (HR = 0.70;  $p < 0.001$ ) (80). It was also associated with prolonged time to first skeletal event and improvement in QoL. The associated toxicity was minimal, specially the hematologic one, and did not differ significantly from that in the placebo arm (80).

#### 20.12.3 **Bisphosphonates**

Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in CRPC. In the largest single phase III trial to date (92), 643 patients who had CRPC with bone metastases were randomized to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44% vs. 33%,  $P = 0.021$ ) and fewer pathological fractures (13.1% vs. 22.1%,  $P = 0.015$ ). Furthermore, the time to first SRE was longer in the zoledronic acid group, thus improving QoL. Patients were initially randomized to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg because of toxicity. No survival benefit was seen in any trial with bisphosphonates, except in a post hoc analysis of an old compound without any significant impact on SREs (93).

Currently, bisphosphonates can be offered to patients with CRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear. At present, it is every 3 weeks or less. The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind (92). Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as intravenous long-term bisphosphonate administration (94).

Pain due to bone metastases is one of the most debilitating complications of CRPC. Bisphosphonates have proven to be highly effective in reducing bone pain, but so far this has been investigated only in small, open trials. Data from these trials suggest that bisphosphonates have a low side-effect profile (95-97). Bisphosphonates should be considered early in the management of symptomatic CRPC. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur (i.e., palliative external beam radiation, cortisone, analgesics and antiemetics).

#### 20.12.4 **RANK ligand inhibitors**

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor  $\kappa$ B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85,  $P = 0.028$ ) (95). However, this benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively). The practical impact of this finding remains under discussion. 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 NTX and BAP were significantly suppressed in the denosumab arm compared with the zoledronic acid arm ( $p < 0.0001$  for both). However, these positive findings were not associated with any survival benefit.

### 20.13 Recommendations for treatment after hormonal therapy (first second-line modality) in metastatic CRPC

Recommendations	LE	GR
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	2b	B
Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.		A
Patients should not be started on second-line therapy unless their PSA serum levels are > 2 ng/mL to ensure correct interpretation of therapeutic efficacy.		B
Men treated with maximal androgen blockade should stop the anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i>	1b	A
No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.	3	A
Second-line salvage hormonal treatment using abiraterone acetate is considered to be a valid option. It must be remembered that one of the 2 coprimary end-points of the pivotal trial has not yet been met.	2b	A
Second-line salvage hormonal treatment using enzalutamide might become a valid option. But a full paper is awaited.	2b	C
In non-metastatic CRPC, secondary hormonal treatment (AA, Enza) should only be used in a clinical trial setting.	3	A

CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen; MAB = maximal androgen blockade.

### 20.14 Recommendations for cytotoxic treatment and pre/post-docetaxel therapy in mCRPC

Recommendations	LE	GR
Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.	3	A
In non-metastatic CRPC, cytotoxic therapy should only be used in a clinical trial setting.	3	B
Prior to treatment, the potential benefits of second-line therapy and expected side effects should be discussed with the patient.		C
In patients with metastatic CRPC who are candidates for cytotoxic therapy, docetaxel at 75 mg/m <sup>2</sup> every 3 weeks has shown a significant survival benefit.	1a	A
Docetaxel chemotherapy improves QoL and provides pain relief for men with symptomatic bone metastases due to mCRPC.	1a	A
In patients with relapse following first-line docetaxel chemotherapy cabazitaxel, abiraterone and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	1a	A
In men with mCRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit.	2a	A

mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.



## 20.15 Recommendations for “non-specific” management of mCRPC

Recommendations	LE	GR
Management of patients with extended symptomatic bone metastases has to be directed at improvement of QoL and mainly pain reduction.	1a	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.	1a	A
Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	1a	A
Calcium and vitamin D supplementation must be systematically considered when using either denosumab or biphosphonates.	1b	A
In the management of painful bone metastases, early use of palliative treatments such as radionuclides, external beam radiotherapy and adequate use of analgesics is recommended.	1a	B
In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must be always initially considered.	1b	A

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## 21. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations*

3D-US	three-dimensional ultrasound
aCGA	abbreviated comprehensive geriatric assessment
ADT	androgen-deprivation therapy
AR	androgen-receptor
ART	adjuvant radiotherapy
AS	active surveillance
ASAP	atypical small acinar proliferation
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
AUA	American Urological Association
BCF	biochemical failure
BCR-FS	biochemical recurrence-free survival
BCR	biochemical recurrence
BDFS	biochemical disease-free survival
BMD	bone mineral density
bNED	biochemically no evidence of disease
BPH	benign prostatic hypertrophy
BPSA	benign PSA
CAB	complete (or maximal or total) androgen blockade
CAD	complete androgen deprivation
CISR-G	cumulative illness score rating-geriatrics
CPA	cyproterone acetate
cPSA	complex PSA
CRT	conformal radiotherapy
CRPC	castration-resistant prostate cancer
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
CTC	circulating tumour cells
DES	diethylstilbestrol
DRE	digital rectal examination
DHT	dihydrotestosterone
DSS	disease-specific survival
DT	doubling time
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EEC	extracapsular extension of carcinoma
EGF	epidermal growth factor
eLND	extended lymph node dissection
EMA	European Medicines Agency
e-MRI	endorectal MRI
EORTC	European Organisation for Research and Treatment of Cancer
EPC	Early Prostate Cancer Trialists' Group
EPE	extraprostatic extension
ER-®	oestrogen receptor-®
ERSPC	European Randomized Screening for Prostate Cancer
FACT-P	Functional Assessment of Cancer Therapy-prostate
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FNAB	fine-needle aspiration biopsy
FSH	follicle-stimulating hormone
GETUG	Groupe d'Etude des Tumeurs Uro-Génitales
GFI	groningen frailty index
GI	gastrointestinal
GR	grade of recommendation
GU	genitourinary
HD EBRT	high-dose EBRT

HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
IAD	intermittent androgen deprivation
IGRT	image-guided radiotherapy
IMRT	intensity modulated radiotherapy
iPSA	intact PSA
IPSS	International Prostatic Symptom Score
LDR	low-dose rate
LE	level of evidence
LET	linear energy transfer
LH	luteinising hormone
LHRH	luteinising hormone-releasing hormone
LHRHa	luteinising hormone-releasing hormone analogue
LND	lymph node dissection
LRP	laparoscopic radical prostatectomy
MAB	maximal androgen blockade
MDM2	mouse double minute 2
MRC	Medical Research Council
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NCCN	National Comprehensive Cancer Network
NCIC	National Cancer Institute of Canada
NHT	neoadjuvant hormonal therapy
NIH	National Institutes of Health
NNT	number needed to treat
NSAA	non-steroidal anti-androgen
NVB	neurovascular bundle
OR	odds ratio
OS	overall survival
PAP	prostatic acid phosphatase
PCa	prostate cancer
PCOS	prostate cancer outcomes study
PET	positron emission tomography
PFS	progression-free survival
PIN	prostatic intraepithelial neoplasia
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colorectal and Ovary
PMB	prostate mapping biopsy
proPSA	precursor isoforms PSA
PSA	prostate-specific antigen
PSADT	PSA doubling time
PSAV	PSA velocity
PSMA	prostate-specific membrane antigen
PTEN	phosphatase and tensin homolog
QoL	quality of life
QUALYs	quality adjusted life years
RADICALS	radiotherapy and androgen deprivation in combination after local surgery
RARP	robot-assisted radical prostatectomy
RANKL	receptor activator of nuclear factor $\kappa$ B ligand
RAVES	radiotherapy adjuvant versus early salvage
RECIST	Response Evaluation Criteria In Solid Tumours
RP	radical prostatectomy
RR	relative risk
RRP	radical retropubic prostatectomy
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group

SCAP	salvage cryoablation of the prostate
SEER	Surveillance, Epidemiology, and End Results
SELECT	selenium and vitamin E cancer prevention trial
SIOG	International Society of Geriatric Oncology
SLN	sentinel lymph node
SLRP	salvage laparoscopic radical prostatectomy
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
SRE	skeletal-related events
SRP	salvage radical prostatectomy
SRT	salvage radiotherapy
STAD	short-term androgen deprivation
SV	seminal vesicle
SVI	seminal vesicle invasion
SWOG	Southwest Oncology Group
TNM	Tumour Node Metastasis
TROG	Trans-Tasman Oncology Group
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UI	urinary incontinence
US PSA	ultra-sensitive PSA
VACURG	Veterans Administration Co-operative Urological Research Group
VES	vulnerable elders survey
WHO	World Health Organization
WW	watchful waiting

### **Conflict of interest**

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