

Guidelines on Prostate Cancer

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Prostate Cancer Guidelines Panel have prepared this guidelines document to assist medical professionals assess the evidence-based management of prostate cancer (PCa).

1.2 Panel composition

The Prostate Cancer Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, a radiologist, a pathologist and a patient stakeholder organisation representative.

1.2.1 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 prostate cancer in senior adults'. As a leading expert in this field, and prominent member of the International Society of Geriatric Oncology, his contribution has been invaluable.

1.2.2 Potential conflict of interest

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the Prostate Cancer guidelines. All documents can be viewed, free access, through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The first EAU Guidelines on Prostate Cancer were published in 2001. This current 2015 document presents a full update of the 2014 full text document. The literature for the complete document has been assessed and updated, whenever relevant.

1.4.2 Summary of changes

Key changes for this 2015 print:

Table 4.1.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	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	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

Conclusions and recommendations have been rephrased and added to throughout the current document. Changed or new conclusions and recommendations can be found in sections:

5.2.4.3 Guidelines for imaging

	LE	GR
When clinical suspicion of PCa persists in spite of negative biopsies, MRI-targeted biopsies are recommended.	2b	B

Table 5.2.4: Recommended terminology for reporting prostate biopsies [3]

• Benign/negative for malignancy. If appropriate, include a description.
• Active inflammation.
• Granulomatous inflammation.
• High-grade PIN.
• High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP).
• Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer.
• Adenocarcinoma.

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

	LE	GR
Transurethral resection of the prostate should not be used as a tool for cancer detection.	2a	A

5.3.4 **Guidelines for staging of prostate cancer**

Any risk group staging	LE	GR
Additional imaging is required only if it changes patient management.	2a	A*
For local staging, CT and TRUS should not be used.	3	A
For up-front staging, PET-scanning should not be used.	2a	A

Low-risk localised PCa	LE	GR
No additional imaging is recommended for staging purposes.	2a	A

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4, bone scan and cross-sectional imaging is required.	2a	A*

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Prostate mpMRI should be used for local staging.	2b	A
CT/MRI and bone-scan should be used in staging.	2b	A
For up-front staging, PET-scanning should not be used.	2a	A

7.1.5 **Guidelines for active surveillance and watchful waiting**

Recommendations - active surveillance	LE	GR
Patients who are suitable for surgery and radiotherapy must have these options discussed with them.	4	A*

7.2.11 Guidelines for radical prostatectomy

	LE	GR
Patients who are suitable for AS and radiotherapy must have these options discussed with them.	4	A*
In patients with low- and intermediate-risk PCa and a life expectancy > 10 years, RP should be offered.	1b	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 may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	2b	B
In patients with high-risk localised PCa and a life expectancy of > 10 yr, RP should be offered in a multimodality setting.	2a	A
In selected patients with locally advanced (cT3a) PCa, and a life expectancy > 10 yr, RP may be offered in a multimodality setting.	2b	B
In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	3	C
NHT before RP is not recommended.	1a	A
Adjuvant HT for pN0 is not recommended.	1a	A
Adjuvant ADT is the standard of care for node-positive (pN+) patients.	1b	A

7.3.10 Conclusion and Guidelines for definitive radiotherapy

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

Recommendations	LE	GR
Patients who are suitable for AS and surgery must have these options discussed with them.	4	A
EBRT should be offered in all risk groups of non-metastatic PCa.	2a	A
In low-risk PCa, the total dose should be 74 to 78 Gy.	1a	A
In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	2a	A
In intermediate-risk PCa, a total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	1b	A
In patients with high-risk localised PCa, a total dose of 76-78 Gy in combination with long-term ADT (2-3 yr) is recommended.	1b	A
In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr).	1a	A
IMRT is the recommended modality for definitive treatment of PCa by EBRT.	2a	A
In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	2b	B
In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	1a	A
Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (See Section 6.10.5.1).	2b	A

Primary treatment of prostate cancer		GR	
General comments	Patients suitable for several treatment modalities (active surveillance, surgery, radiotherapy) must have these options discussed with them.	A*	
	In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable as no single approach has shown clear superiority in terms of functional or oncological results.	A	
	EBRT should be offered in all risk groups of non-metastatic PCa.	A	
	IMRT is the recommended modality for definitive treatment of PCa by EBRT.	A	
	Treatment	Comment	
Low risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
		During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression.	B
	Active surveillance	Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A
		Follow-up should be based on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	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).	B
		LND is not indicated in low-risk PCa.	A
	Radiotherapy	In low-risk PCa the total dose should be 74 to 78 Gy.	A
		In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	A
	Cryotherapy, HIFU	In patients who are unfit for surgery or radiotherapy, cryotherapy or HIFU might be an alternative treatment for PCa. The lack of long-term efficacy compared to standard modality should be discussed with patients.	C
	Focal treatment	Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A
	Androgen suppression	Unsuitable.	A
Intermediate risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
	Active surveillance	Not an option.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	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).	B

		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		eLND should be performed if the estimated risk for positive lymph nodes exceeds 5%.	B
		Limited LND should not be performed.	A
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
		Adjuvant HT for pN0 is not recommended.	
	Radiotherapy	In intermediate-risk PCa, the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A
	Androgen suppression monotherapy	No place in asymptomatic patients.	A
High risk PCa	Watchful waiting	High risk localised: Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	
		High risk locally advanced: In M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSA-DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	A
	Active surveillance	Not appropriate.	A
	Radical prostatectomy	NHT before RP is not recommended.	A
		eLND should be performed in high-risk PCa.	A
		Limited LND should not be performed.	A
		High risk localised: In patients with high-risk localised PCa and a life expectancy of > 10 yr, RP should be offered in a multimodality setting.	B
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (refer to Partin tables/nomograms).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		High risk locally advanced: In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	C
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A

	Radiotherapy	In patients with high-risk localised PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yr is recommended).	A	
		In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr is recommended).	A	
	Androgen suppression monotherapy	Reserved for those unwilling or unable to receive any form of local treatment and either symptomatic or asymptomatic with a PSA-DT < 12 months and a PSA > 50 ng/mL and a poorly differentiated tumour.	A	
N1 patients				
cN1		In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	B	
pN1 after eLND		Adjuvant ADT is the standard of care for node-positive (pN+) patients.	A	
		Adjuvant ADT with additional radiotherapy may have a role.	B	
		Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.	B	
Metastatic PCa	Watchful waiting	In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	B	
	Active surveillance	Unsuitable.	A	
	Radical prostatectomy	Unsuitable outside clinical trial.	A	
	Radiotherapy to the prostate	Unsuitable outside clinical trial.	A	
	Androgen suppression		Surgical- or medical castration (LHRH agonist or antagonist).	A
			No recommendation can be made to define the best population for combining castration with upfront Docetaxel.	A
			Castration combined with local treatment / other new hormonal treatments (abiraterone acetate or Enzalutamide) should not be used outside clinical trials.	A
			In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	A
			In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	A
			In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	A
			In M1 patients short-term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection).	A
		In M1 patients, administration of anti-androgens as monotherapy should not be considered.	A	
		In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	B	

		Based on the schedules in use in clinical trials, treatment is stopped when the PSA is < 4 ng/mL after 6 to 7 months of treatment. Treatment is resumed when the PSA is > 10-20 ng/mL.	C
		Combined treatment with LHRH agonists and NSAA is recommended.	A
		Antagonists might be an option.	B
Castrate resistant status		Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.	A
		There is no evidence for treatment of non-metastatic CRPC outside a clinical trial.	A
		Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.	A
		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>	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.	A
		Salvage hormonal treatment using abiraterone acetate is a valid option.	A
		Salvage hormonal treatment using enzalutamide is a valid option.	A
		In patients with metastatic CRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m ² every 3 weeks has shown a significant survival benefit.	A
		In patients with relapse following salvage docetaxel chemotherapy cabazitaxel, abiraterone acetate and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	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.	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.	A
		Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	A
	In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must always be initially considered.	A	

A* Upgraded following panel consensus.

ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; LHRH = luteinising-hormone-releasing hormone; (e)LND = (extended) lymph node dissection; mCRPC = metastatic castrate-resistant prostate cancer; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSA-DT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

2. METHODS

2.1 Data identification and evidence sources

For all chapters of this 2015 Guidelines document, the literature has been assessed and updated. In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

2.3 Future plans

For their 2016 update, the Guidelines Panel aim to present the results of a number of ongoing systematic reviews.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Prostate cancer (PCa) is the most common cancer in elderly males (> 70 years of age) 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 [4]. There is still a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe [5]. Overall, during the last decade, the 5-year relative survival percentages for PCa steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 [5].

With the expected increase 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 PCa in Europe exceed € 8.43 billion [6], with a high proportion of the costs of PCa 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 PCa patients diagnosed in 2006.

3.2 Risk factors and chemoprevention

The factors that determine the risk of developing clinical 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 [7, 8]. A small subpopulation of men with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before age 55 [8]. Patients with hereditary PCa usually have an onset six to seven years earlier than spontaneous cases, but do not differ in other ways [8].

The frequency of incidentally- and autopsy-detected cancers is roughly the same in different parts of the world [273]. 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 [9].

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 [10, 11] and occupational exposure have all been discussed as being aetiologically important [11]. PCa may be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to the following specific features:

- high prevalence
- long latency
- endocrine dependency
- availability of serum markers (PSA)
- the histological precursor lesion prostatic intraepithelial neoplasia [10].

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 [12]. Similarly, a meta-analysis of eight randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [13].

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 [14]. 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 the 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 [15-17]. 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 the risk of progression. There is, as yet, insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk [18].

3.2.1 **Guideline for preventative measures**

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

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world and to make recommendations on their treatment. Throughout this guideline we made use of the 2009 TNM classification for staging of PCa (Table 4.1.1) [19] and the EAU risk group classification essentially based on D'Amico's classification system for PCa (Table 4.1.2) [20]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after surgery or external beam radiotherapy.

Table 4.1.1: Tumour Node Metastasis (TNM) classification of PCa [19]

T - Primary tumour	
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 ¹
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 ²
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes³	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis ⁴
M - Distant metastasis⁵	
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)

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

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

³ The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.

⁴ Laterality does not affect the N-classification

⁵ When more than one site of metastasis is present, the most advanced category should be used.

Table 4.1.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	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	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

5. DIAGNOSTIC EVALUATION

5.1 Screening and early detection

Population or mass screening is defined as the systematic examination of asymptomatic men (at risk) and is usually initiated by health authorities. In contrast, early detection or opportunistic screening consists of individual case findings, which are initiated by the person being screened (patient) and/or his physician. The co-primary endpoints of both types of screening are:

- reduction in mortality due to 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 industrialised world [21]. Mortality due to PCa has decreased 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 [22]. However, there is still no level 1 evidence that prostate-specific antigen (PSA) screening reduces mortality due to PCa [23].

Currently, screening for PCa is one of the most controversial topics in the urological literature [24]. Three large prospective RCTs published data on screening in 2009 [25-27]. Heated discussions and debates resulted in many conflicting positions and policy papers. Some authors argue that the use of current AUA guidelines recommendations for screening may lead to missing a substantial number of men with aggressive disease [28, 29]. The potential impact of this topic would necessitate the highest level of evidence produced through a systematic literature search of all published trials or cohorts summarised in a structured meta-analysis. Subgroup analyses of cohorts that are part of large trials, or mathematical projections, cannot provide the quality of evidence needed to appropriately address this clinical question.

The main summary of findings from literature published on PCa screening is the Cochrane review published in 2013 [23]. This review was based on an up-to-date systematic literature search until 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 localised disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80; 95% CI: 0.73-0.87).
- From the results of five RCTs, representing more than 341,000 randomised 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 followed by (OS) 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 other known data [16, 17].

The impact on the patient's overall QoL is still unclear. It appears to be minimal in some subgroup analyses [30], but significant in others [31]. This has led to strong advice against population-based systematic screening in all countries, including Europe.

Since 2013, the ERSPC data have been updated with a 13 years of follow up (see Table 5.1.1) [32]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen and to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials [33].

Table 5.1.1 Follow-up data from the ERSPC study [32]

	Number needed to screen	Number needed to treat
9 years of follow-up	1410	48
11 years of follow-up	979	35
13 years of follow-up	781	27

Thus, an individualised risk-adapted strategy for early detection might be offered to a well-informed man with a least 10-15 years of individual life expectancy. However, this approach may still be associated with a substantial risk of overdiagnosis. It is therefore important to carefully identify 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 > 50 years, or with a family history of PCa and age > 45 years, or African-Americans [34]. In addition, men with PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [35, 36] are also at increased risk of PCa metastasis or death several decades later. Recently, as for breast cancer, a genetic abnormality likely to be associated with an increased risk has been shown prospectively [37]. Its everyday use requires further studies and cannot yet be recommended.

Risk calculators may be useful in helping to decide (on an individual basis) the potential risk of cancer whilst reducing the number of unnecessary biopsies. Several tools exist developed from several cohorts (from the PCPT cohort: PCPTRC 2.0: <http://deb.uthscsa.edu/JRORiskCalc/Pages/calcs.jsp>; from the ERSPC cohort: <http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators>, from a local Canadian cohort: <http://sunnybrook.ca/content/?page=occ-prostatecalc>, among others). Since none has clearly shown superiority it is impossible to provide a recommendation and it remains a personal decision which one to use [38].

Early baseline testing could be used to detect men at risk and in need of further follow-up. However, the long-term benefit for survival and QoL of such an approach remains to be proven at a population level.

Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [39]. 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.

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. Furthermore, although there is no simple tool to evaluate individual life expectancy, co-morbidity is at least as important as age. A detailed review can be found in the section on senior adults and in the recently updated SIOG guidelines [40].

Based on the tools currently available, an individualised strategy will diagnose many insignificant lesions (above 50% in some trials), most of which will not require any form of active treatment (Section 7.1, Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only way to decrease overtreatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

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

5.1.1 Guidelines for screening and early detection

	LE	GR
An individualised 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 should be offered to men at elevated risk for PCa. Risk groups are: <ul style="list-style-type: none"> men over 50 years of age men over 45 years of age and a family history of PCa African-Americans men with a PSA level of > 1 ng/mL at 40 years of age men with a PSA level of > 2 ng/mL at 60 years of age 	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

5.2 Clinical diagnosis

Prostate cancer is usually suspected on the basis of digital rectal examination (DRE) and/or prostate-specific antigen (PSA) levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from TURP or prostatectomy for benign prostatic enlargement (BPE).

5.2.1 Digital rectal examination

Most prostate cancers are located in the peripheral zone and may be detected by DRE when the volume is ≥ 0.2 mL. In $\sim 18\%$ of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [41]. Suspect DRE in patients with PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [42]. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy [43, 44].

5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [45]. PSA is organ- but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than DRE or transrectal ultrasound (TRUS) [46].

There are no agreed standards defined for measuring PSA [47]. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [48]. Table 5.2.1 demonstrates the occurrence of Gleason ≥ 7 PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant PCa. The use of nomograms may help in predicting indolent PCa [49].

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

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

5.2.2.1 PSA density

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

5.2.2.2 PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [50];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [51].

PSAV and PSA-DT may have a prognostic role in treated PCa [52], but limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time. These measurements do not provide additional information compared with PSA alone [53-56].

5.2.2.3 Free/total PSA ratio

Free/total (f/t) PSA ratio is widely used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. PCa was detected by biopsy in 56% of men with f/t PSA < 0.10 , but in only 8% with f/t PSA > 0.25 [57]. f/t PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow-up of known PCa.

f/t PSA must be used cautiously because it may be adversely affected by several preanalytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [58].

5.2.2.4 Prostate Health Index (PHI) test

The Prostate Health Index (PHI) test is a recently approved diagnostic blood test, combining free and total PSA and the (-2) pro PSA isoform (p2PSA), intended to reduce the number of unnecessary prostate biopsies in PSA tested men. A few prospective multicentre studies demonstrated that the PHI test not only outperforms free and total PSA PCa detection, but has an improved prediction of clinically significant PCa, both in men with a PSA between 4-10 ng /mL and between 2-10 ng /mL. The PHI test may therefore also have a role in monitoring men under active surveillance [59]. Its clinical impact is, as yet undetermined, given the slight net benefit for clinical decision-making [60].

5.2.2.5 *PCA3 marker*

PCA3 is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The ProgenSA urine test for PCA3 is now commercially available. PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies [61-64].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts Gleason score, and its use for monitoring in active surveillance is unconfirmed [65]. Currently, the main indication for the ProgenSA test is to determine whether repeat biopsy is needed after an initially negative biopsy.

5.2.3 **Prostate biopsy**

5.2.3.1 *Baseline biopsy*

The need for prostate biopsy is based on PSA level and/or suspicious DRE. Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [66]. Risk stratification is a potential tool for reducing unnecessary biopsies [66].

Limited PSA elevation alone, should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory [67, 68]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [69].

Ultrasound-guided biopsy is now the standard of care. A transrectal approach is used for most prostate biopsies, although some urologists prefer a perineal approach. Cancer detection rates are comparable with both approaches [70, 71].

5.2.3.2 *Repeat biopsy after previously negative biopsy*

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2 for risk estimates);
- suspicious DRE, 5-30% cancer risk [41, 42];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 40% risk [72];
- extensive (multiple biopsy sites, i.e., ≥ 3) high grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [72, 73];
- A few atypical glands immediately adjacent to high grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [74].

Isolated high-grade PIN in one or two biopsy sites is no longer an indication for repeat biopsy [75].

5.2.3.3 *Saturation biopsy*

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30-43% and depends on the number of cores sampled during earlier biopsies [76]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback [77].

5.2.3.4 *Sampling sites and number of cores*

On baseline biopsies, the sample sites should be bilateral from apex to base as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS.

Sextant biopsy is no longer considered adequate. For prostate volume 30-40 mL, ≥ 8 cores should be sampled. Ten to 12 core biopsies are recommended [78], with > 12 cores not being significantly more conclusive [79, 80].

5.2.3.5 *Diagnostic transurethral resection of the prostate*

Transurethral resection of the prostate (TURP) should not be used as a tool for cancer detection [81].

5.2.3.6 *Seminal vesicle biopsy*

Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA > 15 ng/mL, the odds of tumour involvement are 20-25% [82]. Seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or radiotherapy. Its added value compared with multiparametric MRI (mpMRI) is questionable.

5.2.3.7 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be confined to repeat biopsies [83].

5.2.3.8 Antibiotics prior to biopsy

Oral or intravenous antibiotics are state-of-the-art. Quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin [84]. Increased quinolone resistance [85] is associated with a rise in severe post-biopsy infection [86].

5.2.3.9 Local anaesthesia prior to biopsy

Ultrasound-guided periprostatic block is state-of-the-art [87]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [88].

5.2.3.10 Fine-needle aspiration biopsy

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

5.2.3.11 Complications

Biopsy complications are listed in Table 5.2.2 [89]. Severe postprocedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [90].

Low-dose aspirin is no longer an absolute contraindication [91].

Table 5.2.2: Percentage of complications per biopsy session, irrespective of the number of cores

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

5.2.4 Role of imaging

5.2.4.1 TRUS

Classic hypoechoogenicity in the peripheral prostate is not always seen. Grey-scale TRUS is not reliable at detecting PCa [92]. Thus, there is no evidence that targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography, contrast-enhanced ultrasound or computerised ultrasound (Histoscanning™) are being investigated. There is not currently enough evidence for their routine use.

5.2.4.2 Multiparametric MRI (mpMRI)

Correlation with radical prostatectomy (RP) shows that mpMRI, associating T2-weighted imaging with diffusion-weighted imaging, dynamic contrast-enhanced imaging, or H1-spectroscopy, has excellent sensitivity for Gleason score ≥ 7 cancers (Table 5.2.3) [93-96].

Table 5.2.3: PCa detection rates (%) by mpMRI by tumour volume and Gleason score [96]

Gleason score	Tumour volume (mL)		
	< 0.5	0.5-2	> 2
GS6	21-29%	43-54%	67-75%
GS7	63%	82-88%	97%
GS > 7	80%	93%	100%

mpMRI may detect anterior tumours missed by systematic biopsy [97, 98]. In 265 patients undergoing repeat biopsy, mpMRI-guided samples were positive in 41%, and 87% of the cancers were clinically significant [99].

Biopsies targeted on MR abnormalities also seem to evaluate PCa aggressiveness better than systematic biopsy [100]. Although some authors proposed mpMRI as a triage test for biopsy candidates, to increase

detection of aggressive cancers and reduce over-detection of non-significant foci [101-103], only a few controlled trials have currently been published [104-106]. A recent systematic review concluded that, whereas there was currently not enough evidence to recommend mpMRI before a first set of prostate biopsies, the use of targeted biopsy often achieved significantly higher cancer detection rate in the repeat biopsy setting [107].

Inter-reader variability remains a concern with mpMRI. The Prostate Imaging Reporting and Data System (PIRADS) scoring system has been recently proposed to standardise mpMRI interpretation [108], but two independent evaluations suggested that it did not improve inter-reader variability as compared to subjective scoring [109, 110].

5.2.4.3 Guidelines for imaging

	LE	GR
When clinical suspicion of PCa persists in spite of negative biopsies, MRI-targeted biopsies are recommended.	2b	B

GR = grade of recommendation; LE = level of evidence; MRI = magnetic resonance imaging.

5.2.5 Pathology of prostate needle biopsies

5.2.5.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with PCa detection rate [111]. To achieve optimal flattening and alignment, a maximum of three cores should be embedded per tissue cassette, and sponges or paper used to keep the cores stretched and flat [3, 112]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [83] and intervening unstained sections are kept for immunohistochemistry.

5.2.5.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [113-115]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [113]. Table 5.2.4 lists the recommended terminology for reporting prostate biopsies [3].

Table 5.2.4: Recommended terminology for reporting prostate biopsies [3]

• Benign/negative for malignancy. If appropriate, include a description
• Active inflammation
• Granulomatous inflammation
• High-grade PIN
• High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)
• Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
• Adenocarcinoma

Each biopsy site should be reported individually, including its location (in accordance with site of sampling) and histopathologic findings, which include the histological type and the International Society of Urological Pathology (ISUP) 2005 Gleason score (i.e., 2005 ISUP Modified Gleason System) [116]. As compared to the traditional Gleason grading, the ISUP 2005 Gleason score improved the concordance of the grading of the corresponding prostatectomy specimens [117].

The (2005 ISUP modified) Gleason score of biopsy-detected PCa comprises the Gleason grade or pattern of the most extensive (primary pattern) pattern, plus the second most common pattern (secondary pattern), if two are present. If one pattern is present, double it to yield the Gleason score. For three grades, the Gleason score comprises the most common grade plus the highest grade, irrespective of its extent. When the carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the Gleason score. A Gleason score ≤ 4 should not be given on prostate biopsies [116]. Intraductal carcinoma, lymphovascular invasion and extraprostatic extension must be reported. In addition to reporting the carcinoma features for each biopsy, an overall Gleason score based on the carcinoma-positive biopsies can be provided.

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core

correlates with the Gleason score, tumour volume, surgical margins and pathologic stage in radical prostatectomy (RP) specimens and predicts BCR, post-prostatectomy progression and radiation therapy failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [118-120]. A pathology report should therefore provide both the proportion of carcinoma-positive cores and the extent of cancer involvement for each core. The length in mm and percentage of carcinoma in the biopsy have equal prognostic impact [121]. An extent of > 50% of adenocarcinoma in a single core is used in some active surveillance protocols as a cut off [122] triggering immediate treatment vs. active surveillance in patients with Gleason score 6.

A prostate biopsy that does not contain glandular tissue should be reported as diagnostically inadequate.

5.2.6 **Histopathology of radical prostatectomy specimens**

5.2.6.1 *Processing of radical prostatectomy specimens*

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded, to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most accepted method includes complete embedding of the posterior prostate, and a single mid-anterior left and right section. Compared with total embedding, partial embedding detected 98% of PCa with a Gleason score ≥ 7 and accurate staging in 96% of cases [123].

Entire RP specimens are inked upon receipt in the laboratory, to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin, which provides more homogeneous fixation and sectioning after 24 h [124]. After fixation, the apex and the base (bladder neck) are removed and cut into (para)sagittal or radial sections; the shave method is not recommended [116]. The remainder of the specimen is cut in transverse, 3-4-mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with preoperative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.2.6.1.1 Guidelines for processing prostatectomy specimens

	LE	GR
Total embedding is preferred, by conventional (quadrant) or whole-mount sectioning.	3	C
The entire surface should be inked before cutting, to evaluate the surgical margin.	3	A
The apex and base should be examined separately using the cone method with sagittal or radial sectioning.	3	A

GR = grade of recommendation; LE = level of evidence.

5.2.6.2 *RP specimen report*

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.5). As a result of the complex information provided on each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.6). Synoptic reporting results in more transparent and complete pathology reporting [125].

Table 5.2.5: Information provided by the pathology report

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

Table 5.2.6: Example checklist: reporting of prostatectomy specimens

Histopathological type
<ul style="list-style-type: none"> Type of carcinoma, e.g. conventional acinar, or ductal
Histological grade
<ul style="list-style-type: none"> Primary (predominant) grade Secondary grade Tertiary grade (if applicable) Global Gleason score Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional)
<ul style="list-style-type: none"> Percentage of prostate involved Size/volume of dominant tumour nodule
Pathological staging (pTNM)
<p><i>If extraprostatic extension is present:</i></p> <ul style="list-style-type: none"> o indicate whether it is focal or extensive o specify sites o Indicate whether there is seminal vesicle invasion <p><i>If applicable, regional lymph nodes:</i></p> <ul style="list-style-type: none"> o location o number of nodes retrieved o number of nodes involved
Surgical margins
<p><i>If carcinoma is present at the margin:</i></p> <ul style="list-style-type: none"> o specify sites
Other
<ul style="list-style-type: none"> Presence of lymphovascular / angio-invasion Location of dominant tumour Presence of intraductal carcinoma

5.2.6.2.1 Gleason score

Grading of conventional prostatic adenocarcinoma using the (modified) Gleason system [116] is the strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is incorporated in nomograms that predict disease-specific survival after prostatectomy [126].

5.2.6.2.2 Interpreting 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 it is not incorporated in the Gleason score (5% rule). The primary and secondary grades are reported in addition to the Gleason score. A global Gleason score is given for multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. Tertiary Gleason grade 4 or 5, particularly if $> 5\%$ of the PCa volume, is an unfavourable prognostic indicator for BCR. The tertiary grade and its approximate proportion of the cancer volume should also be reported [127] in addition to the Gleason score.

5.2.6.2.3 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered extraprostatic extension. It is useful to report the location and extent of extraprostatic extension because the latter is related to recurrence risk [128].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive extraprostatic extension. Some describe focal as a few glands [129] or extension as < 1 high-power field (HPF) [130], whereas others measure the depth of extent in millimetres [131].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute extraprostatic extension. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e., not as pT4, because it does not carry independent prognostic significance for PSA recurrence [132, 133] and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as extraprostatic extension (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [134].

5.2.6.3 Prostate cancer volume

The independent prognostic value of PCa volume in RP specimens has not been established [130, 135-138]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [135]. Improvement in prostatic radioimaging allows more accurate preoperative measurement of cancer volume. It is recommended that at least the diameter/volume of the dominant tumour nodule should be assessed, or a rough estimate of the percentage of cancer tissue provided [139].

5.2.6.4 Surgical margin status

Surgical margin is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [136] or at the surface of the tissue lacking ink.

In tissues that have severe crush artefacts, it may not be possible to determine margin status [140]. Surgical margin is separate from pathological stage, and a positive margin is not evidence of extraprostatic extension [141]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [130]. However, some indication must be given of the multifocality extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [142], or number of blocks with positive margin involvement.

5.2.6.5 Other factors

According to the College of American Pathologists' consensus statement [143], additional potential biomarkers have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting, including perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, and PSA derivatives.

5.2.7 Guidelines for the clinical diagnosis of prostate cancer

	LE	GR
Transurethral resection of the prostate should not be used as a tool for cancer detection.	2a	A
PCa should be graded according to the ISUP 2005 modified Gleason grading system.	2a	A
Biopsy decision should be based on PSA testing and DRE.	2b	A
Transition zone biopsies are not recommended initially due to low detection rates.	2b	B
For initial diagnosis, a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies should be performed under ultrasound 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 sites should be submitted separately for processing and pathology reporting.	3	A
Processing and reporting of prostatectomy specimens should follow the guidelines of the 2010 ISUP consensus meeting.	3	A
One set of repeat biopsies is warranted for persistent indications for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at initial biopsy).	2a	B

DRE = digital rectal examination; GR = grade of recommendation; ISUP = International Society of Urological Pathology; LE = level of evidence; PSA = prostate-specific antigen.

5.3 Diagnosis: Clinical staging

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

5.3.1 T-staging

5.3.1.1 Definitions

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

5.3.1.2 DRE, PSA level and biopsy findings

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

in < 50% of cases [144], although it often underestimates tumour extension. More extensive T-staging is only recommended if it directly affects treatment decisions

Serum PSA levels increase with tumour stage, although they are limited for accurate prediction of final pathological stage. PSA is produced by benign and malignant tissue, thus, there is no direct relationship between serum PSA and clinicopathological tumour stage [145]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [146]. An increase in tumour-positive biopsies is an independent predictor of extraprostatic extension, margin involvement, and lymph node invasion [147]. Serum PSA, Gleason score, and T stage are more useful together than alone in predicting final pathological stage [126, 148]. These models may help to select candidates for nerve-sparing surgery and lymphadenectomy (Section 7.2).

SVI is predictive of local relapse and distant metastatic failure. SV biopsies can improve preoperative staging accuracy [149]. This is not recommended for first-line examination, but is reserved for patients with high risk of SVI, in whom a positive biopsy would modify treatment. Patients with T stage > 2a and serum PSA > 10 ng/mL are candidates for SV biopsy [150, 151]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [152].

Transperineal 3D prostate mapping biopsy (PMB) is an alternative to transrectal biopsies because it provides more accurate tumour localization, extent and Gleason grading [153], and has acceptable morbidity.

5.3.1.3 *Transrectal ultrasound (TRUS)*

Only 60% of tumours are visible with TRUS, and 40% are undetectable due to isoechogenicity. TRUS is no more accurate at predicting organ-confined disease than DRE [154, 155]. Combined DRE and TRUS can detect T3a PCa more accurately than either method alone [156].

3D-TRUS is claimed to have better staging accuracy than 2D techniques [157]. Greater sensitivity for cancer detection is achieved by the addition of power colour Doppler and contrast agents [158-160]. All TRUS techniques are largely operator-dependent and cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine staging.

5.3.1.4 *Multiparametric magnetic resonance imaging (MRI)*

T2-weighted imaging (WI) remains the most useful method for local staging on MRI. At 1.5T (Tesla), MRI has low sensitivity for detecting extraprostatic extension of carcinoma (22-82%) or SVI (0-71%), but higher specificity (61-100% and 62-100%, respectively) [161-176]. Global MRI accuracy for distinguishing T1/T2 stages from T3 stage is 50-85% [163-165, 171, 172, 177-180]. These disappointing results are because MRI cannot detect microscopic extra-prostatic extension. Its sensitivity increases with the radius of extension within periprostatic fat. In one study, the EEC detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [163]. In another study, MRI sensitivity, specificity and accuracy for detecting pT3 stage were, 40, 95 and 76%, respectively, for focal (i.e. microscopic) extra-prostatic extension, and 62, 95 and 88% for extensive extra-prostatic extension [171].

An endorectal coil improves staging accuracy at 1.5T, and accuracy of 77-83% has been shown for combined endorectal and external coils vs. 59-68% for external coil alone [174, 181]. Dynamic contrast-enhanced imaging combined with T2-WI may also improve local staging [172, 175]. The high field strength allows high-resolution T2-WI [182] and results at 3T seem better than at 1.5T [173, 183], even if the experience of the reader remains of paramount importance, MRI accuracy at 3T varies between 67% and 93% depending on the experience of the reader [173]. Even if MRI is not perfect for local staging, it may improve prediction of the pathological stage when combined with clinical data [184, 185].

Given its low sensitivity for focal (microscopic) extra-prostatic extension, mpMRI is not recommended for local staging in low-risk patients [184, 186, 187]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [188].

5.3.2 **N-staging**

5.3.2.1 *PSA level and biopsy findings*

N-staging should be performed only when it might directly influence treatment decisions. High PSA values, T2b-T3 stage, poor tumour differentiation and perineural invasion are associated with high risk of nodal metastases [126, 189, 190]. Measurement of PSA alone is unhelpful in predicting lymph node metastases.

Nomograms or Partin tables can define patients at low risk (< 10%) of nodal metastasis, although nomograms may be more accurate in establishing the extent of nodal involvement [148, 191]. The simple Roach formula can also be used [192]. Patients with low- and intermediate-risk PCa may be spared N-staging before potentially curative treatment [126].

Gleason 4 pattern in sextant biopsies can define the risk of N1 disease. Risk of nodal metastases

was 20-45% if any core had a predominant Gleason 4 pattern, or > 3 cores had any Gleason 4 pattern. For the remaining patients, the risk was 2.5%, suggesting that nodal staging is unnecessary in selected patients [193].

5.3.2.2 *Nodal staging using computed tomography (CT) and magnetic resonance imaging (MRI)*

Abdominal CT and MRI indirectly assess nodal invasion by measuring lymph node diameter. Their sensitivity is low and microscopic invasion cannot be detected. Using a 10-mm threshold, CT or MR sensitivity is < 40% [194-206]. Among 4,264 patients, 654 (15.3%) had positive lymph nodes at lymphadenectomy but only 105 (2.5%) had positive CT. Median estimated CT sensitivity, specificity, NPV and PPV were 7%, 100%, 85% and 100%, respectively [205].

Fine-needle aspiration biopsy (FNAB) may be decisive in cases with positive imaging. The lymph nodes can be difficult to reach because of their position. FNAB is not highly sensitive for staging and has a false-negative rate of 40% [207].

For CT or MRI, detection of microscopic lymph node invasion is < 1% in patients with a Gleason score < 8, PSA < 20 ng/mL, or localised disease [202, 208, 209]. CT and MRI should not be used for nodal staging in low-risk patients and reserved for high-risk cancer.

5.3.2.3 *Lymphadenectomy*

The gold standard for N-staging is open or laparoscopic lymphadenectomy. Pelvic lymph node dissection (LND) limited to the obturator fossa will miss ~50% of metastases [210, 211]. When deciding on pelvic LND, extended lymphadenectomy should be considered (Section 7.2.6).

Primary removal of sentinel lymph nodes aims to improve accuracy of detecting tumour bearing nodes while reducing morbidity associated with extended pelvic LND [212, 213]. Image guidance allows intraoperative sentinel node (SN) detection visually [214]. Difficulty in accessing the SN and the lack of large multicenter cohorts are major limitations of this technique. Therefore, for the time being, this remains experimental [215].

5.3.3 **M-staging**

5.3.3.1 *Alkaline phosphatase*

The axial skeleton is involved in 85% of PCa fatalities [216]. The presence and extent of bone metastases accurately reflect prognosis of PCa. Elevated skeletal alkaline phosphatase (ALP) indicates bone metastasis in 70% of cases [217]. Simultaneous measurement of skeletal ALP and PSA increases clinical effectiveness to ~98% [218]. The extent of bone disease is the only variable influencing serum levels of skeletal ALP and PSA, and the former is significantly correlated with extent of bone disease [219].

5.3.3.2 *Bone scan*

Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. However, it suffers from relatively low specificity [220]. Thus, in patients with equivocal findings or a small number of hot spots, the metastatic nature of the lesions needs to be checked by other imaging modalities.

The NPV for bone scanning is 87-100% [207, 221-229]. Its diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score [221-234] and these three factors were the only independent predictors of BS positivity in a study of 853 patients [235]. BS positivity rate is extremely low (< 1%) in low-risk patients [234, 236-238]. In contrast, it is 6.6-38.5% in patients with PSA level of 20-50 ng/mL [221, 224-227, 229, 230, 236-238], 19-90.7% in patients with stage \geq T3 [221, 225, 227, 228, 230, 236] and 16.9-29.6% in patients with Gleason \geq 8 tumours [232, 233, 236, 238]. The proportion of positive BS in patients with PSA level of 10-20 ng/mL (1-33.3%) or Gleason 7 (2.8-22%) is quite variable from one study to another [207, 221, 222, 224-228, 230, 237-239]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive BS [237, 239].

Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score or clinical stage [205].

5.3.4 **New imaging modalities**

5.3.4.1 *Nodal metastases*

^{11}C - or ^{18}F -choline positron emission tomography (PET)/CT have good specificity for lymph node metastases, but sensitivity of 10-73% [240, 241].

In a meta-analysis of 609 patients pooled sensitivity and specificity of choline PET/CT for pelvic lymph node metastases were 62% (95% CI, 51-66%) and 92% (95% CI, 89-94%), respectively [242]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10-35%), the sensitivity was only 8.2% in a region based and 18.9% at a patient-based analysis, too low to be of clinical interest [243]. PET-choline has no place for up-front staging in nodal metastasis. Currently, psmaPET-CT (prostate-specific membrane antigen-PET CT) remains experimental.

MR sensitivity is low for lymph node metastases and similar to that of ¹¹C-choline PET/CT [244, 245]. Ultra-small particles of iron oxide (USPIOs) improve detection of microscopic lymph node metastases on MRI. This approach is cost-effective [246], but is limited by a lack of availability.

5.3.4.2 Bone metastasis

¹⁸F-fluoride PET or PET/CT shows superior sensitivity to bone scanning [240, 247-250]. It remains unclear whether ¹¹C-choline PET/CT is more sensitive than conventional bone scanning, but it has higher specificity, with fewer indeterminate lesions [240, 242, 251].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scanning and targeted radiography [252-254] in detecting bone metastases in high-risk PCa. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [255]. A recent meta-analysis found MRI to be better than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although PET/CT had the highest specificity [256].

However, as with PET/CT, the cost-effectiveness of these new MR-based approaches remains to be assessed [257]. Bone scan is therefore preferred on the basis of availability and cost.

5.3.5 Guidelines for staging of prostate cancer

Any risk group staging	LE	GR
Additional imaging is required only if it changes patient management.	2a	A*
For local staging, CT and TRUS should not be used.	3	A
For up-front staging, PET-scanning should not be used.	2a	A

*Upgraded following panel consensus.

Low-risk localised PCa	LE	GR
No additional imaging is recommended for staging purposes.	2a	A

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4, bone scan and cross-sectional imaging is required.	2a	A*

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Prostate mpMRI should be used for local staging.	2b	A
CT/MRI and bone-scan should be used in staging.	2b	A
For up-front staging, PET-scanning should not be used.	2a	A

CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

6. DISEASE MANAGEMENT

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

6.1.1 Introduction

Many men with localised PCa will not benefit from definitive treatment [258], and ~45% of men with PSA-detected PCa are candidates for deferred management [259]. In men with comorbidity and limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life (QoL). There are two distinct strategies for conservative management that aim to reduce overtreatment: active surveillance and watchful waiting (Table 7.1.1).

6.1.1.1 Definition

6.1.1.1.1 Active surveillance

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

6.1.1.1.2 Watchful waiting

Watchful waiting (also known as deferred or symptom-guided treatment) arose in the pre-PSA screening era (before 1990). It refers to conservative management, until the development of local or systemic progression with (imminent) disease-related complaints. Patients are then treated palliatively with TURP or other procedures for urinary tract obstruction, and hormonal therapy or radiotherapy for palliation of metastatic lesions. No standardised follow-up is recommended.

Table 6.1.1: Definitions of active surveillance and watchful waiting [261-263]

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

6.1.2 **Deferred treatment of localised PCa (stage T1/T2, Nx/N0, M0)**

Clinical stage T1c currently represents 40-50% of new PCa cases [264]. The incidence of small, localised, well-differentiated PCa is increasing, mainly because of PSA screening and multicore biopsy [259]. One clinical trial [265] did not show any difference in 10-year survival between watchful waiting and RP in screen-detected PCa with PSA < 10 ng/mL.

The lead-time in PSA screening is ~10 years [261, 262]. Mortality from untreated, non-screen-detected PCa in patients with Gleason scores of 6 might be only 10% at 20 years follow-up [263].

6.1.2.1 *Active surveillance*

Active surveillance might mean no treatment for patients aged > 70 years, while in younger patients treatment may be delayed for several years. The aim is to reduce overtreatment in patients with clinically confined, very-low-risk PCa, without relinquishing curative treatment, as happens with watchful waiting [260]. Active surveillance is only proposed for highly selected low-risk patients. Current data are from ongoing prospective or retrospective cohorts, without any available randomised clinical trials and the results of active surveillance (AS) are consistent throughout the published cohorts for survival.

One of the largest cohorts with the longest follow-up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [266]. These men presented with stage T1c or T2a PCa and PSA ≤ 10 ng/mL, age ≤ 70 years and a Gleason score ≤ 6 or age > 70 years with a score of ≤ 7. Initially, six biopsies were performed, but in recent years the 12-core protocol was introduced. After a median follow-up of 6.4 years (21% followed for more than 10 years), the 10- and 15-year OS were 80% and 62%, respectively. At 10 and 15 years, disease-specific survival (DSS) were 98.1% and 94.3% respectively. Twenty-eight men (2.8%) developed metastases during follow-up (all but 2 being Gleason ≥ 7), and 15 died. 63.5% and 55% of men are still alive on active surveillance at 10 and 15 years, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years in (43.5%), a Gleason score progression on repeat biopsies (35%) and patient preference (6%).

Several studies have investigated active surveillance in organ-confined disease, the findings of which were summarized in a systematic review including more than 3,900 patients [267]. There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated.

Selection criteria discussed in this review suggest: low volume intraprostatic non-aggressive disease: Gleason 6, when specified < 2 - 3 positive cores with < 50% cancer involvement of every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc.

A consensus meeting recently suggested also excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoid carcinoma, small cell carcinoma, extraprostatic extension or lymphovascular invasion in needle biopsy [269]. Some studies would include men with a PSA < 20 ng/mL, or up to T2b PCa. Even patients with Gleason score 7 (3 + 4) were considered since only 19% of men with a PSA level < 10 ng/mL, PSA-DT < 0.15 ng/mL/g, T1c, and < 2 positive cores, had unfavourable disease at RP [268]. However these criteria are not yet considered as acceptable for AS and should therefore not be used.

A comprehensive review of the currently available patient selection- and follow-up criteria has been published [270], highlighting that repeat-biopsies should be systematically included in an AS policy, even though they are associated with increased erectile dysfunction [271] and infectious complications [272]. Imaging with mpMRI is of particular interest due to its high negative-predictive value for lesion upgrading and for staging anterior prostate lesions [273]. As yet, mpMRI cannot replace follow-up biopsies and should not be used alone as an assessment tool to prompt active treatment [274]. Biological markers, include urine markers such as PCA3, the TMPRSS2: ERG fusion gene or PSA isoforms such as the Phi index appear promising as does genomics on the tissue sample itself [275]. However, further study data will be needed before such markers can be used in standard clinical practice.

Follow up in AS should be based on repeat biopsy, serial PSA measurements and clinical examination (DRE). There is no agreement on which criteria to use as the basis for the decision to proceed to active treatment [276]. Criteria include a change in the Gleason score, the modification of the biopsy results (number of positive cores, increase in the core involvement). These criteria are recognised in all the published cohorts. T- stage increase is also considered. A PSA change (in particular a PSA-DT < 3 years) is often used which is questionable considering the weak link between PSA-DT and grade progression on repeat biopsy [277].

Active treatment may also be instigated upon a patient's request. This occurs in 10-18% of patients on AS [278]. Self-administered questionnaires show that patients experience anxiety and depression during an AS policy, the extent of which, however, does not significantly differ from anxiety reported by men treated by RP [279]. Overall, the discontinuation rate of AS is between 14% to 40% and 40% to 60% at 5 and 10 years, respectively. Depending on the criteria used, CSS at 10 years is reported to be between 96-100%.

Table 6.1.2: Active surveillance in screening-detected PCa

Studies	n	Median follow-up (mo)	pT3 in RP* patients	OS	CSS
Van As et al, 2008 [280]	326	22	8/18 (44%)	98	100
Carter et al, 2007 [281]	407	41	10/49 (20%)	98	100
Adamy et al, 2011 [282]	533-1,000	48	4/24 (17%)	90	99
Soloway et al, 2010 [283]	99	45	0/2	100	100
Roemeling et al, 2007 [284]	278	41		89	100
Khatami et al, 2007 [285]	270	63		NR	100
Klotz et al, 2015 [266]	993	77	NR	85	98.1
Total	2,130-3,000	43		90	99.7

* Patients receiving active therapy following initial active surveillance.

CSS = case-specific survival; n = number of patients; OS = overall survival

6.1.2.2 Watchful waiting

The rationale behind watchful waiting is that PCa often progresses slowly, and is predominantly diagnosed in older men with a high incidence of comorbidity and other causes of mortality [286]. Watchful waiting is possible in patients with localised PCa and limited life expectancy, or older patients with less aggressive cancer.

Studies of watchful waiting have included patients with up to 25 years follow-up, with endpoints of OS and DSS. Several series showed a consistent DSS rate of 82-87% at 10 years [287-292], and 80-95% for T1/T2 and Gleason score ≤ 7 [293]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [289, 291, 292], and two reported a 20-year DSS of 57% and 32% [289, 291]. It must be highlighted that the used Gleason classification is not the revised version which is associated with a slight increase in the Gleason classification. Practically, many patients classified as Gleason 6 in older studies would now be classified as Gleason 7. Therefore, the current Gleason 6 population has less aggressive disease compared to the patients classified in the above mentioned cohorts.

Patients with well-, moderately- and poorly differentiated tumours had 10-year CSS of 91%, 90% and 74%,

respectively, correlating with data from the pooled analysis [293].

Observation was most effective in men aged 65-75 years with low-risk PCa [258].

In patients with stage cT1a PCa, 10-year CSS rates were 96% and 94% for grade 1 and 2 tumours, respectively [287]. MFS rate was 92% and 78% for patients with grade 1 and 2 tumours, respectively, indicating a higher risk of progression for moderately differentiated tumours. Similar results were found in other studies of stage cT1a disease [294, 295].

Gleason 6-10 tumours carry a continuously increasing mortality risk for up to 15 years follow-up after watchful waiting [296]. Others have shown that the mortality risk of PCa was high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 tumours (Table 6.1.4) [297, 298].

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

Gleason score	Cancer mortality risk* (%)	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

* Figures differ among age groups and represent the true risk in the study population (considering actual competing mortality from other causes)

† Figures compensate for differences in competing mortality and indicate outcome if the patient lives for 15 years

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

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

	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)	NR

CI = confidence interval.

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

Another study randomised 731 men with clinically organ-confined PCa (PSA < 50 ng/mL and age < 75 years) to RP or watchful waiting [265]. Half the patients had non-palpable PCa, compared with only 12% in the other trial [299]. Despite a 10-year life expectancy being an inclusion criterion, > 33% of the men died within 10 years, suggesting that the population was less fit than expected, and reduced the ability to assess survival benefit for active treatment [265].

After a mean follow-up of 10 years, there was no significant difference between the treatments for overall mortality (47% for RP vs. 49.9% for the observation group) and PCa-specific survival (5.8% (RP group) vs. 8.4% (observation group)). There were no significant differences in OS when considering patient age, Gleason score, performance status, and Charlson comorbidity index (CCI) score. Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a relative-risk reduction in mortality of 33% and 31%, respectively. There was a relative-risk and absolute-risk reduction of 31% and 10.5%, respectively, for patients with intermediate/high-risk PCa. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%).

Data from a 1995 study showed a tendency for a higher probability of metastases in the deferred treatment group and shorter CSS was reported after deferred therapy compared with immediate hormone therapy in presumed localised PCa after 15 years of follow-up [300]. Another study showed higher mortality in men with localised PCa treated with 150 mg/day bicalutamide compared with placebo [301].

The data on deferred and conservative management of low-risk disease contrast with the recent increase in the incidence of local treatment from 25 to 34% in the USA in men with life expectancy < 10 years [302]. Swedish data show a higher prevalence of deferred treatment in low-risk disease of 46% [303].

Many small, localised, well-differentiated tumours do not progress, and radical therapy may lead to substantial overtreatment. This was confirmed by a recent analysis at 5 and 10 years in 19,639 patients aged > 65 years who were not given curative treatment. Most men with a CCI score ≥ 2 died from competing causes at 10 years whatever their initial age. However, men without comorbidity or CCI score 1 had a low risk of death at 10 years, especially for well- or moderately differentiated lesions (Table 8.7) [304]. For CCI score ≥ 2 , tumour aggressiveness had little impact on OS, suggesting that patients could have been spared biopsy and diagnosis of cancer. Thus, evaluation of initial comorbidity and survival probability before proposing biopsy or treatment is important [305].

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

The final analysis of the largest RCT focusing on this specific question was published in 2013 [306]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa were treated with androgen-deprivation therapy (ADT) immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up 12.8 years, the OS hazard ratio was 1.21 (95% CI = 1.05-1.39), favouring immediate treatment. The time from randomisation to progression of hormone-refractory disease did not differ significantly, nor did CSS. The median time to start of deferred treatment was 7 years. One hundred and twenty-six patients died without needing treatment (44% of deaths). Immediate ADT resulted in a modest but significant increase in OS, but no significant difference in PCa mortality or symptom-free survival, raising the question of its clinical value. Patients with a baseline PSA > 50 ng/mL had a > 3.5-fold higher mortality risk than those with ≤ 8 ng/mL. If baseline PSA was 8-50 ng/mL, the mortality risk was ~7.5-fold higher in patients with a PSA-DT of < 12 months compared with > 12 months. The time to PSA relapse after response to immediate ADT correlated significantly with baseline PSA.

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

The only candidates for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. Median survival is ~2 years, therefore, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even death from PCa, without receiving any benefit from hormone treatment has been highlighted [307, 308]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.1.5 **Guidelines for active surveillance and watchful waiting**

Recommendations - active surveillance	LE	GR
Patients who are suitable for surgery and radiotherapy must have these options discussed with them.	4	A*
Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 , ≤ 2 positive biopsies, minimal biopsy core involvement ($\leq 50\%$ cancer per biopsy).	2a	A
Follow-up should be based on DRE, PSA and repeat biopsies.		
The optimal follow-up interval is still unclear.	2a	A
Patients should be counselled on the possibility of needing further treatment in the future.	2a	A

Recommendations - watchful waiting for localised prostate cancer	LE	GR
Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy	1b	A
During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression (see section 6.1.2.2).		B

Recommendations - watchful waiting for locally advanced prostate cancer	LE	GR
In locally advanced M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSA DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	1b	A

**Upgraded following panel consensus.*

ADT = androgen-deprivation therapy; DRE = digital rectal examination; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen.

6.2 Treatment: Radical prostatectomy

6.2.1 Introduction

The surgical treatment of 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. The goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency [309]. There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone [305]. However, patients with a life expectancy of ≥ 10 years are more likely to benefit from the procedure. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [304]. An estimation of life expectancy is paramount in counselling a patient about surgery [310] (see also Section 6.6 - Management of prostate cancer in older men).

Currently, RP is the only treatment for localised PCa to show a benefit for OS and cancer-specific survival (CSS), compared with conservative management, as shown in one prospective randomised trial [311]. During 23.2 years of follow-up, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality. The relative risk (RR) of death at 18 years was 0.71 (95% CI, 0.59-0.86). The number needed to treat (NNT) to prevent one death at 18 years of follow-up was 8; the NNT decreased to 4 for men younger than 65 years of age. Radical prostatectomy was also associated with a reduction in PCa-specific mortality at 18 years (RR = 0.56; 95% CI, 0.41-0.77). The benefit of surgery with respect to death from PCa was largest in men younger than 65 years (RR, 0.45) and in those with intermediate-risk PCa (RR, 0.38). However, RP was associated with a reduced risk of metastases among older men (RR, 0.68).

The benefits in OS and CSS were not reproduced in the overall study population (mean age 67 yr) of another prospective randomised 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; 95% CI, 0.71-1.08) or significantly reduce PCa mortality (HR = 0.63; 95% CI, 0.36-1.09) [265].

- Among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR = 0.69; 95% CI, 0.49-0.98).
- Among men with high-risk tumours, RP non-significantly reduced all-cause mortality (HR = 0.40; 95% CI, 0.16-1.00).
- Among men with PSA > 10, RP significantly reduced all-cause mortality (HR = 0.67; 95% CI, 0.48-0.94).

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 localised 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. A recent systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic and robotic radical prostatectomy demonstrated that robotic surgery had lower perioperative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy, although there was considerable uncertainty. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction outcomes [312]. A recent cohort study demonstrated that RALP and RRP had comparable rates of complications and additional cancer therapies. However, although associated with lower risk of blood transfusions and a slightly shorter length of hospital stay, RALP was associated with a higher probability of experiencing 30- and 90-day genitourinary and miscellaneous medical complications [313].

Surgical expertise has decreased the complication rates of RP and improved cancer cure [314-317]. 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 [318, 319]. More evidence for a volume-outcome relationship was provided by a recent systematic review. There was undeniable evidence suggesting that increased surgeon

volume improves outcomes [320].

The main gap in the evidence base are the lack of direct comparative studies of robotic, laparoscopic and open radical prostatectomy with low risk of bias. Moreover, there is a lack of longer-term outcomes allowing comparison of more certain measures of cancer control, such as cancer-specific mortality and overall mortality [312, 321-325]. Even though there appears to be a clear volume-outcome relationship, suggesting that referral of patients to high-volume centres would seem reasonable, the impact of a shift in practice has yet to be fully determined [320].

6.2.2 **Low-risk prostate cancer**

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

The decision to offer RP in cases of low-risk cancer should be based upon the probabilities of clinical progression, side-effects and potential benefit to survival [326]. It might therefore be reasonable to propose active monitoring to selected patients whose tumours are most likely to be insignificant.

Apart from disease characteristics, age, comorbidities and individual patient preferences impact the choice for surgery vs. active monitoring and should be considered in shared decision making. A recent study assessed the effect of age, health status and patient preferences on outcomes of surgery vs. active surveillance for low risk PCa. As expected, older age and worse baseline health status were associated with a smaller benefit in prostate-cancer-specific mortality and life expectancy with surgery, and increased incremental years with treatment side effects [327].

Pelvic lymph node dissection (eLND) is not necessary in low-risk PCa because the risk for positive lymph nodes does not exceed 5% [328].

6.2.3 **Intermediate-risk, localised prostate cancer**

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

When the tumour is palpable or visible on imaging and clinically confined to the prostate, disease progression can be expected. When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year prostate-cancer-specific mortality rates of 13 and 19.6%, respectively [329].

The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [328]. An eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5% [328]. 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 [243].

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

The results achieved in 2 prospective studies involving RP are shown in Table 6.2.1.

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

Study	Year of RP	Median follow-up (mo)	Risk category	12-year CSS (%)	18-year CSS (%)
Bill-Axelson et al, 2014 [311]	1989-1999	160	Low-risk Intermediate-risk	89.8	84.9
Wilt et al, 2012 [265]	1994-2002	120	Low-risk Intermediate-risk	100	94.2

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

6.2.4 **High-risk and locally advanced prostate cancer**

Patients classified with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor

prognosis after RP [330].

There is no consensus regarding the optimal treatment of men with high-risk PCa. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Extended LND should be performed in all high-risk PCa cases, because the estimated risk for positive lymph nodes is 15-40% [328]. Limited LND should no longer be performed, because it misses at least half the nodes involved [243].

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.

6.2.4.1 *High-risk prostate cancer*

6.2.4.1.1 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 [331]. These men, in particular, may benefit most from potentially curative resection.

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

6.2.4.1.2 Prostate-specific antigen > 20 ng/mL

Yossepowitch et al. have reported the results of RP as monotherapy in 275 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 [330]. Thirty-three and 53% of patients with PSA > 20 ng/mL needed secondary treatment at 5 and 10 years, respectively [333]. D'Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP [335]. Spahn et al. published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively [336].

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a BPFS at 5-, 10- and 15-years follow-up, ranging between 40-63%, 25-48% and 25%, respectively. The CSS at 5, 10 and 15 years ranged between 93-97%, 83-91% and 71-78%, respectively [333-338].

6.2.4.2 *Locally advanced prostate cancer:*

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

In recent years, however, there has been 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 [342-344]. In up to 50% of cases this is part of multi-modality treatment (adjuvant or salvage radiotherapy and/or ADT).

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 [345, 346]. Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. It has been shown that continence can be preserved in most cases, and in some cases, potency can also be preserved [347].

Retrospective case series demonstrated 5-, 10- and 15-year biochemical BPFS ranged between 45-62%, 43-51% and 38-49%, respectively. CSS at 5-, 10- and 15-years ranged between 90-99%, 85-92% and 62-84%, respectively. Five- and 10-year OS ranged between 90-96% and 76-77%, respectively [342-344, 346-350].

Only a limited number of cohort studies provided survival data of surgery for cT3b-T4 PCa. In these studies, the CSS was 88-92% at 5 years and 87-92% at 10 years, while the OS was 73-88% at 5 years and 65-71% at 10 years [351-353].

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Clinical lymph node-positive (N+) disease will mostly be followed by systemic disease progression, No good evidence exists supporting RP of cN+ patients, therefore local treatment to N+ patients

in a multimodal approach should be discussed with the patients on an individual basis.

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

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% [354, 355]. Furthermore, a retrospective observational study has shown a dramatic improvement in CSS and OS in favour of completed RP vs. abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and the discontinuation of RP in pN+ cases may not be justified [356]. These findings have been corroborated in a contemporary retrospective analysis [357]. 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 pN+ 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 pN+ PCa.

The incidence of tumour progression is lower in patients with fewer positive lymph nodes [236, 358]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective randomised trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more frequently performed 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 ≤ 2 microscopically involved lymph nodes in an extended nodal dissection. Interestingly, in a retrospective cohort study, maximal local control with RT of the prostatic fossa appeared to be beneficial in PCa patients with pN+ after RP, treated adjuvantly with continuous ADT [359]. The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (≤ 2 lymph nodes) in the presence of intermediate- to high-grade, non-specimen-confined disease and those with intermediate-volume nodal disease (3-4 lymph nodes) represent the ideal candidates for RT after surgery.

Recent studies described survival outcomes after surgery in pN1 PCa, with 5-, 10- and 15-year CSS ranging from 84-95%, 51-86% and 45%, respectively. The OS at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively [236, 354-359].

6.2.6 **Indication and extent of pelvic lymph node dissection (LND)**

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 [244]. Sentinel node mapping studies have shown that aside from the obturator and external iliac lymph nodes, the prostate also drains to the presacral nodes and most commonly to the internal iliac nodes [243, 360]. 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.

The individual risk of finding positive lymph nodes can be estimated using preoperative nomograms. Only a few of these nomograms are based on extended LND templates. One of those, the Briganti nomogram with the cutoff of 5% as proposed in the EAU Prostate Cancer guidelines, has been externally validated in both open and robot-assisted RP series and showed the highest accuracy when compared with other similar prognostic tools [328, 361, 362].

6.2.6.1 *Extent of lymph node dissection*

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. 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 [360]. A recent prospective mapping study confirmed that a template including the external iliac, obturator and internal iliac areas was able to correctly stage 94% of patients. Nevertheless, in pN+ patients, this template was associated with a 24% incomplete clearance from positive nodes [243]. Adding the common iliac area and the presacral area decreased this risk to only 3%.

It is recommended for each region that the nodes should be sent in separate containers for histopathological analysis, because this will usually be associated with a higher diagnostic gain by the uropathologist.

6.2.6.2 Therapeutic role of extended lymph node dissection (eLND)

Besides being a staging procedure, pelvic eLND may be curative, or at least beneficial, in a subset of patients with limited lymph node metastases [363-366]. In some series, the number of nodes removed during lymphadenectomy has been significantly correlated with time to disease progression [211]. 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 [367]. In another series, it was demonstrated that a more extensive LND was associated with improvement in CSS in patients with lymph node invasion [368]. Nevertheless, results from ongoing confirmatory prospective studies are awaited.

6.2.6.3 Morbidity

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended vs. limited LND, three-fold higher complication rates have been reported by some authors [369]. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphocoeles (10.3% vs. 4.6%) being the most common. Other authors have reported more acceptable complication rates [370].

Similar rates of lymphocoeles have been observed in RALP series, however, in one subgroup analysis lymphocoeles were more common in the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [371, 372].

6.2.7 Guidelines for eLND in prostate cancer

	LE	GR
LND is not indicated in low-risk PCa.	2b	A
eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%.	2b	B
eLND should be performed in high-risk PCa.	2a	A
Limited LND should not be performed.	2a	A
When nodal involvement is detected after RP:		
• Adjuvant ADT is the standard of care for node-positive (pN+)	1b	A
• Adjuvant ADT with additional radiotherapy may have a role (see Section 6.3.3.3)	2b	B
• Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.	2b	B

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

6.2.8 Neoadjuvant and adjuvant hormonal therapy and radical prostatectomy

Neoadjuvant hormonal therapy (NHT) is defined as therapy given before definitive local curative treatment. Since PCa is an androgen-dependent tumour, NHT is an appealing concept. A recent review and meta-analysis studied the role of NHT and prostatectomy [373]. NHT significantly reduced positive margin rates (RR = 0.49 $p < 0.00001$), extra-prostatic extension (RR = 1.63; $p < 0.0001$) and lymph node invasion (RR = 0.49; 0.42-0.56; $p < 0.02$). However, this was not associated with improved OS or disease-free survival (DFS).

Regarding adjuvant HT, a Cochrane review has been published [374]: the pooled data showed a non-significant 5-year OS benefit (OR: 1.50 [95% CI: 0.79-2.84]) and no 10-year OS benefit (with again a trend favouring the adjuvant approach). 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. The Early Prostate Cancer Trialists' Group (EPC) trial using bicalutamide 150 mg daily [375] could not be included in the Cochrane review due to missing information. After a median follow-up of 7.2 years, there was a significant improvement in objective PFS that was only significant in the locally advanced disease group (HR: 0.75; 95% CI: 0.61-0.91). There was an OS decrease trend in the localised disease group (HR: 1.16; 95% CI: 0.99-1.37). No OS benefit was observed in both localised and locally advanced groups.

The main limitations of the above data are the mixing of pN0 and pN1 populations. For pN+ patients, 2 RCT are available and drive the main conclusion of the Cochrane review, even if non RCT suggest that the benefit might not be so large in all patients [376]. Regarding pN0 / N0 stages, the only RCT is the EPC project [375]. Using more conventional HT, a large retrospective data base with a median follow up of 10 years [377] suggests that adjuvant HT might be linked to an increased specific, but not OS benefit.

6.2.9 Complications and functional outcomes

The intra- and peri-operative complications of retropubic RP and RALP are listed in Table 6.2.2 [378] and see also section 7.8.3 - Radical prostatectomy.

Table 6.2.2: Intra- and peri-operative complications of retropubic RP and RALP (Adapted from [312])

Predicted probability of event	RALP	Laparoscopic RP	RRP
Bladder neck contracture	0.010	0.021	0.049
Anastomotic leak	0.010	0.044	0.033
Infection	0.008	0.011	0.048
Organ injury	0.004	0.029	0.008
Ileus	0.011	0.024	0.009
Deep-vein thrombosis	0.006	0.002	0.014
Predicted rates of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

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

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 [325]. 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 [324]. 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.

6.2.10 Indications for nerve-sparing surgery

Nerve-sparing RP can be performed safely in most men with localised PCa undergoing RP [379, 380]. 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 [345]. Multiparametric MRI is increasingly being used in the decision-making process to select a nerve-sparing approach [381-383].

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 extending into the inked margin on frozen-section analysis, the NVB is resected; otherwise, the NVB remains *in situ* [384].

Before surgery the patient must be informed 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 use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. Placebo-controlled prospective studies have shown no benefit from daily early administration of vardenafil or sildenafil vs. on-demand vardenafil or sildenafil in the post-operative period [385, 386]. Conversely, another placebo-controlled prospective study has shown that sildenafil has a significant benefit on the return of normal spontaneous erections [387].

6.2.11 Guidelines for radical prostatectomy

	LE	GR
Patients who are suitable for AS and radiotherapy must have these options discussed with them.	4	A*
In patients with low- and intermediate-risk PCa and a life expectancy > 10 years, RP should be offered.	1b	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 may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	2b	B
In patients with high-risk localised PCa and a life expectancy of > 10 years, RP should be offered in a multimodality setting.	2a	A
In selected patients with locally advanced (cT3a) PCa, and a life expectancy > 10 years, RP may be offered in a multimodality setting.	2b	B
In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	3	C
NHT before RP is not recommended.	1a	A
Adjuvant HT for pN0 is not recommended.	1a	A
Adjuvant ADT is the standard of care for node-positive (pN+) patients.	1b	A
In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable because none has clearly shown superiority in terms of functional or oncological results.	1a	A

DFS = disease-free survival; GS = Gleason score; GR = grade of recommendation; LE = level of evidence; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; OS = overall survival; PCa = prostate cancer; RP = radical prostatectomy.

6.3 Treatment: definitive radiotherapy

6.3.1 Introduction

There are no published RCT comparing radiotherapy with watchful waiting or active surveillance. The only randomised trial in the modern era is the ProtecT study which has not yet reported its first results. 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.

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 10);
- Baseline prostate-specific antigen (PSA);
- Age of the patient;
- Patient's comorbidity, life expectancy, and QoL;
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings;
- and the EAU prognostic factor classification.

Additional information on the various aspects of radiotherapy in the treatment of PCa is available in an extensive overview [388].

6.3.2 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 visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field using portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. 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 randomised trials have been published comparing dose escalation using IMRT and 3D-CRT.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [389]. 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 [390].

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.

6.3.3 **Radiotherapy for localised PCa**

6.3.3.1 *Dose escalation*

Several randomised studies (see below) have shown that dose escalation (range 74–80 Gy) has a significant impact on 5-year survival without biochemical relapse [391–397]. 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.

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

If IMRT and IGRT are used for dose escalation, severe late side effects \geq grade III for the rectum is about 2–3% and for the genito-urinary tract is 2–5% [393, 394, 424–437] (see also Section 6.8.4.1 Post-treatment quality of life in patients with localised PCa).

Table 6.3.1: Randomised trials on dose escalation in localised prostate cancer

Trial	n	PCa condition	Radiotherapy Dose	Follow-up	Outcome	Results
MD Anderson study 2011 [391]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs. 78 Gy	Median 9 years	Disease specific mortality (DSM) vs. other cause of death	High risk / PSA >10 16% DSM @ 70 Gy 4% DSM @ 78 Gy (p = 0.05) Higher risk 15% DSM @ 70 Gy 2% DSM @ 78 Gy (p = 0.03)
PROG 95-09 study [392]	393	T1b-T2b PSA 15 ng/mL 75% GLS < 6	70.2 vs. 79.2 Gy including proton boost 19.8 vs. 28.8 Gy	Median 8.9 years for survivors	10-year ASTRO Biochemical failure (BF)	All patients: 32% BF @ 70.2 Gy 17% BF @ 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF @ 70.2 Gy 7% BF @ 79.2 Gy (p < 0.0001)
MRC RT01 study [388]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	Median 10 years	Biochemical progression free survival (BFS); OS	43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch randomised phase III trial [394]	664	T1b-T4 143 pts. with (neo)adjuvant HT	68 vs. 78 Gy	Median 51 mo	Freedom from biochemical- or clinical failure (FFF @ 5 years)	54% FFF @ 68 Gy 64% FFF @ 78 Gy (p = 0.02)

French GETUG 06 randomised trial [395]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	Median 61 mo	Biochemical failure (ASTRO)	39% BF @ 70 Gy 28% BF @ 80 Gy
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HT = hormone therapy; OS = overall survival.

6.3.3.2 Hypofractionation (HFX)

In radiobiology, the linear quadratic model uses two coefficients, alpha (α) and beta (β) to describe the dose-response relationship. In clinical practice, these coefficients are used to calculate the effect of different fractionation schemes. Fractionated radiotherapy utilises differences in the DNA repair capacity of normal and tumour tissue. In fast growing tissue including many tumours, cells have little time to repair photon-induced DNA damage. The α/β ratio is then typically around 10 Gy. In contrast, tissue with a low cell renewal has a good opportunity for repair between fractions of irradiation. In such tissue, the α/β ratio is 3 Gy or lower. Slowly proliferating cells with low α/β ratios are very sensitive to an increased dose per fraction [398].

While the correct α/β ratio is still controversial, a meta-analysis of 25 studies with > 14,000 patients concludes that PCa due to its slow growth has an α/β ratio of approximately 1.5 Gy. Assuming this value, hypofractionated radiotherapy could be more effective than conventional fractions of 1.8 - 2 Gy [399]. Beyond the radiobiological aspects, hypofractionation HFX can increase the convenience for the patient and lower costs for the health care system.

Several studies report on HFX applied in various techniques and in part also including hormone treatment [400-406]. A systematic review concludes that studies on moderate HFX (2.5 - 4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking [407]. Extreme HFX (5-10 Gy/fx) typically requires IGRT and stereotactic body radiotherapy SBRT. Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade genitourinary and rectal toxicity, and long-term side effects may not all be known, yet [407-409].

Taking into account the published results and the uncertainties of the correct α/β ratio, moderate HFX (Table 6.3.2) plus dose escalation should be done by experienced teams, accompanied by meticulous radiotherapy QA and close attention to organ at risk dose constraints until long-term data are available.

For extreme HFX, it seems prudent to restrict this therapy to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.3.2: Phase 3 randomised trials of moderate hypofractionation for intact prostate cancer

Study	n	Risk, GS, or NCCN	Regimen	BED, Gy	Median FU, mo	Outcome	Toxicity
Lukka et al. [400]	466	60% GS 6	52.5 Gy/20 fx	62	68	5 yr FFBF 40% (NS)	Gr \geq 3 2% (NS)
	470	31% GS 7 9% GS 8-10	66 Gy/33 fx	66		5 yr FFBF 43%	Gr \geq 3 1%
Yeoh et al. [401]	108	n.s.	55 Gy/20 fx	66.8	90	7.5 yr FFBF 53%	Late GU; HR: 1.58 (95% CI, 1.01-2.47) favouring hypofractionation
	109		64 Gy/32 fx	64		7.5 yr FFBF 34%	
Dearnaley et al. [402]	151	n.s.	57 Gy/19 fx	73.4	51	n.s.	Gr \geq 2 GU 0% (NS) Gr \geq 2 GI 1% (NS) Gr \geq 2 GU 2% Gr \geq 2 GI 4% Gr \geq 2 GU 2% Gr \geq 2 GI 4%
	153		60 Gy/20 fx	77			
	153		74 Gy/37 fx	74			
Kuban et al. [403]	102	29% low	72 Gy/30 fx	80.2	56	5 yr FFBF 96% (NS)	5 yr Gr \geq 2 GU 19% (NS)
	102	70% intermediate 1% high	75.6 Gy/42 fx	71.4		5 yr FFBF 92%	5 yr Gr \geq 2 GI 14% (NS) 5 yr Gr \geq 2 GU 19% 5 yr Gr \geq 2 GI 6%

Arcangeli et al. [404, 405]	83 85	26% GS 7 74% GS > 7	62 Gy/20 fx 80 Gy/40 fx	81.4 80	70	5 yr FFBF 85% (p = 0.065) *p ss for GS ≥ 4 + 3 5 yr FFBF 79%	3 yr Gr ≥ 2 GU 16% (NS) 3 yr Gr ≥ 2 GI 17% (NS) 3 yr Gr ≥ 2 GU 11% 3 yr Gr ≥ 2GI 14%
Pollack et al. [406]	151 152	34% GS 6 47% GS 7 19% GS 8-10	70.2 Gy/26 fx 78 Gy/36 fx	84 78	68	5 yr BCDF 23% (NS) 5 yr BCDF 21%	5 yr Gr ≥ 2 GU 13% (p = 0.16) 5 yr Gr ≥ 2 GI 9% (NS) 5 yr Gr ≥ 2 GU 13% 5 yr Gr ≥ 2 GI 9%

BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/β of 1.5 Gy; CI = confidence interval; FFBF = freedom from biochemical failure; FU = follow-up; fx = fractions; GI = gastrointestinal; Gr = grade; GS = Gleason score; GU = genitourinary; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; NS = not significant; n.s. = not stated; ss = statistically significant.

6.3.3.3 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of radiotherapy with LHRH ADT has definitively proven its superiority compared with radiotherapy alone followed by deferred ADT on relapse, as shown by phase III randomised trials [410-414] (Table 7.3.3). These trials included high risk PCa patients, mostly by virtue of locally advanced (T3-T4 N0-X) disease, though with a wide range of clinical risk factors, such as PSA level or Gleason grade (high risk localised, T1-2, N0-X PCa). The most powerful conclusion from these studies comes from the EORTC 22863 trial, which is the basis for the combination of radiotherapy and ADT in patients with locally advanced PCa as standard practice today.

In daily practice, ADT starts either at the onset of RT (for adjuvant ADT) or 2 or 3 months before (for neoadjuvant), but the concomitant component is crucial to potentiate RT; Long-term ADT, ranging from 2 to 3 years is recommended for locally advanced disease [397, 415] rather than short term (6-months) [414]. Dose escalation phase III randomised trials are going on to assess its impact on DFS. Cardiovascular mortality may be related to ADT, not radiotherapy, as addressed in Section 12.9.3.3.

Whether these results should be applied to patients with intermediate- or high-risk localised PCa is unclear. The Boston trial has shown an improved 8-year OS rate for patients without moderate or severe comorbidity assigned to 6 months of complete ADT (p=0.01) [413], and the RTOG 94-08 study showed an increased 10-year OS rate for intermediate risk only with 4 months of complete ADT (p=0.003) [396].

The EORTC trial 22961 with 970 patients (78% T3-4, 92% N0) combined radiotherapy (70 Gy) with either 6 months or with 3 years of LHRH analogue treatment. With a median follow-up of 6.4 years, both cancer-specific and overall mortality were lower with long-term androgen suppression [397].

In the RTOG 9910 trial, 1,579 intermediate-risk PCa patients were randomised to LHRH antagonist therapy for 8 weeks before radiotherapy (70.2 Gy in 2-D or 3-D techniques) followed by either another 8 or 28 weeks of anti-hormonal treatment. Extended androgen suppression did not significantly improve 10-year rates of distant (both arms 6%), loco-regional (6% vs. 4%) or biochemical progression (both arms 27%), or disease-specific (96% vs. 95%) or OS (66% vs. 67%). The 8+8 week scheme was confirmed as a standard procedure [417].

Table 6.3.3: Studies of use and duration of ADT in combination with RT for prostate cancer

Trial	Year	TNM stage	n	Trial	ADT	RT	Effect on OS
EORTC 22863 [410]	2010	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist for 3 yrs (adjuvant)	70 Gy RT	Significant benefit at 10 years for combined treatment (HR 0.60, 95% CI 0.45-0.80, p = 0.0004).
RTOG 85-31 [411]	2005	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% radical prostatectomy	65-70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with Gleason score 7-10.
Granfors [419]	2006	T3 N0-1 M0	91	EBRT ± ADT	Orchiectomy	65 Gy RT	Significant benefit (p = 0.02 p = 0.03), mainly caused by lymph-node-positive tumours.
D'Amico [413]	2008	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo	70 Gy 3D-CRT	Significant benefit (HR 0.55, 95% CI 0.34-0.90, p = 0.01) that may pertain only to men with no or minimal comorbidity.
TROG 96-01 Denham 2011 [414]	2011	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in overall survival reported; benefit in prostate-cancer-specific survival (HR 0.56, 95% CI 0.32-0.98, p = 0.04) (10 yrs: HR 0.84, 0.65-1.08; p = 0.18).
RTOG 94-13 [420]	2007	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo neoadjuvant plus concomitant vs. 4 mo adjuvant suppression	Whole pelvic RT vs. prostate only; 70·2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected).
RTOG 86-10 [412]	2008	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo before, plus concomitant therapy	65-70 Gy RT	No significant difference at 10 years.
RTOG 92-02 [415]	2008	T2c-4 N0-1 M0	1554	Short vs prolonged ADT	LHRH agonist given for 2 years as adjuvant after 4 mo as neoadjuvant	65-70 Gy RT	p = 0.73 p=0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with Gleason score 8-10.
EORTC 22961 [397]	2009	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs prolonged ADT	LHRH agonist for 6 mo vs. 3 yrs	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 months (3.8% improvement in survival at 5 years).
Pisansky [417]	2014	intermediate risk (94% T1-T2, 6% T3-4)	1579	Short vs prolonged ADT	LHRH antagonist 8+ 8 vs 8+28 weeks	70.2 Gy 2D / 3D	67 vs 68% p = 0.62, confirms 8+8 weeks LHRH as a standard.
SPCGF-7/ SFUO-3 [416]	2009	T1b-2 Grade 2-3, T3 N0 M0	880	ADT ± EBRT	LHRH agonist for 3 mo plus continuous flutamide	70 Gy 3D-CRT vs. no RT	Significantly better survival with combined treatment (HR 0.68, 95% CI 0.52-0.89, p = 0.04).

NCIC CTG PR.3/ MRC PRO7/ SWOG [421]	2015	T3-4 (88%), PSA > 20 ng/mL (64%), GLS 8-10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRH agonist	65-70 Gy 3D-CRT vs. no RT	10-years OS = 49% vs 55% favouring combined treatment (HR = 0.7, p < 0.001).
Mottet 2012 [422]	2012	T3-4 N0 M0	273 264	ADT ± EBRT	LHRH agonist for 3 yrs	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-years OS 71.4% vs 71.5%.

LHRH = luteinising-hormone-releasing hormone; RT = radiotherapy; HR = hazard ratio; 3D-CRT = three-dimensional conformal radiotherapy.

6.3.3.4 Neoadjuvant chemotherapy plus radiotherapy

The GETUG 12 trial investigated the impact of neoadjuvant chemotherapy with docetaxel on the PFS in a cohort of 413 high-risk patients, defined as having one or more of the following criteria: T3-4, Gleason score ≥ 8 , PSA ≥ 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/m² 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. A PSA response (PSA < 0.2 ng/mL after 3 months of treatment) was obtained in 34% in the ADT+DE arm and 15% in the ADT arm. With a median follow-up period of 4.6 years, the 4-year PFS was 85% in arm 1 vs. 81% in arm 2 ($p = 0.26$), but the data need to mature [423].

6.3.3.5 Combined dose-escalated radiotherapy (RT) and androgen-deprivation therapy (ADT)

Zelefsky et al. [438] reported a retrospective analysis comprising 571 patients with low-risk PCa (22.4%), 1074 with intermediate-risk PCa (42.1%), and 906 with high-risk PCa (35.5%). 3D-conformal radiotherapy or IMRT were administered to the prostate and seminal vesicles. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years of the study using image-guided IMRT. Complete androgen blockade with LHRH agonist plus oral antiandrogen was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before radiotherapy. The 10-year BDFR was significantly improved by dose escalation: 84% (> 75.6 Gy) vs. 70% for low-risk PCa ($p = 0.04$), 76% (> 81 Gy) vs. 57% for intermediate-risk PCa ($p = 0.0001$), and 55% (> 81 Gy) vs. 41% for high-risk patients ($p = 0.0001$). The 6-month ADT also influenced the BDFR in intermediate- and high-risk patients, with 55% for intermediate-risk vs. 36% for high-risk patients ($p < 0.0001$). In the multivariate analysis, a dose > 81 Gy ($p = 0.027$) and ADT ($p = 0.052$) were found to be predictive factors for distant metastasis-free survival, but none of these parameters influenced OS.

6.3.3.6 Recommended external beam radiation therapy (EBRT) treatment policy for localised PCa

6.3.3.6.1 Low-risk PCa

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

6.3.3.6.2 Intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months) [396, 439, 440]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT at an escalated dose (76-80 Gy) or a combination of IMRT and brachytherapy.

6.3.3.6.3 Localised High-risk PCa

The high risk of relapse outside the irradiated volume makes it mandatory to use a combined modality approach, consisting of dose-escalated IMRT, 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. It is important to recognise that EBRT + short-term ADT did not improve OS in high-risk localised PCa, in the Boston and 04-08 RTOG trials, and long-term ADT is currently recommended for these patients.

6.3.3.6.4 Locally advanced PCa: T3-4 N0, M0

The results of radiotherapy alone are very poor [441]. The randomised 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.

6.3.3.3.6.4.1 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 1,205 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) [442, 443].

6.3.3.3.6.4.2 The TAP 32 trial

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to 3 years of ADT using an LHRH agonist (leuprorelin), with or without radiotherapy (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic lymph nodes). After a median follow-up period of 67 months, there was a significant improvement in the 5-year 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 [422].

6.3.3.3.6.4.3 The SPCG-7/SFUO-3 randomised study [416]

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% 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%).

6.3.3.7 *Lymph node irradiation*

6.3.3.7.1 Prophylactic lymph node irradiation in clinically N0 PCa (estimated cN0)

There is no level 1 evidence for prophylactic whole-pelvic irradiation, since randomised trials have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77 06 study (n = 484 with T1b-T2) [441], the Stanford study (n = 91) [444], and the GETUG 01 trial (n = 444 with T1b-T3 N0 pNx M0) [445]. In the RTOG 94-13 study [420], 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 Briganti tables [328] and/or the Roach formula [446]. The results of pelvic lymphadenectomy, especially in young patients, allows radiation oncologists to tailor both the planning target volume and the duration of ADT, particularly ensuring that there is no pelvic irradiation for pN0 patients, while it is possible to irradiate, in combination with long-term ADT. The real impact of such an approach remains, so far, hypothetical, since no randomised trials are available. The benefits of pelvic nodal irradiation at a high dosage using IMRT merit further investigation in a phase II trial. One such trial is currently recruiting through the RTOG, and PIVOTAL, a randomised phase II in the UK, has completed accrual.

6.3.3.7.2 Clinical, or pathological node positive, M0 disease

Outcomes in this group after radiotherapy as a sole modality are poor [397], and as a minimum these patients should receive radiotherapy plus long-term ADT. The RTOG 85-31 randomised phase III trial, with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better 5-year (54%) and 9-year (10%) PFS rates (PSA < 1.5 ng/mL) vs. 33% and 4%, respectively, for radiation alone (p < 0.0001). Multivariate analysis showed that this combination had a statistically significant impact on the OS, disease-specific failure, metastatic failure and biochemical control rates [447]. Evidence concerning the efficacy of pelvic radiotherapy in patients with established lymph node disease is circumstantial. 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. Recent data from the UK STAMPEDE trial suggests that pelvic radiotherapy could be beneficial for N1 disease, but this is not based on a randomised comparison [448].

6.3.4 **Proton 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.

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 [449]; the other study suggested a clearer advantage for protons [450].

One randomised trial on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose, but it cannot be used as evidence for the superiority of proton therapy per se [392]. Thus, unequivocal information that shows an advantage of protons over IMRT photon therapy is still not available.

Studies from the SEER database, and from Harvard [451, 452], describing toxicity and patient reported outcomes, respectively, do not point to an inherent superiority for protons - indeed, in terms of longer term GI toxicity, proton therapy might even be inferior to IMRT [452].

A retrospective 2:1 matched-control analysis of 27,647 US Medicare patients compared 314 men receiving proton therapy with 628 men who had IMRT. Despite the considerably higher costs for proton therapy, there was some improvement in GU-tract toxicity after 6 months, but not after 12 months, and not at the GI tract [453].

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

6.3.5 **Low-dose rate (LDR) and high-dose rate (HDR) brachytherapy**

6.3.5.1 **LDR brachytherapy**

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

- Stage cT1b-T2a N0, M0;
- A Gleason score ≤ 6 assessed on an adequate number of random biopsies;
- An initial PSA level of ≤ 10 ng/mL;
- $\leq 50\%$ of biopsy cores involved with cancer;
- A prostate volume of < 50 cm³;
- An International Prostatic Symptom Score (IPSS) ≤ 12 [454].

Patients with low-risk PCa are the most suitable candidates for LDR brachytherapy. Further guidelines on the technical aspects of brachytherapy have been published recently and are strongly recommended [455]. Outcomes data have been reported for a large population-based cohort in Canada, in which both low- and intermediate-risk patients were treated [456].

There have been no randomised trials comparing brachytherapy with other curative treatment modalities. Outcomes are based on non-randomised case series. The results of permanent implants have been reported from different institutions, with a median follow-up ranging from 36 to 120 months [457]. The recurrence-free survival after 5 and 10 years has been reported to range from 71% to 93% and from 65% to 85%, respectively [458-464]. A significant correlation has been shown between the implanted dose and recurrence rates [465]. Patients receiving a D90 (dose covering 90% of the prostate volume) of > 140 Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years than patients who received less than 140 Gy (92% vs 68%). There is no benefit in adding neoadjuvant or adjuvant ADT to LDR salvage brachytherapy [457].

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%) [466]. A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity [467]. 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 salvage brachytherapy [468], 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 [469].

A small randomised trial has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice [470]. In cases of intermediate- or high-risk localised PCa, brachytherapy + supplemental external irradiation [471] or neoadjuvant hormonal treatment [472] may be considered. The optimum dose of supplemental EBRT is unclear. A randomised trial comparing 44 Gy vs. 20 Gy of EBRT + palladium-103 brachytherapy closed early, showing no difference in the biochemical outcomes [473].

6.3.5.2 HDR brachytherapy

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 [474]. 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 [475].

Data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) [476]. In a retrospective analysis of modern series [477, 478], 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 [479]. However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs 34%). A single randomised trial of EBRT vs. EBRT + HDR brachytherapy has been reported [480]. A total of 220 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the BDFR ($p = 0.03$). 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 [480]. 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. A systematic review of non-randomised trials has suggested the possibility that outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective, randomised trial [481].

For T1-2 N0 M0 disease, the 5-year BDFRs 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 localised 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 [476].

6.3.5.3 Side effects of percutaneous irradiation and brachytherapy

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients [482]. A meta-analysis has shown that the 1-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing RP, and 0.25 after standard RP. When studies with more than 2 years of follow-up were selected (i.e. excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches [483].

Studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT [484, 485]. 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 [484]. Another analysis [485] 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 [486]. 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 [487]. 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 vs. 13% with 3D-CRT. The incidence of grade 2 or higher late

genitourinary toxicity was 20% in patients treated with 81 Gy vs. 12% in patients treated with lower doses. The overall incidences of grade 3 toxicity were 1% for gastrointestinal toxicity and 3% for genitourinary toxicity. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity. Interestingly, with dose escalation, genitourinary toxicity may become the predominant type of morbidity [487].

6.3.6 **Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0) (Table 6.3.5)**

Extracapsular invasion (pT3), Gleason score ≥ 7 and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after 5 years [488]. Three prospective randomised trials have assessed the role of immediate post-operative radiotherapy (adjuvant radiotherapy, ART), as follows:

6.3.6.1 *EORTC 22911*

EORTC 22911 [489], 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 (Tables 6.8.1 and 6.8.2). The rate of grade 3 genitourinary toxicity was 5.3% vs. 2.5% in the observation group after 10 years. For patients younger than 70 years, the study concluded that immediate post-operative radiotherapy after surgery significantly improved the 10-year biological PFS to 60.6% vs. 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 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 [490, 491].

6.3.6.2 *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 112 months, the radiotherapy group demonstrated a significant improvement in BDFR of 56% vs. 35%, respectively ($p = 0.0001$). 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 [491].

6.3.6.3 *SWOG 8794 trial*

Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, $p = 0.016$) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; $p = 0.023$) [492].

6.3.6.4 *Conclusion*

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

- Immediate ART to the surgical bed [489, 491, 493] after recovery of urinary function;
or
- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [494, 495] (see Section 6.10.5.1).

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

Reference	n	Inclusion criteria	Randomization	Definition of BCR PSA (ng/mL)	Median follow-up (mo)	Biochemical Progression-free survival (bNED)	Overall survival
SWOG 8794 [493]	431	pT3 cN0 ± involved SM	60-64 Gy vs observation	> 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
EORTC 22911 [489]	1005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs observation	> 0.2	127	10 years: 60.6% vs 41% (p < 0.001)	81% vs 77% NS
ARO 96-02 [491]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs observation	> 0.05 + confirmation	112	10 years: 56% vs 35% (p = 0.0001)	10 years: 82% vs 86% n.s.

BCR = biochemical recurrence; NS = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.
see Section 6.10.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.

6.3.7 **Immediate (adjuvant) post-operative external irradiation after radical prostatectomy (RP) (pN1)**

In a retrospective matched-pair analysis with 364 pN+ patients, men who received adjuvant RT in addition to androgen deprivation therapy after radical prostatectomy had a 16% better 10-year cancer specific survival as compared to those without ADT [496]. In a recent study comparing lymph node positive prostatectomy patients who received either adjuvant ADT alone (n = 721) or ADT+ART (n = 386), the multimodal treatment reduced 8-year cancer-specific mortality (7.6% vs 13.8%, p = 0.08) [359]. Subgroup analysis in this retrospective study demonstrated a significant benefit from additional ART for patients with intermediate risk (1-2 positive nodes, GLS 7-10 and pT3b/4 or positive surgical margins; 6.9% vs 15.8%, p = 0.03) and for patients with high risk (3-4 positive nodes irrespective of further risk parameters; 3.5% vs 21.2%, p = 0.02). The results could be confirmed with the end-point OS. These data need prospective validation, but could be helpful in individual decision making.

6.3.8 **Conclusion and Guidelines for definitive radiotherapy**

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

	LE	GR
Patients who are suitable for AS and surgery must have these options discussed with them.	4	A
EBRT should be offered in all risk groups of non-metastatic PCa.	2a	A
In low-risk PCa, the total dose should be 74 to 78 Gy.	1a	A
In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	2a	A
In intermediate-risk PCa the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	1b	A
In patients with high-risk localised PCa, a total dose of 76-78 Gy in combination with long-term ADT (2-3 yr) is recommended.	1b	A
In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr).	1a	A
IMRT is the recommended modality for definitive treatment of PCa by EBRT.	2a	A
In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	2b	B
In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation has to be discussed as an option because it improves at least biochemical-free survival	1a	A
Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (see Section 6.10.5.1).	2b	A

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

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

6.4.1 Background

Besides radical prostatectomy (RP), external-beam radiation and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa [497-500]. 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.

6.4.2 Cryosurgery

Cryosurgery uses freezing techniques to induce cell death by:

- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [497-500].

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.

6.4.2.1 Indication for cryosurgery

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 [497-499]. The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobe 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, or intermediate-risk PCa 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.

6.4.2.2 *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 [501-506].

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 old American Society of Therapeutic Radiology and Oncology (ASTRO) criteria, which require three initial consecutive increases in PSA level.

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, BDFS at five years is 60% and 36% for low-risk and high-risk patients, respectively [501, 502].

Long et al. [501] 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 [507].

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 [501-506]. 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. [504], who have analysed the therapeutic results of 590 patients undergoing CSAP for clinically localised 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 [508].

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 [509]. Men in both arms of the study received three to six months of neoadjuvant androgen ablative therapy.

6.4.2.3 *Complications of cryosurgery for primary treatment of PCa*

Erectile dysfunction occurs in about 80% of patients and this remains a consistent complication of the CSAP procedure, independent of the generation of the system used [510]. 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% [501-506]. 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.

6.4.3 *High-intensity focused ultrasound 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 [511]. 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 [507]. 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 7.4.4.2).

6.4.3.1 Results of high-intensity focused ultrasound in PCa

As with CSAP, various PSA thresholds are defined for biochemical cure, and no international consensus exists on objective response criteria. The Stuttgart criteria (> PSA nadir + 1.2 ng/mL) have been proposed to define BCR after HIFU treatment [512]. 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 [513]. According to the review mentioned above [507], HIFU showed PFS (based on PSA \pm 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) [514] (see Table 6.4.1). 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 [515], 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 [516], 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 [517].

Thüroff et al. [516] have summarised 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 [518]. 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 [519] ($p < 0.001$). 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 ± 1.2 years of follow-up, the actuarial DFS rate at five years was 66%, with salvage treatment initiated in 12% of patients [520].

In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU [521]. 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 [522]. 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. [523] 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. 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. [524] 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. [517] 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 6.4.1: Summary of studies addressing HIFU in PCa

Study (reference no.)	n	Median follow-up	Outcome measure
Blana et al. 2004 [518]	137	22.5 mo	87% PSA < 1 at follow-up
Poissonnier et al. 2007 [514]	227	27 mo	66% BCR-free at 5 y
Crouzet et al. 2013 [517]	1,002	6.4 y	76%, 63% and 57% BCR-free (Phoenix) for low-, intermediate- and high-risk disease, respectively DFS at 10 y: 97%; metastasis-free: 94%
Thüroff et al. 2003 [516]	559	6 mo	87% biopsy negative at 6 mo
Uchida et al. 2009 [521]	517	24 mo	72% BCR-free (Phoenix)
Inoue et al. 2011 [522]	137	36 mo	78% BCR-free (Phoenix)
Boutier et al. 2011 [523]	99	6 mo	64% biopsy tumour-free
Komura et al. 2011 [524]	144	47 mo	61% BCR-free (Phoenix)
Thüroff and Chaussy 2013 [525]	704	5.3 y	60%, BCR-free (Phoenix) at 10 y 99% DFS at 10 y; 95% metastasis-free at 10 y
Pfeiffer et al. 2012 [526]	191	53 mo	85%, 65% and 55% biochemical-free survival rate (Stuttgart) for low-, intermediate- and high-risk disease, respectively
Pinthus et al. 2012 [527]	402	24 mo	68% BCR-free (Stuttgart) at 4 y

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

6.4.4 Focal therapy of PCa

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [528-530].

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 [531-533].

6.4.4.1 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 [534-536]. 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 [537]. Thus, the exact anatomical localization of the index lesion - defined as the biologically most aggressive - can be accurately determined.

6.4.4.2 Patient selection for focal therapy

The primary objective of treatment must be the eradication of measurable and biologically aggressive disease with minimal toxicity. However, although treatment is usually intended to be a single session, patients should know that further treatment might be necessary in the future. Standardised 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; multiparametric 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 [538];
- patients should be counselled with caution as 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 [539] and focal electroporation [540].

6.4.5 **Conclusions and guidelines for experimental therapeutic options to treat clinically localised PCa**

Conclusions	LE
HIFU has been shown to have a therapeutic effect in low-stage PCa, but prospective randomised 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 localised 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

CSAP = cryosurgery; GR = grade of recommendation; HIFU = high-intensity focused ultrasound; LE = level of evidence; PSA = prostate specific antigen.

6.5 Treatment: Hormonal therapy - rationale and available drugs

6.5.1 Introduction

6.5.1.2 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) [541].

6.5.2 Testosterone-lowering therapy (castration)

6.5.2.1 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 was < 50 ng/dL (1.7 nmol/L). It was defined more than 40 years ago, when testosterone level testing was limited. Current testing methods have found that the mean value of testosterone after surgical castration is 15 ng/dL [542]. 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). This new definition is important as better results are repeatedly observed with levels around or below 1 nmol/l compared to 1.7 nmol/L [543-545]. However, the castrate level considered by the regulatory authorities is still 50 ng/dL (1.7 mmol/L), which is

also the threshold that has been used in all clinical trials addressing castration in PCa patients.

6.5.2.2 *Bilateral orchiectomy*

Bilateral orchiectomy, either total or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [546] and is the quickest way to achieve a castration level, usually within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

6.5.3 **Oestrogens**

Opposed to castration, oestrogens resultant testosterone suppression is not associated with bone loss [547].

6.5.3.1 *Diethylstilboestrol (DES)*

Early studies by the Veterans Administration (VACURG) tested oral Diethylstilboestrol (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 found to be as effective as bilateral orchiectomy [548], with still more side effects compared to castration.

6.5.3.2 *Strategies to counteract the cardiotoxicity of oestrogen therapy*

Two strategies have been attempted to neutralise oestrogen cardiotoxicity.

- Parenteral oestrogen (polyoestradiol phosphate) to avoid first-pass hepatic metabolism was as effective as CAB for survival, but with still more non-fatal cardiovascular events [549].
- 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 [550, 551].

These results precluded oestrogen as a standard first-line treatment.

6.5.4 **Luteinising-hormone-releasing hormone agonists**

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they 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.

6.5.4.1 *Achievement of castration levels*

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. The castration level is usually obtained within 2-4 weeks [552]. However, about 10% of treated patients fail to achieve castration levels [543], which rise to 15% if the castration threshold is defined as 1 nmol/l. Although there is no formal direct comparison between the various compounds, they are considered to be equally active [548] and comparable to orchiectomy [549].

6.5.4.2 *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 cardiovascular death due to hypercoagulation status.

Clinical flare needs to be distinguished from the biochemical flare and even from asymptomatic radiographic evidence of progression [553]. Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely 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 OS (see Section 6.6.3.1).

6.5.5 **Luteinising-hormone-releasing hormone 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. The practical shortcoming of these compounds is the lack of a long-acting depot formulation.

6.5.5.1 *Abarelix*

Abarelix was as effective as LHRH agonists in achieving and maintaining castration levels of testosterone and in reducing serum PSA [554, 555]. However, 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 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21320_plenaxis_lbl.pdf).

6.5.5.2 *Degarelix*

Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. The standard dosage 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. No allergic reactions were 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, suggesting a better progression-free survival compared to monthly leuporelin [556]. Its definitive superiority over the LHRH analogues remains to be proven. Their use is limited by a monthly formulation.

6.5.6 **Anti-androgens**

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

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

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

6.5.6.1 *Steroidal anti-androgens*

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

6.5.6.1.1 *Cyproterone acetate (CPA)*

This was the first anti-androgen to be licensed, but 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. Only one randomised trial [557] compared 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.

An underpowered monotherapy comparison with flutamide in M1b PCa did not show any difference in specific- and overall survival at a median follow-up of 8.6 years [558].

6.5.6.1.2 *Megestrol acetate and medroxyprogesterone acetate*

Very limited information is available on these two compounds, but they are associated with a poor overall efficacy [559].

6.5.6.2 *Non-steroidal anti-androgens*

Non-steroidal anti-androgens monotherapy have 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 [560]. Non-androgen pharmacological side-effects differ, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide [561]. All three agents share a common liver toxicity (occasionally fatal) and liver enzymes must be monitored regularly.

6.5.6.2.1 *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 exceptional interstitial pneumonitis (potentially life-threatening). Nilutamide is not licensed for monotherapy.

6.5.6.2.2 *Flutamide*

Flutamide has been studied as monotherapy for more than 20 years. No dose-finding studies against a currently accepted endpoint (e.g. PSA response) are available. 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.

6.5.6.2.3 Bicalutamide

The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens [562, 563], prophylactic radiotherapy [559], or surgical mastectomy. However, bicalutamide monotherapy clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists [560, 564].

6.5.7 **New compounds (for the castrate resistant status only)**

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 Section 6.11 - Castrate-resistant Prostate Cancer). 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 [565]. This has led to the development of two new major compounds targeting the androgen axis: abiraterone acetate and enzalutamide.

6.5.7.1 *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 ketoconazole, which is no longer available. By blocking CYP 17, AA significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone (2 x 5 mg).

6.5.7.2 *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 also blocks AR transfer and therefore suppresses any possible agonist-like activity.

Both drugs were developed for use in mCRPC after docetaxel. Both drugs have resulted in a significant overall improvement in survival [566, 567]. Detailed results are presented in section 6.11 - Castrate-resistant Prostate Cancer).

6.5.8 **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, NSAA monotherapy, and CAB using NSAA). 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 [568]. Finally, once ADT is started, if a major response is obtained, IAD might be a useful way to lower treatment costs.

6.6 **Treatment: Metastatic prostate cancer**

6.6.1 **Introduction**

A systematic review of ADT in PCa has recently been published [541].

6.6.2 **Prognostic factors**

In recent years, the median survival of patients with newly diagnosed metastases is 42 months [569]. The M1 population is heterogeneous, with the most convincing data on prognosis produced by the large SWOG 8894 trial [570] discriminating patients into three groups based on the location of metastases (axial bone only compared to appendicular or visceral), the performance status (< 1 compared to ≥ 1), the Gleason score (< 8 compared to ≥ 8) and the PSA (< 65 compared to > 65 ng/mL). Patients with axial bone metastases only or appendicular or visceral metastases, an PS < 1 and a Gleason score < 8 have a median survival of 54 months, compared to those with appendicular or visceral metastases a PS ≥ 1 and a PSA > 65 with only 21 months median survival.

After starting ADT, the PSA level after 7 months of ADT may lead to 3 groups with very different survival expectancy. 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 [571]. 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.

6.6.3 **First-line hormonal treatment**

Primary ADT is the standard of care [541]. 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.

6.6.3.1 *Prevention of flare-up*

Starting with an LHRH analogue results in an initial testosterone flare, which can usually be prevented by starting an anti-androgen at the same time [572]. 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, although 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 [573].

6.6.4 **Combination therapies**

6.6.4.1 *Complete androgen blockade (CAB)*

There are conflicting results from the many studies comparing CAB with monotherapy [572]. The largest RCT in 1,286 M1b patients found no difference between surgical castration plus flutamide compared to surgical castration without flutamide [574]. Systematic reviews have shown that CAB using non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [575, 576] beyond 5 years [577]. 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 vs. orchiectomy alone.

6.6.4.2 *Non-steroidal anti-androgen (NSAA) monotherapy*

A systematic review has been published comparing non-steroidal antiandrogen monotherapy to castration (either medical or surgical) by the Cochrane group [578]. The key message is that use of non-steroidal antiandrogen monotherapy compared with medical or surgical castration monotherapy for advanced PCa is less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events. The evidence quality was rated as moderate.

6.6.4.3 *Intermittent versus continuous androgen deprivation therapy (IAD)*

Long-term castration stimulates prostate cell apoptosis. After an average period of 24 months, the tumour relapses, characterised 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 [579]. It has been suggested that stopping castration prior to progression would mean that 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 Shionoggi 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.

IAD is feasible and accepted by patients [580]. Two independent reviews [581, 582] summarised the clinical efficacy of this attitude. They were based on seven RCTs. Of the seven trials, only three trials were in patients with M1 disease. The three remaining trials were combinations of different relapse situations, mainly locally advanced and metastatic cases.

The design of the seven trials is summarised in Table 6.6.1, while the main results for survival are summarised in Table 6.6.2. The most important survival finding was the lack of a significant difference in OS between continuous and intermittent ADT. Table 6.6.3 summarises the expected treatment benefits of IAD. The most important finding was that the benefit in overall QoL was at best minimal if any. However, some treatment side effects were decreased using IAD.

Table 6.6.1: Patient population and treatment cycles in phase III trials on IAD in M1 patients

Parameter	SEUG9401 [583]	FINN VII [584]	SWOG9346 [585]	TULP [586]	TAP22 [587]	De Leval [588]
n	766	554	1535	193	173	68
Tumour stage	Locally advanced/metastatic	Locally advanced/metastatic	Metastatic	Metastatic	Metastatic	Locally advanced/metastatic/BCR
PSA (ng/mL) at inclusion	4-100	Any value	> 5	Any value	> 20	Any value
Therapy	CAD	CAD	CAD	CAD	CAD	CAD
Induction period (mo)	3	6	7	6	6	6
PSA (ng/mL) level to stop on-phase	< 4	< 10	< 4	< 4	< 4	< 4
PSA (ng/mL) level to restart on-phase	> 10 for symptomatic and > 20 for asymptomatic	> 20	> 20	> 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	0.7-4.9 mo	1.0- 48.9 mo	3.3-8.3 mo
Follow-up (mo) median	50	65	108	31	44	31

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

Table 6.6.2: Oncological results in the 7 phase III trials on IAD

Parameter	SEUG9401 [583]	FINN VII [584]	SWOG9346 [585]	TULP [586]	TAP22 [587]	De Leval [588]
End points considered	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.
PC-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	-	-	-
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 yr. Continuous 5.8 yr. HR 1.09	-	IAD 56.9% dead; 42.2 mo. Continuous 54.2% dead; 52.0 mo p = 0.75	-

HR = hazard ratio; IAD = intermittent androgen deprivation; mo = months.

Table 6.6.3: QoL and safety in the 7 phase III trials on IAD

Parameter	SEUG9401 [583]	FINN VII [584]	SWOG9346 [585]	TULP [586]	TAP22 [587]
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 months 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. Favourable for IAD in sexual function domains	Favourable for IAD in activity limitation, physical capacity and sexual functioning domains	-	No clinically relevant difference	No clinically relevant difference

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

- The SWOG 9346 [585] is the largest-ever conducted trial in M1b patients. Out of 3,040 selected patients, only 1,535 were randomised 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.
- The SWOG 9346 was a non-inferiority trial. The results are inconclusive: (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2.

6.6.4.3.1 Potential other benefits of intermittent androgen deprivation

Other possible long-term benefits include bone protection [589] and/or a protective effect against the metabolic syndrome. Testosterone recovery is seen in most studies [580], leading to an intermittent castration. Finally, IAD is associated with a very significant decrease in the treatment cost.

6.6.4.3.2 Practical aspects for intermittent androgen deprivation

The optimal thresholds at which ADT must be stopped or resumed are empirical [580, 582]. Nevertheless, several points are clear.

- IAD is based on intermittent castration. Therefore, only drugs leading to castration are suitable for use in IAD.
- Most published experiences are based on CAB, which is considered as standard treatment. An LHRH antagonist might be a valid alternative [2], without any significant benefits.
- The induction cycle must last 9 months at the most, 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.
- 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 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 for IAD has still to be fully characterised. However, the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response [582].

IAD might be an option in metastatic situations after a standardised induction period, even if the benefits are fewer compared to those with less advanced situations.

6.6.4.4 *Immediate versus deferred androgen deprivation therapy*

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 variations in ADT modalities and follow-up schedules.

ADT was shown to be the most cost-effective therapy if started at the time the patient developed symptomatic metastases [568].

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 vs. deferred ADT, either as primary therapy or adjuvant to radical prostatectomy [590]. The Cochrane review found that the M1a/b population showed no improvement in OS, although early ADT significantly reduced disease progression and complication rates due to progression.

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 on when to start hormonal therapy in advanced asymptomatic PCa [591]. The ESMO guidelines do not make any statement [592].

6.6.5 *Hormonal treatment combined with chemotherapy*

Two large RCT were conducted, one is fully published [593], the second one just presented recently [594], but representing a cohort twice as large. They both compared ADT alone as standard with AT combined with upfront Docetaxel. They came to different findings regarding survival benefit and it is not possible to make a clear recommendation at the present time.

6.6.6 *Guidelines for the first-line treatment of metastatic prostate cancer*

	Modality	Recommendation	LE	GR
Castration alone	Surgical: agonist, antagonist.	Standard of care	1b	A
	New hormonal treatment (Abiraterone acetate, Enzalutamide)	To be used in an experimental setting only.	4	A
Castration combined with chemotherapy	Docetaxel combined with castration.	No specific recommendation can be made.	1b	A
Castration combined with any other local treatment	Radiotherapy or surgery	To be used in an experimental setting only.	3	A

6.6.7 *Guidelines for hormonal treatment of metastatic prostate cancer*

Recommendations	LE	GR
In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskelatal metastasis).	1b	A
In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b	A
In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	2b	B
Anti-androgens		
In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	2a	A
In M1 patients, short-term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection).	3 4	A B
In M1 patients, administration of anti-androgens as monotherapy should not be considered.	1a	A

Intermittent treatment			
Population	In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	1b	B
Threshold to start and stop ADT	In M1 patients, timing of intermittent treatment should follow the schedules currently in use in clinical trials. Treatment is usually stopped when the PSA level is < 4 ng/mL after 6 to 7 months of treatment. Treatment is resumed when the PSA is > 10-20 ng/mL.	4	C
Drug	Combined treatment with LHRH agonists and NSAA is recommended.	1b	A
	Antagonists might be an option.	4	B

ADT = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence; LHRH = luteinising hormone-releasing hormone; NSAA = non-steroidal anti-androgen; PSA = prostate specific antigen; RCT = randomised controlled trial.

6.6.8 Contraindications for various therapies

Therapy	Contraindications	LE	GR
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 = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence; LHRH = luteinising hormone-releasing hormone.

6.7 Management of prostate cancer in older men

6.7.1 Evaluating health status in senior adults

6.7.1.1 Introduction

With a median age at diagnosis of 68 years, PCa is generally a disease of men aged > 70 years. In the USA, the increase in men aged > 65 years will result in an estimated 70% increase in annual diagnosis of PCa by 2030 [595]. A similar increase is expected in Europe [4].

The Surveillance, Epidemiology and End Results (SEER) database shows that 71% of PCa-related deaths occur in men aged ≥ 75 years [596], probably due to the higher incidence of advanced/metastatic disease [597-599].

Despite the high incidence and mortality rates in senior adults, they may be undertreated in the USA [600] and Europe [601]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease receive curative treatment compared to 88% aged 65-74 [602]. Two large studies showed that PCa-specific mortality was low for localised low- and intermediate-risk PCa, irrespective of age [329, 603]. In contrast, cancer-related mortality of up to 64% was found for high-risk PCa.

6.7.1.2 Evaluation of life expectancy, comorbidity and health status

In localised disease, > 10 years life expectancy is considered mandatory for any benefit from local treatment. Life expectancy varies within each age group. This can be explained by comorbidity, which is more important than age in predicting death in localised PCa [304]. Besides comorbidities, dependence in daily activities, malnutrition and cognitive impairment are associated with worse survival.

6.7.1.2.1 Comorbidity

Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP [604]. This was confirmed in a patient group who did not receive any form of local treatment within 180 days after diagnosis [304]. At 10 years, most men with a Charlson Comorbidity Index (CCI) score > 2 had died from competing causes, irrespective of age or tumour aggressiveness.

Currently, the Cumulative Illness Score Rating-Geriatrics (CISR-G; Table 6.7.1) [605] is the best tool for assessing mortality risk unrelated to PCa [606]. Although CCI measures only potentially lethal comorbidity, the CISR-G also rates non-lethal conditions [607].

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

Cumulative Illness Rating Scale	
Patient	Age
Rater	Date
Rating strategy	
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)
Score	
Heart	
Vascular	
Respiratory	
Eyes, ears, nose, throat and larynx	
Upper GI	
Lower GI	
Hepatic	
Renal	
Genitourinary	
Musculoskeletal/integument	
Neurological	
Endocrine/metabolic	
Psychiatric illness	
Total score	

Patients are considered fit if they have no Grade 3 score

Vulnerable: one or two Grade 3 scores

Frail: > 2 Grade 3, or any Grade 4 scores

Too sick: multiple Grade 4 scores

6.7.1.2.2 Independent daily activities

The level of dependence in daily activities influences survival in senior adults [608-610]. The Activities of Daily Living (ADL) scale rates accomplishment of basic activities of daily living, while the Instrumental Activities of Daily Living (IADL) scale rates activities requiring higher cognition and judgement.

6.7.1.2.3 Malnutrition

Malnutrition is associated with increased mortality in senior patients [611]. Nutritional status can be estimated from body weight during the previous 3 months:

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

6.7.1.2.4 Cognitive impairment

Cognitive impairment is associated with increased mortality risk in senior adults [612]. In patients undergoing major elective surgery, there is an association between baseline cognitive impairment and long-term postoperative complications and mortality [613]. Intervention is unlikely to reverse cognitive impairment, except in depression [40].

6.7.1.2.5 Baseline screening using the G8 screening tool

The International Society of Geriatric Oncology (SIOG) Prostate Cancer Working Group (PCWG) recommends that treatment for senior adults should be based on systematic evaluation of health status [40]. The G8 (Geriatric 8) health status screening tool is described in Table 6.7.2, the Karnofsky and ECOG Scores in Table 6.7.3 [614].

Table 6.7.2: G8 screening tool (Adapted from [615])

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

G8 score > 14 shows that patients should receive the same treatment as younger patients. Patients with $G8 \leq 14$ should undergo full geriatric evaluation, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [615]. Patients with reversible impairment (vulnerable patients) should be treated according to EAU Guidelines. Patients with irreversible impairment (frail patients) should receive adapted treatment [40].

Table 6.7.3: Performance Scales - Karnofsky & ECOG Scores [614]

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

6.7.1.2.6 Conclusions

Systematic assessment, using the G8 tool, is recommended by The SIOG PCWG [40]. Patients with G8 score < 14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [40].

Senior adults can be classified into one of four groups regarding health status based on G8 score > 14 (patient considered fit), or score < 14 (patient considered vulnerable or frail). The treatment policy is then:

- fit or healthy older men should receive standard treatment;
- vulnerable patients may receive standard treatment after resolution of any geriatric problems;
- frail patients should receive adapted treatment;
- patients who are too sick with terminal illness should receive only palliative treatment [40].

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

6.7.1.3 Guidelines for the evaluation of health status in elderly men

	LE	GR
Senior adults with localised PCa should systematically undergo health status screening	1b	A
Health status screening should be performed using the G8 screening tool	2a	A
Patients with G8 score ≤ 14 should undergo full specialist geriatric evaluation	2a	A
Senior adults can be classified as follows: 1. Fit or healthy older men, should receive standard treatment; 2. Vulnerable patients (reversible impairment) may be given standard treatment after resolution of geriatric problems; 3. Frail patients (irreversible impairment) should receive adapted treatment; 4. Patients who are too sick with terminal illness should receive only symptomatic palliative treatment.	3	B

6.7.2 Specific aspects of PCa treatment in older men

6.7.2.1 Localised PCa

6.7.2.1.1 Deferred treatment (active surveillance, watchful waiting)

This has been described in Chapter 8 and 9. Active treatment mostly benefits patients with intermediate- or high-risk disease and longest expected survival. A recent study assessed the effect of age, health status and patient preferences on outcomes of surgery vs active surveillance for low risk PCa. As expected, older age and worse baseline health status were associated with a smaller benefit in prostate-cancer-specific mortality and life expectancy with surgery, and increased incremental years with treatment side effects. Older men and men in poor health were likely to have better quality adjusted life expectancy with active surveillance [327].

6.7.2.1.2 Radical prostatectomy

Senior adults (aged ≥ 75 years) are more likely to present with very advanced disease and have a greater risk of death from PCa, despite higher death rates from competing causes [597]. In the most recent update of the SPCG-4 study, randomising patients with localised PCa to RP vs watchful waiting, the benefit of surgery with respect to death from PCa was largest in the men younger than 65 years of age (relative risk, 0.45). However, radical prostatectomy was associated with a reduced risk of metastases and use of androgen deprivation therapy among older men (relative risk, 0.68 and 0.60, respectively) [311]. Risk of short-term complications after RP is related more to comorbidity severity than age. Conversely, risk of long-term incontinence is influenced more by increasing age [616, 617].

6.7.2.1.3 External beam radiotherapy

External beam radiotherapy (EBRT) and RP have similar cancer control and treatment-related comorbidity, regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided radiotherapy [618].

The drawback of associating ADT with EBRT in senior adults is discussed in Chapter 12. Cardiac status should be assessed because ADT in patients with pre-existing heart conditions is associated with increased morbidity and mortality. Patients with moderate to severe comorbidities might not have a significant survival-benefit when associating ADT with EBRT [413].

6.7.2.1.4 Minimally invasive therapies

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

6.7.2.1.5 Androgen deprivation therapy

In patients with non-metastatic localised PCa not suitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation. In locally advanced T3-T4 disease, immediate ADT may benefit patients with PSA > 50 ng/mL and PSA-DT < 12 months [619, 620].

6.7.2.2 Advanced PCa

6.7.2.2.1 Hormone-naïve metastatic PCa

ADT is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG PCWG recommends evaluation of baseline bone mineral density and prevention of osteoporosis by calcium and vitamin D supplements [40].

Routine bisphosphonates or denosumab to prevent skeletal complications in ADT is not recommended, unless

there is a risk of fracture, or castration-resistant PCa (CRPC) with skeletal metastasis [621].

6.7.2.2.2 Metastatic CRPC

In metastatic CRPC, docetaxel is standard in fit and vulnerable older men [622], with comparable response and tolerance to younger patients [623]. Tolerability has not been specifically studied in frail older men. In elderly and frail patients, granulocyte colony-stimulating factor prophylaxis should be considered.

Cabazitaxel, abiraterone acetate, enzalutamide, and sipuleucel-T increase survival in chemotherapy-treated and chemotherapy-naïve senior adults [566, 567, 624-628].

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

6.7.2.3 Guidelines for the treatment of prostate cancer in older men

Treatment	LE	GR
<i>Localised disease</i>		
Fit and vulnerable senior adults with life expectancy > 10 years and high-risk disease should be offered standard treatment.	2b	A
In frail or 'too-sick' patients, immediate ADT should only be used for symptom palliation.	1b	A
Minimally invasive energy-ablative therapies should not be routine in senior adults. These only have a role in 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 in fit and vulnerable adults.	1b	B

ADT = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence.

6.8 Treatment: Post-treatment quality of life in patients with localised prostate cancer

6.8.1 Introduction

Increased life expectancy in PCa makes post-treatment QoL a key issue. Health-related QoL (HRQoL) refers to the impact of disease and treatment on well-being and physical, emotional and social functioning, including daily functioning [629]. HRQoL is rated by patients, and is important because physicians often underestimate the impact of disease and treatment on patients [630].

PCa-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel and sexual functioning. General HRQoL refers to well-being, vitality, fatigue, pain, general health status, global QoL, and life satisfaction [631].

HRQoL is measured using standardised questionnaires, which provide an objective assessment of general and disease-specific domains [632, 633].

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

6.8.2 Active surveillance and watchful waiting

Although active surveillance (AS) and watchful waiting (WW) avoids treatment-related side effects, they carry an increased risk of psychological distress, which significantly affects HRQoL [634]. Risk factors for not doing well on AS include: patient perception that the physician is making most of the decisions, poor physical health, high anxiety, high PSA, lack of a partner, mental impairment, recent diagnosis of PCa, and lower number of core samples taken at diagnostic biopsy. These factors are significantly associated with low HRQoL [635, 636]. Anxiety and distress remained low during the first 9 months of AS [636].

In contrast to AS, men managed with WW in SPCG-4 were not followed closely to induce curative treatment if needed, which could explain the less favourable anxiety and depression scores compared to the PRIAS results [637].

A long-term comparison of WW and RP [637] found that depression, well-being and psychological status did not differ significantly among treatment groups over 8 years. However, men in the RP group reported more physical symptoms related to leakage, erection and libido.

Apart from psychological distress, untreated men may have a higher level of irritative/obstructive urinary symptoms compared to patients treated with RP or radiotherapy after 1-3 years [638].

6.8.3 **Radical prostatectomy**

RP has a significant negative effect on multiple QoL domains, including sexual and urinary function, and physical HRQoL [639-641]. In the Prostate Cancer Outcomes Study (PCOS), at 2 years 8.7% of men had a lack of urinary control and 41.9% reported sexual dysfunction [642]. Recovery from sexual dysfunction and urinary incontinence occurs over 2-3 years [617, 643], with the latter being at its worst by 2 months after surgery [639].

Although some advances have reduced these side effects, such as nerve-sparing RP or robot-assisted radical prostatectomy (RALP), their impact on HRQoL remains controversial. Preserving neurovascular bundles aims to reduce erectile dysfunction [639, 644] and improves urinary function [645]. RALP and open RP have comparable functional outcomes and similar HRQoL scores [646]. There is no reliable data to compare HRQoL following RALP and laparoscopic RP. General HRQoL domains such as pain and energy worsen immediately post-RP, but usually improve by 12 months [643, 647].

New methods for reporting outcomes after RP combine major outcomes, including continence, potency and cancer control [309] and perioperative complications and positive surgical margins [648]. Pentafecta rates reflect postoperative expectations and satisfaction more accurately and are used in counselling patients with clinically localised PCa. The use of trifecta and pentafecta outcomes in postoperative HRQoL assessment needs further validation.

6.8.4 **External-beam radiotherapy and low-dose rate brachytherapy**

EBRT and I-125 low-dose rate (LDR) brachytherapy may cause urinary, sexual- and bowel dysfunction. Both methods can result in irritative voiding symptoms, such as urgency, frequency, and urge incontinence, that negatively affect overall urinary function and HRQoL [639]. In the radiotherapy group, urinary incontinence was reported to be at its worst by 2 months after surgery, but the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months [639]. Patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence. At 1-2 years after LDR brachytherapy, incontinence was reported by 4-6% of patients. Eighteen percent of the LDR brachytherapy group and 11% of the EBRT group reported distress from overall urinary symptoms at 1 year [639].

EBRT and LDR brachytherapy significantly affected the bowel and rectal HRQoL domains [639], which were almost as important as urinary problems [649, 650]. Symptom onset 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 was reported in 9% of patients at 1 year after EBRT or LDR brachytherapy [639]. At 2 years after dose-escalated EBRT, $\leq 11\%$ of patients had problems with bowel HRQoL. Bowel HRQoL was related to baseline function, $\leq 25\%$ volume of rectum treated with 70 Gy, and aspirin [651]. Bowel and rectal symptoms were less severe after LDR brachytherapy than EBRT [632].

Significant deterioration in HRQoL was reported at 6 years after I-125 LDR brachytherapy, including urinary and bowel symptoms, pain, physical functioning, and sexual activity [652]. HRQoL scores returned close to baseline 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 did not significantly affect gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT [653].

Adjuvant androgen suppression may exacerbate the adverse effects of EBRT or LDR on sexuality, vitality [639] and long-term bowel function [654].

Fatigue is commonly reported following EBRT, with the highest level seen at the end of treatment. 4% of patients reported severe fatigue 5-years post-treatment, adversely affecting QoL [655].

Men treated with interstitial LDR brachytherapy had only slight declines in general HRQoL. Physical and functional status declines have been reported in the first few months after implantation, but pretreatment function was regained by most men after 1 year [652].

6.8.4.1 **Radiotherapy toxicity**

Patients must be informed about acute and late genitourinary or gastrointestinal toxicity and the impact of irradiation on erectile function. In contemporary practice, the NCIC toxicity grading system is increasingly used, but most studies have used the RTOG scales, which are described in Tables 6.8.1 and 6.8.2. Risk factors for acute or late gastrointestinal toxicities after RT include advanced age, preexisting diabetes mellitus, haemorrhoids, inflammatory bowel disease, a history of prior abdominal surgery, larger rectal volume and the concomitant use of androgen deprivation [466].

Pre-treatment genitourinary complaints, prior transurethral resection of the prostate and the presence of acute genitourinary toxicity are suggested as contributing to long-term urinary morbidity.

Table 6.8.1: Acute gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer morbidity scale (adaptations with regard to the original RTOG scale in italics) according to Huang et al. [656]*

	Grade 1	Grade 2	Grade 3	Grade 4
GI	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.	Diarrhoea requiring parasympatholytic drugs. Mucous discharge not necessitating sanitary pads. Rectal or abdominal pain requiring analgesics.	Diarrhoea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distension (flat plate radiograph demonstrates distended bowel loops).	Obstruction, fistula, or perforation GI bleeding requiring transfusion; Abdominal pain or tenesmus requiring tube decompression or bowel diversion.
GU	Frequency of urination or nocturia twice pretreatment habit. Dysuria or urgency not requiring medication.	Frequency of urination is less frequent than every hour (<i>day: 12-16 times; nocturia 5-8 times</i>). Dysuria, urgency, bladder spasm requiring local anaesthetic.	Frequency of urination is more frequent than every hour (<i>day: > 16 times; nocturia: > 8 times</i>). Dysuria, bladder spasm, urgency requiring frequent regular narcotic. Gross haematuria <i>complaints requiring permanent or suprapubic catheter.</i>	Haematuria requiring transfusion. Obstruction not resulting from clots. Ulceration Necrosis

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GI = gastrointestinal; GU = genitourinary.

Table 6.8.2: Late gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scale (adaptations with regard to the original RTOG/EORTC scale in italics) according to Huang et al. [656]*

	Grade 1	Grade 2	Grade 3	Grade 4
GI*	Mild diarrhoea Mild cramping Bowel movements 2-5 per day Slight rectal discharge or bleeding	Moderate diarrhoea Intermittent, severe cramping. Bowel movements (5 per day). <i>Moderate excessive, rectal discharge. Intermittent, frequent bleeding (3 single laser treatments or transfusion).</i>	<i>Watery diarrhoea</i> Obstruction requiring surgery. Bleeding requiring surgery or 2 <i>laser treatments or transfusions.</i>	Necrosis Perforation Fistula <i>Abdominal pain or tenesmus requiring tube decompression or bowel diversion.</i>
GU	<i>Frequency during day 0.5-1 h</i> <i>Nocturia 2-3/night</i> <i>Slight dysuria or microscopic haematuria requiring no medication</i> Slight epithelial atrophy, minor telangiectasia <i>Bladder capacity > 300 mL</i>	<i>Frequency during day: 1-2 h</i> <i>Nocturia 4-6/night</i> <i>Moderate dysuria or intermittent (mild, moderate) haematuria requiring medication†</i> Moderate telangiectasia <i>Bladder capacity: 150-300 mL</i>	<i>Frequency during day: 2 h</i> <i>Nocturia 6/night</i> Severe dysuria Frequent (severe) haematuria Severe telangiectasia Bladder capacity: 100-150 mL <i>Benign urethral strictures requiring TURP, dilation, or suprapubic or permanent catheter</i>	Necrosis Severe haemorrhagic cystitis Bladder capacity > 100 mL
<p>* The difference between grade 1 and grade 2 GI pain, mucosal loss, or bleeding is most easily made when grade 2 is defined as morbidity requiring specific medication: grade 1 = stool softener, diet modification, occasional (< 2/wk) non-narcotic drug, occasional antidiarrhoeal agent (2/wk), occasional use of incontinence pads (1-2 d/wk); grade 2 = regular (> 2/wk) use of (non)narcotic drugs for pain, regular (2/wk) antidiarrhoeals, steroid suppositories, one laser.</p> <p>† With the exception of antibiotics.</p>				

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GI = gastrointestinal; GU = genitourinary; TURP = transurethral resection of the prostate.

6.8.5 Complications of high-intensity focused ultrasound

Urinary retention appears to be one of the most common side-effects of HIFU, developing in almost all patients, with the mean interval of catheterization via a suprapubic tube varying between 12 and 35 days [511, 514, 515]. 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. [657] 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% [517]. Acute urinary retention was seen in 7.6% of men. Even in more recent treatment, the rate of urethral-rectal fistula was 0.7%.

6.8.6 Cryotherapy

Quality of life and sexuality following CSAP were investigated in a clinical phase II trial that recruited 75 men [658]. 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 prospective, randomised clinical trial, 244 men with newly diagnosed organ-confined PCa were randomised to receive either external-beam radiation therapy (EBRT) or to undergo CSAP [659]. After a follow-up of three years, sexual function was significantly less impaired in the EBRT group.

6.8.7 **Hormonal therapy**

There is a lack of data on the effects of hormonal treatment on QoL, with only a single, large, prospective, RCT comparing orchiectomy + flutamide or placebo in M1 patients. Combined therapy resulted in a lower QoL in the first 6 months, with more frequent diarrhoea and worse emotional functioning, compared with castration alone [660]. A small RCT evaluated the health-related quality of life (HRQoL) at 1-year follow-up in patients with non-localised PCa, between various ADT, or no treatment. Both sexual and cognitive function significantly declined with ADT, while emotional distress significantly increased if no treatment [661]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [662]. Another retrospective, non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than did orchiectomised patients. The stage at diagnosis had no effect on health outcome [663].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at 12 months [664]. A post-hoc analysis, including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [665], preserved libido and erectile function [666].

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

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

The many deleterious side-effects of long-term ADT have been well known for years. As the use of ADT increases, it is increasingly important to consider these side-effects. A systematic review of the side-effects of long-term ADT has been recently published [667].

6.8.7.1.1 Sexual function

Loss of libido and erectile dysfunction are usual. The management of acquired erectile dysfunction is mostly non-specific [668].

6.8.7.1.2 Hot flushes

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

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications. Soya phytoestrogens have shown an efficacy in breast cancer patients, but have not been evaluated in men. Progesterone-based treatments have demonstrated efficacy with 80% of patients showing an improvement [669].

Serotonin reuptake inhibitors (e.g. venlafaxine or sertraline) appear to be effective in men, but less than hormonal treatments based on a prospective randomised trial comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or CPA, 100 mg daily [670]. After 6 months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

With a placebo effect influencing up to 30% of patients [671], the efficacy of clonidine, veralipride, gabapentine [672] and acupuncture [673] must be compared in prospective, randomised, controlled trials.

6.8.7.1.3 Other systemic side-effects of androgen-deprivation therapy

They are frequent and may lead to significantly increased morbidity or even mortality.

6.8.7.1.3.1 Non-metastatic bone fractures

Due to increased bone turnover and decreased BMD in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% relative risk with long-term ADT [674]). Hip fractures in men are associated with a significant risk of death [675]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk

factors) indicates a high risk of subsequent non-metastatic fracture. The WHO FRAX tool (<http://www.shef.ac.uk/FRAX>) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) are common and occur during the first year of ADT [676]. Both changes increase the fracture risk.

- **Lifestyle changes before starting long-term androgen-deprivation therapy**
Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption, and to normalise their body mass index. Calcium and vitamin D supplements should be considered if low values are detected. (Normal values: calcium: 2.2-2.6 nmol/L, vitamin D: 100-160 nmol/L). A daily intake of at least 1200 mg/day of calcium and 1000 UI of vitamin D is useful.

- **Hormonal treatment modalities**
Bicalutamide monotherapy could be a bone-protective treatment [677, 678], but is limited by its suboptimal efficacy (see Section 6.6 - Metastatic Prostate Cancer - Hormonal Therapy).
The intermittent modality might be associated with less bone impact [589].

- **Bisphosphonates**
Bisphosphonates increase BMD in the hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid remains unclear: quarterly [679] or yearly [680] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [681]. A quarterly regimen could be considered for a BMD \leq 2.5 as a yearly injection is unlikely to provide sufficient protection [682].

In contrast to breast cancer, a significant benefit in OS has only been demonstrated in PCa in a post-hoc analysis for the oral first-generation clodronate with an absolute 8% OS increase after 8 years of follow-up [683]. This benefit has never been observed with more recent bisphosphonates.

- **Denosumab (a fully human monoclonal antibody against RANKL)**
In M0 patients, Denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after 2 years, using a 60 mg subcutaneous regimen every 6 months [684]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs 3.9%, $p = 0.006$). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every 4 weeks), a delay in bone metastases of 4.2 months has been shown [685] without any impact on OS, and with increased side effects. Therefore, this regimen cannot be recommended.

6.8.7.1.3.2 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [676]. 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 [686], 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 [687]:

- 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 [688].

6.8.7.1.3.3 Cardiovascular morbidity

Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [689]. Several studies showed that ADT, even after only 6 months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [690]. The RTOG 92-02 [691] and 94-08 [396] confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 [692]. 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 [693] or presenting with a metabolic syndrome [694].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [695]. However, the used methodology does not provide convincing evidence to show a clear superiority of these compounds.

These data resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [696]. Preventive advice includes non-specific measures: loss of weight, increased exercise, improved nutrition and smoking cessation.

6.8.7.1.3.4 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure [697, 698], with prolonged efficacy [699] and improved specific survival [700].

Anaemia may be a cause of fatigue. Anaemia requires an etiological diagnosis (medullar invasion, mainly inflammatory, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusion is required if severe anaemia is present. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [667].

6.8.8 **Comparison of health-related quality of life between treatment modalities**

So far, any comparisons between treatment-related QoL were assessed in non-randomised observational cohorts, with limited follow-up. Only a few trials have directly compared treatment modalities but longer follow-up is needed. When comparing general HRQoL for treatments of clinically localised PCa [631, 701] the differences were limited. Data from longitudinal studies show that surgery and radiotherapy have a greater impact on role functioning and vitality/energy with surgery being associated with increased dysfunction [647]. Most men recovered function by 1 year after treatment.

QoL outcomes have been reported for RP or EBRT [642]. At 5 years after diagnosis, sexual function declined similarly in both groups. Erectile dysfunction was more prevalent in the RP group (79.3% vs 63.5%). Incontinence was reported in 14-16% of RP and 4% of EBRT patients at 5 years. Bowel urgency and painful haemorrhoids were more common in the EBRT group. At 15 years, there were no significant differences between RP and EBRT [34]. RP incurred a significantly higher incidence of urinary incontinence (39-49%) and erectile dysfunction (80-91%) compared with radiotherapy (6-7% and 41-55%, respectively) [649]. Bowel problems (urgency) affected 30-35% of the EBRT group vs. 6-7% of the RP group [649].

Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0-6 months after treatment (84.5%) than patients treated with RP (63.3%) [702]. Urinary bother did not differ significantly (67.7% vs. 67.4%, respectively). Decreased sexual function did not return to pretreatment levels in either group.

Urinary incontinence increased at 2 years after RP, whereas bowel problems and urinary irritation-obstruction occurred after EBRT and LDR brachytherapy [632]. Sexual function deteriorated immediately after surgery and then improved, whereas sexual function continued to slowly decline after EBRT and brachytherapy. There was no change in urinary function and little change in bowel function after 1 year. Patients with bowel dysfunction at 1 year after EBRT may expect modest improvement. Although diarrhoea continues to subside, there is little change in tenesmus and rectal urgency, while rectal bleeding becomes more prevalent.

Three years follow-up confirmed long-term changes in adverse effects, e.g., increased urinary symptoms after EBRT or increased sexual dysfunction after LDR brachytherapy, which tended to reduce any differences between treatments over time [703]. RP caused greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive symptoms compared with LDR brachytherapy. Treatment differences persisted for up to 3 years [703].

A comparative trial of RP and LDR brachytherapy was closed after 2 years due to poor accrual [704]. For LDR brachytherapy vs. RP, there were no differences in bowel or hormonal domains. The LDR brachytherapy patients scored better for the urinary QoL and sexual domains, and patient satisfaction.

A study in Norway investigated the relationship between urinary, bowel or sexual dysfunction and global QoL in PCa survivors, including untreated patients [638]. The RP group reported more urinary incontinence than other groups, but had the lowest level of urinary irritative-obstructive symptoms. Untreated patients had the highest level of these symptoms. The radiotherapy group reported more intestinal irritation and faecal leakage than the RP and untreated groups. In all groups, poor sexual drive and erectile function were common, with

the RP group reporting the highest prevalence of erectile dysfunction. Irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global QoL, whereas erectile function and use of medication for erectile dysfunction were not [638].

All typical adverse events (moderate/severe IPSS, urinary incontinence, irritative intestinal symptoms, faecal leakage, poor sexual drive and poor erectile function) were significantly associated with low global QoL in univariate analyses. Low educational level, comorbidity and moderate or high neuroticism were all significantly associated with low global QoL in univariate analyses. No significant associations with global QoL were observed for age, a paired relationship or D'Amico risk group.

LDR brachytherapy and prostate cryoablation were associated with better urinary function and bother scores compared to open RP and laparoscopic and robotic radical prostatectomy in a non-randomised cohort of patients [705]. LDR brachytherapy was associated with higher sexual function and bother scores compared to other treatments. The study used the UCLA-PCI questionnaire, which does not evaluate irritative urinary symptoms, which are often observed after LDR brachytherapy [702]. This may have significantly compromised the results of the HRQoL assessment.

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

6.8.9 Guidelines on quality of life in prostate cancer management

	LE	GR
Patients with low-risk PCa should be informed that functional outcome of active surveillance is better than for local active treatment.	2	B
Patients should be informed that functional outcome after RALP and open prostatectomy are similar.	2	B
Patients should be informed that long-term (15 years) QoL outcomes of EBRT and RP are similar.	2	B

EBRT = external beam radiation therapy; GR = grade of recommendation; LE = level of evidence; RALP; RP = radical prostatectomy; QoL = quality of life.

6.9 Summary of guidelines for the primary treatment of prostate cancer

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

	Low-risk	Intermediate-risk	High-risk	
Definition	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	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

Primary treatment of prostate cancer		Gr	
General comments	Patients suitable for several treatment modalities (active surveillance, surgery, radiotherapy) must have these options discussed with them.	A*	
	In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable as no single approach has shown clear superiority in terms of functional or oncological results.	A	
	EBRT should be offered in all risk groups of non-metastatic PCa.	A	
	IMRT is the recommended modality for definitive treatment of PCa by EBRT.	A	
	Treatment	Comment	
Low risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
		During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression.	B
	Active surveillance	Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A

		Follow-up should be based on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	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).	B
		LND is not indicated in low-risk PCa	A
	Radiotherapy	In low-risk PCa the total dose should be 74 to 78 Gy.	A
		In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	A
	Cryotherapy, HIFU	In patients who are unfit for surgery or radiotherapy, cryotherapy or HIFU might be an alternative treatment for PCa. The lack of long-term efficacy compared to standard modality has to be discussed with patients.	C
	Focal treatment	Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A
	Androgen suppression	Unsuitable.	A
Intermediate risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
	Active surveillance	Not an option.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	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).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		eLND should be performed if the estimated risk for positive lymph nodes exceeds 5%.	B
		Limited LND should not be performed.	A
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
		Adjuvant HT for pN0 is not recommended.	
	Radiotherapy	In intermediate-risk PCa the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A
Androgen suppression monotherapy	No place in asymptomatic patients.	A	
High risk PCa	Watchful waiting	High risk localised: Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	
		High risk locally advanced: In M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSA-DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	A
	Active surveillance	Not appropriate.	A
	Radical prostatectomy	NHT before RP is not recommended.	A

		eLND should be performed in high-risk PCa.	A	
		Limited LND should not be performed.	A	
		High risk localised: In patients with high-risk localised PCa and a life expectancy of > 10 yr, RP should be offered in a multimodality setting.	B	
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (refer to Partin tables/nomograms).	B	
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B	
		High risk locally advanced: In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	C	
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A	
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A	
	Radiotherapy	In patients with high-risk localised PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yr is recommended).	A	
		In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr is recommended).	A	
	Androgen suppression monotherapy	Reserved for those unwilling or unable to receive any form of local treatment and either symptomatic or asymptomatic with a PSA-DT < 12 months and a PSA > 50 ng/mL and a poorly differentiated tumour.	A	
N1 patients				
cN1		In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	B	
pN1 after eLND		Adjuvant ADT is the standard of care for node-positive (pN+) patients.	A	
		Adjuvant ADT with additional radiotherapy may have a role.	B	
		Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.	B	
Metastatic PCa	Watchful waiting	In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	B	
	Active surveillance	Unsuitable.	A	
	Radical prostatectomy	Unsuitable outside clinical trial.	A	
	Radiotherapy to the prostate	Unsuitable outside clinical trial.	A	
	Androgen suppression		Surgical- or medical castration (LHRH agonist or antagonist).	A
			No recommendation can be made to define the best population for combining castration with upfront Docetaxel.	A
			Castration combined with local treatment / other new hormonal treatments (abiraterone acetate or Enzalutamide) should not be used outside clinical trials.	A
			In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	A
		In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	A	

	In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	A
	In M1 patients short-term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection).	A
	In M1 patients, administration of anti-androgens as monotherapy should not be considered.	A
	In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	B
	Based on the schedules in use in clinical trials, treatment is stopped when the PSA is < 4 ng/mL after 6 to 7 months of treatment. Treatment is resumed when the PSA is > 10-20 ng/mL.	C
	Combined treatment with LHRH agonists and NSAA is recommended.	A
	Antagonists might be an option.	B
Castrate resistant status	Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.	A
	There is no evidence for treatment of non-metastatic CRPC outside a clinical trial.	A
	Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.	A
	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>	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.	A
	Salvage hormonal treatment using abiraterone acetate is a valid option.	A
	Salvage hormonal treatment using enzalutamide is a valid option.	A
	In patients with metastatic CRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m ² every 3 weeks has shown a significant survival benefit.	A
	In patients with relapse following salvage docetaxel chemotherapy, cabazitaxel, abiraterone acetate and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	A
	In men with mCRPC and with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit.	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.	A
	Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	A
In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must always be initially considered.	A	

A* Upgraded following panel consensus.

ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; LHRH = luteinising-hormone-releasing hormone; LND = (extended) lymph node dissection; mCRPC = metastatic castrate-resistant prostate cancer; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSA-DT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

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

	GR
Senior adults with localised PCa should systematically undergo health status screening	A
Health status screening should be performed using the G8 screening tool	A
Patients with G8 score ≤ 14 should undergo full specialist geriatric evaluation	A
Senior adults can be classified as follows: 1. Fit or healthy older men, should receive standard treatment; 2. Vulnerable patients (reversible impairment) may be given standard treatment after resolution of geriatric problems; 3. Frail patients (irreversible impairment) should receive adapted treatment; 4. Patients who are too sick with terminal illness should receive only symptomatic palliative treatment.	B

Treatment	LE	GR
<i>Localised disease</i>		
Fit and vulnerable senior adults (after status optimisation) with life expectancy > 10 years and high-risk disease should be offered standard treatment.	2b	A
In frail or 'too-sick' patients, immediate ADT should only be used for symptom palliation.	1b	A
Minimally invasive energy-ablative therapies should not be routine in senior adults. These only have a role in selected fit and vulnerable senior adults with intermediate-risk disease.	3	B
<i>Advanced disease (locally advanced / metastatic 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 in fit and vulnerable adults.	1b	B

DT = doubling time; NHT = neoadjuvant hormonal treatment; GR = grade of recommendation; IPSS = International Prostatic Symptom Score; LE = level of evidence; PSA = prostate specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate.

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

6.10.1 Background

Primary curative procedures such as RP, and RT are well-established therapeutic options in the management of localised PCa. Despite technical improvements, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or RT develop PSA-recurrence (see Sections 6.2 and 6.3). While a rising PSA level universally antedates metastatic progression and prostate-cancer-specific mortality (PCSM), physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a PSA rise is not a surrogate for these survival endpoints. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It has to be emphasised that the treatment recommendations for these patients should be given after discussion with a multidisciplinary team.

6.10.2 Definitions

6.10.2.1 Definition of biochemical failure

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. However, following RP, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL and rising [706]. Although a retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa [707] was used to determine the best PSA cut-off point for defining BCR. Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively [707].

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 [708].

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

6.10.3 **Natural history of biochemical failure**

Once a PSA relapse has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. The risk of subsequent metastases and PCSM may be predicted by the initial clinical factors (e.g. T-category, PSA, biopsy Gleason score). If the patient has undergone RP, the pathological outcomes of the surgery (e.g. pathologic T-category and prostatectomy Gleason score, nodal and margin status) may provide further information. Beyond pre- and posttreatment clinico-pathological factors, PSA kinetics (PSA doubling-time (PSA-DT) and interval to PSA failure) may be used to estimate the risk of metastases and subsequent PCSM.

6.10.3.1 *Post-radical prostatectomy biochemical recurrence*

According to Pound et al. [363], not all patients with BCF after RP develop clinical recurrence. The authors evaluated the follow-up data for 1,997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data were confirmed by Boorjian et al. in a study including approximately 2,400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only a few died of PCa (5.8%) [709]. Overall, these studies demonstrated a general trend among men with PSA-only recurrence after RP (i.e. 7-40% of relapsing men): for every 100 men treated with RP, approximately 15-30 will develop BCR and 2-6 of those will die of PCa.

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. Compiling the results of several studies, a subgroup with a high risk of metastases and PCSM was characterised by a PSA-DT < 3 months, seminal vesicle invasion (pT3b), specimen Gleason score 8-10, or time to PSA-recurrence < 3 years. Furthermore, a low-risk subgroup was defined as patients with a PSA-recurrence > 3 years following surgery, specimen Gleason score ≤ 7, pathologically organ confined disease or limited extracapsular extension (pT3a), and PSA-DT > 12 months [710-713]. Patients in the high-risk subgroup universally have an exponentially higher risk of developing metastases and dying of PCa. In other words, many patients in the high-risk subgroup likely have micro-metastatic disease or significant local recurrence at the time of PSA-rise, while those in the low-risk subgroup likely have a slow-growing local recurrence only. Indeed, patients in the low-risk subgroup typically respond very well to salvage RT with a high probability of PSA being undetectable [714]. However, it must be stressed that most patients within the low-risk subgroup have an excellent outcome even without any salvage treatment. Therefore, the decision to treat these patients should be made after careful consideration of the pro and cons, taking into account the life expectancy of the patient and his expectations. Patients within the high-risk subgroup need early and aggressive salvage treatment [715]. Trock et al. demonstrated that salvage RT was associated with a significant 3-fold increase in prostate-cancer-specific survival relative to those who received no salvage treatment. The increase in prostate-cancer-specific survival associated with salvage RT was limited to men with a PSA-DT of < 6 months and remained after adjustment for pathological stage and other established prognostic factors. Salvage RT initiated > 2 years after recurrence provided no significant increase in prostate-cancer-specific survival [715].

6.10.3.2 *Post-radiotherapy biochemical recurrence*

Similar to patients experiencing PSA-recurrence after RP, patients with a PSA-rise following RT can be subdivided into prognostic categories. A high-risk subgroup with elevated risk of metastases and PCSM are those patients with a PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 and clinical stage cT3b-T4. Conversely, patients at low risk of metastases and PCSM are those with a PSA-DT > 15 months, biopsy Gleason score ≤ 7, clinical stage ≤ cT3a and time to biochemical progression > 3 years [712, 716, 717].

Zumsteg et al. have designed a risk score to further subdivide patients who develop PSA recurrence following RT. Those with either 0, 1 or ≥ 2 high-risk factors (PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 and clinical stage cT3b-T4) have an increased risk of developing metastases and PCSM [717].

Again, the choice of local salvage treatment (salvage RP, salvage cryo, salvage HIFU, salvage brachytherapy) should be guided by the life expectancy and oncological risk profile of each patient, together with the patient's expectations.

6.10.4 **Assessment of metastases**

6.10.4.1 *Bone scan and abdominopelvic computed tomography*

The standard workup to detect PCa metastases usually includes bone scan and abdominopelvic CT. However, because biochemical failure after RP or radiation therapy precedes clinical metastases by 7-8 years on average, the diagnostic yield of usual imaging techniques is poor in asymptomatic patients [718]. In men with

PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [719, 720]. A PSA doubling time (PSA-DT) < 6 months or a PSA velocity > 0.5 ng/mL/month are predictors of positive bone scan [719, 721].

CT sensitivity for detecting local recurrences or lymph node metastases is low. Only 11-14% of patients with biochemical failure after RP have positive CT [719]. In a series of 132 men with biochemical failure after RP, the mean PSA level and PSA velocity associated with positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [721]. 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 high PSA kinetics (PSA-DT < 6 months or PSA velocity > 0.5 ng/mL/month) or in patients with symptoms of bone disease [719].

However, more sensitive methods are needed to detect metastatic patients among candidates for local salvage treatment.

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

¹⁸F-fluorodeoxyglucose (FDG) is of limited value due to low uptake by PCa. In contrast, ¹¹C- or ¹⁸F-Choline and ¹¹C-Acetate have shown promising results in the early detection of local and distant recurrences [240]. However, their accuracy remains difficult to assess because most published studies are retrospective, evaluate heterogeneous populations (often mixing recurrences after various types of primary treatments), use non-standardised 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 [240].

Recent studies report overall sensitivities and specificities of 55-96% and 57-100%, respectively [240, 722-724]. ¹¹C-Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [725] and may be positive for bone metastases in up to 15% of patients with biochemical failure after RP and negative bone scan [726]. The specificity of ¹¹C-Choline PET/CT is also higher than bone scan with less false positive and indeterminate findings [248, 727].

Several studies evaluated ¹¹C-Choline PET/CT in lymph node staging in patients with biochemical failure after primary treatment, using lymph node dissection as the gold standard. They reported conflicting results. One study found a sensitivity of 64%, a specificity of 90%, a positive predictive value of 86% and a negative predictive value of 72% [728]. The main explanation for the low sensitivity was the lack of detection of micrometastases in lymph nodes. In contrast, others found poor specificity with a 30-47% false-positive rate [729-731]. In a meta-analysis of 609 patients with primary or recurrent PCa, the pooled sensitivity and specificity of Choline PET/CT for pelvic lymph node metastases were 62% (95% CI, 51%-66%) and 92% (95% CI, 89%-94%), respectively [242].

Despite these limitations, Choline- or Acetate-PET/CT changed medical management in 28-48% of patients with biochemical failure after primary treatment [732-735].

However, a large body of literature suggests that Choline or Acetate PET/CT sensitivity is strongly dependent on the PSA level and kinetics [240, 722, 724, 736]. In patients with biochemical failure after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL, but rises to 67-100% when the PSA level is > 5 ng/mL. Similarly, PET/CT sensitivity seems much higher when the PSA velocity is high or the PSA-DT is short. In a recent meta-analysis, Choline PET/CT detection rates were 65% (95% CI, 58%-71%) when the PSA-DT was ≤ 6 months, and were 71% (95% CI, 66%-76%) and 77% (95% CI, 71%-82%) when the PSA velocity was > 1 and > 2 ng/mL/year, respectively [722].

Due to its high cost, PET/CT cannot be recommended in all patients with PSA relapse. After RP, the optimal PSA cutoff level seems to be between 1 and 2 ng/mL [724, 736]. It is unclear whether PSA velocity or PSA-DT thresholds can be used to further select groups of patients in whom PET/CT could be recommended.

After RT, the PSA cutoff level is unclear due to the lack of sufficient data and because the PSA level is more difficult to interpret due to the “physiological” amount of measurable PSA produced by the non-tumoural prostate [724]. In a study of 46 patients with PSA relapse after RT or brachytherapy, the ¹⁸F-Choline PET/CT detection rate was 54.5%, 81%, 89% and 100% when the PSA level was 1-2 ng/mL, 2-4 ng/mL, 4-6 ng/mL and > 6 ng/mL, respectively [737]. In another study of 140 patients the ¹¹C-Choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [738].

6.10.4.3 Other radionuclide techniques

A ¹¹¹In-capromab pendetide scan (ProstaScint™) yielded disappointing results in patients with biochemical failure after RP or radiation therapy [718, 719]. Its use is therefore not recommended.

¹⁸F-Fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases [727]. However, ¹⁸F-Fluoride is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [248].

6.10.4.4 Whole-body and axial magnetic resonance imaging (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 [252-254] and seem equally effective as ¹¹C-Choline PET/CT [739] 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 ¹¹C-Choline PET/CT in high-risk patients [244].

However, little is known regarding the accuracy of whole-body or axial MRI in patients with biochemical failure after RP or radiation therapy [740]. Therefore, the role of these techniques in detecting occult bone or lymph node metastases in the case of biochemical failure remains to be assessed.

6.10.4.5 Assessment of local recurrences

6.10.4.5.1 Local recurrence after radical prostatectomy

The precise localisation of the local recurrence by imaging techniques is needed only if histological proof of the recurrence is mandatory before salvage treatment and/or if this localisation could change treatment planning. Transrectal ultrasound is neither sensitive nor specific in detecting local recurrences after RP. Even with TRUS guidance, the sensitivity of anastomotic biopsies remains low: 40-71% for PSA levels > 1 ng/mL and 14-45% for PSA levels < 1 ng/mL [718]. As a consequence, salvage radiation therapy is usually decided on the basis of the BCR, without histological proof of the local recurrence. The dose delivered to the prostatic bed also tends to be uniform as it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Thus, most patients undergo salvage radiation therapy without local imaging.

Nonetheless, several studies have reported promising results in the detection of local recurrences using MRI, particularly dynamic contrast-enhanced MRI which showed sensitivities and specificities of 84-88% and 89-100%, respectively [741-743]. However, the mean PSA level in these studies was 0.8-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Recently, two studies evaluated mpMRI in patients with PSA level < 0.5 ng/mL. One found a sensitivity of only 13% in men with PSA level < 0.3 ng/mL [744], while the other reported a sensitivity of 86% in patients with PSA level < 0.4 ng/mL [745]. Thus, it remains to be defined whether MRI is able to correctly detect local recurrences in patients with PSA level < 0.5 ng/mL in order to allow a stereotaxic boost to the recurrence site during salvage radiation therapy. Choline or Acetate PET/CT can also detect local recurrences, but are less sensitive than MRI [723, 746].

6.10.4.5.2 Local recurrence after radiation therapy

In patients with biochemical failure after radiation therapy, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options, it is thus necessary to obtain histological proof of the local recurrence before treating the patient [718].

TRUS is not reliable in depicting local recurrences after radiation therapy. In contrast, mpMRI has yielded excellent results [718, 747-749] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with Choline and Acetate PET/CT, but PET/CT has poorer spatial resolution than MRI [732, 733, 738, 750].

6.10.4.6 Guidelines for imaging and second-line therapy after treatment with curative intent

Biochemical recurrence (BCR) after RP	LE	GR
In the case of BCR, bone scan and abdominopelvic CT should be performed only in patients with a PSA level > 10 ng/mL, or with high PSA kinetics (PSA-DT < 6 mo or a PSA velocity > 0.5 ng/mL/mo) or in patients with symptoms of bone disease.	3	A
A Choline PET/CT is not recommended in patients with BCR and a PSA-level < 1 ng/mL	3	A
Biochemical recurrence after RT		
In patients with BCR who are candidates for local salvage therapy, prostate mpMRI may be used to localise abnormal areas and guide biopsy.	3	C

BCR = biochemical recurrence; CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; PSA-DT = prostate specific antigen doubling time; RP = radical prostatectomy; RT = radiotherapy.

6.10.5 Treatment of PSA-only recurrences

The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial. After RP, the therapeutic options are:

- Radiotherapy at least to the prostatic bed;

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

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

6.10.5.1 Radiotherapy (Salvage radiotherapy [SRT] - with or without androgen-deprivation therapy for PSA-only recurrence after radical prostatectomy)

Early SRT provides a possibility of cure for patients with an increasing or persistent PSA after RP. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level again [494, 751-753], providing patients with an ~ 80% chance of being progression-free 5 years later [495]. A retrospective analysis based on 635 patients who underwent RP in 1982-2004, followed up through December 2007, who experienced BCR and/or local recurrence and received no salvage treatment (n = 397) or salvage RT alone (n = 160) within 2 years of BCR, 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 short PSA-DT [715]. Despite the indication of salvage RT a “wait and see” strategy is an option in patients with a long PSA-DT of more than 12 months [709]. For an overview see Table 6.10.1.

Table 6.10.1: Selected studies on post-prostatectomy salvage radiotherapy (SRT), sorted by pre-salvage radiotherapy (SRT) PSA level.

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 yr	5-yr results
Siegmann, et al. [754]	2011	301	0	0.28	66.6 / 70.2	74% (2)	55% vs.88% @ 66.6 vs. 70.2 Gy
Wiegel, et al. [495]	2009	162	0	0.33	66.6	54% (3.5)	60% vs. 33% @ PSA ≤ 0.5 vs. > 0.5
Goenka, et al. [755]	2011	285	31	0.4	> 70 (72%)	37% (7)	39%
Cremers, et al. [756]	2010	197	0	0.59	63 / 2.25 frct. (88%)	59% (5)	
Bernard, et al. [757]	2010	364	0	0.6	64.8	50% (5)	
Buskirk, et al. [758]	2006	368	15	0.7	64.8	46% (5)	63% vs. 51% @ PSA < 0.5 vs. 0.5-1.0
Pazona, et al. [759]	2005	223	4.5	0.8	63	40/25% (5/10)	42% vs. 30% @ < 1.3 vs. ≥ 1.3
Pisansky, et al. [760]	2000	166	4	0.9	64	46% (5)	61% vs. 36% @ PSA ≤ 1 vs. > 1
Soto, et al. [761]	2012	441	24	< 1 (58%)	68	63/55% (3) HT / no HT	44/40% HT / no HT
Stephenson, et al. [494]	2007	1540	14	1.1	64.8	32% (6)	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 an additional increase in the CSS compared with SRT alone [715]. So far, adding ADT to SRT has only shown benefit in terms of biochemical PFS after 5 years in retrospective series [755, 762] and in PFS for “high-risk” tumours [761], however data from prospective randomised trials are missing. Results are awaited from recently completed randomised controlled phase III studies: the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting and the French GETUG 16 trial, comparing salvage

EBRT with- or without 6 months of ADT. To date there is no recommendation for patients with primary pN0-stage at RP for a combination of SRT plus additional ADT.

6.10.5.1.1 Dose, target volume, toxicity

To date, the optimal salvage RT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the bed of the seminal vesicles according to the pathological stage after RP) [751]. Similarly, a US guideline panel regarded 64-65 Gy as the minimum dose that should be delivered post RP [763]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at 3-5 years [757]. In a systematic review, the pre-SRT PSA level and SRT dose were correlated with BCR, showing that the relapse-free survival decreased by 2.6% per 0.1 ng/mL PSA and improved by 2% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA [751, 764, 765].

There have been various attempts to define common outlines for “clinical target volumes” of PCa [766-768] and for organs at risk of normal tissue complications [769]. 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 [766].

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 resulted from RP alone [752]. In a retrospective cohort of 285 men receiving 3D-CRT (38%) or IMRT (62%) with 66 Gy in 95% of cases, the high-dose subgroup did not show a significant increase in toxicity [755]. In an analysis involving 30 participating centres, a quality assurance programme assessing target volumes, RT techniques (3D-CRT, IMRT, VMAT) and RT doses (64 vs. 70 Gy) it was found that 3D-CRT was applied in nearly half of the centres and was not associated with significantly worse rectum and bladder DVH parameters, for salvage RT using 70 Gy, when compared with IMRT [770].

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 [771, 772]. 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%) [771]. 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 [772].

6.10.5.1.2 Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy (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 the 10-year bNED after ART was significantly improved compared with non-ART (63 vs. 45%), there was no difference in OS. 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 a median of 5.9 years. Sixty-three percent of the SRT patients achieved an undetectable PSA after salvage RT and the hazard ratio for local recurrence after salvage RT was 0.13. However, similar to that after ART, no improved OS was seen after salvage RT [773].

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 salvage RT, respectively. Subgroup analyses did not yield significant differences for the two approaches. It was concluded that early SRT does not impair PCa control, but clearly helps to reduce overtreatment which is a major issue in ART [774].

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 17).

Decision-making on whether to proceed with adjuvant RT for high risk PCa - pT3-4 pN0 M0 with undetectable PSA after RP, or to postpone RT as an early salvage procedure in the case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before RP that adjuvant RT may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of RT when it is used and

provide justification when it is not, and this will help the discussion between the physician and the patient.

6.10.5.2 *Hormonal therapy*

Currently there is no available RCT comparing the effect of salvage ADT, although retrospective comparative studies are available. Still, salvage ADT is often used and represents one major practice of ADT use [775].

A retrospective study including 1,352 patients with post-RP PSA recurrence showed that early ADT was associated with a delay to clinical metastases only in patients with a Gleason score > 7 and/or a PSA-DT < 12 months. After a median follow-up after relapse of 3.7 yr, ADT had no impact on the PCa-specific mortality [776].

A multivariate analysis performed by Choueiri et al. [777] showed that whereas salvage ADT in univariate analysis was harmful in the whole patient population, it showed a survival benefit in multivariate analysis correcting for risk factors (logPSA, age, pGS, pT, surgical margins, PSA failure and salvage RT). In a subanalysis of patients where PSA-DT was known, if corrected for the same risk factors plus PSA-DT (< 6 months vs \geq 6 months), the survival benefit of salvage ADT increased even more with a HR for death of 0.55 (95% CI 0.36-0.82).

In patients initially treated with radiotherapy, Klayton et al [778] showed there was a clinical benefit of ADT versus observation in patients with a PSA-DT < 6 months. At 7 years follow-up, these patients had a significantly better metastases-free survival and disease-specific survival, whilst this was not the case for patients with a PSA-DT \geq 6 months.

Regarding the timing of salvage ADT, two large comparative studies show no benefit of early vs. late ADT in patients with BCR [377, 779]. After a median of 10-yr follow-up, Siddiqui et al documented that there was no progression-free or disease-specific survival benefit for early ADT. In patients with a PSA \geq 2 ng/mL, early ADT even showed worse CSS. A recent study based on the CAPSURE database of relapsing patients did not show any 5- and 10-year specific or overall survival difference when comparing immediate and deferred ADT [779]. In the deferred ADT group, patients with a PSA-DT < 12 months were included; again suggesting PSA-DT might be an important risk factor.

If salvage ADT is considered, an intermittent strategy may be appealing as it decreased by almost 60% the amount of drug used. In a large non-inferiority RCT of 1,386 patients primarily treated with radiotherapy [780], intermittent treatment was non-inferior compared to continuous treatment (median OS: 8.8 years (intermittent), and 9.1 years (continuous) (HR: 1.02 (0.86 - 1.21)). In the intermittent ADT group, testosterone recovery to the trial-entry threshold occurred in 79% of patients. Intermittent androgen deprivation provided potential benefits with respect to physical function, fatigue, urinary problems, hot flushes, libido, and erectile function. In metastatic patients (see Section 6.8.7), this modality is reserved for responding patients (achieving a PSA at least below 4 ng/mL after 6 to 8 mo of ADT), and treatment is resumed when the PSA is above 10 ng/mL.

In conclusion, not all patients with relapse after primary curative treatment benefit from salvage ADT. A favourable effect is observed in a high-risk group, which may be defined by short PSA-DT and/or tumour characteristics. Intermittent ADT seems non-inferior to continuous hormones.

6.10.5.3 *Observation*

Observation until the development of clinically evident metastatic disease may represent a viable option for patient with low-risk features (PSA-DT > 12 months, time to BCR > 3 years, GS \leq 7 and stage \leq T3a) or unfit patients with a life expectancy < 10 years and/or are unwilling to undergo salvage treatment. In these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [363].

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

Therapeutic options in these patients are ADT or local procedures such as SRP, cryotherapy, interstitial brachytherapy and high-intensity focused US [781-790]. As a general rule, strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of (very) low quality. The following is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

6.10.6.1 *Salvage radical prostatectomy (SRP)*

Salvage 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.

6.10.6.1.1 Oncological outcomes

In a recent systematic review of the literature, Chade et al. showed that SRP gave 5- and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The 10-yr 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 [791].

In most contemporary series, organ-confined disease, negative SMs, and the 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 [790].

Table 6.10.2: Oncological results of selected SRP case series, including at least 30 patients

Reference	Yr	n	Median FU (mo)	Pathologic organ confined, %	PSM, %	Lymph node involvement, %	BCR-free probability, %	CSS, %	Time probability, yr
Sanderson, et al. [792]	2006	51	-	25	36	28	47	-	5
Leonardo, et al. [793]	2009	32	35	53	34	0	75	-	3
Heidenreich, et al. [789]	2010	55	23 (2-56)	73	11	20	87	-	2
Chade, et al. [794]	2011	404	55	55	25	16	37	83	10

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

6.10.6.1.2 Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47% vs 5.8%), urinary retention (25.3% vs 3.5%), urinary fistula (4.1% vs 0.06%), abscess (3.2% vs 0.7%) and rectal injury (9.2% vs 0.6%) [795]. In more recent series, these complications appear to be less common [788, 791]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence (UI) ranging from 21% to 90% and erectile dysfunction in nearly all patients [791].

Table 6.10.3: 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. [788]	2004	100	15 vs 2*	30	33 vs 13*	-
Ward, et al. [796]	2005	138	5	22	-	-
Sanderson, et al. [792]	2006	51	2	41	6	-
Gotto, et al. [795]	2010	98	9	41	25	-
Heidenreich, et al. [789]	2010	55	2	11	3.6	360 (150-1450)

* SRP performed before vs after 1993.

n = number of patients; SRP = salvage radical prostatectomy.

6.10.6.2 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, a pre-SRT PSA < 10 ng/mL and biopsy Gleason score ≤ 7, no lymph node involvement pre-SRT, and whose initial clinical staging was T1 or T2 [791].

6.10.7 Salvage cryoablation of the prostate

6.10.7.1 Oncological outcomes

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [797]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year biochemical recurrence-free survival (BCR-FS) estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [798].

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%) [799].

Table 6.10.4: Oncological results of selected SCAP case series, including at least 50 patients

Reference	Yr	n	Median FU (mo)	BCR-free probability, %	Time probability, yr	Definition of failure
Pisters, et al. [800]	1997	150	17	44	-	Nadir + 0.2
Bahn, et al. [801]	2003	59	82	59	7	PSA > 0.5
Ismail, et al. [797]	2007	100	33	73 (low risk)	5	ASTRO
Pisters, et al. [798]	2008	279	22	58	5	ASTRO and Phoenix
Williams, et al. [802]	2011	187	7.46 yr	39	10	Nadir +2
Spiess, et al. [803]	2010	450	40.8	34	-	PSA > 0.5

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

6.10.7.2 Morbidity

According to Cespedes et al. [804], the risks of urinary incontinence 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 patients underwent surgical procedures for the management of treatment-associated complications. In a recent study by Pisters et al, the UI rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients required transurethral resection of the prostate (TURP) for removal of sloughed tissue [798]. With the use of third-generation technology, complications such as UI and obstruction/retention have significantly decreased during the last decade (see Table 6.10.5) [805].

Table 6.10.5: 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 [800]	1997	150	73	67	1	72
Bahn [801]	2003	59	8	-	3.4	-
Ismail [797]	2007	100	13	4	1	-
Pisters [798]	2008	279	4.4	3.2	1.2	-
Ahmad [806]	2013	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

6.10.7.3 Summary of salvage cryoablation of the prostate

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

6.10.8 Salvage brachytherapy for radiotherapy failure

Following local recurrence after previous definitive RT there is no indication for external beam salvage RT as

the total dose is limited and therefore the chance of cure is low. For carefully selected patients with primary localised PCa and histologically proven local recurrence, high- or low-dose rate (H/LDR) brachytherapy remain effective treatment options with an acceptable toxicity profile [807-809]. However, the published series are relatively small, therefore this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR-brachytherapy over a period of nine years [807]. With a median follow-up of 60 months the 5-year biochemical control was 51% and only 2% grade 3 GU toxicities were reported. Comparable with these data, 42 patients were treated in a phase-II-trial at MSCCC in New York [810]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after 5 years was 69% (median follow-up 36 months). Grade 2 late side effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side effects have been reported [811].

Using LDR-brachytherapy with 103Pd (palladium), long-term outcome was reported in 37 patients with a median follow-up of 86 months [114]. 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 was 11%. These side effects were comparable with a series of 31 patients treated with salvage 125I brachytherapy in the Netherlands. Therefore, in these small series, late side effects seem to be lower with HDR-brachytherapy [812].

In conclusion, freedom from BCR after salvage HDR- and LDR-brachytherapy is promising and the rate of severe side effects in experienced centres seem to be acceptable. Therefore salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

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

6.10.9.1 *Oncological outcomes*

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

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

Reference	Yr	n	Median FU (mo)	BCR-free probability, %	Negative biopsy rate
Colombel, et al. [813]	2006	224	15-18	-	80
Gelet, et al. [814]	2000				
Gelet, et al. [815][121]	2004				
Uchida, et al. [816]	2011	22	24	59 (Phoenix) (24 mo)	92 (only 12 biopsied)
Berge, et al. [817]	2011	46	9	60.9 (9 mo)	

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

6.10.9.2 *Morbidity*

Again, most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

6.10.9.3 *Summary of salvage high-intensity focused ultrasound (HIFU)*

There is a paucity of data which prohibits any recommendation regarding the indications for salvage HIFU.

6.10.10 **Observation**

Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. watchful waiting in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSA-DT of $>$ 12 months after RT. The 5-year metastasis-free survival rate was 88% with hormone therapy versus 92% with watchful waiting ($p = 0.74$) [818].

6.10.11 Guidelines for imaging and second-line therapy after treatment with curative intent

Local salvage treatment	LE	GR
Biochemical recurrence (BCR) after RP		
For patients with a PSA rise from the undetectable range and favourable prognostic factors (\leq pT3a, time to BCR > 3 yr, PSA-DT > 12 mo, Gleason score \leq 7) surveillance and possibly delayed salvage RT (SRT) may be offered.	3	B
Patients with a PSA rise from the undetectable range should be treated with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Biochemical recurrence (BCR) after RT		
Selected patients with localised PCa at primary treatment and histologically proven local recurrence should be treated with salvage RP (SRP).	3	B
Due to the increased rate of side effects, SRP should be performed in experienced centres.	3	A
High intensity focused ultrasound (HIFU), cryosurgical ablation and salvage brachytherapy are treatment options for patients without evidence of metastasis and with histologically proven local recurrence. Patients must be informed about the experimental nature of these approaches.	3	B
Systemic salvage treatment		
In asymptomatic men with BCR, ADT should not be given routinely.	3	A
Patients with a PSA-DT > 12 mo, should not receive ADT.	3	B
If salvage ADT (post-primary RT) is started, intermittent therapy should be considered in responding patients.	1b	A

ADT = androgen-deprivation therapy; BCR = biochemical recurrence; GR = grade of recommendation; LE = level of evidence; PSA-DT = prostate-specific antigen doubling time; RT = radiotherapy; SRP = salvage radical prostatectomy.

6.11 Treatment: Castration-resistant prostate cancer (CRPC)

6.11.1 Background

Our knowledge of the mechanisms involved in the development of castration-resistant prostate cancer (CRPC), remains incomplete [819, 820]. An alteration in normal androgen signaling is thought to be central to the pathogenesis of CRPC [821]. It is mediated through two main, overlapping, mechanisms. These are androgen-receptor (AR)-independent and AR-dependent.

6.11.2 Definition of progressing prostate cancer after castration

Table 6.11.1: Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;
Biochemical progression: Three consecutive rises in 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 new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [822].
Symptomatic progression alone must be questioned and is not sufficient to diagnose CRPC.

Frequent post-treatment PSA surveillance has resulted in earlier detection of progression [823]. In such patients occult micro-metastasis might exist, but are usually undetectable using conventional methods [824]. Although 33% will develop bone metastases within 2 years [825], there are no available studies suggesting a benefit for treatment.

In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity and PSA doubling time have been associated with time to first bone metastasis, bone metastasis-free and overall survival [825, 826]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group [827] suggested a bone scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL and again after every doubling of the PSA based on PSA testing every 3 months.

The rest of this chapter focuses on management of men with proven metastatic CRPC (mCRPC)

6.11.3 Assessing treatment outcome in castration-resistant PCa (CRPC)

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

6.11.3.1 PSA level as marker of response

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

6.11.4 Androgen deprivation in castration-resistant PCa

Eventually men with PCa show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in CRPC is debatable [838].

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 [839, 840]. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients.

Table 6.11.2: Randomised phase III controlled trials - first-line treatment of mCRPC*

Author	Year	Intervention (N)	Comparison (N)	Selection criteria	Main outcomes
DOCETAXEL					
SWOG 99-19 [841]	2004	Docetaxel/EMP, every 3 weeks, 60 mg/m ² , EMP 3 x 280 mg/day	Mitoxantrone, every 3 weeks, 12 mg/m ² prednisone 5 mg BID		OS: 17.52 vs. 15.6 mo. PFS: 6.3 vs. 3.2 mo.
TAX 327 [842]	2004	Docetaxel, every 3 weeks, 75 mg/m ² prednisone 5 mg BID or Docetaxel, weekly, 30 mg/m ² prednisone 5 mg BID	Mitoxantrone, every 3 weeks, 12 mg/m ² , Prednisone 5 mg BID		OS: 18.91 for 3 weekly vs. 17.4 mo for weekly and 16.5 in the control group.
ABIRATERONE					
COU-AA-302 Ryan [843, 844]	2013	Abiraterone + Prednisone (546)	Placebo + Prednisone (542)	No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms. No visceral metastases.	OS: 34.7 vs. 30.3 mo (p= 0.0027). FU: 49.2 mo. PFS: 16.5 vs. 8.3 mo. P < 0.0001) (p = Main side effects outcomes: 48% vs. 42% grade 3-4.

ENZALUTAMIDE					
PREVAIL Beer [845]	2014	Enzalutamide (872)	Placebo (845)	No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms 10% had visceral metastases	<u>OS</u> : 32.4 vs 30.2 mo (p < 0.001). FU: 22 mo. <u>PFS</u> : median not reached vs 3.9 mo (p < 0.001) <u>Main side effects outcomes</u> : Hypertension, fatigue and hot flush
SIPULEUCEL-T					
Kantoff [830]	2010	Sipuleucel-T (341)	Placebo (171)	Some with previous docetaxel. ECOG 0-1. Asymptomatic or minimally symptomatic.	<u>OS</u> : 25.8 vs. 21.7 mo (p.0.03). FU: 34.1 mo. <u>PFS</u> : 3.7 vs 3.6 mo. <u>Main side effects outcomes</u> : 31.7% vs. 35.1%.
Small [829]	2006	Sipuleucel-T (82)	Placebo (45)	ECOG 0-1. No visceral metastases. No bone or cancer pain. No corticosteroids.	<u>OS</u> : 25.9 vs. 21.4 mo (p. 0.01). FU: 36 mo. <u>PFS</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.

ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; PFS = progression-free survival; OS = overall survival.

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

6.11.5.1 Abiraterone

The use of abiraterone in the pre-docetaxel setting was evaluated in the large phase III trial COU-AA-302, in which 1,088 chemo-naïve mCRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone [843]. Patients were mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and were 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 49.2 months, there was significant radiological PFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At that point there was a trend to improved OS, which with further follow-up has become significant [846]. With a median follow-up of 49.4 months OS was 34.7 vs 30.3 months (HR = 0.80, (CI 0.69-0.93) p = 0.0027) 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.

6.11.5.2 Enzalutamide

The Enzalutamide, phase III trial (PREVAIL) has also been unblinded early [845]. In a similar chemo-naïve population of 1717 men this also showed a significant improvement in time to radiological progression (HR 0.186 (CI 0.15-0.23) p < 0.0001) and a marked delay in the initiation of chemotherapy (HR 0.35) with 78% of men seeing at least a 50% decrease in PSA. This also showed statistical improvement in OS (HR 0.706 (CI 0.6-0.84) p < 0.001). The most common clinically relevant adverse events were fatigue and hypertension.

6.11.6 Non-hormonal therapy

6.11.6.1 Docetaxel regimen

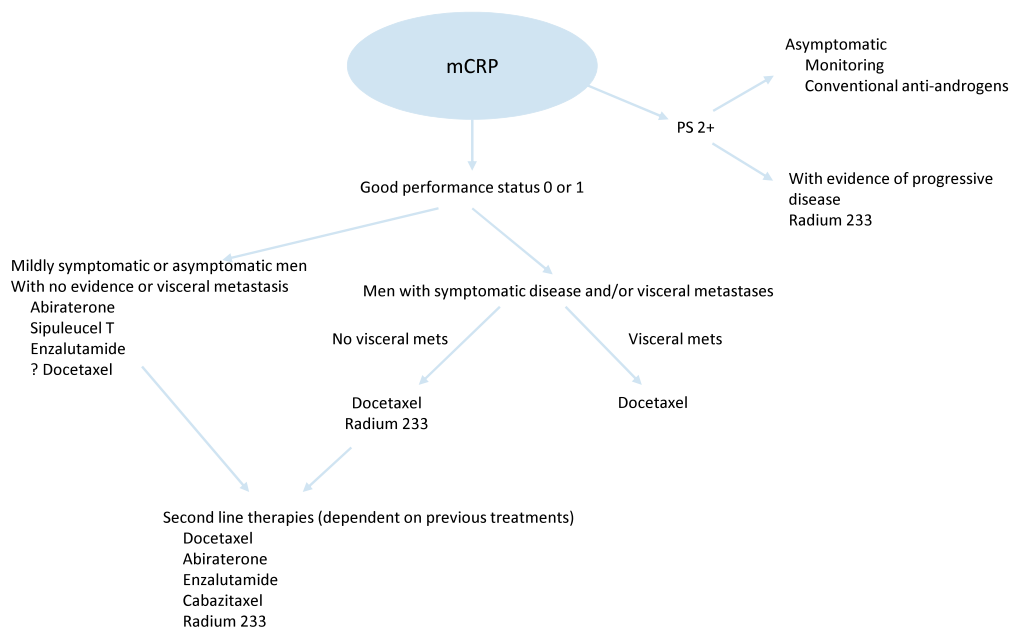
A significant improvement in median survival of 2-2.5 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy [841, 842]. The standard for first-line cytotoxic chemotherapy is docetaxel using the same regimen as in the TAX 327 trial, that is, 75 mg/m² 3 weekly combined with prednisone 5 mg BID, up to 10 cycles, 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, PSA-DT < 55 days, or the presence of visceral metastases [847]. A better risk group definition has recently been 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 categorised 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 [848]. 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) [849, 850]. Age by itself is not a contraindication to docetaxel [851].

6.11.6.2 Vaccine

In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients [626]. This was the first time that a PCa vaccine had shown a benefit and led to FDA and EMA 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. 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. Uptake of Sipuleucel T has been affected by access, cost and questions of timing.

Figure 6.11.1: Flowchart of the potential therapeutic options after PSA progression following initial hormonal therapy



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

Eastern Cooperative Oncology group performance status was used to stratify patients. Generally

men with a performance status of 0-1 are likely to tolerate treatments and those with performance status of 2 or more are less likely to benefit. However, it is important that treatment decisions are individualised and in particular where symptoms related to disease progression are determining performance status it may be appropriate to trial novel treatments in order to see if response is accompanied by improvement in PS.

6.11.7 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 [852, 853].

Available treatments and the setting tested are presented in Table 6.11.3.

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

Author	Year	Intervention (N)	Comparison (N)	Selection criteria	Main outcomes
ABIRATERONE					
Fizazi [625]	2012	Abiraterone + Prednisone (797)	Placebo + Prednisone (398)	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	Overall survival: 15.8 vs. 11.2 mo ($p < 0.0001$). FU: 20.2 mo. Progression-free survival: 5.6 vs. 3.6 mo. Main side effects outcomes: Similar.
de Bono [566]	2011				Overall survival: 14.8 vs. 10.9 mo ($p < 0.001$). FU: 12.8 mo. Progression-free survival: 5.6 vs. 3.6 mo. Main side effects outcomes: More mineralocorticoid adverse events with abiraterone.
ALPHARADIN					
Parker [854]	2013	Alpharadin (614)	Placebo (307)	Previous or no previous docetaxel. ECOG 0-2. Two or more bone metastases. No visceral metastases.	Overall survival: 14.9 vs. 11.3 mo ($p 0.002$). FU: Interim analysis. Progression-free survival: 3.6 vs. 3.4 mo (PSA-progression). Main side effects outcomes: 56% vs. 62% grade 3-4.
CABAZITAXEL					
Bahl [628]	2013	Cabazitaxel + Prednisone (378)	Mitoxantrone + Prednisone (377)	Previous docetaxel. ECOG 0-2.	Overall survival: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI 1.33-3.33). FU: 2 years. Progression-free survival: - Main side effects outcomes: Similar.
deBono [624]	2010 check				Overall survival: 15.1 vs. 12.7 mo ($p < 0.0001$). FU: 12.8 mo. Progression-free survival: 2.8 vs. 1.4 mos. Main side effects outcomes: 82% vs. 58% neutropenia.

ENZALUTAMIDE					
Scher [567]	2012	Enzalutamide (800)	Placebo (399)	Previous docetaxel. ECOG 0-2.	<p><u>Overall survival</u>: 18.4 vs. 13.6 mo ($p < 0.001$). FU: 14.4 mo.</p> <p><u>Progression-free survival</u>: 8.3 vs 2.9 mo.</p> <p><u>Main side effects outcomes</u>: 45.3% vs. 53.1% grade 3-4.</p>

*Only studies reporting survival outcomes have been included.

6.11.7.1 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 [624]. Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) plus prednisone (10 mg/day), respectively. Overall survival was the primary end-point 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 [628]. This drug should be administered by physicians with expertise in handling neutropenia and sepsis, with granulocyte colony-stimulating factor administered prophylactically in the high-risk patient population.

6.11.7.2 Abiraterone acetate

Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [566] and the final results have been reported more recently [625]. A total of 1,195 patients with metastatic CRPC were randomised in a 1/1 fashion to 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). 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.

6.11.7.3 Enzalutamide

The planned preliminary analysis of the AFFIRM study was published in 2012 [567]. This trial randomised 1,199 patients with metastatic CRPC in a 2/1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were 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.

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.

6.11.8 Bone targeted therapies in metastatic castration-resistant PCa

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 [855]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur.

6.11.8.1 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 [856]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [857, 858]. 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 [859]. Otherwise, external beam radiotherapy, with or without systemic therapy, is the treatment of choice.

6.11.8.2 Painful bone metastases

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [860], even as a single fraction [861].

6.11.8.2.1 Radium 223

The only bone-specific drug that is associated with a survival benefit is alfaradin, a radium 223 α -emitter. In a large phase III trial (ALSYMPCA), 921 patients with symptomatic CRPC, who failed or were unfit for docetaxel therapy, were randomised 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; $p < 0.001$) [854]. It was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL. The associated toxicity was minimal, especially haematologic toxicity, and did not differ significantly from that in the placebo arm [854].

6.11.8.2.2 Bisphosphonates

Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption in CRPC and have proven to be highly effective in reducing bone pain. 643 patients who had CRPC [862] with bone metastases were randomised 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 randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg due to toxicity. The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind [859, 860]. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as long-term intravenous bisphosphonate administration [863].

No survival benefit has been seen in any prospective trial with bisphosphonates.

6.11.8.2.3 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ 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, $P = 0.028$) [685]. 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.

6.11.9 **Conclusion and guidelines for treatment after hormonal therapy (first, second-line modality) in metastatic CRPC**

Conclusion	LE	GR
No definitive strategy regarding treatment choice (which drug/drug family first) can be devised.	4	
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.	4	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.	4	B
There is no evidence for treatment of non-metastatic CRPC outside of a clinical trial.	3	A
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>	2a	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
Salvage hormonal treatment using abiraterone acetate is a valid option.	1b	A
Salvage hormonal treatment using enzalutamide is a valid option.	1b	A

CRPC = castration-resistant prostate cancer; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen; MAB = maximal androgen blockade.

6.11.10 **Guidelines 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 salvage cytotoxic therapy, docetaxel at 75 mg/m ² 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 salvage 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.	1b	A

GR = grade of recommendation; LE = level of evidence; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.

6.11.11 **Guidelines 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 bisphosphonates.	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 always be initially considered.	1b	A
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GR = grade of recommendation; LE = level of evidence; mCRPC = metastatic castration-resistant prostate cancer.

7. FOLLOW-UP

7.1 Follow-up: After local treatment

7.1.1 Definition

Local 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. Unestablished alternative treatments, such as HIFU and cryosurgery do not have a well-defined, validated PSA cut-off to define biochemical failure, but do follow the outlines below.

7.1.2 Why follow-up?

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

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

7.1.3 How to follow-up?

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

7.1.3.1 Prostate-specific antigen monitoring

Measurement of PSA is a cornerstone in follow-up after local treatment. Expectations differ after RP and radiotherapy, but PSA recurrence often precedes clinical recurrence [864, 865]. A single, elevated, serum PSA level should be confirmed before starting second-line therapy based solely on PSA elevation.

7.1.3.2 Definition of prostate-specific antigen progression

The PSA level for definition of treatment failure differs between RP and radiotherapy. International consensus defines recurrent cancer after RP by two consecutive PSA values ≥ 0.2 ng/mL [866]. However, others have argued for a higher cut-off of 0.4 ng/mL for patients with a high-risk of clinical progression [865].

Ultrasensitive PSA (US PSA) assay remains controversial for routine follow-up after RP. Men with a US PSA nadir < 0.01 ng/mL have a 4% likelihood of early biochemical relapse [867]. Detectable postoperative US PSA does not predict BCR in all cases, although it adds prognostic value. In men with US PSA > 0.05 ng/mL, 66.8% remained free of biochemical disease at 5 years [868]. If survival is improved by early adjuvant treatment after RP (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 to establish better correlation between definition and clinical outcome, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [708]. It applies to patients with or without hormonal therapy.

After HIFU or cryotherapy, there are various definitions for PSA relapse [507]. Most of these are based on a cut-off PSA level of ~ 1 ng/mL, combined with negative post-treatment biopsy. No end-points have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of biochemical failure.

7.1.3.3 Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP [869]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease.

Rapidly increasing PSA level indicates distant metastases, whereas later, slowly increasing level most likely indicates local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [870]. Local treatment failure and distant metastases occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [871].

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

7.1.3.4 PSA monitoring after radiotherapy

PSA level falls slowly after radiotherapy compared with RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after radiotherapy [872], although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. Biochemical failure after radiotherapy is currently defined as PSA > 2 ng/mL above the nadir [708]. After radiotherapy, PSA-DT is correlated with site of recurrence: patients with local recurrence have a DT of 13 months compared to 3 months for those with distant failure [873].

7.1.3.5 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [871]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. PSA measurement and DRE comprise the most useful combination for first-line examination in follow-up after radiotherapy or RP, but PSA measurement may be the only test in cases with favourable pathology (< pT3, pN0, Gleason < 8) [874].

7.1.3.6 Transrectal ultrasonography (TRUS), bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and ¹¹C-choline positron emission tomography computed tomography (PET/CT)

Imaging techniques have no place in routine follow-up of localised PCa. They are only justified in patients with biochemical failure or in patients with symptoms for whom the findings affect treatment decisions. (See Section 6.19.4 for a more detailed discussion).

7.1.3.6.1 Transrectal ultrasonography/magnetic resonance imaging biopsy

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

7.1.4 When to follow-up?

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. Patients should be followed-up more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually.

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

7.1.5 Conclusions and guidelines for follow-up after treatment with curative intent

Conclusions	LE
After RP, serum PSA level > 0.2 ng/mL is associated with residual or recurrent disease.	
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is the most reliable sign of recurrence.	B
Palpable nodules and increasing serum PSA are signs of local recurrence.	B

Recommendations	GR
In asymptomatic patients, disease-specific history and serum PSA measurement supplemented by DRE are recommended 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
Imaging to detect local recurrence is only recommended if it affects treatment planning. Biopsy is usually not necessary before second-line therapy, except after EBRT when local salvage treatment is considered.	B
Routine bone scans and other imaging are not recommended in asymptomatic patients if there are no signs of biochemical relapse. In patients with bone pain or other symptoms of progression, re-staging should be considered irrespective of serum PSA level.	B

DRE = digital rectal examination; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen; RP = radical prostatectomy.

7.2 Follow-up: During hormonal treatment

7.2.1 Introduction

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

7.2.2 Purpose of follow-up

The main objectives of follow-up in 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 costs. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up procedures following hormonal therapy.

7.2.3 Methods of follow-up

7.2.3.1 Clinical follow-up

Clinical follow-up is mandatory. Neither biology nor imaging modalities can replace face to face clinic visits. Patients should be seen on a regular basis to check for possible troublesome symptoms. Of utmost importance in patients in the M1b stage is to highlight and check for possible early signals of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction, etc) or bone lesions at an increased fracture risk.

7.2.3.1.1 Prostate-specific antigen monitoring

Prostate-specific antigen (PSA) is a good marker for following the course of PCa.

Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa. Patients with a PSA nadir < 0.2 ng/mL after 7 months of treatment have been shown to have the best survival (median 75 months) compared to patients with a value of 0.2-4.0 ng/mL (median 44 months) or > 4.0 ng/mL (median 13 months) [571]. Similar results have been found in locally advanced and metastatic PCa [875, 876], as in salvage ADT for elevated PSA following treatments with curative intent [877].

Patients should be regularly monitored to detect and treat any complications of endocrine treatment as well as disease progression, usually after a median of 12-18 months in patients with stage M1 disease. 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 insufficient as clinical progression (usually bone pain) with normal PSA levels has been reported.

7.2.3.1.2 Creatinine, haemoglobin and liver function monitoring

Creatinine monitoring is good clinical practice as an increase may be linked to silent bilateral ureteral obstruction or bladder retention. Liver function tests may suggest disease progression and/or toxicity of hormonal treatment (especially non-steroidal antiandrogens), which can lead to interruption of hormonal treatment. A decline in haemoglobin after 3 months of ADT is independently associated with a shorter progression-free and OS [878] and might explain significant fatigue.

Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [879]. Therefore, it may be helpful to determine its bone-specific isoenzymes as none are directly influenced by hormonal therapy.

7.2.3.1.3 Bone scan, ultrasound and chest X-ray

Asymptomatic patients with a stable PSA level should not undergo imaging at regular intervals [207].

In the case of bone symptoms or PSA progression under castration, a bone scan might be helpful, if a treatment modification is considered. 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 [880], later confirmed.

Suspicion of disease progression indicates the need for additional imaging modalities, guided by symptoms or subsequent possible treatment decisions. In CRPC, follow-up examinations should be individualised with the aim of maintaining the patient's QoL.

7.2.3.1.4 Testosterone monitoring

Most PCa patients receiving LHRH analogues will achieve serum testosterone values at or below the castration level (< 1 nmol/L). However, approximately 13-38% of patients fail to achieve this therapeutic goal. In addition, up to 24% of men treated with LHRH analogues may experience testosterone surges (testosterone > 50 ng/dL) during long-term treatment, which is described as the 'acute on-chronic effect' or 'breakthrough response'.

The measurement of serum testosterone levels should be considered part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. A 3 to 6-month testosterone level assessment may be performed to ensure the castration level is being maintained. If it is not being maintained, switching to another LHRH agonist or antagonist or to surgical orchiectomy should be considered. In patients with rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

7.2.3.1.5 Monitoring of metabolic complications

Androgen deprivation therapy is beneficial in patients with PCa, but has a greater range of complications than might be expected. The most severe complications are bone problems, the metabolic syndrome and cardiovascular morbidity (see section 7.5). The patient's GP or family physician should probably be more involved.

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months), as for blood lipid levels. In selected cases, glucose tolerance testing may be required. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. A cardiology consultation should be considered in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. Monitoring serum levels of vitamin D and calcium is important. If necessary, supplements should be given to ensure a daily intake of at least 1200 mg/day of calcium and 1000 IU of vitamin D. Preventive therapy with bisphosphonates or denosumab using specific doses (which differ from those used in the CRPC stage) could be considered in patients who have an initial T-score of less than -2.5 on DEXA. It is suggested that bone monitoring should be performed every 2 years after castration, provided there are no other risk factors [881], or yearly if there are risk factors [882, 883]. However, prospective trials are needed.

Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [884, 885]. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT [676].

7.2.4 **When to follow-up**

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

7.2.4.1 *Stage M0 - M1 patients*

If there is a good treatment response, i.e. PSA response (less than 4 ng/mL), 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 (a 3-month schedule can be considered in M1 patients).

7.2.4.2 *Castration-refractory PCa*

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

7.2.5 Guidelines for follow-up 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 fixed 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 treatment, follow-up should be individualised.	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 (< 1 mL/L).	B
Routine imaging of stable patients is not recommended.	B

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

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9. CONFLICT OF INTEREST

All members of the Prostate Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website:
<http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.