

Guidelines on Prostate Cancer

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1. INTRODUCTION

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

Where possible a level of evidence (LE) and/or grade of recommendation (GR) have been assigned (1). Recommendations are graded in order to provide transparency between the underlying evidence and the recommendation given (Tables 1 and 2).

It has to be emphasised that the current guidelines contain information for the treatment of an individual patient according to a standardised general approach.

1.1 Methodology

The recommendations provided in the current guidelines are based on a systemic literature search performed by the panel members (1). MedLine, Embase and Web of Science databases were searched to identify original articles, review articles and editorials addressing “epidemiology”, “risk factors”, “diagnosis”, “staging” and “treatment” of prostate cancer. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a “free-text” protocol, combining “prostate cancer” with the terms “diagnosis”, “screening”, “staging”, “active surveillance”, “radical prostatectomy”, “external beam radiation”, “brachytherapy”, “androgen deprivation”, “chemotherapy”, “relapse”, “salvage treatment”, and “follow-up” to ensure sensitivity of the searches.

All articles published between January 2009 (previous update) and January 2010 were considered for review. A total of 11,834 records were identified in all databases. The expert panel reviewed these records to select the articles with the highest evidence, according to a rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (Table 1) (2).

1.2 Publication history

The Prostate Cancer Guidelines were first published in 2001, with partial updates in 2003 and 2007, followed by a full text update in 2009. This 2010 publication presents a considerable update; all sections, but for Chapters 2 (Background), 4 (Risk Factors), 7 (Staging) and 14 (Follow-up after primary treatment with curative intent), have been revised. A number of different versions of these Prostate Cancer Guidelines are available, including a quick reference guide and several translated documents. All texts can be viewed and downloaded for personal use at the society website: <http://www.uroweb.org/professional-resources/guidelines/>.

Table 1: Level of evidence.

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

Modified from Sackett et al. (2).

Table 2: Grade of recommendation.

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

Modified from Sackett et al. (2).

1.3 REFERENCE

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2. BACKGROUND

Cancer of the prostate (PCa) is now recognized as one of the most important medical problems facing the male population. In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer (1). Furthermore, PCa is currently the second most common cause of cancer death in men (2). In addition, since 1985, there has been a slight increase in most countries in the number of deaths from PCa, even in countries or regions where PCa is not common (3).

Prostate cancer affects elderly men more often than young men. It is therefore a bigger health concern in developed countries with their greater proportion of elderly men. Thus, about 15% of male cancers are PCa in developed countries compared to 4% of male cancers in undeveloped countries (4). It is worth mentioning that there are large regional differences in incidence rates of PCa. For example, in Sweden, where there is a long life expectancy and mortality from smoking-related diseases is relatively modest, PCa is the most common malignancy in males, accounting for 37% of all new cases of cancer in 2004 (5).

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3. CLASSIFICATION

The 2009 TNM (Tumour Node Metastasis) classification for PCa is shown in Table 3 (1).

Table 3: Tumour Node Metastasis (TNM) classification of PCa*.

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
M - Distant metastasis⁴	
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 Metastasis no larger than 0.2 cm can be designated pN1 mi.

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

Prognostic grouping

Group I	T1a-c	N0	M0 PSA < 10	Gleason ≤ 6
	T2a	N0	M0 PSA < 10	Gleason ≤ 6
Group IIA	T1a-c	N0	M0 PSA < 20	Gleason 7
	T1a-c	N0	M0 PSA ≥ 10 < 20	Gleason ≤ 6
	T2a, b	N0	M0 PSA < 20	Gleason ≤ 7
Group IIb	T2c	N0	M0 Any PSA	Any Gleason
	T1-2	N0	M0 PSA ≥ 20	Any Gleason
	T1-2	N0	M0 Any PSA	Gleason ≥ 8
Group III	T3a, b	N0	M0 Any PSA	Any Gleason
Group IV	T4	N0	M0 Any PSA	Any Gleason
	Any T	N1	M0 Any PSA	Any Gleason
	Any T	Any N	M0 Any PSA	Any Gleason

Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA or Gleason is available. When neither is available prognostic grouping is not possible, use stage grouping

3.1 Gleason score

The Gleason score is the most commonly used system for grading adenocarcinoma of the prostate (2). The Gleason score can only be assessed using biopsy material (core biopsy or operative specimens). Cytological preparations cannot be used. The Gleason score is the sum of the two most common patterns (grades 1-5) of tumour growth found. The Gleason score ranges between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. In needle biopsy, it is recommended that the worst grade always should be included, even if it is present in < 5% of biopsy material (3).

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4. RISK FACTORS

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, ethnical origin and 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 5- to 11-fold (1, 2). A small subpopulation of individuals with PCa (about 9%) has 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 (3). Patients with hereditary PCa usually have an onset 6-7 years prior to spontaneous cases, but do not differ in other ways (4).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (5). 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 Southeast Asia (6). 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 (7) (level of evidence: 2).

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation and occupational exposure have all been discussed as being of aetiological importance (8). Prostate cancer is an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to some specific features: high prevalence, long latency, endocrine dependency, availability of serum markers (PSA) and histological precursor lesions (PIN). Dietary/nutritional factors that may influence disease development include total energy intake (as reflected by body mass index), dietary fat, cooked meat, micronutrients and vitamins (carotenoids, retinoids, vitamins C, D, and E), fruit and vegetable intake, minerals (calcium, selenium), and phyto-oestrogens (isoflavonoids, flavonoids, lignans). Since most studies reported to date are case-control analyses, there remain more questions than evidence-based data available to answer them. Several ongoing large randomised trials are trying to clarify the role of such risk factors and the potential for successful prostate cancer prevention (9).

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on this risk. The key question is whether there is enough evidence to recommend lifestyle changes (lowered intake of animal fat and increased intake of fruit, cereals and vegetables) in order to decrease the risk (10). There is some evidence to support such a recommendation and this information can be given to male relatives of PCa patients who ask about the impact of diet (level of evidence: 2-3).

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5. SCREENING AND EARLY DETECTION

Population or mass screening is defined as the examination of asymptomatic men (at risk). It usually takes place as part of a trial or study and is initiated by the screener. In contrast, early detection or opportunistic screening comprises individual case findings, which are initiated by the person being screened (patient) and/or his physician. The primary endpoint of both types of screening has two aspects:

1. Reduction in mortality from PCa. The goal is not to detect more and more carcinomas, nor is survival the endpoint because survival is strongly influenced by lead-time from diagnosis.
2. The quality of life is important 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 (1). Decreased mortality rates due to PCa have occurred in the USA, Austria, UK and France, while in Sweden the 5-year survival rate has increased from 1960 to 1988, probably due to increased diagnostic activity and greater detection of non-lethal tumours (2). However, this trend was not confirmed in a similar study from the Netherlands (3). The reduced mortality seen recently in the USA is often attributed to the widely adopted aggressive screening policy, but there is still no absolute proof prostate-specific antigen (PSA) screening reduces mortality due to PCa (4) (level of evidence: 2).

A non-randomised screening project in Tyrol (Austria) may support the hypothesis that screening can be effective in reducing mortality from PCa. An early detection programme and free treatment have been used to explain the 33% decrease in the PCa mortality rate seen in Tyrol compared to the rest of Austria (5) (level of evidence: 2b). In addition, a Canadian study has claimed lower mortality rates in men randomised to active PCa screening (6), though these results have been challenged (7). Positive findings attributed to screening have also been contradicted by a comparative study between the US city of Seattle area (highly screened

population) and the US state of Connecticut (seldom screened population) (8). The study found no difference in the reduction in the rate of PCa mortality (level of evidence: 2b), even allowing for the very great diversity in PSA testing and treatment.

The long awaited results of two prospective, randomised trials were published in 2009. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomly assigned 76,693 men at 10 US centres to receive either annual screening with PSA and DRE or standard care as the control. After 7 years' follow-up, the incidence of PCa per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group (rate ratio, 1.22) (9). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio, 1.13). The data at 10 years were 67% complete and consistent with these overall findings. The PLCO project team concluded that PCa-related mortality was very low and not significantly different between the two study groups (level of evidence: 1b).

The European Randomized Study of Screening for Prostate Cancer (ERSPC) included a total of 162,243 men from seven countries aged between 55 and 69 years. The men were randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years, the cumulative incidence of PCa was 8.2% in the screened group and 4.8% in the control group (10). The rate ratio for death from PCa was 0.80 in the screened group compared with the control group. The absolute risk difference was 0.71 deaths per 1,000 men. This means that 1410 men would need to be screened and 48 additional cases of PCa would need to be treated to prevent one death from PCa. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from PCa by 20%, but was associated with a high risk of over-diagnosis (level of evidence: 1b).

Both trials have received considerable attention and comments. In the PLCO trial, the rate of compliance in the screening arm was 85% for PSA testing and 86% for DRE. However, the rate of contamination in the control arm was as high as 40% in the first year and increased to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40-52% versus 86% in the ERSPC. Thus, the PLCO trial will probably never be able to answer whether or not screening can influence PCa mortality.

In the ERSPC trial, the real benefit will only be evident after 10-15 years of follow-up, especially because the 41% reduction of metastasis in the screening arm will have an impact.

Based on the results of these two large, randomised trials, most if not all of the major urological societies conclude that at present widespread mass screening for PCa is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man (see also Section 6, Diagnosis). Two key items remain open and empirical:

- at what age should early detection start;
- what is the interval for PSA and DRE.

A baseline PSA determination at age 40 years has been suggested upon which the subsequent screening interval may then be based (11) (grade of recommendation: B). A screening interval of 8 years might be enough in men with initial PSA levels ≤ 1 ng/mL (12). Further PSA testing is not necessary in men older than 75 years and a baseline PSA ≤ 3 ng/mL because of their very low risk of dying from PCa (13).

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6. DIAGNOSIS*

The main diagnostic tools to obtain evidence of PCa include DRE, serum concentration of PSA and transrectal ultrasonography (TRUS). Its definite diagnosis depends on the presence of adenocarcinoma in prostate biopsy cores or operative specimens. Histopathological examination also allows grading and determination of the extent of the tumour.

6.1 Digital rectal examination (DRE)

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger. A suspect DRE is an absolute indication for prostate biopsy. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level (1) (level of evidence: 2a). A suspect DRE in patients with a PSA level of up to 2 ng/mL has a positive predictive value of 5-30% (2) (level of evidence: 2a).

* Acknowledgment: Section 6.4 is partly based on the Guidelines of the AUO Study Group Urologic Oncology of the Austrian Society of Urologists and Andrologists (W. Hörtl, W. Loidl, M. Rauchenwald, M. Müller, M. Klimpfinger, A. Schratzer-Sehn, C. Brössner).

6.2 Prostate-specific antigen (PSA)

The measurement of PSA level has revolutionised the diagnosis of PCa (3). Prostate-specific antigen (PSA) is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. For practical purposes, it is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS (4).

There are many different commercial test kits for measuring PSA, but no commonly agreed international standard exists (5). The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa (Table 4). This means there is no universally accepted cut-off or upper limit. The finding that many men may harbour PCa, despite low levels of serum PSA, has been underscored by recent results from a US prevention study (6) (level of evidence: 2a). Table 4 gives the rate of PCa in relation to serum PSA for 2,950 men in the placebo-arm and with normal PSA values.

Table 4: Risk of PCa in relation to low PSA values.

PSA level (ng/mL)	Risk of PCa
0-0.5	6.6%
0.6-1	10.1%
1.1-2	17.0%
2.1-3	23.9%
3.1-4	26.9%

PSA = prostate-specific antigen.

These findings highlight an important issue about lowering the PSA-level threshold, which is how to avoid detecting insignificant cancers with a natural history unlikely to be life threatening (7). As yet, there is no long-term data to help determine the optimal PSA threshold value for detecting non-palpable, but clinically significant, PCa (level of evidence: 3).

Several modifications of serum PSA value have been described, which may improve the specificity of PSA in the early detection of PCa. They include: PSA density, PSA density of the transition zone, age-specific reference ranges and PSA molecular forms. However, these derivatives and certain PSA isoforms (cPSA, proPSA, BPSA, iPSA) have limited usefulness in the routine clinical setting and have therefore not been considered for inclusion in these guidelines.

6.2.1 Free/total PSA ratio (f/t PSA)

The free/total PSA ratio (f/t PSA) is the concept most extensively investigated and most widely used in clinical practice to discriminate BPH from PCa. The ratio is used to stratify the risk of PCa for men who have total PSA levels between 4 and 10 ng/mL and a negative DRE. In a prospective multicentre trial, PCa was found on biopsy in 56% of men with a f/t PSA < 0.10, but in only 8% of men with f/t PSA > 0.25 (8) (level of evidence: 2a). Nevertheless, the concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA. For example, free PSA is unstable at both 4°C and at room temperature. In addition, assay characteristics may vary and concomitant BPH in large prostates may result in a 'dilution effect' (9). Furthermore, f/t PSA is clinically useless in total serum PSA values > 10 ng/mL and in follow-up of patients with known PCa.

6.2.2 PSA velocity (PSAV), PSA doubling time (PSADT)

There are two methods of measuring PSA over time. These are:

- PSA velocity (PSAV), defined as an absolute annual increase in serum PSA (ng/mL/year) (10) (level of evidence: 1b).
- PSA doubling time (PSADT), which measures the exponential increase of serum PSA over time, reflecting a relative change (11).

These two concepts may have a prognostic role in patients with treated PCa (12). However, they have limited use in the diagnosis of PCa because of background noise (total volume of prostate, BPH), the variations in interval between PSA determinations, and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have shown that these measurements do not provide additional information compared to PSA alone (13-16).

6.2.3 PCA3 marker

In contrast to the serum markers discussed above, the prostate specific non-coding mRNA marker, PCA3, is

measured in urine sediment obtained after prostatic massage. The main advantages of PCA3 over PSA are its somewhat higher sensitivity and specificity. The level of PCA3 shows slight but significant increases in the AUC for positive biopsies (17), but is not influenced by prostate volume or prostatitis (18-20). There is conflicting data about whether PCA3 levels are related to tumour aggressiveness. Although PCA3 may have potential value for identifying prostate cancer in men with initially negative biopsies in spite of an elevated PSA, the determination of PCA3 remains experimental. In the near future, several molecular diagnostic tests may move out of the laboratory into the clinical setting, e.g. detection of prostate cancer specific TMPRSS2-erg fusion genes in urine sediments after massage (21,22).

So far, none of the above biomarkers are being used routinely to counsel an individual patient on the need to perform a prostate biopsy to rule out PCa.

6.3 Transrectal ultrasonography (TRUS)

The classic picture of a hypoechoic area in the peripheral zone of the prostate will not always be seen (23). Gray-scale TRUS does not detect areas of PCa with adequate reliability. It is therefore not useful to replace systematic biopsies with targeted biopsies of suspect areas. However, additional biopsies of suspect areas may be useful.

6.4 Prostate biopsy

6.4.1 Baseline biopsy

The need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious DRE. The patient's biological age, potential co-morbidities (ASA Index and Charlson Comorbidity Index) and the therapeutic consequences should also be considered.

The first elevated PSA level should not prompt an immediate biopsy. The PSA level should be verified after a few weeks by the same assay under standardised conditions (i.e. no ejaculation and no manipulations, such as catheterisation, cystoscopy or TUR, and no urinary tract infections) in the same diagnostic laboratory, using the same methods (24,25) (level of evidence: 2a).

It is now considered the standard of care to perform prostate biopsies guided by ultrasound. Although a transrectal approach is used for most prostate biopsies, some urologists prefer to use a perineal approach. The cancer detection rates of perineal prostate biopsies are comparable to those obtained of transrectal biopsies (26,27) (level of evidence: 1b).

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

6.4.2 Repeat biopsy

The indications for a repeat biopsy are:

- rising and/or persistent PSA, suspicious DRE;
- atypical small acinar proliferation (ASAP).

The optimal timing of a repeat biopsy is uncertain. It depends on the histological outcome of the baseline ASAP biopsy and the index of a persistent suspicion of PCa (high or dramatically rising PSA, suspect DRE, family history). The later the repeat biopsy is done, the higher the detection rate (28).

High-grade prostatic intraepithelial neoplasia (PIN) as an isolated finding is no longer considered an indication for re-biopsy (29) (level of evidence: 2a). A repeat biopsy should therefore be prompted by other clinical features, such as DRE findings and PSA level. If PIN is extensive (i.e. in multiple biopsy sites), this could be a reason for early re-biopsy as the risk of subsequent prostate cancer is slightly increased (30). If clinical suspicion for prostate cancer persists in spite of negative prostate biopsies, MRI may be used to investigate the possibility of an anterior located prostate cancer, followed by TRUS or MRI-guided biopsies of the suspicious area (31).

6.4.3 Saturation biopsy

The incidence of PCa detected by saturation repeat biopsy is between 30% and 43% and depends on the number of cores sampled during earlier biopsies (32) (level of evidence: 2a). In special situations, saturation biopsy may be performed with the transperineal technique. This will detect an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback (3D-stereotactic biopsy) (33) (level of evidence: 2b).

6.4.4 Sampling sites and number of cores

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

Sextant biopsy is no longer considered adequate. At a glandular volume of 30-40 mL, at least eight cores should be sampled. More than 12 cores are not significantly more conclusive (34) (level of evidence: 1a). The British Prostate Testing for Cancer and Treatment Study has recommended 10-core biopsies (35) (level of evidence: 2a).

6.4.5 Diagnostic transurethral resection of the prostate (TURP)

The use of diagnostic TURP instead of repeat biopsies is of minor importance. Its detection rate is no better than 8% and makes it a poor tool for cancer detection (36) (level of evidence: 2a).

6.4.6 Seminal vesicle biopsy

Indications for seminal vesicle biopsies are poorly defined. At PSA levels > 15-20 ng/mL, a biopsy is only useful if the outcome will have a decisive impact on treatment, i.e. if the biopsy result rules out radical removal for tumour involvement or radiotherapy with intent to cure. At PSA levels > 15-20 ng/mL, the odds of tumour involvement are 20-25% (37) (level of evidence: 2a).

6.4.7 Transition zone biopsy

Transition zone (TZ) sampling during baseline biopsies provides a very low detection rate and TZ sampling should therefore be confined to repeat biopsies (38) (level of evidence: 1b).

6.4.8 Antibiotics

Oral or intravenous antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin superior to ofloxacin (39) (level of evidence: 1b).

6.4.9 Local anaesthesia

Ultrasound-guided peri-prostatic block is state-of-the-art (40) (level of evidence: 1b). It does not make any difference whether the depot is apical or basal. Intrarectal instillation of a local anaesthetic is clearly inferior to peri-prostatic infiltration (41) (level of evidence: 1b).

6.4.10 Fine-needle aspiration biopsy

Fine-needle aspiration biopsy is not as effective as TRUS-guided transrectal core biopsy because of the lack of uropathologists experienced in cytology. In addition, TRUS-guided transrectal core biopsies provide more information on the Gleason score and on the extent of the tumour.

6.4.11 Complications

Complication rates are low (Table 5) (42). Minor complications include macrohaematuria and haematospermia. Severe post-procedural infections have been reported in < 1% of cases. The recent increase in the number of biopsy cores performed has not increased the rate of severe complications requiring treatment.

Low-dose aspirin is no longer an absolute contraindication (43) (level of evidence: 1b).

Table 5: Percentage given per biopsy session, irrespective of the number of cores*.

Complications	% of biopsies
• Haematospermia	37.4
• Bleeding from urethra, urinary bladder (> 1 day)	14.5
• Fever	0.8
• Urosepsis	0.3
• Rectal bleeding	2.2
• Urine retention	0.2
• Prostatitis	1.0
• Epididymitis	0.7

* Adapted from Consensus Guidelines NCCN, Version 1.2007 (33).

6.5 Pathology of prostate needle biopsies

6.5.1 Grossing and processing

Prostate core biopsies taken from different sites are usually sent to the pathology laboratory in separate vials and should be processed in separate cassettes. Before processing, record the number of cores per vial and length of each core. There is a significant correlation between the length of prostate biopsy tissue on the histological slide and the detection rate of PCa (44). To achieve optimal flattening and alignment of individual

cores, embed a maximum of three cores per cassette and use sponges or paper to keep the cores stretched and flat (45,46). To optimise the detection of small lesions, blocks should be cut in three levels (38). It is helpful to routinely mount intervening tissue sections in case additional immunostaining is needed.

6.5.2 Microscopy and reporting

Diagnosis of prostate cancer is based on histological examination. However, immunostaining may also be helpful (47,48). Ancillary staining techniques (e.g. basal cell staining) and additional (deeper) sections should be considered if a suspect glandular lesion is identified (48,49). For suspicious lesions in biopsies, diagnostic uncertainty may often be resolved by intradepartmental consultation and a second opinion from an external institution (47). Use concise clear terminology to report prostate biopsies (46) (Table 6) and avoid terms such as 'atypia', 'atypical glands' or 'possibly malignant'.

Table 6: Diagnostic terms used to report prostate biopsy findings*.

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

*From Van der Kwast, 2003 (36).

PIN = prostatic intra-epithelial neoplasia.

For each biopsy site, report the proportion of biopsies positive for carcinoma and the Gleason score, using the system adopted in 2005 (50).

According to current international convention, the (modified) Gleason score of cancers detected in a prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component plus the highest grade, irrespective of its extent (no 5% rule). When the carcinoma largely consists of grade 4/5 carcinoma, identification of a small portion (< 5% of the carcinoma) of Gleason grade 2 or 3 glands should be ignored. A diagnosis of Gleason score 4 or lower should not be given on prostate biopsies (50). The presence of intraductal carcinoma and extraprostatic extension should be reported. In addition to a report of the carcinoma features for each biopsy site, provide an overall Gleason score based on findings in the individual biopsies. The presence of perineural invasion is usually reported, even though there is conflicting evidence about its usefulness as a prognostic indicator (51,52). The proportion (%) or length (mm) of tumour involvement per biopsy site correlates with tumour volume, extraprostatic extension and prognosis after prostatectomy (52-54) and should therefore be recorded. The length of carcinoma (mm) and the percentage of carcinoma involvement of the biopsy have equal prognostic impact (55).

The extent of a single, small focus of adenocarcinoma, which is located in only one of the biopsies, should be clearly stated (e.g. < 1 mm or < 1%), as this might be an indication for further diagnostic work-up before selecting therapy. In some studies, a finding of < 3 mm carcinoma in one biopsy with a Gleason score 5-6 has often been associated with insignificant cancer and with an increased risk of vanishing cancer (56-58). A prostate biopsy that does not contain glandular prostate tissue could be reported as inadequate for diagnostics, except on staging biopsies.

A recent study evaluated the concordance of pattern and change of prognostic groups for the conventional and the modified Gleason grading (59). The evaluation was based on 172 prostatic needle biopsies of patients who subsequently underwent RP. Four prognostic Gleason grading groups were considered, divided into scores of 2-4, 5-6, 7, and 8-10. To check the discriminative power of the modified Gleason grading, the time of biochemical progression-free outcome, according to prognostic groups, was compared between standard and revised grading. The greatest impact of the International Society of Urological Pathology consensus recommendations for Gleason grading was seen on the secondary pattern, which had the lowest percentage of concordance and was reflected in a change toward higher Gleason prognostic groups. Of 172 patients in whom the Gleason prognostic group was changed (to higher grades) based solely on the consensus criteria, 46 (26.7%) had a higher pre-operative PSA level, more extensive tumours and positive surgical margins, and a higher pathological stage. In this series, the revised Gleason grading identified more patients in the aggressive prognostic group Gleason score 8-10, who had a significantly shorter time to biochemical progression-free

outcome after radical prostatectomy (log rank $p = 0.011$). These findings have shown that the International Society of Urological Pathology's recommendations are a valuable refinement of the standard Gleason grading system.

6.6 Pathohistology of radical prostatectomy (RP) specimens

6.6.1 Processing of the RP specimen

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

However, for cost-efficiency purposes, partial embedding using a standard method may also be considered, particularly for large-sized prostates (> 60 g). The most acceptable method includes the complete embedding of the posterior (dorsal) part of the prostate in addition to a single mid-anterior left and right section. Compared to total embedding, this method of partial embedding permitted detection of 98% of prostate cancers with a Gleason score ≥ 7 and accurate staging in 96% of cases (60).

Upon receipt in the histopathology lab, the entire RP specimen is inked in order to appreciate the surgical margin status. The specimen is fixed in buffered formalin, preferably prior to incision of the sample, as incision causes distortion of the tissue. Generally, appropriate fixation is achieved by immersing the RP specimen in fixative for a few days. Fixation can be enhanced by injecting formalin using 21-gauge syringes, which provides a more homogeneous fixation and sectioning after 24 hours (61). After fixation, the apex is removed and cut with (para)sagittal or radial sections; the shave method is not recommended (62). Separate removal and sagittal sectioning of the bladder neck is optional. The remainder of the RP specimen is generally cut in transverse sections at 3-4 mm steps, perpendicularly to the posterior surface. The resulting tissue slices can be embedded and processed either as whole-mounts or after quadrant sectioning. Whole-mount processing provides better topographic visualisation of the carcinoma and a faster histopathological examination. However, it is a more time-consuming and more expensive technique requiring specialised equipment and personnel. Although whole-mount sectioning may be necessary for research, its advantages do not outweigh its disadvantages for routine sectioning.

6.6.1.1 Recommendations for processing a prostatectomy specimen

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

6.6.2 RP specimen report

The pathology report provides essential information on the prognostic characteristics relevant for making clinical decisions (Table 7). Because of the complex information provided on each RP specimen, the use of a synoptic-(like) or checklist reporting is recommended (Table 8). Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (63).

Table 7: Information provided by the pathology report.

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

Table 8: Example checklist – reporting of prostatectomy specimens.

Histological type
• Type of carcinoma, e.g. conventional acinar, ductal, etc.
Histological grade
• Primary (predominant) grade
• Secondary grade
• Tertiary grade (if applicable)
• Total/global Gleason score
• Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional)
• Percentage of prostatic gland involved
• Tumour size of dominant nodule (if identified), greatest dimension in mm
Pathological staging (pTNM)
• Presence of extraprostatic extension (focal or extensive)
o If present, specify site(s)
• Presence of seminal vesicle invasion
• If applicable, regional lymph nodes
o Location
o Number of lymph nodes retrieved
o Number of lymph nodes involved
Surgical margins
• Presence of carcinoma at margin
o If present, specify site(s) and extra- or intraprostatic invasion
Other
• If identified, presence of angioinvasion
• Location (site, zone) of dominant tumour (optional)
• Perineural invasion (optional)
o If present, specify extra- or intra-prostatic invasion

6.6.2.1 Gleason score

Grading of conventional prostatic adenocarcinomas using the (modified) Gleason score system (50) is the single strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is therefore one of the parameters incorporated in nomograms that predict the risk of recurrence after prostatectomy (64).

6.6.2.2 Interpreting the Gleason score

The Gleason score is the sum of the most dominant and second most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises $\leq 5\%$ of the cancer volume, this grade is not incorporated in the Gleason score (5% rule). Both the primary and the secondary grade should be reported in addition to the Gleason score (e.g. Gleason score 7 [4 + 3]). A global Gleason score is given when there are multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. A tertiary Gleason grade 4 or 5, particularly if exceeding 5% of the prostate cancer volume, is an unfavourable prognosticator for biochemical recurrence. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported (65), in addition to the Gleason score.

6.6.2.3 Definition of extraprostatic extension

The TNM staging system of the International Union Against Cancer (UICC) is recommended for pathological staging of carcinomas of the prostate (62,66). It measures the anatomical extension of the cancer, which may (e.g. pT3 substaging) or may not (e.g. pT2 substaging) be prognostic.

Extraprostatic extension is the recommended term for the presence of tumour beyond the confines of the prostate. Extraprostatic extension is defined as carcinoma admixed with periprostatic adipose tissue, or bulging out beyond the contour of the prostate gland, e.g. at the neurovascular bundle or the anterior prostate. Bladder neck invasion is also considered to be an extraprostatic extension.

It is useful to report not only the location, but also the extent of extraprostatic extension because extension is related to the risk of recurrence (67,68). There are no well-established and internationally accepted definitions of the terms ‘focal’ and ‘non-focal’ or ‘extensive extraprostatic extension’. Some authors describe focal as ‘a

few glands' (69) or extension less than 1 high power field (68), while others measure the depth of extent in mm (70). Currently, it is considered clinically useful to measure the extent of extraprostatic extension (e.g. less or more than 1 high power field or 1 mm).

At the apex of the prostate gland: there is no agreed definition on how to determine extraprostatic extension at the site of the apex. Here, tumour admixed with skeletal muscle does not constitute extraprostatic extension. It should be noted that at the apex, there is no diagnosis of stage pT4. In the bladder neck, microscopic invasion of small fibres of smooth muscle is not equated to (gross) bladder wall invasion as it does not carry independent prognostic significance for PSA recurrence (71,72) and should now be recorded as an extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as an extraprostatic extension (pT3a) with positive margin and not as pT4 disease. Some consider tumour invasion of the large bundles of smooth muscle to be a gross invasion (73), as determined by the urologist.

6.6.3 Prostate cancer volume

The prognostic value of determining the volume of PCa in RP specimens is controversial, with several conflicting studies either demonstrating or refuting its independent prognostic impact (68,74-77). Nevertheless, a prostate cancer volume cut-off of 0.5 mL continues to be an important parameter to distinguish insignificant from clinically relevant cancers (74). Furthermore, continued improvement in radio-imaging of the prostate glands has allowed more accurate measurements of cancer volume before surgery. For these reasons, it may be recommended that, if present, the greatest dimension of the dominant tumour nodule should be provided in millimetres.

6.6.4 Surgical margin status

Surgical margin status is an independent risk factor for biochemical recurrence. It is usually possible to provide clear information about the surgical margin status.

- Margin status is positive if tumour cells are in touch with the ink on the surface of the specimen.
- Margin status is negative if tumour cells are very close to the inked surface of the margin (75) or when they are at the surface of the tissue lacking any ink.

If the tissue has severe crush artifacts (usually at the apex), it may not be possible to assign a surgical margin status (78). Surgical margin status is independent of the pathological stage and a positive margin is not evidence of extraprostatic extension (79). There is insufficient evidence to prove a relationship between the extent of positive margin and the risk of recurrence (68). However, some indication must be given of the (multi-)focality and extent of margin positivity, such as the linear extent in millimetres, or number of blocks with positive margin involvement.

6.6.5 Other factors

According to the College of American Pathologists consensus statement (80), additional potential biomarkers have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting (category III), including perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, prostate-specific antigen derivatives, and other factors (oncogenes, tumour suppressor genes, apoptosis genes, etc).

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7. STAGING

The primary extension assessment of prostate cancer (PCa) is usually made by digital rectal examination (DRE), prostate-specific antigen (PSA) measurement and bone scan, supplemented with computed tomography (CT) or magnetic resonance imaging (MRI) and chest X-ray in specific situations.

7.1 T-staging

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

Serum PSA levels increase with advancing stage. Nevertheless, when PSA level is measured in an individual patient, it appears to have a limited ability to predict the final pathological stage accurately. Due to the production of PSA by benign and malignant prostatic tissue, there is no direct relationship between serum PSA concentration and the clinical and pathological tumour stage (2-4). A combination of serum PSA level, Gleason score on prostate biopsy and clinical T-stage, however, has been proven to be more useful in predicting the final pathological stage than the individual parameters per se (5).

The ability of the molecular forms of PSA to predict T-stage is still controversial. Percentage-free serum PSA did not appear to be able to predict organ-confined disease in the overall population: it could significantly predict favourable pathology in a subset of patients where DRE is normal and total PSA ranges from 4.1-10.0 ng/mL (6). Total PSA and PSA complexed to antichymotrypsin (PSA-ACT) may be superior to their density derivatives in the prediction of post-surgical pathological stage, but it does not seem to justify the substitution of PSA-ACT data in the Partin's nomogram (7). Large multicentre studies are needed before any form of PSA can be used as a single modality for staging.

The most commonly used method for viewing the prostate is transrectal ultrasound (TRUS). However, only 60% of tumours are visible with TRUS, and the remainder are not recognised due to their echogenicity. A combination of DRE and TRUS can detect T3a PCa more accurately than either method alone (8). TRUS is not able to determine tumour extension with sufficient accuracy to be recommended for routine use in staging. About 60% of pT3 tumours will not be detected pre-operatively by TRUS (9) (level of evidence: 3).

Three-dimensional ultrasound (3D-US) is a non-invasive method of reproducing whole volume images of solid structures with a suggested staging accuracy of 91% (10). Several adjuncts to 3D greyscale TRUS have been investigated. A greater sensitivity for cancer detection has been achieved with the addition of power colour Doppler and contrast agents: the presence or absence of vessels crossing the capsule to determine an extracapsular extension was considered a significant predictive sign (11,12). Unfortunately, recognition of these findings is largely operator-dependent. Thus, differentiation between T2 and T3 tumours should not be based on TRUS alone (13,14).

Furthermore, in a large multi-institutional study, TRUS was no more accurate at predicting organ-confined disease than was DRE (15). These findings were supported by another large study, which showed that there was no meaningful superiority of TRUS over DRE (16).

Seminal vesicle invasion is predictive of local relapse and distant failure. Seminal vesicle biopsies may be used to increase the accuracy of pre-operative staging (17). This is not recommended as a first-line examination, but should be reserved for patients with a substantial risk of seminal vesicle invasion in whom a positive seminal vesicle biopsy would modify treatment decisions. Patients with a clinical stage greater than T2a and a serum PSA level of more than 10 ng/mL could be candidates for seminal vesicle biopsies (18,19).

Patients with any of the basal biopsies positive for cancer are more likely to have positive seminal vesicle biopsies (20). The biopsy Gleason score, serum PSA level and clinical stage are known to be independent predictors of adverse pathological features after radical prostatectomy (RP).

Of the prostate needle biopsy parameters examined, the percentage of tissue with cancer was the strongest predictor for positive surgical margins, seminal vesicle invasion and non-organ-confined disease (21). An increased number of biopsies involved with tumour independently predicts extracapsular extension, margin involvement and lymph node invasion (22).

In a multivariate analysis, the best risk predictors of extracapsular extension on one side were the overall average of positive biopsy cores being 15% or greater, and the average from three ipsilateral biopsies being 15% or greater. When used in combination, these two factors yielded a model with a positive predictive value of 37%, and a negative predictive value of 95%. The high negative predictive value of the side-specific model identifies patients who are good candidates for nerve-sparing surgery (23). Furthermore, it may be useful to correlate the bioptic Gleason score with the final pathological stage: about 70% of patients have localised disease when the biopsy Gleason score is ≤ 6 (24).

Both CT and MRI are now of a high technical standard, but neither modality is sufficiently reliable to make their use mandatory in the assessment of local tumour invasion (25-27). Endorectal MRI (e-MRI) may allow for more accurate local staging by complementing the existing clinical variables by improvements in spatial characterisation of the prostatic zonal anatomy and molecular changes (28). Image quality and localisation improves significantly with e-MRI compared with external coil MRI (29). When compared with DRE and TRUS prostate biopsy findings, e-MRI contributes significant incremental value for local PCa staging (30), particularly in the pre-operative identification of extracapsular extension (ECE) and seminal vesicle invasion (SVI) when interpreted by dedicated genitourinary radiologists (31,32,33).

E-MRI could impact on the decision to preserve or resect the neurovascular bundle (NVB) at the time of radical surgery (34). Similarly, e-MRI could be accurate in evaluating the presence of SVI (35). Features associated with the identification of SVI include low signal intensity within the seminal vesicle, and lack of preservation of normal seminal vesicle architecture. Combining these features with the presence both of tumour at the base of the prostate and ECE is highly predictive for the presence of SVI (35,36).

When assessed for the ability to predict organ-confined PCa, the contribution of e-MRI to staging nomograms was significant in all risk categories, but the greatest benefit was seen in the intermediate and high risk groups (37). The combination of dynamic contrast-enhanced MR imaging and T2-weighted MR imaging yields improved assessment of ECE and better results for PCa staging compared with either technique independently (38) (level of evidence: 3).

MR spectroscopic imaging (MRSI) allows for the assessment of tumour metabolism by displaying the relative concentrations of citrate, choline, creatinine and polyamines. Differences in the concentrations of these chemical metabolites between normal and malignant prostate tissues allow for better tumour localisation within the peripheral zone, increasing the accuracy of ECE detection among less-experienced readers, and decreasing interobserver variability (39). Furthermore, correlations have been demonstrated between the metabolic signal pattern and a pathological Gleason score, suggesting the potential for a non-invasive assessment of PCa aggressiveness (40).

Despite the proposed accuracy and benefit of e-MRI and MRSI in PCa characterisation and localisation, e-MRI has several limitations that hamper its widespread application in PCa staging, e.g. difficulties in interpreting signal changes related to post-biopsy haemorrhage and inflammatory changes of the prostate, and the unquantifiable but significant inter- and intra-observer variability seen between both non-dedicated and dedicated radiologists that may lead to under- or overestimation of tumour presence and the local extent of disease (level of evidence: 3). The overall accuracy of ^{11}C -choline positron emission tomography (PET) in defining local tumour stage (pT2 and pT3a-4) has been reported to be around 70%. PET tends to understage PCa, and has a limited value for making treatment decisions in patients with clinically localised PCa, especially if a nerve-sparing procedure is being considered (41) (level of evidence: 2b).

7.2 N-staging

N-staging should be performed only when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatments are planned. High PSA values, stages T2b-T3 disease, poor tumour differentiation and peri-neural tumour invasion have been associated with a higher risk of the presence of nodal metastases (5,42,43). The measurement of PSA level alone is unhelpful in predicting the presence of lymph node metastases for an individual patient.

The nomograms could be used to define a group of patients with a low risk of nodal metastasis (< 10%, see *reference number 44*). In such cases, patients with a serum PSA level of less than 20 ng/mL, stage T2a or less, and a Gleason score of 6 or less may be spared N-staging procedures before potentially curative treatment (5).

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

In the current published literature, the results indicate that CT and MRI perform similarly in the detection of pelvic lymph node metastases, although CT seems to be slightly superior (46) (level of evidence: 2a). In either case, the decision about whether nodal involvement is present rests solely on whether there is enlargement of the investigated lymph nodes. The centimetre threshold used to decide whether a lymph node is pathologically involved varies between 0.5 cm and 2 cm. A threshold of 1 cm in the short axis for the oval nodes, and 0.8 cm for the round nodes, has been recommended as the criteria for the diagnosis of lymph node metastases (47).

A fine-needle aspiration biopsy (FNAB) might provide a decisive answer in cases of positive imaging results. However, the lymph node can be difficult to reach because of the anatomical position. In addition, FNAB is not a highly sensitive staging procedure, and a false-negative rate of 40% has been reported (47).

High-resolution MRI with lymphotropic ultra-small super-paramagnetic iron oxide particles (USPIO) was more recently suggested in the detection of small and otherwise occult lymph node metastases in patients with PCa (48,49). These iron nanoparticles are taken up by circulating macrophages, which travel to normal nodal tissue. The presence of the nanoparticles causes normal nodal tissue to turn black, and because malignant nodal tissue is unable to take up the agent, metastases will have a signal intensity higher than normal nodes, even in those that do not meet the standard size criteria for metastasis (50).

In asymptomatic patients with newly diagnosed PCa and a serum PSA level of less than 20 ng/mL, the likelihood of positive findings on CT or MRI is approximately 1% (37). CT scanning may therefore be warranted in patients with a very high risk of harbouring lymph node metastases, as the specificity of a positive scan is high (93-96%). Patients with nodal metastases on CT can thus be spared operative lymphadenectomy (51).

Radio-immunoscintigraphy and PET have been investigated in order to improve the diagnosis of metastatic disease to the lymph nodes. Both methods are still under investigation, and further evaluation is needed before they can be recommended for routine use in clinical practice, especially as negative results should be interpreted with caution (52). The results obtained using ¹⁸F-choline PET/CT scans for initial N-staging were discouraging, especially in terms of inability to detect small metastases/micrometastases (< 5 mm) (53). Furthermore, ¹¹C-choline PET/CT has quite a low sensitivity for the detection of lymph node metastases, but performed better than clinical nomograms, with equal sensitivity and better specificity (54).

The gold standard for N-staging is operative lymphadenectomy, either by open or laparoscopic techniques. It is worth pointing out that recent studies with more extensive lymphadenectomy have shown that the obturator fossa is not always the primary site for metastatic deposits in the lymph nodes, and pelvic lymph node dissection that is limited to the obturator fossa will therefore miss about 50% of lymph node metastases (55,56). When deciding on pelvic lymph node dissection, extended lymphadenectomy should be considered, despite its disadvantages: it requires surgical experience; it is time-consuming; and it often leads to more complications than the limited procedures. Furthermore, it may fail to identify lymph node metastases, however present, even outside the region of extended dissection (57).

The primary removal of the so-called sentinel lymph node (SLN), defined as the first lymph node that receives lymphatic drainage from PCa, has the main aim of reducing the eventual morbidity associated with an extended pelvic node dissection, while preserving maximal sensitivity for diagnosis of metastatic disease (58) (level of evidence: 3) (see *section 9.5.2.1 'Treatment: radical prostatectomy, indication and extent of LND'*).

7.3 M-staging

The axial skeleton is involved in 85% of patients who die from PCa (59). The presence and extent of bone metastases accurately reflect the prognosis for an individual patient. Elevated skeletal alkaline phosphatase levels may indicate the presence of bony metastasis in 70% of affected patients (60). Furthermore, the measurement of skeletal alkaline phosphatase and PSA at the same time increases clinical effectiveness to approximately 98% (61). In a prospective study, multiple regression analysis showed the extent of bone disease to be the only variable influencing the serum levels of skeletal alkaline phosphatase and PSA. However, in contrast to serum PSA, skeletal alkaline phosphatase demonstrated a statistical correlation with the extent of bone disease (62).

Early detection of bone metastases will alert the clinician to the possible complications inherent in skeletal destruction. Bone scintigraphy remains the most sensitive method of assessing bone metastases, being superior to clinical evaluation, bone radiographs, serum alkaline phosphatase measurement and prostatic acid phosphatase (PAP) determination (63,64). Technetium diphosphonates are the optimum radiopharmaceuticals currently available because of their extremely high bone-to-soft tissue ratio (65). A semi-quantitative grading system based on the extent of disease observed on the bone scan was found to correlate with survival (66).

Increased ¹⁸F-fluoride uptake in malignant bone lesions reflects the increase in regional blood flow and bone turnover that characterise these lesions.

Studies have shown that ¹⁸F-fluoride PET/CT is a highly sensitive and specific imaging modality for detection of bone metastases (67,68). However, no definitive results have been obtained and therefore no final recommendations can be made (69).

Besides bone, PCa may metastasise to any organ, but most commonly it affects distant lymph nodes, lung, liver, brain and skin. Clinical examination, chest X-ray, ultrasound, CT and MRI scans are appropriate methods of investigation, but only if symptoms suggest the possibility of soft-tissue metastasis.

The need for reliable serum markers to improve the pre-treatment staging of patients with PCa has long been recognised. At present, PSA is the marker of choice. A pre-treatment serum PSA level greater than 100 ng/mL has been found to be the single most important indicator of metastatic disease, with a positive predictive value of 100% (70). Furthermore, it has helped to reduce the number of patients with newly diagnosed PCa who require a bone scan. Patients with a low serum PSA concentration have only rarely been found to harbour detectable skeletal metastases. The correlation between serum PSA and bone scintigraphy in patients with newly diagnosed untreated PCa has been further investigated (71-75). Results suggest that a staging bone scan may be superfluous if the serum PSA concentration is less than 20 ng/mL in asymptomatic patients with well or moderately differentiated tumours. In contrast, in patients with poorly differentiated tumours and locally advanced disease, a staging bone scan should be obtained irrespective of the serum PSA value (76,77).

7.4 Guidelines for the staging of PCa

		GR
1.	An abnormal DRE result or elevated serum PSA measurement could indicate PCa. The exact cut-off level of what is considered to be a normal PSA value has not been determined, but values of approximately < 2-3 ng/mL are often used for younger men.	C
2.	The diagnosis of PCa depends on histopathological (or cytological) confirmation. • Biopsy and further staging investigations are only indicated if they affect the management of the patient.	B C
3.	TRUS-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 10 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volume prostates: • transition zone biopsies are not recommended in the first set of biopsies due to low detection rates • one set of repeat biopsies is warranted in cases with persistent indication (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy) for prostate biopsy • overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	B C B C
4.	Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies.	A

5.	Local staging (T-staging) of PCa is based on findings from DRE and possibly MRI. Further information is provided by the number and sites of positive prostate biopsies, the tumour grade and the level of serum PSA.	C
	Despite its high specificity in the evaluation of ECE and SVI, TRUS is limited by poor contrast resolution, resulting in low sensitivity and tendency to understage PCa. Even with the advent of colour and power Doppler to assist in identifying tumour vascularity, the accuracy of TRUS in local staging remains inadequate. In comparison with DRE, TRUS, and CT, MRI demonstrates higher accuracy for the assessment of uni- or bilobar disease (T2), ECE and SVI (T3), as well as the invasion of adjacent structures (T4). However, the literature shows a wide range in the accuracy of T-staging by MRI, from 50-92%. The addition of dynamic contrast-enhanced MRI (DCE-MRI) can be helpful in equivocal cases. The addition of MRSI to MRI also increases accuracy and decreases interobserver variability in the evaluation of ECE.	C
6.	Lymph node status (N-staging) is only important when potentially curative treatment is planned. Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score ≤ 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation. Given the significant limitations of pre-operative imaging in the detection of small metastases (< 5 mm), pelvic lymph node dissection remains the only reliable staging method in clinically localised PCa.	B
	Currently, it seems that only methods of histological detection of lymph node metastases with high sensitivity, such as sentinel lymph node dissection or extended pelvic lymph node dissection, are suitable for lymph node staging in PCa.	C
7.	Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is less than 20 ng/mL in the presence of well or moderately differentiated tumours.	B
	In equivocal cases, ¹¹ C-choline or PET/CT could be of value, especially to differentiate active metastases and healing bones.	C

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8. TREATMENT: DEFERRED TREATMENT (WATCHFUL WAITING/ACTIVE MONITORING)

8.1 Introduction

The therapeutic management of prostate cancer (PCa), even in clinically localised disease, has become increasingly complex due to the various therapeutic options available, which have equal oncological efficacy but significantly different, treatment-related, side-effects.

Treatment decisions for each clinical stage and risk group of PCa should be based on national or European guidelines, with the guideline used for the decision-making process clearly indicated. Furthermore, a multidisciplinary approach may be advisable from the beginning in patients with high-risk PCa because it is very likely that adjuvant treatment will be necessary for locally advanced disease. It is therefore advisable to:

- Counsel patients with clinically localised or intermediate-risk PCa in an interdisciplinary setting with a urologist and a radiation oncologist, considering the therapeutic options of nerve-sparing radical prostatectomy (RP), permanent low-dose brachytherapy, external beam radiation therapy and active surveillance (AS).
- Discuss neoadjuvant and adjuvant treatment options in patients with high-risk PCa in a pre-therapeutic multidisciplinary tumour board to recommend the most appropriate treatment option, considering all pathohistological, functional and individual parameters of a given PCa.
- Thoroughly document which guidelines have been used for the decision-making process if no multidisciplinary approach was possible.

8.1.1 Definition

There is a great difference between the incidence of and mortality from PCa: in the USA in 2007, there were 218,900 new cases with only 27,050 deaths (1). Several autopsy studies of people dying from different causes have shown that while 60-70% of older men have histological PCa (2,3), a large proportion of these tumours

will not progress. Prostate cancer is diagnosed in only 15-20% of men during their lifetime, with a 3% lifetime risk of death (4).

The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of prostate-specific antigen (PSA) screening and 'multi-core' schemes of prostate biopsy. These data suggest that a lot of the men with localised PCa would not, in fact, benefit from a definitive treatment. With the aim of reducing the risk of overtreatment in this subgroup of patients, two conservative management strategies of 'watchful waiting' and 'active surveillance' have been proposed.

8.1.1.1 Watchful waiting (WW)

Also known as 'deferred treatment' or 'symptom-guided treatment', this term was coined in the pre-PSA screening era (before 1990) and referred to the conservative management of PCa until the development of local or systemic progression, at which point the patient would be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction and hormonal therapy or radiotherapy for the palliation of metastatic lesions.

8.1.1.2 Active surveillance (AS)

Also known as 'active monitoring', this is the new term for the conservative management of PCa. Introduced in the past decade, it includes an active decision not to treat the patient immediately and to follow him with close surveillance and treat at pre-defined thresholds that classify progression (i.e. short PSA doubling time and deteriorating histopathological factors on repeat biopsy). In these cases, the treatment options are intended to be curative.

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

8.2.1 Watchful waiting (WW)

The rationale behind WW is the observation that PCa often progresses slowly, and is diagnosed in older men in whom there is a high incidence of co-morbidity and related high competitive mortality (5). Watchful waiting can be considered as an option for treating patients with localised PCa and a limited life expectancy or for older patients with less aggressive cancers.

There have been several attempts to summarise the key papers dealing with deferred treatment in patients with presumed localised PCa (6-10). Most of them present the same results as they analyse roughly the same series, but with a somewhat different methodology.

The outcome studies on WW usually include patients whose PSA readings are not always available, and in whom the lesions are predominantly palpable and which would currently be defined as intermediate-risk tumours, as described by D'Amico et al. (11). These studies include patients with a follow-up of up to 25 years, for whom the endpoints are overall survival (OS) and disease-specific survival (DSS).

Several WW series show a very consistent DSS ratio at 10 years, ranging from 82-87% (6,12-17). In three studies with data beyond 15 years, the DSS was 80%, 79% and 58%, respectively (14,16,17). Two of them reported a 20-year DSS of 57% and 32%, respectively (14,16).

Chodak and co-workers reported a pooled analysis of the original data from 828 patients treated by WW (6). The paper is based on patients from six non-randomised studies (10,18-23). The results describe cancer-specific survival (CSS) and metastasis-free survival after 5 and 10 years of follow-up (6) (level of evidence: 2b).

Tumour grade is clearly significant, with very low survival rates for grade 3 tumours. Although the 10-year CSS rate is equally good (87%) for grade 1 and 2 tumours, the latter have a significantly higher progression rate, with 42% of these patients developing metastases (Table 9).

Table 9: Outcome of deferred treatment in localised PCa in relation to tumour grade (6): percentage of patients (95% confidence interval) surviving at 5 and 10 years.

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

The importance of tumour grade on survival after conservative management of PCa was also underlined in a large register study utilising the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute in the USA (12) (level of evidence: 3). Patients with grade 1, 2 and 3 tumours had 10-year CSS rates of 92%, 76% and 43%, respectively, correlating with the data from the pooled analysis.

The paper by Chodak and co-workers also specifically described the outcome for stage T1a patients (6), with cancer-specific 10-year survival rates of 96% and 94%, respectively, for grade 1 and 2 tumours. The metastasis-free survival rate was 92% for patients with grade 1 tumours, but 78% for those with grade 2 tumours, indicating a higher risk of progression in individuals with moderately differentiated tumours. This difference in progression rate correlates with other studies on stage T1a disease (24,25).

In order to stage patients accurately and not overlook the presence of more extensive and/or more poorly differentiated tumours, repeat examinations with PSA measurement, transrectal ultrasound (TRUS) and needle biopsy of the prostate remnant have been advocated, especially in younger males with a long life expectancy (26).

The impact of grade on the risk of tumour progression and ultimately death from PCa is also described in a paper by Albertsen and co-workers (27). They re-evaluated all biopsy specimens using the more widely accepted Gleason score, and showed that the risk of PCa death was very high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 cancers (Table 10) (28,29) (level of evidence: 3).

This paper also showed that Gleason 6-10 tumours carry a continuously increasing risk of ending the patient's life for up to 15 years of follow-up after conservative management. The CSS curves for this group of patients have been published in a recent discussion article on different methods of assessing outcome in treatment for localised PCa (28).

Table 10: The 15-year risk of dying from PCa in relation to Gleason score at diagnosis in patients with localised disease aged 55-74 years (27,28).

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

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

† The cancer-specific mortality compensates for differences in competing mortality and indicates the outcome if the patient actually lived for 15 years.

Three randomised clinical trials have reported long-term follow-up of patients randomised to WW or RP: the first was in the pre-PSA screening era (29); the second was at the beginning of PSA screening (30); and the third was a recent study, the results from which are not yet mature (1).

The Veterans Administration Cooperative Urological Research Group between 1967 and 1975, randomised 142 patients affected by clinical localised PCa. The study was underpowered to detect treatment differences (31).

Between 1989 and 1999, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomised 695 patients with clinical stage T1-T2 to WW (348) or RP (347) (Table 11) (30). This study began after PSA screening was introduced into clinical practice, but only 5% of men were diagnosed by screening. After a median follow-up of 10.8 years, this study showed a significant decrease in cancer-specific mortality, overall mortality, metastatic risk progression and local progression in patients treated with RP versus WW (level of evidence: 1b).

Table 11: Outcome of Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) at 10 years of follow-up (median of 8.2 years) (30).

	RP (n 347) % (n)	WW (n 348) % (n)	Relative risk (95% CI)	p value
• Disease-specific mortality	9.6 (30)	14.9 (50)	0.56 (0.36-0.88)	0.01
• Overall mortality	27 (83)	32 (106)	0.74 (0.56-0.86)	0.04
• Metastatic progression	15.2 (50)	35.4 (79)	0.60 (0.42-0.44)	0.004
• Local progression	19.2 (64)	44.3 (149)	0.33 (0.25-0.44)	< 0.001

The results of three more years of follow-up were published recently. At 12 years' follow-up, the group of patients treated with RP presented a favourably significant difference of 5.4% in PCa-specific mortality and 6.7% in non-metastatic progression (Table 12) (32) (level of evidence: 1b).

Table 12: Outcome of Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) at 12 years of follow-up (median of 10.8 years) (32).

	RP (n 347) % (n)	WW (n 348) % (n)	Relative risk (95% CI)	p value
• Disease-specific mortality	12.5 (43)	17.9 (68)	0.65 (0.2-11.1)	0.03
• Metastatic progression	19.3	26	0.65 (0.47-0.88)	0.006

The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT) (1) is an ongoing controlled multicentre randomised clinical trial comparing RP with WW in patients with clinical stage T1-T2 disease. Between 1994 and 2002, 731 patients with a median age of 67 years were enrolled. The median PSA was 7.8 ng/mL (mean 10.2 ng/mL). Three-quarters of the men had clinical stage T1c disease. Using previously developed tumour risk categorizations, incorporating PSA levels, Gleason histological grade and tumour stage, approximately 43% of men had low-risk, 36% had medium-risk, and 20% had high-risk PCa. Follow-up is planned for 15 years, and the primary endpoint is the overall mortality. PIVOT enrollees are more representative of men being diagnosed and treated in contemporary clinical practice than were those enrolled in SPCG-4.

In summary:

- Clinical stage T1c currently represents 40-50% of new cases of PCa (33). The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of PSA screening and 'multi-core' schemes of prostate biopsy.
- The SPCG-4 study demonstrated significant advantages for RP over WW, but only 5% of those studied were PSA-screened patients.
- During the past 20 years, there has apparently been a shift towards higher Gleason scoring levels (34), even in cases evaluating microscopic foci of PCa. Some tumours previously given a Gleason score of 6 (3 + 3), might be scored as 7 (3 + 4), or more, today.
- The lead time in PSA screening is about 10 years (35,36). It is therefore possible that the cancer mortality from untreated, non-screen-detected PCa in patients with contemporary Gleason scores of 6 might be as low as 10% at 20-year follow-up (37).

It would seem that many small, localised, well-differentiated PCas will not progress, and radical therapy may lead to substantial overtreatment with consequent problems in terms of quality of life and socio-economic costs.

8.2.2 Active surveillance

Active surveillance was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined low-risk PCa, without giving up radical treatment, as happened with the WW strategy. Only data from non-mature randomised clinical trials of AS with follow-up < 10 years are currently available.

A multicentre clinical trial of AS versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025.

Choo, Klotz and co-workers were the first to report on a prospective AS protocol (38,39). They enrolled 331 patients with clinical stage T1c or T2a, PSA \leq 10 ng/mL and a Gleason score \leq 6 (PSA \leq 15 and Gleason score \leq 7 [3 + 4] in patients above the age of 70 years). At a median follow-up of 8 years, the overall survival was 85%, while disease-specific survival and metastasis-free survival were 99%. The median value of the PSA doubling time was 7 years; in 42% of patients it was $>$ 10 years, and in 22% $<$ 3 years. Thirty-three per cent of the patients subsequently underwent a radical treatment: 20% for a PSA doubling time $<$ 3 years; 5% for Gleason score progression on repeat biopsies; and 10% because of patient preference.

Soloway et al., evaluating 157 patients with a median follow-up of 4 years, reported no PCa deaths or metastatic disease and a ratio of only 8% having delayed treatment (40). Carter et al., looking at 407 patients with a median follow-up of 3.4 years, reported no PCa deaths (41).

A variety of additional studies have been performed on active surveillance in clinically organ confined disease (Table 13). All these studies confirm that, in well-selected patients with low-risk disease, there is a very low rate of progression and cancer-specific death, and only a few patients require delayed radical intervention. However, another 5-7 more years of follow-up will be necessary in order to obtain definitive results.

Table 13: Clinical trials of AS for organ-confined PCa.

Author	n	Follow-up (years)	Overall survival	Cancer-specific survival	Progression / Intervention	Inclusion criteria
Klotz (2009) [42]	453	6.8 (1-13)	78.6%	97.2%	30%	PSA \leq 10 Gleason score \leq 6
Van den Bergh (2008) [43]	616	3.9 (0-11)	91%	99.8%	32% intervention; only 14% due to progressive PCA	PSA \leq 10, PSA-density \leq 0.2, cT1C/T2, Gleason score \leq 6, \leq 2 biopsies positive
Soloway (2008) [40]	99	4 (1- 14.9)	No data	100%	9%	$<$ 80 years, Gleason score \leq 6, PSA \leq 0,15 ng/mL, cT \leq 2, \leq 50% cancer in \leq 2 biopsies
Dall'Era (2008) [44]	321	3.6 (1-17)	100%	100%	24%	PSA $<$ 10 ng/mL, Gleason score \leq 6, no Gleason grade $>$ 3, $<$ 33% positive biopsies, cT 1-2a
Berglund (2008) [45]	104	3 (1-6)	No data	100%	27%	PSA $<$ 10, cT1-2a, Gleason grade \leq 3, \leq 3 positive biopsies, $<$ 50% cancer in biopsy
Al Otaibi (2008) [46]	186	6.4 (2.5-14)	No data	100%	36%	\leq cT2a, \leq 2 positive biopsies, \leq 50% cancer in biopsy, no Gleason grade 4
Takehi (2008) [47]	134	4.5	2.5%	100%	17.7%	cT1cN0M0, 50-80 years, PSA \leq 20ng/mL, \leq 2 positive out of 6-12 biopsies Gleason score \leq 6, \leq 50% cancer

Different series have identified several eligibility criteria for enrollers:

- clinically confined PCa (T1-T2)
- Gleason score \leq 7
- PSA $<$ 15-20 ng/mL (5).

Moreover, different criteria were applied to define cancer progression (5), although all groups used:

- PSA doubling time with a cut-off value ranging between \leq 2 and \leq 4 years;

- Gleason score progression to ≥ 7 at re-biopsy, at intervals ranging from 1-4 years.

These indicators are poorly validated. Currently, it is impossible to make evidence-based recommendations on when to intervene in patients with a long life expectancy.

Data that include PSA and PSA changes over time are relatively sparse in the literature. In a recent review article, it was pointed out that patients with a PSA of < 3 ng/mL had no mortality from PCa within the first 10 years, and that PSA changes over time were relatively unreliable in determining the risk for tumour progression (48).

The data above indicate a high risk of tumour progression after conservative treatment for some patients with apparently localised PCa. This has been supported by the results of other studies in which patients with a life expectancy exceeding 10 years have been shown to have a higher mortality rate from PCa when left without curative treatment (49-51). Long-term follow-up of the Johansson series shows the same outcome: there is a higher risk of dying from PCa in patients surviving more than 15 years with well- and moderately differentiated tumours at diagnosis (52) (level of evidence: 3).

For patients who choose deferred treatment, the risk of delaying hormone therapy until disease progression has occurred appears to be modest, although shorter CSS times have been reported after deferred therapy compared with immediate hormone therapy in presumed localised PCa (not utilising PSA for staging) after 15 years of follow-up (53).

In contradiction of Lundgren et al. (53), the report of the Casodex Early Prostate Cancer Trialists' Group programme showed a higher mortality in a group of men with localised PCa treated with bicalutamide 150 mg than in those who received placebo (54).

In summary, it seems that hormonal therapy should be withheld until there is definitive proof of disease activity (progression), but it is open to speculation whether there might be some benefit in delivering it before the patient develops metastatic disease (55) (see below).

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

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

Most patients whose disease progresses after deferred treatment of locally advanced PCa will be candidates for hormone therapy. There are reports from non-randomised studies showing that hormone treatment may safely be delayed until metastatic progression occurs, as no survival advantage was noted between patients treated with immediate orchiectomy compared with delayed treatment (56,57).

In a recent prospective randomised clinical phase III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0 PCa were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic disease progression or occurrence of serious complications (58,59). After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% confidence interval [CI]: 1.05-1.48; non-inferiority $p > 0.1$) favouring immediate treatment, seemingly due to fewer deaths of non-prostatic cancer causes ($p = 0.06$).

The time from randomisation to progression of hormone-refractory disease did not differ significantly, nor did prostate cancer-specific survival. The median time to the start of deferred treatment after study entry was 7 years. In this group, 126 patients (25.6%) died without ever needing treatment (44% of the deaths in this arm). The conclusion drawn from this study is that immediate ADT resulted in a modest but statistically significant increase in overall survival but no significant difference in PCa mortality or symptom-free survival. Furthermore, the authors identified significant risk factors associated with a significantly worse outcome: in both arms, patients with a baseline PSA > 50 ng/mL were at a > 3.5 -fold higher risk of dying of PCa than patients with a baseline PSA ≤ 8 ng/mL. If the baseline PSA was between 8 ng/mL and 50 ng/mL, the risk of PCa death was approximately 7.5-fold higher in patients with a PSA doubling time < 12 months than in patients with a PSA doubling time > 12 months. The time to PSA relapse following a response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA may also reflect disease aggressiveness.

However, when early and delayed treatments were compared in a large randomised trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormone therapy was demonstrated (60), comparable with the results of the Lundgren et al. study mentioned above (53) (level of evidence: 1b).

Also, a comparison of bicalutamide, 150 mg/day, with placebo showed that progression-free survival (PFS) was better with early treatment in patients with locally advanced PCa (54) (level of evidence: 1b).

Fifty selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 PCa were followed up for 169 months (61). The 5- and 10-year CSS rates were 90% and 74%, respectively, and the likelihood of being without treatment at 5 and 10 years was 40% and 30%, respectively. The authors concluded that WW might be a treatment option for selected patients with non-poorly differentiated T3 tumours and a life expectancy of less than 10 years (level of evidence: 3).

8.4 Deferred treatment for metastatic PCa (stage M1)

There are only very sparse data on this subject. The only candidates for such treatment should be asymptomatic patients with a strong wish to avoid treatment-related side-effects (level of evidence: 4). As the median survival time is about 2 years, the time without any treatment (before symptoms occur) is very short in most cases. The MRC trial highlighted the risk of developing symptoms (pathological fractures, spinal cord compression), and even death from PCa, without receiving the possible benefit from hormone treatment (60,62) (level of evidence:1b). If a deferred treatment policy is chosen for a patient with advanced PCa, close follow-up must be possible.

8.5 Summary of deferred treatment

8.5.1 Indications	LE
In presumed localised PCa (Nx-N0, M0):	
<ul style="list-style-type: none"> Stage T1a: well and moderately differentiated tumours. In younger patients with a life expectancy of > 10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended 	2a
<ul style="list-style-type: none"> Stage T1b-T2b: well and moderately differentiated tumours. In asymptomatic patients with a life expectancy of < 10 years 	2a
<ul style="list-style-type: none"> Inclusion criteria for active surveillance with the lowest risk of cancer progression are: PSA ≤ 10 ng/ml, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, ≤ 50% cancer per biopsy, cT1c-2a. 	
8.5.2 Options	
In presumed localised PCa (Nx-N0, M0):	
<ul style="list-style-type: none"> Stage T1b-T2b patients who are well informed and have well-differentiated (or Gleason 2-4) PCa and a life expectancy of 10-15 years. 	
<ul style="list-style-type: none"> All patients not willing to accept side-effects of active treatment. 	
<ul style="list-style-type: none"> Well-informed, asymptomatic patients with high PSA levels for whom cure is unlikely 	3
In locally advanced disease (stage T3-T4):	
<ul style="list-style-type: none"> Asymptomatic patients with well- or moderately differentiated cancer, PCa and a short life expectancy 	3
<ul style="list-style-type: none"> PSA < 50 ng/mL and PSA doubling time > 12 months 	1
In metastatic disease (M1):	
<ul style="list-style-type: none"> A very rare patient without any symptoms and the possibility of close follow-up 	4

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9. TREATMENT: RADICAL PROSTATECTOMY

9.1 Introduction

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

Radical prostatectomy was first applied at the beginning of the 20th century by Young (5) using a perineal approach, while Memmelaar and Millin were the first to perform retropubic RP (6). In 1982, Walsh and Donker described the anatomy of the dorsal venous complex and the neurovascular bundles (NVBs). This resulted in a significant reduction in blood loss and improved continence and potency rates (7). Currently, RP is the only treatment for localised PCa to show a benefit for cancer-specific survival (CSS) compared with conservative management, as shown in a prospective, randomised trial (8). Surgical expertise has decreased the complication rates of RP and improved cancer cure (9-12).

Total surgical removal is an excellent treatment option in well-selected patients with localised PCa. If performed by an experienced surgeon, the patient's subsequent quality of life should be satisfactory. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can decrease positive surgical margin rates and improve cancer control with RP (13).

Radical retropubic prostatectomy (RRP) and perineal prostatectomy are performed through open incisions, while more recently minimally invasive laparoscopic (LRP) and robot-assisted radical prostatectomy (RALP) have been developed. The retropubic approach is more commonly performed over the perineal procedure, as it enables simultaneous pelvic lymph node assessment. It has been suggested that perineal RP might result in positive surgical margins more often than the retropubic approach (14), but this has not been confirmed (15). In the past decade, several European centres have acquired considerable experience with LRP (16-19). More recently, RALP has been developed.

A recent in-depth systematic review of the literature compared the results of RRP versus LRP/RALP. It was concluded that LRP and RALP were followed by a significantly lower blood loss and transfusion rate, but the available data were not sufficient to prove the superiority of any surgical approach in terms of functional and oncological outcomes (20). It has been suggested that the need for salvage therapy (with external beam radiation therapy [EBRT] or androgen-deprivation therapy) within 6 months of LRP and RALP is much higher than following RRP (21). In a more recent study (22), those who underwent LRP or RALP versus RRP experienced:

- shorter length of stay;
- fewer respiratory and miscellaneous surgical complications and strictures;
- similar post-operative use of additional cancer therapies;
- more genitourinary complications, incontinence, and erectile dysfunction.

Clearly, even though RALP is displacing RRP as the gold standard surgical approach for clinically localised PCa in the USA and some regions in Europe, it is still not clear which technique is superior in terms of oncological and functional results and cost-effectiveness. Prospective trials are urgently needed.

9.2 Low-risk, localised PCa: cT1-T2a and Gleason score 2-6 and PSA < 10

Patients with low-risk, localised PCa should be informed about the results of the randomised trial comparing retropubic RP versus watchful waiting in localised PCa. In this study, RP reduced prostate cancer mortality and the risk of metastases in men younger than 65 years with little or no further increase in benefit 10 or more years after surgery (8).

9.2.1 Stage T1a-T1b PCa

Stage T1a PCa is defined as an incidental histological finding of cancer in 5% or less of resected prostatic tissue (transurethral resection of the prostate [TURP] or open adenectomy). Stage T1b PCa is defined as > 5% cancer. Published series have shown a pT0 stage of 4-21% and an organ-confined stage in 47-85% at subsequent RP (23).

A Swedish register-based study of 23,288 men with incidental PCa detected at TURP or open adenoma enucleation largely before the prostate-specific antigen (PSA)-era showed a 10-year PCa mortality of 26.6%. There were no details of the PSA level or Gleason score nor the numbers of cases with cT1a or cT1b PCa (24). Other older studies have shown that, even though the risk of disease progression of untreated T1a PCa after 5 years is only 5%, these cancers can progress in about 50% of cases after 10-13 years (25). Thus, it was believed that in younger patients with a life-expectancy of 15 years or more, the chance of disease progression was real. In contrast, most patients with T1b tumours were expected to show disease progression after 5 years, and aggressive treatment was often warranted (25). Patients with T1b lesions were offered RP when they have a life expectancy of 10 years or more.

Nevertheless, it remained unclear whether these findings would still be valid in the PSA era. In a recent analysis of T1a/b PCa:

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

A predictive model has been proposed, which incorporates the PSA level before and after surgery and the Gleason score at surgery for BPH. The model has a predictive accuracy of 83.2% for estimating residual tumour and 87.5% for estimating biochemical progression, but needs external validation before it can be used in daily practice (26).

Systematic prostate biopsies of the remnant prostate may be useful in detecting residual cancer or concomitant peripheral zone cancer, or to ascertain a more correct tumour grade. Radical prostatectomy may be very difficult after a thorough TURP, when almost no residual prostate is left behind (27).

9.2.2 Stage T1c and T2a PCa

Clinically unapparent tumour identified by needle biopsy because of an elevated PSA (cT1c) has become the most prevalent type of PCa. In an individual patient, it is difficult to differentiate between clinically insignificant and life-threatening PCa. Most reports, however, stress that cT1c tumours are mostly significant and should not be left untreated as up to 30% of cT1c tumours are locally advanced disease at final histopathology (28). The proportion of insignificant tumours varies between 11% and 16% (29,30). Increasing the number of biopsies may carry the risk of detecting a higher number of insignificant cancers. However, a recent study has shown that increasing the number of biopsies to 12 did not increase the number of insignificant tumours (31). The major problem is how to recognise those tumours that do not need RP. The biopsy findings and the free PSA ratio are helpful in predicting insignificant disease (32). Partin tables may be very helpful in better selecting patients requiring surgical treatment because of their ability to provide an estimation of the final pathological stage (33). Other authors have suggested the incorporation of biopsy information, such as the number of cores or the percentage of cores invaded (34). When only one or a few cores are invaded and the percentage of invasion in one core is limited, the chance of finding an insignificant PCa is more likely, certainly when the lesion is of low Gleason grade (35). It might be reasonable to follow up some patients whose tumours are most likely to be insignificant.

In general, however, RP should be advocated for patients with T1c tumours, bearing in mind that significant tumours will be found in most of these individuals. Stage T2a patients with a 10-year life expectancy should be offered RP since 35-55% of them will have disease progression after 5 years if not treated. If active monitoring is proposed for low-grade T2 cancer, it should be remembered that pre-operative assessment of tumour grade by needle biopsy is often unreliable (36).

An extended pelvic lymph node dissection (eLND) is not necessary in low-risk, localised PCa, as the risk for positive lymph nodes does not exceed 7% (37).

9.3 Intermediate-risk, localised PCa: cT2b-T2c or Gleason score = 7 or PSA 10-20

Patients with intermediate-risk, localised PCa should be informed about the results of the randomised trial comparing RRP versus watchful waiting in localised PCa. In this study, RP reduced prostate cancer mortality and risk of metastases in men younger than 65 years with little or no further increase in benefit 10 or more years after surgery (8).

Radical prostatectomy is one of the recommended standard treatments for patients with intermediate-risk PCa and a life expectancy of more than 10 years (38). The prognosis is excellent when the tumour is confined to the prostate based on pathological examination (39,40). A policy of WW has been proposed for some patients with intermediate-risk localised tumours (41). However, when the tumour is palpable or visible on imaging and clinically still confined to the prostate, disease progression can be expected in most long-term survivors. The median time to progression of untreated T2 disease is reported to be 6-10 years. Stage T2b cancer still confined to the prostate, but involving more than half of a lobe or both lobes, will progress in more than 70% of patients within 5 years (42). These data have been confirmed by a large randomised trial comparing RP and WW that included mostly T2 PCa patients showing a significant reduction in disease-specific mortality in favour of RP (8).

An eLND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 7% (37). In all other cases, an eLND can be omitted, which means accepting a low risk of missing positive nodes. A limited lymph node dissection should no longer be performed, as this will miss at least half of the nodes involved.

9.3.1 Oncological results of RP in low- and intermediate-risk PCa

The results achieved in a number of studies involving RP are shown in Table 14.

Table 14: Oncological results of RP in organ-confined disease

Reference	No. of patients	Year of RP	Median follow-up (months)	10-year PSA-free survival	10-year cancer-specific survival
• Isbarn et al. (2009) (43)	436	1992-97	122	60	94
• Roehl et al. (2004) (44)	3478	1983-2003	65	68	97
• Han et al. (2001) (45)	2404	1982-99	75	74	96
• Hull et al. (2002) (46)	1000	1983-98	53	75	98
• Porter et al. (2006) (47)	752	1954-94	137	71	96

Recently, the first externally validated nomogram predicting prostate cancer-specific mortality after RP for patients treated in the PSA era was published. The nomogram predicted that few patients will die from PCa within 15 years of RP, despite the presence of adverse clinical features. This nomogram can be used in patient counselling and clinical trial design (48).

9.4 High-risk localised PCa: cT3a or Gleason score 8-10 or PSA > 20

The widespread use of PSA testing has led to a significant migration in stage and grade of PCa, with > 90% of men in the current era diagnosed with clinically localised disease (49). Despite the trends towards lower-risk PCa, 20-35% of patients with newly diagnosed PCa are still classified as high risk, based on either PSA > 20 ng/mL, Gleason score > 8, or an advanced clinical stage (50). Patients classified with high-risk PCa are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk patients have a uniformly poor prognosis after RP (51).

There is no consensus regarding the optimal treatment of men with high-risk PCa. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence.

9.4.1 Locally advanced PCa: cT3a

Stage T3a cancer is defined as cancer that has perforated the prostate capsule. In the past, locally advanced

PCa was seen in about 40% of all clinically diagnosed tumours. This figure is lower today, although its management remains controversial. Surgical treatment of clinical stage T3 PCa has traditionally been discouraged (52), mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse (53,54). Several randomised studies of radiotherapy combined with androgen-deprivation therapy (ADT) versus radiotherapy alone have shown a clear advantage for combination treatment, but no trial has ever proven combined treatment to be superior to RP (55). Another problem is 'contamination' by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal therapy (HT) in most series reporting the treatment of clinical T3 PCa. In recent years, there has been renewed interest in surgery for locally advanced PCa, and several retrospective case-series have been published. Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease (56-61).

Over-staging of cT3 PCa is relatively frequent and occurs in 13-27% of cases. Patients with pT2 disease and patients with specimen-confined pT3 disease have similarly good biochemical and clinical PFS (60,61). In about 33.5-66% of patients, positive section margins will be present, and 7.9-49% will have positive lymph nodes (62). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or HT (60,61). Nevertheless, excellent 5-, 10- and 15-year overall survival (OS) and cancer-specific survival (CSS) rates have been published (Table 15). These rates surpass radiotherapy-alone series and are no different from radiotherapy combined with adjuvant hormonal therapy series (55). 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 (33,62). In addition, nodal imaging with computed tomography (CT or MRI), and seminal vesicle imaging with magnetic resonance imaging (MRI), or directed specific puncture biopsies of the nodes or seminal vesicles can help to identify those patients unlikely to benefit from a surgical approach (63). Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. Increased overall surgical experience must contribute to a decreased operative morbidity and to better functional results after RP for clinical T3 cancer (60,64). It has been shown that continence can be preserved in most cases, while in selected cases, potency can also be preserved (65).

Table 15: Overall and cancer-specific survival rates for prostate cancer.

Survival rate	no. of patients	Median and/or mean survival rate	OS (%)			CSS (%)			BPFS (%)			CPFS (%)		
			5 y	10 y	15 y	5 y	10 y	15 y	5 y	10 y	15 y	5 y	10 y	15 y
Yamada et al. (1994) (56)	57	Median, 5.4 y	91.2 (77.6 at 7.5 y)	-	-	-	-	-	45.5 (PSA > 0.4)	-	-	81.4	-	-
Gerber et al. (1997) (57)	242	Mean, 39 m Median, 26 m	-	-	-	85	57	-	-	-	-	72	32 (meta free)	-
Van den Ouden et al. (1998) (58)	83	Median, 52 m	75	60	-	85	72	-	29 (PSA > 0.1)	-	-	59	31	-
Isorna Martinez de la Riva et al. (2004) (59)	83	Mean, 68.7 m (cT3a only)	97.6	94.8	-	100	-	-	-	59.8 (PSA > 0.3)	-	-	-	-
Ward et al. (2005) (60)	841	Median, 10.3 y	90	76	53	95	90	79	58 (PSA > 0.4)	43	38	85	73	67
Hsu et al. (2007) (61)	200	Mean, 70.6 m (cT3a only)	95.9	77	-	98.7	91.6	-	59.5 (PSA > 0.2)	51.1	-	95.9	85.4	-

BPFS = biochemical progression-free survival; CSS = cancer-specific survival; CPFS = clinical progression-free survival; OS = overall survival; PSA = prostate-specific antigen.

9.4.2 High-grade PCa: Gleason score 8-10

Although most poorly differentiated tumours extend outside the prostate, the incidence of organ-confined disease is between 26% and 31%. Patients with high-grade tumours confined to the prostate

at histopathological examination still have a good prognosis after RP. Furthermore, one-third of patients with a biopsy Gleason score ≥ 8 may in fact have a specimen Gleason score ≤ 7 with better prognostic characteristics. The PSA value and percentage of positive prostate biopsies may help to select men with high-grade PCa most likely to benefit from RP (66).

9.4.3 PCa with PSA > 20

Yossepowitch et al. reported the results of RP as a monotherapy in men with PSA > 20 ng/mL in a cohort with mostly clinically organ-confined tumours and found a PSA failure rate of 44% and 53% at 5 and 10 years, respectively (51). 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 (67). Tiguert and co-workers presented the outcome for an identical cohort of patients who had a disease-free survival of 65% at 5 years after RP (68). More recently, Inman and co-workers described the long-term outcomes of RP with multimodal adjuvant therapy in men with PSA ≥ 50 . Systemic progression-free survival rates at 10 years were 83% and 74% for PSA 50-99 and ≥ 100 , respectively, while CSS was 87% for the whole group. These results argue for aggressive management with RP as the initial step (69).

- An eLND should be performed in all high-risk cases, as the estimated risk for positive lymph nodes will be in the range 15-40% (37). A limited lymph node dissection should no longer be performed, as this will miss at least half of the nodes involved.

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

9.5.1 cT3b-T4 N0

Men with very high-risk PCa generally have a significant risk of disease progression and cancer-related death if left untreated. Very high-risk patients present two specific challenges. There is a need for local control as well as a need to treat any microscopic metastases likely to be present but undetectable until disease progression. The optimal treatment approach will therefore often necessitate multiple modalities. The exact combinations, timing and intensity of treatment continue to be strongly debated. A recent US study showed that patients who underwent RP ($n = 72$) for cT4 disease had a better survival than those who received HT alone or RT alone and comparable survival to that of men who received RT plus HT (70).

Another study compared the outcomes of RP in very high-risk PCa (T3-T4 N0-1, N1, M1a) with those in localised PCa. The two groups did not differ significantly in surgical morbidity except for blood transfusion, operative time, and lymphoceles, which showed a higher rate in patients with advanced disease. Overall survival and CSS at 7 years were 76.69% and 90.2% in the advanced disease group and 88.4% and 99.3% in the organ-confined disease group, respectively (71).

Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, oncologists, radiologists and pathologists), and after the balance of benefits and side-effects of each therapy modality has been considered by the patient with regard to his own individual circumstances.

9.5.2 Any T, N1

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

Nevertheless, the combination of RP and early adjuvant hormonal treatment in N+ PCa has been shown to achieve a 10-year CSS rate of 80% (72,73). Most urologists are reluctant to perform RP for clinical N+ disease, or will cancel surgery if a frozen section shows lymph node invasion. However, a recent study has shown a dramatic improvement in CSS and OS in favour of completed RP versus abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and the abandonment of RP in node-positive cases may not be justified (74).

It should also be noted that the definitive pathological examination after RP could show microscopic lymph node invasion. The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only (75,76). In patients who prove to be pN+ after RP, early adjuvant HT has been shown to improve significantly 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 applied in the present era of increased detection of microscopic involvement as a result of more extensive lymph node dissection. The benefits should be judged against the

side-effects of long-term HT. Follow-up of PSA and HT in the case of an increase in PSA level is therefore an acceptable option in selected cases.

9.6 Summary of RP in high-risk localised disease

- RP is a reasonable treatment option in selected patients with cT3a PCa, Gleason score 8-10 or PSA > 20.
- If RP is performed, an extended pelvic lymphadenectomy must be performed, as lymph node involvement is common.
- The patient must be informed about the likelihood of a multimodal approach. In case of adverse tumour characteristics (positive section margin, extracapsular extension, seminal vesicle invasion), adjuvant RT may be reasonably used after recuperation from surgery.
 - o Recently, Thompson and colleagues reported the results of a trial enrolling 431 men with pT3N0M0 PCa treated with RP. Patients were randomised to receive 60-64 Gy adjuvant RT or observation. Metastasis-free survival and OS were significantly better with radiotherapy (77). In cases of positive lymph nodes at final histopathology, adjuvant ADT may be considered.
 - o Messing et al. examined the role of immediate ADT versus observation in patients with positive lymph nodes at initial surgery. At a median follow-up of 11.9 years, those receiving immediate ADT had a significant improvement in OS over those managed with observation (73).

9.7 Indication and extent of extended pelvic lymph node dissection (eLND)

Although it is generally accepted that eLND provides important information for prognosis (number of nodes involved, tumour volume within the lymph node, capsular perforation of the node) that cannot be matched by any other current procedure, consensus has not been reached as to when eLND is indicated and to what extent it should be performed. When making such decisions, many physicians rely on nomograms based on pre-operative biochemical markers and biopsies (33).

According to these nomograms, patients with a PSA value < 10 ng/mL and a biopsy Gleason score < 7 have a low risk of lymph node metastasis and, therefore, eLND might not be beneficial. However, the fact that most nomograms are based on a limited eLND (obturator fossa and external iliac vein) probably results in underestimation of the incidence of patients with positive nodes (37). Lymphography studies have shown that the prostate drains not only to the obturator and external iliac but also to the internal iliac and pre-sacral lymph nodes. Performing an eLND results in removal of all lymph nodes in these particular anatomical regions, producing a higher yield of removed lymph nodes (mean of 20 nodes) compared with limited LND (mean of 8-10 nodes).

In patients with a PSA value < 10 and a Gleason score ≥ 7 , an incidence of 25% nodal involvement was reported (78). Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (79,80). Clearly, the removal of a greater number of nodes results in improved staging. In the largest study of its kind, a cut-off ≤ 2 versus > 2 affected nodes was shown to be an independent predictor of CSS (75).

9.7.1 Conclusions

An extended pelvic lymph node dissection (eLND) is not necessary in low-risk, localised PCa, as the risk for positive lymph nodes does not exceed 7% (37).

An eLND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 7%, as well as in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes will be in the range 15-40% (37). A limited lymph node dissection should no longer be performed, as this will miss at least half of the nodes involved.

9.7.2 Extent of eLND

Extended pelvic lymph node dissection (eLND) includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa cranially and caudally to the obturator nerve, and the nodes medially and laterally to the internal iliac artery. According to lymph node mapping studies, some 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 (81). For an eLND to be representative, a mean of 20 lymph nodes should be removed (82). It is recommended that the nodes should be sent in separate containers per region for histopathology, as this will usually be associated with a higher diagnostic gain by the uro-pathologist.

9.7.3 Therapeutic role of eLND

Besides being a staging procedure, (extended) pelvic lymph node dissection can be curative, or at least beneficial, in a subset of patients with limited lymph node metastases (83-85). In some series, the number of nodes removed during lymphadenectomy correlated significantly with time to progression (86). In one population-based study with a 10-year follow-up, patients undergoing excision of at least four lymph nodes (node-positive and node-negative patients) or more than 10 nodes (only node-negative patients) had a lower risk of prostate cancer-specific death at 10 years than did those who did not undergo lymphadenectomy (87). Further studies should confirm these results.

9.7.4 Morbidity

Extended pelvic lymph node dissection remains a surgical procedure, which adds morbidity to the treatment of PCa. When comparing extended versus limited LND, threefold higher complication rates were reported by some authors (88). Complications consist of lymphocele, lymphoedema, deep venous thrombosis, and pulmonary embolism. Other authors, however, reported more acceptable complication rates (89,90).

9.7.5 Summary of eLND

- eLND may play a role in the treatment of a subset of intermediate-risk cases with > 7% nomogram predicted risk of positive lymph nodes, and in all high-risk cases.
- eLND may increase staging accuracy and influence decision-making with respect to adjuvant therapy.
- The number of lymph nodes removed correlates with the time to progression.
- Surgery-related morbidity has to be balanced against the therapeutic effects, and a decision will have to be made based on individual cases.

9.8 Neoadjuvant hormonal therapy and RP

Generally, neoadjuvant or up-front hormonal therapy is defined as therapy given prior to definitive local curative treatment (e.g. surgery or radiation therapy). As PCa is an androgen-dependent tumour, neoadjuvant hormonal therapy (NHT) is an appealing concept. Attempts to decrease the size of the prostate before RP were first reported by Vallett as early as 1944 (91). In a recent review and meta-analysis, the role of NHT and prostatectomy were studied (92). Neoadjuvant hormonal therapy prior to prostatectomy did not improve overall or disease-free survival, but did significantly reduce positive margin rates (relative risk [RR]: 0.49; 95% confidence interval [CI]: 0.42-0.56, $p < 0.00001$), organ confinement (RR: 1.63; 95% CI: 1.37-1.95, $p < 0.0001$) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, $p < 0.02$). Thus, the absence of improvement in clinically important outcomes (overall, disease-specific survival or biochemical disease-free survival) was demonstrated despite improvements in putative pathological surrogate outcomes, such as margin-free positive status. This calls into question the use of these pathological markers of treatment outcomes as valid surrogates for clinically relevant outcomes.

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

It is noteworthy that the Early Prostate Cancer Trialists' Group (EPC) trial was not included in the Cochrane review. The third update from this large randomised trial of bicalutamide, 150 mg once daily, in addition to standard care in localised and locally advanced, non-metastatic PCa was published in November 2005 (93). Median follow-up was 7.2 years. There was a significant improvement in objective progression-free survival in the RP group. This improvement was only statistically significant in the locally advanced disease group (hazards ratio [HR] 0.75; 95% CI: 0.61-0.91). There was no significant improvement in OS in the RP-treated groups (localised and locally advanced disease). In the WW group, there was an OS trend in favour of WW alone in the localised disease group (HR 1.16; 95% CI: 0.99-1.37).

9.8.1 Summary of neoadjuvant and adjuvant hormonal treatment and RP

- Neoadjuvant hormonal therapy before RP does not provide a significant OS advantage over prostatectomy alone.
- Neoadjuvant hormonal therapy before RP does not provide a significant advantage in disease-free survival over prostatectomy alone.
- Neoadjuvant hormonal therapy before RP does substantially improve local pathological variables such as organ-confined rates, pathological down-staging, positive surgical margins and rate of lymph node involvement.
- Adjuvant hormonal therapy following RP shows no survival advantage at 10 years.
- Adjuvant hormonal therapy following RP: the overall effect estimate for disease-free survival was highly statistically significant ($p < 0.00001$) in favour of the hormonal therapy arm.

9.9 Complications and functional outcome

The post-operative complications of RP are listed in Table 16. The mortality rate is 0-1.5% (87); urinary fistulas are seen in 1.2-4% of patients (94); and urinary incontinence persists after 1 year in 7.7% (95). In men undergoing prostatectomy, the rates of post-operative and late urinary complications are significantly reduced if the procedure is performed in a high-volume hospital and by a surgeon who performs a large number of such procedures (96-98). Erectile dysfunction used to occur in nearly all patients, but nerve-sparing techniques can be applied in early-stage disease (99). Patients who benefit from nerve-sparing RP may have a higher chance of local disease recurrence and should therefore be selected carefully.

Table 16: Complications of RP.

Complication	Incidence (%)
• Peri-operative death	0.0-2.1
• Major bleeding	1.0-11.5
• Rectal injury	0.0-5.4
• Deep venous thrombosis	0.0-8.3
• Pulmonary embolism	0.8-7.7
• Lymphocele	1.0-3.0
• Urine leak, fistula	0.3-15.4
• Slight stress incontinence	4.0-50.0
• Severe stress incontinence	0.0-15.4
• Impotence	29.0-100.0
• Bladder neck obstruction	0.5-14.6
• Ureteral obstruction	0.0-0.7
• Urethral stricture	2.0-9.0

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

Reference name	Sofer (100)	Walsh (101)	Alsikafi (102)	Graefen (103)	Bianco (104)
Pre-operative selection criteria					
• Stage > T2	+	+	+	+	+
• PSA > 10	+				
• Biopsy Gleason score 7			+		
• Biopsy Gleason score 8-10	+			+	
• Partin tables		+			+
• Side with > 50% tumour in biopsy			+		
• Side with perineural invasion		+/-	+		
Intra-operative selection criteria					
• Side of palpable tumour			+		
• Side of positive biopsy				+	
• Induration of lateral pelvic fascia		+			+
• Adherence to neurovascular bundles		+			+
Positive section margins	24%	5%	11%	15.9%	5%

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

Nerve-sparing RP can be performed safely in most men undergoing RP (104,105). 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 those patients in whom there is a high risk of extracapsular disease, such as any cT3 PCa, cT2c, any Gleason score > 7 on biopsy, or more than one biopsy > 6 at the ipsilateral side. Partin tables will help to guide decision-making (33).

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 lesion palpable close to the capsule during nerve-sparing RP. A wedge of the prostate can then be resected and inked differently. In case of presence of carcinoma adherent to the capsule on frozen section analysis, the NVB is resected; otherwise, the NVB remains *in situ*. In patients with intra-operatively detected tumour lesions during a nerve-sparing, planned RP, frozen section analysis objectively supports the decision of secondary NVB resection as well as preservation (106).

The patient must be informed before surgery about the risks of nerve-sparing surgery, the potency rates achieved by the surgeon, and the possibility that, to ensure adequate cancer control, the nerves may be sacrificed despite any pre-operative optimism favouring the potential for their salvage.

The early administration of intracavernous injection therapy could improve the definitive potency rates (107,108) and the significance of sural nerve transplant needs further multicentre study (109). Finally, the early use of PDE-5 inhibitors in penile rehabilitation remains controversial. A recent placebo-controlled prospective study showed no benefit from daily early administration of vardenafil versus on-demand vardenafil in the post-operative period (110), while another placebo-controlled prospective study showed sildenafil to have a significant impact on return of normal spontaneous erections (111).

9.11 Guidelines and recommendations for radical prostatectomy

Indications	LE
• In patients with low and intermediate risk localised PCa (cT1a-T2b and Gleason score 2-7 and PSA ≤ 20) and a life expectancy > 10 years	1b
Optional	
• Selected patients with low-volume high-risk localised PCa (cT3a or Gleason score 8-10 or PSA > 20)	3
• Highly selected patients with very high-risk localised PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment	3
Recommendations	
• Short-term (3 months) neoadjuvant therapy with gonadotrophin releasing-hormone analogues is not recommended in the treatment of stage T1-T2 disease	1a
• Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables/nomograms)	3
• Unilateral nerve-sparing procedures are an option in stage T2a disease	4

LE = level of evidence

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10. TREATMENT: DEFINITIVE RADIATION THERAPY

10.1 Introduction

There are no randomised studies comparing radical prostatectomy (RP) with either external beam radiation therapy (EBRT) or brachytherapy for localised prostate cancer. However, the National Institutes of Health (NIH) consensus set up in 1988 (1) remains available: external irradiation offers the same long-term survival results as surgery; moreover, EBRT provides a quality of life at least as good as that provided by surgery (2).

Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard and, at the beginning of the third millennium, intensity modulated radiotherapy (IMRT), an optimised form of 3D-CRT, is gradually gaining ground in centres of excellence.

In addition to external irradiation, there has been continued and growing interest in transperineal low-dose or high-dose brachytherapy. In localised and locally advanced prostate cancer (PCa), several randomised phase III trials conducted by radiation therapy scientific societies, such as the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC), have established the indications for the combination of external irradiation and androgen deprivation treatment (ADT).

Whatever the technique used, the choice of treatment – after the appropriate assessment of tumour extension – must be based on a multidisciplinary approach and should consider the following:

- 2002 and 2009 tumour node metastasis (TNM) classification;
- Gleason score defined on a sufficient number of core biopsies (at least 12);
- baseline prostate-specific antigen (PSA);
- age of the patient;
- patient's co-morbidity, life expectancy and quality of life;
- d'Amico's prognostic factor classification.

Obtaining a patient's consent is essential after giving full information regarding diagnosis, the therapeutic modalities, and morbidity. Additional information on the various aspects of radiotherapy in the treatment of prostate cancer is available in a newly published extensive overview (3).

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

Anatomical data, acquired by scanning the patient in a treatment position, are transferred to the 3D treatment planning system, which visualises the clinical target volume and then adds a (surrounding) safety margin. At the time of irradiation, a multi-leaf collimator automatically and, in the case of IMRT, continuously, adapts to the contours of the target volume seen by each beam. Real-time verification of the irradiation field by means of portal imaging allows for 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 increasing the risk of morbidity.

The use of IMRT is possible with linear accelerators equipped with the latest multileaf collimators and specific software. Movement of the leaves during the course of the irradiation 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 to spare the rectum.

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

10.3 Localised prostate cancer T1-2c N0, M0

10.3.1 T1a-T2a, N0, M0 and Gleason score ≤ 6 and PSA < 10 ng/mL (low-risk group)

Retrospective, non-randomised studies have shown that biochemical disease-free survival (BDFS) is significantly higher with a radiation dose ≥ 72 Gy compared with < 72 Gy ($p = 0.04$) (4).

Two randomised trials focused on clinical stages T1-3 N0 M0 paved the way for dose escalation:

- The MD Anderson study compared 78 Gy with 70 Gy conventional radiotherapy: it included 305 stage T1-3 patients with a pre-treatment PSA level of more than 10 ng/mL and, with a median follow-up of

8.7 years, showed a significant increase in freedom from biochemical and/or clinical failure for low-risk patients ($p = 0.04$) (5).

- The PROG 95-09 study evaluated 393 T1b-T2b patients, of whom 75% had a Gleason score ≤ 6 and a PSA < 15 ng/mL. Patients were randomised to receive an initial boost to the prostate alone, using conformal protons of either 19.8 Gy or 28.8 Gy, and then 50.4 Gy to a larger volume. With a median follow-up of 5.5 years, there was a significant increase in 5-year freedom from biochemical failure ($p < 0.001$) in favour of low-risk patients given a higher dose (79.2 Gy) versus those given a conventional dose (70.2 Gy) (6).

In daily practice, a minimum dose of ≥ 74 Gy is recommended (7).

10.3.2 T2b or PSA 10-20 ng/mL, or Gleason score 7 (intermediate-risk group)

Many non-randomised studies have shown that dose escalation (range, 76-81 Gy) has a significant impact on 5-year survival without biochemical relapse for patients classified as cT1c-T3 (4,8,9).

- A Dutch randomised phase III trial comparing 68 Gy with 78 Gy showed a significant increase in 5-year freedom from clinical or biochemical failure for patients in an intermediate-risk group (10).
- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in 306 patients with a pelvic lymph node involvement risk of $< 10\%$ (Partin) or pN0, with no hormonal therapy allowed before, during, or after radiotherapy. With a median follow-up of 59 months, a high dose should provide a better 5-year biological outcome in intermediate-risk patients, especially if the initial PSA > 15 ng/mL (11).
- Patients who are reluctant to accept short-term hormonal treatment (12) can receive definitive radiotherapy alone, provided that a dose escalation up to 78-80 (76-80 Gy) Gy is proposed.

10.3.3 T2c or Gleason score > 7 or PSA > 20 ng/mL (high-risk group)

External irradiation with dose escalation is mandatory since it improves the 5-year BDFS, as shown in several phase III randomised trials.

- A Dutch study comparing 68 Gy with 78 Gy showed a 10% increase in the 5-year freedom from clinical or biochemical failure ($p = 0.02$) (10).
- The MRC RT01 study, comparing a dose of 64 Gy with 74 Gy, both with neoadjuvant hormonal therapy, showed an 11% difference in 5-year BDFS (13).
- The PROG 95-09 study showed a significant increase in 5-year freedom from biochemical failure ($p < 0.02$) in favour of high-risk patients given a higher dose (79.2 Gy) versus those receiving a conventional dose (70.2 Gy) (10).
- An MD Anderson study showed a significant increase in freedom from biochemical and/or clinical failure for high-risk patients ($p = 0.004$) (5).
- The EORTC trial 22991, comparing 3D-CRT +/- IMRT with a choice of three levels of dose (70 Gy, 74 Gy or 78 Gy), with or without 6 months of neoadjuvant and concomitant hormonal therapy, was closed in April 2008 after recruiting 800 patients; its results are awaited (14).

In daily practice, a combination of external irradiation with short-term androgen deprivation therapy (ADT) is recommended, based on the results of a phase III randomised trial. The trial, which included 206 patients with a PSA level of at least 10 ng/mL (maximum 40 ng/mL), a Gleason score of at least 7 (range 5-10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with 6 months of ADT. After a median follow-up of 7.6 years, intermediate- or high-risk patients without moderate or severe co-morbidity, who had been randomised to receive 3D-CRT + ADT, showed a 13% improvement in overall survival rate ($p < 0.001$) (12). In contrast, there are data from the EORTC-22961 randomised phase III trial, comparing 36 months of hormonal treatment + radiotherapy with 6 months of hormonal treatment + radiotherapy, which showed that increased hormonal treatment improved overall survival in patients with high-risk PCa at 5 years (13).

10.3.4 Prophylactic irradiation of pelvic lymph nodes in high-risk localised PCa

Invasion of the pelvic lymph nodes is a poor prognostic factor and mandates systemic medical treatment because radiotherapy alone is insufficient (14). Prophylactic whole-pelvis irradiation has been abandoned since randomised trials failed to show that patients benefited from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77 06 study with 484 T1b-T2 patients (15), the Stanford study with only 91 patients (16), and the GETUG-01 trial, which included 444 T1b-T3 N0 pNx M0 patients (17). Pelvic lymphadenectomy may be needed to improve the selection of patients who might benefit from pelvic lymph node irradiation and to supplement the use of Partin's tables (18) and/or the Roach formula (19). The results of pelvic lymphadenectomy, particularly for young patients, will enable radiation oncologists to tailor both the planning target volume and the duration of ADT: specifically, no pelvic irradiation for pN0

patients, but pelvic irradiation for pN1 patients with long-term ADT.

10.4 Innovative techniques

10.4.1 Intensity modulated radiotherapy

Intensity modulated radiotherapy enables radiation oncologists to increase radiation doses homogeneously, up to as much as 86 Gy within the target volume, while respecting the tolerance doses in organs at risk. Certainly, IMRT is the only safe means of treatment delivery for dose escalation beyond 80 Gy using conventional 2 Gy fraction sizes, or for dose escalation using hypofractionated radiotherapy, in which there has been renewed interest. However, both treatment scenarios should be performed only within the confines of a properly designed clinical trial.

The Memorial Sloan-Kettering Cancer Center has the largest experience with this technique, and its results have now been updated, reporting on disease control and toxicity in two cohorts of patients.

- In the first cohort, 561 patients with organ-confined disease were treated with a dose of 81 Gy. The 8-year actuarial PSA relapse-free survival rates for patients in favourable-, intermediate- and unfavourable-risk groups were 85%, 76% and 72%, respectively, according to the then-current American Society for Radiation Oncology (ASTRO) definition (21).
- In the second cohort, 478 patients with organ-confined disease were treated with a dose of 86.4 Gy. The five-year actuarial PSA relapse-free survival according to the nadir plus 2 ng/mL definition was 98%, 85% and 70% for the low-, intermediate-, and high-risk groups, respectively (22).

To date, no randomised trials have been published comparing dose escalation using IMRT and 3D-CRT. However, several such trials are ongoing (UK NCRI, MD Anderson, Fox Chase, and Ottawa Health Research Institute), although one (Ottawa) is studying helical tomotherapy (see *below*), and two (NCRI and MD Anderson) are studying hypofractionated, dose-escalated radiotherapy.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of image-guided radiotherapy (IGRT), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear (23).

Another evolving technique for the delivery of IMRT is tomotherapy, 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 computed tomography (CT) scanning. Preliminary data suggest that this technique is feasible in PCa treatment (24).

10.4.2 Proton beam and carbon ion beam therapy

In theory, proton beams are an attractive alternative to photon beam radiotherapy for PCa because 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. Additionally, there is 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.

In practice, however, this has the disadvantage that dose distributions from protons are highly sensitive to changes in internal anatomy, such as might occur with bladder or rectal filling, and prostate proton therapy is usually delivered with lateral beams. It is also possible that high linear energy transfer (LET) radiation therapy using protons or carbon ions offers inherent biological advantages over photons, having more capacity for DNA damage dose-for-dose.

Only one randomised trial has incorporated proton therapy in one arm: the Loma Linda/Massachusetts General Hospital trial mentioned above compared standard-dose conformal radiotherapy with dose-escalated radiotherapy using protons for the boost dose (6). This trial cannot, however, be used as evidence for the superiority of proton therapy *per se*, as its use here could be viewed merely as a sophisticated method for dose escalation. In order to compare the efficacy of protons versus photons, a randomised trial using equivalent doses, comparing proton beam therapy with IMRT, would be needed, and such a study is under consideration by the RTOG.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing (25); the other study suggested a clearer advantage to protons (26). Further studies are clearly needed, and in the interim, proton therapy must be regarded as a promising, but experimental, alternative to photon beam therapy. Theoretically, proton therapy might be associated with a

lower risk of secondary cancers compared with IMRT, because of the lower integral dose of radiation, but there are no data in patients treated for PCa to support this.

Carbon ions offer similar theoretical advantages as protons, as an alternative to photon beam therapy. In a phase II study, 175 patients with T1-3, N0-1, M0 PCa were treated with carbon ions in a dose equivalent to 66 Gy in 20 fractions over 5 weeks (27). Treatment appeared to be well tolerated, with no RTOG grade 3 or 4 bowel or genitourinary toxicity, and an overall four-year BDFR of 88% (26). As with protons, a randomised trial comparing carbon ions with IMRT and using equivalent doses is required.

10.5 Transperineal brachytherapy

Transperineal brachytherapy is a safe and effective technique that generally requires fewer than 2 days of hospitalisation. There is consensus on the following eligibility criteria:

- stage cT1b- T2a N0, M0;
- a Gleason score ≤ 6 assessed on a sufficient 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 ≤ 12 (IPSS) (28).

Patients with low-risk PCa are the most suitable candidates for low-dose rate (LDR) brachytherapy. Further guidelines on the technical aspects of brachytherapy have been published recently, and are strongly recommended (29).

In 1983, Holm et al. described the transperineal method with endorectal sonography in which the patient is positioned in a dorsal decubitus gynaecological position (30). Implantation is undertaken under general anaesthesia or spinal block, and involves a learning curve for the whole team: the surgeon for delineation of the prostate and needle placement, the physicist for real-time dosimetry, and the radiation oncologist for source loading. The sonography probe introduced into the rectum is fixed in a stable position.

There are no randomised trials comparing brachytherapy with other curative treatment modalities, and outcomes are based on unrandomised case series. Results of permanent implants have been reported from different institutions, with a median follow-up ranging between 36 and 120 months (31). Recurrence-free survival after 5 and 10 years was reported to range from 71% to 93% and from 65% to 85%, respectively (32-39).

A significant correlation has been shown between the implanted dose and recurrence rates (40). Patients receiving a D90 of > 140 Gy demonstrated a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at 4 years than patients receiving less than 140 Gy (92% vs 68%). There is no benefit from adding neoadjuvant or adjuvant ADT to LDR brachytherapy (31).

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implant transurethral resection of the prostate (TURP) (up to 8.7%), and incontinence (0-19%). A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity (41). 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 symptoms prior to brachytherapy. Previous TURP for benign prostatic hyperplasia increases the risk of post-implant incontinence and urinary morbidity.

Brachytherapy-induced rectal morbidity with grade II/III proctitis occurs in 5-21% of patients. Erectile dysfunction develops in about 40% of patients after 3-5 years. In a recent retrospective analysis of 5,621 men who had undergone LDR brachytherapy (42), 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 cases of permanent implants, iodine-125 in granular form is the radio-element of reference, while palladium-103 may be used for less differentiated tumours with a high doubling time. The dose delivered to the planning target volume is 160 Gy for iodine-125, and 120 Gy for palladium-103. A Gleason score of 7 remains a 'grey area', but patients with a Gleason score of 4 + 3 show no difference in outcome (43).

A small randomised trial has suggested that the use of stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice (44).

In cases of intermediate- or high-risk localised PCa, brachytherapy in combination with supplemental external irradiation (45) or neoadjuvant hormonal treatment (46) may be considered.

The optimum dose of supplemental EBRT is unclear. A randomised trial comparing 44 Gy with 20 Gy of EBRT + palladium-103 brachytherapy closed early, showing no difference in biochemical outcomes (47).

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 (48). Higher doses of supplemental EBRT than this may best be delivered with IMRT; a report from Memorial Sloan-Kettering indicates that this approach is safe and feasible (49).

Recent data suggest an equivalent outcome in terms of BDFS compared with high-dose EBRT (HD EBRT) (50). In a retrospective analysis of modern series (51,52), BDFS rates of 85.8%, 80.3% and 67.8% in men with low-, intermediate- and high-risk PCa, respectively, are reported after a mean follow-up of 9.43 years.

Quality-of-life changes are similar between high-dose EBRT and high-dose rate (HDR) brachytherapy in terms of diarrhoea and insomnia (53). However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs 34%). A single randomised trial of EBRT versus EBRT + HDR brachytherapy has been reported (54). 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. Compared to EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in biochemical relapse-free survival ($p = 0.03$). There were no differences in the rates of late toxicity. Patients randomised to EBRT + brachytherapy had a significantly better quality of life 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 (54). There is still a need to compare dose-escalated EBRT + hormone therapy, with the same followed by a brachytherapy boost, in intermediate- and high-risk patients.

For T1-2 N0 M0 disease, the 5-year biochemical failure rates are similar for permanent seed implantation, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and RP, according to a study of 2,991 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 of 1-year follow-up (50).

10.6 Late toxicity

Patients must be informed about the potential late genitourinary or gastrointestinal toxicity that may occur, as well as the impact of irradiation on erectile function. Late toxicity was analysed using a dose of 70 Gy in the prospective EORTC randomised trial 22863 (1987-1995) (55), in which 90% of patients were diagnosed as stage T3-4. A total of 377 patients (91%) out of 415 enrolled were evaluable for long-term toxicity, graded according to a modified RTOG scale. Eighty-six (22.8%) patients had grade ≤ 2 urinary or intestinal complications or leg oedema, of which 72 had grade 2 (moderate) toxicity, 10 had grade 3 (severe) toxicity, and four died due to grade 4 (fatal) toxicity. Although four (1%) late treatment-related deaths occurred, long-term toxicity was limited, with fewer than 5% grade 3 or 4 late complications being reported (Table 17). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT or IMRT.

Table 17: Incidence of late toxicity by RTOG grade (from EORTC trial 22863).

Toxicity	Grade 2		Grade 3		Grade 4		Any significant toxicity (> grade 2)	
	No.	%	No.	%	No.	%	No.	%
Cystitis	18	4.7	2	0.5	0	0	20	5.3
Haematuria	18	4.7	0	0	0	0	18	4.7
Urinary stricture	18	4.7	5	1.3	4	1	27	7.1
Urinary incontinence	18	4.7	2	0.5	0	0	20	5.3
Overall GU toxicity	47	12.4	9	2.3	4[†]	1[†]	60	15.9
Proctitis	31	8.2	0	0	0	0	31	8.2
Chronic diarrhoea	14	3.7	0	0	0	0	14	3.7
Small bowel obstruction	1	0.2	1	0.2	0	0	2	0.5
Overall GI toxicity	36	9.5	1	0.2	0	0	37	9.8
Leg oedema	6	1.5	0	0	0	0	6	1.5
Overall toxicity*	72	19.0	10	2.7	4	1	86	22.8

GU = genitourinary; GI = gastrointestinal.

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

[†] Two of the grade 4 patients were irradiated with cobalt-60.

Note: There was no other significant (\leq grade 2) toxicity among patients irradiated with cobalt-60 ($n = 15$) except for two patients with grade 4 genitourinary toxicity (stated above) and only one patient with grade 2 gastrointestinal toxicity.

Radiotherapy affects erectile function to a lesser degree than surgery according to retrospective surveys of patients (2). A recent meta-analysis has shown that the 1-year rate of probability for maintaining erectile function was 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing radical prostatectomy, and 0.25 after standard radical prostatectomy.

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 (56).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (57,58). 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 1.7-fold in comparison with the surgery group (57). Another analysis (58) showed that the relative risk of developing bladder cancer increased by 2.34-fold compared with a healthy control population. On the other hand, a re-analysis of the SEER-data with 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 (59).

Corresponding data on late toxicity has also been reported by the Memorial Sloan-Kettering Cancer Center group, from its experience in 1571 patients with T1-T3 disease treated with either 3D-CRT or IMRT in doses of between 66 Gy and 81 Gy, with a median follow-up of 10 years (59). Both acute GI and GU toxicity appeared to predict for corresponding late toxicity. The overall rates of NCIC-CTC grade 2 or more GI toxicity was 5% with IMRT, compared with 13% with 3D-CRT. The incidence of grade 2 or more late GU toxicity was 20% in patients treated with 81 Gy, compared with 12% in patients treated with lower doses. The overall incidence of grade 3 GI toxicity was 1%, and grade 3 GU toxicity was 3%. These data suggest that IMRT can successfully protect against late GI toxicity, but, interestingly, with dose escalation, GU toxicity may become the dominant morbidity (60).

10.7 Immediate post-operative external irradiation for pathological tumour stage T3 N0 M0

Extracapsular invasion (pT3) is associated with a risk of local recurrence, which can be as high as 30% (61). In a multifactorial analysis, the predictors of biochemical relapse are:

- PSA level ($p = 0.005$);
- Gleason score of the surgical specimen ($p = 0.002$);
- positive surgical margins ($p < 0.001$) (62).

Three prospective randomised trials have assessed the role of immediate post-operative radiotherapy.

The EORTC study 22911, 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 proved to be well tolerated, with a risk of grade 3-4 urinary toxicity of less than 3.5% (63), without significant differences regarding the rate of incontinence and/or stricture of anastomosis (64). The study concludes that immediate post-operative radiotherapy after surgery significantly improves 5-year clinical or biological survival: 72.2% versus 51.8% ($p < 0.0001$) (65). After re-evaluation by central pathological review, the highest impact (30%) was seen in patients with positive margins (R1), but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors (66,67).

However, the EORTC study has not yet demonstrated improved metastasis-free and cancer-specific survival in this cohort of patients. The most suitable candidates for immediate radiation therapy might be those with multifocal positive surgical margins and a Gleason score > 7 . The conclusions of the ARO trial 96-02 ($n = 385$) appear to support those of the EORTC study. After a median follow-up of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical progression-free survival of 72% versus 54%, respectively ($p = 0.0015$). However, of major interest and in contrast to other studies, patients were randomised after achieving an undetectable PSA after RP (< 0.1 ng/mL) and only pT3-tumours were included. This finding indicates that adjuvant radiotherapy works even in the setting of an undetectable PSA after RP and additional risk factors (67).

On the other hand, the SWOG 8794 trial randomised 425 pT3 patients, and the updated results, with a median follow-up of more than 12 years, showed that adjuvant radiation significantly improved metastasis-free survival, with a 10-year metastasis-free survival of 71% versus 61% (median: 1.8 years prolongation, $p = 0.016$) and a 10-year overall survival of 74% versus 66% (median: 1.9 years prolongation, $p = 0.023$) (67,68).

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 within the framework of an informed consent:

- *either* an immediate radiotherapy to the surgical bed (66) upon recovery of urinary function
- *or* clinical and biological monitoring followed by salvage radiotherapy when the PSA exceeds 0.5 ng/mL (70,71).

Early salvage radiotherapy provides the possibility of cure to patients with an increasing PSA after RP. More than 60% of patients who are treated before the PSA level rises to more than 0.5 ng/mL will achieve an undetectable PSA level again (70,71), so providing patients with the chance of about 80% being progression-free 5 years later (71). A retrospective analysis based on 635 patients undergoing RP from 1982-2004, followed up through to December 2007, who experienced biochemical and/or local recurrence and received no salvage treatment [397] or salvage radiotherapy alone [160] within 2 years of biochemical recurrence, has shown that salvage radiotherapy was associated with a threefold increase in prostate cancer-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage radiotherapy has also been effective in patients who have a rapid PSA-doubling time (72).

These two approaches, together with the efficacy of neoadjuvant hormone therapy, are currently being compared in the UK MRC RADICALS randomised trial. The role of short-term hormone therapy in combination with radiotherapy is being investigated in the EORTC 22043 randomised trial.

10.8 Locally advanced PCa: T3-4 N0, M0

The incidence of locally advanced PCa has declined as a result of individual or mass screening. Pelvic lymph node irradiation is optional for N0 patients, but the results of radiotherapy alone are very poor (73,74). Because of the hormonal dependence of PCa (75), ADT has been combined with external irradiation with the aim of:

- reducing the risk of distant metastases by potentially sterilising micrometastases already present at the moment of diagnosis;
- decreasing the risk of non-sterilisation and/or local recurrence as a source of secondary metastases (74) through the effect of radiation-induced apoptosis (76,77).

Numerous randomised trials have confirmed the value of long-term administration.

10.8.1 Neoadjuvant and concomitant hormonal therapy

The RTOG study 86-10 included 471 patients with bulky (5 x 5 cm) tumours T2-4N0-X M0. Androgen

deprivation therapy was administered 2 months before irradiation and during irradiation, or in the case of relapse in the control arm. Thirty-two per cent of patients were diagnosed as T2, 70% as T3-4, and 91% as N0. The hormone treatment consisted of oral eulexine, 250 mg three times daily, and goserelin acetate (Zoladex), 3.6 mg every 4 weeks by subcutaneous injection. The pelvic target volume received 45 Gy, and the prostatic target volume received 20-25 Gy. The 10-year overall survival estimates were 43% for ADT + irradiation versus 34% for hormonal treatment, though the difference was not significant ($p = 0.12$). There was a significant improvement in the 10-year disease-specific mortality (23% vs 36%; $p = 0.01$), disease-free survival (11% vs 3%; $p < 0.0001$) and in biochemical failure (65% versus 80%; $p < 0.0001$), with the addition of ADT having no statistical impact on the risk of fatal cardiac events (78).

10.8.2 Concomitant and long-term adjuvant hormonal therapy

The EORTC study 22863 recruited 415 patients diagnosed with T1-2 grade 3 WHO (World Health Organization) or T3-4 N0 M0 and any histological grade, and compared radiotherapy + adjuvant ADT, with radiotherapy alone. The use of ADT was allowed in cases of relapse. A total of 82% of patients was diagnosed as T3, 10% as T4, and 89% as N0.

Hormonal treatment consisted of oral cyproterone acetate (CPA), 50 mg three times daily for 1 month, beginning 1 week before the start of radiotherapy, and goserelin acetate (Zoladex), 3.6 mg subcutaneously every 4 weeks for 3 years, starting on the first day of radiotherapy. The pelvic target volume received was 50 Gy, and the prostatic target volume was 20 Gy. With a median follow-up of 66 months, combination therapy compared with radiotherapy alone yielded significantly better survival (78% vs 62%, $p = 0.001$) (79). At a median follow-up of 9.1 years, the 10-year overall survival remained significantly higher – 58.1% vs 39.8% ($p < 0.0001$) – as did clinical progression-free survival – 47.7% vs 22.7% ($p < 0.0001$). The 10-year cumulative incidence of PCa mortality was 11.1% versus 31% ($p < 0.0001$), and the 10-year cumulative incidence of cardiovascular mortality was 11.1% versus 8.2% ($p = 0.75$) (80).

10.8.3 Long-term adjuvant hormonal therapy

The RTOG study 85-31 recruited 977 patients diagnosed with T3-4 N0-1 M0, or pT3 after RP. Androgen deprivation therapy was begun in the last week of irradiation and continued up to relapse (Group I) or was started at recurrence (Group II). A total of 15% of patients in Group I and 29% in Group II had undergone RP, while 14% of patients in Group I and 26% in Group II were pN1.

Goserelin acetate, 3.6 mg subcutaneously, was administered every 4 weeks. The pelvis was irradiated with 45 Gy, while the prostatic bed received 20-25 Gy. Patients diagnosed with stage pT3 received 60-65 Gy. With a median follow-up time of 7.6 years for all patients, the 10-year overall survival was significantly greater for the adjuvant arm, at 49% versus 39% ($p = 0.002$) (81).

The results are awaited from another long-term comparison study – The National Cancer Institute (NCI) of Canada/Medical Research Council intergroup PR3/PR07 study – in which patients diagnosed with stage cT3-4 N0 M0 have been treated with complete androgen blockade (CAB) (goserelin acetate 3.6 mg subcutaneously every 4 weeks and flutamide 750 mg/day) alone versus CAB + radiation 65-69 Gy (82,83).

The SPCG-7/SFUO-3 randomised study (84) compared hormonal treatment alone (i.e. 3 months of CAB followed by continuous flutamide treatment ($n = 439$ patients) with the same treatment combined with radiotherapy [436 patients]. After a median follow-up of 7.6 years, the 10-year cumulative incidence for prostate cancer-specific mortality was, respectively, 23.9% and 11.9% (95% CI: 4.9-19.1), and the 10-year cumulative incidence for overall mortality was 39.4% in the hormonal treatment-only group, and 29.6% in the hormonal + radiotherapy group (95% CI: 0.8-18%).

10.8.4 Neoadjuvant, concomitant and long-term adjuvant hormonal therapy

The RTOG 92-02 trial closed in 1995 after accruing 1,554 patients. Statistically significant improvements were observed in actuarial biochemical freedom from disease control, distant metastatic failure, local control, and disease-free survival in patients receiving long-term ADT (before, during, and 2 years after radiotherapy), compared with short-term androgen deprivation (2 months before and during radiotherapy). With a median follow-up of 11.27 years of all survival patients, the long-term ADT arm showed significant improvement over the short-term ADT arm in all efficacy endpoints, except 10-year overall survival, which was 51.6% versus 53.9% ($p = 0.36$), respectively. In a subset of patients that was not part of the original study design, with Gleason score 8-10 tumours, the long-term ADT arm showed significantly better overall survival after 10 years than the short-term ADT arm, with 45% versus 32% ($p = 0.006$) (85).

10.8.5 Short-term or long-term adjuvant hormonal treatment

Following the EORTC trial 22863, the EORTC equivalence trial 22961 was set up to test whether similar survival could be achieved in patients who underwent irradiation (to 70 Gy) and 6 months of combined ADT without further ADT, i.e. short-term ADT arm, compared with patients with 2.5 years of further treatment with luteinising hormone-releasing hormone analogue (LHRHa), i.e. long-term ADT arm. Eligible patients had T1c-2b N1-2 or pN1-2, or T2c-4 N0-2 (UICC 1992) M0 PCa with PSA < 150 ng/mL.

Non-inferior survival was defined as a mortality hazard ratio (HR) = 1.35 for short-term ADT versus long-term ADT. A total of 970 patients were randomised. With a 5.2-year median follow-up, the 5-year overall survival rate was 85.3% on long-term ADT, and 80.6% on short-term ADT (HR = 1.43; 96.4% CI; 1.04-1.98), and failed to prove non-inferiority (86).

10.8.6 Dose escalation with hormonal therapy

For bulky locally advanced PCa, there might be a role for dose escalation as suggested by the excellent results of a retrospective series by the Memorial Sloan-Kettering Cancer Center devoted to 296 patients: 130 cT3a N0-X M0 and 166 cT3bN0-X M0. The prescribed doses to the prostate gland ranged from 66 Gy to 86.4 Gy; 95 patients received IMRT with dose escalation beyond 81 Gy. Androgen deprivation therapy was given for 3 months prior to radiotherapy to 189 patients (64%), and was continued during the course of radiotherapy for patients with high-grade disease. With a median follow-up of 8 years, the 5- and 10-year overall survival and cause-specific survival were, respectively, 91% and 65%, and 95% and 83% (87).

10.9 Very high-risk PCa: c or pN1, M0

Patients with a pelvic lymph node involvement lower than the iliac regional nodes, younger than 80 years old, with a WHO performance status 0-1, and no severe co-morbidity may be candidates for EBRT plus immediate long-term hormonal manipulation. The RTOG 85-31 randomised phase III trial has shown, with a median follow-up of 6.5 years, that 95 patients out of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better 5- and 9-year progression-free survival (PSA < 1.5 ng/mL), with 54% and 10% respectively versus 33% and 4% with radiation alone and hormonal manipulation instituted at the time of relapse ($p < 0.0001$). Multivariate analysis revealed this combination as having a statistically significant impact on overall survival, disease-specific failure, metastatic failure and biochemical control (88).

10.10 Summary of definitive radiation therapy

		LE
•	In localised prostate cancer T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention. There is fairly strong evidence that low-, intermediate- and high-risk patients benefit from dose escalation	1a
	For patients in the high-risk group, short-term ADT prior to and during radiotherapy results in increased overall survival, but three years of adjuvant ADT are better according to the results of EORTC 22961	2a
•	Transperineal interstitial brachytherapy with permanent implants is an option for patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS	2b
•	Immediate post-operative external irradiation after RP for patients with pathological tumour stage T3 N0 M0 improves overall survival, biochemical and clinical disease-free survival with the highest impact in cases of positive margins (R1)	1b
	An alternative option is to give radiation at the time of biochemical failure, but before PSA rises above 0.5 ng/mL	3
•	In locally advanced prostate cancer T3-4 N0 M0, overall survival is improved by concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external beam irradiation for patients with a WHO 0-2 performance status.	1a
	For a subset of patients with T2c-T3 N0-x and a Gleason score of 2-6, short-term ADT before and during radiotherapy may favourably influence overall survival	1b
•	In very high-risk prostate cancer, c-pN1 M0 with no severe co-morbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment improve overall survival, disease-specific failure, metastatic failure and biochemical control	2b

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11. EXPERIMENTAL LOCAL TREATMENT OF PROSTATE CANCER

11.1 Background

Besides radical prostatectomy (RP), external beam radiation and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) have emerged as alternative therapeutic options in patients with clinically localised PCa (1-4).

Whereas HIFU is still considered to be an experimental treatment, CSAP has been recognised as a true therapeutic alternative according to the guidelines of the American Urological Association. Both HIFU and CSAP have been developed as minimally invasive procedures, which have potentially the same therapeutic efficacy as established surgical and non-surgical options with reduced therapy-associated morbidity.

11.2 Cryosurgery of the prostate (CSAP)

Cryosurgery uses freezing techniques to induce cell death by:

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

Freezing of the prostate is ensured by placement of 12 to 15 17G-cryoneedles under transrectal ultrasound (TRUS) guidance, placement of thermosensors at the level of the external sphincter and the 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.

11.2.1 Indication for CSAP

Patients who are ideal candidates for CSAP are those who have organ-confined PCa and those identified as having minimal tumour extension beyond the prostate (1-3). The prostate should be ≤ 40 mL in size. Prostate glands > 40 mL should be hormonally downsized in order to avoid any technical difficulty in placing cryoprobes under the pubic arch. Prostate-specific antigen (PSA) serum levels should be < 20 ng/mL, and the biopsy Gleason score should be < 7 . It is important that patients with a life expectancy > 10 years should be fully informed that there are no data, or only minimal data, on the long-term outcome for cancer control at 10 and 15 years.

11.2.2 Results of modern cryosurgery for PCa

When comparing treatment modalities, it is important to bear in mind that, in modern RP series of patients with clinically organ-confined PCa, there is a very low risk (2.4%) of dying from PCa at 10 years after surgery (5). Therapeutic results have improved over time with enhanced techniques, such as gas-driven probes and transperineal probe placement, as used in third-generation cryosurgery (6-11).

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, while others use the American Society of Therapeutic Radiology and Oncology (ASTRO) criteria, which requires three consecutive increases in PSA level.

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, biochemical disease-free survival (BDFR) at 5 years is 60% and 36% for low-risk and high-risk patients, respectively (6,7).

Long et al. (6) 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 5-year actuarial BDFR 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.

However, according to a recent meta-analysis of 566 cryosurgery-related publications, there were no controlled trials, no survival data and no validated biochemical surrogate end-points available for analysis (12). Cryosurgery showed a progression-free survival (PFS) of 36-92% (projected 1- to 7-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72-87%, 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%) of patients (6-11). Of these, 80 (73%) patients still had a PSA nadir < 0.4 ng/mL, while 42/65 (64.6%) low-risk patients remained free from biochemical progression using the 0.4 ng/mL cut-off.

A longer follow-up was reported by Bahn et al. (9), who 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 7-year BDFR for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively.

Nerve-sparing cryosurgery, as reported recently (13), must still be considered an experimental therapeutic option. Nerve-sparing surgery was performed in nine patients with unilateral PCa confirmed on repeated biopsies; CSAP was carried out on the side of the positive biopsy, while the negative biopsy side was spared from freezing.

11.2.3 Complications of CSAP for primary treatment of PCa

Erectile dysfunction occurs in about 80% of patients and remains a consistent complication of the CSAP procedure, independent of the generation of the system used. The complication rates described with the third generation of cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% (6-11). The development of fistula is usually rare, being less than 0.2% in modern series. About 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.

Quality of life and sexuality following CSAP have been investigated in a clinical phase II trial recruiting 75 men (14). Quality-of-life analysis by the prostate-specific FACT-P questionnaire revealed that most subscales had returned to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes were determined when comparing data at 36 months with data obtained at 12 months. With regard to sexuality, 37% of men were able to have intercourse at 3 years after CSAP.

In a recent, 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 (15). After a follow-up of 3 years, sexual function was significantly less impaired following EBRT.

11.2.4 Summary of CSAP

- Patients with low-risk PCa (PSA < 10 ng/mL, \leq T2a, Gleason score \leq 6) or intermediate-risk PCa (PSA > 10 ng/mL, or Gleason score \geq 7, or stage \geq 2b) represent potential candidates for CSAP.
- Prostate size should be < 40 mL at the time of therapy.
- Long-term results are lacking, while 5-year BDFR rates are inferior to those achieved by RP in low-risk patients. Patients must be informed accordingly.

11.3 HIFU of the prostate

High-intensity focused ultrasound consists of focused ultrasound waves emitted from a transducer, which cause tissue damage by mechanical and thermal effects as well as by cavitation (16). The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis.

High-intensity focused ultrasound is performed under general or spinal anaesthesia, with the patient lying in the lateral position. The procedure is time-consuming, with about 10 g prostate tissue treated per hour. In a recent review, 150 papers related to HIFU were identified and evaluated with regard to various oncological

and functional outcome parameters (12). No controlled trial was available for analysis, and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy.

11.3.1 Results of HIFU in PCa

As with CSAP, it appears to be difficult to interpret oncological outcome in patients undergoing HIFU since various PSA thresholds are defined and no international consensus exists on objective response criteria. The results of HIFU are limited, with outcome data from less than 1,000 PCa cases published in the literature.

According to the recent review mentioned above (12), HIFU showed PFS (based on PSA +/- biopsy data) of 63-87% (projected 3- to 5-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) (17). The projected 5-year BDFR 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% to 9% and 6%, respectively. In one of the studies (18), 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 another study (19), a complete response rate (i.e. PSA < 4 ng/mL) and six negative biopsies were achieved in 56% of the patients.

Summarising the efficacy results of a European multicentre study comprising the data of 559 patients with mainly low- and intermediate-risk PCa, Thüroff et al. (19) reported a negative biopsy rate of 87.2% in 288 men with a follow-up of at least 6 months. A PSA nadir after 6 months' follow-up could be determined in 212 patients, and was as high as 1.8 ng/mL. However, following the initial procedure, it could be demonstrated that the PSA nadir might be reached at 12-18 months.

Blana et al. reported on the results of 146 patients undergoing HIFU with a mean follow-up of 22.5 months (20). The mean PSA level at initiation of therapy was 7.6 ng/mL; the PSA nadir achieved after 3 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 appears to be strongly associated with treatment failure (21) ($p < 0.001$). Patients with a PSA nadir of 0.0-0.2 ng/mL have 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 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 disease-free survival rate at 5 years was 66%, with salvage treatment initiated in 12% of patients (22).

In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU (23). Biochemical failure was defined as the PSA nadir + 2 ng/mL according to the Phoenix guidelines with regard to radiation therapy. After a median follow-up of 24 months, the BDFR was 72% for the entire cohort. The BDFR in patients with stage T1c, T2a, T2b, T2c and T3 groups at 5 years was 74%, 79%, 72%, 24% and 33%, respectively ($p < 0.0001$). The BDFR in patients in the low-, intermediate- and high-risk groups at 5 years were 84%, 64% and 45%, respectively ($p < 0.0001$). The BDFR in patients treated with or without neoadjuvant hormonal therapy at 7 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.

11.3.2 Complications of HIFU

Urinary retention appears to be one of the most common side-effects of HIFU, developing in almost all patients, with the mean interval of catheterisation via a suprapubic tube varying between 12 and 35 days (16-18). 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 will occur in approximately 55-70% of patients.

11.4 Focal therapy of PCa

During the past two decades, there has been a trend towards earlier diagnosis of PCa due to 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 with smaller tumours at an earlier stage, which occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease (24-26).

Most focal therapies to date have been achieved with ablative technologies; cryotherapy, HIFU or with photodynamic therapy. So far, three groups have proposed that non-diseased prostate tissue be left untreated in both the hope and expectation that genitourinary function might be preserved and the tumour treated adequately (27-29). Although focal therapy is currently not the standard treatment for men with organ-confined PCa, it is the therapeutic approach with the most important future potential.

11.4.1 Pre-therapeutic assessment of patients

The high random and systematic errors associated with TRUS-guided biopsy regimens mean that this procedure is not sufficiently accurate for selecting candidates for focal therapy. The current standard for characterising men considering focal therapy is transperineal prostate biopsy using a template-guided approach (30,31). When used with a 5-mm sampling frame, this approach can rule-in and rule-out PCa foci of 0.5 mL and 0.2 mL volume with 90% certainty (32). Thus the exact anatomical localisation of the index lesion – defined as the biologically most aggressive lesion – can be accurately determined.

11.4.2 Patient selection for focal therapy

The primary objective of treatment must be the eradication of measurable and biologically aggressive disease. However, although treatment is usually intended to be a one-off therapy, patients should know that further treatment might be necessary in the future.

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. However, a state-of-the-art multifunctional MRI with TRUS biopsy at expert centres may be acceptable.
- Focal therapy should be limited to patients with a low to moderate risk. The tumour's clinical stage should be \leq cT2a and the radiological stage \leq cT2b.
- Patients with previous prostate surgery should be counselled with caution because no data on functional and oncological outcomes are available. Patients who have undergone radiation therapy of the prostate are not candidates for focal therapy.
- Patients must be informed that the therapy is still experimental and that there is a possibility of repeat (re-do) treatment.

11.5 Summary of experimental therapeutic options to treat clinically localised PCa

Recommendation	GR
CSAP has evolved from an investigational therapy to a possible alternative treatment for PCa in patients who are unfit for surgery or with a life expectancy < 10 years	C
All other minimally invasive treatment options – such as HIFU microwave and electro-surgery – are still experimental or investigational. For all of these procedures, a longer follow-up is mandatory to assess their true role in the management of PCa	
Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials	C

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12. HORMONAL THERAPY

12.1 Introduction

In 1941, Huggins and Hodges assessed the favourable effect of surgical castration and oestrogen administration on the progression of metastatic prostate cancer (PCa). They demonstrated for the first time the responsiveness of PCa to androgen deprivation (1,2).

Since Huggins and Hodges' pivotal studies, androgen-suppressing strategies have become the mainstay of management of advanced PCa. More recently, however, there has been a move towards the increasing use of hormonal treatment in younger men with earlier disease (i.e. non-metastatic) or recurrent disease after definitive treatment, either as the primary single-agent therapy or as a part of a multimodality approach (3).

Even if hormonal treatment effectively palliates the symptoms of advanced disease, there is no conclusive evidence at present that it extends life.

12.1.1 Basics of hormonal control of the prostate

Prostate cells are physiologically dependent on androgens to stimulate growth, function and proliferation. Testosterone, although not tumorigenic, is essential for the growth and perpetuation of tumour cells (4). The testes are the source of most of the androgens, with only 5-10% (androstenedione, dihydroepiandrosterone and dihydroepiandrosterone sulphate) being derived from adrenal biosynthesis.

Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. The hypothalamic luteinising

hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). Luteinising hormone stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cells, testosterone is converted by the enzyme 5- α -reductase into 5- α -dihydrotestosterone (DHT), which is an androgenic stimulant about 10 times more powerful than the parent molecule (5). Circulating testosterone is peripherally aromatised and converted into oestrogens, which together with circulating androgens, exert a negative feedback control on hypothalamic LH secretion.

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

12.1.2 Different types of hormonal therapy

Androgen deprivation can be achieved by:

- suppressing the secretion of testicular androgens by surgical or medical castration

or

- inhibiting the action of the circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens.

In addition, these two methods of androgen deprivation can be combined to achieve what is commonly known as complete (or maximal or total) androgen blockade (CAB).

12.2 Testosterone-lowering therapy (castration)

12.2.1 Castration level

Surgical castration is still considered the 'gold standard' for ADT against which all other treatments are rated. Removal of the testicular source of androgens leads to a considerable decline in testosterone levels and induces a hypogonadal status, although a very low level of testosterone (known as the 'castration level') persists.

The standard castrate level is < 50 ng/dL. It was defined more than 40 years ago, when testosterone level testing was limited. However, according to current testing methods using chemiluminescence, the mean value of testosterone after surgical castration is 15 ng/dL (6). This has led to a revisiting of the current definition of castration, with some authors suggesting a more appropriate level to be < 20 ng/dL.

12.2.2 Bilateral orchiectomy

Bilateral orchiectomy, either total or by means of a subcapsular technique (i.e. with preservation of tunica albuginea and epididymis), is a simple and virtually complication-free surgical procedure easily performed under local anaesthesia (7). It is the quickest way to achieve a castration level, usually within less than 12 hours.

The main drawback of orchiectomy is that it may have a negative psychological effect: some men consider it to be an unacceptable assault on their manhood. In addition, it is irreversible and does not allow for intermittent treatment. The use of bilateral orchiectomy has declined recently, probably because of stage migration towards earlier disease and the introduction of equally effective pharmacological modalities of castration (8).

12.3 Oestrogens

Oestrogens have several mechanisms of action:

- down-regulation of LHRH secretion;
- androgen inactivation;
- direct suppression of Leydig cell function;
- direct cytotoxicity to the prostate epithelium (in-vitro evidence only) (9).

12.3.1 Diethylstilboesterol (DES)

Diethylstilboesterol (DES) is the most commonly used oestrogen in PCa. Early studies by the Veterans Administration Co-operative Urological Research Group (VACURG) (10) tested oral DES at a dosage of 5 mg/day (as this was the dosage used in CAB). However, this dosage treatment was associated with high cardiovascular morbidity and mortality due to first-pass hepatic metabolism and the formation of thrombogenic metabolites. Lower oral dosages (1 mg and 3 mg) were therefore tested (11). Both dosages provided a therapeutic efficacy comparable to that of bilateral orchiectomy, though DES, 3 mg, was still associated with high cardiotoxicity. However, even though DES, 1 mg, had much fewer adverse cardiovascular events than DES, 5 mg, the side-effects of 1 mg of DES were still significantly greater than with castration. Because of these concerns, and the advent of LHRH agonists and anti-androgens, until recently the use of DES had fallen out of favour.

12.3.2 *Renewed interest in oestrogens*

There are three main reasons for the renewed interest in using oestrogens to treat PCa.

1. LHRH agonists have a number of deleterious side-effects and their long-term widespread use is costly, while oestrogens suppress testosterone levels and do not seem to lead to bone loss and cognitive decline (12) (level of evidence: 3).
2. In phase II trials with patients diagnosed with hormone-refractory PCa (HRPC), oestrogenic compounds (DES, DES-diphosphate) have induced prostate-specific antigen (PSA) response rates as high as 86%.
3. A new oestrogen receptor- β (ER- β), possibly involved in prostate tumorigenesis, has been discovered (9).

12.3.3 *Strategies to counteract the cardiotoxicity of oestrogen therapy*

Two strategies have been used to try to neutralise the cardiotoxicity that is the main drawback of oestrogen therapy:

- parenteral route of administration – so avoiding first-pass hepatic metabolism;
- cardiovascular-protecting agents.

The Scandinavian Prostatic Cancer Group Study 5 was a prospective randomised trial of more than 900 men with metastatic PCa, comparing a parenteral oestrogen (polyoestradiol phosphate) with CAB (orchiectomy, or an LHRH agonist + flutamide). No significant difference was shown in disease-specific survival and OS between the treatment groups, while the oestrogen-treated group showed no significant increase in cardiovascular mortality. However, the oestrogen-treated group showed a significantly higher incidence of non-fatal adverse cardiovascular events, particularly ischaemic and heart decompensation events (13, for update see 14).

In addition, thromboembolic complications were observed in three recent (though small) phase II trials of patients with advanced PCa or HRPC. The trials were evaluating the combination of DES, 1 mg/day or 3 mg/day, with either a low dose of warfarin sodium, 1 mg/day, or a low dose of aspirin, 75-100 mg/day, for the prevention of cardiovascular toxicity (15-17).

12.3.4 *Conclusions*

Diethylstilboesterol is one of the classic forms of hormonal therapy. Its efficacy was demonstrated many years ago and was recently re-confirmed in a meta-analysis as comparable to that of bilateral orchiectomy (18) (level of evidence: 1a). However, there is still concern about the significant cardiovascular side-effects of DES, even at lower dosages. Further data are needed before oestrogens can be re-admitted into clinical practice as a standard first-line treatment option.

12.4 **LHRH agonists**

Long-acting LHRH agonists (busereline, gosereline, leuproreline and triptoreline) have been used in advanced PCa for more than 15 years and are currently the main forms of ADT (3,19). They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, or 6-monthly basis by initially stimulating pituitary LHRH receptors, inducing a transient rise in LH and FSH release. This then elevates testosterone production (known as the 'testosterone surge' or 'flare up' phenomenon), which begins within approximately 2-3 days of the first injection and lasts through approximately the first week of therapy (20).

12.4.1 *Achievement of castration levels*

Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors. This then suppresses pituitary LH and FSH secretion and testosterone production so that testosterone levels decrease to castration levels usually within 2-4 weeks (21,22). However, about 10% of patients treated with LHRH agonists fail to achieve castration levels (23). This proportion rises to 15% if the castration threshold is defined as 20 ng/dL.

A recent meta-analysis evaluating single-therapy ADT for advanced PCa showed that LHRH agonists have comparable efficacy to orchiectomy and DES (18) (level of evidence: 1a). This finding questions the clinical impact of changing the definition of the castrate testosterone level from 50 ng/dL to 20 ng/dL. In addition, although only based on indirect comparison, the LHRH agonists seemed equally effective whatever their formulation (18) (level of evidence: 3).

12.4.2 *Flare-up phenomenon*

Today, LHRH agonists have become the 'standard of care' in hormonal therapy because they avoid the physical and psychological discomfort associated with orchiectomy and lack the potential cardiotoxicity

associated with DES. However, the main concerns associated with the administration of LHRH agonists are the potentially detrimental effects associated with the 'flare phenomenon' in advanced disease, namely increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and fatal cardiovascular events due to hypercoagulation status.

A recent review (24) concluded that clinical flare needs to be distinguished from the more common biochemical flare (i.e. increasing levels of PSA), and even from asymptomatic radiographic evidence of progression. The review also identified that patients at risk for clinical flare are overwhelmingly patients with high-volume, symptomatic, bony disease, which account for only 4-10% of M1 patients.

Anti-androgen treatment

Concomitant therapy with an anti-androgen decreases the incidence of clinical relapse, but does not completely remove the possibility of its occurrence. Anti-androgens should be started on the same day as the depot LHRH injection and should be continued for a 2-week period.

However, in patients with impending spinal cord compression, other strategies for immediately ablating testosterone levels must be used, such as bilateral orchiectomy or LHRH-antagonists. Except in this group of patients, the clinical impact of the flare-up observation is unknown.

Mini-flares with long-term use of LHRH agonists

Some mini-flares have also been observed with the long-term use of LHRH agonists; the clinical impact is unknown.

12.5 LHRH antagonists

In contrast to LHRH agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. This seemingly more desirable mechanism of action has made LHRH antagonists very attractive. However, practical shortcomings have limited clinical studies. Many LHRH antagonists have been associated with serious and life-threatening histamine-mediated side-effects and, until recently, no depot formulation was available.

12.5.1 Abarelix

Two recently published phase III randomised multicentre trials compared the LHRH antagonist, abarelix, with the LHRH agonist, leuporelin acetate (25), and with CAB (26), in patients with metastatic or recurrent PCa. Both trials showed no difference in achieving and maintaining castration levels of testosterone and in reducing serum PSA. The biochemical 'flare up' phenomenon was not reported in the abarelix arm and the overall incidence of severe adverse events (including allergic reactions) was similar across all treatment groups. Data on survival end-points and long-term safety are not yet available.

The US Food and Drug Administration has recently licensed the clinical use of abarelix, but only in metastatic and symptomatic PCa for which no other treatment option is available (27).

12.5.2 Degarelix

Degarelix is another LHRH antagonist that has shown promising preliminary results in a monthly subcutaneous formulation. Following phase II trials (28), a large, randomised, non-inferiority, dose-finding study (n = 610) compared two degarelix dosages with 7.5 mg monthly leuporelin injections (29). The study showed that the standard dosage of degarelix should be 240 mg the first month, followed by 80 mg monthly injections. More than 95% of patients achieved a castrate level at day 3 with degarelix, which was associated with a quicker decline in PSA as soon as day 14. No allergic reaction was observed. The main criterion (testosteronemia < 0.5 ng/mL at all monthly measurements) was similar in the three treatment groups at 1 year. The main specific side-effect of degarelix was a painful injection (moderate or mild) reported in 40% of patients, mainly after the first injection.

12.5.3 Conclusions

Overall, this new family of agents seems appealing, but their advantages over LHRH agonists are far from proven. Further trials are needed to confirm the preliminary, observed, increased efficacy compared to leuporelin. The use of LHRH agonists is limited by a monthly formulation, compared with 3-month and 6-month depot formulations for leuporelin. Suppression of the initial flare up with monotherapy is only clinically relevant in a few, symptomatic, metastatic patients. Long-term efficacy must be proven, with most available trials limited to a 1-year follow-up period.

12.6 Anti-androgens

Anti-androgens compete with testosterone and DHT at the receptor level in the prostate cell nucleus, thus promoting apoptosis and inhibiting PCa growth (30).

These oral compounds are classified according to their chemical structure as steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate, and non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide. Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal anti-androgens. However, in addition, steroidal anti-androgens have progestational properties due to central inhibition of the pituitary gland. As a consequence, non-steroidal anti-androgens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

12.6.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. In addition to peripherally blocking androgen receptors, they have progestational properties and inhibit the release of gonadotrophins (LH and FSH) and suppress adrenal activity. At high doses, megestrol acetate is cytotoxic. Since steroidal anti-androgens lower testosterone levels, the main pharmacological side-effects are loss of libido and erectile dysfunction, while gynaecomastia is quite rare. The non-pharmacological side-effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

12.6.1.1 Cyproterone acetate (CPA)

Cyproterone acetate was the first anti-androgen to be licensed and is the most widely used. However, it is the least studied, with most questions about its use unanswered, e.g. the optimal dose, or unclear, e.g. comparison with standard forms of castration, surgical or with an agonist.

Comparison of CPA with medical castration

There has been only one randomised trial (31) comparing CPA with standard hormonal therapy, i.e. medical castration. Patients in arm A (no contraindications to DES) were randomly assigned to CPA, goserelin or DES, while patients in arm B (contraindications to DES) were assigned to CPA or goserelin. In arm A, treatment with CPA was associated with significantly poorer median overall survival (OS) than goserelin only; adjusting for baseline characteristics did not account for this difference.

Two other studies in CPA monotherapy have been performed. However, one study did not report survival data (32), and the other used a non-standard treatment combination of DES and medroxyprogesterone acetate (33). It is therefore difficult to draw any definite conclusions from these data about the relative efficacy of CPA and castration.

Dosage regimen of CPA

Because there have been no dose-finding studies of CPA monotherapy, the most effective dose 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 (34).

Comparative study of CPA with flutamide

The only comparative study on anti-androgens as monotherapy was recently published by the European Organisation for Research and Treatment of Cancer (EORTC). The final analysis of Protocol 30892 (a randomised trial of 310 patients comparing CPA with flutamide in metastatic PCa) showed no difference in cancer-specific survival and OS at a median follow-up of 8.6 years, although the study was underpowered (35) (level of evidence: 1b).

12.6.1.2 Megestrol acetate and medroxyprogesterone acetate

Very limited information is available on these two compounds. Early studies with megestrol acetate demonstrated a symptomatic and partially beneficial clinical response, both in previously untreated metastatic PCa (36-38) and, to a lesser extent, in HRPC (39). No apparent dose-response correlation was shown to exist in a recent trial (40). The overall poor efficacy has prevented megestrol acetate and medroxyprogesterone acetate from being recommended for either primary- or second-line hormonal therapy.

The only prospective randomised trial evaluating medroxyprogesterone acetate as primary therapy in advanced (M0-1) PCa is the EORTC 30761 study (41), in which 236 patients were given CPA, DES or medroxyprogesterone acetate. Although there was no difference in cancer-specific survival and OS between CPA and DES, treatment with medroxyprogesterone acetate had a less favourable course with a shorter survival time and time to progression than either of the other CPA or DES.

12.6.2 Non-steroidal anti-androgens

The use of non-steroidal anti-androgens as monotherapy has been promoted on the basis of improved quality of life (QoL) and compliance compared with castration. They do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density are preserved (42).

Although they have not been directly compared in a monotherapy setting, the severity of pharmacological side-effects, namely gynaecomastia, breast pain and hot flashes, appears similar for the three available non-steroidal anti-androgens. However, there are differences in non-pharmacological side-effects, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide (43). All three agents share a common liver toxicity and liver enzymes must be monitored regularly.

12.6.2.1 Nilutamide

There are no comparative trials of nilutamide monotherapy with castration or with other anti-androgens (44). Only one non-comparative study has been carried out, including 26 patients with M1 PCa who received nilutamide, 100 mg three times daily. Only 38.5% of patients experienced an objective response. The median progression-free survival (PFS) time was 9 months and the median OS was 23 months (45).

A large randomised controlled trial in 457 patients with M1 PCa showed a significant benefit for cancer-specific survival and OS with orchiectomy + nilutamide, 300 mg/day, versus orchiectomy + placebo (46). Nilutamide has recently shown encouraging results as a second-line hormonal therapy in HRPC (47,48).

Non-pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, hepatotoxicity, and interstitial pneumonitis. The latter, even if exceptional, is potentially life-threatening and is specific to nilutamide. Nilutamide is not licensed for monotherapy.

12.6.2.2 Flutamide

Flutamide was the first non-steroidal anti-androgen available for clinical use. Although it has been studied as monotherapy for more than 20 years, there are no dose-finding studies against a currently accepted end-point (e.g. PSA response). Flutamide is a pro-drug, and the half-life of the active metabolite is 5-6 hours, so it must be administered three times daily to maintain therapeutic serum levels. The recommended daily dosage is 750 mg (34).

Early phase II trials demonstrated the efficacy of flutamide in the treatment of advanced PCa, even though the reported response rates cannot be correlated with currently recommended end-points. The main advantage shown in these studies was the preservation of sexual function, which was maintained in up to 80% of patients with no pre-treatment erectile dysfunction (49-52). This rate has not been confirmed in the above-mentioned EORTC trial 30892 (35), in which as few as 20% of men treated with flutamide maintained sexual activity for up to 7 years.

Although several phase III studies have been conducted, the results are often difficult to evaluate because of several drawbacks, such as the use of non-standard combinations, short-term follow-up and underpowering. Of these studies, survival data for advanced PCa has been reported in only two phase III randomised trials comparing flutamide monotherapy with standard therapy, i.e. CAB (54) and orchiectomy (53). Both studies showed no significant difference in OS for flutamide or castration in patients with a PSA < 100 ng/mL (53). At a higher PSA, flutamide was inferior. However, both trials were underpowered. Results are eagerly awaited from an ongoing Swedish study, which has randomised 700 patients with M1 PCa to flutamide, 250 mg three times daily, or CAB (42). The non-pharmacological side-effects of flutamide are diarrhoea and hepatotoxicity (occasionally fatal).

12.6.2.3 Bicalutamide

Dose-finding studies of bicalutamide

Early studies with bicalutamide monotherapy used the 50 mg dosage licensed for use in CAB. Although bicalutamide 50 mg/day had clinical benefits, a dosage of 50 mg/day resulted in a poorer OS than castration (median difference 97 days) (55). Subsequent dose-finding studies established that bicalutamide, 150 mg once daily, achieved a similar PSA response to castration, while maintaining a good tolerability profile (56). Accordingly, the 150 mg dosage was chosen for further evaluation as both primary and adjuvant monotherapy.

Primary monotherapy with bicalutamide

Bicalutamide, 150 mg/day, has been compared as first-line monotherapy with medical or surgical castration in two large prospective randomised trials with identical study designs, including a total of 1,435 patients with locally advanced M0 or M1 PCa (57). A pooled analysis showed:

- In M1 patients, an improvement in OS with castration, although the difference in median survival between the groups was only 6 weeks (57); a further post hoc analysis showed a survival benefit only for patients with higher PSA levels (> 400 ng/mL) at study entry (58).
- In M0 patients (n = 480), no significant difference was noted in OS (59) based on the Kaplan-Meier test, with median survival being 63.5 months in the bicalutamide arm compared with 69.9 months in the castration one.

In two smaller randomised trials, high-dose bicalutamide was compared with CAB. In the first trial (251 patients with predominantly M1 stage), no difference in OS was apparent (60). In the second trial (220 patients with M0 and M1 stage), there was no difference in OS for well- or moderately-well-differentiated tumours (61) (level of evidence: 1b). However, both studies were underpowered, and the first one has not yet been fully published.

Adjuvant therapy with bicalutamide

In the adjuvant setting, the ongoing Early Prostate Cancer Programme (EPCP) is a study comprising three different clinical trials (known as Trials 23, 24 and 25) of similar design. The programme included 8,113 patients worldwide and evaluated the efficacy and tolerability of high-dose (150 mg/day) bicalutamide versus placebo, given in addition to standard primary care (i.e. radical prostatectomy, radiotherapy and watchful waiting) in either localised PCa (T1-2, N0-X) or locally advanced PCa (T3-4, any N, or any T N+). The first combined analysis of the programme showed that, after a median follow-up of 3 years, adjuvant bicalutamide reduced the risk of objective disease progression by 42% compared with standard care alone (62).

After a median follow-up of 5.4 years, the positive effects of bicalutamide were obvious in patients with locally advanced disease (stage M0). Bicalutamide significantly improved PFS, irrespective of standard care. However, survival appeared to be reduced in patients with localised disease treated with bicalutamide versus those given placebo (63). After a median follow-up of 7.4 years, there appeared to be no benefit to PFS from the addition of bicalutamide to standard care in localised PCa, with a trend towards decreased survival in patients otherwise undergoing watchful waiting (WW) (hazard ratio [HR], 1.16; 95% CI: 0.99-1.37; p = 0.07).

The same overall results were observed in the most recent analysis of the bicalutamide treatment arm of the EPCP 24 trial (64). Bicalutamide significantly improved OS in patients receiving radiotherapy (HR, 0.65; 95% CI: 0.44-0.95; p = 0.03), mainly due to a lower risk of PCa-related deaths. Bicalutamide produced a trend towards improved OS in patients with locally advanced disease otherwise undergoing WW (HR, 0.81; 95% CI: 0.66-1.01; p = 0.06). No survival difference was evident in the subgroup undergoing radical prostatectomy (63).

Even though the EPCP is a combination of three trials and among the largest conducted in PCa patients, it is difficult to draw clear conclusions because of problems with the protocols (65), including:

- The three trials grouped for analysis were different in terms of patients; 80% of patients underwent prostatectomy in trial 23 versus 13% in trial 25. In addition, treatment duration was 2 years in trial 23, but prolonged until progression in Trials 24 and 25.
- The OS benefit claimed with radiotherapy is mainly driven by a respiratory or cardiovascular improvement, and not by a cancer-specific survival benefit, which is different to other trials with LHRH agonists (66).
- Furthermore, the EPCP trials are underpowered for locally advanced patients, compared with oriented trials such as the Bolla (67) or Pilepich (68) trials.
- Direct protocol analysis revealed quite different results, such as those from EPCP Trial 23 (80% prostatectomy, 19% radiotherapy) (69). At a median 7.7 years of follow-up, no PFS benefit was observed (HR, 1.00; 95% CI: 0.84; 1.19; p = 0.991). Likewise, OS did not differ. Even after stratifying for disease stage, no PFS benefit was apparent.
- The OS benefit must be balanced by the very prolonged (mainly permanent) use of bicalutamide combined with radiotherapy in contrast to the more limited use of agonists (6 months to 3 years in most studies).
- Although a QoL benefit has been claimed, in fact a QoL benefit cannot be demonstrated because none of the EPCP trials used a systematic, validated QoL questionnaire. The only QoL data was derived from a specific questionnaire and a limited population. The observed benefit was only significant for physical capacity and sexual interest (not function!). For all other QoL items (emotional well-being, vitality, social function, pain, activity limitation and bed disability), there was no difference compared with castration (70). The breast problems related to bicalutamide are also important, as they can lead to a 16.4% treatment cessation (71).

The lack of data means that many questions are still debatable with bicalutamide, such as the practical management after progression under bicalutamide.

Furthermore, the clear trend (even if not statistically significant) suggesting a decreased OS in localised disease treated with WW is a clear argument against the use of bicalutamide in such situations (63). The mechanisms involved remain unclear.

Conclusions for the use of bicalutamide in primary and adjuvant therapy

- High-dose bicalutamide has emerged as an alternative to castration for patients with locally advanced (M0) if PFS is the target, and in highly selected, well-informed cases of M1 PCa with a low PSA (72).
- Bicalutamide should be avoided in patients with localised PCa.
- The expected benefit of bicalutamide for QoL compared with castration is far from being proven.
- The survival benefit observed with adjuvant use after radiotherapy in locally advanced PCa must be considered with caution, as the EPCP trials do not have the clear power of trials conducted with LHRH agonists. The lack of any direct comparison between both bicalutamide and LHRH agonists in combination with radiotherapy leads to a major limitation of any guidelines, which should therefore be based on unquestionable trials, which are mainly those with analogues.

Side-effects of bicalutamide

Non-pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens (73-75), prophylactic radiotherapy (76), or treatment with surgical mastectomy or radiotherapy (77). However, bicalutamide clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists (78,79).

12.7 Combination therapies

12.7.1 Complete androgen blockade (CAB)

Although castration reduces serum testosterone levels by up to 95%, an intraprostatic androgen stimulus is sustained by the conversion of circulating androgens of adrenal origin into DHT within the prostate cells. However, the action of these adrenal androgens can be blocked by the addition of an anti-androgen to either surgical or pharmacological castration, a concept known as complete (or maximal or total) androgen blockade (CAB).

The many studies comparing CAB with monotherapy have produced contrasting results (80). According to the most recent systematic reviews and meta-analyses, at a follow-up of 5 years, CAB appears to provide a small survival advantage (< 5%) versus monotherapy (81-85, level of evidence: 1a). However, some of the largest trials included were methodologically flawed (86). It remains debatable whether this small advantage, if any, is useful in everyday clinical practice, as the survival benefit seems limited to patients taking non-steroidal anti-androgens (87) and only appears after 5 years of follow-up.

Gastrointestinal, ophthalmological, and haematological side-effects are worse with CAB. Although LHRH analogues and non-steroidal anti-androgens have the highest estimated quality-adjusted survival, there is an incremental cost of more than US\$1 million per quality-adjusted live-year for CAB over orchiectomy alone.

12.7.2 Minimal androgen blockade (or peripheral androgen blockade)

Minimal androgen blockade is produced by combining finasteride with a non-steroidal anti-androgen. Finasteride reduces intraprostatic levels of DHT by inhibiting 5- α -reductase, while the anti-androgen competes with the binding of the residual DHT to its receptor. This enables testosterone levels to be maintained within normal ranges to ensure acceptable sexual function and a reasonable QoL.

Several phase II trials (88-92) have evaluated the association of finasteride and flutamide, either given together or sequentially, using the PSA response rate in patients with advanced or biochemically recurrent PCa. Notwithstanding the small sample and short follow-up, nearly all patients experienced a substantial decline in PSA (by up to 96% compared with the baseline level at entry). In a long-term follow-up of one study, stronger end-points were reported, including castration-free survival (median: 37 months), androgen-independent PCa-free survival (median: 48.6 months) and OS (65% at 5 years). These results indicated that combination therapy was able to induce an overall period of hormone-responsive disease exceeding 4 years (93). In all these trials, sexual function was preserved in 55-86% of men studied.

The preliminary data make minimal androgen blockade a most attractive option in the management of patients for whom QoL is the main concern. However, while awaiting the results of follow-up and larger controlled trials, this treatment should be considered investigational.

12.7.3 Intermittent versus continuous ADT

For reasons still unclear, long-term CAB, which stimulates prostate cell apoptosis, fails to eliminate the entire malignant cell population. Thus, after a variable period (averaging 24 months), the tumour inevitably relapses, characterised by an androgen-independent state of growth. Experimental data indicate that androgen-independent progression may begin early after the administration of hormonal therapy, coinciding with the cessation of androgen-induced differentiation of stem cells (94). It has therefore been suggested that stopping androgen deprivation prior to progression of androgen-independent cells would mean any subsequent tumour growth would be solely sustained by the proliferation of androgen-dependent stem cells. The stem cells should therefore be susceptible once again to androgen withdrawal. Thus, intermittent androgen blockade (IAD) would delay the emergence of the androgen-independent clone.

Other possible benefits of IAD include the preservation of QoL in off-treatment periods and a reduction in the cost of treatment.

Phase II results

A detailed systematic review was recently published (95), with no other trials published since this review. According to the review, several phase II trials demonstrated the feasibility of IAB in metastatic or biochemically recurrent disease (95). Both PSA response rates and symptom improvement were similar to those seen with CAB. However, these trials included very heterogeneous patients and used different PSA thresholds for decisions regarding castration. This should be borne in mind when considering the main findings:

- Most patients were treated with an LHRH agonist, with or without an anti-androgen;
- The cycle lengths were quite stable regarding the off-treatment periods;
- Testosterone recovery, when tested, was frequent during the first cycle, but tended to decrease during subsequent cycles;
- Early occurrence of early refractory status was quite uncommon;
- Overall tolerability was acceptable, and sometimes there was a QoL benefit, especially for sexual function.

These findings suggest a potential benefit for IAD. However, randomised trials are required to clarify the potential survival benefit suggested by animal models.

Randomised controlled trials

Overall, eight randomised trials are underway, only some of which have published findings. Most of the trials included a mixed patient population, i.e. both locally advanced and metastatic disease. Only three trials included only metastatic patients, and two trials only relapsing patients. The two largest trials each contained more than 1,300 patients, with one trial focused only on metastatic patients (SWOG 9346) and the other on relapsing patients after radiotherapy (SWOG JPR7).

A short summary of the most important published findings from these trials follows:

- The South West Oncology Group (SWOG) trial 9346 randomised 1,134 men with stage D2 PCa to intermittent and continuous ADT after 7 months' induction ADT with PSA reduction < 4 ng/mL. A very preliminary analysis has identified no significant differences with regard to survival between treatment groups (96). A PSA reduction to < 0.2 ng/mL, < 4 ng/mL and > 4 ng/mL was identified as a significant prognostic factor with regard to survival, achieving 13 months, 44 months and 75 months, respectively.
- In another trial, 75 patients were considered for IAD after 9 months' treatment with ADT, provided they had achieved PSA serum levels < 4 ng/mL or at least a 90% reduction in pre-treatment levels (97). Treatment with 9 months of ADT was only repeated when PSA values rose > 20 ng/mL. 86% of the men were alive at a median of 134 months, with a median survival of 95 months from the initial ADT cycle. At 5 years, 100% and 70% survival rates were calculated for those presenting with locally advanced disease and metastases, respectively.
- In a similar patient population and using a quite similar protocol, no difference was observed in OS nor PFS between IAD and CAB in 173 randomised patients (98), with a mean follow-up of 47 months. No QoL benefit was observed in any treatment arm.
- The same lack of OS difference was observed using CPA in another randomised study of 366 patients (99), after a mean follow-up of 66 months.
- The only trial with results available on relapse after a local treatment is clearly underpowered with a short follow-up. But once again, no difference in PFS was seen (100).

Mixed populations

The same overall results have been observed for trials with mixed populations. A prospective, randomised,

multicentre trial (n = 68) with a mean follow-up of 31 months was reported (101). In the IAD-treated group, the median cycle length was 9.5 months and the median percentage of time off-treatment was 59.5%. The median 3-year progression rate was significantly lower in the IAD group (7%) than in the CAD group (38.9%), suggesting that IAD maintains the androgen-dependent state of advanced PCa at least as long as does CAD.

In a prospective trial, which included 478 patients with either M1 disease (40%) or N+ (N1-3) disease (102), 335 patients were randomised to IAD after 6 months of CAB if the PSA decreased to < 4 ng/mL or a decrease of > 90% was observed. The mean initial PSA was 158 ng/mL in the IAD-treated group, and 139 ng/mL in the CAB-treated group, respectively. In the IAD group, treatment was resumed if the PSA rose > 10 ng/mL and stopped when it decreased < 4 ng/mL. However, after a median follow-up of 50.5 months, no significant difference was observed in the median PFS (16.6 months in the IAD group vs 11.5 months in the CAB group, p = 0.17) in either the total study population or in the N+ or M1 subgroup populations. In the IAD arm, 88% of patients were off-treatment for more than 50% of the time and normalised their testosterone in a mean of 70 days after stopping treatment.

SEUG trial results

To date, the largest trial (n = 766) with published results has been carried out by the South European Uro-Oncological Group (SEUG) (103). After a 3-months' induction regimen (CPA for 2 weeks followed by monthly LHRH + CPA), patients with a PSA < 4 ng/ml, or a decrease > 80% were randomised to IAD or CAB. In the IAD-treated group, treatment was resumed according to the PSA nadir (< 4 ng/mL or above), and symptoms, to either PSA > 10 or 20 ng/mL, or if there was a PSA rise \geq 20% above the nadir. The primary end-point was time to progression. After a median follow-up of 51 months, there was no difference in either time to progression (HR, 0.81; p = 0.11) or OS (HR, 0.99). Metastatic status and PSA at randomisation were associated with specific death rates.

No overall QoL benefit was seen, except for more frequent side-effects in the CAB-treated group. However, there was a clear benefit for improved sexual function in the IAD group versus the CAB group (28% sexually active vs 10% at 15 months after randomisation, respectively).

Alternative IAD regimen

Recently, a published randomised trial (n = 129) suggested an alternative IAD regimen involving fixed 6-month periods of treatment (CAB) and surveillance (104). The PSA response was not used to guide treatment in the heterogeneous study population. After a mean follow-up of 44.8 months, no difference was observed in OS, cancer-specific survival or PFS. The QoL also showed no difference between the two groups, except that painkillers were required more often in the IAD arm, and the ability to get and maintain an erection was better in the IAD arm.

Other benefits of IAD

Intermittent androgen deprivation has not been shown to be associated with prolonged hormone-sensitive status or OS increase. This modality is well accepted by patients, urologists and oncologists. Although the QoL benefit is less than expected or absent except in one study (99), IAD is better tolerated and sometimes benefits sexual functioning (102,103). Other possible long-term benefits, which are not clearly proven, include bone protection (105), cognitive and mood changes (106), or protective effect against metabolic syndrome. Testosterone recovery is seen in most studies (95), leading to an intermittent castration (not just an intermittent treatment delivery).

Optimal threshold for stopping or resuming ADT

The optimal thresholds at which ADT must be stopped or resumed are empirical (95). The best candidates for IAD have still not been completely defined (95,107,108), but are probably patients with locally advanced or relapsing disease, provided a perfect response is obtained (see below). Nevertheless, several points are clear (95,109):

- IAD is based on intermittent castration. Thus, only drugs leading to castration should be considered for use in IAD.
- It is unclear if an LHRH agonist may be used alone, as published experiences are based on CAB. An LHRH antagonist might be a valid alternative, provided clear results are obtained from randomised trials.
- The initial (induction) cycle must last between 6 and 9 months, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
 - o well-informed and compliant patient
 - o no clinical progression, i.e. a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease, or 0.5 ng/mL in relapsing disease.

- Strict follow-up must be applied once treatment has stopped, with clinical examination every 3-6 months (the more advanced the disease, the closer the follow-up). At the same time, PSA should be measured, and by the same laboratory to ensure standardisation of testing.
- Treatment is resumed when the patient reaches either a clinical progression, or a PSA value above a predetermined, empirically fixed threshold (usually 4 ng/mL in non-metastatic situations, or 10-15 ng/mL in metastatic patients) (107).
- 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 of hormone-refractory status.

In conclusion, IAD is currently widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational (level of evidence: 2).

Increased duration of off-treatment periods in IAD

Recently, attempts have been made to increase the duration of the off-treatment periods in IAD. Although hormonal manipulations using finasteride (110) were suggested, finasteride has never been tested in randomised trials, and its use in PCa has been recently questioned (111). Instead, non-hormonal compounds have been tested, such as a COX-2 inhibitor or anti-angiogenic drugs.

The first preliminary trial (112) included 44 relapsing patients after surgery, who were randomised to intermittent bicalutamide alone or to etoricoxib in the off-treatment periods. With a median follow-up of 62 weeks, etoricoxib showed a clear benefit in prolonging the off-treatment period. The second, more mature, study (113) randomised 159 patients, relapsing after local treatment, to two treatment arms: LHRH antagonist for 6 months, followed by placebo or thalidomide, 200 mg daily. When PSA progression occurred, a cross-over was done, using the same regimen. A clearly prolonged time to PSA progression was seen with thalidomide: there was a non-significant difference during the first round (15 vs 9.6 months), but a highly significant difference after the cross-over (17.1 vs 6.6 months, $p = 0.0002$). This finding was not linked to any hormonal effect, based on the time taken to reach testosterone normalisation after the LHRH antagonist was stopped. This proof of principle warrants further larger studies, as thalidomide, even with an acceptable tolerance, required dose reduction in 47% of patients.

12.7.4 Immediate vs deferred ADT

There is still controversy over the most appropriate time to introduce hormonal therapy in patients with advanced PCa. Should ADT be given immediately upon diagnosis in locally advanced and asymptomatic metastatic disease or deferred until there are signs and symptoms of clinical progression? (This has been partly discussed in *Section 8.3*.)

The controversy over whether immediate treatment with ADT has a positive effect on survival and QoL has arisen because of the lack of properly conducted, randomised, controlled trials. Many of the trials are methodologically flawed because of small size and underpowering, heterogeneity of patient enrolment with advanced PCa (i.e. locally advanced, nodal and metastatic stages of disease), and variability in the hormonal treatments administered and of follow-up schedules and modalities used.

Bearing these limitations in mind, the evidence for immediate versus deferred ADT is provided by three systematic reviews of the literature (one of which is a meta-analysis). A report by the Agency for Health Care Policy and Research (AHCPR) indicated a possible survival advantage for early ADT in single studies where hormonal treatment was the primary therapy, while the combined analysis showed no significant benefit. Furthermore, androgen suppression was shown to be the most cost-effective therapy if initiated after patients had experienced symptoms from metastatic disease (81,114).

The Cochrane Library review extracted four, good-quality, randomised, controlled trials, i.e. namely VACURG I and II studies (10,11), the MRC trial (115) and the Eastern Cooperative Oncology Group (ECOG) 7887 study (116), which were all conducted in the pre-PSA era. The studies included patients with advanced PCa, who received early versus deferred ADT, either as primary therapy or adjuvant to radical prostatectomy (but not to radiotherapy). According to the analysis, early androgen suppression significantly reduced disease progression and complication rates due to the progression itself. However, it did not improve cancer-specific survival and provided a relatively small benefit in OS, with an absolute risk reduction of 5.5% after 10 years (117).

Since 2002, the level 1 evidence suggesting immediate ADT in every pN+ patient after a prostatectomy has been questioned for several reasons. Some have been discussed elsewhere (see *Section 9.7*), such as the impact of a micronodal metastasis in a single node (118), which is far from being equivalent to a massive

nodal involvement as described in the Messing trial (116). Recently, the analysis of 719 patients from the SEER database (Surveillance, Epidemiology and End Results, part of the US National Cancer Institute) questioned the real impact of immediate ADT in pN+ patients after a radical prostatectomy (119).

In the PSA era, the EORTC 30891 study (120) has produced the same results, namely a small benefit in OS, but no CSS benefit. Furthermore, only young patients with a high PSA might clearly benefit.

Based on a systematic review of the literature, recently published ASCO guidelines on initial hormonal treatment for androgen-sensitive, metastatic, recurrent or progressive PCa concluded that no recommendation can be made on when to start hormonal therapy in advanced asymptomatic PCa until data becomes available from studies using modern diagnostic and biochemical tests and standardised follow-up schedules (72).

Based on meta-analysis published, treatment appears to be most cost-effective when started after the onset of symptoms. Based on exploratory analysis, treatment with anti-androgen monotherapy does not lead to a survival benefit in men with localised PCa managed with non-definitive therapy, and the impact is still questionable after external beam therapy. This was explored in detail above with regard to the EPCP trials (see Section 12.6.2.3).

For asymptomatic patients with locally or regionally advanced PCa who undergo radiotherapy, several randomised controlled trials have produced good evidence to show that concomitant and/or adjuvant hormonal therapy provides longer time-to-disease progression and/or longer OS than radiotherapy alone followed by androgen suppression at progression (121-124) (level of evidence: 1b).

12.8 Indications for hormonal therapy

Table 18 lists the indications for hormonal therapy.

Table 18: Indications for hormonal therapy.

Hormonal therapy Indications for castration	Benefits	LE
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskelatal metastasis)	1
	Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence	1
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications (115)	1b
	An active clinical surveillance protocol might be an acceptable option in clearly informed patients if survival is the main objective	3
N+	Immediate castration to prolong PFS and even OS (116)	1b
	Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy (125)	3
Locally advanced M0	Immediate castration to improve cancer-free survival	1b
• Locally advanced disease treated with radiotherapy	High-risk d'Amico: combined and prolonged ADT	1
	Intermediate-risk d'Amico	1b
	– If low dose (< 75 Gy) radiotherapy: 6 months of ADT	
	– If high dose (> 75 Gy) radiotherapy: ADT questionable	2
• Locally advanced asymptomatic unfit for local definitive treatment	Limited OS improvement not related to a CSS benefit (120)	1
Anti-androgens		
Short-term administration	To reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist (126,127)	1b
Non-steroidal anti-androgen monotherapy	Primary monotherapy as an alternative to castration in patients with locally advanced PCa (T3-4, any N, or any T)	2
	No place in localised disease as a single-treatment modality	
	Combined with radiotherapy: no clear recommendation is possible at the present time	
	Combined with radical prostatectomy: no place so far in an adjuvant setting	

12.9 Contraindications for various therapies (Table 19)

Table 19 lists the contraindications for various therapies.

Table 19: Contraindications for various therapies.

Therapy	Contraindications
• Bilateral orchiectomy	Psychological reluctance to undergo surgical castration
• Oestrogens	Known cardiovascular disease
• LHRH agonists alone	Patients with metastatic disease at high risk for clinical 'flare up' phenomenon
• Anti-androgens	Localised PCa as primary therapy

12.10 Outcome

Outcome depends on the stage and grade of disease at diagnosis.

In M1 cases, the median OS ranges between 28 and 53 months (81); only 7% of patients with metastatic cancer treated with hormonal therapy have been reported alive at 10 years or longer (128). Survival is likely to depend on the PSA level at diagnosis, the Gleason score, the volume of metastatic disease, and the presence of bony symptoms.

In locally advanced M0 patients, the median OS is frequently reported to exceed 10 years (82).

12.11 Side-effects, QoL, and cost of hormonal therapy

The many deleterious side-effects of long-term ADT have been well known for years. Some can have a detrimental effect on QoL, especially in young men, while others may contribute to an increased risk of serious health concerns associated with ageing.

Many patients with PCa for whom long-term ADT is indicated are still young and physically and sexually active. Quality of life is an issue of paramount importance when considering the various hormonal treatment options. Thus, in selected patients, monotherapy with a non-steroidal anti-androgen (e.g. bicalutamide) is becoming more popular because it maintains normal (or even higher) serum testosterone levels and has a good tolerability profile.

12.11.1 Sexual function

Loss of libido and erectile dysfunction are well-known side-effects of hormonal therapy. The management of erectile dysfunction is not specific.

12.11.2 Hot flashes

Hot flashes are probably the most common side-effect of ADT. They appear 3 months after starting ADT, persist long term in most patients, and have a significant impact on QoL (129). Treatments include hormonal therapy and antidepressants.

12.11.2.1 Hormonal therapy

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flashes. Both treatments carry a risk of cardiovascular complications (130). Soya phytoestrogens have shown efficacy for hot flashes in breast cancer patients (131), but have not been evaluated in men. Progesterone-based treatments, such as megestrol acetate, medroxyprogesterone acetate, and CPA, have also demonstrated efficacy, with 80% of patients showing an improvement with CPA (132) or chlormadinone (133).

12.11.2.2 Antidepressants

Antidepressants may have some efficacy. For example, venlafaxine (a non-specific selective noradrenaline and serotonin reuptake inhibitor) has shown efficacy in breast cancer patients, while the selective serotonin reuptake inhibitor, sertraline, appears to be effective in men with PCa (134). Recently, a randomised trial (n = 919) compared three drugs considered to be effective: venlafaxine, 75 mg daily, medroxyprogesterone, 20 mg daily, or CPA, 100 mg daily (135). After 6 months of LHRH, only 311 men had significant hot flashes and were randomized. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

Other products have also been tested, including clonidine and veralipride, and even acupuncture (136). With a placebo effect influencing up to 30% of patients (137), few treatments are approved for the control of hot flashes in men with PCa. There is a lack of large, prospective randomised controlled trials in this area.

12.11.3 Other systemic side-effects of ADT

More recently, other systemic side-effects have been described and require increased attention, including bone problems, obesity and sarcopenia, lipid alterations and insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease (138).

12.11.3.1 Non-metastatic bone fractures

Androgen deprivation therapy increases the risk of non-metastatic bone fracture as a result of increased bone turnover and decreased bone mineral density (BMD) in a time-dependent manner. This leads to an increased risk of fracture of up to 45% relative risk long term (139). This is an important side-effect, as hip fractures in

men are associated with a significant risk of death (140). Increased exercise and calcium supplementation are protective.

Bisphosphonates

Recently, bisphosphonates such as pamidronate, alendronate or zoledronic acid have been shown to increase BMD in hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid is unclear. One study recommends treatment every 3 weeks (141), while another trial has produced similar results with an annual injection (142). The optimal regimen is very important because of the risk of jaw necrosis, which may be both dose- and time-related (143). The initial BMD could be used to guide the choice of regimen (144). Thus, a 3-month injection might be given in osteoporotic patients, for whom a yearly injection is likely to provide insufficient protection.

As previously observed in breast cancer, a significant OS benefit has recently been demonstrated for bisphosphonates in PCa, particularly oral first-generation clodronate compared to placebo. After at least 10 years of follow-up, an absolute 8% increase in OS at 8 years was observed in a clodronate-treated group of PCa patients, who had an OS of 22% versus 14% in the placebo group (145). The OS benefit was only apparent for M1, but not for M0, patients. This result highlighted again the potential impact of bone-targeted drugs and the need for continuous trials, such as the Zeus trial using a more recent bisphosphonate.

Denosumab

In 2009, a major advance in bone protection was made with the introduction of denosumab, a fully human monoclonal antibody against RANKL, which is a key mediator for osteoclast function, activation and survival. A total of 1,468 men with non-metastatic PCa receiving ADT were randomised to denosumab, 60 mg subcutaneous every 6 months, or placebo (146). The primary end-point was the percentage change in lumbar spine BMD at 2 years. Denosumab was associated with 5.6% increase in the lumbar BMD versus 1% decrease in the placebo arm. There were also significant BMD increases at the total hip, femoral neck and distal third of the radius. The vertebral fracture rate was less in the denosumab-treated group versus the placebo-treated group (1.5% vs 3.9%, $p = 0.006$). This benefit was similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the weight or the initial BMI (144). This benefit was not associated with any significant toxicity, as rates of adverse events were the same in both groups, without any jaw osteonecrosis or delayed healing in vertebral fractures. This compound may therefore represent a major advance in bone protection.

Lifestyle changes

Before starting long-term ADT, patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption and normalisation of their body mass index (BMI). A precise evaluation of BMD should be performed by dual X-ray absorptiometry before starting long-term ADT. An initial low BMD (T-score above 2.5, or above 1 if other risk factors are present) indicates a high risk of subsequent non-metastatic fracture, suggesting the need for early use of preventive bisphosphonate therapy.

Obesity and sarcopenia

Obesity and sarcopenia are common and often occur early, during the first year of ADT. There is an expected increase in body fat mass by up to 10%, and a decrease in lean tissue mass by up to 3% (147). Both changes are linked to an increased risk of fracture.

12.11.3.2 Lipid levels

Lipid alterations are also frequent, and occur as early as the first 3 months of treatment (147). Androgen deprivation therapy also decreases insulin sensitivity and increases fasting plasma insulin levels (148), which is a marker of insulin resistance. Once again, exercise must be recommended as a protective tool.

12.11.3.3 Metabolic syndrome

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. These include:

- waist circumference > 102 cm
- serum triglyceride > 1.7 mmol/L
- blood pressure > 130/80 mmHg
- HDL cholesterol < 1 mmol/L
- glycaemia > 6.1 mmol/L.

The prevalence of metabolic syndrome is higher during ADT compared with untreated men (149).

12.11.3.4 Cardiovascular disease

Androgen deprivation therapy has been associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction in one study (150), and with a 20% increased risk of new cardiovascular disease after 1 year of treatment in another (151). Recently, the analysis of the RTOG 92-02 data confirmed the increase in cardiovascular risk (152), with no relationship with the duration of ADT. However, these observations have been much discussed recently, as no increased cardiovascular mortality was demonstrated in RTOG 8610 (153), EORTC 30891 (120) or EORTC 22863 (66).

In summary, if even 6 or fewer months of ADT might be associated with increased cardiovascular morbidity, the data on cardiovascular mortality are so far inconsistent. Again, prevention is associated with non-specific measures, such as loss of weight, increased exercise, better nutrition and the cessation of smoking.

12.12 Quality of life (QoL)

Data on QoL during hormone treatment are scant because of a lack of solid evidence. The only large, prospective, randomised study is a double-blind, placebo-controlled trial including 739 patients with M1 PCa, which compared orchiectomy + flutamide versus orchiectomy + placebo. The QoL was assessed in the first 6 months of treatment. Combined therapy resulted in a lower QoL, with statistically significant differences in two QoL parameters, namely more frequent diarrhoea and worse emotional functioning, compared with castration alone (154).

A prospective, non-randomised, observational study including 144 patients with locally advanced PCa or PSA failure after definitive local treatment showed that patients who received immediate ADT (by means of bilateral orchiectomy, LHRH agonist or CAB) reported a lower overall QoL (increased fatigue, emotional distress, and decreased physical functioning) than patients in the deferred hormone treatment arm (155) (level of evidence: 2a).

A retrospective, non-randomised study included 431 patients with stage PCa who received orchiectomy or LHRH agonists as their primary therapy within 12 months of initial diagnosis. The study assessed health-related quality of life (HRQoL) outcomes at 12-months' follow-up. 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 were orchiectomised patients. The stage at diagnosis had no significant independent effect on health outcome. However, the study was insufficiently powered (156) (level of evidence: 2b).

A recent, small, randomised, controlled trial evaluated the HRQoL of patients with non-localised PCa allocated to leuprorelin, goserelin, CPA or no treatment at 1-year follow-up. Both sexual and cognitive function significantly declined in men on all forms of androgen suppression, while emotional distress significantly increased in those assigned to CPA and no treatment (157) (level of evidence: 1b).

Intermittent androgen deprivation may be associated with an improved overall QoL based on the normal testosterone levels during the off-treatment periods. So far, the results are inconclusive, showing either no benefit, or only a marginal one, in QoL.

As for LHRH agonists, QoL was evaluated in the previously mentioned studies of bicalutamide monotherapy using a specific questionnaire covering 10 domains (sexual interest, sexual function, physical capacity, emotional well-being, vitality, social function, activity limitation, pain, bed disability and overall health). Separate analyses of data for M0 and M1 patients were performed at 12-months' follow-up. In both patient categories, bicalutamide showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) (59) (level of evidence: 1b).

A further post hoc analysis, including only patients with sexual interest at study entry, found that significantly more patients receiving bicalutamide, 150 mg/day, maintained their interest in sex and felt that they were still sexually attractive than did those randomised to castration (157,158).

Data on QoL are also available from an early report from Boccardo et al. (159) and support the findings of the two larger combined trials. More men in the bicalutamide group than in the castration group reported a preserved libido and erectile function.

Furthermore, a recent, small, prospective, randomised trial, including 103 patients with localised or locally advanced PCa, who received bicalutamide 150 mg/day or medical castration, evaluated the changes in BMD after 96 weeks of treatment and showed it to be maintained with bicalutamide therapy (160) (level of evidence: 1b).

The most common side-effects during non-steroidal anti-androgen monotherapy are gynaecomastia and breast pain, which are caused by an imbalance in the androgen:oestrogen ratio within the breast tissue. In

bicalutamide studies, these events were reported by up to 66% and 73% of patients, respectively, and may lead to treatment cessation in 16.4% of patients.

12.13 Cost-effectiveness of hormonal therapy options

A recent formal meta-analysis and literature review evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa (e.g. bilateral orchiectomy, DES, LHRH-agonist, non-steroidal anti-androgen monotherapy, and CAB using non-steroidal anti-androgens).

For the analysis, a sophisticated statistical model was generated, assuming the base case at entry to be a 65-year-old man with a clinically evident, local recurrence of PCa and no distant metastases, followed for a 20-year time horizon. The study concluded that, for men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits for a high relative cost. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred (114) (level of evidence: 1a).

Finally, once ADT is started, if a clear response is obtained (see Section 12.3.3), then IAD might be a useful way to lower treatment costs.

12.14 Guidelines for hormonal therapy in prostate cancer	LE
• In advanced PCa, androgen deprivation therapy (ADT) delays progression, prevents potentially catastrophic complications, and palliates symptoms effectively, but does not prolong survival.	1b
• In advanced PCa, all forms of castration used as monotherapy (e.g. orchiectomy, LHRH and DES) have equivalent efficacy.	1b
• Non-steroidal anti-androgen monotherapy (e.g. bicalutamide) is an alternative to castration in patients with locally advanced disease.	2
• In metastatic PCa, the addition of a non-steroidal anti-androgen to castration (CAB) results in a small advantage in OS over castration alone, but is associated with increased adverse events, reduced QoL, and high costs.	1a
• Intermittent ADT should no longer be regarded as experimental, even though long-term data from prospective clinical trials are still awaited. 'Minimal' ADT should, however, continue to be seen as experimental.	2
• In advanced PCa, immediate ADT (given at diagnosis) significantly reduces disease progression, as well as the complication rate due to progression itself, compared with deferred ADT (delivered at symptomatic progression). However, the survival benefit is at best marginal and not related to cancer-specific survival.	1b
• Bilateral orchiectomy might be the most cost-effective form of ADT, especially if initiated after the occurrence of symptoms from metastatic disease.	3

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13. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF PCa

Stage	Treatment	Comment	GR
T1a	Active Surveillance	Standard treatment for well-, and moderately, differentiated tumours and < 10-year life expectancy. In patients with > 10-year life expectancy, re-staging with TURP and biopsy is advised	B
	Radical prostatectomy	Optional in young patients with a long life expectancy, especially for poorly differentiated tumours	B
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation	B
	Hormonal	Not an option	A
	Combination	Not an option	C
T1b-T2b	Active surveillance	Treatment option in patients with cT1c-cT2a, PSA < 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 biopsies positive, ≤ 50% cancer involvement of each biopsy. Patients with a life expectancy < 10 years. Patients who do not accept treatment-related complications	B
	Radical prostatectomy	Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications	A
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below)	B
	Brachytherapy	LDR Brachytherapy can be considered in low risk PCa, patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.	B
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment Anti-androgens are associated with a poorer outcome compared to 'watchful waiting' and are not recommended	C A
	Combination	For high-risk patients, neoadjuvant hormonal treatment (NHT) and concomitant hormonal therapy + radiotherapy results in increased overall survival	A
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumours, and a life expectancy < 10 years who are unfit for local treatment	C
	Radical prostatectomy	Optional for selected patients with T3a, PSA < 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy > 10 years	C
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation > 74 Gy seems to be of benefit. A combination with hormonal therapy should be recommended (see below)	A
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSA-DT < 1 year. Patient-driven, unfit patients	A
	Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation NHT + radical prostatectomy: no indication	A B
N+, M0	Watchful waiting	Asymptomatic patients. Patient driven (PSA < 20-50 ng/mL), PSA DT > 12 months. Requires very close follow-up	B
	Radical prostatectomy	Optional for selected patients with a life expectancy of > 10 years as part of a multimodal treatment	C
	Radiotherapy	Optional in selected patients with a life expectancy of > 10 years, combination therapy with adjuvant androgen deprivation for 3 years is mandatory	C
	Hormonal	Standard therapy in N > N1	A
	Combination	No standard option. Patient-driven	B
M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up	B
	Radical prostatectomy	Not an option	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms	C
	Hormonal	Standard therapy. Mandatory in symptomatic patients	A

GR = grade of recommendation; TURP = transrectal urethral resection of prostate; NHT = neoadjuvant hormonal therapy; PSA = prostate-specific antigen; PSA-DT = prostate-specific doubling time.

14. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

14.1 Definition

Curative treatment is defined as radical prostatectomy or radiotherapy, either by external beam radiation or an interstitial technique, or any combination of these. Alternative treatment options that are not fully established, such f.i. HIFU, do not have a well-defined, validated PSA-cut-point to define biochemical failure but do generally follow the outlines given below.

14.2 Why follow-up?

The first question to be answered is: 'If failure after curative treatment is so common, are follow-up efforts worthwhile?' The answer to this question is definitely 'Yes'. Recurrences will occur in a substantial number of patients who received treatment with intent to cure at various time points after the primary therapy.

The second question to be answered is: 'What is the reason for follow-up?' Reasons may vary depending on the treatment given, patient age, comorbidity and the patient's own wishes. In general, patients who receive curative therapy may be followed-up for any of the following reasons:

- good responsible patient care;
- possibility of second-line treatment with curative intent;
- possibility of early hormonal therapy after failure;
- as part of a study protocol.

Section 16 discusses treatment options after failure of primary therapy.

14.3 How to follow-up?

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

14.3.1 PSA monitoring

The measurement of PSA level is a cornerstone in the follow-up after curative treatment. There is a difference in what can be expected after radical prostatectomy and radiotherapy, but PSA recurrence nearly always precedes clinical recurrence after either treatment, in some cases by many years (1-5). It is recommended that the finding of a single, elevated, serum PSA level should be re-confirmed before second-line therapy is started solely based on the PSA elevation.

14.3.2 Definition of PSA progression

The level of PSA at which to define treatment failure differs between radical prostatectomy cases and radiation treated cases. Following radical retropubic prostatectomy, two consecutive values of 0.2 ng/mL or greater appear to represent an international consensus defining recurrent cancer (6,7). Other authors have argued for an even higher cut-off of 0.4 ng/mL to better define patients with a high risk for clinical progression (5). It has been shown that patients with a PSA level between 0.1 ng/mL and 0.2 ng/mL after radical prostatectomy had neither clinical nor biochemical disease progression (8). Therefore, the use of an ultra-sensitive PSA assay is not justified for routine follow-up after radical prostatectomy (4). If ongoing randomized trials show that early adjuvant treatment after radical prostatectomy (given before PSA reaches > 0.2 ng/mL) improves survival, this issue should be reconsidered.

Following radiation therapy, until recently, the definition of biochemical relapse was three consecutive increases according to the recommendation of ASTRO from 1996 (9). At the 2006 RTOG-ASTRO Consensus conference a new definition of radiation failure was established with as the main aim to establish a better correlation between the definition and clinical outcome. The new definition of radiation failure is a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value) (10). This definition is applicable for patients treated with or without hormonal therapy.

After HIFU or cryotherapy, a variety of definitions for PSA-relapse have been used (11). Most of these are based on a cut-off of around 1 ng/mL, eventually combined with a negative post-treatment biopsy. As yet, none of these end-points have been validated against clinical progression or survival and therefore it is not possible to give firm recommendations on the definition of biochemical failure.

14.3.3 PSA monitoring after radical prostatectomy

PSA is expected to be undetectable within 6 weeks after a successful radical prostatectomy (12). A persistently elevated PSA level means that PSA-producing tissue remains in the body. In patients treated with radical prostatectomy, this is generally thought to be residual cancer due to either micrometastases that were not detected or undetectable beforehand, or residual disease in the pelvis possibly due to positive surgical margins.

A rapidly increasing PSA level (high PSA velocity, short PSA doubling time) indicates distant metastases, while a later and slowly increasing concentration of PSA is most likely to indicate local disease recurrence. The time to PSA recurrence and tumour differentiation are also important predictive factors distinguishing between local and systemic recurrence (13,14). Both local treatment failure and distant metastases have been shown to occur with undetectable PSA levels. This is very rare and occurs almost only in patients with unfavourable pathology (undifferentiated tumours) (15,16).

This means that, in patients with a relatively favourable pathology (< pT3, pN0, Gleason score < 8), PSA measurement, together with the disease-specific history, could stand as the single test in follow-up after radical prostatectomy.

14.3.4 PSA monitoring after radiation therapy

The PSA level falls slowly after radiotherapy compared with radical prostatectomy. The optimal cut-off value for a favourable PSA nadir after radiotherapy is somewhat controversial. Achieving a PSA nadir of less than 0.5 ng/mL seems to be associated with a favourable outcome (17). The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. A PSA rising more than 2 ng/mL above the nadir PSA is the current definition of biochemical failure after radiotherapy (10). Also, after radiotherapy, the PSA doubling time has been shown to correlate to the site of recurrence; patients with local recurrence had a doubling time of 13 months compared to 3 months for those with distant failure (18).

14.3.5 Digital rectal examination (DRE)

DRE is performed to assess whether or not there is any sign of local disease recurrence. It is very difficult to interpret the findings of DRE after curative therapy, especially after radiotherapy. A newly detected nodule should raise the suspicion of local disease recurrence.

As mentioned previously, a local disease recurrence after curative treatment is possible without a concomitant rise in PSA level (15,16). However, this has only been proven in patients with unfavourable pathology, i.e. those with undifferentiated tumours. Thus, PSA measurement and DRE comprise the most useful combination of tests as first-line examination in follow-up after radiotherapy or radical prostatectomy, but PSA measurement may well be the only test in cases with favourable pathology (19).

14.3.6 Transrectal ultrasonography (TRUS) and biopsy

TRUS and biopsy have no place in the routine follow-up of asymptomatic patients and nowadays only rarely after biochemical failure. TRUS cannot stand alone as a diagnostic tool, but must usually be combined with biopsy to establish the presence of local disease recurrence. The purpose of the investigation is to confirm a histological diagnosis of local disease recurrence. It is only warranted if the finding of a local recurrence affects the treatment decision (see Section 16 for a more detailed discussion).

14.3.7 Bone scintigraphy

The purpose of bone scintigraphy is to detect skeletal metastases. It is not recommended for the routine follow-up of asymptomatic patients, but may be indicated in individuals with elevated PSA levels for whom the findings will affect the treatment decision. It is also indicated in patients with symptoms arising from the skeleton, since metastatic disease may occur even if PSA is undetectable (15,16).

14.3.8 Computed tomography (CT) or magnetic resonance imaging (MRI)

CT or MRI have no place in the routine follow-up of asymptomatic patients. They may be used selectively in the evaluation after biochemical failure before treatment decisions are made (see Section 16).

14.4 When to follow-up?

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

margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimen-confined tumour. Obviously, advanced age or associated comorbidity may make further follow-up in asymptomatic patients superfluous.

14.5 Guidelines for follow-up after treatment with curative intent

	GR
• In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	B
• After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.	B
• After radiation therapy, a rising PSA level over 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.	B
• Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.	B
• Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases TRUS and biopsy are not necessary before second-line therapy.	B
• Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be omitted if the serum PSA level is less than 120 ng/mL but data on this topic are sparse.	C
• Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.	B

GR = grade of recommendation

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15. FOLLOW-UP AFTER HORMONAL TREATMENT

15.1 Introduction

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

15.2 Purpose of follow-up

The main objectives of following-up these patients are:

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

However, the usefulness of complementary investigations at various stages of the disease must be clarified in order to avoid unnecessary examinations and excessive economic cost to the community. On the other hand, strict recommendations for follow-up procedures are only useful if effective therapeutic strategies can be offered to patients in cases of disease progression. To date, the issue of early vs late initiation of non-hormonal treatment in castration-refractory PCa (CRPC) has still not been resolved, so follow-up should be performed on an individual basis. Based on current knowledge, it is not possible to formulate strict guidelines for follow-up procedures following hormonal therapy.

15.3 Methods of follow-up

15.3.1 Prostate-specific antigen monitoring

Prostate-specific antigen (PSA) is a good marker for following the course of metastatic prostate cancer (PCa). The prognostic value of PSA (the prediction of the duration of response to endocrine treatment), based on either the initial pre-treatment value or the PSA decrease during the first three to six months, has been used to monitor prostate cancer over the past few decades (1, 2).

The initial PSA level can reflect the extent of metastatic disease, although some poorly differentiated tumours do not secrete PSA. The prognostic value of the pre-treatment PSA value is variably assessed in the literature and should not be used solely to predict the duration of response to treatment (3).

Treatment response may be assessed utilising the change in serum PSA level as a surrogate end-point for survival in patients with newly diagnosed metastatic PCa after hormonal treatment has been initiated. Patients with the lowest absolute value of serum PSA (< 0.2 ng/mL) also had the best survival compared with those obtaining a value of 0.2-4.0 ng/mL or > 4.0 ng/mL (4). Similar results have been seen in other studies of locally advanced and metastatic PCa (5, 6). The PSA response has been shown to be equally important for patients treated with hormonal therapy because of a rising PSA after treatments with curative intent (radical prostatectomy, radiation therapy). Patients with the best response also had the best survival (7, 8).

Despite its usefulness in determining treatment response in individual patients, the role of PSA as a surrogate end-point in clinical trials is more controversial (9). After the initial phase of response to endocrine treatment, patients should be regularly monitored in order to detect and treat any complications of endocrine escape, as clinical disease progression occurs after a median interval of about 12-18 months of treatment in patients with stage M1 disease. It is well established that regular PSA control in asymptomatic patients allows the earlier detection of biochemical escape, as the rise in PSA level usually precedes the onset of clinical symptoms by several months. However, it must be stressed that the PSA level is not a reliable marker of escape and cannot stand alone as a follow-up test. Clinical disease progression (usually bone pain) with normal PSA levels has been reported to occur.

15.3.2 Creatinine, haemoglobin and liver function monitoring

Creatinine monitoring has some value because it can detect upper urinary tract obstruction in cases of advanced cancer that might need to be relieved by, for example, percutaneous nephrostomy or double J-stent.

Haemoglobin and liver function tests could suggest disease progression and/or toxicity of hormonal treatment, which can lead to interruption of hormonal treatment (i.e. liver toxicity from non-steroidal anti-androgens).

The fact that haemoglobin levels will decrease by about 20% with androgen deprivation must be taken into consideration (10).

Alkaline phosphatase and its bone-specific isoenzymes may be used to monitor patients with stage M1b disease. These markers have the advantage of not being directly influenced by hormonal therapy compared with PSA. It should be remembered that increases in serum concentrations of alkaline phosphatase might also be due to osteoporosis induced by androgen deprivation (11). In this scenario, the determination of bone-specific alkaline phosphatase might be helpful.

15.3.3 Bone scan, ultrasound and chest X-ray

In routine practice, asymptomatic patients with a normal PSA level should not have a bone scan at regular intervals as disease progression is more reliably detected by PSA monitoring, which also has a lower cost (12-14).

Moreover, the interpretation of bone scans is sometimes difficult, and the appearance of a new site of uptake or deterioration of pre-existing lesions in an asymptomatic patient does not modify the therapeutic approach.

In cases where there is a clinical or laboratory suspicion of disease progression, a chest X-ray or renal and hepatic ultrasound may be indicated. Imaging modalities must also be guided by symptoms. However, these examinations are not recommended for routine use in asymptomatic patients. In CRPC disease, follow-up examinations should be individualised with the aim of maintaining the patient's quality of life.

During long term androgen deprivation therapy (ADT), regular measurement of bone mineral density (BMD) might be recommended (level of evidence: 3) based on the initial T-score (15): every two years if the initial T-score < 1.0, or yearly if the T-score is between 1.0 and 2.5 in the absence of associated risk factors. Otherwise an active treatment should have started at the initiation of ADT.

15.4 Testosterone monitoring

Most PCa patients receiving LHRH analogues will achieve serum testosterone values at or below the castration level (< 20 ng/dL). However, about 13-38% of patients fail to achieve this therapeutic goal, while 2-17% of patients do not achieve a serum testosterone level below 50 ng/dL (16-18). Furthermore, some men may experience testosterone surges during long-term treatment upon re-administration of the agonist drug, which is described as the 'acute on-chronic effect' (19). Testosterone surges may also be seen at any time during treatment, when they are referred to as 'breakthrough responses'; these may occur in 2-13% of patients on LHRH agonists (20-22).

There is limited information about the optimal level of testosterone necessary to achieve in the treatment of PCa. Recent studies have suggested lower testosterone levels may be associated with improved outcomes. In a study of 73 men with non-metastatic PCa treated with LHRH androgen suppression (23), patients experiencing testosterone breakthroughs had a reduced biochemical survival rate. The mean survival without androgen-independent progression in patients with testosterone breakthroughs (increase > 32 ng/dL) was 88 months (95% CI: 55-121) versus 137 months (95% CI: 104-170) in those without breakthrough increases ($p < 0.03$). In a retrospective series of 129 men with metastatic PCa treated with LHRH agonists, the risk of death was significantly correlated in multivariate analysis with serum testosterone level at 6 months (24).

In view of these findings, the measurement of serum testosterone levels, as well as serum PSA levels, should be considered as part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. The first evaluation of testosterone level can be recommended at 1 month after initiating LHRH therapy to check the nadir testosterone level achieved before re-administration of the agonist drug. A 6-month testosterone level assessment might be performed to evaluate the effectiveness of treatment and to ensure the castration level is being maintained.

Switching to another LHRH agent or surgical orchiectomy can be attempted if this is not the case. In patients with a rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

15.5 Monitoring of metabolic complications

Androgen deprivation therapy (ADT) is beneficial in patients with prostate cancer, but has a greater range of complications than might be expected. The most common side-effects of low testosterone levels include hot flushes, lack of libido, erectile dysfunction, gynaecomastia and loss of bone mineral density. However, in addition, recent studies have suggested that men with low testosterone levels have a higher prevalence of metabolic complications such as insulin resistance (25-27), arterial stiffness (25,26), diabetes (28-30), and metabolic syndrome (31,32). Short-term ADT (3-6 months) leads to the development of insulin resistance (25-27), while long-term ADT (12 months or longer) is associated with hyperglycaemia and frank diabetes (29). Research has shown that the metabolic syndrome is present in more than 50% of the men undergoing long-term ADT, predisposing them to a higher cardiovascular risk (33). Men with metabolic syndrome are almost three times more likely to die of coronary heart disease and other cardiovascular diseases (34), which have now become the most common cause of death in prostate cancer patients, even exceeding prostate cancer mortality (35).

In view of these findings, a cardiology consultation may be beneficial in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months). In selected cases, glucose tolerance testing may be required. Men with impaired glucose tolerance and/or diabetes should be referred for endocrine consultation. Patients on ADT should be given advice on modifying their lifestyle (diet, exercise, smoking cessation, etc) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension (36,37). The monitoring of fasting glucose, lipids profile and blood pressure is recommended in all patients receiving long-term ADT. 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 (38,39).

15.6 When to follow-up

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

15.6.1 Stage M0 patients

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

15.6.2 Stage M1 patients

If there is a good treatment response, i.e. good symptomatic improvement, good psychological coping, good treatment compliance and a serum PSA level of less than 4 ng/mL, follow-up is scheduled every three to six months. Patients should be advised of clinical symptoms that could suggest spinal cord compression and told to consult a physician immediately should they occur.

15.6.3 Castration-refractory PCa

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

15.7 Guidelines for follow-up after hormonal treatment

Recommendation	GR
Patients should first be evaluated at three and six months after the initiation of treatment. As a minimum, tests should include serum PSA measurement, digital rectal examination (DRE), serum testosterone and careful evaluation of symptoms in order to assess the treatment response and the side-effects of the treatments given	B
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given	C
In patients with stage M0 disease with a good treatment response, follow-up is scheduled every six months, and should include as a minimum a disease-specific history, DRE and serum PSA determination	C
In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every three to six 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	C
Patients (especially if M1b status) should be advised on the clinical signs that could suggest spinal cord compression	
When disease progression occurs, or if the patient does not respond to the treatment given, the follow-up needs to be individualised	C
Routine imaging of stable patients is not recommended	B

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16. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENT WITH CURATIVE INTENT

16.1 Background

Primary curative procedures, such as radical prostatectomy (RP) and radiotherapy, are well-established therapeutic options in the management of localised prostate cancer (PCa). Technical advances in surgery have improved therapeutic efficacy, while improvements in radiation therapy have decreased treatment-associated morbidity and toxicity. However, there still remains a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing radiation therapy or RP will develop local or distant recurrences within 10 years of initial therapy, and 16-35% of patients will receive second-line treatment within 5 years of initial therapy (1-6).

16.2 Definitions

16.2.1 Definition of treatment failure

In previous years, treatment failure was defined as a recurrence on digital rectal examination (DRE) or the development of metastatic disease. Currently, treatment failure is defined as a rising PSA level, following a study by Pound et al. (7), which showed that no patient followed up for more than 5 years developed any recurrence without a concomitant rise in PSA.

The PSA level that defines treatment failure differs between patients treated with RP and those treated with radiotherapy. Following radical retropubic prostatectomy (RRP), two consecutive values of PSA > 0.2 ng/mL appear to represent an international consensus defining recurrent cancer (6,8). However, the most appropriate definition of biochemical progression after RP is still uncertain.

In a retrospective analysis of 2,782 men who had undergone RP for clinically localised PCa, Amling et al. (9) determined the best PSA cut-off point for defining biochemical recurrence. Once PSA recurrence was detected, a subsequent increase in PSA was noted in 49%, 62% and 72% of patients who had PSA levels of 0.2 ng/mL, 0.3 ng/mL and 0.4 ng/mL, respectively. These data indicate that only half of patients with a PSA of 0.2 ng/mL will progress further, and that these patients can therefore initially be managed by surveillance (9). Similar data have been presented by Stephenson et al. (2006) (10), who identified a PSA value \geq 0.4 ng/mL as the best cut-off point to explain the development of distant metastases from among 10 candidate definitions, which were derived from a retrospective review of 75 patients who had developed distant metastases after RP. A cut-off of 0.4 ng/mL is therefore appropriate for defining progression with clinical relevance necessitating salvage treatment.

Following radiotherapy, a reasonable definition of biochemical relapse is three consecutive increases, according to the recommendation of the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel (11). The new definition indicates a relapse if the PSA increase is \geq 2 ng/mL higher than the PSA nadir value, independent of the serum concentration of the nadir (12).

16.2.2 Definition of recurrence

- Following RP, PSA values > 0.2 ng/mL confirmed by two consecutive measures represent recurrent cancer.

- Following radiotherapy, a PSA value of 2 ng/mL above the nadir after radiotherapy represents recurrent cancer.

16.3 Local or systemic relapse

With regard to further management, once PSA relapse has been diagnosed, it is of major importance to determine whether the recurrence has developed at local or distant sites. About 50% of patients who underwent RRP will have local disease, and the remainder will have either distant disease alone, or distant and local disease (11).

Important parameters to help differentiate between local or distant relapse include:

- timing of the PSA increase after surgery
- PSA velocity (PSA Vel);
- PSA DT;
- pathohistological stage;
- Gleason score of the prostatectomy specimen.

Elevations in PSA level that develop within the first 2 years following surgery are more likely to be associated with distant recurrences (12). Research has shown that a median PSA doubling time (PSA DT) of ≤ 4 months might be associated with distant relapse, whereas a median PSA DT of ≥ 12 months predicts local failure (13). According to a recent study (14), PSA velocity of < 0.75 ng/mL/year was observed in 94% of patients with local recurrence, whereas 56% of patients with distant metastases demonstrated a PSA velocity of > 0.75 ng/mL/year. There is no indication for performing ultrasound-guided biopsies of the vesicourethral anastomosis to diagnose local relapse because of the low sensitivity and low predictive accuracy of this method in men with rising PSA levels < 1.0 ng/mL.

With radiotherapy, any continuously rising PSA following a nadir after radiation therapy is an indicator for local recurrence, systemic metastatic spread, or a combination of both (11,14-16). However, due to the well-known PSA bounce phenomenon, biochemical recurrence is defined by a PSA rise 2 ng/mL above the PSA nadir according to ASTRO guidelines. After radiotherapy, a late and slowly rising PSA is a sign of local failure only.

Local recurrence is defined by:

- Prostatic biopsy demonstrating malignant cells 18 months or longer after initial radiotherapy together with an associated rise in PSA. Prostate biopsy, however, is only indicated if the patient is being considered for a secondary local salvage therapy with curative intent
- and**
- No evidence of metastatic spread documented by computed tomography (CT) or magnetic resonance imaging (MRI) and bone scintigraphy.

16.3.1 Definition of local and systemic failure

- Local failure following RP is predicted with an 80% probability by PSA increase > 3 years after RP, a PSA DT ≥ 11 months, a Gleason score ≤ 6 , and stage \leq pT3a pN0, pTx R1.
- Systemic failure following RP is predicted with $> 80\%$ accuracy by a PSA increase < 1 year after RP, a PSA DT of 4-6 months, a Gleason score of 8-10, and stage pT3b, pTxpN1.
- Local failure after radiotherapy is documented by a positive prostatic biopsy and negative imaging studies.
- Prostatic biopsy after radiotherapy is necessary only if local procedures such as salvage prostatectomy are indicated in an individual patient.

16.4 Evaluation of PSA progression

Prior to extensive diagnostic work-up in patients with PSA relapse following local treatment, men must be stratified into patients who are candidates for salvage therapy and those who are not. Patients must then be further stratified into candidates for local salvage treatment and those who might need systemic therapy. All diagnostic procedures only have to be performed if they are likely to have therapeutic consequences.

In recent years, disease recurrence would be confirmed in patients, who showed PSA progression following initial therapy with curative intent, by further investigations, including physical and sonographic examinations, as well as radiographic studies or biopsies of the prostatic fossa and the vesicourethral anastomosis.

For patients with asymptomatic, PSA-only progression, the yield is very low. Lange et al. (14) have shown that biochemical failure precedes clinical disease by 6-48 months. In general, DRE is not useful in men with

undetectable or very low PSA levels. In a recent study by Öbek et al. (17), only 4/72 patients (5.5%) with a PSA recurrence following RP had an abnormal DRE.

Imaging studies are performed to differentiate local from systemic relapse to ensure the most appropriate treatment modality is used. However, it must be remembered that most imaging studies may not be sensitive enough to identify the anatomical location of relapsing PCA at PSA levels below 0.5 ng/ml or 1.0 ng/mL.

16.4.1 Diagnostic procedures for PSA relapse following RP

Traditionally, bone scans and abdominal CT scans have been used to evaluate PSA elevations following primary treatment. Both imaging studies, however, are characterised by a low sensitivity and specificity and might be safely omitted in the routine work-up of relapsing patients. Recently, Cher et al. (18) studied 144 bone scans in 93 patients with PSA recurrence after RRP, of which 122 patients had undergone RP without any hormone treatment, whereas 22 patients had received either neoadjuvant or adjuvant androgen-deprivation therapy (ADT). Only 4.1% and 27% of the bone scintigrams were positive for metastatic disease; the lowest PSA associated with positive findings was 46 ng/mL in the absence of adjuvant ADT, whereas the lowest PSA value was 15.47 ng/mL in patients who had received hormonal therapy (HT).

The likelihood of a positive bone scan remains $\leq 5\%$ until the serum PSA level reaches at least 40 ng/mL. Similar data have been achieved by other groups, who demonstrated that patients with a true positive bone scan had an average PSA level of > 60 ng/mL and a PSA velocity of 22 ng/mL/year (19,20). On logistic regression analysis, PSA and PSA velocity predicted the findings on bone scan, and PSA velocity predicted the CT scan result. The probability of a positive bone scan and a positive CT scan was 9.4% and 14%, respectively, among the 132 patients with biochemical recurrence. However, there might be a slight difference between patients after RRP compared with patients after radiation therapy, as demonstrated by Johnstone et al. (21) in whose study 5% and 30%, respectively, of the bone scans, were positive.

In summary, bone scintigraphy and CT scans are of no additional diagnostic value unless the PSA serum levels are higher than 20 ng/mL or the PSA velocity is more than 20 ng/mL/year.

Endorectal coil imaging has been described as a useful technique to detect local recurrences after RP (22). In a series of 48 patients, local recurrence was correctly identified in 81%, with the mean PSA being 2 ng/mL at the time of diagnosis.

In another series of 72 men with PSA relapse following RP, the diagnostic accuracy of endorectal MRI was evaluated (23). The mean total PSA was 1.23 \pm 1.3 ng/mL and men underwent endorectal MRI on a 1.5-T system. These data were compared to various references for local recurrence:

- Prostatectomy bed biopsy results;
- Choline positron emission tomography results;
- PSA reduction or increase after pelvic radiotherapy;
- PSA modification during active surveillance.

Sensitivity, specificity, predictive positive value, negative predictive value and accuracy were 61.4%, 82.1%, 84.4%, 57.5%, and 69.4% for unenhanced endorectal MRI and 84.1%, 89.3%, 92.5%, 78.1%, and 86.1% for enhanced-endorectal MRI. A statistically significant difference was found between the accuracy and sensitivity of the two evaluations ($\chi^2 = 5.33$; $p = 0.02$ and $\chi^2 = 9.00$; $p = 0.0027$).

Although endorectal MRI appears to be very sensitive and predictive in identifying local recurrences following RP, it is currently not a routine imaging modality to be performed in each individual case. This is because local versus systemic relapses are differentiated at PSA levels below 0.5 ng/mL (see Section 16.6). At these PSA levels, endorectal MRI is still too insensitive and too inaccurate.

Positron emission tomography (PET) has been successfully applied in many human cancers for early identification of local or systemic recurrences. In PCa, there are few, but promising, published data on the clinical efficacy of PET in detecting local recurrences after RP (23,24). However, it must be remembered that the uptake of ^{11}C -choline is not specific for PCa and may sometimes be due to inflammatory intraprostatic lesions.

In a series of 31 patients with biochemical progression after RP, (^{11}C)acetate-PET demonstrated a high sensitivity and specificity for detecting local recurrences at PSA serum levels > 1 ng/mL (24). In another recent series of 43 patients with newly diagnosed PCa, there was a significant correlation between the ^{11}C -choline

uptake and the intraprostatic location of PCa as analysed in RP specimens (25). Similar results have been reported for the detection of locally recurrent PCa after radiation therapy (26). However, sensitivity with regard to extraprostatic extension was significantly lower for ^{11}C -PET when compared with MRI.

The most recent series to evaluate the role of ^{11}C -choline PET/CT in patients with biochemical recurrence after RP identified a significant PSA relationship: the sensitivity to identify the localisation of metastases was 20-36% at PSA levels ≤ 1 ng/mL, and increased to 63-83% in men with PSA levels ≥ 3 ng/mL (27-30).

Castelucci et al. (2009) (31) evaluated the effect of total prostate-specific antigen (PSA) at the time of (11)C-choline PET/CT (trigger PSA), PSA Vel, and PSA DT on (11)C-choline PET/CT detection rate in 190 patients with PSA relapse following RP (mean, 4.2; median, 2.1; range, 0.2-25.4 ng/mL). (11)C-choline PET/CT detected disease relapse in 74 of 190 patients (38.9%). The detection rate of (11)C-choline PET/CT was 25%, 41%, and 67% in the four PSA subgroups:

- 19% in the PSA group, ≤ 1 ng/mL (51 patients)
- 25% in the PSA group, $1 < \text{PSA} \leq 2$ ng/mL (39 patients)
- $2 < \text{PSA} \leq 5$ ng/mL (51 patients)
- $\text{PSA} > 5$ ng/mL (49 patients).

Trigger PSA values were statistically different between PET-positive patients (median PSA, 4.0 ng/mL) and PET-negative patients (median PSA, 1.4 ng/mL) ($p = 0.0001$) with the optimal cut-off point for a trigger PSA of 2.43 ng/mL. In 106 patients, the PSA DT and PSA Vel values were statistically different between patients with PET-positive ($p = 0.04$) and PET-negative scan findings ($p = 0.03$). The (11)C-choline PET/CT detection rate was 12%, 34%, 42%, and 70%, respectively, in patients with PSA Vel < 1 ng/mL/year (33 patients), $1 < \text{PSA Vel} \leq 2$ ng/mL/years (26 patients), $2 < \text{PSA Vel} \leq 5$ ng/mL/years (19 patients), and $\text{PSA Vel} > 5$ ng/mL/y (28 patients). The (11)C-choline PET/CT detection rate was 20%, 40%, 48%, and 60%, respectively, in patients with PSA DT > 6 months (45 patients), $4 < \text{PSA DT} \leq 6$ months (20 patients), $2 < \text{PSA DT} \leq 4$ months (31 patients), and $\text{PSA DT} \leq 2$ months (10 patients).

The role of choline PET/CT in detecting local or systemic recurrences in men with PSA relapse following radiotherapy is unclear and based on very few studies (32,33). Thus, no final recommendations can be made. Its sensitivity and specificity with regard to the detection of lymph node metastases is less reliable, and the routine use of ^{11}C -PET cannot therefore be recommended, especially not for PSA values < 1 ng/mL.

Immunoscintigraphy, which uses a radiolabelled monoclonal antibody based on prostate-specific membrane antigen for messenger RNA (PSMA), known as ^{111}In -indium capromab pendetide, might represent an innovative diagnostic approach. Its overall accuracy is up to 81% to detect the site of relapse in PSA-only recurrences following RRP (34-37). Independent of the PSA serum concentration, a capromab pendetide scan shows a diagnostic yield of 60-80%, and may help to stratify therapy according to the location of positive sites. A recent study (35) investigating 255 patients with PSA-only recurrence < 4.0 ng/mL after RP, showed capromab pendetide uptake in 72% throughout the range of post-operative PSA serum levels (0.1-4.0 ng/mL). Approximately 31%, 42% and 25% of patients exhibited local uptake, locoregional uptake and distant uptake, respectively, enabling therapy to be targeted according to the differentiation of local versus systemic relapse.

However, immunoscintigraphy is not widely available and due to sparse results it can only be regarded as an experimental imaging modality not to be used in daily clinical routine.

It was common practice to exclude local recurrence after RRP or radiotherapy by performing transrectal ultrasound (TRUS)-guided biopsies of the prostatic fossa, the anastomosis or the prostate gland. However, available studies indicate that routine biopsy of the vesicourethral anastomosis is not justifiable based on a verification rate of only 54% (33-37). The diagnostic yield of the biopsy improves to approximately 80% only in the presence of a palpable lesion or a hypoechoic lesion on TRUS. Furthermore, a strong correlation has been shown between the PSA serum level and a positive biopsy (36-40); 28% and 70% of the biopsies were positive if the PSA level was, respectively, < 0.5 ng/mL or > 2.0 ng/mL.

These findings therefore indicate that the use of PSA and PSA DT is sufficient for clinical practice and routine anastomotic biopsy is not necessary. In addition, PSA-free survival in biopsy-proven recurrences does not differ significantly compared with PSA-only recurrences.

16.4.2 Diagnostic studies for PSA relapse following radiation therapy

With regard to PSA relapses following radiation therapy, routine prostate biopsy should no longer be performed

for the evaluation of PSA-only recurrences, according to an ASTRO consensus recommendation (15). However, prostate biopsy documenting local recurrence represents the main cornerstone in the decision-making process for salvage radical prostatectomy in patients with rising PSA levels following a nadir after radiation therapy (41). It is a general recommendation to wait about 18 months after radiation therapy or seeds and 3 months after cryotherapy or high-intensity focused ultrasound (HIFU). Patients with rising PSA and viable cancer on biopsy 2 years after radiation therapy have true locally recurrent disease and may be candidates for radical salvage prostatectomy.

Recent studies have evaluated the role of endorectal MRI, MRI spectroscopy and dynamic-contrast enhanced MRI in the identification of locally recurrent PCA following radiation therapy (42-44). These studies demonstrated that locally recurrent PCA could be differentiated from benign nodules due to the low T2-weighted signal intensity. Endorectal MRI and MR spectroscopy were more sensitive than TRUS or TRUS-guided prostate biopsies to detect viable PCA. Endorectal MRI also contributed important information with regard to the presence of extracapsular extension and seminal vesicle invasion with sensitivity and a specificity of 86% and 96%, respectively.

It is therefore strongly recommended that endorectal MRI is part of the diagnostic work-up of men with PSA relapse after radiation therapy, who might be candidates for secondary local salvage therapy with curative intent.

16.4.3 Diagnostic procedures in patients with PSA relapse

- Following RP, CT scans of the pelvis and abdomen are of low sensitivity and specificity in patients with PSA levels < 20 ng/mL or a PSA velocity of < 2 ng/mL/year.
- Endorectal MRI or PET scans may help to detect local recurrences if PSA is > 1-2.0 ng/mL, but are not routine clinical practice for the early detection of local relapses.
- Following radiation therapy, local recurrence is documented by a positive biopsy > 18 months after the procedure.
- Endorectal MRI is of valuable importance for men who are candidates for radical salvage prostatectomy.

16.5 Treatment of PSA-only recurrences

The timing and mode of treatment of PSA-only recurrence after RP or radiation therapy remains controversial. After RRP observation, the therapeutic options are:

- radiation therapy to the prostatic bed;
- (complete) androgen blockade (CAB);
- intermittent androgen deprivation (IAD);
- combination of antiandrogens with 5- α -reductase inhibitors;
- early chemohormonal approaches.

These same therapeutic options may be applied to PSA recurrences following radiation therapy. In addition, salvage prostatectomy, cryotherapy or brachytherapy may be indicated in carefully selected patients.

16.5.1 Radiation therapy for PSA-only recurrence after radical prostatectomy

Three large randomised controlled trials in adjuvant radiation have now been published (45-48). All three trials showed a benefit with adjuvant radiotherapy of at least 15% at 5 years in biochemical recurrence-free survival. The largest trial (EORTC-22911, n = 1005) and the smallest trial (ARO-96-02, n = 307) trial were powered to detect a benefit in biochemical disease recurrence-free survival, while metastasis-free survival was the primary endpoint of the third trial, SWOG-S8794 (n = 431). The three trials had similar inclusion criteria; however, the EORTC trial also included pT2R1 patients, while the other two trials allowed only pT3 cancers with or without a positive resection margin. In all three trials, quite a high proportion of patients (63-68%) had a positive surgical margin.

It should be noted that the post-operative PSA level of men before they were randomised to adjuvant radiotherapy was different between the three trials. In the German ARO-96-02 trial, only men with a PSA < 0.1 ng/mL were eligible for randomisation. In the EORTC trial, 11% of men had a PSA level > 0.2 ng/mL prior to randomisation and 34% in the SWOG trial. Thus, a substantial number of patients in the EORTC and SWOG trials received 'salvage' radiation rather than adjuvant radiotherapy for a non-normalised PSA.

It is therefore interesting that not all men in the non-adjuvant arms of the trials were treated with salvage radiotherapy by the time of a biochemical recurrence: delayed or salvage radiotherapy to the prostatic fossa was administered to 55% of men with a rising PSA level in the EORTC trial and to 33% of men in the SWOG trial. Thus, the trials were not able to evaluate whether adjuvant radiation was superior to salvage radiation as, in the control arm, only half of the men at most received radiation at the time of PSA recurrence.

Indeed, the authors of the EORTC trial suggested that salvage radiation may be equivalent to adjuvant therapy, provided the PSA is lower than 1 ng/mL (46). However, only the SWOG trial was powered to address the effect of delayed radiation since it was the only trial with metastasis-free survival as the primary endpoint. In the SWOG trial, men in the control arm were less likely to receive salvage radiation (33%). However, it took a median follow-up of over 12 years before metastasis-free survival improved in the adjuvant treatment arm, suggesting that adjuvant therapy may not be helpful in men with a life expectancy < 10 years (45,47).

There have been many studies on the use of radiation therapy for PSA-only recurrence following RRP. As a result, there is a growing body of parameters predicting outcome that may help to differentiate between the need for observation, radiation or HT. As confirmed by various studies, the pre-radiation PSA level is critically important for optimal treatment results (41-44,49-53):

- Applying a pre-radiation cut-off of < 2.5 ng/mL, Wu et al. (49) and Schild et al. (50) reported disease-free survival rates of 53% and 76%, compared with 8% and 26%, respectively, for patients with PSA serum levels > 2.5 ng/mL.
- Forman et al. (1997) (51) demonstrated a disease-free survival rate of 83% versus 33% in patients with a PSA-only recurrence of < 2.0 ng/mL and greater than 2.0 ng/mL, respectively.
- Nudell et al. (1999) (44) even reported progression-free survival rates of 58% and 21% in patients having undergone radiation of the prostate bed if PSA serum levels were below 1.0 ng/mL or greater than 1.0 ng/mL, respectively.

Based on these data, ASTRO has published a consensus paper recommending a dose of at least 64 Gy when the PSA level is < 1.5 ng/mL after RRP (15). Furthermore, recent papers (53-58) have corroborated the data of early salvage radiation therapy, demonstrating a significant difference in 5-year biochemical-free and OS rates in patients treated for PSA-recurrence only or for palpable local recurrence. In another study, Stephenson et al. (2007) (59) evaluated prognostic models to predict the outcome of salvage radiation therapy on a cohort of 1,603 men with PSA progression after RP and operated on in 17 North American tertiary referral centres. The authors identified a significant relationship between PSA serum concentration at the time of radiation therapy and therapeutic outcome: the 6-year biochemical-free survival was 48% in men with PSA < 0.5 ng/mL, whereas it was only 40%, 28%, and 18% in men with PSA levels of 0.51-1 ng/mL, 1.01-1.5 ng/mL and > 1.5 ng/mL, respectively.

For the SWOG and EORTC non-adjuvant radiotherapy arms, the median interval to salvage radiotherapy was 2 and 2.2 years, respectively. In the SWOG 8974 study, 23% of men had a PSA > 1.5 ng/mL prior to salvage radiation. In a subanalysis of the SWOG 8974 trial, Swanson et al. (2007) (60) showed that men in all categories of post-prostatectomy PSA level (< 0.2, 0.2-1.0, > 1.0 ng/mL) showed an improvement with salvage radiotherapy in metastasis-free survival. However, the therapeutic benefit was most evident in the presence of minimal PSA serum levels. These data suggest that, although less effective, salvage radiation may help improve metastasis-free survival.

In a recent, multi-institutional, matched-control analysis of adjuvant and salvage post-operative radiation for pT3-4N0 PCa, Trabulsi et al. (2008) (61) have demonstrated a biochemical recurrence-free survival advantage in favour of adjuvant radiotherapy versus salvage radiotherapy. Interestingly, in a multivariate Cox regression analysis, adjuvant versus salvage radiotherapy were not independent predictors in metastatic progression-free survival, when corrected for adverse clinical and pathological factors.

Recently, data on overall survival and salvage radiation have become available. In a group of men with a median follow-up of 9 years after prostatectomy, the benefit of salvage radiation for prostate cancer-specific mortality was seen particularly in men with a PSA DT of less than 6 months, who had been given salvage radiation to the prostate fossa within 2 years after a rise in PSA (62). This suggests that local disease control may prolong prostate cancer-specific survival in men formerly thought to be at risk for systemic disease progression and less likely to benefit from (salvage) radiation. It has been suggested that men with slowly progressing disease, even though still at risk of systemic progression, may not benefit from salvage radiotherapy because they have a low risk of development of lethal PCa. Certainly, longer follow-up is needed to answer this question.

However, more data are required from prospective randomised trials.

16.5.1.1 Dose, target volume, toxicity

The three randomised trials on adjuvant radiation therapy all used dosages less than 66 Gy, which is currently the most frequently used dose for adjuvant and salvage radiation. However, it is important to note that, as with dose escalation studies in primary radiation for PCa, an increased dose in the salvage setting may improve

the biochemical response without worsening local toxicity (63,64). Dosages up to 70 Gy showed better biochemical recurrence-free rates at higher doses, with 66.8 Gy radiation found to be the dose required for 50% biochemical recurrence-free survival (TCD50). Even higher doses may be considered, particularly when using improved imaging techniques, such as fiducial markers (65). The finding that 9% of men develop a local recurrence after adjuvant radiation of 60 Gy provides support for an increase in dosage and target volume (60).

Target volume delineation has been found to vary by up to 65% between different radiotherapists administering adjuvant or salvage radiation to the prostatic fossa (66,67), despite the presence of guidelines (68). It is therefore important not to overlook local toxicity. In the EORTC 22911 study, 3.1% of men had to interrupt adjuvant radiation because of local complaints, mainly diarrhoea. Although grade 3 or 4 toxicity is rare for either adjuvant or salvage radiation to the prostate fossa, it was almost doubled in the adjuvant arm of the EORTC 22911 study (2.6% vs 4.2%) and the SWOG S8794 study, particularly urethral stricture (relative risk [RR], 9) and incontinence (RR, 2.3).

16.5.2 Hormonal therapy

Systemic failure following RP is predicted with $\geq 80\%$ accuracy by PSA relapse ≤ 1 year, PSA DT of 4-6 months, Gleason score 8-10 and stage pT3b, pT4pN1. There is some evidence that early HT may help to delay progression and possibly achieve a survival benefit (69,70).

16.5.2.1 Adjuvant hormonal therapy after radical prostatectomy

In the absence of randomised controlled trials for post-operative PSA recurrence, it is necessary to rely on retrospective data or to extrapolate data from other clinical settings, such as men with metastatic disease or locally advanced non-metastatic disease. It is uncertain whether or not such data are relevant to men with rising post-operative PSA levels.

Two randomised studies have compared immediate HT (after diagnosis) with deferred HT (on progression) in patients with PCa. The Medical Research Council study in locally advanced or asymptomatic metastatic PCa and the European Organisation for Research and Treatment study in newly diagnosed PCa (T0-4N0M0) illustrate that, although immediate HT after diagnosis can delay disease progression in men with PCa, it does not necessarily result in an improved CSS (71,72).

The survival advantage for immediate (adjuvant) ADT after RP has only been proven in patients with positive-lymph-node PCa in a single randomised study (69,70). The updated results of this multicentre Eastern Cooperative Oncology Group study after a median follow-up of 11.9 years showed a significant improvement in overall survival (OS), cancer-specific survival (CSS) and progression-free survival (PFS) in lymph-node-positive (N+) patients treated with immediate ADT (70).

Adjuvant bicalutamide, 150 mg, could decrease progression in men with locally advanced PCa, but did not result in an OS benefit (73). Several retrospective analyses from the Mayo Clinic showed that adjuvant HT after RP had a positive effect on time to progression and cancer death in patients with pT3b and N+ PCa (74-76). However, a recent large series from the Mayo Clinic with a median follow-up of 10.3 years showed that adjuvant HT in patients with surgically managed N+ PCa decreased the risk of biochemical recurrence and local recurrence, but did not significantly impact systemic progression or CSS (77). A recent retrospective study with a median follow-up of 5.2 years showed that immediate and delayed HT (at PSA recurrence) in patients with surgically managed N+ PCa provided similar outcomes (78).

An observational study showed that deferring immediate ADT in men with positive lymph nodes after RP may not significantly compromise survival. There was no statistically significant difference in survival with 90, 150, 180 and 365 days as the definition of adjuvant ADT. These results need to be validated in a prospective study (79).

16.5.2.2 Post-operative HT for PSA-only recurrence

Androgen deprivation

Although patients with post-operative PSA recurrence often undergo ADT before evidence of metastatic disease, the benefit of this approach is uncertain. A retrospective study including 1352 patients with post-operative PSA recurrence showed no significant difference in the time to clinical metastases with early ADT (after PSA recurrence, but before clinical metastases) versus delayed ADT (at the time of clinical metastases). However, upon risk stratification, early ADT could delay the time to clinical metastases in high-risk patients with a Gleason score > 7 and/or a PSA DT ≤ 12 months. Androgen deprivation therapy had no overall impact on prostate cancer-specific mortality (80).

A recent retrospective study from the Mayo Clinic showed that adjuvant ADT (within 90 days of surgery)

slightly improved the CSS and systemic PFS after RP in a large group of high-risk patients with PCa. However, the survival advantage was lost when ADT was delivered farther in the disease process, at the time of PSA recurrence or systemic progression. It should be emphasised that there was no OS advantage (83% for both groups) and that the difference in CSS and systemic PFS was only 3% and 5%, respectively (81). In a recent retrospective study, including 422 patients with post-operative PSA recurrence, 123 developed distant metastasis, of whom 91 patients with complete data received deferred ADT at the time of documented metastasis after RP. The authors concluded that patients when closely followed after PSA recurrence may have an excellent response to deferred ADT and a long survival with a median failure time of 168 months from RP to death (82). However, these three studies are limited by their retrospective design and in assessing the side-effects of long-term ADT. Evidence from well-designed, prospective, randomised studies is needed before the use of early HT can be advocated in clinical practice.

Antiandrogens

Although gynaecomastia and breast tenderness were the most predominant side-effects for the treatment of organ-confined and locally advanced PCa, the incidence of hot flushes, loss of libido and impotence was significantly lower than expected for luteinising hormone-releasing hormone (LHRH) agonists and CAB (83). Antiandrogens may represent a viable alternative to other modes of androgen deprivation for the management of PSA-only recurrences, especially in young and otherwise healthy men.

In a prospective, placebo-controlled, randomised trial of adjuvant bicalutamide, 150 mg, following RP in patients with locally advanced disease, the risk of objective progression of the disease was significantly reduced in patients receiving bicalutamide. However, OS did not differ between groups (84). Low-dose flutamide, 250 mg daily, is currently being investigated in men with PSA recurrence. Bicalutamide, 150 mg daily, has not yet been studied in this clinical setting (85).

Intermittent androgen deprivation

Intermittent androgen deprivation has been examined as a potential alternative to CAD:

- to delay the time to androgen independence and hormone-refractory disease;
- to minimise the side-effects;
- to reduce the costs of prolonged therapy.

Recently, the Cochrane Collaboration revealed that there were no long-term data of large-scale randomised controlled trials that proved the superiority of IAD over CAD in terms of its effect on survival. Limited information suggests that IAD may result in a slight reduction of adverse effects (86). In the setting of PSA-only recurrences, however, there are no prospective randomised trials and no clinical studies with sufficient data on long-term efficacy to justify a routine clinical application of IAD, despite its potential benefits. Summarising the series in which PSA-only recurrences were treated by IAD (87-91), PSA threshold levels at study-entry varied significantly, as did the PSA level at discontinuation of HT. Only the study of 150 patients by Tunn et al. (2003) (91) had a sufficiently appropriate study design to allow the drawing of important clinical conclusions. Patients were started on IAD for 9 months when the post-prostatectomy PSA serum level was greater than 3.0 ng/mL, and all patients reached a nadir of less than 0.5 ng/mL. Intermittent androgen deprivation was re-started when PSA increased to more than 3.0 ng/mL. After a mean follow-up of 48 months, and a mean duration of HT of 26.6 months, none of the patients had progressed to hormone-refractory disease. In the meantime, IAD remains attractive to selected, closely monitored and well-informed patients with post-operative PSA recurrence.

Minimal androgen blockade

In some studies, finasteride and flutamide have been combined to manage PSA-only recurrences since both agents work additively by blocking the intraprostatic conversion of testosterone to dihydrotestosterone (DHT), and blocking the intracytoplasmic DHT receptor (92-94). In the latest report (93), including 73 patients, the application of finasteride (10 mg/day) and low-dose flutamide (250 mg/day) resulted in a mean PSA nadir of 1.35 ng/mL within 6 months. However, only 62% of the patients studied reached a PSA nadir of < 0.2 ng/mL. After a mean follow-up of 15 months, none of the patients had progressed to traditional HT. However, longer follow-up of a larger patient cohort is needed, and randomised phase III trials using modern antiandrogens with fewer gastrointestinal and hepatic side-effects are mandatory.

HT after RP combined with RT and/or chemotherapy

The addition of HT to salvage RT (n = 78) was not associated with any additional increase in CSS (94). A recent phase II trial including 74 patients with post-operative PSA recurrence showed that combined treatment with salvage RT plus 2 years' maximum androgen blockade (castration + oral antiandrogen) had relatively

minor long-term effects on QOL (95). However, more efficacy data are needed and the potential increase in side-effects should be considered when combining therapies. Results are eagerly awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo versus the combination of RT + bicalutamide, 150 mg daily, in the post-operative setting.

Radiotherapy and Androgen Deprivation in Combination after Local Surgery is a recently started, large, randomised, controlled study, sponsored by the Medical Research Council. The study addresses the timing of RT (adjuvant vs early salvage) and the duration of HT (none vs short-term vs long-term) used together with post-operative RT. The primary outcome measures will be CSS. Secondary outcome measures will include OS, ADT administered outside the protocol, and reported treatment toxicity. The study also aims to assess the long-term effect of RT after RP on sexual, urinary and bowel function, and the long-term effect of ADT on sexual function and overall QOL. Patients will be asked to complete four short questionnaires. These assessments will be done at baseline, and at 5 and 10 years (96).

Currently, there is no indication for chemotherapy in patients with PSA-recurrence only. Chemotherapy should be considered as a treatment option for patients with hormone-refractory PCa, but when to initiate a cytotoxic regime remains controversial (97).

16.5.3 Observation

Observation until the development of clinically evident metastatic disease might represent a viable option for patients with a Gleason score ≤ 7 , PSA recurrence longer than 2 years after surgery, and a PSA DT longer than 10 months. In these patients, the median actuarial time for the development of metastasis will be 8 years, and the median time from metastasis to death will be another 5 years (7).

16.5.4 Management of PSA relapse after RP

Recommendations	GR
Local recurrences are best treated by salvage radiation therapy with 64-66 Gy at a PSA serum level ≤ 0.5 ng/mL	B
Expectant management is an option for patients with presumed local recurrence who are too unfit or unwilling to undergo radiation therapy	B
PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases	B
Luteinising hormone releasing hormone (LHRH) analogues/orchiectomy or bicalutamide, 150 mg/day, can both be used when there is an indication for hormonal therapy	A

GR = grade of recommendation

16.6 Management of PSA failures after radiation therapy

In a recent review of the data of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) comprising 2336 patients with PCa, Grossfeld et al. (2002) (98) demonstrated that 92% of patients initially irradiated received ADT for secondary treatment of PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 years.

Therapeutic options in these patients are ADT or local procedures, such as salvage RP, cryotherapy and interstitial radiation therapy (41,99-108). Salvage RRP has not, however, gained widespread acceptance because of its associated morbidity, namely incontinence, local recurrences and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

16.6.1 Salvage RP

Previously, most series reporting on salvage RP have included patients treated in the pre-PSA era without modern radiotherapeutic techniques, when local recurrences were usually detected at a late stage. Complications associated with the procedure were therefore quite high, with up to 65% of patients suffering from treatment-related morbidities. Up to 60% of patients who underwent salvage RP had to undergo anterior or total exenteration for locally extensive disease associated with a high rate of local recurrences and a mean time to progression of only 1.3 years.

Recent reports analysing patients who were operated on during the past decade, have described far more optimistic outcomes after salvage RP. In the series examined by Gheiler et al. (1998) (103), 40 patients with a

mean PSA of 14 ng/mL underwent salvage RP. When stratified by PSA \leq 10 ng/mL, the 3-year disease-specific survival was 68% and 26%, respectively.

In the series reported by Garzotto and Wajzman 1998) (104), 24 patients underwent radical cystoprostatectomy or RP with neoadjuvant ADT. Neoadjuvant ADT was associated with a lower rate of positive surgical margins (21%) compared with patients in whom androgen deprivation failed and who exhibited a positive surgical margin rate of 80%. The authors demonstrated that disease-specific survival correlated strongly with the surgical margin status. At a mean follow-up of 5 years, the disease-specific survival rate was 95% and 44% for those with negative and positive surgical margins, respectively.

Vaidya and Soloway (2000) (105) demonstrated a low rate of complications, good post-operative continence and only one biochemical recurrence at 36 months after salvage RP.

Similar data have been achieved by Stephenson et al. (2004) (106), who reported on 100 consecutive patients undergoing salvage RP associated with a very low rate of peri-operative complications. The 5-year progression-free rates have improved, with results similar to those of standard RP in cases of similar pathological stages. In contemporary series, the 10-year CSS and OS rates are in the ranges of 70-75% and 60-66%, respectively. In most contemporary series, organ-confined disease, negative surgical margins and the absence of seminal vesicle and/or lymph node metastases are favourable prognostic indicators associated with a better disease-free survival of approximately 70-80%, compared with 40-60% in patients with locally advanced PCa (107).

Recently, Heidenreich et al. (2010) (108) reported on the oncological and functional outcome of 55 patients who underwent radical salvage therapy for locally recurrent PCA after various types of modern state-of-the-art radiation therapy, performed in or after the year 2000. Forty (72.7%) and 15 (27.3%) patients demonstrated organ-confined and locally advanced PCa, respectively. Eleven patients (20%) and seven patients (14%) had lymph node metastases and positive surgical margins (PSM), respectively. On multivariate analysis, significant predictors of organ-confined PCa with negative surgical margins were:

- biopsy Gleason score prior to salvage RP ($p = 0.02$)
- $< 50\%$ positive biopsy cores ($p = 0.001$)
- PSA DT > 12 months ($p = 0.001$)
- low-dose brachytherapy ($p = 0.001$).

Urinary continence was achieved after a mean of 8 months in basically all men after low-dose-radiation brachytherapy; incontinence persisted in about 20% of patients who underwent external beam radiation therapy or high-dose radiation brachytherapy. Salvage RP is a surgically challenging but effective secondary local treatment of radio-recurrent PCa with curative intent. The identified predictive parameters will help to select patients most suitable for salvage RP with long-term cure and good functional outcome.

16.6.1.1 Summary of salvage RRP

In general, salvage RRP should be considered only in patients with a low co-morbidity, a life expectancy of at least 10 years, an organ-confined PCa $< T2$, Gleason grade < 7 , and pre-surgical PSA < 10 ng/mL. In all other patients, accurate pre-surgical staging is not easily defined after radiation therapy, increasing the risk not only for anterior and total extirpation procedures, but also for associated complications and decreased long-term disease-specific survival.

16.6.2 Salvage cryosurgical ablation of the prostate (CSAP) for radiation failures

Salvage cryosurgery has been proposed as an alternative to salvage RP, as it has the potential advantage of less morbidity but equal efficacy. However, only a very few studies are available, and the results are not very promising. Pisters et al. (1997) (109) reported on 150 patients who had undergone CSAP for PSA recurrences following radiotherapy ($n = 110$) or other extensive pre-treatment ($n = 40$). After a mean follow-up of 13.5 months, 58% of patients exhibited biochemical failure, while only 31% demonstrated undetectable PSA serum levels. The complications associated with salvage CSAP were significant, and occurred in virtually all patients, with the main complications being urinary incontinence (73%), obstructive symptoms (67%), impotence (72%) and severe perineal pain (8%). After 1-year follow-up, incontinence resolved in most patients, with persistent significant incontinence in 22% of patients (53%).

According to a recent study by Cespedes et al. (1997) (110), the risk for urinary incontinence and impotence at least 12 months after CSAP are as high as 28% and 90%, respectively. In addition, 8-40% of patients complained about persistent rectal pain, and an additional 4% of men had undergone surgical procedures for the management of treatment-associated complications.

With regard to oncological outcome, recent studies demonstrated that a durable PSA-response can be achieved in about 50% of patients with a pre-cryosurgery PSA of < 10 ng/mL (111).

In a recent multicentre study, the contemporary results of CSAP in 279 patients treated at a large number of centres, participating in the Cryo On-Line Data Registry, were analysed (112). Pre-treatment PSA was 7.6 +/- 8.2 ng/mL and Gleason score was 7.5 +/- 1.1 (median 7). Patients were followed for 21.6 +/- 24.9 months and 47 were followed longer than 5 years. The 5-year actuarial biochemical disease-free rate was 54.5% +/- 4.9% (Phoenix). As predicted, based on the preservation of some prostatic tissue, 83% +/- 3.5% of patients had a detectable PSA level \geq 0.2 ng/mL at 5 years. Positive biopsies were observed in 15 of the 46 patients (32.6%) who underwent prostate biopsy after salvage cryotherapy. The incontinence rate (requiring pad use) was 4.4%. The rectal fistula rate was 1.2% and 3.2% of patients underwent transurethral prostate resection to remove sloughed tissue.

16.6.3 Salvage brachytherapy for radiation failures

The experience with salvage brachytherapy for radiation failures is very limited and there is only one study that includes a representative number of patients and a mean follow-up of 64 months (113-118). Grado et al. (1999) (114) treated 49 patients with transperineal TRUS-guided brachytherapy and reported 3- and 5-year disease-free survival rates of 48% and 43%, respectively. Beyer (1999) (115) reported a 5-year biochemical freedom from relapse in 34-53% of patients, with local cancer control achieved in 98% of patients. However, the complication rate was quite severe:

- 27% became incontinent
- 14% needed palliative transurethral resection due to acute urinary retention
- 4% developed rectal ulcers
- 2% required permanent colostomy.

Burri et al. (2010) (116) reported on the long-term outcomes and toxicity after salvage brachytherapy with palladium-103 or iodine-125 for local failure after initial radiotherapy for PCA in 37. Median follow-up was 86 months (range, 2-156). The median dose to 90% of the prostate volume was 122 Gy (range, 67-166). The 10-year biochemical disease-free survival and CSS were 54% and 96%, respectively. There were three Grade 3 toxicities and one Grade 4 toxicity (10.8%). Careful patient selection for salvage BT may result in improved outcomes and reduced toxicity.

In a similar approach, Moman et al. (2009) (117) retrospectively evaluated the outcome and toxicity after salvage iodine-125 implantation in 31 patients with locally recurrent PCa after primary iodine-125 implantation and external beam radiotherapy. The mean follow-up was 9 years (SD +/-4). The freedom from biochemical failure after 1- and 5-year follow-up were 51% and 20%, respectively. Fourteen (45%) patients died of PCa after a mean (+/-SD) follow-up of 73 (+/-39) months. Grade 1, 2, or 3 toxicity of the genitourinary tract was reported in 29%, 58% and 3% of the patients, respectively, in the acute phase, and in 16%, 39%, and 19%, respectively, in the late phase. Grade 1, 2, or 3 toxicity of the gastrointestinal tract was reported in 45%, 10%, and 0% of the patients, respectively, in the acute phase, and in 48%, 3%, and 6%, respectively, in the late phase. Freedom from biochemical failure after salvage iodine-125 implantation for locally recurrent PCa after radiotherapy is limited, and both genitourinary and gastrointestinal toxicity occur frequently.

16.6.4 Observation

Patients with signs of local recurrence only (i.e. low-risk patients with late recurrence and a slow PSA rise) who are not opting for second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT versus watchful waiting (WW) in 248 men with PSA failure after radiotherapy showed no advantage for HT in the subgroup of men with a PSA DT of > 12 months after radiotherapy. The 5-year metastasis-free survival rate was 88% with HT versus 92% with WW ($p = 0.74$) (118).

16.6.5 High-intensity focused ultrasound (HIFU)

The experience of HIFU for the treatment of locally recurrent PCa after radiation therapy is limited to a few retrospective studies only. Zacharakis et al. (119) investigated the oncological and functional outcome of HIFU in a cohort of 31 men with biopsy -proven locally recurrent PCa following EBRT. The mean (range) pre-operative PSA level of 7.73 (0.20-20) ng/mL. The patients were followed for a mean (range) of 7.4 (3-24) months. Side-effects included stricture or intervention for necrotic tissue in 11 of the 31 patients (35%), urinary tract infection or dysuria syndrome in eight (26%), and urinary incontinence in two (6%). Recto-urethral fistula occurred in two men (7%). Overall, 71% had no evidence of disease following salvage HIFU.

In a similar approach Murat et al. (2009) (120) evaluated the safety and efficacy of salvage HIFU in 167 patients with local PCA recurrence after EBRT and to determine prognostic factors for optimal patient selection. Local cancer control was achieved with negative biopsy results in 122 (73%) patients. The median PSA nadir was 0.19 ng/mL. The mean follow-up period was 18.1 months (range, 3-121 months). Seventy-four patients required no HT. The actuarial 5-year OS rate was 84%. The actuarial 3-year PFS was significantly lower in three circumstances:

1. Worsening of the pre-EBRT stage with 53%, 42%, and 25% for low-, intermediate-, and high-risk patients, respectively
2. An increase in the pre-HIFU PSA
3. Use of AD during PCa management.

In multivariate analyses, the risk ratios for intermediate- and high-risk patients were 1.32 and 1.96, respectively. The risk ratio was 2.8 if patients had received AD. No rectal complications were observed. Urinary incontinence accounted for 49.5% of the urinary sphincter implantations required in 11% of patients.

Urinary incontinence and the development of rectourethral fistula are the most significant complications of salvage HIFU therapy (119-124). About 30% of men develop some type of incontinence, with significant urinary incontinence requiring implantation of an artificial urinary sphincter occurring in about 10% of patients. The oncological control rate after a short median follow-up of about 2 years is in the range of 30-40%.

16.6.6 Recommendation for the management of PSA relapse after radiation therapy

Recommendation	GR
Local recurrences may be treated by salvage radical prostatectomy in carefully selected patients, who presumably demonstrate organ-confined disease, i.e. PSA < 10 ng/ml, PSA-DT > 12 months, low-dose-radiation brachytherapy, biopsy Gleason score ≤ 7	B
Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery	B
High-intensity focused ultrasound might be an alternative option, however, patients have to be informed about the experimental nature of this treatment modality due to the short follow-up periods reported	
ADT is an option in patients with presumed systemic relapse	B

16.7 Guidelines for second-line therapy after treatment with curative intent

Recommendation	GR	
Presumed local failure after radical prostatectomy	Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably before PSA has risen above 0.5 ng/mL. Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on	B
Presumed local failure after radiotherapy	Selected patients may be candidates for salvage radical prostatectomy and patients should be informed about the higher risk of complications, such as incontinence and erectile dysfunction. Salvage prostatectomy should only be performed in experienced centres. Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on	C
Presumed distant failure	There is some evidence that early hormonal therapy may be of benefit in +/- local failure, delaying progression, and possibly achieving a survival benefit in comparison with delayed therapy. The results are not without controversy. Local therapy is not recommended except for palliative reasons	B

GR = grade of recommendation

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17. CASTRATION-REFRACTORY PCa (CRPC)

17.1 Background

Cancer of the prostate is a heterogeneous disease. Our knowledge of the mechanisms involved in androgen independence remains incomplete (1-5), but is starting to become clearer (6,7). It is known that androgen ablation provides a selective advantage to androgen-independent cells that grow and eventually comprise most of the tumour. An alteration in normal androgen signalling is thought to be central to the pathogenesis of androgen-independent PCa (8).

It is thought that androgen independence is mediated through two main, overlapping, mechanisms, which are androgen-receptor(AR)-independent and AR-dependent.

17.1.1 *Androgen-receptor-independent mechanisms*

Androgen-receptor-independent mechanisms may be associated with the deregulation of apoptosis through the deregulation of oncogenes. High levels of *bcl-2* expression are seen with greater frequency as PCa progresses and the regulation of microtubule integrity may be a mechanism through which *bcl-2* induces its anti-apoptotic effect (9-11). Indeed, most active chemotherapeutics in castration-refractory prostate cancer

(CRPC) work by inhibiting microtubule formation. The tumour suppressor gene *p53* is more frequently mutated in androgen-independent PCa. Over-expression of *bcl-2* and *p53* in prostatectomy specimens has been shown to predict an aggressive clinical course (12-14). Clinical trials are underway to target the *bcl-2* pathway (15), as the MDM2 oncogene (16) and the PTEN (phosphatase and tensin homolog) suppressor gene may also be involved (17).

17.1.2 AR-dependent mechanisms

Direct AR-dependent mechanisms comprise the main pathway. Ligand-independent AR activation has been suspected, such as the tyrosine kinase activated pathway (IGF-1, KGF, EGF). Epidermal growth factor (EGF) is a potent mitogen of prostate stromal and epithelial cells. It is produced in high levels locally and acts as a paracrine stimulator. In AR-independent tumours, autocrine stimulation may become more important, which could allow unregulated growth (18-20).

Androgen receptor amplification and overexpression are observed in one-third of HRPC tissues (21-23) and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in AR function (3-5,24). At the same time, there is an intracellular increase in androgens from in-situ conversion (25,26). This increase may be secondary to an increase in the intracellular enzymes involved in intracellular androgen synthesis (27).

Because AR mutations are found in only a subpopulation of tumour cells, they are unlikely to be responsible for the entire spectrum of the AR-independent state (28). The AR mutations might be related to the selective pressure of anti-androgens (29). The recent discovery of gene fusion between the androgen-driven *TMPRSS2* and the *EGR-ETS* oncogene family (30) raises the question of oncogene regulation through androgen regulation pathways. In gene fusion, an androgen-responsive element from an androgene-regulated gene becomes associated with genes that are usually not androgen-regulated, so that they too become subject to androgen regulation. Currently, their implication in CRPC is hypothetical. Even in castrated patients, metastatic tissues have repeatedly shown high levels of androgens, suggesting a high level of intracrine synthesis (27,31). It is possible that a high intraprostatic cholesterol level can activate specific androgen pathways (1).

17.2 Definition of relapsing prostate cancer after castration

The previously term, 'hormone-refractory prostate cancer' referred to a very heterogeneous disease. It included different patient cohorts with significantly different median survival times (Table 20).

Table 20: Estimated natural mean survival of patients with HRPC presenting with different clinical scenarios.

Patient characteristics	Estimated mean survival
<i>Asymptomatic PSA</i>	
• No metastases	24-27 months
• Minimal metastases	16-18 months
• Extensive metastases	9-12 months
<i>Symptomatic PSA</i>	
• Minimal metastases	14-16 months
• Extensive metastases	9-12 months

The precise definition of recurrent or relapsed PCa remains controversial and several groups have recently published practical recommendations for defining CRPC (31-34).

Various different terms have been used to describe prostate cancers that relapse after initial hormonal ablation therapy, including HRPC, androgen-independent cancers and hormone-independent cancers (1). The castrate-resistant, but still hormone-sensitive, PCa (CRPC) has been clearly characterised, with the new drugs targeting either the AR, such as the MDV3100, or androgen synthesis, via the CYP 17 inhibitor (see below Section 17.8.5.2) (35,36). It is important to differentiate CRPC from true HRPC. Although CRPC responds to secondary hormonal manipulations, including anti-androgen withdrawal, oestrogens and corticosteroids, true HRPC is resistant to all hormonal measures. Table 21 lists the key defining factors of CRPC.

Table 21: Definition of CRPC.

* Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for CRPC.

† Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) and with nodes ≥ 2 cm in diameter.

17.3 Assessing treatment outcome in androgen-independent PCa

In general, the therapeutic outcome should be assessed using the guidelines for the evaluation of treatment response in solid tumours, recently published by the RECIST group (Response Evaluation Criteria In Solid Tumours) (37). However, 80-90% of patients do not have bi-dimensionally measurable disease. Patients with primarily soft tissue cancers often have a different prognosis to those with only osseous metastases.

Osteoblastic bone metastases remain difficult to quantify accurately. Magnetic resonance imaging (MRI) might be useful for assessing axial metastases (38). Since the cause of death in PCa patients is often unreliable, a more valid end-point might be overall survival (OS) rather than a disease-specific one (39).

17.3.1 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 new agents for activity, there is conflicting evidence about the role of PSA as a response marker. Both the vaccine trials, Sipuleucel-T (Provenge) (40) and the TRICOM (PROSTVAC) study (41), demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs (42).

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 (43-50).

Nevertheless, it has been reproducibly shown that $\geq 50\%$ PSA decline in pre-treatment PSA following therapy carries a significant survival advantage (51,52). Kelly et al. (51) reported a statistically significant survival advantage in 110 patients with $\geq 50\%$ PSA decline (> 25 months) versus those without a $\geq 50\%$ PSA decline (8.6 months). Smith et al. (52) showed that a PSA decline $\geq 50\%$ for at least 8 weeks resulted in a longer mean survival time of 91 weeks versus 38 weeks in patients showing a smaller PSA reduction.

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) versus 15.8 months for an abnormal PSA. This study also showed that a PSA response was not a surrogate marker for survival; even though the same PSA response rate was found in both docetaxel arms (45%), improved survival only occurred with the 3-weekly docetaxel regimen. According to the most recent evaluation of the TAX 327 study, a PSA detection of $\geq 30\%$ is associated with a significant survival benefit (103).

17.3.2 Other parameters

The evaluation of molecular markers is just beginning. It includes a possible correlation between the positive findings of reverse transcriptase-polymerase chain reaction (RT-PCR) and poor survival (53), though these data must be corroborated before any clinical recommendations can be made. Another, probably more interesting, tool is the circulating tumour cell count (CTC count), which has been developed in parallel with abiraterone. The CTC count has been clearly related to survival in several trials (54-56) and may become a surrogate marker for survival. The FDA has recently approved an assay for CTC.

In patients with symptomatic osseous lesions, pain reduction or complete pain relief may be used as parameters to assess palliative therapeutic response (57).

17.3.3 Trial end-points

An increasing number of investigators advocate subjective end-points. However, investigators should currently apply the following:

- Use clearly defined end-points in trials, sufficiently powered to answer the hypothesis.
- Report each response parameter individually, rather than as a complete or partial response.
- Only use PSA response with other clinical parameters of response.
- Consider QoL end-points independently in symptomatic patients.

However, in everyday practice, the evaluation of treatment response must be based on symptom improvement, prolonged survival, or other pre-defined targets.

17.4 Recommendations for assessing therapeutic response

Recommendations	LE
PSA decline \geq 30% maintained for 8 weeks is associated with a significantly better outcome compared to a PSA decline $<$ 30%	1a
In non-osseous metastases from HRPC, assessment should adhere to the RECIST criteria	1b
In patients with advanced symptomatic metastatic HRPC, therapeutic response can be assessed best by improvement of symptoms	1b

RECIST = Response Evaluation Criteria in Solid Tumours

17.5 Androgen deprivation in castration-independent PCa

The existence of androgen-independent PCa shows that disease progression occurs despite castration. The castration levels of testosterone must therefore be documented and a serum testosterone level $<$ 50 ng/dL (1.7 nmol/L) should be documented at initial relapse on hormonal therapy (32,58).

Continued testicular androgen suppression in CRPC has a minimal overall effect. The recommendation to continue androgen deprivation therapy (ADT) with LHRH analogues, despite PSA progression, is based on the data of Manni et al. (59). This study demonstrated significantly lower survival rates in patients without complete androgen blockade (CAB). However, these data have been challenged by two recent trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies (60,61).

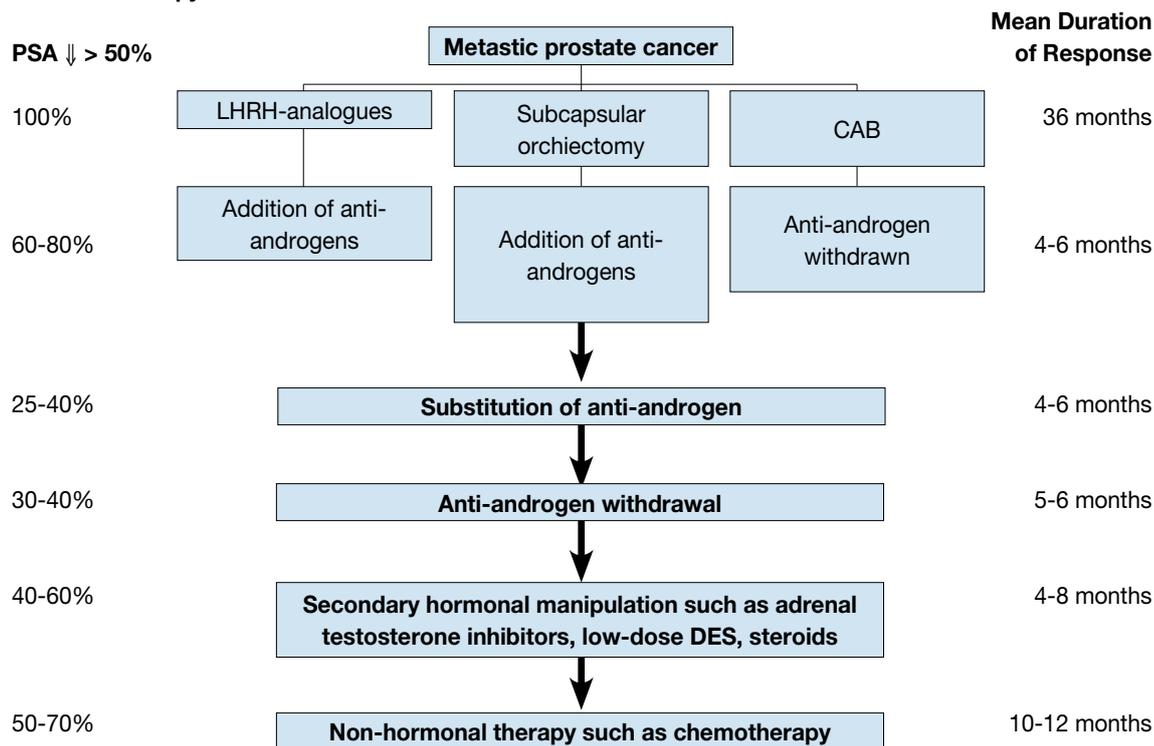
In addition, a provocative experimental approach towards testosterone replacement in CRPC has raised questions regarding the true benefits of continuing with LHRH analogues. The rationale behind testosterone replacement is the repression of tumour growth by high doses of testosterone. At least two phase I trials have been recently published (62,63) demonstrating the feasibility of this experimental approach. Some PSA-based responses have been observed and a phase III trial is currently underway.

However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. Androgen suppression should therefore be continued indefinitely in these patients.

17.6 Secondary hormonal therapy

For the patient with progressive disease after ADT, there are many therapeutic options. They include anti-androgen withdrawal, addition of anti-androgens, anti-androgen replacement, oestrogenic compounds, adrenolytic agents, and novel approaches (64). Figure 1 summarises the treatment modalities and expected responses.

Figure 1: Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy.



LHRH = luteinising hormone releasing hormone; CAB = complete androgen blockade; DES = diethylstilboesterol.

17.7 Anti-androgen withdrawal syndrome

In 1993, Kelly and Scher (65) reported clinical and PSA responses in men who discontinued flutamide therapy upon development of progressive disease. The anti-androgen withdrawal syndrome was a critical discovery in understanding the biology of androgen independence, interpreting clinical trials, and treating patients (66-69).

Approximately one-third of patients respond to anti-androgen withdrawal, as indicated by a $\geq 50\%$ PSA decrease, for a median duration of approximately 4 months (Table 22). Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (70-76). Recently, in the SWOG 9426 trial, PSA progression despite CAB was reported in a subgroup of 210 patients with a tumour stage of M0 or M1 (77). A response was observed in 21%, even though there was no radiographic response. Median progression-free survival (PFS) was 3 months, with 19% (all M0) having 12 months' or greater PFS. Factors associated with increased PFS and OS were a longer period of non-steroidal use, lower PSA at baseline and M0-stage. These results were obtained with patients on CAB following androgen withdrawal treatment. No data were available on the withdrawal effect following second-line anti-androgen treatment.

In conclusion, androgen withdrawal should be systematically considered as a first-line modality in relapsing patients, even if its efficacy is limited (level of evidence: 2).

Table 22: Frequency and duration of PSA response following anti-androgen withdrawal.

Anti-androgen	No. of patients	> 50% decrease in PSA No. of patients (%)	Duration (months)
• Flutamide	57	16 (28%)	4.0
• Flutamide	82	12 (15%)	3.5
• Flutamide	39	11 (28%)	3.7
• Flutamide	21	7 (33%)	3.7
• Bicalutamide	17	5 (29%)	5.0
• Combined results	210	44 (21%)	3 (median)

17.8 Treatment alternatives after initial hormonal therapy

Except in patients with non-castration testosterone levels, it is difficult to predict which subset of patients is most likely to respond to secondary hormonal strategies.

17.8.1 Bicalutamide

Bicalutamide is a non-steroidal anti-androgen with a dose response, with higher doses producing a greater reduction in PSA level (78). The largest cohort so far is based on 52 CRPC patients treated with bicalutamide, 150 mg (79). A palliative effect was clear and a 20% PSA response (at least 50% decrease) was observed, without any link to the palliative effect. Based on the affinity of dihydrotestosterone (DHT) for the androgen receptor, a large randomised trial (TARP) is ongoing comparing the effectiveness of bicalutamide 50 mg combined with either dutasteride or placebo in non-metastatic CRPC (80). Addition of an anti-androgen, such as bicalutamide or flutamide, to gonadal suppression at the time of PSA failure appears to result in declining PSA in only a few patients (81-83).

17.8.2 Switching to an alternative anti-androgen therapy

There has been recent interest in another simple modality: the alternative anti-androgen therapy (84). After CAB was stopped in 232 progressing patients (76% being M1b), a withdrawal effect was observed in 31 men (15.1%). A second-line hormonal treatment was performed by giving an alternative non-steroidal drug (i.e. initial flutamide was replaced by bicalutamide and vice versa). An overall > 50% decline in PSA was observed in 83 men (35.8%), irrespective of any previous withdrawal effect, which lasted more than 6 months. The higher the PSA at the start of second-line therapy, the shorter was the progression-free survival and the lower was the PSA response rate.

17.8.3 Anti-androgen withdrawal accompanied by simultaneous ketoconazole

The adrenal glands secrete approximately 10% of circulating androgen in humans. Some tumour cells in androgen-independent states must retain androgen sensitivity, as a clinical response is induced by a further decrease in circulating androgen levels following bilateral adrenalectomy or administration of drugs inhibiting adrenal steroidogenesis.

Aminoglutethimide, ketoconazole and corticosteroids act mainly via this mechanism (85-89) to produce a PSA response in about 25% of patients for about 4 months. However, the simultaneous addition of ketoconazole to anti-androgen withdrawal, produced a significantly increased PSA response (32% vs 11%) and a longer time to PSA progression (8.6 vs 5.9 months) compared to anti-androgen withdrawal alone (89).

17.8.4 Oestrogens

Prostate cancer usually expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. In-vitro oestrogens can activate mutant androgen receptors isolated from androgen-independent PCa, while high-dose oestrogens have achieved objective salvage responses. This may be due to the mitotic arrest of direct cytotoxic effects on the cells, perhaps through an apoptotic mechanism (90,91). Recently, diethylstilboestrol (DES) (92-94) achieved a positive PSA response between 24% and 80%, with an overall estimated survival of 63% at 2 years. However, even at low doses of DES, about one-third (31%) of patients developed deep venous thrombosis and 7% experienced myocardial infarction.

17.8.5 The future for anti-androgen agents

In the last 2 years, potential drugs have appeared in early phase I/II trials in CRPC and should be considered as potential major new tools, provided the randomised phase III trials confirm the early results. Furthermore, they confirm that the castrate-resistant status is far from meaning an hormonal-resistant status (see above Section 17.2).

17.8.5.1 MDV3100

The first agent, MDV3100, is a novel anti-androgen which blocks AR transfer to the nucleus, in contrast to currently available drugs where AR is able to transfer to the nucleus. This means that no agonist-like activity should ever occur. At the ASCO 2009 meeting, a phase I/II trial on 140 CRPC was reported (95). In this dose-finding study, a PSA decline > 50% was seen in 57% chemo-naïve patients, and in 45% chemo-refractory patients. Based on these results, a large phase III trial has been recently launched in metastatic CRPC patients after chemotherapy, on more than 1,000 patients, with OS being the primary end-point.

17.8.5.2 Abiraterone acetate

The second agent is the CYP17 inhibitor, abiraterone acetate. In CRPC patients, this drug is able to decrease PSA > 50% in 85% chemo-naïve patients (96), by 50% after docetaxel (97,98), and even by 33% after

ketoconazole (98). In chemo-naïve patients, a PSA decline of > 90% is seen in up to 40% of patients (96).

The largest cohort so far is based on 96 chemo-naïve men included in a phase I/II trial. At a dose of 1000 mg, a PSA decline > 50% was observed in 67% and > 90% in 19% of patients. A partial response (RECIST-based) was seen in 37% of patients. The median time to progression was about 1 year (7). These very promising results have led to two large phase 3 trials: one in chemo-refractory patients (n = 1158, trial is closed), the other in chemo-naïve patients (n = 1000, accrual is ongoing). In both trials, OS is the primary end-point.

In conclusion, there are only preliminary results for both drugs, which are currently only available in clinical trials. However, these agents represent a strong opportunity for the future treatment of CRPC based on the level of response obtained (PSA and RECIST-based).

17.9 Non-hormonal therapy (cytotoxic agents)

Several proven chemotherapeutic options are available for metastatic disease in HRPC (Table 23). Multiple trials are underway, using very different approaches through all the known pathways. A detailed review is far beyond the scope of these guidelines (6), as most drugs are experimental, except perhaps docetaxel.

A significant improvement in median survival of about 2 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy (99,100). In the SWOG 99-16 trial, pain relief was similar in both groups, though side-effects occurred significantly more often with docetaxel than with mitoxantrone.

Table 23: PSA response rates, mean survival, time to progression, and pain reduction in the large, prospective, randomised phase III trials of chemotherapy in patients with HRPC.

Study	n	PSA decrease > 50%	Decrease in pain	Survival (months)	Time to progression
TAX 327					
Mitoxantrone		32%	22%	16.5	–
Docetaxel, 75 mg/m ²		45% ¹	35% ³	18.9 ¹	–
Docetaxel, 30 mg/m ²		48% ¹	31%	17.4	–
SWOG 99-16					
Mitoxantrone	336	50% ¹	–	17.5 ²	6.3 months ¹
Docetaxel/EMP	338	27%	–	15.6	3.2 months
CALGB 9182					
Hydrocortisone	123	38% ⁴	–	12.3	2.3 months
Mitoxantrone/HC	119	22%	–	12.6	3.7 months ⁴
Tannock et al.					
Prednisone	81	22%	12%	–	43 weeks ¹
Mitoxantrone/Pred	80	33%	29% ²	–	18 weeks

EMP = estramustine; HC = hydrocortisone; Pred = prednisone. ¹p < 0.000; ²p = 0.001; ³p = 0.01; ⁴p < 0.03.

17.9.1 Timing of chemotherapy in metastatic HRPC

The timing of chemotherapy varies in metastatic HRPC. It is advisable to start it immediately in symptomatic patients, if possible every 3 weeks, as this schedule is associated with an improvement in survival. However, a weekly regimen will result in the same symptom improvement and must be considered in patients unable to receive the optimal regimen (level of evidence: 1b), as it is more effective than best supportive care (101). In asymptomatic patients, timing is not so clear and must be discussed individually.

Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, PSA doubling time (PSA-DT) < 55 days, or the presence of visceral metastases (102). A better risk group definition has been recently presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorised into three risk groups: good risk (0-1 factor), intermediate (2 factors) and high risk (3-4 factors), leading to three different median OS: 25.7, 18.7 and 12.8 months, respectively (103). In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (hazard ratio [HR], 2.96) (104,105). Age by itself is not a contraindication to docetaxel (106).

Currently, the only indication for chemotherapy in HRPC non-metastatic patients is inside clinical trials and patients should be advised to participate.

17.9.2 Taxanes in combination therapy for HRPC

In an effort to improve treatment results further, several phase I and phase II trials are underway combining taxanes with anti-*bcl-2*, calcitriol (trial stopped due to unexpected toxicity), exisulind, and thalidomide, resulting in PSA responses of about 60% (107-110).

In a randomised phase II trial of docetaxel alone versus docetaxel + thalidomide (107), 75 men with chemo-naïve HRPC were randomised to receive either docetaxel, 30 mg/m² for 5 of every 6 weeks, or docetaxel, at the same dose and schedule, plus thalidomide, 200 mg orally each day. A decline in the level of PSA \geq 50% appeared more likely in the combination-treated group (53%) compared to the docetaxel-alone treated group (37%) (not statistically significant). At 18 months, the median PFS and OS with docetaxel + thalidomide were 5.9 months and 68%, respectively, versus 3.7 months and 43% in the docetaxel-alone group (not statistically significant). However, there were considerable side-effects, with thromboembolic events occurring in 28% of the combination arm compared to no such events in the docetaxel arm. A recent phase III trial in HRPC patients confirmed the potential interest of thalidomide compared to placebo in non-metastatic patients with a PFS of 15 months versus 9.6 months ($p = 0.0002$) (111).

Small molecules are also being tested in combination with docetaxel, especially but not exclusively those targeting the vascular endothelial growth factor (VEGF) pathway. Following interesting results from phases I/II trials, several large phase III trials (each including about 1,000 patients) are underway, using either bevacizumab (a monoclonal antibody), aflibercept (VEGF trap), sunitinib (anti-VEGFR), or dasatinib (anti-Src).

17.9.3 Mitoxantrone combined with corticosteroids

Mitoxantrone combined with corticosteroids (112, 113) has been extensively studied primarily in patients with symptomatic osseous lesions due to HRPC. In the CALGB 9182 study (113), 244 patients with symptomatic metastatic HRPC were randomised to receive either mitoxantrone + hydrocortisone, 12 mg/m² every 3 weeks, or hydrocortisone alone. No differences were observed with regard to survival, PSA response, and median time to progression. However, the QoL was significantly improved in the combination arm. In another trial (112), 161 men with painful osseous metastases due to HRPC were randomised to receive mitoxantrone + prednisone versus prednisone alone. There was a significant benefit in pain reduction in the combination group (29%) versus prednisone alone (12%, $p = 0.01$). Furthermore, the duration of palliation was longer in patients who received mitoxantrone (43 weeks vs 18 weeks, $p < 0.0001$). There were no significant differences with regard to PSA response and median survival time. However, again, QoL was improved significantly due to pain reduction.

17.9.4 Alternative combination treatment approaches

Encouraging results have been seen with alternative treatments evaluated in prospective clinical phase II trials (114-117), including pegylated doxorubicin, vinorelbine, a combination of paclitaxel, carboplatin + estramustine, a combination of vinblastine, doxorubicin + radionuclides, and a combination of docetaxel + mitoxantrone. The lack of representative randomised phase III trials and unknown long-term efficacy are major problems associated with all these studies.

17.9.5 Estramustine in combination therapies

The synergy observed for estramustine combined with other drugs that target microtubule action has generated promising results in prospective clinical trials.

Estramustine + vinblastine is the most studied estramustine combination. Although different doses of estramustine and vinblastine have been used in prospective randomised trials, significant PSA and measurable responses have been reported in three separate studies. Although time to progression and frequency of \geq 50% PSA decrease was significantly higher in the estramustine + vinblastine treatment arm, median survival did not differ significantly between the estramustine and the estramustine + vinblastine arms (118). A recent meta-analysis (119) concluded that the addition of estramustine to chemotherapy increased the time to PSA progression and OS. However, there was a significant increased risk of thromboembolic events, up to 7% (120), requiring systematic prevention with coumadin.

17.9.6 Oral cyclophosphamide

Intravenous cyclophosphamide has been tested in many trials. However, there is currently interest in oral cyclophosphamide, which seems to be less toxic than intravenous cyclophosphamide and may have greater activity. A study of oral cyclophosphamide + oral etoposide in 20 patients was similarly encouraging (121,122).

17.9.7 Cisplatin and carboplatin

Cisplatin and carboplatin have activity as single agents against PCa. They also have a well-documented

synergy with etoposide or paclitaxel in vitro in other malignancies, such as lung and ovarian cancer. As estramustine is also synergistic with these drugs, combinations of these three agents are now being tested. A combination of estramustine, etoposide and cisplatin (or carboplatin) has significant activity against poorly differentiated HRPC. A combination of estramustine, etoposide and paclitaxel has produced high response rates (116).

17.9.8 *Suramin*

Suramin activity against HRPC is likely to be mediated through the inhibition of binding of growth factors (e.g. transforming growth factor beta) to their receptors. Recent results have renewed interest in suramin's initial promise in the treatment of HRPC (123-125).

17.9.9 *Non-cytotoxic drugs: the vaccines*

Vaccines have been studied for a long time in prostate cancer, with initially disappointing results. Recently, a large phase III study (n = 500) confirmed the results from a previous phase III trial, which demonstrated an OS survival benefit not linked to a PSA response or PFS (see above Section 17.3.1). In the first phase III trial, a total of 127 CRPC patients were randomised to Sipuleucel-T (Provenge) or placebo (40), with cross-over at progression allowed. The primary end-point was not reached (time to progression), but there was a significant difference in OS (HR, 1.7), leading to the proof of principle of such an approach and to a second randomised trial of 500 patients, with OS as the primary end-point. Again, a statistical benefit was observed (25.8 months compared to 21.7 months; HR, 0.77; p = 0.03). Together with results from TRICOM (PROSTVAC), these are the only positive results with PCa vaccines. However, the results point to a possible future for vaccination, particularly as tolerability was very acceptable (no grade 3, and only transient grade 1 or 2 vaccine-related adverse events).

17.9.10 *Specific bone targets*

Bone is a primary target for prostatic metastatic cells, leading to a rational for bone-protective drugs, preventing cancer cells from colonising and developing bone. Besides zoledronic acid and denosumab (see above Section 12.7.1), there are other promising drugs, mainly those targeting the endothelin-1 axis. The first of these agents (atrasentan) resulted in clear biological responses, but questionable clinical results (126), possibly secondary to an inappropriate trial design. However, the proof of principle has been made, and second-generation blockers are under development after encouraging phase II trials (127), with large phase III trials in CRPC, either without metastases (> 1,000 patients), with metastases (> 500 patients), or with docetaxel (> 1,000 patients).

17.9.11 *Salvage chemotherapy*

Since all patients who receive docetaxel-based chemotherapy for HRPC will progress within 6 to 8 months, there have been many clinical trials investigating the role of salvage chemotherapy. The results suggest the most appropriate approaches are intermittent docetaxel chemotherapy (128,129), molecular-targeted therapy (131,132) and second-line satraplatin (133).

Several groups have used second-line intermittent docetaxel in patients who had clearly responded to first-line docetaxel (128-130). 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. Another, recently identified approach is molecular-targeted therapy (131-136) though more research is needed in larger groups of patients.

Platinum-based chemotherapeutic regimes have been investigated in patients with HRPC. Although the platinum complex, satraplatin, has shown activity against HRPC and some promise in clinical trials, the FDA rejected it for HRPC in 2008.

Many new drugs, such as gefitinib, bevasusimab (phase III trial CALB 90401), oblimersen (phase III trial EORTC 30021), and also a vaccine, G-Vax (136), are being tested in phase III trials. However, the G-Vax trial has been stopped prematurely because of a significantly higher mortality in the treatment arm as compared to the docetaxel control arm.

Positive results have been recently published from a prospective, randomised, phase III trial comparing the therapeutic efficacy of the taxane derivate, cabazitaxel, + prednisone versus mitoxantrone + prednisone in 755 patients with castration-resistant PCa, who had progressed after or during docetaxel-based chemotherapy (137).

Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m²) and mitoxantrone (12 mg/2), respectively. In both treatment arms, patients also received 10 mg prednisone daily for the entire treatment

period. Overall survival was the primary endpoint and progression-free survival, treatment response and safety were secondary endpoints.

Patients in the cabazitaxel arm experienced a significantly increased overall survival of 15.1 versus 12.7 months ($p < 0.0001$) in the mitoxantrone arm. The cabazitaxel treatment arm also showed significant improvement in progression-free survival (2.8 vs 1.4 months, $p < 0.0001$), the objective response rate according to RECIST criteria (14.4% vs 4.4%, $p < 0.005$), and the 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 hematological (68.2% vs 47.3%, $p < 0.0002$) and non-hematological toxicities (57.4% vs 39.8%, $p < 0.0002$), respectively.

Conclusion:

According to the positive results of this prospective randomised clinical phase III trial (level of evidence: 1), cabazitaxel should be considered in the management of progressive CRPCA following docetaxel therapy.

17.10 Palliative therapeutic options

17.10.1 Painful bone metastases

Most patients with HRPC have painful bone metastases. External beam radiotherapy is highly effective (138), even as single fraction (139). The two radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients, but should not be given too late when pain is intractable. Early use can give rise to myelosuppression, making subsequent chemotherapy more difficult (140), even though a recent phase I trial has demonstrated manageable hematological toxicity with repeated administration of docetaxel and samarium-153. The use of samarium-153 as consolidation therapy, following a clear docetaxel response, may also help with initially painful bone metastases (141). Palliative treatment with another radioisotope emitter, radium-223, has shown very promising phase II results in patients with painful bone metastases in terms of palliation and OS, and only a mild hematological toxicity (142).

17.10.2 Common complications due to bone metastases

Common complications due to skeletal metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Osteoporosis may also cause fractures and should be prevented (see above). Cementation is an effective treatment of painful fracture, clearly improving both pain and QoL (143). However, it is still important to offer standard palliative surgery, which can be very effective at managing osteoblastic metastases (144,145).

Impending spinal cord compression is an emergency. It must be recognised early and patients educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and an MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression (146). Otherwise, external beam radiotherapy is the treatment of choice.

17.10.3 Bisphosphonates

Recently, bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in HRPC to provide effective treatment of skeletal complications and to reduce pain or provide total pain relief. In the largest single phase III trial (147), 643 patients who had HRPC with bone metastases were randomised to receive zoledronic acid, 8 mg or 4 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with only 4 mg of zoledronic acid had fewer skeletal-related events 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 skeletal-related event was longer in the zoledronate group, so 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 because of toxicity.

Currently, bisphosphonates can be proposed to patients with HRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear. At present, it is every 3 weeks or less. The toxicity, e.g. jaw necrosis, of these drugs, especially aminobisphosphonate, must always be kept in mind (148). Patients should have a dental examination before starting a bisphosphonate. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as intravenous long-term bisphosphonate administration (149).

Pain due to osseous metastases is one of the most debilitating complications of HRPC. Bisphosphonates have been highly effective with a response rate of 70-80% in small, open trials, which, associated with a low frequency of side-effects, makes bisphosphonates an ideal medication for palliative therapy of advanced

HRPC (150-152). Bisphosphonates should be considered early in the management of symptomatic HRPC. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur (i.e. palliative external beam radiation, cortisone, analgesics and anti-emetics).

Hormone-refractory PCa 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 (153).

17.11 Summary of treatment after hormonal therapy

(There is currently no real change in treatment after hormonal therapy, provided the novel agents, MDV3100 and abiraterone, do not become available once randomised controlled trial results are published (34).

Recommendations	GR
It is recommended to stop anti-androgen therapy once PSA progression is documented	B
Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect is apparent	B
No clear-cut recommendation can be made for the most effective drug for secondary hormonal manipulations because data from randomised trials are scarce	C

17.12 Recommendations for cytotoxic therapy in CRPC.

Recommendations	GR
Ideally, patients with CRPC should be counselled, managed and treated in a multidisciplinary team	
In non-metastatic CRPC, cytotoxic therapy should only be considered in clinical trials	
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented (31)	B
Prior to treatment, PSA serum levels should be > 2 ng/mL to assure correct interpretation of therapeutic efficacy	B
Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient	C
In patients with metastatic CRPC, and who are candidates for cytotoxic therapy, docetaxel at 75 mg/m ² every 3 weeks has shown a significant survival benefit	A
In patients with symptomatic osseous metastases due to CRPC, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options	A
Second-line docetaxel should be considered in previously responding patients to docetaxel. Otherwise, treatment is tailored to the individual patient	B
Cabazitaxel should be considered as effective second-line treatment following docetaxel	A

17.13 Recommendations for palliative management of CRPC.

Recommendations	Grade
Patients with symptomatic and extensive osseous metastases cannot benefit from medical treatment with regard to prolongation of life	A
Management of these patients has to be directed at improvement of QoL and mainly pain reduction	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy	A
Bisphosphonates may be offered to patients with skeletal masses (mainly zoledronic acid has been studied) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, in particular jaw necrosis must be avoided	A
Palliative treatments such as radionuclides, external beam radiotherapy, adequate use of analgesics should be considered early in the management of painful osseous metastases	B
Spinal surgery or decompressive radiotherapy are emergency surgeries which have to be considered in patients with neurological symptoms might be an emergency	A

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18. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

3D-US	three-dimensional ultrasound
ADT	androgen-deprivation therapy
AS	active surveillance
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
AUA	American Urological Association
BDFS	biochemical disease-free survival
BMD	bone mineral density
bNED	actuarial biochemical freedom from disease
CAB	complete (or maximal or total) androgen blockade
CaP	cancer of the prostate
CPA	cyproterone acetate
CRT	conformal radiotherapy
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
DES	diethylstilboestrol
DRE	digital rectal anticipation
DHT	dihydrotestosterone
DSS	disease-specific survival
EBRT	external beam radiation therapy
ECE	extracapsular extension
ECOG	Eastern Cooperative Oncology Group
eLND	extended lymph node dissection
ELND	elective lymph node dissection
e-MRI	endorectal MRI
EORTC	European Organisation for Research and Treatment of Cancer
EPC	Early Prostate Cancer Trialists' Group
EPCP	Early Prostate Cancer Programme
ER- β	oestrogen receptor- β
ESRPC	European Randomized Screening for Prostate Cancer
FACT-P	Functional Assessment of Cancer Therapy-prostate
FNAB	fine-needle aspiration biopsy
FSH	follicle-stimulating hormone
GI	gastrointestinal
GR	grade of recommendation
GU	genitourinary
HD EBRT	high-dose EBRT
HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
IAD	intermittent androgen deprivation
IGRT	image-guided radiotherapy
IMRT	intensity modulated radiotherapy
IPSS	International Prostatic Symptom Score
LDAT	long-term ADT
LDR	low-dose rate (LDR)
LE	level of evidence
LET	linear energy transfer
LH	luteinising hormone
LHRH	luteinising hormone-releasing hormone
LHRHa	luteinising hormone-releasing hormone analogue
LND	lymph node dissection
LRP	laparoscopic radical prostatectomy

MRC	Medical Research Council
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopy imaging
NHT	neoadjuvant hormonal therapy
NIH	National Institutes of Health
NVB	neurovascular bundle
OR	odds ratio
OS	overall survival
PAP	prostate acid phosphatase
PCa	prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PIN	prostatic intraepithelial neoplasia
PIVOT	Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407
PLCO	Prostate, Lung, Colorectal and Ovary
PSA	prostate-specific antigen
PSA-ACT	PSA complexed to antichymotrypsin
PSADT	PSA doubling time
PSAV	PSA velocity
PSMA	prostate-specific membrane antigen for messenger RNA
QoL	quality of life
QUALYs	quality of life adjusted gain in life
RALP	robot-assisted radical prostatectomy
RITA	radio-frequency interstitial tumour ablation
RP	radical prostatectomy
RRP	radical retropubic prostatectomy
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results
SLN	sentinel lymph node
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
STAD	short-term androgen deprivation
SVI	seminal vesicle invasion
SWOG	South West Oncology Group
TNM	Tumour Node Metastasis
TZ	transition zone
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UICC	Union Against Cancer
USPIO	ultra-small super-paramagnetic iron oxide particles
VACURG	Veterans Administration Co-operative Urological Research Group
WHO	World Health Organization
WW	watchful waiting

Conflict of interest

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