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.

The recommendations provided in the current guidelines are based on a systemic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles. 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).

Prior to publication external review has taken place.

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

Publication history information:
The Prostate Cancer Guidelines were first published in 2001, with partial updates in 2003 and 2007, followed by the current full text update. But for one section (Chapter 14), all topics have been revised. Additionally, a quick reference guide is available. 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. (1).

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. (1).

1.1 REFERENCE

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
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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 2002 TNM (Tumour Node Metastasis) classification for PCa is shown in Table 3 (1). The new TNM system is due to be published early in 2009, but was not yet available for citation.

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)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall	
N - Regional lymph nodes[3]		
	NX	Regional lymph nodes cannot be assessed

N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant metastasis[4]		
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 T3, but as T2.

[3] Metastasis no larger than 0.2 cm can be designated pN1mi.

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

**At the time of the publication of this document the updated TNM system was not yet available for citation.*

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.

Prospective, preferably population-based, randomised trials are needed to properly evaluate the efficacy of PCa screening. Two large trials are underway, the PLCO (Prostate, Lung, Colorectal and Ovary) trial in the USA and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe (9, 10). The main endpoint of these trials is difference in PCa mortality, with first results due in 2009 (level of evidence: 1b).

Thus, there is currently no evidence for introducing widespread, population-based, screening programmes for early PCa detection in all men in a given population (4) (level of evidence: 2). A less controversial programme, which is also recommended by most guidelines, is using PSA with digital rectal examination (DRE) as an aid to early diagnosis (11) *(see Section 6.1)* (level of evidence: 3). Nevertheless, a few conclusions about screening intervals can be deduced from the ERSPC study (12):

- A screening interval of 2 or 4 years had no impact on outcome in a cohort of 17,505 men aged 55-74 years
- The rate of interval cancer, especially aggressive interval cancer, was low in this study (0.43% vs 0.74%)
- Although the 2-year screening interval had a higher detection rate for PCa than the 4-year interval (13.14% vs 8.42%), it did not lead to lower incidences of interval PCa (0.11%) and aggressive interval PCa (0.12%)
- A screening interval of 8 years might be enough in men with initial PSA levels ≤ 1 ng/ml (13)
- A total of 1703 men had a PSA level ≤ 1 ng/ml when they first presented for screening. A total of 1327 men (79.3%) attended the second screening visit during which 13 men (0.98%) had PSA levels ≥ 3.0 ng/mL and three cancers were detected (0.23%)
- A total of 1017 men (76.8%) attended the third screening visit during which 34 men (3.3%) had a PSA level ≥ 3.0 ng/mL and five cancers were detected (0.49%)
- The 2344 subsequent PSA determinations during an 8-year period following the initial screening visit resulted in the detection of eight cancers (0.47%)
- Thus, PSA screening every 8 years for men with PSA levels ≤ 1.0 ng/mL would mean fewer screening visits (with less cost and stress), with a minimal risk of missing aggressive cancer at a curable stage.

The decision to undergo early PSA testing should be a shared decision between the patient and his physician (14, 15). PSA testing and digital rectal examination should be offered from the age of 45 years to men with a life expectancy of at least 10 years. The most recent research suggests further PSA testing is unnecessary in men ≥ 75 years and a PSA level ≤ 3 ng/mL at their first screening visit. This is because these men have a very low risk of dying from PCa (16).

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6. DIAGNOSIS*

The main diagnostic tools used to look for evidence of PCa include DRE, serum concentration of PSA and transrectal ultrasonography (TRUS). Diagnosis depends on the presence of adenocarcinoma in operative specimens, prostate biopsy cores or aspiration needle cytology. Histopathological examination also allows grading 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).

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 2950 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, and has been used to stratify the risk of PCa for men with total PSA levels between 4 and 10 ng/mL and with 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,

* 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. Höltl, W. Loidl, M. Rauchenwald, M. Müller, M. Klimpfinger, A. Schratter-Sehn, C. Brössner).

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/mLyear) (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 several unresolved issues, including background noise (total volume of prostate, BPH), the interval between PSA determinations, and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have not shown these measurements can provide additional information compared to PSA alone (13, 14).

6.2.3 PCA3 marker

In contrast to the serum markers discussed above, PCA3 is measured in urine sediment obtained after prostatic massage (15). Determination of this PCa-specific gene is experimental. In the near future, several molecular diagnostic tests may move out of the laboratory into the clinical setting (16).

So far, none of the above biomarkers can be used 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 (17). Gray-scale TRUS does not detect areas of PCa with adequate reliability. Replacing systematic biopsies by targeted biopsies of suspect areas is therefore unproductive. 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 (18, 19) (level of evidence: 2a).

The ultrasound-guided perineal approach is a useful alternative in special situations, e.g. after rectal amputation. Its detection rates are comparable to those of the transrectal approach (20) (level of evidence: 1b).

6.4.2 Repeat biopsy

Indications are rising and/or persistent PSA, suspicious DRE and atypical small acinar proliferation (ASAP). The optimal timing is uncertain and 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 (21). High-grade prostatic intraepithelial neoplasia (PIN) is no longer considered an indication for re-biopsy (22) (level of evidence: 2a). A repeat biopsy should therefore be prompted by other clinical features, like DRE findings and PSA level. If PIN is extensive (i.e. in several biopsies) this could be a reason for early re-biopsy.

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 (23) (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) (24) (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 in the peripheral gland as possible.

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 (25) (level of evidence: 1a). The British Prostate Testing for Cancer and Treatment Study has recommended 10-core biopsies (26) (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 (27) (level of evidence: 2a).

6.4.6 Seminal vesicle biopsy
Indications for seminal vesicle biopsies are not well 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/L, the odds of tumour involvement are 20-25% (28) (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 (29) (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 (30) (level of evidence: 1b).

6.4.9 Local anaesthesia
Ultrasound-guided peri-prostatic block is state-of-the-art (31) (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 (32) (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 extent of the tumour.

6.4.11 Complications
Complication rates are low (Table 5) (33). 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 (34) (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 (35). 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 (36, 37). To optimise the detection of small lesions, blocks should be cut in three levels (38). It may be of help if intervening tissue sections are routinely mounted 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 (39, 40). Ancillary staining techniques (e.g. basal cell staining) and additional (deeper) sections should be considered if a suspect glandular lesion is identified (38, 40). For suspicious lesions in biopsies, diagnostic uncertainty may often be resolved by intradepartmental consultation and a second opinion from an external institution (39). Use concise clear terminology to report prostate biopsies (37) (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 (41). 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 (41). The presence of high-grade PIN 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 prognosticator of unfavourable disease (42, 43). The proportion (%) or length (mm) of tumour involvement per biopsy site correlates with tumour volume, extraprostatic extension and prognosis after prostatectomy (43-45) and should therefore be recorded. The length of carcinoma (mm) and the percentage of carcinoma involvement of the biopsy have equal prognostic impact (46).

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 (47-49). 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 (50). 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 recommendations of the International Society of Urological Pathology 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 (51).

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 (52). After fixation, the apex is removed and cut with (para)sagittal or radial sections; the shave method is not recommended (53). Separate 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.

Recommendations

- 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. The report includes:

- typing (> 95% of PCa represent conventional (acinic) adenocarcinomas)
- grading according to the Gleason score
- (sub)staging and surgical margin status of the tumour
- if appropriate, location and extent of extraprostatic extension, 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.

Given the complex information to be provided on each RP specimen, the use of synoptic-(like) or checklist reporting is recommended (see table 7). Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (54).

Table 7: Example checklist - reporting of prostatectomy specimens

Histologic type
Type of carcinoma (e.g. conventional acinar, ductal, etc.)
Histologic 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
Pathologic staging (pTNM)
Presence of extraprostatic extension (focal or extensive) If present: specify site(s)
Presence of seminal vesicle invasion
If applicable: Regional lymph nodes: - Location - Number of lymph nodes retrieved - Number of lymph nodes involved
Surgical margins
Presence of carcinoma at margin If present: specify site(s) and extra- or intraprostatic
Other
If identified: presence of angioinvasion
Location (site, zone) of dominant tumour (optional)
Perineural invasion (optional) If present: specify extra-or intra-prostatic

6.6.2.1. Gleason score

Grading of conventional prostatic adenocarcinomas using the (modified) Gleason score system (41) 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 (55).

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 ≤ 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 (56), 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 (53, 57). 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. It is useful to report not only the location, but also the extent of extraprostatic extension because the extension is related to the risk of recurrence (58, 59). 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‘ (60) or extension less than 1 high power field (59), while others measure the depth of extent in mm (61). 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 site of the apex, there is no agreed definition on how to determine extraprostatic extension. Here,

tumour admixed with skeletal muscle does not constitute extraprostatic extension, and it should be noted that at the apex, a diagnosis of stage pT4 is not rendered. In the bladder neck, microscopic invasion of small fibres of smooth muscle is not equated to bladder wall invasion (62). Some consider tumour invasion of large bundles of smooth muscle to be gross invasion (63), as determined by the urologist, or a positive bladder neck margin to be equivalent to pT4 (64).

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 (59, 65-68). Nevertheless, a prostate cancer volume cut-off of 0.5 mL continues to be an important parameter to distinguish insignificant from clinically relevant cancers (65). 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 millimeters.

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: positive if tumour cells are in touch with the ink on the surface of the specimen, and negative if not. The margin is negative if tumour cells are very close to the inked surface of the margin (66) 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 (69). Surgical margin status is independent of the pathological stage and a positive margin is not evidence of extraprostatic extension (70). There is insufficient evidence to prove a relationship between the extent of positive margin and the risk of recurrence (59). However, it is recommended that some indication is given of the (multi)-focality and extent of margin positivity (e.g. linear extent in millimeters, or number of blocks with positive margin involvement).

6.6.5 Other factors

According to the College of American Pathologists consensus statement (71), additional potential biomarkers, such as perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, prostate-specific antigen derivatives, and other factors (oncogenes, tumor suppressor genes, apoptosis genes, etc) have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting (category III).

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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 lymphotrophic 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 ^{18}F-choline PET/CT scans for initial N-staging were discouraging, especially in terms of inability to detect small metastases/micrometastases (< 5 mm) (53). Furthermore, ^{11}C-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 ^{18}F-fluoride uptake in malignant bone lesions reflects the increase in regional blood flow and bone turnover that characterise these lesions.

Studies have shown that ^{18}F-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:	B
	• transition zone biopsies are not recommended in the first set of biopsies due to low detection rates	C
	• 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	B
	• overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	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.	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, ^{18}F-fluorodeoxyglucose-PET or PET/CT could be of value, especially to differentiate active metastases and healing bones.	C

GR = grade of recommendation

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

8.1 Introduction

8.1.1 Definition

There is a great difference between the incidence of and mortality from prostate cancer (PCa): in the USA in 2007, there were 218,900 new cases with only 27,050 deaths (1).

Several autoptic 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. PCa 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 have been proposed:

- **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 (transurethral resection of the prostate [TURP] or other procedures for urinary tract obstruction, and hormonal therapy or radiotherapy for the palliation of metastatic lesions).
- **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; to follow him with close surveillance and treat at pre-defined thresholds that classify progression (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). WW can be considered as an option for treating patients with localised PCa in whom life expectancy is limited, or 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, 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, having as endpoints 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 five 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 8).

Table 8: Outcome of deferred treatment in localised PCa in relation to tumour grade (6)**: percentage of patients (95% confidence interval) surviving at five 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 9) (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 9: 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 radical prostatectomy (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 detected 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 10) (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 vs WW (level of evidence: 1b).

Table 10: 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 11) (32) (level of evidence: 1b).

Table 11: 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 categorisations incorporating PSA levels, Gleason histological grade and tumour stage, approximately 43% 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 enrolees 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

AS 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 ≤ 10 ng/mL and a Gleason score ≤ 6 (PSA ≤ 15 and Gleason score ≤ 7 [3 + 4] in patients above the age of 70 years). At a median follow-up of eight years, the overall survival was

85%, DSS 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 175 patients with a median follow-up of four 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).

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 five to seven more years of follow-up will be necessary in order to obtain definitive results.

Different series have identified several eligibility criteria for enrollers:

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

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

- a PSA doubling time with a cut off ranging between ≤ 2 and ≤ 4years
- Gleason score progression to ≥ 7 at re-biopsy, at intervals ranging from one to four years.

These indicators are poorly validated and, 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 (42).

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 (43-45). 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 (46) (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 (47).

In contradiction of Lundgren et al. (47), the report of the Casodex Early Prostate Cancer Trialists' Group programme showed higher mortality in a group of men with localised PCa treated with bicalutamide 150 mg than in those who received placebo (48).

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 (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 (49, 50).

In a recent prospective randomised clinical phase III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0 prostate cancer were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT

only on symptomatic disease progression or occurrence of serious complications (51, 52). After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% 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 seven 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 prostate cancer 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 ≤ to 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 after 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 (53), comparable with the results of the Lundgren et al. study mentioned above (47) (level of evidence: 1b).
Also, a comparison of bicalutamide, 150 mg/day, with placebo showed that progression-free survival was better with early treatment in patients with locally advanced PCa (48) (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 (54). The five- and 10-year CSS rates were 90% and 74%, respectively, and the likelihood of being without treatment at five and 10 years was 40% and 30%, respectively. The authors concluded that 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 two years, the time without any treatment (before symptoms occur) is very short in most cases. The MRC trial highlighted the risk of developing symptoms (pathological fractures, spinal cord compression), and even death from PCa, without receiving the possible benefit from hormone treatment (53, 55) (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

In presumed localised PCa (Nx-N0, M0):

- 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 (level of evidence: 2a).
- Stage T1b-T2b: well and moderately differentiated tumours. In asymptomatic patients with a life expectancy of < 10 years (level of evidence: 2a).

8.5.2 Options

In presumed localised PCa (Nx-N0, M0):

- 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
- all patients not willing to accept side-effects of active treatment
- well informed, asymptomatic patients with high PSA levels for whom cure is unlikely (level of evidence: 3).

In locally advanced disease (stage T3-T4):

- asymptomatic patients with well or moderately differentiated cancer, PCa and a short life expectancy (level of evidence: 3)
- PSA < 50 ng/mL and PSA doubling time > 12 months (level of evidence: 1).

In metastatic disease (M1):

- a very rare patient without any symptoms and the possibility of close follow-up (level of evidence: 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 is the removal of the entire prostate gland between the urethra and the bladder, with resection of both seminal vesicles. In men with localised PCa and a life expectancy of 10 years or more, the goal of an RP by any approach must be eradication of the disease (1). There is no age threshold for RP. A patient should not be denied this procedure on the grounds of age alone (2). In fact, increasing co-morbidity with age greatly increases the risk of dying from non-PCa related causes (3, 4). Life expectancy estimation is paramount in the counselling of a patient for 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. This resulted in a significant reduction of blood loss and improved continence and potency rates (7).

Currently, radical prostatectomy is the only treatment for localised PCa that has shown a cancer-specific survival benefit when compared with conservative management in a prospective, randomised trial (8). Surgical expertise has decreased the complication rates and improved cancer cure (9-12). The retropubic approach is more commonly performed, as it enables simultaneous pelvic lymph node assessment to be carried out, which is an advantage over the perineal approach. It has been suggested that perineal radical prostatectomy might result in positive surgical margins more often than the retropubic approach (13), but this has not been confirmed (14).

In the past 5-10 years, several European centres have acquired considerable experience with laparoscopic radical prostatectomy (15-18). More recently, the robotic-assisted laparoscopic RP has been developed. It is

likely that laparoscopic, robot-assisted and perineal prostatectomies have lower morbidity than the retropubic operation, but randomised studies are as yet unavailable. Functional and short-term oncological outcomes of laparoscopic and robot-assisted RP seem comparable with the open technique in high-volume centres. However, long-term oncological outcomes are still unavailable (19).

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

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 adenomectomy). Stage T1b PCa is defined as > 5% cancer.

A recent Swedish register-based study in 23,288 men with incidental PCa detected at TURP or open adenoma enucleation showed a 10-year PCa mortality of 26.6%. No details on prostate-specific antigen (PSA) or Gleason score were provided. Neither were details available on the numbers of cases with cT1a or cT1b PCa (20).

Although the risk of disease progression of untreated T1a PCa after five years is only 5%, these cancers can progress in about 50% of cases after 10-13 years (21). Thus, in younger patients with a life-expectancy of 15 years or more, the chance of disease progression is real. An RP may also be offered when the Gleason score is > 6.

In contrast, most patients with T1b tumours are expected to show disease progression after five years, and aggressive treatment is often warranted (21). Patients with T1b lesions are offered RP when they have a life expectancy of 10 years or more.

It is consequently very important to distinguish between T1a and T1b tumours. Systematic prostate biopsies of the remnant prostate may be useful to detect concomitant peripheral zone cancer, or to ascertain a more correct tumour grade. RP may be very difficult after a thorough TURP, when almost no residual prostate is left behind (22).

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 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 since up to 30% of cT1c tumours are locally advanced disease at final histopathology (23). The proportion of insignificant tumours varies between 11% and 16% (24, 25). Increasing the number of biopsies might 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 (26).

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 (27). 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 (28). Other authors have suggested the incorporation of biopsy information, such as the number of cores or the percentage of cores invaded (29). 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 (30). 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. T2a patients with a 10-year life expectancy should be offered RP since 35-55% of them will have disease progression after five years if not treated.

If watchful waiting (WW) is proposed for low-grade T2 cancer, it should be remembered that pre-operative assessment of tumour grade by needle biopsy is often unreliable (31).

As a rule of thumb, 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% (32). A limited lymph node dissection should no longer be performed, as this will miss at least half of the nodes involved.

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

RP is one of the recommended standard treatments for patients with intermediate-risk PCa and a life

expectancy of more than 10 years (33). The prognosis is excellent when the tumour is confined to the prostate based on pathological examination (34, 35). A policy of WW has been proposed for some patients with intermediate-risk localised tumours (36). 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. 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 five years (37). 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). Total surgical removal is an excellent option, and, 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 (38).

As a rule of thumb, an eLND should be performed if the estimated risk for positive lymph nodes exceeds 7% (32). In all other cases, an eLND can be omitted, 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 12.

Table 12: Oncological results of RP in organ-confined disease

Reference (no.)	No. of patients	Mean follow-up (months)	5-year PSA-free survival (%)	10-year PSA-free survival (%)
Han et al. (2001) (39)	2404	75*	84	74
Catalona and Smith (1994) (40)	925	28	78	65
Hull et al. (2002) (41)	1000	53	–	75
Trapasso et al. (1994) (42)	601	34	69	47
Zincke et al. (1994) (43)	3170	60	70	52

** = 15-year, 66%.*

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 of stage and grade of PCa, with > 90% of men in the current era diagnosed with clinically localised disease (44). 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 (45). There is no consensus regarding the optimal treatment of men with high-risk PCa.

9.4.1 Locally advanced PCa: cT3a

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 (46), mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse (47, 48).

Several randomised studies on radiotherapy with androgen-deprivation therapy (ADT) vs radiotherapy alone showed a clear advantage for the combination treatment. However, no trial has ever shown this approach to be superior to RP (49). Another problem is 'contamination' by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal treatment in most of the 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 (50-55).

Overstaging of cT3 PCa is relatively frequent and occurs in 13-27% of cases. These pT2 patients and patients with specimen-confined pT3 disease have similarly good biochemical and clinical PFS (54, 55). In about 33.5-

66% of patients, positive section margins will be present, and 7.9-49% will have positive lymph nodes (56). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or hormonal therapy (54, 55). Nevertheless, excellent 5-, 10- and 15-year overall survival (OS) and cancer-specific survival (CSS) rates have been published (Table 2). These rates surpass radiotherapy-alone series and are no different from radiotherapy combined with adjuvant hormonal therapy series (49).

The problem remains the selection of patients before surgery that have neither lymph node involvement nor seminal vesicle invasion. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease (28, 56). In addition, nodal imaging with computed tomography (CT), and seminal vesicle imaging with magnetic resonance imaging (MRI), or directed specific puncture biopsies of the nodes or seminal vesicles can be helpful in recognising those patients unlikely to benefit from a surgical approach (57).

RP 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 (54, 58).

Table 13: 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) (50)	57	Median, 5.4 y	91.2 (77.6 at 7.5 y)	-	-	-	-	-	45.5 (PSA > 0.4)	-	-	81.4	-	-
Gerber et al. (1997) (51)	242	Mean, 39 m Median, 26 m	-	-	-	85	57	-	-	-	-	72 (meta free)	32	-
Van den Ouden et al. (1998) (52)	83	Median, 52 m	75	60	-	85	72	-	29 (PSA > 0.1)			59	31	-
Isorna Martinez de la Riva et al. (2004) (53)	83	Mean, 68.7 m (cT3a only)	97.6	94.8	-	100	-	-	(PSA	59.8 > 0.3)	-	-	-	-
Ward et al. (2005) (54)	841	Median, 10.3 y	90	76	53	95	90	79	58 (PSA	43 > 0.4)	38	85	73	67
Hsu et al. (2007) (55)	200	Mean, 70.6 m (cT3a only)	95.9	77	-	98.7	91.6	-	59.5 (PSA	51.1 > 0.2)	-	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. PSA value and the % of positive prostate biopsies may be helpful in selecting men with high-grade prostate cancer most likely to benefit from RP (59).

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 five and 10 years, respectively (60). D'Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at five years after RP (61). Tiguert and co-workers presented the outcome for an identical cohort of patients who had a disease-free survival of 65% at five years after RP (62). 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 overall CSS was 87%. These results argue for aggressive management with RP as initial step (63).

As a rule of thumb, 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% (32). 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. 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.

Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP may be considered a reasonable first step in a selection of patients with low tumour volume.

9.5.2 Any T, N1

The indication for RP in all previously described stages assumes the absence of 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 simultaneous hormonal treatment has been shown to achieve a 10-year CSS rate of 80% (64). However, it is questionable whether or not these results could also have been obtained with hormonal treatment alone. Most urologists are reluctant to perform RP for clinical N+ disease, or will cancel surgery if a frozen section shows lymph node invasion. It should also be noted that the definitive pathological examination after RP can 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 (65, 66). Clinical N+ patients usually have significant nodal involvement and will be treated with hormonal manipulation only. In patients who prove to be pN+ after RP, adjuvant hormonal treatment can be advocated, but the benefits should be judged against the side-effects of long-term hormonal therapy. PSA follow-up and hormonal treatment in the case of an increase in PSA level is therefore an acceptable option in selected cases.

The most accurate staging method for the assessment of lymph node involvement is eLND. This includes removal of al node-bearing tissue from the area bounded by the external iliac vein anteriorly, the lateral pelvic side wall, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. During recent years, there has been increasing interest in eLND, but controversy regarding indication and extent of ELND, its therapeutic role and morbidity remain.

9.5.2.1 Indication and extent of extrended pelvic lymph node dissectiori (eLND)

Although it is generally accepted that eLND provides important information for prognosis (number of nodes involved, tumour volume, capsular perforation) that cannot be matched by any other current procedures, 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 (28). 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 of these 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 (32).

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 (67). Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (68, 69).

9.5.2.2 Therapeutic role of eLND

Besides being a staging procedure, (extended) pelvic lymph node dissection might be curative, or at least beneficial, in a subset of patients with limited lymph node metastases (70-72). For an eLND to be representative, a mean of 20 lymph nodes should be removed (73). In some series, the number of nodes removed during lymphadenectomy correlated significantly with time to progression (74). At present, however, lymph node metastases are considered to be a sign of systemic disease. Whenever lymph node metastases are found, prognosis worsens and systemic therapy is advised.

9.5.2.3 Morbidity

An eLND remains a surgical procedure, which adds morbidity to the treatment of PCa. When comparing limited vs extended LND, threefold higher complication rates were reported by some authors (75). Complications consist of lymphocoeles, lymphoedema, deep venous thrombosis and pulmonary embolism. Other authors, however, reported more acceptable complication rates (76, 77).

9.5.2.4 Summary of eLND

- eLND can play a role in the treatment of PCa for a subset of patients.
- The number of lymph nodes removed correlates with the time to progression.
- Concomitant morbidity has to be balanced against the therapeutic effects, and a decision will have to be made based on individual 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 frequent.
- 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.

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 (78). In cases of positive lymph nodes at final histopathology, adjuvant ADT may be considered. Messing et al. examined the role of immediate ADT vs observation in patients with positive lymph nodes found 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 (79).

9.7 Neoadjuvant hormonal therapy and RP

Generally, neoadjuvant or up-front 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 (80).

In a recent Cochrane review and meta-analysis, the role of neoadjuvant and adjuvant hormonal therapy and prostatectomy were studied (81). Patients had predominantly localised T1 and T2 disease, low- and intermediate-grade, with Gleason scores < 7, and PSA < 20 ng/mL in most patients. The Cochrane review made the following observations:

- Neoadjuvant hormonal therapy before RP does not provide a significant OS advantage over prostatectomy alone (pooled odds ratio [OR] 1.11; 95% confidence interval [CI] 0.67-1.85).
- Neoadjuvant hormonal therapy before RP does not provide a significant advantage in disease-free survival over prostatectomy alone (pooled OR 1.24; 95% CI 0.97-1.57).
- 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: the pooled data for five-year OS showed an OR of 1.50 and 95% CI 0.79-2.84. This was not statistically significant, although there was a trend favouring adjuvant hormonal therapy. Similarly, there was no survival advantage at 10 years.
- Adjuvant hormonal therapy following RP: 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 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 (82). Median follow-up was 7.2 years. There was a significant improvement in objective progression-free survival (PFS) in the RP group.

- This improvement was only statistically significant in the locally advanced disease group (HR 0.75; 95% CI 0.61-0.91). There was no significant improvement in OS in the RP group, both the localised and locally advanced disease groups. 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).

9.7.1 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 was highly statistically significant ($p < 0.00001$) in favour of the hormonal arm.

9.8 Complications and functional outcome

The post-operative complications of RP are listed in Table 14. The mortality rate is 0-1.5% (75); urinary fistulas are seen in 1.2-4% of patients (83); and urinary incontinence persists after one year in 7.7% (84). 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 (85-87). Erectile dysfunction used to occur in nearly all patients, but nerve-sparing techniques can be applied in early-stage disease (88). Patients who benefit from nerve-sparing RP may have a higher chance of local disease recurrence and should therefore be selected carefully.

Table 14: 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
• Lymphocoele	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

9.9 Summary of indications for nerve-sparing surgery*

Reference name	Sofer (89)	Walsh (90)	Alsikafi (91)	Graefen (92)	Bianco (93)
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 peri-neural invasion		+/-	+		

Intra-operative selection criteria					
Side of palpable tumour			+		
Side of positive biopsy				+	
Induration of lateral pelvic fascia		+			+
Adherent 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 (94, 95). 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 guide decision-making (28).

If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle. Alternatively, the use of intra-operative frozen-section analysis can help guide these decisions. The patient must be informed before surgery about the risks of nerve-sparing surgery, the potency rates of 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 (96, 97) and the significance of sural nerve transplant needs further multicentre study (98). Finally, the early use of PDE-5 inhibitors in penile rehabilitation remains controversial. A recent study showed no benefit of daily early administration of vardenafil versus on-demand vardenafil in the postoperative period (99).

9.10 Guidelines and recommendations for RP

	LE
Indications	
• In patients with low and intermediate risk localised PCa (cT1b-T2 and Gleason score 2-7 and PSA < 20) and a life expectancy > 10 years.	1b
Optional	
• Patients with stage T1a disease and a life expectancy > 15 years or Gleason score 7.	3
• 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 (three 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 with either external beam therapy or brachytherapy for localised prostate cancer, but 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, external irradiation 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, 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, the choice of treatment after the appropriate assessment of tumour extension must be based on a multidisciplinary approach taking account of:

- the 2002 tumour node metastasis (TNM) classification
- the Gleason score defined on a sufficient number of core biopsies (at least 12)
- the baseline prostate-specific antigen (PSA)
- the age of the patient
- his 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 and intensity modulated external beam radiotherapy

Anatomical data acquired by scanning the patient in a treatment position, are transferred to the 3D treatment planning system where the clinical target volume is visualised, following which a (surrounding) safety margin is added. At the time of irradiation, a multileaf collimator automatically and, in the case of IMRT, continuously, adapts to the contours of the target volume seen by each beam. 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, mandating 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 is significantly higher with a radiation dose ≥ 72 Gy compared with < 72 Gy (p = 0.04) (4).

Two randomised trials focusing 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 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 five-year freedom from biochemical failure ($p < 0.001$) in favour of low-risk patients, who were given a higher dose (79.2 Gy), compared with those receiving a conventional dose (70.2 Gy) (6).

In daily practice, a minimum dose of 74 Gy is recommended.

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

Many non-randomised studies have shown dose escalation to have a significant impact on five-year survival without biochemical relapse for patients classified as cT1c-T3, with a dose ranging from 76-81 Gy (4, 7, 8).

A Dutch randomised phase III trial comparing 68 Gy with 78 Gy showed a significant increase in five-year freedom from clinical or biochemical failure for patients in an intermediate-risk group (9).

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, high dose should provide a better five-year biological outcome in intermediate-risk patients, especially if the initial PSA > 15ng/mL (10).

Patients who are reluctant to accept short-term hormonal treatment (11) can receive definitive radiotherapy alone provided that a dose escalation up to 78-80 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 five-year biochemical disease-free survival, as shown in several phase III randomised trials.

- The Dutch study comparing 68 Gy with 78 Gy showed a 10% increase in the five-year freedom from clinical or biochemical failure ($p = 0.02$) (9).
- The MRC study comparing 64 Gy with 74 Gy, with neoadjuvant hormonal therapy, has shown an 11% difference in five-year biochemical disease-free survival (12).
- The PROG 95-09 study, with a significant increase in five-year freedom from biochemical failure ($p < 0.02$) in favour of high-risk patients given a higher dose (79.2 Gy) vs those receiving a conventional dose (70.2 Gy) (9).
- The 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 and 78 Gy), with or without six months of neoadjuvant and concomitant hormonal therapy, was closed in April 2008 after recruiting 800 patients, and its results are awaited (13).

In daily practice, a combination of external irradiation with short-term androgen deprivation is recommended, based on the results of a phase III randomised trial. This trial, which included 206 patients with a PSA 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 six months of ADT. After a median follow-up of 7.6 years, intermediate- or high-risk patients without moderate or severe co-morbidity randomised to receive 3D-CRT plus ADT had a 13% improvement in overall survival rate ($p < 0.001$) (11).

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

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 of the pelvic lymph nodes in high-risk cases (46-50 Gy). Such studies include the RTOG study with 484 T1b-T2 patients (15), the Standford study with only 91 patients (16), and the GETUG-01 trial, which included 444 T1b-T3 N0 pNx M0 patients (17). In order better to select 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), pelvic lymphadenectomy might be required, particularly for young patients, because its results 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

IMRT 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, 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, IMRT is the only safe means of treatment delivery, although 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, 561 patients with organ-confined disease were treated with a dose of 81 Gy. The eight-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 (20).

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 (21). 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, and evolving techniques will 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 (22).

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 prostate cancer treatment (23).

10.4.2 Proton beam and carbon ion beam therapy

In theory, proton beams are an attractive alternative to photon beam radiotherapy for prostate cancer 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 to photon beams, which will continue to deposit energy up to and including an exit dose as they leave the body.

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 discussed 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 suggesting that the two are equivalent in terms of rectal dose sparing, but IMRT is actually superior in terms of bladder sparing (24), and the other suggesting a clearer advantage to protons (25). 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 prostate cancer 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 prostate cancer were treated with carbon ions in a dose equivalent to 66 Gy in 20 fractions over five weeks (26). Treatment appeared to be well tolerated, with no RTOG grade 3 or 4 bowel or genitourinary toxicity, and an overall four-year biochemical disease-free rate of 88% (25). 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 two 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
- ≤ 50% of biopsy cores involved with cancer
- a prostate volume of < 50 cm^3
- a good International Prostatic Symptom Score (IPSS) (27).

Patients with low-risk prostate cancer are the most suitable candidates for low-dose rate (LDR) brachytherapy. Further guidelines on technical aspects of brachytherapy have been published recently, and are strongly recommended (28).

In 1983, Holm et al. described the transperineal method with endorectal sonography in which the patient is positioned in a dorsal decubitus gynaecological position (29). Implantation is undertaken under general anaesthesia or spinal block, and involves a learning curve for the whole team: the surgeon for the delineation of the prostate and the placement of the needles, 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.

No randomised trials have been performed 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 (30). Recurrence-free survival after five and 10 years was reported to range from 71-93% and from 65-85%, respectively (31-38).

A significant correlation has been shown between the implanted dose and recurrence rates (39). Patients receiving a D90 of > 140 Gy demonstrated a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at four years than patients receiving less than 140 Gy (92% vs 68%). There is no benefit from adding neoadjuvant or adjuvant androgen deprivation to LDR brachytherapy (30).

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 (40). This observation could usefully be further studied 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 three to five years. In a recent retrospective analysis of 5621 men who had undergone LDR brachytherapy (41), 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 (42).

A small randomised trial has suggested that, as one might expect, 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 (43).

In cases of intermediate or high-risk localised prostate cancer, its combination with supplemental external irradiation (44) or neoadjuvant hormonal treatment (45) may be considered.

The optimum dose of supplemental external beam radiation therapy (EBRT) is unclear. A randomised trial comparing 44 Gy with 20 Gy of EBRT plus palladium-103 brachytherapy closed early, showing no difference in biochemical outcomes (46).

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

Recent data suggest an equivalent outcome in terms of biochemical disease-free survival compared with high-dose EBRT (HD EBRT) (49). In a retrospective analysis of modern series (50, 51), biochemical disease-free survival rates of 85.8%, 80.3% and 67.8% in men with low-, intermediate- and high-risk prostate cancer, respectively, are reported after a mean follow-up of 9.43 years.

Quality-of-life changes are similar between HD EBRT and high-dose rate (HDR) brachytherapy in terms of diarrhoea and insomnia (52). However, the frequency of erectile dysfunction is significantly increased with HDR brachytherapy (86% vs 34%). A single randomised trial of EBRT versus EBRT plus HDR brachytherapy has been reported (53). A total of 220 patients with organ-confined prostate cancer 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. A significant improvement in biochemical relapse-free survival was seen in favour of the combined brachytherapy schedule ($p = 0.03$). There were no differences in the rates of late toxicity. Patients randomised to brachytherapy had significantly better quality of life as measured by their Functional Assessment of Cancer Therapy-prostate (FACT-P) score at 12 weeks (53). There is still a need to compare dose escalated EBRT plus hormone therapy, with the same plus a brachytherapy boost, in intermediate- and high-risk patients.

For T1-2 N0 M0 disease, the five-year biochemical failure rates are similar for permanent seed implantation, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and radical prostatectomy. These were the results from a study that included 2991 patients diagnosed with T1-2 consecutive localised prostate cancer treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Center with a minimum of one-year follow-up (49).

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) (54), 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 15). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT or IMRT.

Table 15: 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	31	8.2

Chronic diarrhoea	14	3.7	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 (≥ 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 one-year rate of probability for maintaining erectile function was 0.76 after brachytherapy, 0.60 after brachytherapy plus 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 two 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 (55).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (56, 57). In a retrospective evaluation of 30,552 and 55,263 men who had undergone either EBRT or radical prostatectomy, the risk of being diagnosed with rectal cancer increased 1.7-fold in comparison with the surgery group (56).

Another analysis (57) showed that the relative risk of developing bladder cancer increased by 2.34-fold compared with a healthy control population.

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 (58). 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 take over as the dominant morbidity (58).

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% (59). 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 ($p < 0.001$) (60).

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 after retropubic radical prostatectomy. Immediate post-operative radiotherapy proved to be well tolerated, with a risk of grade 3-4 urinary toxicity of less than 3.5% (61), without significant differences regarding the rate of incontinence and/or stricture of anastomosis (62). The study concludes that immediate post-operative radiotherapy after surgery significantly improves five-year clinical or biological survival: 72.2% vs 51.8% ($p < 0.0001$) (63).

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 – based on a cohort of 385 patients – echoed those of EORTC since after a median follow-up of 54 months, biochemical progression-free survival was significantly improved in the radiotherapy group: 72% vs 54% ($p = 0.0015$) (64).

In the same way, the SWOG 8794 trial randomised 425 pT3 patients, and the updated results (65), with a median follow-up of 11.5 years, show that adjuvant radiation significantly improved metastasis-free survival, with a 15-year metastasis-free survival of 46% vs 38% ($p = 0.036$) and a 15-year overall survival of 47% vs 37% ($p = 0.053$).

Thus, for patients classified as T1-2 N0 (or T3 N0 with selected prognostic factors), pT3 pN0 with a high risk of local failure after radical prostatectomy due to capsular rupture, positive margins and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL one month after surgery, two options can be offered within the frame 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 (67); 1.0 ng/mL seems to be a breakpoint above which the likelihood of local control is significantly reduced (68).

A retrospective analysis based on 635 patients undergoing prostatectomy 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 two 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 ($p < 0.001$) (69).

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

10.8 Locally advanced prostate cancer: T3-4 N0, M0

The incidence of locally advanced prostate cancer 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 (70). Because of the hormonal dependence of prostate cancer (71), 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 (72) through the effect of radiation-induced apoptosis (73, 74).

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. ADT was administered two 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 four 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 – 43% vs 34% – favoured ADT and irradiation, but 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 biochemical failure (65% vs 80%; $p < 0.0001$), with the addition of ADT having no statistical impact on the risk of fatal cardiac events (75).

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), T3-4, N0 M0 and any histological grade, and compared radiotherapy plus adjuvant ADT, with radiotherapy alone. ADT was allowed in cases of relapse. A total of 82% of patients was diagnosed as T3, 10% as T4, and 89% as N0.

The hormone treatment consisted of oral cyproterone acetate (CPA), 50 mg three times daily for one month, beginning one week before the start of radiotherapy, and goserelin acetate (Zoladex), 3.6 mg subcutaneously every four weeks for three 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%, $p = 0.001$) (76). 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 prostate cancer mortality was 11. 1% vs 31% ($p < 0.0001$), and the 10-year cumulative incidence of cardiovascular mortality was 11.1% vs 8.2% ($p = 0.75$) (77).

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 radical prostatectomy. ADT 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 radical prostatectomy, while 14% of patients in group I and 26% in group II were pN1.

Goserelin acetate, 3.6 mg subcutaneously, was administered every four weeks. The pelvis received 45 Gy and 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% vs 39% ($p = 0.002$) (78). National Cancer Institute (NCI) of Canada /Medical Research Council intergroup PR3/PR07 study, including patients diagnosed with stage cT3-4 N0 M0, compared complete androgen blockade (CAB) (goserelin acetate 3.6 mg subcutaneously every four weeks and flutamide 750 mg/day) alone and in combination with radiation 65-69 Gy (79, 80). The results are awaited.

The SPCG-7/SFUO-3 randomised study (81) compared endocrine treatment alone, three months of CAB followed by continuous endocrine treatment using flutamide (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% (difference 12%; 95% CI; 4.9-19.1%), and the 10-year cumulative incidence for overall mortality was 39.4% in the endocrine treatment alone group, and 29.6% in the endocrine plus radiotherapy group (difference 9.8%; 0.8-18%).

10.8.4 Neoadjuvant, concomitant and long-term adjuvant hormonal therapy

The RTOG 92-02 trial closed in 1995 after accruing 1554 patients. Statistically significant improvements were observed in actuarial biochemical freedom from disease (bNED) control, distant metastatic failure, local control, and disease-free survival in patients receiving long-term ADT (LDAT) (before, during, and two years after radiotherapy), compared with short-term androgen deprivation (STAD) (two months before and during radiotherapy). With a median follow-up of 5.8 years, the LTAD treatment arm showed significant improvement over the STAD arm in all efficacy end-points except five-year overall survival, which was 80% vs 78.5% ($p = 0.73$), respectively. In a subset of patients that was not part of the original study design, with Gleason score 8-10 tumours, the LTAD arm showed significantly better overall survival after five years than the STAD arm, with 81% vs 70.7% ($p = 0.04$) (82).

10.8.5 Short-term or long-term adjuvant hormonal treatment

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

Non-inferior survival was defined as a mortality hazard ratio (HR) = 1.35 for SADT vs LADT. A total of 970 patients were randomised. With a 5.2-year median follow-up, the five-year overall survival rate was 85.3% on LADT, and 80.6% on SADT (HR = 1.43; 96.4% CI; 1.04-1.98), and failed to prove non-inferiority (83).

10.8.6 Dose escalation with hormonal therapy

For bulky locally advanced prostate cancer, 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. ADT was given for three 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 eight years, the five- and 10-year overall survival and cause-specific survival were respectively 91% and 65%, 95% and 83% (84).

10.9 Very high-risk prostate cancer: c or pN1, M0

Patients with a pelvic lymph node involvement lower than the iliac regional nodes, younger than 80 years old with WHO performance status 0-1 and no severe co-morbidity may be candidates for external beam irradiation 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 five and nine-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 (85).

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	2
	For patients in the high-risk group, short-term ADT prior to and during radiotherapy results in increased overall survival.	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 radical prostatectomy for patients with pathological tumour stage T3 N0 M0 improves biochemical and clinical disease-free survival.	1
	An alternative option is to give radiation at the time of biochemical failure, but before PSA rises above 1ng/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 three years, with external irradiation for patients with a WHO 0-1 performance status.	1
	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

LE = level of evidence

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11. EXPERIMENTAL LOCAL TREATMENT OF PROSTATE CANCER

11.1 Background

Besides radical prostatectomy, 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 prostate cancer (PCa) (1-4).

Whereas HIFU is still considered to be an experimental treatment, CSAP has been recognised as a true therapeutic alternative as recommended by the guidelines of the American Urological Association. Both techniques have been developed as minimally invasive procedures that potentially have the same therapeutic efficacy as the established surgical and non-surgical options associated 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 the placement of 12-15 17 G 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 to have minimal extension beyond the prostate (1-3). The prostate should be ≤ 40 mL in size. Prostate glands that are > 40mL should be hormonally downsized in order to prevent technical difficulties 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. Since there are no, or only very few, data on the long-term outcome in terms of cancer control at 10 and 15 years, patients with a life expectancy > 10 years must be informed accordingly.

11.2.2 Results of modern cryosurgery for PCa

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

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

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, biochemical-free survival at five years is 60% and 36% for low-risk and high-risk patients, respectively (6, 7). The seven-year biochemical-free survival, however, is 92% if ASTRO criteria are used.

Long et al. (6) retrospectively analysed the multicentre pooled CSAP results of 975 patients who were stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL at a mean follow-up of 24 months, the five-year actuarial biochemical progression-free rate was 76% and 60%, respectively, for the low-risk group, 71% and 45%, respectively, for the intermediate-risk group, and 61% and 36%, respectively, for the high-risk group. However, in a recent meta-analysis of 566 publications related to cryosurgery, it was demonstrated that no controlled trial was available for analysis, no survival data were presented, and no validated biochemical surrogate end-points were available (12). Cryosurgery showed a progression-free survival of 36-92% (projected one- to seven-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72-87%, 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 only 110/175 (63%) patients having a PSA follow-up at 12 months (6-11). Of these, 80 (73%) patients remain with a PSA nadir < 0.4 ng/mL, and 42/65 (76%) low-risk patients remain free from biochemical progression using the 0.4 ng/mL cut-off.

A longer follow-up was reported by Bahn et al. (9) analysing the therapeutic results of 590 patients undergoing CSAP for clinically localised and locally advanced PCa. Using a PSA cut-off level of < 0.5 ng/mL, the seven-year biochemical-free survival for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively.

Nerve-sparing cryosurgery, as reported recently (13), must still be considered to be an experimental therapeutic option. Nerve-sparing surgery was performed in nine patients with unilateral PCa confirmed on repeated biopsies, with CSAP being carried out on the side of the positive biopsy, whereas 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, with < 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 could be determined when comparing the 36-month with the 12-month data. With regard to sexuality, 37% of the men were able to have intercourse at three years after CSAP.

11.2.4 Summary of CSAP

- Patients with low-risk PCa (PSA < 10 ng/mL, ≤ T2a, Gleason score ≤ 6) or intermediate-risk PCa (PSA > 10 ng/mL, or Gleason score ≥ 7, or stage ≥ 2b) represent potential candidates for CSAP.
- Prostate size should be < 40 mL at the time of therapy.
- Long-term results are lacking, and five-year biochemical progression-free rates are inferior to those achieved by radical prostatectomy in low-risk patients. Patients must be informed accordingly.

11.3 High-intensity focused ultrasound (HIFU)

HIFU consists of focused ultrasound waves emitted from a transducer to cause tissue damage by mechanical and thermal effects as well as by cavitation (15). The goal of HIFU is to heat malignant tissues above 65 °C in order to destroy them by coagulative necrosis.

HIFU is performed under general or spinal anesthesia, with the patient in the lateral (Ablatherm®) or supine (Sonablate® 500) position; the procedure is time-consuming, with about 10 g prostate tissue being treated in one 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 fewer than 1000 PCa cases having been published in the literature.

According to the recent review paper mentioned above (12), HIFU showed progression-free survival (based on PSA +/- biopsy data) of 63-87% (projected three- to five-year data), but median follow-up in the studies ranged from 12-24 months only.

In one of the largest single-centre studies, 227 patients with clinically organ confined PCa were treated with HIFU and their outcome data were analysed after a mean follow-up of 27 months (range = 12-121 months) (16). The projected five-year biochemical disease-free survival was 66%, and 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 (17), 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 (18), a complete response rate defined by PSA < 4 ng/mL and six negative biopsies was 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. (18) reported on a negative biopsy rate of 87.2% in 288 men with a follow-up of at least six months. A PSA nadir after six months follow-up could be determined in 212 patients, and it was as high as 1.8 ng/mL. However, it could be demonstrated that the PSA nadir might be reached at 12-18 months following the initial procedure.

Blana et al. reported on 146 patients undergoing HIFU with a mean follow-up of 22.5 months (19). The mean PSA level at initiation of therapy was 7.6 ng/mL; the PSA nadir achieved after three months was 0.07 ng/mL. However, after 22 months the median PSA level was 0.15 ng/mL. Of the 137 men available for analysis, 93.4% demonstrated a negative control biopsy. The PSA nadir appears to be strongly associated with treatment failure (20) ($p < 0.001$). 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 five years was 66%, with salvage treatment initiated for 12% of the patients (21).

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 (15-17). 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 Radio-frequency interstitial tumour ablation (RITA)

Radio-frequency interstitial tumour ablation (RITA) is a recently developed minimally invasive therapeutic option delivering radio-frequency energy via a needle electrode placed inside the prostate and resulting in coagulative necrosis by heating the tissue up to 100 °C. Clinical application so far has been limited to two small studies demonstrating the feasibility and safety of the procedure (22, 23). However, there are reliable data with regard to oncological control of PCa.

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, RITA, 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	C

GR = grade of recommendation

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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), demonstrating for the first time the responsiveness of PCa to androgen deprivation (1, 2).

Since their pivotal studies, androgen-suppressing strategies have become the mainstay of the management of

advanced PCa. Recently, however, there has been an evolution towards the use increasing use of hormonal treatment in younger men with earlier (i.e. non-metastatic) stages of disease 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 can extend life.

12.2 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). LH stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cells, testosterone is converted by the enzyme 5-∝-reductase into 5-∝-dihydrotestosterone (DHT), which is an androgenic stimulant approximately 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 ultimately resulting in the suppression of androgen activity is referred to as androgen deprivation therapy (ADT).

12.3 Different types of hormonal therapy

Androgen deprivation can be achieved either by suppressing the secretion of testicular androgens by means of surgical or medical castration, or by inhibiting the action of the circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens.

Alternatively, these two modalities can be combined to achieve what is commonly known as complete (or maximal or total) androgen blockade (CAB).

12.3.1 Testosterone-lowering therapy (castration)

12.3.1.1 Bilateral orchiectomy

Surgical castration is still considered the ‘gold standard’ for ADT against which all other treatments are rated. By removing the testicular source of androgens, a hypogonadal status with a considerable decline of testosterone concentrations is induced, although a very low level of testosterone (known as the ‘castration level’) persists.

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

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 that can easily be performed under local anaesthesia (7). It is the quickest way to achieve a castration level, which is usually obtained in 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, which can be attributed to the effects of stage migration towards earlier disease, and the introduction of equally effective pharmacological modalities of castration (8).

12.3.1.2 Oestrogens

There are 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).

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

There are three main reasons for the renewed interest in oestrogens.

- First, as a response to the number of deleterious side-effects and high cost of long-term ADT with the widespread use of LHRH agonists: oestrogens suppress testosterone levels and do not seem to lead to bone loss and cognitive decline (12) (level of evidence: 3).
- Second, in phase II trials with patients diagnosed with hormone-refractory prostate cancer (HRPC), oestrogenic compounds (DES, DES-diphosphate) have been shown to induce prostate-specific antigen (PSA) response rates as high as 86%.
- Third, a new oestrogen receptor-β (ER-β), possibly involved in prostate tumorigenesis, has been discovered (9).

Two different strategies have been used to try to neutralise the cardiotoxicity that is the main drawback of oestrogen therapy. These strategies use the parenteral route of administration, which avoids first-pass hepatic metabolism, plus the addition of cardiovascular protecting agents.

The final analysis of the Scandinavian Prostatic Cancer Group Study 5, a prospective randomised trial of more than 900 men with metastatic PCa that compared a parenteral oestrogen (polyoestradiol phosphate) with CAB (orchiectomy or LHRH agonist plus flutamide), showed neither a significant difference in disease-specific and overall survival between the treatment arms, nor a significant increase in cardiovascular mortality in the oestrogen arm, although the occurrence of non-fatal adverse cardiovascular events was significantly higher in this group (increase in ischaemic heart and heart decompensation events) (13, for update see 14).

On the other hand, three recent, though small, phase II trials of patients with advanced PCa or HRPC evaluated the combination of DES (1 mg/day or 3 mg/day), with either low dose (1 mg/day) warfarin sodium or low dose (75-100 mg/day) aspirin for the prevention of cardiovascular toxicity, and found a persistent rate of thromboembolic complications (15-17).

In conclusion, DES is one of the classic forms of hormonal therapy. Although its efficacy was demonstrated many years ago and recently reconfirmed in a meta-analysis as comparable to that of bilateral orchiectomy (18) (level of evidence: 1a), the significant cardiovascular side-effects, even at lower dosages, remain a concern. Further data are needed before oestrogens will be readmitted into clinical practice as a standard first-line treatment option.

12.3.1.3 LHRH agonists

Long-acting LHRH agonists (buserelin, goserelin, leuprorelin and triptorelin) have been used in advanced PCa for more than 15 years and are currently the predominant forms of ADT (3, 19). They are synthetic analogues of LHRH, generally delivered as depot injections on a one-, two-, three-, or six-monthly basis, that interfere with the hypothalamic-pituitary-gonadal axis. They initially stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release, and consequently elevate testosterone production (known as ‘testosterone surge’ or ‘flare up’ phenomenon), which begins within approximately two or three days of the first injection and lasts through approximately the first week of therapy (20).

Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors, with subsequent suppression of pituitary LH and FSH secretion and testosterone production. The level of testosterone decreases to castration levels usually within two to four weeks (21, 22). However, approximately 10% of patients treated with LHRH agonists fail to achieve castration levels (23), or up to 15% if the threshold is defined as 20 ng/dL.

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

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) addressing these issues 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, and that patients at risk for clinical flare are overwhelmingly those with high volume, symptomatic, bony disease, accounting for only 4-10% of M1 patients.

Concomitant therapy with an anti-androgens definitely decreases the incidence of clinical relapse, but it does not completely remove the possibility of its occurrence. Based on pharmacokinetic considerations, it is recommended that administration of anti-androgens should be started on the same day as the depot injection, and treatment should be continued for a two-week period. However, for patients with impending spinal cord compression, alternative strategies for immediately ablating testosterone levels must be considered, such as bilateral orchiectomy or LHRH-antagonists. Apart from those patients, the clinical impact of the flare up observation is unknown.

Finally, some mini-flares have also been observed with the long-term use of analogues, with an unknown clinical impact.

12.3.1.4 LHRH antagonists

In contrast to the 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 since their introduction, but practical shortcomings have limited clinical studies. Indeed, many of these compounds have been associated with serious and life-threatening histamine-mediated side-effects and, until recently, no depot formulation was available.

Two recently published phase III randomised multicentre trials comparing the LHRH antagonist abarelix with the LHRH agonist leuprorelin acetate (25) and with CAB (26) in patients with metastatic or recurrent PCa 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 arms, 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.

Abarelix has recently been licensed for clinical use by the US Food and Drug Administration, but its use is restricted to those patients with metastatic and symptomatic PCa for whom no other treatment option is available (27).

Recently, another antagonist, called degarelix, has been presented with preliminary promising results. In a phase II dose-finding study of 187 men, most patients had a testosterone level below 0.5 ng/mL at day 3, with a sustained effect at one year and no testosterone surge. The median testosterone value at one year for the 78.6% of patients with a level below 0.5 ng/mL was 0.12 ng/mL. No patient reported any systemic allergic reaction (28).

Overall, even if this new family appears appealing, its real advantages over LHRH agonists are far from being proven. So far its use is limited by a monthly formulation, compared with three-month and six-month depot formulations. The clinical advantage of the suppression of the initial flare up is only clinically relevant in a minority of metastatic patients, and finally antagonists must confirm their efficacy in the long-term, most available trials being limited to a one-year follow-up period.

12.3.2 Anti-androgens

Anti-androgens compete with testosterone and DHT for binding sites on their receptors in the prostate cell nucleus, thus promoting apoptosis and inhibiting PCa growth (29). These orally administered 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, but while this is the sole action of non-steroidal anti-androgens, steroidal anti-androgens additionally have progestational properties with 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.

12.3.2.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. In addition to peripherally blocking androgen receptors, they have progestational properties and inhibit gonadotrophin (LH and FSH) release 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; gynaecomastia is quite rare. The non-pharmacological side-effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

Cyproterone acetate (CPA)

CPA was the first anti-androgen to be licensed. It is the most widely used drug, but the less studied one, leaving most questions unanswered (such as the optimal dose), or unclear (e.g. comparison with standard forms of castration – surgical or with an agonist).

There is only one randomised trial (30) 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 on CPA monotherapy have been performed, but one did not report survival data (31), and the other used a non-standard treatment combination (DES and medroxyprogesterone acetate [32]). It is therefore difficult to draw any definite conclusions from these data about the relative efficacy of CPA and castration.

As no dose-finding studies of CPA monotherapy have been conducted, the most effective dose is still unknown. Although CPA has a relatively long half-life (30-40 hours), it is usually administered in two or three fractionated doses of 100 mg each (33).

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 (CSS) and OS at a median follow-up of 8.6 years, although the study was underpowered (34) (level of evidence: 1b).

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 (35-37) and, to a lesser extent, in HRPC (38). No apparent dose response correlation was shown to exist in a recent trial (39). The overall poor efficacy precluded megestrol acetate and medroxyprogesterone acetate from being recommended as a primary or second-line hormonal therapy option.

The only prospective randomised trial evaluating medroxyprogesterone acetate as primary therapy in advanced (M0-1) PCa is the EORTC 30761 study mentioned above (31), in which 236 patients were assigned to receive CPA, DES or medroxyprogesterone acetate. While no difference in CSS and OS was evident 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 two drugs tested.

12.3.2.2 Non-steroidal anti-androgens

Non-steroidal anti-androgens have been promoted in monotherapy for quality of life (QoL) and compliance benefits over castration: since they do not suppress testosterone secretion, it is claimed that libido, overall physical performance and bone mineral density are preserved (40).

Although no direct comparisons have been undertaken in a monotherapy setting, the three available drugs do not appear to differ in the severity of pharmacological side-effects, namely gynaecomastia, breast pain and hot flashes. However, there are differences in the non-pharmacological side-effects, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide (41). They all share a common liver toxicity, and liver enzymes must be checked on a regular basis when they are used.

Nilutamide

There are no comparative trials on nilutamide monotherapy with castration or with other anti-androgens (42). Only one non-comparative study has been carried out, including 26 patients with M1 PCa who received nilutamide 100 mg three times daily. The results showed that as few as 38.5% of patients experienced an objective response; the median progression-free survival (PFS) time was nine months and the median OS was 23 months (43).

One large randomised controlled trial of 457 patients with M1, which compared orchiectomy plus nilutamide, 300 mg/day, with orchiectomy plus placebo, showed a significant benefit in CSS and OS for the combined therapy (44).

Recently, nilutamide has been tested as a second-line hormonal therapy in HRPC with encouraging results (45, 46). 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 this drug. Nilutamide is not licensed for monotherapy.

Flutamide

Flutamide was the first non-steroidal anti-androgen available for clinical use, and has been studied as monotherapy for more than 20 years, but no dose-finding studies against a currently accepted end-point (e.g. PSA response) have been published. Flutamide is a pro-drug, and the half-life of the active metabolite is five to six hours, so it must be administered three times per day in order to maintain therapeutic serum levels. The recommended daily dosage is 750 mg (33).

Early phase II trials demonstrated flutamide to be effective in the treatment of advanced PCa, albeit that 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 (47-50). This rate has not been confirmed in the above mentioned EORTC trial 30892 (34), in which as few as 20% of men treated with flutamide maintained sexual activity for up to seven 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, only two phase III randomised trials comparing flutamide monotherapy with standard therapy (orchiectomy [51] and CAB [52]) for advanced PCa have reported survival data; both showed no significant difference in OS for flutamide or castration for patients with a PSA < 100 ng/mL (52). At higher PSA, flutamide was inferior. Both trials were underpowered, however. Results are eagerly awaited from an ongoing Swedish study in which 700 patients with M1 PCa have been randomised to flutamide 250 mg three times daily or CAB (40). The non-pharmacological side-effects are diarrhoea and hepatotoxicity (occasionally fatal).

Bicalutamide

Early reports with bicalutamide monotherapy related only to the 50 mg dosage, which was that licensed for use in CAB. An overall analysis of these studies showed that, although bicalutamide 50 mg/day had clinical benefits, it was inferior to castration in terms of OS (median difference 97 days) (53). Subsequent dose-ranging studies established that bicalutamide 150 mg once daily achieved a PSA response similar to that seen with castration while maintaining a good tolerability profile (54). Accordingly, the 150 mg dosage was chosen for further evaluation as both primary and adjuvant monotherapy.

As primary monotherapy, bicalutamide 150 mg/day has been compared with medical or surgical castration in two large prospective randomised trials with identical study designs, including a total of 1435 patients with locally advanced M0 or M1 PCa (55). A pooled analysis showed:

- In M1 patients, an improvement in OS with castration, although the difference in median survival between the groups was only six weeks (55); a further post hoc analysis showed a survival benefit only for patients with higher PSA levels (> 400 ng/mL) at study entry (56).

- In M0 patients (N = 480), no significant difference was noted in OS (57) 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 (58). In the second trial (220 patients with M0 and M1 stage), there was no difference in OS for well or moderately well differentiated tumours (59) (level of evidence: 1b), but both studies were underpowered, and the first one has not yet been fully published.

As for the adjuvant setting, the ongoing Early Prostate Cancer Programme (EPCP), a study comprising three different clinical trials of similar design and including 8113 patients worldwide, was designated to evaluate the efficacy and tolerability of high-dose (150 mg/day) bicalutamide vs placebo given in addition to standard primary care (i.e. radical prostatectomy, radiotherapy and watchful waiting) in localised (T1-2, N0-X) or locally advanced (T3-4, any N, or any T N+) PCa. The first combined analysis of the programme showed that, after a median follow-up of three years, adjuvant bicalutamide provided a reduction of 42% in the risk of objective disease progression compared with standard care alone (60).

After a median follow-up of 5.4 years, the positive effects of bicalutamide were obvious in patients with locally advanced disease (stage M0), but patients with localised disease given bicalutamide appeared to have a reduced survival compared with those given placebo (61). However, results obtained after a median follow-up of 7.4 years showed there was no benefit to PFS from the addition of bicalutamide to standard care in localised PCa, and identified a trend (hazard ratio [HR] 1.16, 95% CI 0.99-1.37, $p = 0.07$) towards decreased survival in patients otherwise undergoing watchful waiting (WW). However, in locally advanced disease, bicalutamide significantly improved PFS, irrespective of standard care.

The same overall results were observed in the most recent arm 24 analysis (62). Bicalutamide significantly improved OS in patients receiving radiotherapy (HR 0.65, 95% CI 0.44-0.95, $p = 0.03$), which was driven by 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 prostatectomy subgroup (61).

Even though the EPCP is a combination of three trials and among the largest ever conducted in prostate cancer patients, clear conclusions are difficult to present as many problems are apparent with these protocols (63). For example, three trials were grouped for analysis, but they are different in terms of patients (80% prostatectomy in trial 23 compared with 13% in trial 25). The treatment duration was two 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 CSS benefit, which is different from other trials with LHRH agonists (64). Furthermore, the trials are underpowered for locally advanced patients, compared with oriented trials such as the Bolla (65) or Pilepich (66) trials. Finally, direct protocol analysis reveals quite different results, such as those from the EPCP 23 (80% prostatectomy, 19% radiotherapy) (67). At a median 7.7 years of follow-up, no PFS benefit was observed (HR 1.00; CI 0.84, 1.19, $p = 0.991$). Likewise, OS did not differ. Even after stratifying for disease stage, no PFS benefit was apparent.

No QoL benefit has been demonstrated, as is claimed, as the EPCP trial did not use a QoL questionnaire. The only QoL data come 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 items considered (emotional well-being, vitality, social function, pain, activity limitation and bed disability), there was no difference compared with castration (68). The breast problems related to bicalutamide must also be discussed, as they might lead to a 16.4% treatment cessation (69).

The clear trend (even if not statistically significant) suggesting a decreased OS in localised disease treated with WW is a clear argument against its use in such situations (61). The mechanisms remain unclear.

Many questions are still debatable with this drug, such as the practical management after progression under bicalutamide, as no data are available.

In conclusion, 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, but should be avoided in patients with localised PCa. The QoL benefit over castration that was expected is, however, far from being proven. The survival benefit observed with an adjuvant use after radiotherapy in locally

advanced situations must be considered with caution, as these three trials are far from having the power of any trial conducted with LHRH agonists.

Non-pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). These might be prevented by anti-oestrogens (70, 71), prophylactic radiotherapy (72), or treatment with surgical mastectomy or radiotherapy (73).

12.3.3 Combination therapies

12.3.3.1 Complete androgen blockade

Although serum testosterone levels are reduced by up to 95% by castration, the intraprostatic androgen stimulus is sustained by the conversion of circulating androgens of adrenal origin into DHT within the prostate cells. The action of these adrenal androgens is 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).

A plethora of studies evaluating CAB over monotherapy have been carried out with contrasting results. From the most recent systematic reviews and meta-analyses it appears that at a follow-up of five years, CAB provides a small survival advantage (less than 5%) when compared with monotherapy (74-78, level of evidence: 1a), although some of the largest trials included are methodologically flawed (79). It remains debatable whether this small advantage, if any, can be meaningful when applied to everyday clinical practice. The benefit seems to be limited to patients taking non-steroidal anti-androgens and to appear only after five years of follow-up.

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

12.3.3.2 Minimal androgen blockade (or peripheral androgen blockade)

This derives from the combination of finasteride and a non-steroidal anti-androgen. The rationale behind the combination is that finasteride reduces intraprostatic levels of DHT by inhibiting 5-∝-reductase, while anti-androgen competes with the binding of the residual DHT to its receptor. The result is that testosterone levels are maintained within normal ranges to ensure acceptable sexual function and a reasonable QoL.

In several phase II trials (80-84), the association of finasteride and flutamide, either in a concomitant or sequential regimen, has been evaluated in terms of 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 level at entry). An update of one of these studies, at a long-term follow-up, reported on stronger end-points, such as castration-free survival (median: 37 months), androgen-independent PCa-free survival (median: 48.6 months) and OS rate (65% at five years). It was concluded that combination therapy can induce an overall period of hormone responsive disease exceeding four years (85). In all these trials, sexual function was reported to be preserved in between 55% and 86% of the men studied.

The preliminary data make this treatment option most attractive in the management of patients for whom QoL is the primary issue. However, while awaiting the results of follow-up and larger controlled trials, this treatment is still regarded as investigational.

12.3.3.3 Intermittent vs continuous androgen deprivation therapy

For reasons that as yet remain unclear, long-term CAB, which stimulates prostate cell apoptosis, fails to eliminate the entire malignant cell population, so that after a variable period (averaging 24 months) the tumour inevitably relapses, being 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 (86). It is therefore theoretically possible that if androgen deprivation is stopped prior to the progression of androgen-independent cells, any subsequent tumour growth would then be solely sustained by the proliferation of androgen-dependent stem cells, which should be susceptible once again to androgen withdrawal. In this way, cyclical ADT would delay the emergence of the androgen-independent clone. Thus, intermittent ADT may result in two other benefits: namely the preservation of QoL in the off-therapy periods and the reduction of cost.

Several phase II trials have demonstrated the feasibility of intermittent androgen blockade (IAB) in metastatic

or biochemically recurrent disease, with PSA response rates and symptom improvement similar to that of CAB, but phase III prospective, randomised controlled trials are still underway, and data on survival endpoints and QoL are not mature (87). Preliminary results of clinical phase III trials have demonstrated not significantly different efficacy for intermittent vs continuous ADT in men with PSA progression following radical prostatectomy and in advanced metastatic PCa (88-90).

The South West Oncology Group (SWOG) trial 9346 randomised 1134 men with stage D2 PCa to intermittent and continuous ADT after seven months' induction ADT with PSA reduction < 4 ng/mL. No significant differences with regard to survival in a very preliminary analysis were identified between treatment groups (88). 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 some other trials, 75 patients were considered for IAD if they had achieved PSA serum levels < 4 ng/mL or at least 90% reduction of pre-treatment levels after 9 months of ADT (89). Patients went on when PSA values rose > 20 ng/mL at which the 9-month cycle of ADT was repeated. 86% of the men are alive at a median of 134 months, with a median survival of 95 months from the initial ADT cycle. A 100% and 70% survival at 5 years was calculated for those presenting with locally advanced disease and metastases at initial presentation, respectively.

A prospective randomised multicentre trial including 68 patients with a mean follow-up of 31 months have been reported (90). In the intermittent androgen deprivation (IAD) group, the median cycle length was 9.5 months and the median percentage of time off therapy was 59.5%. The median three-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. Another trial came to the same conclusions, but, once again this presented-only German study was underpowered and had too short a follow-up (91).

The most recent and convincing data were presented during the 2007 American Society of Clinical Oncology (ASCO) meeting (92). In a prospective trial including 478 patients with M1 (40%) or N+ (N1 to 3) disease, 335 were randomised after six months of maximal androgen blockade if the PSA was below 4 ng/mL or if a decrease of more than 90% was observed. The mean initial PSA was 158 ng/mL in the intermittent arm, and 139 ng/mL in the continuous arm, respectively. In the intermittent arm, the treatment was resumed if the PSA was above 10 ng/mL and stopped when it went below 4 ng/mL. The main question was PFS. After a median follow up of 50.5 months, no significant difference was observed in the median PFS (16.6 months in the intermittent arm compared with 11.5 months in the continuous arm [$p = 0.17$], neither in the entire population nor in the N+ or M1 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.

Recently a published randomised trial suggested a different IAD regimen, with fixed six-month periods of treatment (CAB) and surveillance (93). The PSA was not used to direct the treatment in this heterogeneous population (N = 129). After a mean of 44.8 months of follow up, no difference was observed in either OS, CSS or PFS. The QoL was also no different 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.

IAD has not been shown to be associated with prolonged hormone-sensitive status. This treatment modality is well accepted by patients and increases their QoL during the periods without treatment, although still to a questionable level (94-96), and testosterone levels recover in most studies (97, 98), leading to an intermittent castration (not just an intermittent treatment delivery). Other benefits, such as a reduction in impact on the bones (99) or sexual activity (96), are also suspected.

It must be acknowledged that, so far, IAD raises more questions than it has precise answers for, especially with regard to defining the best candidates, (100, 101). In addition, the threshold at which the ADT must be stopped or resumed are empirical (100). Nevertheless, several points are clear (102):

- IAD is based on intermittent castration, and therefore only drugs leading to castration should be considered.
- It is unclear if an LHRH agonist may be used alone, as the published experiences are based on CAB.
- The initial (induction) cycle must last between six and nine months, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
  - well informed and compliant patient
  - no clinical progression

- a clear PSA response, empirically defined as a PSA below 4 ng/mL in metastatic patients, or 0.5 ng/mL in relapsing patients.

- A strict follow-up must then be applied, with clinical examination every three to six months (the more advanced the disease, the closer the follow-up), with PSA measurements at the same time and always performed in the same laboratory.
- The 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).
- The same treatment is used for at least three to six months.
- The next cycles 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).

12.3.3.4 Immediate vs deferred ADT

The most appropriate time to introduce hormonal therapy in patients with advanced PCa is still controversial, particularly whether ADT for locally advanced and asymptomatic metastatic disease delivered immediately at diagnosis favourably influences survival and QoL compared with ADT deferred while signs and symptoms of clinical progression remain a matter of debate. This point was partially discussed in section 8.3.

The dispute derives from the lack of properly conducted, randomised, controlled trials, with many being methodologically flawed because of small size and underpowering, and the heterogeneity of patient enrolment with advanced PCa (i.e. locally advanced, nodal and metastatic stages of disease), as well as variability in the hormone treatments administered and of follow-up schedules and modalities used.

Bearing these limitations in mind, evidence on immediate vs 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 indicated that a possible survival advantage for early ADT existed in single studies where hormone treatment was the primary therapy, while the combined analysis showed no significant benefit. Furthermore, androgen suppression was shown to be the most cost-effective if initiated after patients had experienced symptoms from metastatic disease (74, 103).

The Cochrane Library review extracted four good quality randomised controlled trials (namely VACURG I and II studies [10, 11], the MRC trial (104) and the Eastern Cooperative Oncology Group [ECOG] 7887 study [105]), which were all conducted in the pre-PSA era and included patients with advanced PCa who received early vs deferred ADT as primary therapy or adjuvant to radical prostatectomy, but not to radiotherapy. According to the analysis, early androgen suppression significantly reduces disease progression and complication rates due to the progression itself, but does not improve CSS, and provides a relatively small benefit in OS, with an absolute risk reduction of 5.5%, which does not become evident until after 10 years (106).

Since 2002, the level 1 evidence suggesting immediate ADT in every pN+ patient after a prostatectomy has been questioned for several reasons. Some were discussed earlier (*see section 9.7*) such as the impact of a micronodal metastasis in a single node (107), which is far from being equivalent to a massive nodal involvement, as present in the Messing trial. Recently, the analysis of 719 patients from the SEER (Surveillance, Epidemiology and End Results, part of the US National Cancer Institute) database questioned the real impact of immediate ADT in pN+ patients after a radical prostatectomy (108).

In the PSA era, the EORTC 30891 (109) gave 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, the recently published ASCO guidelines on initial hormonal treatment for androgen-sensitive metastatic, recurrent or progressive PCa concluded that no recommendation on when to start hormonal therapy in advanced asymptomatic PCa can be made until data from studies using modern diagnostic and biochemical tests and standardised follow-up schedules become available (110).

Based on the meta-analysis, published treatment was 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 in section 12.3.2.2 with regard to the EPCP trials.

For asymptomatic patients with locally or regionally advanced PCa who undergo radiotherapy, there is good evidence from several randomised controlled trials 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 (111-114) (level of evidence: 1b).

12.4 Indications for hormonal therapy

Table 16 lists the indications for hormonal therapy.

Table 16: Indications for hormonal therapy

Hormonal therapy	Benefits	LE
Indications for castration		
M1 symptomatic	• To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis)	1
	• Even without controlled randomised trail, 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 (104)	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 (105)	1b
	• Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy (115)	3
Locally advanced M0	• Immediate castration to improve cancer-free survival	1b
Locally advanced symptomatic	• (116)	4
Locally advanced treated with radiotherapy	• High risk d'Amico: combined and prolonged ADT	1
	• Intermediate risk d'Amico:	1b
	• if low dose (< 75 Gy) radiotherapy: six 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 (109)	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 (117, 118)	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 N+) (57) (level of evidence: 2)	2
	• No place in localised disease as 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	

LE = level of evidence

12.5 Contraindications for various therapies (Table 17)

Table 17 lists the contraindications for various therapies.

Table 17: 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 • Known hepatic dysfunction

12.6 Outcome

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

In M1 cases, the median OS ranges between 28 and 53 months (74); only 7% of patients with metastatic cancer treated with hormonal therapy are reported to live 10 years or more (119). 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 (75).

12.7 Side-effects, QoL and cost of hormonal therapy

Many patients with PCa for whom long-term ADT is indicated are still young and physically and sexually active, so QoL is an issue of paramount importance when considering the various hormonal treatment options. In view of this, in selected patients, monotherapy with a non-steroidal anti-androgen (e.g. bicalutamide) is gaining increasing popularity because of its ability to maintain normal (or even higher) serum testosterone levels and its good tolerability profile.

12.7.1 Side-effects

The many deleterious side-effects of long-term ADT have been well known for years. Some of these 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 age.

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

Hot flashes are probably the most common side-effect of ADT. They appear three months after starting the treatment, persist in the long term in most patients, and have a significant impact on the QoL (120). Treatment modalities include hormonal therapy and antidepressants. Oestrogen receptor modulators or low-dose oestrogen therapies (0.5-1 mg/day), such as diethylstilboestrol, reduce their frequency and severity, but both are associated with a risk of cardiovascular complications (121).

Soya phytoestrogens have shown efficacy for hot flushes in breast cancer patients (122), but have not yet been evaluated in men. Progesterone-based treatments, such as megestrol acetate, medroxyprogesterone acetate and CPA, have also demonstrated efficacy, with 80% of patients having shown improvement with CPA (123) or chlormadinone (124).

Antidepressants may also 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 (125).

Other products have also been tested, including clonidine and veralipride, and even acupuncture (126). With a placebo effect influencing up to 30% of patients (127), 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.

More recently, other systemic side-effects have been described and must be paid increased attention. These include: bone problems, obesity and sarcopenia, lipid alterations and insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease (128).

ADT increases the non-metastatic fracture risk as a result of increased bone turn-over 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 in the long term (129). This is a significant side-effect, as hip fractures in men are associated with a significant risk of death (130). Increased exercise and calcium supplementation are protective.

Recently, bisphosphonates such as pamidronate, alendronate or zoledronic acid have been shown to increase the BMD in hip and spine by up to 7% in one year. The optimal regimen for zoledronic acid is still unclear. It is recommended once every four weeks in one study (131), while a yearly injection gave similar results in another (132). The optimal regimen is a very important question because of the risk of jaw necrosis, which might be dose and time-related (133).

Before starting long term ADT, patients should be encouraged to adopt lifestyle changes (e.g. increase physical activity, stop smoking, decrease alcohol consumption and normalise their body mass index). A precise evaluation of the 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 in conjunction with other risk factors) indicates a high risk of subsequent non-metastatic fracture, suggesting the early use of preventive bisphosphonate therapy.

Obesity and sarcopenia are common and often occur early on during the first year of ADT. An increase in body fat mass by up to 10%, and a decrease in lean tissue mass by up to 3% are expected (134). Both are linked to an increased risk of fracture.

Lipid alterations are also frequent, and occur as early as the first three months of treatment (135). ADT also decreases insulin sensitivity and increases fasting plasma insulin levels (135), a marker of insulin resistance. Once again, exercise must be recommended as a protective tool.

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.

Its prevalence is higher during ADT compared with untreated men (136).

ADT has been associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction in one study (137), and with a 20% increased risk of new cardiovascular disease after one year of treatment in another (138). Recently the analysis of the RTOG 92-02 data confirmed this increased cardiovascular risk (139) with no relationship with the duration of the ADT. These observations have, however, been up for discussion recently, as no increased cardiovascular mortality was demonstrated in RTOG 8610 (140), EORTC 30891 (109) or EORTC 22863 (64).

In summary, if even six 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.

12.7.2 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 plus flutamide vs orchiectomy plus placebo. The QoL was assessed in the first six months of treatment. Combined therapy resulted in lower QoL, with statistically significant differences in two QoL parameters, namely more frequent diarrhoea and worse emotional functioning, than castration alone (141).

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 (142) (level of evidence: 2a).

A retrospective, non-randomised study including 431 patients with stage PCa who received orchiectomy or LHRH agonists as their primary therapy within 12 months of initial diagnosis, 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 (143) (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 one-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 (144) (level of evidence: 1b).

IAD might 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 or a marginal QoL benefit.

As for LHRH agonists, QoL was evaluated in the previously mentioned studies of bicalutamide monotherapy by means of 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-month follow-up, and in both patient categories bicalutamide showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) (57) (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 (145, 146).

Data on QoL are also available from the early report of the study of Boccardo et al. (147), and support the findings of the two larger combined trials in that 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 (148) (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 the bicalutamide studies, these events were reported by up to 66% and 73% of patients, respectively, and might lead to a 16.4% treatment cessation.

12.7.3 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, CAB with 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 (103) (level of evidence: 1a).

Finally, once ADT is started, if a clear response is obtained *(see section 11.3.3. above)*, then IAD might be a useful way to lower treatment costs.

12.8 Summary of hormonal therapy

		LE
•	In advanced PCa, ADT delays progression, prevents potentially catastrophic complications, and palliates symptoms effectively, but it does not prolong survival.	1b
•	In advanced PCa, all forms of castration as monotherapy (e.g. orchiectomy, LHRH and DES) have equivalent therapeutic 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 randomised clinical trials are still awaited.	2
	'Minimal' ADT should, however, continue to be seen as experimental	
•	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).	1b

	However, the survival benefit is at best marginal and not related to an increased CSS.	1b
•	Bilateral orchiectomy might be the most cost-effective form of ADT, especially if initiated after the occurrence of symptoms from metastatic disease.	3

LE = level of evidence

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13. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF PCa

Stage	Treatment	Comment	GR
T1a	Watchful waiting	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	Watchful waiting	Asymptomatic patients with well-, and moderately, differentiated tumours and 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
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment	C
		Anti-androgens are associated with a poorer outcome compared to 'watchful waiting' and are not recommended	A
	Combination	For high-risk patients, neoadjuvant hormonal treatment (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	C
	Radical prostatectomy	Optional for selected patients with T3a and a life expectancy > 10 years	C
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation > 70 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 irradiation	A
		NHT + radical prostatectomy: no indication	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	No standard option	C
	Radiotherapy	No standard option	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 (given for cure)	C
	Hormonal	Standard therapy. Mandatory in symptomatic patients Must be otherwise systematically discussed	A
	Combination	Not an option	C

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 3 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 Guidlines 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 30 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 hormone-refractory prostate cancer (HRPC) 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 hormone-refractory 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 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.

15.4.1 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.

15.4.2 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.

15.4.3 Hormone-refractory patients

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

15.5 Guidelines for follow-up after hormonal treatment

Recommendation	GR
• Patients should 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), 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

GR = grade of recommendation

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16. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENT WITH CURATIVE INTENT

16.1 Background

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

16.2 Definitions

16.2.1 Definition of treatment failure

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

The level of PSA that defines treatment failure differs between radical prostatectomy cases and those treated with radiotherapy. Following radical retropubic prostatectomy, 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 radical prostatectomy is still uncertain. In a retrospective analysis of 2782 men who had undergone radical prostatectomy for clinically localised PCa, Amling et al. (9) determined the best PSA cut-off point to be used to define biochemical recurrence. The authors demonstrated that 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 the patients with a PSA of 0.2 ng/mL will progress further, and that they can therefore initially be managed by surveillance.

Similar data have been presented by Stephenson et al. (10), who identified a PSA value ≥ 0.4 ng/mL as the best cut-off to explain the development of distant metastasis among 10 candidate definitions based on retrospective review of 75 patients who developed distant metastases after radical prostatectomy. Therefore, a cut-off of 0.4 ng/mL is appropriate for the definition of 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 ≥ 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 radical prostatectomy, PSA values > 0.4 ng/mL 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 radical retropubic prostatectomy 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 (Table 18) include:
- the timing of the PSA increase after surgery
- PSA velocity
- PSA doubling time (PSADT)
- the pathohistological stage
- the Gleason score of the prostatectomy specimen.

PSA elevations developing within the first two years following surgery are associated with distant recurrences (12). It has been shown that a median PSADT of 4.3 months is associated with distant relapse, whereas a median PSADT of 11.7 months predicts local failure (13). According to a recent study (14), PSA velocity of < 0.75 ng/mL/y 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/y.

Table 18: Important clinical and pathohistological parameters predicting local and systemic relapse following radical prostatectomy

Parameter	Local recurrence	Systemic recurrence
• Interval to PSA relapse		
≤ 1 year	7%	93%
1-2 years	10%	90%
> 2 years	61%	39%
> 3 years	74%	26%
• PSA doubling time	11.7 months	4.3 months
• Gleason score		
2-4	0%	0%
5-6	55%	45%
7	39%	61%
8-10	11%	89%
• Pathological stage		
Organ confined (≤ pT2b)	40%	60%
pT3a, R0	54%	46%
pT3a, R1	48%	52%
pT3b	16%	84%
pTxpN1	7%	93%

With radiotherapy, any continuously rising PSA following a nadir after radiation 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 three consecutive PSA rises above the nadir level according to ASTRO guidelines. After radiotherapy, a late and slowly rising PSA is a sign of local failure only.

Local recurrence is defined by:
- a prostatic biopsy demonstrating malignant cells 18 months or longer after initial radiotherapy
- plus an associated rise in PSA
- plus 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 radical prostatectomy is predicted with an 80% probability by PSA increase > three years after radical prostatectomy, a PSADT ≥ 11 months, a Gleason score ≤ 6, and stage ≤ pT3a pN0, pTx R1.
- Systemic failure following radical prostatectomy is predicted with > 80% accuracy by a PSA increase < one year after radical prostatectomy, a PSADT of four to six 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

In recent years, most patients with PSA progression following initial therapy with curative intent underwent physical and sonographic examinations, radiographic studies or biopsies of the prostatic fossa and the vesicourethral anastomosis to confirm the recurrence identified by serological studies.

For patients with asymptomatic PSA-only progression, the yield is very low, and 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), it was shown that only 4/72 patients (5.5%) with a PSA recurrence following radical prostatectomy had an abnormal DRE.

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 radical retropubic prostatectomy, of which 122 patients had undergone radical prostatectomy 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.

The probability of a positive bone scan remains ≤ 5% until serum PSA reaches at least 40 ng/mL. Similar data have been achieved by other groups that have 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/y (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 radical retropubic prostatectomy 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/y.

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

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 radical prostatectomy (23, 24). However, it must be borne in mind that the uptake of ^{11}C-choline is not specific for PCa and might also be due to inflammatory intraprostatic lesions.

In a series of 31 patients with biochemical progression after radical prostatectomy, (^{11}C)acetate-PET demonstrated a high sensitivity and specificity for the detection of local recurrences if the PSA serum level was > 1 ng/mL (23). In another recent series of 43 patients with newly diagnosed prostate cancer, there was a significant correlation between the ^{11}C-choline uptake and the intraprostatic location of PCa as analysed in radical prostatectomy 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 radical prostatectomy 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).

The role of choline PET/CT to detect local or systemic recurrences in men with PSA relapse following radiotherapy is unclear and based on very few studies (31). 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 using a radiolabelled monoclonal antibody based on prostate-specific membrane antigen for messenger RNA (PSMA), called 111-indium capromab pendetide, might represent an innovative diagnostic approach, with an overall accuracy of up to 81% to detect the site of relapse in PSA-only recurrences following radical retropubic prostatectomy (23, 24, 32, 33). 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 (33) investigating 255 patients with PSA-only recurrence < 4.0 ng/mL after radical prostatectomy, 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.

It has been common practice to perform transrectal ultrasound- (TRUS) guided biopsies of the prostatic fossa, the anastomosis or the prostate gland to exclude local recurrence after radical retropubic prostatectomy or radiotherapy. However, according to available studies, routine biopsy of the vesicourethral anastomosis appears not to be justified based on a verification rate of only 54% (34-38). Only in the presence of a palpable lesion or a hypoechoic lesion on TRUS can the diagnostic yield of the biopsy be improved to approximately 80%. Furthermore, there is a strong correlation between the positive biopsy rate and PSA serum concentrations (34-38); 28% and 70% of the biopsies were positive if the PSA level was, respectively, below 0.5 ng/mL or greater than 2.0 ng/mL.

It is common sense, nowadays, that routine anastomotic biopsy is not indicated, and the use of PSA and PSADT is sufficient for clinical practice. In addition, PSA-free survival in biopsy-proven recurrences does not differ significantly compared with PSA-only recurrences.

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 (39-41). It is a general recommendation to wait about 18 months and three months following radiation therapy or seeds, and cryotherapy or high-intensity focused ultrasound (HIFU), respectively.

16.5 Diagnostic procedures in patients with PSA relapse

- Following radical prostatectomy, 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 < 20 ng/mL/y
- Endorectal MRI or PET scans may help to detect local recurrences if PSA is > 1-2.0 ng/mL, but is not yet routine clinical practice
- If available, a capromab pendetide scan shows a diagnostic yield of 60-80% independent of the PSA serum level
- Following radiation therapy, local recurrence is documented by a positive biopsy > 18 months after the procedure.

16.6 Treatment of PSA-only recurrences

The timing and mode of treatment of PSA-only recurrence after radical prostatectomy or radiation therapy remains controversial. After radical retropubic prostatectomy observation, radiation therapy to the prostatic bed, (complete) androgen blockade, intermittent androgen deprivation (IAD), a combination of anti-androgens with 5-α-reductase inhibitors, and even early chemohormonal approaches are therapeutic options. The same therapeutic options may be applied for PSA recurrences following radiation therapy. In addition, salvage prostatectomy, cryotherapy and brachytherapy might be indicated in carefully selected patients.

16.6.1 Radiation therapy for PSA-only recurrence after radical prostatectomy

Considering the numerous studies on the use of radiation therapy for PSA-only recurrence following radical retropubic prostatectomy, there is a growing body of parameters predicting outcome that might be helpful to differentiate between observation, radiation and hormonal therapy. As confirmed by various studies, the pre-radiation PSA level appears to be of critical importance for obtaining optimal treatment results (42-50). Applying a pre-radiation cut-off of < 2.5 ng/mL, Wu et al. (42) and Schild et al. (43) 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. (44) demonstrated a disease-free survival rate of 83% compared with 33% in patients with a PSA-only recurrence of less than 2.0 ng/mL and greater than 2.0 ng/mL, respectively. Nudell et al. (45) 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 radical retropubic prostatectomy (15). These data of early salvage radiation therapy are corroborated by recent papers (51-53) demonstrating a significant difference with regard to the five-year biochemical-free and overall survival rates in patients being treated for PSA recurrence only or for palpable locally recurrent cancer.

The analysis of patterns of treatment failure in SWOG 8974, a prospective randomised clinical trial to address whether high-risk post-prostatectomy patients benefited from immediate radiation therapy to the prostate fossa, identified a 77% freedom from PSA failure in a subgroup of patients with post-operative PSA levels ≤ 0.2 ng/mL (52). In men with PSA levels of > 0.2 ng/mL and ≤ 1.0 ng/mL, the five-year PSA recurrence-free survival was 34%, and 0% in patients post-operative PSA serum levels > 1.0 ng/mL. These data indicated that adjuvant radiation therapy is effective even in high-risk patients, and that the therapeutic benefit is most evident in the presence of minimal PSA serum levels.

In another study, Stephenson et al. (53) evaluated prognostic models to predict the outcome of salvage radiation therapy on a cohort of 1603 men with PSA progression after radical prostatectomy who were 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 six-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.

Egewa et al. (49) reported five-year biochemical-free and overall survival rates of 69% and 96%, compared with 45% and 78%, respectively, in the group with palpable disease. However, there is still a lack of data from prospective randomised trials, and all of the studies being performed lack long-term follow-up, so the impact on survival is unknown.

16.6.2 Hormonal therapy

In patients with a high pre-radical prostatectomy PSA > 20 ng/mL, a Gleason grade > 7, an extensive positive surgical margin and extensive extraprostatic tumour growth (pT3b, pTxpN1), immediate hormonal therapy might be indicated (46-50). The impact of early ADT on long-term survival is still unknown, however.

In a retrospective observational multicentre study including 1352 patients with PSA recurrence following radical prostatectomy (51), early ADT resulted in a significant reduction of the development of clinical metastases compared with delayed ADT. There was, however, no significant effect on long-term survival.

These recommendations are corroborated by a study (54) demonstrating that none of the patients with a Gleason score of 8, pT3b or pTxpN1 PCa remained disease-free following radiation therapy for PSA-only recurrence after radical prostatectomy.

It is difficult to make recommendations for the optimal therapeutic management for PSA-only recurrences following radical prostatectomy or radiation therapy because of the lack of prospective randomised trials. There are only very few studies analysing the clinical utility of early androgen deprivation in locally advanced (M0) and metastatic PCA (54, 55). It is believed that for the M0 category of patients with pTxN1 disease who have undergone radical prostatectomy reflecting PSA-only recurrences, hormonal therapy would appear to be beneficial for some with a high probability of occult systemic metastases.

There is some evidence that combined androgen blockade (CAB) has a pronounced survival benefit in patients with minimal metastatic disease, so patients with PSA-only recurrences might have a similarly improved survival with combined androgen deprivation (56, 57). Considering the speculative benefits, the side-effects of traditional hormonal therapy – such as hot flushes, loss of libido, impotence, decreased muscle mass and osteoporosis – must not be underestimated.

The use of anti-androgens alone might overcome these side-effects as demonstrated in recent studies. 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 (58). Furthermore, the risk of objective progression of the disease was significantly reduced in patients receiving bicalutamide 150mg (59). Anti-androgens 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.

Non-traditional ways of using hormonal therapy for PSA-only recurrence include IAD and oral therapies combining anti-androgens with 5-α-reductase inhibitors (60-67). In the setting of PSA-only recurrences, however, no prospective randomised trials and no clinical studies with sufficient data on long-term efficacy

are available to justify a routine clinical application of IAD, despite its potential benefits. Summarising the series in which PSA-only recurrences were treated by IAD (60-64), PSA threshold levels at study-entry varied significantly, as did the PSA level at discontinuation of hormonal therapy.

Only the study of 150 patients by Tunn (64) had a sufficiently appropriate study design to allow the drawing of important clinical conclusions. Patients were started on IAD for nine 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. IAD was restarted when PSA increased to more than 3.0 ng/mL. After a mean follow-up of 48 months, and a mean duration of hormonal therapy of 26.6 months, none of the patients had progressed to hormone-refractory disease.

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 (65-67). In the latest report (66), 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 six 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 hormonal therapy. However, longer follow-up of a larger patient cohort is needed, and randomised phase III trials using modern anti-androgens with fewer gastrointestinal and hepatic side-effects are mandatory.

16.6.3 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 two years after surgery, and a PSADT longer than 10 months. In these patients, the median actuarial time for the development of metastasis will be eight years, and the median time from metastasis to death will be another five years.

16.6.4 Management of PSA relapse after radical prostatectomy

Recommendations	GR
• Local recurrences are best treated by salvage radiation therapy with 64-66 Gy at a PSA serum level ≤ 1.5 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
• LHRH analogues/orchiectomy or bicalutamide 150 mg/day can both be used when there is indication for hormonal therapy	A

GR = grade of recommendation

16.7 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. (68) 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 three years.

Therapeutic options in these patients are ADT or local procedures, such as salvage radical prostatectomy, cryotherapy and interstitial radiation therapy (69-74). Salvage radical retropubic prostatectomy 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 might result in long-term disease-free survival. One has to consider that most series reporting on salvage radical prostatectomy include patients who were treated in the pre-PSA era without modern radiotherapeutic techniques, and 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 in whom salvage radical prostatectomy was planned, 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 (46, 49, 52, 53).

Recent reports analysing patients who were operated on during the past decade, have described far more optimistic outcomes after salvage radical prostatectomy. In the series examined by Gheiler et al. (73), 40 patients with a mean PSA of 14 ng/mL underwent salvage radical prostatectomy. When stratified by PSA less than or greater than 10 ng/mL, the three-year disease-specific survival was 68% and 26%, respectively.

In the series reported by Garzotto and Wajsman (74), 24 patients underwent radical cystoprostatectomy or radical prostatectomy 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 five years, the disease-specific survival rate was 95% and 44% for those with negative and positive surgical margins, respectively.

Vaidya and Soloway (75) demonstrated a low complications rate, good post-operative continence and only one biochemical recurrence 36 months after salvage radical prostatectomy.

Similar data have been achieved by Stephenson et al. (76), who reported on 100 consecutive patients undergoing radical salvage prostatectomy associated with a very low rate of peri-operative complications. The five-year progression-free rates have improved, and the results are similar to those of standard radical prostatectomy in cases of similar pathological stages. The 10-year cancer-specific and overall survival rates are in the ranges 70-75% and 60-66%, respectively, in contemporary series. In most contemporary series, organ-confined disease, negative surgical margins and the absence of seminal vesicle and/or lymph node metastases are favourable prognosticators associated with a better disease-free survival of approximately 70-80%, compared with 40-60% in patients with locally advanced PCa (77).

In general, salvage radical retropubic prostatectomy 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 the necessity of anterior and total extirpation procedures, but also for associated complications and decreased long-term disease-specific survival.

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

Salvage cryosurgery has been proposed as an alternative to salvage prostatectomy as it has the potential advantage of less morbidity but equal efficacy. Only very few studies are available, and the results are not very promising. Pisters et al. (78) 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, and 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 a one-year follow-up, incontinence resolved in the majority of patients, with persistent significant incontinence in 22% of patients (53%).

According to a recent study by Cespedes et al. (79), 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 (80).

16.7.2 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 (81-84). Grado et al. (83) treated 49 patients with transperineal TRUS-guided brachytherapy and reported three- and five-year disease-free survival rates of 48% and 43%, respectively. Beyer (84) reported a five-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, with 27% of the patients becoming incontinent, 14% needing palliative transurethral resection of the prostate (TURP) due to acute urinary retention, another 4% suffering from rectal ulcers, and 2% requiring permanent colostomy.

16.7.3 Observation

Patients with signs of local recurrence only (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 hormonal therapy versus watchful waiting in 248 men with PSA failure after radiotherapy showed no advantage for hormonal therapy in the subgroup of men with a PSADT of > 12 months after radiotherapy. The five-year metastasis-free survival rate was 88% with hormonal therapy vs 92% with watchful waiting (p = 0.74) (85).

16.7.4 Management of PSA relapse after radiation therapy

Recommendation	GR
• Local recurrences may be treated by salvage radical prostatectomy in carefully selected patients	C
• CSAP and interstitial brachytherapy are alternative procedures in patients not suitable for surgery	C
• ADT is an option in patients with presumed systemic relapse	B

GR = grade of recommendation

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

Recommendation		GR
• Presumed local failure after radical radiotherapy	Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 66 Gy and preferably prostatectomy before PSA has risen above 1.0 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 although patients should be informed about the comparatively high risk of complications. 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. HORMONE REFRACTORY PROSTATE CANCER (HRPC)

17.1 Background

Cancer of the prostate is a heterogeneous disease and our knowledge of the mechanisms involved in androgen independence remains incomplete (1-5). 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 in the pathogenesis of androgen-independent PCa (6).

Androgen independence is thought to be mediated through two main, overlapping, mechanisms, which are androgen-receptor (AR)-independent and AR-dependent. 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 progress and the regulation of microtubule integrity may be a mechanism through which *bcl-2* induces its anti-apoptotic effect (7-9). Indeed, most active chemotherapeutics in hormone-resistant prostate cancer (HRPC) 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 (10-12). Clinical trials are underway to target the *bcl-2* pathway (13) as the MDM2 oncogene (14). The PTEN (phosphatase and tensin homolog) suppressor gene may also be involved (15). However, direct AR-dependent mechanisms comprise the main pathway. Ligand-independent AR activation has been suspected, such as 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 (16).

Androgen receptor amplification is observed in one-third of HRPC tissues (17) and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in AR function (3-5) (18). 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 (19). The AR mutations might be related to the selective pressure of anti-androgens (20). The recent discovery of gene fusion between the androgen-driven TMPRSS2 and the EGR-ETS oncogene family (21) raises the question of oncogene regulation through androgen regulation pathways. The mechanism of gene fusion is based on the association of an androgen-responsive element from an androgene-regulated gene with genes that are usually not androgen-regulated leading to their androgen regulation. Their implication in HRPC is currently only theoretical. Even in castrated patients, metastatic tissues have repeatedly shown high levels of androgens, suggesting a high level of intracrine synthesis (22, 23). It is possible that a high intraprostatic cholesterol level can activate specific androgen pathways (1).

17.2 Definition of HRPC

Hormone-refractory prostate cancer is a very heterogeneous disease. It includes different patient cohorts with significantly different median survival times (Table 19).

Table 19: Estimated natural mean survival of patients with HRPC presenting with different clinical scenarios

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

The precise definition of recurrent or relapsed CaP remains controversial and several groups have recently published practical recommendations for defining HRPC (23, 24, 25, 26).

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). Androgen-independent, but hormone-sensitive PCa, must be differentiated from true HRPC. Although the former responds to secondary hormonal manipulations, such as anti-androgen withdrawal, oestrogens and

corticosteroids, true HRPC is resistant to all hormonal measures, including ketoconazole and, in the future, abiraterone *(see below)* (27, 28). Table 20 lists the key defining factors of HRPC.

Table 20: Definition of HRPC

• Serum castration levels of testosterone (testosterone < 50 ng/dL, or < 1.7 nmol/L)
• Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with a PSA > 2 ng/mL
• Anti-androgen withdrawal for at least 4 weeks*
• PSA progression, despite secondary hormonal manipulations*
• Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using the RECIST criteria** and with nodes ≥ 2 cm in diameter

** Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for HRPC.*
*** From Therasse et al., 2000 (29).*

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) (29). 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 an interesting tool for axial metastases (30). Because the cause of death in PCa patients is often unreliable, a more valid end-point may be an overall survival rate rather than a disease-specific one (31).

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 decline in PSA level. Prostate-specific antigen is being used as a rapid screening tool to test new agents for activity. However, conflicting evidence is emerging regarding the role of PSA as a marker for response. In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effects of drugs on PSA expression need to be considered when interpreting PSA response data, which must be viewed together with other clinical data (32-39).

Nevertheless, it has been reproducibly shown that ≥ 50% PSA decline in pre-treatment PSA following therapy is associated with a significant survival advantage (40, 41). Kelly et al. (40) reported a statistically significant survival advantage in 110 patients with ≥ 50% PSA decline (> 25 months) compared to those who did not (8.6 months), while Smith et al. (41) showed that a PSA decline ≥ 50% for at least 8 weeks resulted in a longer mean survival time of 91 weeks versus only 38 weeks in patients with 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 abnormal PSA levels. However, it was clear in this trial that a PSA response was not a surrogate marker because the same PSA response rate was found in both docetaxel arms (45%), while improved survival was only apparent with the 3 weeks' docetaxel regimen.

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 (42); however, these data have to be corroborated in other trials before clinical recommendations can be made.

In patients with symptomatic osseous lesions, pain reduction or complete pain relief may be used as parameters to assess palliative therapeutic response (43).

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
- use PSA response, only 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 ≥ 50% maintained for 8 weeks is associated with a significantly better outcome compared to a PSA decline < 50%	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

LE = level of evidence

17.5 Androgen deprivation in androgen-independent PCa

The existence of androgen-independent PCa demonstrates that disease progression occurs despite castration. The castration levels of testosterone must therefore be documented and a serum testosterone level < 50 ng/mL (1.7 nmol/L) should be documented at initial relapse on hormonal therapy (24, 44).

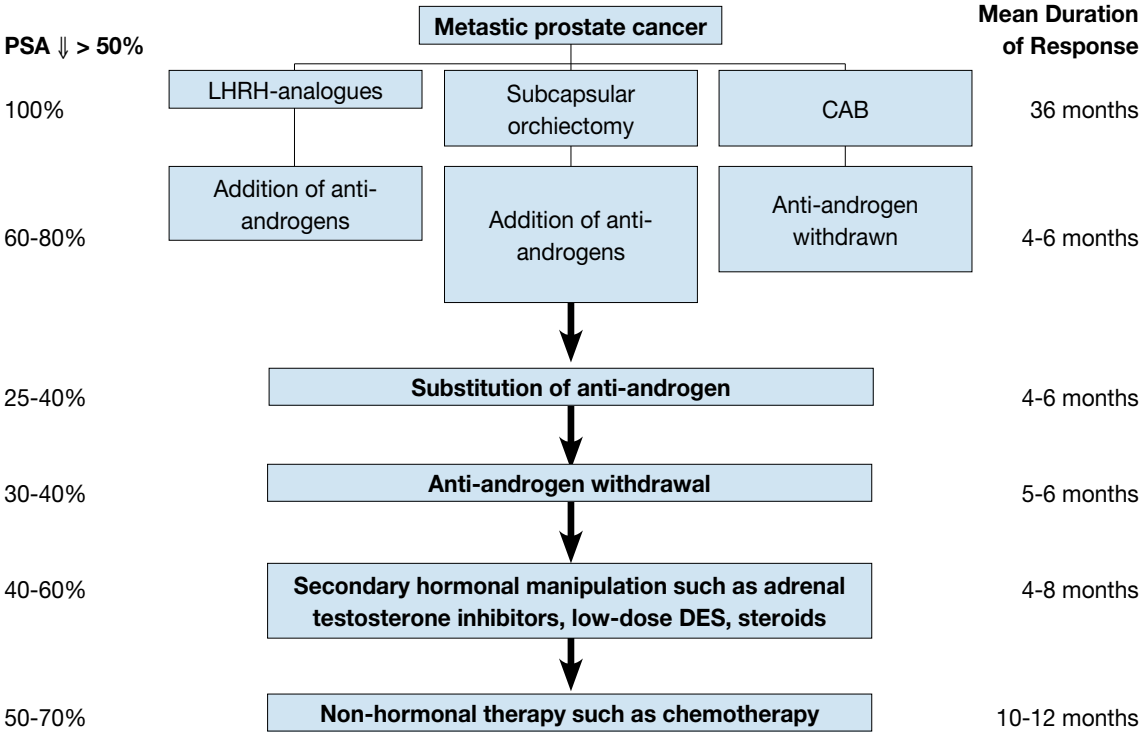
The overall effect of continued testicular androgen suppression in HRPC is minimal. The recommendation to continue androgen deprivation with LHRH analogues, despite PSA progression, is based on the data of Manni et al. (45), which demonstrated significantly lower survival rates in patients without continuous androgen blockade. Two recent trials have challenged these data by showing only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies (46, 47).

However, in the absence of prospective data, the modest potential benefits outweigh the minimal risk of treatment and androgen suppression should be continued indefinitely in these patients.

17.6 Secondary hormonal therapy

For the patient with progressive disease after androgen deprivation, there are many therapeutic options. They include anti-androgen withdrawal, addition of anti-androgens, anti-androgen replacement, oestrogenic compounds, adrenolytic agents and novel approaches (48). 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 (49) 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

terms of understanding the biology of androgen independence, interpreting clinical trials, and treating patients (50-53).

Approximately one-third of patients respond to anti-androgen withdrawal, as indicated by a ≥ 50% PSA decrease, for a median duration of approximately 4 months (Table 21). Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (54-60). Recently, in the SWOG 9426 trial, the results were reported of a subgroup of 210 patients, with a tumour stage of M0 or M1, who showed PSA progression despite CAB. A PSA response was observed in 21%, even though there was no radiographic response. Median progression-free survival was 3 months, with 19% (all MO) having 12 months' or greater progression-free survival. Factors associated with increased progression-free and overall survival 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 21: 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 (61).

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 (62). 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 (63-65).

17.8.2 Switching to an alternative anti-androgen therapy

There has been recent interest in another simple modality: the alternative anti-androgen therapy (66). After CAB 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, and lasting more than 6 months. The higher the PSA at the start of second-line therapy, the shorter the efficacy.

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 (67-71) 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 (71).

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 (72, 73). Recently, DES (74-76) 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.

A very promising drug, the CYP17 inhibitor abiraterone acetate, has achieved more 50% PSA decrease in clinical trials in patients with HRPC (77), including patients previously treated with ketokonazole (78) or even by docetaxel (79). A large phase III trial is underway, enrolling 1158 men, with overall survival as the primary objective. This new compound raises questions about HRPC definition status, as a clear response is apparent even in highly pretreated patients initially considered to be hormone-refractory.

17.9 Non-hormonal therapy (cytotoxic agents)

Several proven chemotherapeutic options are available for metastatic disease in HRPC (Table 22). A significant improvement in median survival of about 2 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy (80, 81). 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 22: 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	TTP
Tax 327					
Mitoxantrone		32%	22%	16.5 months	__
Docetaxel, 75 mg/m^2		45%[1]	35%[3]	18.9 months[1]	__
Docetaxel, 30 mg/m^2		48%[1]	31%	17.4 months	__
SWOG 99-16					
Mitoxantrone	336	50%[1]	__	17.5 months[2]	6.3 months[1]
Docetaxel/EMP	338	27%	__	15.6 months	3.2 months
CALGB 9182					
Hydrocortisone	123	38%[4]	__	12.3 months	2.3 months
Mitoxantrone/HC	119	22%	__	12.6 months	3.7 months[4]
Tannock et al.					
Prednisone	81	22%	12%	__	43 weeks[1]
Mitoxantrone/Pred	80	33%	29%[2]	__	18 weeks

TTP = median time to progression; EMP = estramustine; HC = hydrocortisone; Pred = prednisone.
[1]p < 0.000; [2]p = 0.001; [3]p = 0.01; [4]p < 0.03.

17.9.1 Timing of chemotherapy in metastatic HRPC

The timing of chemotherapy varies in metastatic HRPC. In symptomatic patients, immediate use is advisable, every 3 weeks if possible as this schedule is associated with a survival improvement. However, a weekly regimen will result in the same symptom improvement. It must be considered in patients unable to receive the optimal regimen (level of evidence: 1b), as it is more effective than the best supportive care (82). In asymptomatic patients, timing is not so clear and must be discussed individually.

Several poor prognostic factors have been described, such as PSA level > 114 ng/mL, a PSA doubling time (PSA–DT) < 55 days, or the presence of visceral metastases (83). A C-reactive protein (CRP) level below 8 mg/L (HR, 2.96) has also been suggested as predicting better survival if (84). Age by itself is not a contraindication to docetaxel (85).

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

Taxanes in combination therapy

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), exisulid, and thalidomide, resulting in PSA responses of about 60% (86-89). In a randomised phase II trial of docetaxel + thalidomide (86), 75 men with chemotherapy-naïve HRPC were randomised to receive either docetaxel at 30 mg/m^2 for 5 of every 6 weeks or docetaxel at the same dose and schedule plus thalidomide at 200 mg orally each day. A PSA decline of ≥ 50% was higher in the combination-treated group (53%) compared to the docetaxel-alone treated group (37%) (not statistically significant). Median progression-free survival and overall survival with combination treatment were 5.9 months and 68%, respectively, at 18 months 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 progression-free survival of 15 months versus 9.6 months (p = 0.0002) (90).

Mitoxantrone combined with corticosteroids

Mitoxantrone combined with corticosteroids (37, 91) has been extensively studied primarily in patients with symptomatic osseous lesions due to HRPC. In the CALGB 9182 study (91), 244 patients with symptomatic metastatic HRPC were randomised to receive either mitoxantrone + hydrocortisone, 12 mg/m^2 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 (37), 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 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.

Alternative combination treatment approaches

Encouraging results have been seen with alternative treatments evaluated in prospective clinical phase II trials, including pegylated doxorubicin, vinorelbine, a combination of paclitaxel, carboplatin and estramustine, a combination of vinblastine, doxorubicin and radionuclides, and a combination of docetaxel and mitoxantrone (92-98). The lack of representative randomised phase III trials and unknown long-term efficacy are major problems associated with all these studies.

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 (99). Estramustine + vinblastine has been 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 ≥ 50% PSA decrease was significantly higher in the combination arm, median survival did not differ significantly between the estramustine and the estramustine + vinblastine arms (100). A recent meta-analysis on estramustine (101) concluded that the addition of estramustine to chemotherapy increased the time to PSA progression and overall survival. However, there was a significant increased risk of thromboembolic events, up to 7% (102), requiring systematic prevention with coumadin.

Oral cyclophosphamide

Intravenous cyclophosphamide has been tested in many trials. However, there is currently interest in on oral cyclophosphamide, which seems to be less toxic than intravenous cyclophosphamide and may have greater activity (103, 104). A study of the oral cyclophosphamide + oral etoposide in 20 patients was similarly encouraging (105, 106). Cisplatin and carboplatin have activity against PCa as single agents and a well-documented synergy with etoposide or paclitaxel in vitro in the treatment of other malignancies, such as lung and ovarian cancer. As estramustine is also synergistic with these drugs, combinations of 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 (107).

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 (108-110).

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 (111, 112), molecular-targeted therapy 113, 114) and second-line satraplatin (115).

Second-line intermittent docetaxel has been used by several groups in clearly responding patients to first-line docetaxel (111, 112, 116). 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 (111-117, 118), 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 (39, 41), it was rejected for HRPC by the FDA 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 (119), are being tested in phase III trials. Patients should be advised to participate.

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 (120), even as single fraction (121). 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 the pain is intractable. Early use can give rise to myelosuppression making subsequent chemotherapy more difficult (106, 122), even though a recent phase I trial has demonstrated manageable haematological toxicity with repeated administration of docetaxel and samarium-153 (123). The use of samarium-153 as consolidation therapy, following a clear docetaxel response, may also help with initially painful bone metastases (124). Palliative treatment with another radioisotope emitter, radium-233 has shown very promising phase II results in patients with painful bone metastases in terms of palliation and overall survival, and only a mild haematological toxicity (125).

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 (126). However, it is still important to offer standard palliative surgery, which can be very effective at managing osteoblastic metastases (127, 128).

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 (129). 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 (130), 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 could be proposed to patients with HRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear, but at present is every 3 weeks or less. The toxicity, e.g. jaw necrosis, of these drugs, especially aminobisphosphonate, must always be kept in mind (131). 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 (132).

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 (43, 133). 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 antiemetics).

Hormone-refractory PCa is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers (134).

17.11 Summary of treatment after hormonal therapy

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

GR = grade of recommendation

17.12 Guidelines and recommendations for cytotoxic therapy in HRPC

Guidelines and recommendations	GR
• Cytotoxic therapy should only be used to treat non-metastatic HRPC 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	B
• Prior to treatment, PSA serum levels should be > 5 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 HRPCA, 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 HRPCA, 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

GR = grade of recommendation

17.13 Guidelines for palliative management of HRPC

Recommendations
• Patients with symptomatic and extensive osseous metastases cannot benefit from medical treatment with regard to prolongation of life
• Management of these patients has to be directed at improvement of QoL and mainly pain reduction
• Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy

17.14 Recommendations for palliative management of HRPC

Recommendations	GR
• 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
• Spine surgery or decompressive radiotherapy might be an emergency	A

GR = grade of recommendation

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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
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	dihydrostestosterone
DSS	disease-specific survival
EBRT	electron 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
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
MRC	Medical Research Council
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopy imaging

NHT	neoadjvant 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
RITA	radio-frequency interstitial tumour ablation
RP	radical 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

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Conflict of interest

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