Guidelines on
Prostate Cancer

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1. BACKGROUND

Cancer of the prostate (CaP) is now recognized as one of the principal medical problems facing the male population. In Europe, an estimated 2.6 million new cases of cancer are diagnosed each year. Prostate cancer constitutes about 11% of all male cancers in Europe (1), and accounts for 9% of all cancer deaths among men within the European Union (EU) (2). In most countries, irrespective of whether prostate cancer is common or not in the country/region, a slight increase in prostate cancer mortality has been seen in most, but not all, countries since 1985 (3).

Prostate cancer does more often affect elderly men and is thus a bigger health concern in developed countries, in which about 15% of male cancers are prostate cancer, in contrast to developing countries in which 4% of male malignancies are prostate cancer (4). It is worth mentioning that there are comparatively large regional differences. For example, in Sweden, where there is a long life-expectancy and a comparatively modest mortality from smoking-related diseases, CaP is the most common malignancy in males, accounting for 36.8% of all new cases of cancer in 2004 (5).

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2. CLASSIFICATION

The 2002 TNM (Tumour Node Metastasis) classification for CaP is shown in Table 1 (1).

Table 1: Tumour Node Metastasis (TNM) classification of CaP

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.*

2.1 Gleason score

The most commonly used system for grading adenocarcinoma of the prostate is the Gleason score (2). Biopsy material (core biopsy or operative specimens) is required to be able to assess the Gleason score; cytological preparations cannot be used. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. This score is the sum of the two most common patterns (grades 1-5) of tumour growth found. In needle biopsy, it is now recommended that the worst grade always should be included even if present in < 5% (3).

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3. RISK FACTORS

The factors that determine the risk of developing clinical CaP are not well known; however, a few have been identified. An important risk factor seems to be heredity. If one first-line relative has the disease, 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 CaP (about 9%) has true hereditary CaP, defined as three or more relatives affected or at least two who have developed early-onset disease, i.e. before the age of 55 (3). Patients with hereditary prostate cancer usually have an onset 6-7 years prior to spontaneous cases but to not differ in other ways from these (4).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (5). This finding is in sharp contrast with the incidence of clinical CaP, 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 CaP increases, and if they move to California their risk increases even more and approaches that of American men (7).

These findings indicate that exogenous factors affect the risk of progression from so-called latent CaP to clinical CaP. 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). The identity of these factors is still under debate, but a high content of animal fat in the diet may be important in increasing the risk of developing CaP (9). Tomatoes contain lycopenes, a strong antioxidant, which has been extensively studied as a possible protective agent for the development of prostate cancer. A meta-analysis review identified 11 case-control and 10 cohort studies in which the intake of tomatoes had been correlated to the prostate cancer risk (10). The results showed a decrease in the relative risk to 0.81 (CI 0.71-0.92), for those with the highest intake of tomatoes. Other factors increasing risk include low intakes of vitamin E, selenium, lignans and isoflavenoids (11).

In summary, hereditary factors are important in determining the risk of developing clinical CaP and exogenous factors may have an important impact on this risk. The key question is whether or not 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 (12). There is some evidence for this, and this information could be given to male relatives of CaP patients who ask about the impact of diet (level of evidence: 3-4).

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4. SCREENING AND EARLY DETECTION

Population or mass screening is defined as the examination of asymptomatic men (at risk). Usually, screening takes place within the framework of a trial or study and is initiated by a screener. Contrary to that, early detection or opportunistic screening represents individual case findings. It is initiated by the screenee (patient) and/or his physician. The primary endpoint of both is two-fold: first, the reduction of CaP-specific mortality. The goal is not to detect more and more carcinomas nor is survival the endpoint because survival is heavily influenced by lead-time. Secondly, quality of life is important as expressed by quality of life adjusted gain in life years (QUALYs).

The trends in mortality from CaP show a wide variety from country to country all over the industrialized world (1). A decrease in mortality rates due to CaP is currently seen in the USA and Austria, but also in the UK and France, which share a similar decrease in CaP mortality rates (1). Similarly, in Sweden, the relative 5-year survival rates increased in the period from 1960 to 1988, which was attributed to increased diagnostic activities and the detection of more non-lethal tumours (2). However, this trend could not be confirmed in a similar study from the Netherlands (3).

The reduction in mortality seen lately in the USA is often attributed to the widely adopted aggressive screening policy. However, there is still no absolute proof that the concept of prostate-specific antigen (PSA) screening is the cause for reduced mortality due to CaP (4,5).

A non-randomized screening project in Tyrol (Austria) may support the hypothesis that screening can be effective in reducing CaP mortality. The early detection programme in combination with the availability of free treatment was used as an explanation for the 33% decrease in the CaP mortality rate seen in Tyrol as compared with the rest of Austria (6) (level of evidence: 2b). In addition, Labrie and co-workers from Quebec (Canada) claim lower mortality rates in men randomized to active CaP screening (7), even though these results have been challenged (8). Other studies have contradicted the positive findings attributed to screening, with a comparative study between the Seattle area (highly screened population) and Connecticut (seldom screened population) by Lu-Yao and coworkers (9) showing that, notwithstanding the very large diversity in PSA testing and in use of curative treatments, there was no difference in the reduction in the rate of CaP mortality (level of evidence: 2b).

In order to be able to really evaluate the efficacy of CaP screening, prospective, preferably population-based, randomized trials are needed. 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 (10). The first analysis of the main endpoint of these trials – differences in CaP mortality – is scheduled for 2008 (level of evidence: 1b).

Thus, at the present time, there is a lack of evidence to support or disregard widely adopted, population-based screening programmes for early detection of CaP aimed at all men in a given population (level of evidence: 3).

Less controversial, and recommended in most guidelines, is the use of PSA in combination with digital rectal examination (DRE) as an aid to early diagnosis (11) (see chapter 5) (level of evidence: 3).

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5. DIAGNOSIS

The main diagnostic tools used to look for evidence of CaP include DRE, serum concentration of PSA and transrectal ultrasonography (TRUS) (1). 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. Multiple systematic ultrasound-guided biopsies will detect more cancers than digital or ultrasound-guided biopsies of suspicious areas (2,3).

5.1 Digital rectal examination (DRE)

Most CaPs 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. The risk of a positive DRE turning out to be cancer is heavily dependent on the PSA value (Table 2) (4-6).

Table 2: PSA value and risk of CaP

PSA ng/mL	PPV for cancer
0-1	2.8-5%
1-2.5	10.5-14%
2.5-4	22-30%
4-10	41%
> 10	69%

PPV = positive predictive value; PSA = prostate-specific antigen.

5.2 Prostate-specific antigen (PSA)

The measurement of PSA level has revolutionized the diagnosis of CaP (7). 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, and serum levels may be elevated in the presence of benign prostatic hypertrophy, prostatitis and other non-malignant conditions. PSA level, as an independent variable, is a better predictor of cancer than suspicious findings on DRE or TRUS (6).

Currently, many different commercial test kits for the measurement of PSA are available, but no common international standard exists (8). For the diagnosis of CaP, levels of other tumour markers, such as prostatic acid phosphatase (PAP) do not yield additional information if they are measured in addition to PSA (9). A threshold level of PSA that indicates the highest risk of CaP needs to be defined (10). The cumulative 7-year risk of being diagnosed with CaP in a screening programme based on PSA measurement only was 34% for men with PSA values between 3 and 6 ng/mL, 44% for those with PSA values between 6 and 10 ng/mL, and 71% for those with PSA values > 10 ng/mL (11).

Thus, the detection of non-palpable CaP is dependent on the serum level of PSA. There is no universally accepted lower cut-off value, although > 4 ng/mL has been used in many studies. In younger men, aged 50-66 years, the CaP detection rate was 13.2% in the PSA interval 3-4 ng/mL; the majority of these cancers were judged to be clinically significant (12). Even lower cut-off levels have been proposed by some authors, still with a relatively high detection rate (13). The finding that many men may harbour CaP despite low levels of serum PSA has been underscored by recent results from a US prevention study (14). The rate of CaP in relation to serum PSA for 2950 men in the placebo-arm and with normal PSA values is presented in Table 3. The age range at biopsy was 62-91 years.

Table 3: Risk of CaP in relation to low PSA values

PSA level (ng/mL)	Risk of CaP
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 touch on an important issue associated with lowering the PSA level threshold and that is the avoidance of detecting insignificant cancers whose natural history is unlikely to be life-threatening (15). Long-

term data are not yet available from which to make a recommendation for the optimal PSA threshold value needed to detect non-palpable but clinically significant CaP (level of evidence: 3).

The following modifications of serum PSA value, which may improve the specificity of PSA in the early detection of CaP, have been described:

- PSA density (16)
- PSA density of the transition zone (17)
- Age-specific reference ranges (18)
- PSA molecular forms (19-21)
- PSA velocity (22)
- PSA doubling time (23).

All of the above modifications may help to distinguish between CaP and benign disorders of the prostate, particularly in the intermediate PSA range (4-10 ng/mL). Consensus has not been reached, however, on the application of these modifications in routine practice.

In routine clinical practice, a free-to-total PSA ratio of < 20% and PSA velocity > 0.75 ng/mL/year have been accepted as valid parameters, which are associated with a higher risk of CaP and which facilitate the indication to perform a prostate biopsy. In a recent retrospective study of 12,078 men undergoing a prostate biopsy (24), threshold values of PSA and PSA velocity were identified to improve the assessment of CaP risk in men aged < 50 years. The prevalence of CaP was 4.4% and 14.2% in men aged < 50 years and > 50 years, respectively. For the group with cancer, the median PSA value was significantly lower in men aged < 50 years compared to men aged > 50 years (1.3 vs 6.3 ng/mL). Receiver operating characteristics curve (ROC) analysis demonstrated a breakpoint at a PSA level of 2.3 ng/mL and a PSA velocity of 0.60 ng/mL/year to identify men with CaP. Based on these data, a PSA threshold level of < 2.5 ng/mL and a PSA velocity threshold level > 0.60 ng/mL/year appear to be appropriate for clinical practice.

Stage T1c describes tumours recognized by biopsies performed because of an elevated PSA level only, with a normal DRE and TRUS. A review of the clinical relevance and pathological correlation of this tumour stage in European patients indicates that between 11% and 26% of cases are insignificant cancers, but between 18% and 49% represent locally advanced disease (25).

5.3 Transrectal ultrasonography (TRUS)

Different CaPs appear differently on TRUS. The classic picture of a hypoechoic area in the peripheral zone of the prostate will not always be seen (26). It must be stressed that many cancers are isoechoic and only detectable through systemic biopsies. Ellis and co-workers noted that 37.6% of their detected cancers were diagnosed in isoechoic areas of the prostate (3). Similar findings have been reported from several early detection studies.

TRUS has two potential roles in the diagnosis of CaP:

1. To identify lesions suspected of malignancy.
2. To improve the accuracy of prostate biopsy.

It appears that, in a self-referred population, TRUS detects 50% more patients with CaP than does physical examination (27,28). However, the ultrasonic appearance of CaP is variable, and it seems that only a very small number of cancers will be detected if DRE and PSA levels are normal (3,28,29). Thus, the main role of grayscale TRUS is to direct biopsies in order to obtain a systemic sampling of the gland.

5.4 Relationship between DRE, PSA, TRUS and CaP

The positive predictive value of various combinations of diagnostic procedures used in a screening population ranges from 20% to 80% (3,28,29). If a result using any one of the three modalities is abnormal, the positive biopsy rate is 6-25%; with two abnormalities it is 18-60%; and, if all three modalities are positive, it is 56-72%.

5.5 Prostate biopsies

Digitally guided fine-needle aspiration allows the diagnosis and cytological grading of the tumour with a minimal risk of complications (30). However, the method requires a specially trained cytologist to yield reproducible results and has never gained widespread use outside Scandinavian countries.

Ultrasound-guided transrectal 18G core biopsy has become the standard way to obtain material for histopathological examination. Multiple cores can be taken with a low risk of complications if antibiotic prophylaxis is used (31,32).

Lesion-guided biopsies can be used in cases where there is a palpable nodule in combination with a high PSA-level. Targeted biopsies directed by contrast-enhanced Doppler ultrasound have been shown to have a detection rate similar to that seen with systemic biopsies (33), but the method has not yet gained widespread

acceptance (level of evidence: 2b).

Early studies indicated that the detection rate decreased when the number of cores decreased. Only patients with a PSA > 10 ng/mL and a palpable nodule seemed to have an adequate detection rate with few, directed biopsies (34). For other patients, a more extensive sampling (more cores) was recommended.

Sextant biopsies, as described by Hodge et al., have been used in this situation (2). Recently, the standard way of obtaining sextant biopsies has been replaced by laterally directed sextant biopsies in order to optimize the CaP detection rate (35,36). Biopsy cores obtained this way include biopsies from the posterolateral aspect of the peripheral zone, which is the most common location for early CaP. The number of biopsies required for the optimal detection of CaP is controversial. Several studies have examined the detection rate with more biopsy cores at primary biopsy. Nearly all have shown a higher cancer detection rate in comparison with the standard sextant technique described by Hodge. For example, Eskew and co-workers demonstrated that the five-region biopsy protocol with 13 to 18 cores increased the detection rate by 35% when compared to standard, mid-lobar sextant biopsies (37). Studies clearly show that the transition zone should not be the target area for a first set of prostate biopsies because of a consistently low cancer detection rate, which may be as low as 2% or less (38,39). The vast majority of the extra cancers were detected in the far-lateral mid-lobar region, an area well sampled by the technique of laterally directed sextant biopsy. It seems that the direction of the biopsies may well be as important as the number of cores.

If the first set of biopsies is negative, repeated biopsies can be recommended. In the second set of biopsies, a detection rate of about 10-35% has been reported in cases with a negative first set of biopsies (40-42). In cases where high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) is present, as many as 50-100% of prostates harbour a concomitant cancer and re-biopsy is indicated (43,44). Djavan and co-workers found that two sets of biopsies detected most clinically significant cancers (42). Even patients who have undergone more extensive biopsies may still have a significant detection rate at repeat biopsy (40,45). Today, there is no proven biopsy scheme that omits the need for re-biopsy in the case of a persistent indication (level of evidence: 3).

There is potential to reduce further this diagnostic dilemma. Treatment with 5-alpha-reductase inhibitors may unmask prostate cancer by preferential suppression of BPH-derived PSA. After 1 year of finasteride, prostate cancer detection is more likely in men with a smaller decrease in PSA (46). This hypothesis is supported by a meticulous analysis of the Prostate Cancer Prevention Trial (PCPT), which found that diagnostic accuracy of prostate cancer was greater in the finasteride group than the placebo group (14).

Results of several phase II and phase III studies for primary diagnosis of prostate cancer with 11C-choline and 18F-choline positron emission tomography (PET)/computerized tomography (CT) have been summarized (47). Preliminary results indicate that differentiation of prostate cancer from BPH and from focal chronic prostatitis may be difficult. Functional imaging with metabolic substrates may be more promising in recurrent disease (48).

With an increasing number of men undergoing more extensive biopsies on possibly two or even more occasions, the need for analgesia has become more important in clinical practice. Of various methods examined, the use of a periprostatic injection with a local anaesthetic seems to combine best high-efficacy with easy application and low complication rates. Of 23 studies, 20 showed good efficacy when compared to placebo or intrarectal gel with local anaesthetic (49-71) (level of evidence: 1a).

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6. STAGING

The primary extension assessment of CaP is usually made by DRE, PSA measurement and bone scan, supplemented with CT or magnetic resonance imaging (MRI) and chest X-ray in specific situations.

6.1 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; in one study, a positive correlation between DRE and pathological tumour stage was found in fewer than 50% of tumours (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 proved 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. Although the free-to-total PSA ratio has been found to be useful for staging localized CaP (6), other studies have shown opposite results. 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 TRUS. However, only 60% of tumours are visible at TRUS and the remainder are not recognized due to their echogenicity. TRUS may reveal unsuspected extracapsular extension, but it does not determine tumour extent with sufficient accuracy to be recommended for routine use in staging. About 60% of pT3 tumours will not be detected pre-operatively by TRUS (7). TRUS criteria for extracapsular extension of CaP include irregularity, bulging and discontinuity of boundary echo. TRUS criteria for seminal vesicle invasion are suggested by fullness and loss of normal tapering near the base of the prostate. However, the recognition of these findings is largely operator-dependent. Thus, differentiation between T2 and T3 tumours should not be based on TRUS alone (8,9). Furthermore, in a multi-institutional large study, TRUS was no more accurate at predicting organ-confined disease than DRE (10). These findings were supported by another large study, which showed that there was no meaningful superiority of TRUS over DRE (11).

Seminal vesicle invasion is predictive of local relapse and distant failure. Biopsies of the seminal vesicles may be used to increase the accuracy of pre-operative staging (12). 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 alter the treatment decision. It is worth mentioning that a negative seminal vesicle biopsy does not exclude the presence of microscopic invasion. In general, patients with a clinical stage greater than T2a and a serum PSA level of more than 10 ng/mL are candidates for seminal vesicle biopsies (13,14). Patients with any of the basal biopsies positive for cancer are more likely to have positive seminal vesicle biopsies (15). Improvements in the pre-treatment staging of CaP are required. More detailed analysis of multiple prostate biopsies (the number, grade and extent of CaP foci, capsular perforation) may prove helpful pending further evaluation (16-19). Furthermore, it may be useful to correlate the biopsy Gleason score with the final pathological stage; about 70% of patients have localized disease when the biopsy Gleason score is $\leq$ 6 (20).

Both CT and MRI are now of a high technical standard, but neither modality is sufficiently reliable to make it mandatory to use them to assess local tumour invasion (21-23). MRI of the prostate appears to be the

most accurate non-invasive method of identifying locally advanced disease (24). Several studies have compared the imaging findings of endorectal MRI and pathohistological data after radical prostatectomy with regard to extracapsular extension (ECE) and seminal vesicle invasion (25-27). In one trial (25), 106 patients with biopsy-proven CaP had undergone radical prostatectomy within 1 month after endorectal MRI. Sextants of the prostate were analysed for the presence of ECE and correlated with the MRI findings of three reviewers using ROCs. A total of 41 patients and 135 sextants were positive for ECE; ROC analysis yielded an area under the curve (AUC) ranging from 0.776 to 0.832, revealing a moderate prediction for the localization of ECE. In another trial (26), including 573 patients with CaP who had undergone radical prostatectomy, the validity of endorectal MRI to predict seminal vesicle invasion (SVI) was evaluated. At pathohistological analysis, 28 men demonstrated SVI. The Kattan nomogram plus endorectal MRI (0.87) had a significantly larger AUC than either endorectal imaging alone (AUC 0.76) or the Kattan nomogram alone (0.80) and therefore added substantially to the preoperative identification of SVI. However, its routine use for the pre-treatment staging of CaP remains controversial and MRI is not always available. For dose planning before external-beam radiation, CT is most useful.

6.2 N-staging

N-staging should only be performed when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatments are planned. High PSA values, stages T2b-T3 disease, poor tumour differentiation and perineural tumour invasion have been associated with a higher risk of the presence of nodal metastases (5,28,29). The measurement of PSA level alone is unhelpful in predicting the presence of lymph node metastases for an individual patient.

The nomograms (Partin tables) may be used to define a group of patients with a low risk of nodal metastasis (< 10%). In such cases, patients with a serum PSA level 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 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 > 3 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 that nodal staging is unnecessary in selected patients (30).

The gold standard for N-staging is operative lymphadenectomy, by either 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 (31,32). Both CT and MRI have limited use due to their low sensitivity, which varies from 0% to 70% (22,33,34), although CT accuracy increases when fine-needle aspiration biopsies are applied to virtually all visible and asymmetrical lymph nodes (35). Even the combined use of endorectal MRI and MRI spectroscopy has a positive predictive value of only 50% (36). In asymptomatic patients with newly diagnosed CaP and a serum PSA level of less than 20 ng/mL, the likelihood of positive findings on CT is approximately 1% (37). Therefore, CT scanning may 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 metastasis on CT or with a positive aspiration biopsy may thus be spared operative lymphadenectomy (38). However, a recent retrospective analysis found that lymph node size might only be used with caution as a surrogate for the presence of lymph node metastases (39).

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 (40-42), especially as negative PET results should be interpreted with caution (43).

6.3 M-staging

The axial skeleton is involved in 85% of patients dying from CaP (44). 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 (45). Furthermore, measurement of skeletal alkaline phosphatase and PSA at the same time increases clinical effectiveness to approximately 98% (46). 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 (47). 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 PAP determination (48,49). Technetium diphosphonates are the optimum radiopharmaceuticals currently available due to their extremely high bone-to-soft-tissue ratio (50). A semi-quantitative grading system based upon the extent of disease observed on the bone scan was found to correlate with survival (51). Besides bone, CaP may metastasize 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 all 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 CaP has long been recognized. At present, PSA is the marker of choice. A pre-treatment serum PSA level greater than 100 ng/mL was found to be the single most important indicator of metastatic disease, with a positive predictive value of 100% (52). Furthermore, it has helped to reduce the number of patients with newly diagnosed CaP 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 CaP has been further investigated (53-57). 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 (58,59).

6.4 GUIDELINES FOR DIAGNOSIS AND STAGING OF CAP

1. An abnormal DRE result or elevated serum PSA measurement may indicate CaP. 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 (grade C recommendation).
2. The diagnosis of CaP depends on histopathological (or cytological) confirmation (grade B recommendation). Biopsy and further staging investigations are only indicated if they affect the management of the patient (grade C recommendation).
3. Transrectal ultrasound guided systemic biopsies is the recommended method in most cases with the suspicion of CaP. A minimum of 6-10 systemic, laterally directed, cores are recommended, eventually with more cores in larger glands (grade B recommendation):
   - Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates (grade C recommendation)
   - One set of repeat biopsies are warranted in cases with persistent indication (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy) for prostate biopsy (grade B recommendation)
   - Overall recommendations for further (third or more) sets of biopsies cannot be made; the decision has to be made based on an individual patient (grade C recommendation)
4. Transrectal periprostatic injection with a local anaesthetic may be offered to patients as effective analgesia when undergoing prostate biopsies (grade A recommendation).
5. Local staging (T-staging) of CaP is based on findings from DRE and possibly MRI. Further information is provided by the number and sites of positive prostate biopsies, tumour grade and level of serum PSA (grade C recommendation).
6. Lymph node status (N-staging) is only important when potentially curative treatment is planned for. Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score ≤ 6 have less than a 10% likelihood of having node metastases and may be spared nodal evaluation. Accurate lymph node staging can only be determined by operative lymphadenectomy (grade B recommendation).
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 (grade B recommendation).

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7. TREATMENT: DEFERRED TREATMENT (WATCHFUL WAITING; ACTIVE MONITORING)

7.1 Introduction

7.1.1 Definition

The term deferred treatment or watchful waiting (WW) is used to describe a treatment strategy that includes an active standpoint to postpone treatment until it is required. This does not only mean that treatments, such as palliative or hormonal, are withdrawn until symptomatic progression occurs (local or systemic). In rare, selected cases, this approach may also include younger patients with localized disease for whom potentially curative treatments are withheld until an indication for tumour activity occurs (i.e. rising serum PSA level, deteriorating histopathological factors on repeat biopsy). Patients who are offered WW must be followed-up carefully. It is worth mentioning that a patient's anxiety is also a symptom that might warrant active treatment.

7.2 Deferred treatment of localized CaP (stage T1-T2, Nx-N0, M0)

There have been several attempts to summarize the key papers dealing with deferred treatment in patients with presumed localized CaP (1-6). Most of these papers present the same results as they analyze roughly the same series, but with a somewhat different methodology.

The paper by Chodak and co-workers is a pooled analysis of the original data from 828 patients treated by WW (1). It is based on patients from six non-randomized studies (6-13). The results describe cancer-specific survival (CSS) and metastasis-free survival after 5 and 10 years of follow-up (1) (level of evidence: 2b). The importance of tumour grade is clear, with very low survival rates for grade 3 tumours. Even if 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 the patients having developed metastases (Table 4).

Table 4: Outcome of deferred treatment in localized CaP in relation to tumour grade (1)

	Percentage of patients (95% confidence interval)	
	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 CaP was also underlined in a large register study utilizing the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute in the USA (14) (level of evidence: 3). Patients with grade 1, 2 and 3 tumours had 10-year CSS rates of 92%, 76% and 43%, respectively, in agreement with the data from the pooled analysis.

The paper by Chodak and co-workers also specifically described the outcome for stage T1a patients (1), 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 is in accordance with other studies on stage T1a disease (15,16). To stage patients accurately and not overlook the presence of more extensive and/or more poorly differentiated tumours, repeat examinations with PSA measurement, TRUS and needle biopsy of the prostatic remnant have been advocated, especially in younger males with a long life expectancy (17).

The impact of grade on the risk of tumour progression and ultimately death from CaP is also described in a paper by Albertsen and co-workers (18). They re-evaluated all biopsy specimens using the more widely accepted Gleason score and showed that the risk of CaP death was very high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 cancers (Table 5) (18,19) (level of evidence: 3). This paper also shows 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 to assess outcome in treatment for localized CaP (19).

Table 5: The 15-year risk of dying from CaP in relation to Gleason score at diagnosis in patients with localized disease aged 55-74 years (17,18)[1]

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%

[1] *The figures on the risk of cancer death differ for different age groups and represent the true risk (taking actual competing mortality from other causes into consideration) in the studied population. The cancer-specific mortality compensates for differences in competing mortality and indicates the outcome if the patient actually lived for 15 years.*

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 CaP within the first 10 years and that PSA changes over time were relatively unreliable in determining the risk for tumour progression (20).

The data above indicate a high risk of tumour progression after conservative treatment for some patients with apparently localized CaP. 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 CaP when left without curative treatment (21-23). Long-term follow-up of the Johansson series renders the same outcome: there is a higher risk of dying from CaP in patients surviving more than 15 years with well- and moderately differentiated tumours at diagnosis (24) (level of evidence: 3). Recently, a prospective randomized

controlled trial comparing radical prostatectomy with conservative management showed a significant reduction in disease-specific mortality for the treatment group assigned to surgery (25) (level of evidence: 1b).

For patients who choose deferred treatment, the risk of delaying hormonal therapy until disease progression occurs appears to be modest, although shorter CSS times have been reported after deferred therapy compared with immediate hormonal therapy in presumed localized CaP (not utilising PSA for staging) after 15 years of follow-up (26). In contradiction to Lundgren et al., a recent report from the EPC (Early Prostate Cancer Trial) programme showed a higher mortality in a group of men with localized CaP treated with bicalutamide 150 mg compared to those who received placebo (27).

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

7.3 Deferred treatment for locally advanced CaP (stage T3-T4, Nx-N0, M0)

The literature reporting on deferred treatment for locally advanced CaP is sparse. There are no randomized studies that compare more aggressive treatments, such as radiation therapy or surgery, eventually in combination with hormones. Most patients whose disease progresses after deferred treatment of locally advanced CaP will be candidates for hormonal therapy. There are reports from non-randomized studies showing that hormonal 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 (28,29). However, when early and delayed treatments were compared in a large randomized trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormonal therapy was demonstrated (30), comparable with the results of Lundgren et al. mentioned above (26) (level of evidence: 1b).
Also, a comparison of bicalutamide, 150 mg/day, with placebo showed that progression-free (PFS) survival was better with early treatment in patients with locally advanced CaP (27) (level of evidence: 1b).

Fifty selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 CaP were followed up for 169 months (31). The 5- and 10-year CSS rates were 90% and 74%, respectively, and the likelihood of being without treatment at 5 and 10 years was 40% and 30%, respectively. The authors concluded that WW may 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).

7.4 Deferred treatment for metastatic CaP (stage M1)

There are only very sparse data on this subject. The only candidates for such treatment should be asymptomatic patients with a strong wish to avoid treatment-related side-effects (level of evidence: 4). As the median survival time is about 2 years, the time without 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 CaP, without receiving the possible benefit from hormonal treatment (30,32) (level of evidence:1b). If a deferred treatment policy is chosen for the patient with advanced CaP, there must be a possibility of close follow-up.

7.5 SUMMARY ON DEFERRED TREATMENT

7.5.1 Indications

In presumed localized CaP (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).

7.5.2 Options

In presumed localized CaP (Nx-N0, M0):

- Stage T1b-T2b patients, who are well informed and have well-differentiated, or Gleason 2-4, CaP 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, CaP and a short life expectancy (level of evidence: 3)

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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8. TREATMENT: RADICAL PROSTATECTOMY

8.1 Introduction

The surgical treatment of CaP consists of radical prostatectomy, meaning the removal of the entire prostate gland between urethra and bladder, with resection of both seminal vesicles. The procedure is routinely performed either retropubically or using a transperineal approach, although some centres have gained experience with laparoscopic radical prostatectomy (1-3).

But in the last 5-7 years several European centres have acquired considerable experience with laparoscopic radical prostatectomy (4). More recently, the robotic-assisted laparoscopic radical prostatectomy has been developed. Functional and short-term oncological outcomes seem comparable with the open technique in high-volume centres. However, long-term oncological outcomes are still unavailable.

Radical prostatovesiculectomy was first applied at the beginning of the 20th century by Young (5) who used a perineal approach, while Memmelaar and Millin performed retropubic radical prostatectomy for the first time (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 the blood loss and improved continence and potency rates (7).

Currently, radical prostatectomy is the only treatment for localized CaP that has shown a cancer-specific survival benefit when compared to conservative management in a prospective, randomized trial (8).

Surgical expertise has decreased the complication rates and improved cancer cure (9). In the hands of an experienced urological surgeon, the procedure is associated with minimal intra-operative and postoperative morbidity (10-12). The retropubic approach is more commonly performed, as it enables simultaneous pelvic

lymph node assessment to be carried out – 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). It is likely that laparoscopic prostatectomy and perineal prostatectomy have lower morbidity than the retropubic operation, but randomized studies are as yet unavailable.

In men with localized CaP and a life expectancy of 10 years or more, the goal of a radical prostatectomy by any approach must be eradication of the disease (15). In fact, there is no rigid age limit for radical prostatectomy and a patient should not be denied this procedure on the grounds of age alone (16). However, it is worth pointing out that increasing comorbidity with increasing age substantially decreases the actual risk of dying from localized CaP in men over the age of 70 years (17).

8.2 Stage T1a-T1b CaP

Stage T1a CaP 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 CaP is defined as > 5% cancer, or when the tumour is poorly differentiated. Although the risk of disease progression of untreated T1a CaP after 5 years is only 5%, these cancers can progress in about 50% of cases after 10-13 years (18). Thus, in younger patients with a life-expectancy of 15 years or more, the chance of disease progression is real, especially when a higher-grade tumour is present.

In contrast, most patients with T1b tumours are expected to show disease progression after 5 years and aggressive treatment is often warranted (18). Consequently, it is very important to distinguish between T1a and T1b tumours and systematic prostate puncture biopsy of the remnant prostate 3 months after surgery is useful. Patients with T1b lesions are offered radical prostatectomy when they have a life expectancy of 10 years or more. Radical prostatectomy can become very difficult after a thorough TURP when almost no residual prostate is left behind (19), and external beam radiotherapy can be a valuable alternative treatment modality.

8.3 Stage T1c CaP

The clinically inapparent tumour identified by needle biopsy because of an aberrant PSA level has become the most frequent clinical stage in the actual radical prostatectomy population. In an individual patient, it is difficult to differentiate between clinically insignificant and life-threatening CaP. Most reports, however, stress that PSA-detected tumours are mostly significant and should not be left untreated since up to 30% of T1c tumours are locally advanced (20). The proportion of insignificant tumours detected because of PSA elevation varies between 11% and 16% (21,22). Increasing the number of biopsies (sextant, octant, etc) might carry the risk of detecting more insignificant cancers, but a recent study has shown that increasing the number of biopsies to 12 did not increase the number of detected insignificant tumours (23).

The expected incidence of HGPIN detected using needle biopsies is 5-8%. The median risk for cancer on follow-up biopsies is 24.1%, which is not much higher than the risk upon repeat biopsy following a benign diagnosis. LGPIN should not be documented in pathology reports due to poor interobserver reproducibility and the relatively low risk of cancer on repeat biopsies. The risk for cancer upon follow-up biopsy after the diagnosis of ASAP is 40% (24). Repeat biopsies are recommended in both HGPIN and ASAP, although the best interval for further repeat biopsies is not clear (25). The occurrence of PIN or ASAP is not considered to be an indication for treatment.

The major problem is how to recognize tumours on prostate puncture biopsy that do not need radical prostatectomy as they will be insignificant on the definitive pathological examination of the resected specimen. The needle biopsy findings and the free PSA ratio are helpful in predicting insignificant disease (26). Using the Partin tables (updated in 2001) may be very helpful in determining the final pathological stage to better select patients requiring surgical treatment (27). Other authors have suggested the incorporation of biopsy information, such as the number of cores or the percentage of cores invaded (28). 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 CaP is more likely, certainly when the lesion is of low Gleason grade (29). It might be reasonable to follow-up some patients whose tumours are most likely to be insignificant. In general, however, radical prostatectomy should be advocated for patients with T1c tumours, keeping in mind that significant tumours will be found in most of these individuals.

8.4 Stage T2 CaP

Radical prostatectomy is one of the recommended standard treatments for patients with stage T2 CaP and a life expectancy of more than 10 years (30). The prognosis is excellent when the tumour is confined to the prostate based on pathological examination (31,32). Although most poorly differentiated tumours extend outside the prostate, patients with high-grade tumours confined to the prostate at histopathological examination still have a good prognosis after radical prostatectomy (33). A WW policy has been proposed for T2 tumours (34). If 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 (35).

When the tumour is palpable or visible 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. T2a patients with a 10-year life expectancy should be offered radical prostatectomy since 35-55% of them will have disease progression after 5 years if not treated. T2b cancer still confined to the prostate but involving more than half of a lobe or both lobes will progress in more than 70% of patients within 5 years (36). These data have been confirmed by a large randomized trial comparing radical prostatectomy and WW that included mostly T2 CaP patients showing a significant reduction in disease specific mortality (8).

In young men with localized CaP who are otherwise healthy, total surgical removal is an excellent option, and if it is performed by an experienced surgeon, the patient's subsequent quality of life should be more satisfactory. However, in an older patient or one with clinically significant co-existing conditions, radiation therapy could be the best option (37).

Lower rates of positive surgical margins for high-volume surgeons suggest that experienced and careful attention to surgical details, adjusted for the characteristics of a cancer being treated, can decrease positive surgical margin rates and improve cancer control with radical prostatectomy (38).

8.5 Oncological results of radical prostatectomy in organ-confined disease.

The results achieved in a number of studies involving radical prostatectomy are shown in Table 6.

Table 6: Oncological results of radical prostatectomy in organ-confined disease

Study	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 & 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%.*

8.6 Stage T3 CaP

T3a cancer is defined as capsular perforation and T3b cancer as invasion of the seminal vesicles. In the past, locally advanced CaP was seen in about 40% of all clinically diagnosed tumours. This figure must be lower today, but its management remains controversial. In extracapsular tumours, radical prostatectomy often results in incomplete tumour excision. Higher morbidity and a substantially higher risk of local disease recurrence may be associated with these tumours compared with those confined to the prostate.

Surgical treatment of clinical stage T3 CaP is traditionally discouraged (44), mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse (45,46).

Combination treatment with hormonal and radiation therapy is gaining popularity, although it has not been demonstrated that this approach is superior to surgical treatment. A randomized study on radiotherapy with hormones vs radiotherapy alone showed a clear advantage for combination treatment, but did not show its superiority over radical prostatectomy (47). 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 CaP.

In recent years, there has been renewed interest in surgery for locally advanced prostate cancer, 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 (48-53). Overstaging of cT3 prostate cancer 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 (52,53). In about 33.5-66% of patients, positive-section margins will be present and 7.9-49% will have positive lymph nodes (54). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or hormonal therapy (52,53).

Nevertheless, excellent 5-, 10- and 15-year overall and CSS rates have been published (Table 7). These rates surpass radiotherapy-alone series and are no different from radiotherapy combined with adjuvant hormonal therapy series (47). Adjuvant radiotherapy to the prostatectomy bed improves biochemical and clinical-relapse-free survival, but does not improve overall survival (OS) and disease-specific survival (55).

Table 7: 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) (48)	57	Median, 5.4 y	91.2 (77.6 at 7.5 y)	-	-	-	-	-	45.5 (PSA > 0.4)	-	-	81.4	-	-
Gerber et al. (1997) (49)	242	Mean, 39 m Median, 26 m	-	-	-	85	57	-	-	-	-	72 (meta free)	32	-
Van den Ouden et al. (1998) (50)	83	Median, 52 m	75	60	-	85	72	-	29 (PSA > 0.1)			59	31	-
Martinez de la Riva et al. (2004) (51)	83	Mean, 68.7 m (cT3a only)	97.6	94.8	-	100	-	-	(PSA	59.8 > 0.3)	-	-	-	-
Ward et al. (2005) (52)	841	Median, 10.3 y	90	76	53	95	90	79	58 (PSA	43 > 0.4)	38	85	73	67
Hsu et al. (2007) (53)	200	Mean, 70.6 m (cT3a only)	95.9	77	-	98.7	91.6	-	59.5 (PSA > 0.2)	51.1	-	95.9	85.4	-

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

8.6.1 Summary of radical prostatectomy in locally advanced prostate cancer

- Radical prostatectomy can be performed in patients with locally advanced CaP, PSA serum levels < 20 ng/mL, ≤ cT3a, biopsy Gleason score ≤ 8
- If radical prostatectomy is performed, an extended pelvic lymphadenectomy has to be done
- The patient has to be informed about the highly likelihood of a multimodal approach postoperatively.

As there are no randomized clinical trials comparing treatments in these patients, only single or multicentre reports can be used to define the role of radical prostatectomy. For clinical T3 cancer, the overall PSA-free survival rate is about 50% after 5 years. The Gleason score of the tumour has a definite impact on progression (33), but there is not always a reliable correlation between the biopsy and the specimen Gleason score. On the other hand, seminal vesicle invasion, lymph node invasion, positive surgical margins and high PSA level are independent prognostic factors of PSA-free survival. Therefore, surgery has to be considered a therapeutic option for some patients with clinical T3a CaP.

Not only clinically overstaged patients (pT2), but also individuals whose tumours actually are pT3a, can benefit from this treatment option. The problem remains in selecting patients before surgery without lymph node involvement or seminal vesicle invasion. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease (27,54). In addition, nodal imaging with CT scan and seminal vesicle imaging with MRI or directed specific puncture biopsies of the nodes or of the seminal vesicles can be helpful in recognizing those patients unlikely to benefit from a surgical approach (56).

Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. Increased overall surgical experience must contribute to a decreased operative morbidity and to better functional results after radical prostatectomy for clinical T3 cancer (52,57).

8.7 Nodal disease

The indication for radical prostatectomy 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 radical prostatectomy and simultaneous hormonal treatment has been shown to achieve a 10-year CSS rate of 80% (58). However, it is questionable whether or not these results could be obtained with hormonal treatment alone.

Most urologists are reluctant to perform radical prostatectomy for clinical N+ disease or will cancel surgery if a frozen section shows lymph node invasion. It should be noted that the definitive pathological examination after radical prostatectomy 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.

Clinical N+ patients usually have significant nodal involvement and will be treated with hormonal manipulation only.

In patients who prove to be pN+ after radical prostatectomy, 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 surgical pelvic lymph node dissection (LND). This procedure has gained interest during recent years. It is mainly advised in patients at risk for locally advanced disease, but there remains controversy regarding indication and extent of LND, its therapeutic role and morbidity.

8.7.1 Indication and extent of LND

Although it is generally accepted that LND 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 LND 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 (27). 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, LND might not be beneficial. However, the fact that these nomograms are based on a limited LND (obturator fossa and external iliac vein) probably results in underestimation of the incidence of patients with positive nodes (59).

Lymphography studies have shown that the prostate drains not only to the obturator and external iliac but also to the internal iliac and presacral lymph nodes. Performing an extended LND (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 to limited LND (mean of 8 to 10 nodes). In patients with a PSA value < 10 and a Gleason score > 7, an incidence of 25% nodes was reported (60). Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (61,62).

8.7.2 Therapeutic role of extended LND

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 (63-65). For an eLND to be representative, a mean of 20 lymph nodes should be removed (66). In some series, the number of nodes removed during lymphadenectomy correlated significantly with time to progression (67). 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.

8.7.3 Morbidity

An eLND remains a surgical procedure, which adds morbidity to the treatment of prostate cancer. When comparing limited vs extended LND, 3-fold higher complication rates were reported by some authors (68). Complications consist of lymphocoeles, lymphoedema, deep venous thrombosis and pulmonary embolism. Other authors, however, reported more acceptable complication rates (69,70).

8.7.4 Summary of extended lymphadenectomy

- LND can play a role in the treatment of CaP 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.

8.8 Neoadjuvant hormonal therapy and radical prostatectomy

Generally, neoadjuvant or up-front therapy is defined as therapy given prior to definitive local curative treatment (e.g. surgery or radiation therapy). As CaP is an androgen-dependent tumour, neoadjuvant hormonal therapy

(NHT) is an appealing concept. Attempts to decrease the size of the prostate before radical prostatectomy were first reported by Vallett as early as 1944 (71).

In a recent Cochrane review and meta-analysis, the role of neoadjuvant and adjuvant hormonal therapy and prostatectomy were studied (72). Patients had predominantly localized 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 radical prostatectomy 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 radical prostatectomy 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 radical prostatectomy 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 radical prostatectomy: the pooled data for 5 years 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 radical prostatectomy: the pooled data for disease-free survival gave an overall OR of 3.73 and 95% CI 2.3-6.03. The overall affect estimate was highly statistically significant ($p < 0.00001$) in favour of the hormonal arm.
- It is noteworthy that the EPC trial was not included in the Cochrane review. The third update from this large randomized trial of bicalutamide, 150 mg once daily, in addition to standard care in localized and locally advanced, non-metastatic CaP was published in November 2005 (73). Median follow-up was 7.2 years. There was a significant improvement in objective PFS in the radical prostatectomy 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 radical prostatectomy 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 localized disease group (HR 1.16; 95% CI 0.99-1.37).

8.8.1 Summary of neoadjuvant and adjuvant hormonal treatment and radical prostatectomy

- Neoadjuvant hormonal therapy before radical prostatectomy does not provide a significant OS advantage over prostatectomy alone
- Neoadjuvant hormonal therapy before radical prostatectomy does not provide a significant advantage in disease-free survival over prostatectomy alone
- Neoadjuvant hormonal therapy before radical prostatectomy 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 radical prostatectomy shows no survival advantage at 10 years
- Adjuvant hormonal therapy following radical prostatectomy: the overall effect estimate was highly statistically significant ($p < 0.00001$) in favour of the hormonal arm.

8.9 Complications and functional outcome

The postoperative complications of radical prostatectomy are listed in Table 8. The mortality rate is 0-1.5% (74); urinary fistulas are seen in 1.2-4% of patients (75); and urinary incontinence persists after 1 year in 7.7% (76). In men undergoing prostatectomy, the rates of postoperative 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 (77-79).

Erectile dysfunction used to occur in nearly all patients, but nerve-sparing techniques can be applied in early-stage disease (80). Patients who benefit from nerve-sparing radical prostatectomy may have a higher chance of local disease recurrence and should therefore be carefully selected.

8.10 Summary of indications for nerve-sparing surgery

- Nerve-sparing radical prostatectomy can be performed safely in most men undergoing radical prostatectomy (81,82). In the last 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 prostate cancer, cT2c, any Gleason score > 7 on biopsy, or more than 1 biopsy ≥ 7 at the ipsilateral side. Partin tables will help guide decision-making (27)

- If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle
- Alternatively, the use of intraoperative frozen-section analysis can help guide these decisions. The patient must be informed before surgery regarding 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 (89) and the significance of sural nerve transplant needs further multicentre study (90).

Table 8: Complications of radical prostatectomy

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

8.11 SUMMARY OF RADICAL PROSTATECTOMY

8.11.1 Indications

- In patients with stage T1b-T2, Nx-N0, M0 disease and a life expectancy > 10 years (level of evidence: 1b)

8.11.2 Optional

- Patients with a long life expectancy and stage T1a disease (level of evidence: 3)
- Patients with stage T3a disease, a Gleason score of > 8 and a PSA of < 20 ng/mL

8.11.3 Comments

- Short-term (3 months) neoadjuvant therapy with gonadotropin releasing-hormone analogues is not recommended in the treatment of stage T1-T2 disease (level of evidence: 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) (level of evidence: 3)
- Unilateral nerve-sparing procedures is an option in stage T2a disease (level of evidence: 4)
- The role of radical prostatectomy in patients with high-risk features, lymph node involvement (stage N1 disease) or as a part of a planned multimodality treatment (with long-term hormonal and/or adjuvant radiation therapy), has not been evaluated (level of evidence: 4).

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9. TREATMENT: DEFINITIVE RADIATION THERAPY

9.1 Introduction

There are no randomized studies that compare radical prostatectomy with either external beam therapy or brachytherapy for localized CaP, 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). In Europe, the 1990s saw the introduction of three-dimensional conformal radiotherapy (3D-CRT) and a growing interest in transperineal brachytherapy. At the onset of the third millennium, intensity modulated radiotherapy (IMRT), an optimized form of 3D-CRT, is gradually gaining ground in centres of excellence.

After the appropriate assessment of tumour extension, the choice of treatment must be made based on a multidisciplinary approach, taking into account the 2002 TNM classification, Gleason score, baseline PSA, age of the patient, comorbidity, life expectancy and quality of life. Obtaining a patient's consent is essential after providing exhaustive information regarding diagnosis, the therapeutic modalities and morbidity.

Additional information on the various aspects of radiotherapy in the treatment of CaP is made available in a newly published extensive overview (3).

9.2 Technical aspects

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 visualized, following which a (surrounding) safety margin is added. At the time of irradiation, a multileaf collimator, automatically and continually, adapts to the contours of the target volume seen by each beam. The 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 is a high-precision technique that 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. The movement of the leaves during the course of the irradiation allows for the adaptation of the dose to be delivered within the treatment field and provides concave isodose curves.

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

9.3 Localized CaP T1-2c N0, M0

9.3.1 T1a-T2a, N0, M0 and Gleason score $\leq$ 6 and PSA < 10 ng/mL (low-risk group)

For external radiotherapy, at least 72 Gy is recommended as it has been shown that the biochemical disease-free survival is significantly higher with a radiation dose $\geq$ 72 Gy as compared to < 72 Gy (69% vs 63%, p = 0.046) (4).

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

Many series have shown a significant impact of dose escalation on 5-year survival without biochemical relapse for patients classified as cT1c-T3, with a dose ranging from 76 to 81 Gy with no grade 3 or 4 late toxicity (4-6). This is the reason why intermediate-risk group patients may benefit from dose escalation, as shown by two randomized trials. The MD Anderson Cancer Centre randomized study compared 78 Gy 3D-CRT to a 70 Gy conventional radiotherapy including 305 stage T1-3 patients with a pre-treatment PSA level of more than 10 ng/mL (median follow-up of 40 months). A significantly higher 5-year free-from-failure rate was found in 75% of patients who received 78 Gy vs 48% of those who received 70 Gy (p = 0.01) (7). This study has been confirmed by the PROG 95-09 interim analysis that evaluated 393 T1b-T2b patients, of whom 75% had a Gleason score of $\leq$ 6 and a PSA < 15 ng/mL. Patients were randomized to receive an initial boost to the prostate alone using conformal protons of either 19.8 or 28.8 GyE, and then 50.4 Gy to a larger volume. With a median follow-up of 4 years, there was a significant decrease of the 5-year biochemical failure rate (p = 0.00001) in favour of patients given a higher dose (79.2 GyE) vs those receiving a conventional dose (70.2 GyE) (8). In daily practice, although a consensus has not been reached yet concerning the level of dose escalation, 78 Gy seems to represent a good compromise.

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

External irradiation with dose escalation improves 5-year biochemical disease-free survival (7), but seems insufficient to cover the risk of relapse outside the pelvis. Several studies have aimed to evaluate the dose escalation, with or without adjuvant hormonal therapy, including:

- The MRC study comparing neoadjuvant hormonal therapy comparing conventional radiotherapy of 64 Gy to high-dose (74 Gy) radical conformal radiotherapy (9)
- The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) study comparing 70 to 80 Gy doses without hormonal therapy (10)
- The European Organization for Research and Treatment of Cancer (EORTC) study comparing dose stratification (70, 74 and 78 Gy), with or without neoadjuvant and concomitant hormonal therapy (11).

A prospective randomized 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 6 months of androgen deprivation therapy (ADT). After a median follow-up of 4.5 years, patients randomized to receive 3D-CRT plus ADT had a significantly higher survival rate ($p = 0.04$), lower CaP-specific mortality rate ($p = 0.02$), and a higher survival rate free of salvage ADT ($p = 0.002$) (12).

9.3.4 Prophylactic irradiation of pelvic lymph nodes in intermediate- or high-risk localized CaP

Invasion of the pelvic lymph nodes is a poor prognostic indicator (13). Randomized trials held in the 1970s and 1980s failed to show that patients benefited from prophylactic irradiation of the pelvic lymph nodes in high-risk cases. The Radiation Therapy Oncology Group (RTOG) randomized study (1978-1983) with 484 patients T1b-T2 demonstrated that irradiation of the pelvic lymph node chains neither improved the rate of local recurrence nor survival (14), obtaining similar results to those of a Stanford study (1970-1986) of only 91 patients (15).

Nowadays, due to individual screening, comprehensive clinical work-up and new imaging modalities, the risk of pelvic lymph node invasion, may be assessed by Partin's tables (16) or the Roach formula (17). The Roach formula estimates the risk of pelvic lymph node involvement to be higher than 15%: positive lymph node = 2/3 PSA + (GS - 6) x 10, where PSA is prostate-specific antigen and GS is Gleason score. Selective sampling at coelioscopy (18) or mini-laparotomy is another modality used to decide upon treatments.

9.4 Innovative techniques

9.4.1 Intensity modulated radiotherapy (IMRT)

IMRT enables radiation oncologists to increase homogeneously the doses up to 80 Gy within the target volume, while respecting the threshold doses in organs at risk. The Memorial Sloan-Kettering Cancer Centre has the largest experience with this technique, reporting on 772 patients treated between 1996 and 2001 with doses ranging from 81 to 86.4 Gy using an inverse planning approach. With a median follow-up time of 24 months (6-60 months), the 3-year actuarial likelihood of $\geq$ late grade 2 rectal toxicity was 4%; the 3-year actuarial likelihood of $\geq$ grade 2 urinary toxicity was 15%; and the 3-year actuarial PSA relapse-free survival rates for favourable-, intermediate- and unfavourable-risk group patients were 92%, 86% and 81%, respectively (19). The use of IMRT is opening the way to hypofractionated treatment, with a shorter duration for the overall treatment time, by delivering 70 Gy in 28 fractions over 5.5 weeks, with 2.5 Gy per fraction (20).

9.4.2 Transperineal brachytherapy

Transperineal brachytherapy is a safe and efficient technique, which generally requires less than 2 days of hospitalization. There is a consensus on the following eligibility criteria: stage cT1b- T2a N0, M0, a Gleason score $\leq$ 6 assessed on a sufficient number of random biopsies, an initial PSA level of $\leq$ 10 ng/mL, $\leq$ 50% of biopsy cores involved with cancer and a prostate volume of < 50 cm^3 and a good International Prostatic Symptom Score (IPSS) (21). Patients with low-risk CaP are the most suitable candidates for low-dose rate (LDR) brachytherapy.

In 1983, Holm et al. described the transperineal method with endorectal sonography in which the patient is positioned in a dorsal decubitus gynaecological position (22). Implantation is undertaken under general anaesthesia or spinal block and requires a learning curve from 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.

Results of permanent implants have been reported from different institutions with a median follow-up ranging between 36 and 120 months (23). Recurrence-free survival after 5 and 10 years was reported to range from 71% to 93% and from 65% to 85%, respectively (24-30). A significant correlation has been shown between the implanted dose and recurrence rates (31). Patients receiving a D90 of > 140 Gy demonstrated a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at 4 years than patients receiving less than

140 Gy (92% vs 68%). There is no benefit from adding neoadjuvant or adjuvant androgen deprivation to LDR brachytherapy (23). Most patients experience acute urinary symptoms shortly after implantation, such as urinary retention (1.5–22%), post-implant TURP (up to 8.7%), and incontinence (0-19%). 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 the patients after 3 to 5 years. In a recent retrospective analysis of 5,621 men having undergone LDR brachytherapy (32), 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 granule 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 zone', but patients with a Gleason score of 4+3 show no difference in outcome (33).

In cases of intermediate or high-risk localized CaP, the combination with external irradiation (34) or neoadjuvant hormonal treatment (35) may be considered, but the potential positive impact of these treatments needs to be assessed with randomized trials. 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 to 20 Gy in two to four fractions combined with fractionated external radiotherapy of 45 Gy (36). Recent data suggest an equivalent outcome in terms of biochemical disease-free survival as compared to high-dose external beam radiation therapy (HD EBRT) (37). In a retrospective analysis of modern series (38,39) biochemical disease-free survival rates of 85.8%, 80.3% and 67.8% in men with low-, intermediate- and high-risk CaP, respectively, are reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar between HD EBRT and HDR brachytherapy in terms of diarrhoea and insomnia (40). However, the frequency of erectile dysfunction is significantly increased with HDR brachytherapy (86% vs 34%).

For T1-2 N0 M0, the 5-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 including 2,991 patients diagnosed with T1-2 consecutive localized CaP treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Centre with a minimum 1-year follow-up (37).

9.5 Late toxicity

Patients have to be informed about the potential late genitourinary or intestinal 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 randomized trial 22863 (1987-1995) (41), 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 $\geq$ 2 urinary or intestinal complications or leg oedema, of which 72 had grade 2 (moderate) toxicity, 10 had grade 3 (severe) toxicity, and 4 died due to grade 4 (fatal) toxicity. Although 4 (1%) late treatment-related deaths occurred, long-term toxicity was limited, with less than 5% grade 3 or 4 late complications being reported (Table 9). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT or IMRT. Radiotherapy affects erectile function to a lesser degree than surgery according to retrospective surveys of patients (2). A recent meta-analysis has shown that the 1-year rate of probability for maintaining erectile function was 0.76 after brachytherapy, 0.60 after brachytherapy 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 2 years of follow-up were selected (i.e. excluding brachytherapy), the rates became 0.60, 0.52, 0.25, 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches (42).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (43,44). In a retrospective evaluation of 30,552 and 55,263 men having undergone either EBRT or radical prostatectomy, the risk to be diagnosed with rectal cancer increased 1.7-fold as compared to the surgery group (43). Another analysis (44) showed that the relative risk of developing bladder cancer increased by 2.34-fold compared to a healthy control population.

Table 9: 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**	**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**	**31 (8.2)**
Chronic diarrhoea	**14 (3.7)**	**0**	**0**	**14 (3.7)**
Small bowel obstruction	**1 (0.2)**	**1 (0.2)**	**0**	**2 (0.5)**
Overall GI Toxicity	36 (9.5)	1 (0.2)	0	37 (9.8)
Leg Oedema	**6 (1.5)**	**0**	**0**	**6 (1.5)**
*Overall Toxicity**	*72 (19)*	*10 (2.7)*	*4 (1)*	*86 (22.8)*

** Overall toxicity included GU and GI toxicity and leg oedema. As most patients had more than one type of toxicity, the overall toxicity do 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 GU toxicity (stated above) and only one patient with grade 2 GI toxicity.

9.6 Immediate postoperative external irradiation for pathological tumour stage T3 N0 M0

Extracapsular invasion (pT3) is burdened with a risk of local recurrence, which can be as high as 30% (45). 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 ($p < 0.001$) (46).

Only one prospective randomized trial has assessed the role of immediate postoperative radiotherapy; EORTC study 22911 compared immediate postoperative radiotherapy (60 Gy) to radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 after retropubic radical prostatectomy. Immediate postoperative radiotherapy proved to be well tolerated with a risk of grade 3-4 urinary toxicity of under 3.5% (47), without significant differences regarding the rate of incontinence and/or stricture of anastomosis (48). The study concludes that immediate postoperative radiotherapy after surgery significantly improves 5-year clinical or biological survival: 72.2% vs 51.8% ($p < 0.0001$) (49). However, it has not been demonstrated that immediate radiation therapy improves metastasis-free survival and CSS in this cohort of patients. Most suitable candidates for immediate radiation therapy may be those with multifocal positive surgical margins and a Gleason score > 7.

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 1 month after surgery, the following may be recommended:

- Immediate radiotherapy upon recovery of urinary function; or
- Clinical and biological monitoring followed by salvage radiotherapy, when the PSA exceeds 0.5 ng/mL (50); 1.0 ng/mL seems to be a breakpoint, above which the likelihood of local control is significantly reduced (51).

9.7 Locally advanced CaP: T3-4 N0, M0, T1-4 N1 M0

The incidence of locally advanced CaP declined as a result of individual or mass screening. Pelvic lymph node irradiation is optional for N0 patients, due to the likelihood of infraclinical disease and N1 patients (inter-iliac nodes). However, the results of radiotherapy alone are very poor (52). Because of the hormonal dependence of CaP (53), ADT has therefore been combined with external irradiation with the aims of:

- Reducing the risk of distant metastases by potentially sterilizing micrometastases already present at the moment of diagnosis
- Decreasing the risk of non-sterilization and/or local recurrence as a source of secondary metastases (54) through the effect of radiation-induced apoptosis (55,56).

Numerous randomized trials have assessed the value of this combination.

9.7.1 Neoadjuvant hormonal therapy

The RTOG study 86-10 included 471 patients with stage T2-4N0-X M0. Androgen deprivation therapy was administered 2 months before irradiation and during irradiation, or in the case of relapse in the control arm. Thirty-two per cent of patients were diagnosed as T2, 70% as T3-4 and 91% as N0. The hormone treatment consisted of oral eulexine, 250 mg 3 times daily, and goserelin acetate (Zoladex), 3.6 mg every 4 weeks by subcutaneous injection. The pelvic target volume received 45 Gy and the prostatic target volume received 20-25 Gy. At 8 years, ADT was associated with an improvement in local control (42% vs 30%, $p = 0.016$), disease-free survival (33% vs 21%, $p = 0.004$) and biochemical disease-free survival (PSA < 1.5 ng/mL, 24% vs 10% ($p < 0.0001$)). In patients with Gleason score 2-6, there was a significant improvement in survival of 70% vs 52% ($p = 0.015$) (57).

9.7.2 Concomitant and 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 histologic grade and compared radiotherapy with adjuvant ADT to radiotherapy alone. Androgen deprivation therapy was allowed in cases of relapse. 82% of patients were diagnosed as T3, 10% as T4 and 89% as N0. The hormone treatment consisted of oral cyproterone acetate, 50 mg 3 times daily for 1 month, beginning 1 week before the start of radiotherapy and goserelin acetate (CPA), 3.6 mg subcutaneous every 4 weeks for 3 years, starting on the first day of radiotherapy.

The pelvic target volume received was 50 Gy and the prostatic target volume was 20 Gy. With a median follow-up of 66 months, combination therapy compared with radiotherapy alone was significantly better for both survival (78% vs 62%, $p = 0.001$) and survival without clinical relapse (78% vs 40%, $p < 0.001$) (58). The 5-year cumulative incidence of locoregional failure was 1.7% vs 16.4% in the radiotherapy alone arm ($p < 0.0001$) and survival without clinical or biological failure (nadir of 1.5 ng/mL) was 81% for the combined treatment arm vs 43% in the radiotherapy alone arm ($p < 0.001$).

9.7.3 Adjuvant hormonal therapy

The RTOG study 85-31 recruited 977 patients diagnosed with T3-4 N0-1 M0, or pT3 after radical prostatectomy. Androgen deprivation therapy was begun in the last week of irradiation and continued up to relapse (Group I) or was started at recurrence (Group II). A total of 15% of patients in Group I and 29% in Group II had undergone radical prostatectomy, while 14 % of patients in Group I and 26% in Group II were pN1. Goserelin acetate, 3.6 mg subcutaneous, was administered every 4 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 7.3 years, a statistical significance was reached for 5-year and 10-year OS in favour of the adjuvant hormonal therapy arm, with 76 vs 71% and 53 vs 38%, respectively (59). In this study, 95 of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had a significantly better survival rate without biochemical relapse at 5 years (PSA < 1.5 ng/mL) than those in the arm with delayed hormonal therapy ($p = 0.0001$) (60).

The National Cancer Institute (NCI) Canada study, including patients diagnosed with stage cT3-4 N0 M0, compared complete androgen blockade (CAB) (goserelin acetate 3.6 mg subcutaneous every 4 weeks and flutamide 750 mg/day) alone and in combination with radiation 65-69 Gy (61). The results are awaited.

9.7.4 Neoadjuvant, concomitant and adjuvant hormonal therapy

The RTOG 92-02 trial closed in 1995 after accruing 1,554 patients. Statistically significant improvements were observed in bNED (actuarial biochemical freedom of disease) control, distant metastatic failure, local control, and disease-free survival in patients receiving long-term ADT (LDAT) (before, during, and 2 years after radiotherapy), compared with short-term androgen deprivation (STAD) (2 months before, and during, radiotherapy). With a median follow-up of 5.8 years, the LTAD treatment arm vs STAD arm showed significant improvement in all efficacy end-points except 5-year OS, which was 80% vs 78.5 % ($p = 0.73$), respectively. In a subset of patients who were not part of the original study design, with Gleason score 8-10 tumours, the LTAD arm showed significantly better OS after 5 years than the STAD arm, with 81% vs 70.7% ($p = 0.04$) (62).

9.8 SUMMARY OF DEFINITIVE RADIATION THERAPY

1. In localized CaP 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 intermediate-risk patients benefit from dose escalation (level of evidence: 2). For patients in the high-risk group, short-term ADT prior to, and during, radiotherapy may result in increased OS (level of evidence: 2a).
2. Transperineal interstitial brachytherapy with permanent implants may be proposed to patients 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 (level of evidence: 2b).
3. Immediate postoperative external irradiation after radical prostatectomy for patients with pathological tumour stage T3 N0 M0 prolongs biochemical and clinical disease-free survival (level of evidence: 2a). An alternative option is to give radiation at the time of biochemical failure but before PSA reaches above 1-1.5 ng/mL (level of evidence: 3).
4. In locally advanced CaP, OS is improved by concomitant and adjuvant hormonal therapy (with a total duration of 2-3 years) with external irradiation (level of evidence: 1). For a subset of patients, T2c-T3 N0-x with Gleason score 2-6, short-term ADT before, and during, radiotherapy may favourably influence OS (level of evidence: 1b).

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10. LOCAL TREATMENT OF PROSTATE CANCER

10.1 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 localized CaP (1-4). Whereas HIFU is still considered to be an experimental treatment, CSAP has been recognized as a true therapeutic alternative, as recommended by the guidelines of the American Urological Association. Both techniques have been developed as minimally invasive procedures potentially resulting in the same therapeutic efficacy as the established surgical and non-surgical options associated with reduced therapy-associated morbidity.

10.2 Cryosurgery of the prostate (CSAP)

Cryosurgery uses freezing techniques to induce cell death by:

1. Dehydration resulting in protein denaturation
2. Direct rupture of cellular membranes by ice crystals
3. Vascular stasis and microthrombi resulting in stagnation of the microcirculation with consecutive ischaemia 4. Apoptosis (1-4).

Freezing of the prostate is ensured after placement of 12-15 17G cryoneedles under 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.

10.2.1 Indications for CSAP

Patients ideally suitable for CSAP are those with organ-confined CaP and those with minimal extension beyond the prostate (1-3). Prostate size should be ≤ 40mL. Prostate glands > 40mL should be hormonally downsized in order to prevent technical difficulties in placing cryoprobes under the pubic arch. 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 should be informed accordingly.

10.2.2 Results of modern cryosurgery for CaP

When comparing treatment modalities, it is important to keep in mind that in modern radical prostatectomy series of patients with clinically organ-confined CaP, the risk of dying from CaP 10 years after surgery is as low as 2.4% (5).

Therapeutic results have improved over time with improved techniques in terms of gas-driven probes and transperineal probe placement as used in third-generation cryosurgery (6-12). Objective assessment of PSA outcome cannot be performed easily because some institutions have used PSA values < 0.1 ng/mL as an indicator of therapeutic success and others have used 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 5 years is 60% and 36% for low-risk and high-risk

patients, respectively (6,7). The 7-year biochemical-free survival, however, is 92% if ASTRO criteria are used. Long et al. (6) retrospectively analyzed 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 5-year actuarial biochemical PFS 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, a recent meta-analysis of 566 cryosurgery-related publications found that no controlled trial was available for analysis and that neither survival data nor validated biochemical surrogate end-points were available (13). Cryosurgery showed a PFS of 36-92% (projected 1-7 years' data), depending on risk groups and 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 (6-12). A total of 80 (73%) patients remained with a PSA nadir < 0.4 ng/mL and 42/65 (76%) low-risk patients remained free from biochemical progression using the 0.4 ng/mL cut-off. A longer follow-up was reported by Bahn et al. (9), analyzing the therapeutic results of 590 patients undergoing CSAP for clinically localized and locally advanced CaP. Using a PSA cut-off level of < 0.5 ng/mL, the 7-year biochemical-free survivals for low-, medium- and high-risk groups were 61%, 68% and 61%, respectively.

Nerve-sparing cryosurgery, as reported recently (14), must still be considered an experimental therapeutic option. Nerve-sparing surgery was performed in nine patients with unilateral CaP confirmed on repeated biopsies, with CSAP performed on the side of the positive biopsy while the negative biopsy side was spared from freezing.

10.2.3 Complications of CSAP for primary treatment of CaP

Erectile dysfunction occurs in about 80% of patients and remains a consistent complication of the CSAP procedure, independent of the system generation used. The complication rates described with third-generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% (6-12). The development of fistula is usually rare with < 0.2% in modern series. About 5% of all patients require TURP for subvesical obstruction.

Quality of life and sexuality following CSAP have been investigated in a clinical phase II trial recruiting 75 men (15). 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 36-month data to 12-month data. With regard to sexuality, 37% of men were able to have intercourse at 3 years after CSAP.

10.2.4 Summary of CSAP

- Patients with low-risk CaP (PSA < 10 ng/mL, ≤ T2a, Gleason score ≤ 6) or intermediate-risk CaP (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 5-year biochemical PFS rates are inferior to those achieved by radical prostatectomy in low-risk patients. Patients must be informed accordingly

10.3 High-intensity focused ultrasound (HIFU) of the prostate

High-intensity focused ultrasound consists of focused ultrasound waves emitted from a transducer inducing tissue damage by mechanical and thermal effects as well as by cavitation (16). The goal of HIFU is to destroy malignant tissues through coagulative necrosis by heating the tissues above 65°C. HIFU is performed under general or spinal anaesthesia with the patient in the lateral position; the procedure is time-consuming with about 10 g prostate tissue treated in 1 hour. In a recent review, 150 HIFU-related publications were evaluated with regard to various oncological and functional outcome parameters (13). No controlled trial was available for analysis and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy.

10.3.1 Results of HIFU in CaP

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.

Results of HIFU are limited with the outcome data of less than 1,000 CaP cases published in the literature. According to a recent review paper (13), HIFU showed a PFS (based on prostate-specific antigen +/- biopsy data) of 63-87% (projected 3- to 5-year data). However, 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 CaP were treated with HIFU and their outcome data were analyzed after a mean follow-up of (27 (12-121) months (17). The projected 5-year biochemical disease-free survival was 66%, with only 57% of patients exhibiting a

pre-treatment PSA value of 4-10 ng/mL. Incontinence and bladder neck stricture decreased over time from 28% and 31% to 9% and 6%, respectively. In one of the studies (18), a significant decrease in pre-treatment PSA serum levels from 12 ng/mL to 2.4 ng/mL was observed. However, 50% of the 14 patients demonstrated positive prostate biopsies during follow-up. In another study (19), a complete response rate defined by PSA < 4 ng/mL and six negative biopsies was achieved in 56% of patients.

Summarizing the efficacy results of a European multicentre study comprising the data of 559 patients with mainly low- and intermediate-risk CaP, Thuroff et al. (19) reported a negative biopsy rate of 87.2% in 288 men with a follow-up of at least 6 months. The PSA nadir after 6 months follow-up was determined in 212 patients, with the lowest level being 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 146 patients undergoing HIFU with a mean follow-up of 22.5 months (20). The mean PSA level at initiation of therapy was 7.6 ng/mL, while the PSA nadir achieved after 3 months was 0.07 ng/mL. However, after 22 months, the median PSA level was 0.15 ng/mL. Of 137 men available for analysis, 93.4% demonstrated a negative control biopsy. The PSA nadir appears to be strongly associated with treatment failure ($p < 0.001$) (21). Patients with a PSA nadir of 0.0-0.2 ng/mL have a treatment failure rate of only 11%, compared to 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.

10.3.2 Complications of HIFU

Urinary retention appears to be one of commonest side-effects of HIFU, developing in basically all patients, with the mean interval of catheterization via a suprapubic tube varying between 12 and 35 days (16-18). Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common and sometimes even performed at the time of HIFU. Postoperative impotence will occur in approximately 55-70% of patients.

10.4 Radiofrequency interstitial tumour ablation (RITA)

RITA is a recently developed minimally invasive therapeutic option. It delivers radiofrequency energy via a needle electrode placed inside the prostate, resulting in coagulative necrosis by heating the tissue up to 100°C. So far, clinical application 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 CaP.

10.5 SUMMARY OF EXPERIMENTAL THERAPEUTIC OPTIONS TO TREAT CLINICALLY LOCALIZED CAP

1. CSAP has evolved from an investigational therapy to a possible alternative treatment method for CaP in patients unfit for surgery or in those with a life expectancy < 10 years (grade C recommendation)
2. All other minimally invasive treatment options, such as HIFU, RITA, microwaves and electrosurgery, 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 CaP (grade C recommendation).

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11. HORMONAL THERAPY

11.1 Introduction

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

Since their pivotal studies, androgen-suppressing strategies have become the mainstay for the management of advanced CaP. In recent years, however, there has been an evolution towards increasing hormonal treatment of 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.

11.2 Basics of hormonal control of the prostate

Prostate cells are physiologically dependent on androgens to stimulate growth, function and proliferation. Testosterone, although not tumourigenic, 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) derived from adrenal biosynthesis.

Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. The hypothalamic luteinizing hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Luteinizing hormone stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cells, testosterone is converted by the enzyme 5-alpha-reductase into 5-alpha-dihydrotestosterone (DHT), which is an androgenic stimulant approximately 10 times more powerful than the parent molecule (5). Circulating testosterone is peripherally aromatized 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).

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

11.3.1 Testosterone-lowering therapy (castration)

11.3.1.1 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, though a very low level of testosterone (known as the 'castration level') persists. Bilateral orchiectomy, either by means of total or subcapsular (i.e. with preservation of tunica albuginea and epididymis) technique, is a simple and virtually complication-free surgical procedure, which can easily be performed under local anaesthesia (6).

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 recent years, a decline in the utilization of bilateral orchiectomy can be witnessed which can be attributed to effects of stage migration towards earlier disease and the introduction of equally effective pharmacological modalities of castration (7).

11.3.1.2 Oestrogens

The mechanism of action is multifold: down-regulation of LHRH secretion, androgen inactivation, direct suppression of Leydig cell function and direct cytotoxicity to the prostate epithelium (only in-vitro evidence) (8).

The most commonly used oestrogen is diethylstilboestrol (DES). In early studies by the Veterans Administration Co-operative Urological Research Group (VACURG) (9), oral DES at a dosage of 5 mg/day was tested, but 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 (10) 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 less cardiovascular adverse events than the 5 mg dosage, the side-effects were still significantly increased compared to castration. Due to these concerns and the advent of LHRH agonists and antiandrogens, the use of DES had fallen out of favour until recently.

Renewed interest in oestrogens can be ascribed to three main reasons:

- Firstly, as a response to the number of deleterious side-effects and high costs 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 (11) (level of evidence: 3).
- Secondly, oestrogenic compounds (DES, DES-diphosphate, and the herbal supplement, PC SPES) have been shown to induce PSA-response rates as high as 86% in phase II trials with patients diagnosed with hormone-refractory prostate cancer (HRPC).
- Thirdly, a new oestrogen receptor-beta (ER-b), possibly involved in prostate tumourigenesis, has been discovered (8).

Two different strategies have been used to try to neutralize the cardiotoxicity, which is the main drawback of oestrogen therapy. These strategies use the parenteral route of administration, which avoids hepatic first-pass metabolism, and the addition of cardiovascular protecting agents. The final analysis of the Scandinavian Prostatic Cancer Group Study 5 (a prospective randomized trial of more than 900 men with metastatic CaP that compared a parenteral oestrogen (polyestradiol phosphate) vs CAB [orchiectomy or LHRH agonist plus flutamide]) showed neither a significant difference in disease-specific and OS between the treatment arms nor a significant increase in cardiovascular mortality in the oestrogen arm, although the occurrence of non-fatal cardiovascular adverse events was considerably higher in this group (12). On the other hand, three recent, though small, phase II trials of patients with advanced CaP or HRPC evaluated the combination of DES, 1 or 3 mg/day, with either low-dose (1 mg/day) warfarin sodium or low-dose (75-100 mg/day) aspirin in the prevention of cardiovascular toxicity and found a persistent rate of thromboembolic complications (13-15).

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 (16) (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.

11.3.1.3 Luteinizing hormone-releasing hormone (LHRH) agonists

Long-acting LHRH agonists (buserelin, goserelin, leuprorelin and triptorelin) have been used in advanced CaP for more than 15 years and are currently the predominant forms of ADT (3,17).

They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2- or 3-month 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 approximately within 2 or 3 days after the first injection and lasts through approximately the first week of therapy (18). 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 2 to 4 weeks (19,20). However, approximately 10% of patients treated with LHRH agonist fail to achieve castration levels (21).

In a recent meta-analysis evaluating single-therapy ADT for advanced CaP, LHRH agonists have shown comparable efficacy to orchiectomy and DES (16) (level of evidence: 1a). In addition, although only based on an indirect comparison, all seemed equally effective (16) (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 (22) 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 antiandrogen definitely decreases the incidence of clinical relapse, but it does not completely remove the possibility of their occurrence. Based on pharmacokinetic considerations, it is recommended that administration of antiandrogens should be started on the same day as the depot injection and treatment should be continued for a 2-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.

11.3.1.4 LHRH antagonists

In contrast to the agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pitutitary 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 randomized multicentre trials comparing the LHRH antagonist abarelix with the LHRH agonist leuprorelin acetate (23) and with CAB (24) in patients with metastatic or recurrent CaP 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 United States Food and Drug Administration, but its use is restricted to those patients with metastatic and symptomatic CaP for whom no other treatment option is available (25).

11.3.2 Antiandrogens

Antiandrogens compete with testosterone and DHT for binding sites on their receptors in the prostate cell nucleus, thus promoting apoptosis and inhibiting CaP growth (26).

These orally administered compounds are classified according to their chemical structure as steroidal (e.g. CPA, megestrol acetate and medroxyprogesterone acetate) and non-steroidal or pure (e.g. nilutamide, flutamide and bicalutamide). Both classes act as competitors of androgens at the receptor level, but while this is the sole action of non-steroidal antiandrogens, steroidal antiandrogens additionally have progestational properties with central inhibition of the pituitary gland. As a consequence, non-steroidal antiandrogens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

11.3.2.1 Steroidal antiandrogens

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 antiandrogens 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 was the first antiandrogen to be licensed and is the most widely used. There is only one randomized trial (27) comparing CPA to 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 OS than goserelin only: adjusting for baseline characteristics did not account for this difference.

Two other studies on CPA monotherapy were performed, but one did not report survival data (28) and the other used non-standard treatment combination (DES and medroxyprogesterone acetate [29]). It is therefore difficult to draw any definite conclusions from these data about the relative efficacy of CPA and castration. Since 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 fractional doses of 100 mg each (30).

The only comparative study on antiandrogens as monotherapy was recently published by the European Organization for Research and Treatment of Cancer (EORTC) Protocol 30892 (a randomized trial of 310 patients comparing CPA vs flutamide in metastatic CaP), which showed no difference in CSS and OS at a median follow-up of 8.6 years, though the study was underpowered (31) (level of evidence: 1b).

Megesterol acetate and medroxyprogesterone acetate

Very limited information is available on these two compounds.

Early studies with megestrol acetate demonstrated symptomatic and partial beneficial clinical response both in previously untreated metastatic CaP (32-34) and, to a lesser extent, in HRPC (35). No apparent dose response correlation was shown to exist in a recent trial (36). 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 randomized trial evaluating medroxyprogesterone acetate as primary therapy in advanced (M0-1) CaP is the EORTC 30761 study mentioned above (28), 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.

11.3.2.2 Non-steroidal antiandrogens

Non-steroidal antiandrogens 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 (37).

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 (38).

Nilutamide

There are no comparative trials on nilutamide monotherapy with castration or with other antiandrogens (39).

Only one non-comparative study has been carried out, including 26 patients with M1 CaP 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 PFS time was 9 months and the median OS was 23 months (40).

One large randomized controlled trial of 457 patients with M1, which compared orchiectomy plus nilutamide, 300 mg/day, vs orchiectomy plus placebo, showed a significant benefit in CSS and OS for the combined therapy (41).

Recently nilutamide has been tested as a second-line hormonal therapy in HRPC with encouraging results (42,43). Non-pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, hepatotoxicity and interstitial pneumonitis. Nilutamide is not licensed for monotherapy.

Flutamide

Flutamide was the first non-steroidal antiandrogen available for clinical use and has been studied as monotherapy for over 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 5-6 hours, so it has to be administered three times daily to maintain therapeutic serum levels; the recommended daily dosage is 750 mg (30).

Early phase II trials demonstrated flutamide to be effective in the treatment of advanced CaP, 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 (44-47). This rate has not been confirmed in the above mentioned EORTC trial 30892 (31), in which as few as 20% of men treated with flutamide maintained sexual activity for up to 7 years.

Although several phase III studies have been conducted, 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 randomized trials comparing flutamide monotherapy to standard therapy (orchiectomy [48] and CAB [49]) for advanced CaP have reported survival data; both showed no significant difference in OS for flutamide or castration. Results are eagerly awaited from an ongoing Swedish study in which 700 patients with M1 CaP have been randomized to flutamide 250 mg three times daily or CAB (37).

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 the dosage 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) (50). 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 (51). 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 to medical or surgical castration in two large prospective randomized trials with identical study design, including a total of 1,435 patients with locally advanced M0 or M1 CaP (51). A pooled analysis showed:

- In M1 patients, an improvement in OS with castration, although the difference in median survival between the groups was only 6 weeks (52); a further post-hoc analysis showed a survival benefit only for patients with higher PSA level (> 400 ng/mL) at study entry (53).
- In M0 patients, no significant difference was noted in OS (54,55).

In two smaller randomized trials, high-dose bicalutamide was compared to CAB. In the first trial (251 patients with predominantly M1 stage), no difference in OS was apparent (56). In the second trial (220 patients with M0 and M1 stage), there was no difference in OS for well- or moderately well-differentiated tumours (57) (level of evidence: 1b), but both studies were underpowered.

As for the adjuvant setting, the ongoing Early Prostate Cancer Programme (a study comprising three different clinical trials of similar design and including 8,113 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 WW) in localized or locally advanced CaP. The first combined analysis of the programme showed that, after a median follow-up of 3 years, adjuvant bicalutamide provided a reduction of 42% in the risk of objective disease progression compared to standard care alone (58). 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 localized disease given bicalutamide appeared to have a reduced survival compared to those given placebo (59). However, results obtained after a median follow-up of 7.4 years showed there was no benefit to PFS by adding bicalutamide to standard care in localized CaP, and identified a trend (HR 1.16, 95% CI 0.99-1.37, p = 0.07) towards decreased survival in patients otherwise undergoing WW. However, in locally advanced disease, bicalutamide significantly improved PFS irrespective of standard care. 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 CaP-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.

In conclusion, high-dose bicalutamide has emerged as an alternative to castration for patients with locally advanced (M0) and in highly selected, well-informed cases of M1 CaP, but should be avoided in patients with localized CaP.

11.3.3 Combination therapies

11.3.3.1 Complete androgen blockade (CAB)

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 antiandrogen 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 5 years, CAB provides a small survival advantage (less than 5%) when compared to monotherapy (60-64, level of evidence: 1a), even if some the largest trials included are methodologically flawed (65). 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 antiandrogens and to appear only after 5 years of follow-up. Gastrointestinal, ophthalmological, and hematologic side-effects are worse on combined androgen blockade. LHRH analogues and non-steroidal antiandrogens have the highest estimated quality-adjusted survival but have an incremental cost over US$1 million per quality-adjusted live-year over orchiectomy alone.

11.3.3.2 Minimal androgen blockade (or peripheral androgen blockade)

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

In several phase II trials (66-70), 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 CaP. Notwithstanding the small sample and short follow-up, nearly all patients experienced a substantial decline in PSA (by up to 96% compared to 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 CaP-free survival (median: 48.6 months) and overall survival rate (65% at 5 years). It was concluded that combination therapy can induce an overall period of hormone-responsive disease exceeding 4 years (71). In all these trials, sexual function was reported to be preserved in most (55-86%) men.

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, the treatment is still regarded as investigational.

11.3.3.3 Intermittent vs continuous androgen deprivation therapy (ADT)

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 characterized 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 (72). 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, cyclic 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, randomized controlled trials are still underway and data on survival end-points and QoL are not mature (73). Recent clinical phase III trials have demonstrated equal efficacy of intermittent vs continuous ADT in men with PSA progression following radical prostatectomy and in advanced metastatic CaP (74-76). The SWOG trial 9346 randomized 1,134 men with stage D2 CaP to intermittent and continuous ADT after 7 months' induction ADT with PSA reduction < 4 ng/mL. No significant differences with regard to survival were identified between treatment groups (74). 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 (75). 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.

Finally, the results of a prospective randomized multicentre trial including 68 patients with a mean follow-up of 31 months have been reported (76). In the IAD group, median cycle length was 9.5 months and median percentage of time off therapy was 59.5%. The median 3-year progression rate was significantly lower in the IAD group (7%) compared to the CAD group (38.9%), suggesting that IAD maintains the androgen-dependent state of advanced CaP at least as long as CAD.

In conclusion, IAB is at present widely offered to patients with CaP in various clinical settings, and its status should no longer be regarded as investigational.

11.3.3.4 Immediate vs deferred ADT

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

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

Bearing in mind these limitations, evidence on immediate vs deferred ADT is provided by three systematic reviews of the literature (one of which is a meta-analysis). The Agency for Health Care Policy and Research report 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 most cost-effective if initiated after patients experienced symptoms from metastatic disease (60,77). The Cochrane Library review extracted four good-quality randomized controlled trials (namely, VACURG I & II studies (9,10), the MRC trial (78) and the Eastern Cooperative Oncology Group (ECOG) 7887 study (79)), which were all conducted in the pre-PSA era and included patients with advanced CaP 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 (80).

Based on a systematic review of the literature, the recently published American Society of Clinical Oncology guidelines on the initial hormonal treatment for androgen-sensitive metastatic, recurrent or progressive CaP concluded that no recommendation can be made when to start hormonal therapy in advanced asymptomatic CaP until data from studies using modern diagnostic and biochemical tests and standardized follow-up schedules become available (81). Based on the meta-analysis, published treatment was most cost-effective when started after the onset of symptoms. Based on exploratory analysis, treatment with antiandrogen monotherapy does not lead to a survival benefit in men with localized CaP managed with non-definitive therapy.

For asymptomatic patients with locally or regionally advanced CaP who undergo radiotherapy, there is good evidence from several randomized 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 (82-85) (level of evidence: 1b).

11.4 Indications for hormonal therapy (Table 10)

Table 10: Indications for hormonal therapy

Castration		Indications
•	M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis) (level of evidence: 3)
•	M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications (78) (level of evidence: 1b)
•	N+ Immediate castration to prolong PFS and even OS	Refs. 79,82 (level of evidence: 1b) Ref. 86 (level of evidence: 3)
•	Locally advanced M0	Immediate castration to improve cancer-free survival (79) (level of evidence: 1b)
•	Locally advanced symptomatic	Ref. 87 (level of evidence: 4)
•	Locally advanced asymptomatic unfit for local definitive treatment	Ref. 88
Antiandrogens		
•	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 (89,90) (level of evidence: 1b)
•	Non-steroidal antiandrogens	Primary monotherapy as an alternative to castration in patients with locally advanced CaP (55,91,92) (level of evidence: 1b)

11.5 Contraindications for various therapies (Table 11)

Table 11: Contraindications for various therapies

	Therapy	Contraindications
•	Bilateral orchiectomy	Psychological reluctance to surgical castration
•	Oestrogens	Known cardiovascular disease
•	LHRH agonists	Patients with metastatic disease at high risk for clinical "flare up" phenomenon
•	Antiandrogens	Localized CaP as primary therapy Known hepatic dysfunction

11.6 Outcome

Outcome depends on the stage and grade of disease at diagnosis. In M1 cases, the median OS ranges between 28 and 53 months (60); only 7% of patients with metastatic cancer treated with hormonal therapy are reported to live 10 years or more (93). Survival is likely to depend on PSA level at diagnosis, Gleason score, volume of metastatic disease and presence of bony symptoms. In locally advanced M0 patients, the median OS is frequently reported exceeding 10 years (61).

11.7 Side-effects, QoL and cost of hormonal therapy

Many patients with CaP 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 antiandrogen (i.e. bicalutamide) is gaining increasing interest due to its appeal in maintaining normal (or even higher) serum testosterone levels and in showing a good tolerability profile.

11.7.1 Side-effects

The number of deleterious side-effects during long-term ADT has been well known for years (Table 12). Some of these can have a detrimental effect on QoL, especially in young men, while others may contribute to increased risk for serious health concerns associated with age.

Table 12: Side-effects of hormonal treatment*

Side-effects of therapy	Treatment/prophylaxis
Castration	
• Loss of libido	None
• Erectile dysfunction	Phosphodiesterase-5 (PDE5)-inhibitors, intracavernosal injection (ICI), vacuum device
• "Hot flashes" (55-80% of patients during androgen deprivation therapy)	Diethylstilboestrol (DES), cyproterone acetate (CPA), venlafaxine, clonidine
• Gynaecomastia and breast pain (49-80% DES 50% complete androgen blockade (CAB), 10-20% castration)	Prophylactic radiotherapy, mammectomy, tamoxifene, aromatase inhibitors
• Increase in body fat	Exercise
• Muscle wasting	Exercise
• Anaemia (severe in 13% CAB)	Erythropoietin (EPO)
• Decrease in bone mineral density (not DES)	Exercise, calcium+ vitamin D, bisphosphonates
• Cognitive decline (not DES)	None
Oestrogens	
• Cardiovascular toxicity (acute myocardial infarction, congestive heart failure, cerebrovascular accident, deep vein thrombosis, pulmonary embolism)	Parenteral administration, anticoagulants
Antiandrogens	
Steroidal	
• Pharmacological side-effects: loss of libido, erectile dysfunction, rarely gynaecomastia	
• Non-pharmacological side-effects: see individual drugs	
Non-steroidal	
• Pharmacological side-effects: gynaecomastia (49-66%), breast pain (40-72%), 'hot flashes' (9-13%)	Prophylactic radiotherapy, mammectomy, tamoxifen, aromatase inhibitors
• Non-pharmacological side-effects: see individual drugs	

11.7.2 Quality of life (QoL)

Data on QoL during hormone treatment are scant because of lack of solid evidence. The only large prospective randomized study is a double-blind placebo-controlled trial including 739 patients with M1 CaP, which compared orchiectomy plus flutamide vs orchiectomy plus placebo. The QoL was assessed in the first 6 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 (95).

A prospective non-randomized observational study, including 144 patients with locally advanced CaP 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 (96) (level of evidence: 2a).

A retrospective non-randomized study, including 431 patients with stage CaP who received orchiectomy or LHRH agonists as their primary therapy within 12 months after 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 compared with orchiectomized patients; the stage at diagnosis had no significant independent effect on health outcome. However, the study was insufficiently powered (97) (level of evidence: 2b).

A recent, small, randomized controlled trial evaluated HRQoL of patients with non-localized CaP allocated to leuprorelin, goserelin, CPA and no treatment at 1-year follow-up; both sexual and cognitive function significantly declined in men on all forms of androgen suppression, while emotional distress significantly increased in those assigned to CPA and no treatment (98) (level of evidence: 1b).

As for antiandrogen monotherapy, QoL was evaluated in the previously mentioned combined studies of bicalutamide monotherapy by means of a validated 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 (55) (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 compared with those randomized to castration (99,100). Data on QoL are also available from the early report of the study of Boccardo et al. (101) 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 randomized trial, including 103 patients with localized or locally advanced CaP who received bicalutamide 150 mg/day or medical castration, evaluated the changes in bone mineral density after 96 weeks of treatment and showed that bone mineral density is maintained with bicalutamide therapy (92) (level of evidence: 1b). The most common side-effects during non-steroidal antiandrogen monotherapy are gynaecomastia and breast pain, which are caused by an imbalance in the androgen-to-oestrogen ratio within the breast tissue; in the bicalutamide studies, these events were reported by up to 66% and 73% of patients, respectively, but they were generally well tolerated, with a low withdrawal rate from therapy (58).

11.7.3 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 CaP (i.e. bilateral orchiectomy, DES, LHRH-agonist, non-steroidal antiandrogen monotherapy, CAB with a non-steroidal antiandrogens). 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 CaP 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 (77) (level of evidence: 1a).

11.8 SUMMARY OF HORMONAL THERAPY

1. In advanced CaP, ADT delays progression, prevents potentially catastrophic complications and effectively palliates symptoms, but does not prolong survival (level of evidence: 1b)
2. In advanced CaP, all forms of castration as monotherapy (orchiectomy, LHRH and DES) have equivalent therapeutic efficacy (level of evidence: 1b)
3. Non-steroidal antiandrogen monotherapy (e.g. bicalutamide) is an effective alternative to castration in patients with locally advanced disease (level of evidence: 1b)
4. In advanced CaP, the addition of a non-steroidal antiandrogen 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 (level of evidence: 1a)
5. Intermittent and 'minimal' ADT should still be regarded as experimental therapies (level of evidence: 3)
6. In advanced CaP, immediate (given at diagnosis) androgen suppression significantly reduces disease progression and complication rate due to progression itself compared to deferred (delivered at symptomatic progression) androgen deprivation (level of evidence: 1b)
7. Bilateral orchiectomy may be the most cost-effective form of ADT, especially if initiated after occurrence of symptoms from metastatic disease (level of evidence: 3).

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12. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF CANCER OF THE PROSTATE

Stage	Treatment	Comment
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 TRUS and biopsy is advised (grade B recommendation)
	Radical prostatectomy	Optional in young patients with a long life expectancy, especially for poorly differentiated tumours (grade B recommendation)
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation (grade B recommendation)
	Hormonal	Not an option (grade A recommendation)
	Combination	Not an option (grade C recommendation)
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 (grade B recommendation)
	Radical prostatectomy	Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications (grade A recommendation)
	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) (grade B recommendation)
	Hormonal	Symptomatic patients who needs palliation of symptoms unfit for curative treatment (grade C recommendation). Antiandrogens are associated with poorer outcome in comparison with watchful waiting and are not recommended (grade A recommendation)
	Combination	Neoadjuvant hormonal therapy (NHT) + radical prostatectomy: no proven benefit (grade A recommendation) NHT + radiotherapy: better local control. No proven survival benefit (grade B recommendation). Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumours (grade A recommendation)
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumours, and a life expectancy < 10 years (grade C recommendation)
	Radical prostatectomy	Optional for selected patients with T3a and a life expectancy > 10 years (grade C recommendation)
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation > 70 Gy seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (see below) (grade A recommendation)
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25 ng/mL), unfit patients. Better than watchful waiting (grade A recommendation)
	Combination	Radiotherapy + hormonal seems better than radiotherapy alone (grade A recommendation). NHT + radical prostatectomy: no proven benefit (grade B recommendation)
N+, M0	Watchful waiting	Asymptomatic patients. Patient driven. May have worse survival (grade C recommendation)
	Radical prostatectomy	No standard option (grade C recommendation)
	Radiotherapy	No standard option (grade C recommendation)
	Hormonal	Standard therapy (grade A recommendation)
	Combination	No standard option. Patient driven (grade B recommendation)
M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy (grade B recommendation)
	Radical prostatectomy	Not an option (grade C recommendation)
	Radiotherapy	Not an option (given for cure) (grade C recommendation)
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment (grade B recommendation)
	Combination	Not an option (grade C recommendation)

13. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

13.1 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 as CSAP and HIFU, does not have a well-defined, validated PSA-cut-point to define biochemical failure but do generally follow the outlines given below.

13.2 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 the first question is therefore 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 will. 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 15 discusses treatment options after failure of primary therapy.

13.3 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 CaP 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.

13.3.1 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.

13.3.2 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). Recently, a new RTOG-ASTRO Consensus conference decided upon a new definition of radiation failure with the main aim of getting away from the backdating associated with the 1996 definition and also 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 high intensity focused ultrasound (HIFU) or cryotherapy, a variety of definitions for PSA-relapse have been used (11). Most of them are based on a cut-off of around 1 ng/mL, eventually combined with a negative post-treatment biopsy. None of these end-points have been validated against clinical progression or survival and it is thus not possible to give firm recommendations on the definition of biochemical failure as of today.

13.3.3 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 rather 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.

13.3.4 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).

13.3.5 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).

13.3.6 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 15 for a more detailed discussion).

13.3.7 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).

13.3.8 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 15).

13.4 When to follow-up?

Most patients who fail treatment for CaP 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.

13.5 GUIDELINES FOR FOLLOW-UP AFTER TREATMENT WITH CURATIVE INTENT

1. 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 (grade B recommendation).
2. After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease (grade B recommendation).
3. 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 (grade B recommendation).
4. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence (grade B recommendation).
5. 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 (grade B recommendation).
6. 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 (grade C recommendation).
7. 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 (grade B recommendation).

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14. FOLLOW-UP: AFTER HORMONAL TREATMENT

14.1 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.

14.2 Why follow-up?

The main objectives of follow-up in 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 useless examinations and an 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 the patient in case of disease progression. To date, the issue of early vs late initiation of non-hormonal treatment in HRPC has still not been resolved so that follow-up should be performed on an individual basis. Based on current knowledge, strict guidelines for follow-up procedures following hormonal therapy cannot be formulated.

14.3 How to follow-up?

14.3.1 PSA monitoring

Prostate-specific antigen is a good marker with which to follow the course of metastatic CaP. The prognostic value of PSA (prediction of the duration of response to endocrine treatment) based on either the initial pre-treatment value or the PSA decrease during the first 3-6 months Have been used to monitor prostate cancer during the last 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 utilizing the change in serum PSA level as a surrogate end-point for survival in patients with newly diagnosed metastatic CaP after hormonal treatment has been initiated. Patients with the lowest absolute value of serum PSA (< 0.2 ng/mL) also had the best survival as compared to those obtaining a value of 0.2-4 ng/mL or > 4 ng/mL (4). Similar results have been seen in other studies on locally advanced and metastatic CaP (5,6). Also for patients treated with hormonal therapy due to a rising PSA after treatments with curative intent (radical prostatectomy, radiation therapy), the same importance of the PSA-response have been documented. Patients with the best response also had the best survival (7,8).

Even if useful to determine 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 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.

14.3.2 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 antiandrogens).

The fact that haemoglobin levels will decrease by about 20% with androgen deprivation has to 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.

14.3.3 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 or hepatic ultrasound may be indicated as well as TRUS. However, these examinations are not recommended for routine use in asymptomatic patients. In hormone-refractory disease, follow-up examinations should be individualized with the aim of maintaining the patient's quality of life.

14.4 When to follow-up?

After initiation of hormonal treatment, it is recommended that patients be followed-up at 3 and 6 months.

14.4.1 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 6 months.

14.4.2 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 3-6 months. Patients on antiandrogen treatment may need closer follow-up as they might benefit from antiandrogen withdrawal at the time of disease progression.

14.4.3 Hormone-refractory patients

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

14.5 GUIDELINES FOR FOLLOW-UP AFTER HORMONAL TREATMENT

1. Patients should be evaluated at 3 and 6 months after initiating treatment. Tests should include at least serum PSA measurement, DRE and careful evaluation of symptoms in order to assess the treatment response and the side-effects of treatments given (grade B recommendation).
2. Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given (grade C recommendation).
3. In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and should include at least a disease-specific history, DRE and serum PSA determination (grade C recommendation).
4. In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3-6 months. A minimal follow-up should include a disease-specific history, DRE and serum PSA determination, frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements (grade C recommendation).
5. When disease progression occurs or if the patient does not respond to the treatment given, the follow-up needs to be individualized (grade C recommendation).
6. Routine imaging in stable patients is not recommended (grade B recommendation).

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15. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENT WITH CURATIVE INTENT

15.1 Background

Primary curative procedures, such as radical prostatectomy and radiotherapy, are well-established therapeutic options in the management of localized CaP. 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 and up to 27-53% of all patients undergoing radiation therapy or radical prostatectomy will develop local or distant recurrences within 10 years after initial therapy and 16-35% of patients will receive second-line treatment within 5 years of initial therapy (1-6).

15.2 Definitions

15.2.1 Definition of treatment failure

In previous years, treatment failure was defined as recurrence on DRE or the development of metastatic disease. Currently, treatment failure is defined as a rising PSA level based on a study of Pound et al. (7) who demonstrated that no patient followed for more than 5 years developed any recurrence without a concomitant PSA rise.

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 PSA $\geq$ 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 2,782 men having undergone radical prostatectomy for clinically localized CaP, 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 0.2, 0.3, and 0.4 ng/mL, respectively. These data indicate that only half of patients with a PSA of 0.2 ng/mL will further progress and may initially be managed by surveillance. However, a cut-off of 0.2 ng/mL will still be appropriate for the definition of progression with clinical relevance necessitating salvage treatment. Based on the data given by the papers listed it might still be an option to monitor patients exceeding 0.2 ng/mL for further PSA increase and to initiate salvage radiation therapy below a PSA level of 1.0 ng/mL. Following radiation therapy, a reasonable definition of biochemical relapse has been three consecutive increases, according to the recommendation of the ASTRO (10). The new definition indicates a relapse if the PSA increase is $\geq$ 2 ng/mL higher than the PSA nadir value independent of the serum concentration of the nadir (11).

15.2.2 Definition of recurrence

- Following radical prostatectomy, PSA values > 0.4 ng/mL represent recurrent cancer.
- Following radiation therapy, a PSA value 2 ng/mL above the nadir after radiation therapy represent recurrent cancer.

15.3 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 the patients having undergone radical retropubic prostatectomy will have local disease and the remainder will have either distant disease alone, or distant and local disease (10).

Important parameters to help differentiate between local or distant relapse (Table 13) include: timing of PSA increase after surgery, PSA velocity, PSA doubling time (PSADT), pathohistological stage and Gleason

score of the prostatectomy specimen. PSA elevations developing within the first 2 years following surgery are associated with distant recurrences (12). It was 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/year was observed in 94% of patients with local recurrence, whereas 56% of patients with distant metastases demonstrated a PSA velocity of > 0.75 ng/mL/year.

Table 13: 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 radiation therapy, any continuously rising PSA following a nadir after radiation is an indicator for local recurrence, systemic metastatic spread or a combination of both (15-18). 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 after 18 months or longer following initial radiotherapy, associated with a PSA rise, and no evidence of metastatic spread documented by CT/MRI and bone scintigraphy.

15.3.1 Definition of local and systemic failure

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

15.4 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 it has been shown by Lange et al. (14) 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. (19), it was shown that only 4 out of 72 patients (5.5%) with a PSA recurrence following radical prostatectomy had an abnormal DRE.

Traditionally, bone scans and abdominal CT scans have been applied to evaluate PSA elevations following primary treatment. Both imaging studies, however, are characterized by a low sensitivity and specificity and might be safely omitted in the routine work-up of relapsing patients. Recently, Cher et al. (20) studied 144 bone scans in 93 patients with PSA recurrence after radical retropubic prostatectomy. 122 patients

had undergone radical prostatectomy without any hormonal treatment whereas 22 patients received either neoadjuvant or adjuvant 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 androgen deprivation, whereas the lowest PSA value was 15.47 ng/mL in patients receiving hormonal therapy. The probability of a positive bone scan remains $\leq$ 5% until serum PSA reaches at least 40 ng/mL. Similar data have been achieved by other groups (21,22) demonstrating that patients with a true positive bone scan had an average PSA level of > 60 ng/mL and a PSA velocity of 22 ng/mL/year. 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 to patients after radiation therapy, as demonstrated by Johnstone et al. (23) with 5% and 30% of the bone scans being positive, respectively.

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 unless the PSA velocity is more than 20 ng/mL/year.

Endorectal coil imaging has been described as a useful technique to detect local recurrences after radical prostatectomy (24). 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 CaP, there are only a few, but promising, data published on the clinical efficacy of PET in detecting local recurrences after radical prostatectomy (25,26). However, one has to consider that the uptake of 11C-choline is not specific for CaP but might also be due to inflammatory intraprostatic lesions. In a series of 31 patients with biochemical progression after radical prostatectomy, (11C)Acetate-PET demonstrated a high sensitivity and specificity for the detection of local recurrences if the PSA serum level was > 1 ng/mL. In another recent series of 43 patients with newly diagnosed prostate cancer there was a significant correlation between the 11C-choline uptake and the intraprostatic location of CaP as analysed in radical prostatectomy specimens (26). Similar results have been reported for the detection of locally recurrent CaP after radiation therapy (26). However, sensitivity with regard to extraprostatic extension was significantly for 11C-PET when compared to magnetic resonance imaging. The sensitivity and specificity with regard to the detection of lymph node metastases is less reliable and therefore, the routine use of 11C-PET cannot be recommended, especially not in 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 penetide 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 (27-30). Independent of the PSA serum concentration, the capromab pendetide scan shows a diagnostic yield of 60% to 80% and may help to stratify therapy according to the location of positive sites. In a recent study (30), 255 patients with PSA-only recurrence < 4.0 ng/mL after radical prostatectomy were investigated and capromab pendetide uptake was seen in 72% throughout the range of postoperative 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 a targeted therapy due to the differentiation of local vs systemic relapse.

It has been common practice to perform TRUS-guided biopsies of the prostatic fossa, the anastomosis or the prostate gland to exclude local recurrence after radical retropubic prostatectomy or radiation therapy. However, according to available studies, routine biopsy of the vesicourethral anastomosis appears not to be justified based on a verification rate of only 54% (31-35). Only in the presence of a palpable lesion or a hypoechoic lesion on transrectal ultrasound, 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 (31-35). 28% and 70% of the biopsies were positive if the PSA level was 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 as compared to 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 (16). 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 (36-38). It is a general recommendation to wait about 18 months and 3 months following radiation therapy or seeds and cryotherapy or HIFU, respectively.

15.5 Diagnostic procedures in patients with PSA relapse

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

15.6 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), combination of antiandrogens 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.

15.6.1 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 which might be helpful to stratify between observation, radiation and hormonal therapy.

As confirmed by various studies the pre-radiation PSA level appears to be of critical importance in order to obtain optimal treatment results (39-47). Applying a pre-radiation cut-off of ≤ 2.5 ng/mL, Wu et al. (39) and Schild et al. (40) reported disease-free survival rates of 53% and 76% as compared to 8% and 26%, respectively, for patients with PSA serum levels > 2.5 ng/mL. Forman et al. (41) demonstrated a disease-free survival rate of 83% vs 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. (42) even reported a PFS rate 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 (16).

These data of early salvage radiation therapy are corroborated by a recent paper (48) demonstrating a significant difference with regard to the 5-year biochemical-free and OS rates in patients being treated for PSA recurrence only or for palpable locally recurrent cancer. The 5-year biochemical-free and overall survival rates were 69% and 96% compared to 45% and 78%, respectively, in the group with palpable disease. However, data of prospective randomized trials are still lacking and all studies being performed lack long-term follow-up so that the impact on survival is unknown.

15.6.2 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 (43-47). The impact of early ADT on long-term survival, however, is still unknown. In a retrospective observational multicentre study including 1,352 patients with PSA recurrence following radical prostatectomy (49,50), early ADT resulted in a significant reduction of the development of clinical metastases compared to delayed ADT. There was however no significant effect on long-term survival. These recommendations are corroborated by a recent study (51) demonstrating that none of the patients with a Gleason score 8, pT3b or pTxpN1 CaP 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 randomized trials. There are only very few studies analyzing the clinical utility of early androgen deprivation in locally advanced (M0) and metastatic PCA (51,52). It is believed that for the M0 category of the patients with pTxN1 disease having undergone radical prostatectomy reflecting PSA-only recurrences, hormonal therapy would appear to be beneficial for some patients with a high probability of occult systemic metastases. There is some evidence that CAB has a pronounced survival benefit in patients with minimal metastatic disease so that patients with PSA-only recurrences might have a similar improved survival with combined androgen deprivation (53,54). 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 antiandrogens 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 CaP, the incidence of hot flushes, loss of libido and impotence was significantly lower than expected for LHRH-agonists and CAB (55). Furthermore, the risk of objective progression of the disease was significantly reduced in patients receiving bicalutamide 150 mg (56). Antiandrogens may represent a viable alternative to other modes of androgen deprivation for the management of PSA-only recurrences especially in young and otherwise healthy men.

Non-traditional ways of using hormonal therapy for PSA-only recurrence include IAD and oral therapies combining antiandrogens with 5-α-reductase inhibitors (57-64). In the setting of PSA-only recurrences, however, no prospective randomized trials and no clinical studies with sufficient data on long-term efficacy are available to justify a routine clinical application of IAD despite potential benefits. Summarizing the series in which PSA-only recurrences were treated by IAD (57-61), PSA threshold levels at study entry varied significantly as did the PSA level at discontinuation of hormonal therapy. Only the study by Tunn et al (61) involving 150 patients had an appropriate study design from which to draw important clinical conclusions. Patients were started on IAD for 9 months when the postprostatectomy 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 DHT and blocking the intracytoplasmic DHT receptor (62-64). In the latest report (64), including 73 patients, the application of finasteride (10 mg/day) and low-dose flutamide (250 mg/day) resulted in a mean PSA nadir of 1.35 ng/mL within 6 months. However, only 62% of the patients 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 randomized phase III trials using modern antiandrogens with fewer gastrointestinal and hepatic side-effects are mandatory.

15.6.3 Observation

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

15.6.4 MANAGEMENT OF PSA RELAPSE AFTER RADICAL PROSTATECTOMY

1. Local recurrences are best treated by salvage radiation therapy with 64-66 Gy at a PSA serum level $\leq$ 1.5 ng/mL (grade B recommendation)
2. Expectant management is an option for patients with presumed local recurrence unfit for, or unwilling to undergo, radiation therapy (grade B recommendation)
3. PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases (grade B recommendation)
4. LHRH analogues/orchiectomy or bicalutamide at 150 mg/day can both be used when there is indication for hormonal therapy (grade A recommendation).

15.7 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 2,336 patients with CaP, Grossfeld et al. (65) demonstrated that 92% of patients initially irradiated received ADT for secondary treatment of PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 years. Therapeutic options in these patients are ADT or local procedures, such as salvage radical prostatectomy, cryotherapy and interstitial radiation therapy (66-71). Salvage radical retropubic prostatectomy, however, has not gained widespread acceptance due to its associated morbidity, namely incontinence, local recurrences and rectal injuries. However, in well-selected patients, salvage radical retropubic prostatectomy might result in long-term disease-free survival. One has to consider that most series reporting on salvage radical prostatectomy included patients who were treated in the pre-PSA era without modern radiotherapeutic techniques and local recurrences were usually detected at a late stage. Therefore, complications associated with the procedure were quite high with up to 65% of the patients suffering from treatment-related morbidities. Up to 60% of the patients planned for salvage radical prostatectomy 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).

Recent reports analyzing patients being operated upon in the last decade have described far more optimistic outcomes after salvage radical prostatectomy. In the series of Gheiler et al. (71), 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 3-year disease-specific survival was 68% and 26%, respectively. In the series reported by Garzotto and Wajsman (70), 24 patients underwent radical cystoprostatectomy or radical prostatectomy with neoadjuvant ADT. Neoadjuvant ADT was associated with a lower rate of positive surgical margins (21%) as compared to patients in whom androgen deprivation failed and who exhibited a positive surgical margin rate of 80%. The authors demonstrated that the disease-specific survival strongly correlated with the surgical margin status. At a mean follow-up of 5 years the disease-specific survival rate was 95% and 44% for those with negative and positive surgical margins, respectively. Vaidya and Soloway (72) demonstrated a low complications rate, good postoperative continence and only one biochemical recurrence 36 months after salvage radical prostatectomy. Similar data have been achieved by Stephenson et al. (73), who reported on 100 consecutive patients undergoing radical salvage prostatectomy associated with a very low rate of perioperative complications. The 5-year PFS 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 OS rates are in the range of 70% to 75% and 60% to 66% 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% as compared to 40-60% in patients with locally advanced CaP (74).

In general, salvage radical retropubic prostatectomy should only be considered in patients with a low comorbidity, a life expectancy of at least 10 years, an organ-confined CaP $\leq$ T2, Gleason grade < 7, and presurgical PSA < 10 ng/mL. In all other patients, accurate presurgical 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.

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

Salvage cryosurgery has been proposed as an alternative to salvage prostatectomy with the potential advantage of less morbidity and equal efficacy. There are only very few studies available and the results are not very promising. Pfisters et al. (75) report on 150 patients having 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 basically all patients, with the main complications being urinary incontinence (73%), obstructive symptoms (67%), impotence (72%) and severe perineal pain (8%). After a 1-year follow-up, incontinence resolved in the majority of patients with a persistent significant incontinence in 22% of the patients (53%). According to a recent study by Cespedes et al. (75), the risk for urinary incontinence and impotence at least 12 months following CSAP are as high as 28% and 90%, respectively. In addition, 8% to 40% of the patients complained about persistent rectal pain and an additional 4% of men have undergone surgical procedures for the management of treatment-associated complications.

15.7.2 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 (77-80).

Grado et al. (79) treated 49 patients with transperineal TRUS-guided brachytherapy and reported 3- and 5-year disease-free survival rates of 48% and 43%, respectively. Beyer et al. (80) reported a 5-year biochemical freedom from relapse in 34% to 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% having the need for a palliative TURP due to acute urinary retention and another 4% and 2% suffering from rectal ulcers and permanent colostomy.

15.7.3 Salvage HIFU therapy for radiation failures

High-intensity focused ultrasound represents another potential treatment option for patients with recurrent CaP after radiation therapy. However, the reports published comprise only small patient numbers and follow-up is short so that no final conclusions regarding clinical efficacy can be drawn. In one series Gelet et al. (81) report on the outcome of 71 patients with a mean follow-up of 14.8 months at which 56% of the patients demonstrated a new PSA progression. The complications included recto-urethral fistulas in 6%, grade 3 incontinence in 7% and bladder neck stenosis in 17%.

15.7.4 Observation

Patients with signs of local recurrence only (low-risk patients with late recurrence and a slow PSA rise) and who are not opting for second-line curative options are best managed by observation alone. A retrospective cohort analysis of hormonal therapy vs 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 $\geq$ 12 months after radiotherapy. The 5-year metastasis-free survival rate was 88% with hormonal therapy vs 92% with watchful waiting (p=0.74) (82).

15.7.5 MANAGEMENT OF PSA RELAPSE AFTER RADIATION THERAPY

1. Local recurrences may be treated by salvage radical prostatectomy in carefully selected patients (grade C recommendation).
2. CSAP and interstitial brachytherapy are alternative experimental procedures in patients not suitable for surgery (grade C recommendation).
3. ADT is an option in patients with patients with presumed systemic relapse (grade B recommendation).

15.8 GUIDELINES FOR SECOND-LINE THERAPY AFTER CURATIVE TREATMENT

1. Presumed local failure after radical prostatectomy	Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably before PSA has risen above 1.5 ng/mL. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade B recommendation).
2. Presumed local failure after radiotherapy	Selected patients may be candidates for salvage radical prostatectomy although patients should be informed concerning the comparatively high risk of complications. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade C recommendation).
3. Presumed distant +/- local	There is some evidence that early hormonal therapy may be of benefit in failure delaying progression and possibly achieve a survival benefit in comparison with delayed therapy. The results are not without controversy. Local therapy is not recommended except for palliative reasons (grade B recommendation).

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16. HORMONE-REFRACTORY PROSTATE CANCER (HRPC)

16.1 Background

Cancer of the prostate is a heterogeneous disease and our understanding of the mechanism of androgen independence remains incomplete (1-5). Androgen ablation provides a selective advantage to androgen-independent cells that grow and eventually comprise the majority of the tumour. An alteration in normal androgen signalling probably has a central role in the pathogenesis of androgen-independent CaP. Androgen independence may be mediated through mutations of the androgen receptor gene that alter expression of the androgen receptor or its sensitivity to androgens (3-5). The fact that androgen receptor mutations are found in only a subpopulation of cells in the tumour suggests that these changes alone are unlikely to account fully for the entire spectrum of the androgen-independent state (6).

Many studies have focused on the deregulation of apoptosis in the development of androgen-independent disease. High levels of *bcl-2* expression are seen with greater frequency as CaP progress, and a

mechanism whereby *bcl-2* induces its antiapoptotic effect may be the regulation of microtubule integrity (7-9). The fact that the most active chemotherapeutics in HRPC work by inhibiting microtubule formation suggests that these findings may be clinically relevant. The tumour suppressor gene *p53* is more frequently mutated in androgen-independent CaP. Over-expression of *bcl-2* and *p53* in prostatectomy specimens have been shown to predict an aggressive clinical course (10-12).

Peptide growth factors may have an important role in the progression of CaP. Epidermal growth factor is a potent mitogen of prostate stromal and epithelial cells. It is produced in high levels locally and acts as a paracrine stimulator. In androgen-independent tumours, autocrine stimulation may become more important, which, with epidermal growth factor, could allow unregulated growth (13).

16.2 Definition of HRPC

Hormone-refractory prostate cancer is a very heterogeneous disease including a variety of different patient cohorts with significant different median survival times (Table 14). Many different terms have been used to describe cancers that relapse after initial hormonal ablation therapy, including HRPC, androgen-independent cancers and hormone-independent cancers (1).

Table 14: 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. Recently, the various groups have published practical recommendations that should be adhered to when defining HRPC (14-16). Androgen-independent, but hormone-sensitive CaP, has to be differentiated from true HRPC from the outset. Whereas the first group still responds to secondary hormonal manipulations, such as antiandrogen withdrawal, oestrogens and corticosteroids, the latter is resistant to all hormonal measures (17,18). Table 15 lists key defining factors of HRPC.

Table 15: Definition of HRPC

1.	Serum castration levels of testosterone
2.	Three consecutive rises of PSA 2 weeks apart resulting in two 50% increases over the nadir
3.	Antiandrogen withdrawal for at least 4 weeks*
4.	PSA progression despite secondary hormonal manipulations*
5.	Progression of osseous or soft tissue lesions (3)

** Either antiandrogen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for HRPC.*

16.3 Assessing outcome of treatment in androgen-independent CaP

In general, therapeutic outcome should be assessed according to the guidelines for the evaluation of response to treatment in solid tumours recently published by the RECIST group (Response Evaluation Criteria In Solid Tumours) (19). However, 80-90% of patients do not have bidimensionally 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. There remains no general agreement regarding the methodology of measuring response (20-25). Determination of the cause of death in CaP patients is often unreliable, suggesting that an overall, rather than disease-specific, survival rate may be a more valid end-point (24).

Many contemporary studies use PSA as a marker of response, although there is no general consensus about the magnitude and duration of decline in PSA level. The greatest use of PSA in this context is 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, and wide fluctuations have been seen in PSA values, indicating a transient effect of drugs on PSA production. Knowledge of the effects of a drug on PSA expression is therefore key to

interpreting PSA response data, which must be viewed together with other clinical data (25-32).
Despite these considerations, it has been reproducibly shown that ≥ 50% PSA decline in pre-treatment PSA following therapy is associated with a significant survival advantage (26,33). Kelly et al. (26) reported a statistically significant survival advantage in 110 patients if they had ≥ 50% PSA decline compared to those who did not (8.6 months vs > 25 months, respectively). Likewise, Smith et al. (33) demonstrated an increase in survival if a PSA decline ≥ 50% was maintained for at least 8 weeks, resulting in a mean survival time of 91 weeks as compared to only 38 weeks in those without this decrease.

Molecular markers are just beginning to be evaluated. In a promising study, positive findings using reverse transcriptase-polymerase chain reaction (RT-PCR) were correlated with poor survival (34); however, these data have to be corroborated in other trials before recommendations can be made with regard to their clinical use.

In patients with symptomatic osseous lesions, pain reduction or complete pain relief might also be used as parameters to assess palliative therapeutic response (35).

An increasing number of investigators advocate subjective end-points. Since a significant survival benefit from chemotherapy in HRPC has not just been demonstrated in a subset of patients, the success of treatment may rely on redefining the goals of therapy (15,24,36). Currently, investigators should rely on clearly defined end-points in trials, which are sufficiently powered to answer the question posed, report each response parameter individually (rather than as a complete or partial response), use PSA response only with other clinical parameters of response, and consider QoL end-points in symptomatic patients.

16.4 RECOMMENDATIONS FOR ASSESSING THERAPEUTIC RESPONSE

1. PSA decline ≥ 50% maintained for 8 weeks is associated with a significantly better outcome as compared to a PSA decline < 50% (level of evidence: 1a)
2. In non-osseous metastases from HRPC, assessment should adhere to the RECIST criteria (level of evidence: 1b)
3. In patients with advanced symptomatic metastatic HRPC, therapeutic response can be assessed best by improvement of symptoms (level of evidence: 1b).

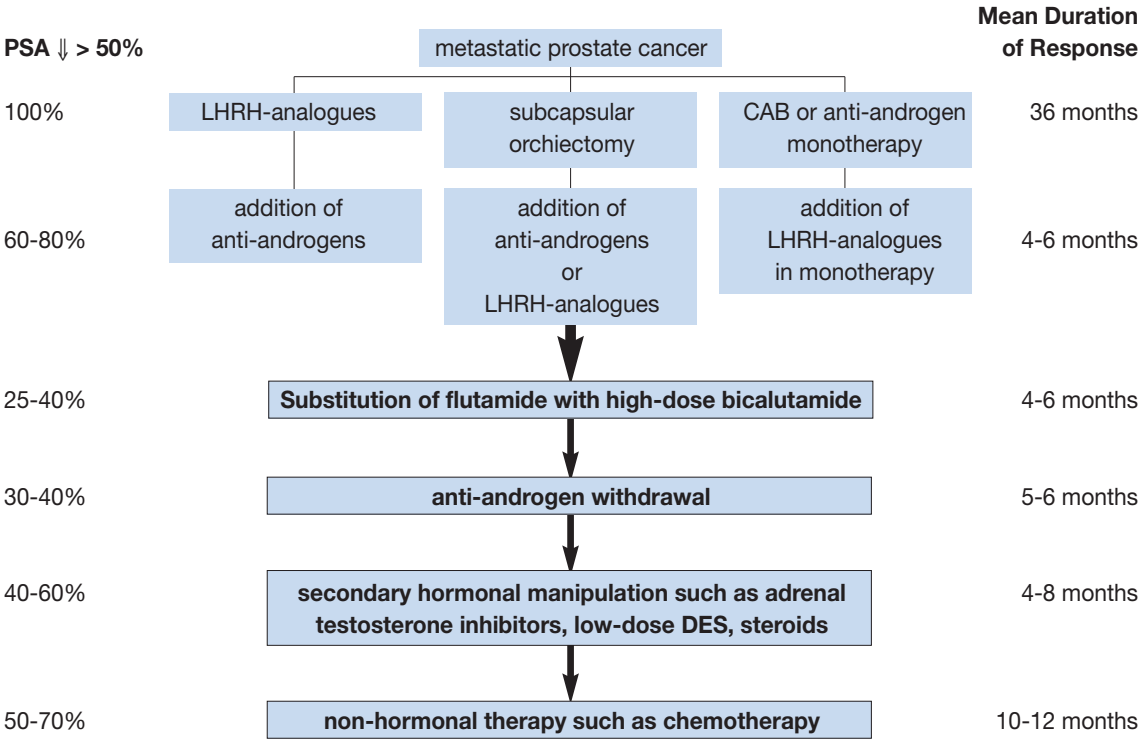
16.5 Androgen deprivation in androgen-independent CaP

Androgen-independent CaP implies that disease progression occurs despite castration. Therefore, castration levels of testosterone must first be documented. A serum testosterone level < 20 to 50 ng/mL should be documented at initial relapse on hormonal therapy (15,37). The overall effect of continued testicular androgen suppression in HRPC is minimal at best. The recommendation to continue androgen deprivation with LHRH analogues despite PSA progression is based on the data of Manni et al. (38), which demonstrated significantly lower survival rates in patients without continuous androgen blockade. However, two recently published trials have challenged these data by showing only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies (39,40). However, in the absence of prospective data, it seems appropriate to view the modest potential benefits against the minimal risk of treatment and to continue androgen suppression indefinitely in these patients.

16.6 Secondary hormonal therapy

For the patient with progressive disease after androgen deprivation, multiple therapeutic options are available. They include antiandrogen withdrawal, addition of antiandrogens, oestrogenic compounds, adrenolytic agents and novel approaches (41). The therapeutic algorithm given in Figure 1 summarizes the various treatment modalities and the responses to be expected.

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



16.7 Antiandrogen withdrawal syndrome

In 1993, Kelly and Scher (42) reported clinical and PSA responses in men who discontinued flutamide therapy upon development of progressive disease. The antiandrogen withdrawal syndrome was a critical discovery in terms of understanding the biology of androgen independence, interpreting clinical trials and treating patients (42-46). Approximately one-third of patients will respond to antiandrogen withdrawal as indicated by a ≥ 50% PSA decrease with a median duration of response of approximately 4 months (Table 16). Antiandrogen withdrawal responses have also been reported after treatment with bicalutamide and megestrol acetate (47-53). The availability and more favourable toxicity profile of secondary hormonal therapies allow the clinician to consider these drugs for the growing category of asymptomatic patients for whom chemotherapy is difficult to justify, but who, due to increasing serum PSA level, want treatment outside clinical trials. However, WW remains a viable choice for asymptomatic patients.

Table 16: Frequency and duration of PSA response following antiandrogen withdrawal

Antiandrogen		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

16.8 Treatment alternatives after initial hormonal therapy

Except in patients with non-castration testosterone levels, it remains difficult to predict which subset of individuals is most likely to respond to secondary hormonal strategies (46). Bicalutamide is a non-steroidal antiandrogen that demonstrates a dose response, which means that 200 mg of bicalutamide normalizes PSA more effectively than 50 mg of bicalutamide in patients with androgen-dependent CaP (54). The benefits of adding an antiandrogen, such as bicalutamide or flutamide, to gonadal suppression at the time of PSA failure seems to result in declining PSA in only a few patients (55-57).

Approximately 10% of circulating androgen in humans is secreted by the adrenal glands. In androgen-independent states, some tumour cells must retain sensitivity to androgens, as a further decrease in circulating androgen levels by bilateral adrenalectomy or drugs that inhibit adrenal steroidogenesis can induce a clinical response. Aminoglutethimide, ketoconazole and corticosteroid act primarily via this mechanism (58-62)

resulting in a PSA response in about 25% of patients treated lasting for about 4 months. The simultaneous addition of ketokonazole to antiandrogen withdrawal, however, results in a significantly increased PSA response (32% vs 11%) and a longer time to PSA progression (8.6 vs 5.9 months) compared to antiandrogen withdrawal alone (62), as has been documented in a recent, prospective, randomized phase III trial including 260 patients with androgen-independent CaP.

Prostate cancer normally expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. In-vitro oestrogens can activate mutant androgen receptors that have been isolated in androgen-independent CaP. Anti-oestrogens in CaP have been reported to have measurable response rates of only 0–10% (63). Alternatively, high-dose oestrogens have been reported to have salvage objective responses. The mechanism for the effect has been postulated to be due to the mitotic arrest of direct cytotoxic effects on the cells, perhaps through an apoptotic mechanism (64,65). Recently, DES has been evaluated in two studies (66,67) including 21 and 32 patients. A positive PSA response was achieved in 43% and 80%, respectively; the estimated survival at 2 years was 63%. However, even at low doses, 31% of the patients developed deep venous thrombosis and 7% experienced myocardial infarction. In another prospective randomized phase II trial, the clinical efficacy of the herbal supplement PC-SPES and DES were tested in a cohort of 90 patients, with PSA progression following initial androgen deprivation (68). A PSA decline $\geq$ 50% was noted in 40% with PC-SPES and in 24% with DES. Median time to progression was 5.5 months with PC-SPES and 2.9 months with DES; the differences were statistically not significant.

16.9 Non-hormonal therapy (cytotoxic agents)

Based on prospective randomized clinical phase III trials, several proven chemotherapeutic options are available for the management of HRPC with metastatic disease (Table 17). In two recent phase III trials, a significant improvement in median survival of approximately 2 months could be demonstrated for docetaxel-based chemotherapy as compared to a combination of mitoxantrone and prednisone (69,70). In the TAX 327 study (70), 1,006 patients with metastatic HRPC were randomly assigned to mitoxantrone at 12 mg/m^2 every 3 weeks, docetaxel at 75 mg/m^2 every 3 weeks, or docetaxel at 30 mg/m^2 weekly for 5 of every 6 weeks. The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the docetaxel group treated with 75 mg/m^2 every 3 weeks, and 17.4 months in the docetaxel group treated with 30 mg/m^2 for 5 of every 6 weeks ($p < 0.001$). A $\geq$ 50% PSA decline was achieved in 45% and 48% of men in the docetaxel-treated groups compared to 32% in the mitoxantrone group ($p < 0.001$). Significant pain reduction was achieved in 22% of the patients in the mitoxantrone group compared to 35% ($p = 0.01$) and 31% ($p = 0.08$) in the docetaxel-treated groups. Adverse events were similar among the different treatment groups. However, QoL was significantly improved in both docetaxel-treated groups.

In the SWOG 99-16 trial (69), 674 patients with metastatic HRPC were randomly assigned to receive mitoxantrone at 12 mg/m^2 every 3 weeks or docetaxel and estramustine at 60 mg/m^2 every 3 weeks. In an intention-to-treat analysis, the median survival was 17.5 months and 15.6 months ($p = 0.02$) in the docetaxel and the mitoxantrone groups, respectively. Also, the median time to progression was significantly longer in the docetaxel group with 6.3 months compared with 3.2 months in the mitoxantrone group ($p < 0.001$). A PSA decline of $\geq$ 50% was achieved in 50% and 27% patients of the docetaxel and the mitoxantrone group, respectively. Pain relief was similar among both groups, though side-effects occurred significantly more often in the docetaxel group.

Table 17: PSA response rates, mean survival and time to progression, and pain reduction in the large prospective randomized phase III trials documenting clinical efficacy 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 < 0.0001, [2]p=0.001, [3]p=0.01, [4]p < 0.03.

Despite these encouraging results, the time-point at which to initiate a cytotoxic regime in patients with HRPC remains controversial. Although it appears evident that chemotherapy should be started in patients with metastatic HRPC, there are no data available with regard to the therapeutic efficacy of early chemotherapy in patients with a PSA rise only. There, at least, exists the recommendation that two consecutive increases in PSA over a previous reference value should exist and that the PSA level should exceed 5 ng/mL (15). Therefore, the indication for the initiation of chemotherapeutic regimes has to be made on an individual basis.

To further improve treatment results, some experimental phase I and phase II trials combining taxanes with anti-*bcl*-2, calcitriol, exisulid, and thalidomide are underway resulting in a PSA response of about 60% (71-74). In a randomized phase II trial of docetaxel plus thalidomide (71), 75 men with chemotherapy-naïve HRPC were randomized 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%) without reaching statistical significance. Median PFS survival and OS were 5.9 months and 68% at 18 months as compared to 3.7 months and 43% in the docetaxel-alone group without reaching statistical significance. However, side-effects were significant, with thromboembolic events occurring in 28% of the combination arm compared to no such events in the docetaxel arm.

Mitoxantrone with corticosteroids (30,75) has been extensively studied primarily in patients with symptomatic osseous lesions due to HRPC. In the CALGB 9182 study (75), 244 patients with symptomatic metastatic HRPC were randomized to either receive mitoxantrone plus hydrocortisone at 12 mg/m^2 every 3 weeks or to hydrocortisone alone. Although no differences were observed with regard to survival, PSA response, and median time to progression, the QoL was significantly improved in the combination arm. In the other trial (30), 161 men with painful osseous metastases due to HRPC were randomized to receive mitoxantrone plus prednisone compared to prednisone alone. A significant benefit in terms of pain reduction was observed in the combination group (29%) compared to prednisone alone (12%, p = 0.01); furthermore, 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. Although none of the studies demonstrated any survival benefit for the patients, QoL was improved significantly due to pain reduction.

Alternative treatments evaluated in prospective clinical phase II trials, including pegylated doxorubicin, a combination of paclitaxel, carboplatin and estramustine, a combination of vinblastine, doxorubicin and radionuclides and a combination of docetaxel and mitoxantrone, have demonstrated encouraging results (76-81). The lack of representative randomized phase III trials and still unknown long-term efficacy are major problems associated with all these studies.

The synergy observed for estramustine combined with other drugs that target microtubule action has generated promising results in prospective clinical trials (82). Estramustine plus vinblastine has been the most studied estramustine combination; although different doses of estramustine and vinblastine have been used in prospective randomized 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 plus vinblastine arms (83).

Intravenous cyclophosphamide has been tested in multiple trials. Current interest has focused on oral cyclophosphamide, which appears to be less toxic than when given intravenously and may have greater activity (84,85). A study of the combination of oral cyclophosphamide and oral etoposide in 20 patients was similarly encouraging (86,87). Cisplatin and carboplatin have activity against CaP as single agents, but their synergy with etoposide or paclitaxel in vitro and in the treatment of other diseases, such as lung and ovarian cancer, is well documented. 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 also recently been reported to produce high response rates (77).

Suramin activity against HRPC is likely to be mediated through the inhibition of binding of growth factors, such as transforming growth factor beta, to their receptors. Although the ultimate role of suramin in the treatment of HRPC is still undetermined, recent results have renewed interest in suramin's initial promise (78-80).

Quite recently, platinum-based chemotherapeutic regimes have been analyzed in patients with HRPCA in clinical phase II and phase III trials, which will have a major impact on daily clinical practice. Satraplatin is a novel oral platinum (IV) complex that shows activity against HRPC. In a small clinical phase III trial, the median OS was 14.9 months on the satraplatin plus prednisone arm and 11.9 months on prednisone alone. Progression-free survival was 5.2 months on the satraplatin plus prednisone arm compared to 2.5 months on the prednisone-alone arm ($p = 0.023$).

Since all patients who have received docetaxel-based chemotherapy for the management of HRPC will progress within 6 to 8 months, the role of salvage chemotherapy has been addressed in many clinical phase II and phase III trials. Intermittent docetaxel chemotherapy (82,83), molecular targeted therapy (84,85) and second-line satraplatin (86) appear to be the most appropriate approaches for clinical use. Second-line intermittent docetaxel has been used by several authors (82,83). In general, a PSA response can be achieved in about 60% of patients with a median time to progression of about 6 months; treatment-associated toxicity is minimal and resembles the toxicity data of first-line docetaxel. Molecular-targeted therapy represents another approach identified recently with promising results (82,85). However, no valid data with regard to PFS and CSS in large cohorts of patients are available currently. In the SPARC trial, 950 men with PSA progression occurring after at least one cytotoxic regime were prospectively randomized to receive either satraplatin and prednisone or to receive placebo and prednisone. There was a 40% reduction in the risk of disease progression in favour of satraplatin resulting in a benefit of 1.3 weeks at the 50th percentile and 17 weeks benefit at the 75th percentile.

16.10 Palliative therapeutic options

Most patients with HRPC have painful bone metastases. The two beta-emitting radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients. Early use can make subsequent administration of chemotherapy more difficult because of myelosuppression (87,90). Critical issues of palliation must be addressed while considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which frequently occur (i.e. palliative external beam radiation, cortisone, analgesics and antiemetics).

Common complications due to skeletal metastases include bone pain, vertebral collapse or deformity pathological fractures and spinal cord compression. Recently, the use of bisphosphonates to inhibit osteoclast-mediated bone resorption and the activity of osteoclast precursors has demonstrated a clinically significant effect in terms of prevention of skeletal complications and reduction of pain, or even total pain relief, in patients with HRPC. In the largest single phase III trial (94), 643 men with HRPC metastatic to the bone were randomized to receive zoledronic acid at 8 mg or 4 mg every 3 weeks for 15 consecutive months or placebo. At 15 months and at 24 months of follow-up, there was a significant reduction in skeletal-related events in the zoledronic acid treated group compared to the placebo group (44% vs 33%, $p = 0.021$). The frequency of pathological fractures was significantly lower in the zoledronic acid group compared with the placebo group (13.1% vs 22.1%, $p = 0.015$). Furthermore, the time to first skeletal-related event was significantly prolonged in the zoledronate group thereby significantly improving QoL. Currently, bisphosphonates could be proposed to patients with HRPC bone metastases in order to prevent skeletal complications.

Pain due to osseous metastases is one of the most debilitating complications of HRPC. Bisphosphonates have been proven to be highly effective with a response rate of 70-80%, which, associated with a low frequency of side-effects, makes bisphosphonates to be an ideal medication for palliative therapy of advanced HRPC (35,95). Bisphosphonates should be considered early in the management of symptomatic HRPC.

Hormone-refractory CaP is usually a debilitating disease, often affecting the elderly male.

A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses and social workers (96).

16.11 SUMMARY OF TREATMENT AFTER HORMONAL THERAPY

1. It is recommended to cease antiandrogen therapy once PSA progression is documented (grade B recommendation).
2. Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual antiandrogen withdrawal effect will become apparent (grade B recommendation).
3. No clear-cut recommendation can be made regarding the most effective drug for secondary hormonal manipulations since data from randomized trials are scarce (grade C recommendation).

16.12 GUIDELINES AND RECOMMENDATIONS FOR CYTOTOXIC THERAPY IN HRPC

1. In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented (grade B recommendation).
2. Prior to treatment, PSA serum levels should be > 5 ng/mL to assure correct interpretation of therapeutic efficacy (grade B recommendation).
3. Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient (grade C recommendation).
4. 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 (grade A recommendation).
5. In patients with symptomatic osseous metastases due to HRPCA, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options (grade A recommendation).

16.13 GUIDELINES FOR PALLIATIVE MANAGEMENT OF HRPC

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

16.14 RECOMMENDATIONS FOR PALLIATIVE MANAGEMENT OF HRPC

1. Bisphosphonates may be offered to patients with skeletal metastases (mainly zoledronic acid has been studied) to prevent osseous complications (grade A recommendation).
2. Palliative treatments such as radionuclides, external beam radiotherapy, adequate use of analgesics should be considered early in the management of painful osseous metastases (grade B recommendation).

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17. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AAW	antiandrogen withdrawal effect
ADT	androgen deprivation therapy
ASAP	atypical small acinar proliferation
ASTRO	American Society of Therapeutic Radiology and Oncology
AUC	area under the curve
bNED	actuarial biochemical freedom of disease/biochemical non-evidence of disease
BPFS	biochemical progression-free survival.
3D-CRT	three-dimensional conformal radiation therapy
CAB	complete androgen blockade
CaP	cancer of the prostate
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavor
CPA	cyproterone acetate
CPFS	clinical progression-free survival
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
DES	diethylstilboestrol
DHT	dihydrotestosterone
DRE	digital rectal examination
ECE	extracapsular extention
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EPC	Early Prostate Cancer Trial
EPO	erythropoietin
ER-β	oestrogen receptor-beta
ERSPC	European Randomized Screening for Prostate Cancer
EU	European Union
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
FSH	follicle-stimulating hormone
HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
IAB	intermittent androgen blockade
IAD	intermittent androgen deprivation
ICI	intracavernosal injection
IMRT	intensity modulated radiotherapy
IPPS	International Prostatic Symptom Score
LDR	low-dose rate
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LND	lymph node dissection
LTAD	long-term androgen deprivation (ablation)
MRC	Medical Research Council
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHT	neoadjuvant hormonal therapy
NIH	National Institutes of Health
PAP	prostatic acid phosphatase
PET	positron emission tomography
PFS	progression-free survival
PIN	prostatic intraepithelial neoplasia
PLCO	Prostate, Lung, Colorectal, Ovary trial
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time

PSMA mRNA	prostate specific membrane antigen for messenger RNA
QoL	quality of life
QUALYs	quality of life adjusted gain in life years
RECIST group	Response Evaluation Criteria In Solid Tumours group
RITA	radiofrequency interstitial tumour ablation
ROC	receiver operating characteristics curve
RTOG	Radiation Therapy Oncology Group
RT-PCR	reverse transcriptase-polymerase chain reaction
SEER (database)	Surveillance, Epidemiology, and End Results database of the National Cancer Institute (USA)
STAD	short-term androgen deprivation (ablation)
SVI	seminal vesicle invasion
TNM	Tumour Node Metastasis (classification)
TRUS	transrectal ultrasonography
TURP	transurethral resection of the prostate
VACURG	Veterans Administration Cooperative Urological Research Group
WHO	World Health Organization
WW	watchful waiting (deferred treatment)

17.1 Levels of evidence and grades of recommendations

Levels of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
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

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Grades of guideline recommendations

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

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