



European Association of Urology

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). 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, prostate cancer is the most common malignancy in males, accounting for 31.5% of all new cases in 1999 (3).

By the time of diagnosis, only 55% of tumours are clinically localized in the absence of an organized screening programme (4). Even in modern series, 30-45% of patients with clinically localized disease are found to have extracapsular extension at pathological staging (5, 6).

2. CLASSIFICATION

The 1997 TNM (Tumour Node Metastasis) classification for CaP is shown in Table 1.

Table 1: Tumour Node Metastasis (TNM) classification of cancer of the prostate

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 level)
T2	Tumour confined within the prostate ¹
T2a	Tumour involves one lobe
T2b	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 ani and/or pelvic wall
N	Regional lymph nodes³
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis⁴
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

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

² Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as T3, but as T2.

³ The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.

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 of adenocarcinoma of the prostate is the Gleason score (7). 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. To be counted, a pattern (grade) needs to occupy more than 5% of the biopsy specimen. The scoring system requires biopsy material (core biopsy or operative specimens) in order to be helpful; cytological preparations cannot be used.

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 (8, 9). 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 develop early-onset disease, i.e. before the age of 55 (10).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (11). 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 South-East Asia (12, 13). However, if Japanese men move from Japan to Hawaii their risk of CaP increases, and if they move to California their risk approaches that of American men (14).

These findings indicate that exogenous factors affect the risk of progression from so-called latent CaP to clinical CaP. 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 (15). Other factors include low intakes of vitamin E, selenium, lignans and isoflavonoids (16). The impact of sunlight has also been discussed; it has been proposed that the risk of developing clinical CaP is inversely related to sun exposure. Sunlight might be protective against CaP mediated via increased vitamin D levels (17).

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 (18). 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.

4. DIAGNOSIS

The main diagnostic tools used to look for evidence of CaP include digital rectal examination (DRE), serum concentration of prostate-specific antigen (PSA) and transrectal ultrasonography (TRUS) (19). 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 (20, 21).

4.1 Digital rectal examination (DRE)

The majority of 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 (22-24):

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

4.2 Prostate-specific antigen (PSA)

The measurement of PSA level has revolutionized the diagnosis of CaP (25). 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 (24).

Currently, many different commercial test kits for the measurement of PSA are available, but no common international standard exists (26). 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 (27). A threshold level of PSA that indicates the highest risk of CaP needs to be defined (28). The positive predictive value of PSA is approximately 25-35% for levels between 4 ng/mL and 10 ng/mL (using monoclonal antibody assays) and 50-80% for those above 10 ng/mL, depending on findings on DRE (29).

The detection of non-palpable prostate cancer 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 (30). Even lower cut-off levels have been proposed by some authors, still with a relatively high detection rate (31).

One important issue associated with lowering the PSA level threshold is the avoidance of detecting insignificant cancers whose natural history is unlikely to be life-threatening (32). 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.

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 (33)
- PSA density of the transition zone (34)
- Age-specific reference ranges (35)
- PSA molecular forms (36-38)
- PSA velocity (39)
- PSA doubling time (40).

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.

Stage T1c describes tumours recognized by biopsies performed because of an elevated PSA level 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 (41).

4.3 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 (42). It must be stressed that many cancers are isoechoic and only detectable from systemic biopsies. Ellis and co-workers noted that 37.6% of their detected cancers were diagnosed in isoechoic areas of the prostate (21).

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 physical examination (43, 44). 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 (21, 44, 45).

4.4 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% (21, 43, 44). 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%.

4.5 Prostate biopsies

Digitally guided fine-needle aspiration allows the diagnosis and cytological grading of the tumour with a minimal risk of complications (46). However, the method needs a specially trained cytologist to produce 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 without anaesthesia and with a low risk of complications if antibiotic prophylaxis is used (47, 48).

Lesion-guided biopsies can be used in cases where there is a palpable nodule in combination with a PSA level greater than 10 ng/mL. However, if the patient is a candidate for curative treatment, if lesions are absent or if the serum PSA level is less than 10 ng/mL, systemic biopsies are a better choice (49). Sextant biopsies, as described by Hodge et al. have been used in this situation (20). Lately, the standard way of obtaining sextant biopsies has been replaced by laterally directed sextant biopsies in order to optimize the CaP detection rate (50, 51). Biopsy cores obtained in this way include the posterolateral aspect of the peripheral zone, the most common location for early CaP. The number of biopsies required for the optimal detection of cancer is controversial. 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 (52). However, the vast majority of these extra cancers were detected in the far-lateral mid-lobar region, an area well sampled by the technique of laterally directed sextant biopsy. Furthermore, a patient who has undergone one set of five-region biopsy has the same rate of cancer at re-biopsy as those who have been biopsied with the sextant technique (53).

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 (53-55). In cases where high-grade prostatic intraepithelial neoplasia (PIN) is present, as many as 50-100% of prostates harbour a concomitant cancer and immediate re-biopsy is indicated (56, 57).

In summary, even if more cores at the primary biopsy may increase the detection rate, at least when compared to the mid-gland sextant technique, one set of repeat biopsies seems always to be warranted if the indication persists.

5. STAGING

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

5.1 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, and in one study a positive correlation between DRE and pathological tumour stage was found in fewer than 50% of tumours (58). 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 (59-61). 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 (62). The ability of the molecular forms of PSA to predict T-stage is still controversial and large multicentre studies are needed before any form of PSA is used as a 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 (63). TRUS criteria for extracapsular extension of CaP include irregularity, bulging and discontinuity of boundary echo. TRUS criteria for seminal vesicle invasion is 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 (64, 65). Furthermore, in a recent multi-institutional large study, TRUS was no more accurate at predicting organ-confined disease than DRE (66). These findings were supported by another large study, which showed that there was no meaningful superiority of TRUS over DRE (67).

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 (68). 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 (69, 70). Patients with any of the basal biopsies positive for cancer are more likely to have positive seminal vesicle biopsies (71). 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 (72-75). 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 ≤ 6 (76).

Computerized tomography and MRI are now of a high technical standard, but neither modality is sufficiently reliable to make their use in assessing local tumour invasion mandatory (77-79). Dynamic, contrast-enhanced, endorectal MRI provides extremely high-resolution images of the prostate and peri-prostatic tumour infiltration, so it might be superior to TRUS. Staging accuracy with the endorectal coil compared with whole-body MRI was improved by up to 16% (80). MRI of the prostate with an endorectal surface coil appears to be the most accurate non-invasive method of identifying locally advanced disease, especially seminal vesicle involvement (80). 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.

5.2 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 (62, 81, 82). The measurement of PSA level alone has been found to be of little help in predicting the presence of lymph node metastases for an individual patient (27). The same is true of the other pre-operatively known prognostic factors. The risk of harbouring lymph node metastases may be estimated more reliably by combining findings of serum PSA estimations, DRE and tumour grade (62, 81, 82). These findings 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 safely be spared N-staging procedures before potentially curative treatment (62). The amount 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 20-45%. In the remaining patients, the risk was 2.5% making nodal staging unnecessary (83).

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 (84, 85). Both CT and MRI are considered of limited use due to their low sensitivity, which varies from 0% to 70% (78, 86, 87), although CT accuracy increases when fine-needle aspiration biopsies are applied to virtually all visible and asymmetric lymph nodes (88). 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 and is in the range 93-96%. Patients with nodal metastasis on CT or with a positive aspiration biopsy may thus be spared operative lymphadenectomy (89). 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 (90).

Radio-immunoscintigraphy and positron emission tomography 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 (91-93).

5.3 M-staging

The axial skeleton is involved in 85% of patients dying from CaP (94). 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 (95). 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 (96, 97). Technetium diphosphonates are the optimum radiopharmaceuticals currently available due to their extremely high bone-to-soft-tissue ratio (98). A semi-quantitative grading system based upon the extent of disease observed on the bone scan was found to correlate with survival (99). 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% (100). Furthermore, it has helped to reduce the number of patients with newly diagnosed CaP who require a bone scan - only on very rare occasions have patients with a low serum PSA concentration 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 (101-105). 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.

Molecular staging of CaP employing reverse transcriptase-polymerase chain reaction (RT-PCR) for PSA-messenger RNA or prostate-specific membrane antigen (PSMA) mRNA appears to be a new tool for staging, but at present it is still experimental and requires further evaluation (106-107).

5.4 Guidelines on diagnosis and staging

1. An abnormal DRE result or elevated serum PSA measurement may indicate CaP.
2. The diagnosis of CaP depends on histopathological (or cytological) confirmation. Biopsy and further staging investigations are only indicated if they do affect the management of the patient.
3. Local staging (T-staging) of CaP is based on findings from DRE and imaging studies. Further information is provided by the number and sites of positive prostate biopsies, tumour grade and level of serum PSA.
4. Lymph node status (N-staging) is only important when potentially curative treatment is planned. Patients with Stage T2 or less, PSA < 20 ng/ml and a Gleason score of 6 or less 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.
5. 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.

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

6.1 Summary

6.1.1 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). 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.

6.1.2 Indications

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

- Stage T1a - well and moderately differentiated tumours. In younger patients with a life expectancy of more than 10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended.
- Stage T1b-T2b - well and moderately differentiated tumours. In patients with a life expectancy of less than 10 years and asymptomatic.

6.1.3 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.

In locally advanced disease (stage T3-T4):

- Asymptomatic patients with well or moderately differentiated cancer, CaP and a short life expectancy.

In metastatic disease (M1):

- A very rare patient without any symptoms and the possibility of close follow-up.

6.2 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 them give the same results as they analyze roughly the same series, but with 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 the patients from six non-randomized studies (6-13). The results describe cancer-specific survival and metastasis-free survival after 5 and 10 years of follow-up (Table 2) (1). The importance of tumour grade is clear, with very low survival rates for grade 3 tumours. Even if the 10-year cancer-specific survival 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 2: Outcome of deferred treatment in localized cancer of the prostate 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 (USA) (14). Patients with grade 1, 2 and 3 tumours had 10-year cancer-specific survival 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 describes the outcome for stage T1a patients (1). They had 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 upon 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 3) (18, 19). 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 cancer-specific survival 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 3: The 15-year risk of dying from cancer of the prostate 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 prostate cancer 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).

For patients who choose deferred treatment, the risk of delaying hormonal therapy until disease progression occurs seems modest, although shorter cancer-specific survival times have been reported after deferred therapy compared with immediate hormonal therapy in localized CaP after 15 years of follow-up (24).

6.3 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 (25, 26). 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 (27), comparable with the results of Lundgren et al. mentioned earlier (24).

Fifty selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 CaP were followed up for 169 months (28). The 5- and 10-year cancer-specific survival 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.

6.4 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. 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 (27, 29). If a deferred treatment policy is chosen for the patient with advanced CaP, there must be a possibility of close follow-up.

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7. TREATMENT: RADICAL PROSTATECTOMY

7.1 Summary

7.1.1 Definition

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

7.1.2 Indications

Presumably curable CaP in patients with a life expectancy of more than 10 years:

- Stage T1a, when the expected survival is 15 years or more, or when high grade
- Stage T1b, T2
- Stage T1c, when presumably not insignificant
- Stage T3, when there is limited unilateral extracapsular extension, a Gleason score below 8 and a PSA level below 20 ng/mL.

7.2 General considerations

The standard surgical technique for the treatment of localized CaP is radical prostatovesiculectomy. This procedure was applied at the beginning of the 20th century by Young (4), who used a perineal approach, while Memmelaar and Millin performed retropubic radical prostatectomy (RRP) for the first time (5). In 1982, Walsh and Donker described the anatomy of the dorsal venous complex and the technical aspects of surgery needed to reduce blood loss dramatically and to spare the neurovascular bundles, avoiding definitive erectile dysfunction (6).

Currently, radical prostatectomy is the only treatment for localized prostate cancer that has indicated a cancer-specific survival benefit when compared to conservative management in a prospective, randomized trial (7). Surgical expertise has decreased the complication rates and improved cancer cure (8). In the hands of an experienced urological surgeon, the procedure is associated with minimal intra-operative and post-operative morbidity (9). 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 should result in positive surgical margins more often than the retropubic

approach (10, 11), but this has not been confirmed. It is likely that laparoscopic lymphadenectomy and perineal prostatectomy have lower morbidity than the retropubic operation, but randomized studies are not available. Recently, some European centres have gained considerable experience with laparoscopic radical prostatectomy, but long-term data on oncological outcome and complications are lacking (1-3).

The post-operative complications of radical prostatectomy are listed in Table 4. The mortality rate is 0-1.5% (12), urinary fistulas are seen in 1.2-4% of patients (13) and urinary incontinence that persists after 1 year in 7.7% (14). Erectile dysfunction used to occur in nearly all patients, but nerve-sparing techniques can be applied in early-stage disease (15). Patients who benefit from nerve-sparing radical prostatectomy have a higher chance of local disease recurrence and should therefore be carefully selected. Patients with poorly differentiated tumours, apical tumour extension and an intra-operatively palpable tumour are not suitable candidates for a nerve-sparing approach (16).

Table 4: 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

7.3 Indications for radical prostatectomy

In men with localized CaP and a life expectancy of 10 years or more, the goal of management must be eradication of the disease (17). 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 (18). However, it is worth pointing out that increasing co-morbidity with increasing age decreases the actual risk of dying from localized prostate cancer substantially in men over the age of 70 years (19).

7.3.1 Stage T1a-T1b CaP

Stage T1a CaP is an incidental histological finding of cancer in 5% or less of resected prostatic tissue (transurethral resection of the prostate [TURP] or open adenomectomy), while it is a T1b stage when more than 5% contains 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 (20). Thus, in younger patients who are expected to survive for 15 years or more, the chance of disease progression is real, especially when a high-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 (20). Consequently, it is very important to distinguish between T1a and T1b tumours. Systematic prostate puncture biopsy of the remaining prostate 3 months after surgery is useful. As for poorly differentiated T1a tumours, 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 (21).

7.3.2 Stage T1c CaP

The clinically inapparent tumour identified by needle biopsy because of an aberrant PSA level has become the most frequent 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 most frequently significant and should not be left untreated (22). The proportion of insignificant tumours detected because of PSA elevation varies between 11% and 16% (23, 24). Moreover, 30% of T1c tumours are locally advanced.

The occurrence of PIN is not considered to be an indication for treatment, although 30% of patients with high-grade PIN will present an invasive adenocarcinoma within 5 years and 80% within 10 years (25). Nevertheless, without proof of an invasive carcinoma, radical prostatectomy is not indicated because PIN may

be a reversible phenomenon (26).

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 (27, 28). 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 the majority of these individuals.

7.3.3 Stage T2 CaP

When the tumour clinically involves one lobe or fewer and is confined to the prostate, disease progression can be expected in most patients who are 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 because, after 5 years, 35-55% of them will have disease progression if not treated (29). 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.

Radical prostatectomy is one of the recommended standard treatments for patients with stage T2 CaP and a life expectancy of more than 10 years. The prognosis is excellent if the diagnosis is made early enough, when the tumour is confined to the prostate based on pathological examination (30, 31).

A WW policy has been proposed for T2 tumours (32). If WW is proposed for low-grade T2 cancer, it should be remembered that pre-operative assessment of tumour grade by needle biopsy is frequently unreliable (33). Alternatively, it has been clearly shown that most poorly differentiated tumours extend outside the prostate. Patients with high-grade tumours that are confined to the prostate at histopathological examination still have a good prognosis after radical prostatectomy (34).

7.3.4 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 as controversial (35). In extracapsular tumours, radical prostatectomy often results in incomplete tumour excision. Higher morbidity and a substantially higher risk of local disease recurrence could be associated with those tumours compared with those confined to the prostate. In most patients, disease will finally progress systemically. Whether or not T3 CaP should be considered an indication for surgical treatment has therefore been questioned. The published reports on treatment outcomes in patients with clinical T3 cancer are few (36-42).

Surgical treatment of clinical stage T3 CaP is traditionally discouraged (43), mainly because patients have an increased risk of both lymph node metastases and local or distant relapse (44). Combination treatment with hormonal and radiation therapy is gaining popularity (43, 44), although it was not demonstrated that this approach was better than a surgical one. The randomized study on radiotherapy with hormones versus radiotherapy alone showed a clear advantage for the combination treatment, but did not show the superiority over radical prostatectomy (45). Another problem is 'contamination' by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal treatment in most of the series that reported on the treatment of clinical T3 CaP.

In the absence of sufficient data from randomized clinical trials comparing possible options for definitive therapy in these patients, only single or multicentre reports can be used to define the role of radical prostatectomy in this stage. Most studies have demonstrated that about 15% of all clinical stage T3 tumours were overstaged (cT3, pT2), while only 8% were understaged (cT3, pT4) (37). Patients who were overstaged obviously did very well, while most of those with pT3b cancer showed early disease progression.

For clinical T3 cancer, the overall PSA-free survival rate is about 20% after 5 years. The Gleason score of the tumour has a definite impact on progression (34), 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. Some authors have used a serum PSA level of 25 ng/mL as the discriminator for outcome (27, 41). Others have shown that radical prostatectomy for clinical T3a cancer with a PSA below 10 ng/mL can achieve a 5-year PSA-free survival rate exceeding 60% (42).

Thus, 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 those patients before surgery who have no 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 (28). In addition, nodal imaging with CT scans and seminal vesicle imaging with MRI or directed specific puncture biopsies to the nodes or to the seminal vesicles can be helpful in recognizing those patients who would not benefit from a surgical approach (46).

Radical prostatectomy for clinical T3 cancer necessitates sufficient surgical expertise in order 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 (47).

7.3.5 Nodal disease

The indication for radical prostatectomy in all previously described stages assumes the pathologically proven absence of nodal involvement. Lymph node-positive (N+) disease will be followed by systemic disease progression. All patients with significant N+ disease will ultimately fail. Nevertheless, the combination of radical prostatectomy and simultaneous hormonal treatment has been shown to achieve a 10-year cancer-specific survival rate of 80% (48). 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 could show microscopic lymph node invasion. The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only. 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 side-effects of long-term hormonal therapy. PSA follow-up and hormonal treatment in case of PSA rise is therefore an acceptable option in selected cases.

7.3.6 Results of radical prostatectomy

The results achieved in a number of studies involving radical prostatectomy are shown in Table 5 (49-53).

Table 5: Results of radical prostatectomy

Study	No. of patients	Mean follow-up (months)	5-year PSA-free survival (%)	10-year PSA-free survival (%)
Han et al., 2001 (49)	2404*	75	84	74
Catalona and Smith, 1994 (50)	925	28	78	65
Hull et al. 2002 (51)	1000	53	-	75
Trapasso et al., 1994 (52)	601	34	69	47
Zincke et al., 1994 (53)	3170	60	70	52

* 15-year, 66%.

7.4 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, radiation, brachytherapy). 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 (54).

In several studies of NHT in clinical stage T2 and T3 cancer, decreased prostate volume and serum PSA levels have been reported after hormonal manipulation (55, 56). However, these trials were not randomized, there was no standard treatment protocol and the lengths of NHT varied considerably.

Five prospective, randomized studies have shown a decrease in positive surgical margin rates, with the use of a short-term (6 weeks-4 months) course of NHT (57-62). Follow-up of these randomized trials has indicated that this has not resulted in any difference in PSA-free failure after 3-5 years of follow-up (63-66). Thus far, no data are available on disease-free or overall survival rates.

When surgical technique was considered, it was noted that surgery tended to be more difficult in pre-treated patients (59, 67), but that the duration of radical prostatectomy, blood loss and number of transfusions were similar in NHT-treated patients and controls (58, 59, 67).

With these results in mind, a 3-month course of NHT cannot be recommended for routine clinical use prior to radical prostatectomy. Further studies on the duration and type of androgen ablation are needed in order to define its role in the treatment of localized or locally advanced prostate cancer (68).

7.5 Conclusions

Radical prostatectomy should be reserved for CaP patients who have a high probability of cure and who will live long enough (10 years) to benefit from treatment. Surgery alone cures most men with organ-confined disease or with well-, to moderately well-, differentiated tumours which have perforated the prostate capsule to an extent where it is still possible to obtain clear surgical margins. A short-term (3 months) course of NHT has not been proven to be of any use in the routine management of these patients. The role of radical prostatectomy in margin-positive disease and in poorly differentiated extracapsular tumours remains doubtful. Furthermore, the usefulness of combination treatments with hormonal manipulation and/or radiotherapy in a

neoadjuvant or adjuvant setting is still controversial. Well-designed, prospective, randomized studies will be of help in defining the role of these multimodality therapeutic approaches.

Radical prostatectomy is an efficient and safe treatment modality for localized CaP. The detection of cancers by reference to PSA level is becoming increasingly important. In T1 tumours that warrant treatment, nerve-sparing radical prostatectomy can be offered when PSA is relatively low and the number of positive biopsies or the extent of biopsy involvement is limited. In T2a cancers, which are often understaged, a contralateral nerve-sparing procedure can be proposed. In T2b cancer, a nerve-sparing attempt can result in positive surgical margins and give rise to local failure. Some well-, or moderately-well, differentiated T3 cancers with a low PSA level can be cured by radical prostatectomy.

Radical prostatectomy, like most cancer surgery, is a one-chance treatment and should therefore be performed by experienced urologists who can achieve a good balance between limited or extensive local resection and avoidance of oncological failure or surgical complications.

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8. TREATMENT: DEFINITIVE RADIATION THERAPY

8.1 Conventional external beam radiation therapy

8.1.1 Clinically localized CaP (T1-T2, Nx-N0, M0-MX)

Radiation therapy may be effective in the treatment of patients with localized prostate cancer. This statement is supported by a number of older prospective and retrospective studies in which local control was obtained in 70-90% of patients (1, 2). Likewise, the long-term (10-15 years), disease-free survival rate was 70-90%. Even more interesting are the results from selected series analyzing 10-year cause-specific survival rates (Table 6) (3-10).

Table 6: Selected conventional radiotherapy series by clinical stage

Study	No. of patients	Stage	Disease-free survival	Cause-specific survival
Hanks et al., 1994 (3)	104	T1b-T2	67% 10-year	86% 10-year
Fowler et al., 1995 (4)	138	A2	43% 10-year	86% 10-year
Zietman et al., 1995 (5)	504	T1-T2	65% 10-year	
Perez et al., 1995 (6)	16	A1	100% 10-year	
	112	A2	69% 10-year	
	373	B	57% 10-year	
Kuban et al., 1995 (7)	27	A2	66% 10-year	83% 10-year
	60	B1	57% 10-year	93% 10-year
	246	B2	48% 10-year	78% 10-year
Hahn et al., 1996 (8)	16	T1a	100% 10-year	
	135	T1b	98% 10-year	
	77	T2a	88% 10-year	
	269	T2b	63% 10-year	
Zagars et al., 1997 (9)	643	T1-T2	66% 6-year	
Pollack-Zagars and Pollack, 1998 (10)	643	T1-T2	> 67 Gy: 87% 4-year freedom from failure < 67 Gy: 67% 4-year freedom	

Compared to clinical disease-free survival, the number of patients who can be defined as free from biochemical (PSA) failure is obviously lower (Table 7). The upper limit of PSA level for biochemical control has been defined differently by a number of investigators (1.1 ng/mL [11]; 1.0 ng/mL [12, 13]). Other workers have observed that the PSA nadir value predicts the risk of relapse, which rises progressively as nadir values increase to greater than 1.0 ng/mL (14, 15).

The optimal post-irradiation PSA level that predicts freedom from failure has not yet been clearly defined. However, the American Society of Therapeutic Radiology and Oncology (ASTRO) Consensus Panel definition of biochemical failure (three consecutive increases in post-treatment PSA level after achieving a nadir) correlates well with clinical distant metastases-free survival, disease-free survival and cause-specific survival (16). The definition of biochemical failure can significantly influence the reporting of potential treatment failures following radiation therapy and radical prostatectomy. As demonstrated by Gretzer et al., the definition of treatment failure might have a significant impact on the probability of being biochemically disease free. The application of the ASTRO criteria to a cohort of surgically treated patients resulted in an improvement of the biochemical failure rate at 15 years from 31% to 10% (17). It appears to be of utmost importance to apply a uniform definition of failure when comparing different therapies.

Table 7 summarizes selected series expressing and comparing survivals and biochemical control (4, 5, 7, 9, 16, 18).

Table 7: Selected conventional radiotherapy series: clinically localized disease

Series	No. of patients	Disease-free survival	Cause-specific survival	PSA bFFF criteria
Fowler et al., 1995 (4)	138	43% 10-year	67% 10-year	34% PSA < 1 ng/mL after 10-year nadir
Zietman et al., 1995 (5)	504	65% 10-year		52% PSA < 4 ng/mL 10-year 40% PSA < 1 ng/mL 10-year
Kuban et al., 1995 (7)	27 (A2)	66% 10-year	83% 10-year	35% PSA < 4 ng/mL
	60 (B1)	57% 10-year	93% 10-year	18% PSA < 4 ng/mL
	246 (B2)	48% 10-year	78% 10-year	21% PSA < 4 ng/mL
Zagars, 1997 (9)	643	66% 6-year DFS and bFFF (< 2 ng/ mL after nadir)		
Horwitz et al., 1998 (17)	568	99% ¹ 5-year	98% 5-year	¹ bFFF ASTRO criteria
		64% ¹ 5-year	89% 5-year	¹ Failed ASTRO criteria
Kupelian et al., 2000 (18)	509 (< 72 Gy 8 year)			51% ¹ bFFF ASTRO
	222 (≥ 72 Gy 8 year)			87% ¹ bFFF ASTRO

PSA = prostate-specific antigen; bFFF = biochemical freedom from failure; ASTRO = American Society of Therapeutic Radiology and Oncology.

¹ p < 0.001 comparing those who failed biochemically with those who did not fail according to ASTRO criteria.

The long natural history observed in prostate cancer patients who receive no initial treatment makes it difficult to assess reliably the impact of radiotherapy on survival. As well as the informed choice of the patient and his life expectancy, the Gleason score and PSA pre-treatment value are considered powerful prognostic factors suitable for determining which patients are most likely to benefit from treatment. Zagars et al. analyzed the outcome of 283 T1, 360 T2 and 295 T3-T4 patients who received external beam radiotherapy (box technique; elective lymph node irradiation not performed) as the only initial treatment (9). In multivariate regression analysis, pre-treatment PSA value, T-classification and Gleason score were each independently highly significantly correlated with the incidence of relapse/rising PSA level, local recurrence and metastases. The authors formulated a Hazard Index that related the risk of a rising PSA level to pre-treatment PSA and Gleason score (Table 8).

Table 8: Hazard Index by factors significantly correlated with relapse or rising prostate-specific antigen level in T1-T2 tumours. Adapted from Zagars et al., 1997 (9)

Gleason score	PSA < 4 ng/mL	PSA 4-10 ng/mL	PSA 10-20 ng/mL	PSA > 20 ng/mL
2-6	1	2.7	4.3	11.1
7	1.3	3.5	5.7	14.5
8-10	2	5.3	8.6	22

PSA = prostate-specific antigen.

On this basis, the authors suggested grouping patients with clinical T1-T2 CaP into prognostic categories as shown in Table 9.

Table 9: Prognostic categories for patients with cancer of the prostate stage T1-T2 disease treated with external beam radiotherapy. Adapted from Zagars et al., 1997 (9)

Category	Gleason score	PSA (ng/mL)	At 6 years after radiotherapy		
			Relapse or rising PSA	Local failure	Metastases
I	2-6	≤ 4	6%	3%	0%
II	7-10	≤ 4	30%	24%	1%
	2-7	4-10			
III	8-10	4-10	40%	26%	4%
	2-7	10-20			
IV (unfavourable)	8-10	10-20	88%	43%	12%
	2-10	> 20			

8.1.2 Locally advanced CaP (T3-T4, Nx-N0)

Historical selected series with locally advanced tumours involving radiotherapy alone as the initial treatment without hormonal blockade are summarized in Table 10 (5, 7-9, 19-21).

Table 10: Selected definitive radiotherapy alone series - locally advanced disease

Series	Overall survival (years)			Disease-free survival (years)		
	5	10	15	5	10	15
Bagshaw et al., 1988 (19): T3	64%	35%	18%	46%	28%	3%
Perez et al., 1993 (20): T3	65%	42%		58%	38%	
Arcangeli et al., 1995 (21): T3				39%		
Zietman et al., 1995 (5): T3-4					18% (PSA < 1 ng/mL)	
Kuban et al., 1995 (7): T3-4					29%	
					11% (PSA ≤ 4 ng/mL)	
Hahn et al., 1996 (8): T3				44%	44%	22%
Zagars et al., 1997 (9): T3-4	IPSA < 10 ng/mL			46% 6-year RRPSA		
	IPSA 10-20 ng/mL and Gleason score < 8			57% 6-year RRPSA		
	IPSA > 20 ng/mL or Gleason score 8-10			88% 6-year RRPSA		

PSA = prostate-specific antigen; IPSA = initial PSA; RRPSA = relapsing or rising PSA.

In 1988, Zagars and co-workers (22) reported the advantages of diethylstilbestrol (DES) as adjuvant therapy following radiotherapy for stage C cancer in terms of disease-free survival. Patients receiving adjuvant oestrogen had disease-free survival rates of 63% at 10 and 15 years compared with 43% and 35%, respectively, in patients irradiated only ($p = 0.008$). However, overall survival was not improved because of greater cardiovascular mortality found in patients receiving oestrogen.

In a prospective, randomized study, Laverdiere et al. reported a 2-year positive biopsy rate of 65% with radiotherapy alone (23). This compared with 28%, when 3 months of luteinizing hormone releasing hormone (LHRH) agonist plus flutamide were given prior to radiotherapy, and with 5%, if combined androgen blockade was continued for 6 months after radiotherapy ($p = 0.00001$).

The long-term results of three Radiation Therapy Oncology Group (RTOG) studies have been recently published.

RTOG 85-31 included 977 patients with clinical or pathological T3 or N+ disease, M0, randomized to receive long-term hormonal therapy with goserelin, starting in the last week of radiotherapy and continuing indefinitely (Arm I), or radiotherapy only (Arm II). Statistically significant differences in outcome were observed between Arm I and Arm II for local failure (23% vs 37%), distant metastases (27% vs 37%), and NED (no evidence of disease) survival (36% vs 25%). Cause-specific failure rate and overall survival rate were not statistically different between the two arms. A significant improvement in survival was limited to patients with a Gleason score of 8-10 who had not undergone prostatectomy (24).

RTOG 86-10 evaluated 471 patients with bulky tumours, clinical stage T2-T4, N0 or N+, M0, randomized to receive goserelin and flutamide for 2 months before and during radiation therapy (Arm I) or radiation therapy alone (Arm II). At 8 years, this short-term androgen ablation has been associated with an improvement in local control (42% vs 30%), distant metastases rate (34% vs 45%), disease-free survival (33% vs 21%), biochemical disease-free survival (PSA < 1.5 ng/ml; 24% vs 10%), and cause-specific mortality (23% vs 31%). However, the differences were highly significant in all endpoints in patients with Gleason score 2-6. (25).

The RTOG 92-02 study addressed the issue regarding the optimal duration of hormonal manipulation with radiation therapy. A total of 1554 patients received 4 months of goserelin and flutamide and were randomized to no further therapy or 24 months additional goserelin alone. The long-term androgen deprivation (LTAD) group showed significant improvement in disease-free survival (54% vs 34%), clinical local progression (6% vs 13%), freedom from distant metastases (11% vs 17%) and ASTRO defined biochemical control (21% vs 46%). Five-year overall survival (80% vs 69%) and disease-free survival (90% vs 78%) were significantly increased in the Gleason 8-10 subset treated with LTAD. The authors concluded that LTAD should be standard practice for Gleason 8-10 prostate cancer (26).

Bolla et al. have updated the results of the Phase III trial 22863 of the European Organization for Research and Treatment of Cancer (EORTC). In this trial, there were 415 patients, with staging T1-T2, G3/T3-T4, Nx-N0, N0-X, who received radiotherapy ± goserelin for a period of 3 years + cyproterone acetate (CPA) for 1 month (27). After a median follow-up of 66 months, the combination group had a better outcome compared to the radiation-only group. The 5-year clinical disease-free survival was improved from 40% to 74%, cancer-specific survival from 79% to 94% and overall survival from 62% to 78%.

8.2 Three-dimensional conformal radiation therapy (3D-CRT)

8.2.1 Normal dose 3D-CRT

Recent advances in diagnostic imaging, tumour markers and biopsy techniques allow more accurate pre-operative staging than in the past, with improved understanding of the spatial relationship between tumour and normal tissues. These developments increase our ability to tailor the prescription dose to target volumes, sparing neighbouring critical normal tissues and reducing treatment toxicity, while delivering higher doses of radiation to the volume of interest. This is the goal of 3D-CRT and of its technological development - intensity-modulated radiation therapy.

Some authors suggest the use of neoadjuvant androgen deprivation to reduce the pre-radiotherapy target volume. This would allow a decrease in the dose delivered to adjacent normal tissues and would thereby minimize the risk of morbidity from high-dose radiotherapy (28). Table 11 summarizes recent series of 3D-CRT (13, 28, 29).

Table 11: Summary of results in recent three-dimensional conformal radiation therapy (3D-CRT) series

Series	Patients	Biochemical freedom from failure (prostate-specific antigen < 1 ng/mL)
Roach et al., 1996 (13)	501 T1-T2	
	IPSA < 4 ng/mL	90% 4-year
	IPSA 4-10 ng/mL	60% 4-year
	IPSA 10-20 ng/mL	35% 4-year
Zelevsky et al., 1998 (28)	213 T1-T2 (leuprolide and flutamide given 3 months before 3D-CRT)	
	IPSA ≤ 10 ng/mL	93% 5-year
	IPSA > 10 ≤ 20 ng/mL	60% 5-year
	IPSA > 20 ng/mL	40% 5-year
Anderson et al., 1998 (29)	172 T1-T2a,b; Gleason score 2-6; no PNI	91%* 5-year
	94 T2c-T3 or Gleason score 7-10 or PNI	74%* 5-year

IPSA = initial PSA; PNI = perineural invasion.
* p = 0.0024 (definition of failure was PSA ≥ 1.5 ng/mL and two consecutive rises).

There is no doubt that conformal techniques significantly lowered the risk of late radiation-induced proctitis after radiotherapy for prostate cancer in a randomized trial involving 225 men after a follow-up of 3.6 years (30).

8.2.2 Dose escalation studies

In their large series, Zelevsky et al. (31) reported on a total of 743 T1-T2 patients treated with dose escalation;

the tumour response was evaluated by a PSA value of 1 ng/mL or less and by sextant biopsies at 2 years or more after treatment. The clinical response was dose-dependent, with 90% of patients who received 75.6 or 81 Gy achieving a PSA nadir of 1 ng/mL or less compared with 76% and 56% of those treated with 70.2 Gy and 64.8 Gy, respectively ($p < 0.001$). The 5-year PSA relapse-free survival rate correlated with prognostic indicators (pre-treatment PSA level and Gleason score), and was significantly improved in patients with pre-treatment PSA levels of more than 10 ng/mL and/or a Gleason score greater than 6 receiving 75.6 Gy or more ($p < 0.05$). A positive biopsy was observed in only 7% (1/15) of patients receiving 81 Gy versus 48% (12/25) after 75.6 Gy, 45% (19/42) after 70.2 Gy, and 57% (13/23) after 64.8 Gy ($p < 0.05$). However, the 5-year actuarial risk of potency loss was 60%; doses of 75.6 Gy or more were correlated with late toxicity (RTOG scale 2 and 3: gastrointestinal 11% and 0.75%; genitourinary 10% and 3%).

Hanks et al. (32), also reporting on a dose-escalation study, concluded that patients with pre-treatment PSA levels less than 10 ng/mL did not benefit from dose escalation, and that the serious late morbidity of conformal radiation at 70 Gy was less than 3%. Patients with PSA values greater than 10 ng/mL benefitted from dose escalation beyond 70 Gy, but doses beyond 75 Gy resulted in more than 10% serious morbidity. Horwitz et al. (33), in a series of 160 patients with T1c tumours (non-palpable PSA detected), reported an 86% 5-year biochemical disease-free survival rate (ASTRO criteria), with 4% (6/160) having toxicities grade 3-4. A recent paper questioned the validity of the dose-response relationship. Twenty-two articles from the medical literature were reviewed and categorized into four groups based upon the endpoint analyzed (local control, biochemical control, pathological control, survival), underlining the lack of prospective randomized studies (two of 22 studies only). The authors concluded that the absolute improvement in outcome due to dose escalation, the subset of patients benefitting most, and the optimal dose remain to be defined (34).

8.3 Adjuvant post-operative radiotherapy

In some series, as many as 50% of all patients undergoing surgery are found to have pathological stage pT3 cancer. Among them the local failure rate has been estimated to be 25-68% (35). Post-operative radiotherapy appears to reduce both local recurrence rates and PSA levels (35, 36, 37); however, the impact on survival remains unproven. Valicenti and co-workers (38) matched 52 patients who received adjuvant radiotherapy within 3-6 months after surgery against 97 patients who underwent radical prostatectomy alone and were observed until PSA failure; 72 patients were included in the analysis. The 5-year freedom from PSA relapse rate was 89% (95% confidence interval (CI): 76-100%) for patients receiving adjuvant radiotherapy compared with 55% (95% CI: 34-79%) for those undergoing radical prostatectomy alone.

8.4 Interstitial radiotherapy (brachytherapy)

In order to deliver higher radiation doses to the prostate while sparing the surrounding tissue, the technique of interstitial radiotherapy has been refined and popularized during the last few years. There are two main ways to deliver brachytherapy.

Treatment with high-dose rate (HDR) interstitial radiotherapy involves leaving the radiation source within the prostate for a very short time to deliver its radiation. The isotope iridium-92 (Ir-92) is most often used, and HDR is commonly used in combination with external beam therapy to boost the dose. For patients, this means a few weeks of external beam therapy initially, then one operative procedure with the placement of needles and Ir-92 radiation, which is repeated after 2 weeks, and then another 2 weeks of external beam radiation (39). The results seem better than those of conventional external beam therapy, but only short-term results are available (39, 40). The incidence of side-effects, especially proctitis, seems to be higher than that seen after seed implants only and it has been stated that the method may have its best application in patients with T3 tumours (41).

Treatment with low-dose rate (LDR) interstitial radiotherapy provides a more convenient, single-session procedure. The radiation sources are permanently placed within the prostate. The two most commonly used isotopes are palladium-103 (Pd-103) and iodine-125 (I-125). They have a half-life of 17 days (Pd-103) to 60 days (I-125) days, and will thus have given off most of their radiation within 3-10 months, depending on the isotope used. The radioactive seeds are placed under ultrasound guidance. The operative procedure takes 1-2 hours and may be performed as an out-patient procedure. The short-term urethral symptoms may be severe (including acute urinary retention), but the long-term side-effect profile seems advantageous, with < 1-2% of patients reporting urinary incontinence and 1-2% experiencing proctitis (42). However, it must be stressed that patients who have undergone previous transurethral surgery are poor candidates for this treatment due to a high risk of developing incontinence. Impotence rates are reported to be around 25% but these may be age-dependent (43). A biochemical control rate of 83.5% at 9 years was achieved by Pd-103 monotherapy in patients with stage T1-T2 CaP (44). A seed implant as a single treatment may be recommended for patients with stage T1c-T2a disease, a Gleason score of less than 3 + 4 and a PSA level of less than 10 ng/mL (45).

The following selection criteria (Table 12) and contraindications (Table 13) for prostate brachytherapy have been proposed by the ASTRO/EAU/EORTC.

Table 12: Selection criteria for prostate brachytherapy

	Recommended Do well	Optional Fair	Investigational Do poorly
PSA (ng/mL)	< 10	10-20	> 20
Gleason score	5-6	7	8-10
Stage	T1c-T2a	T2b-T2c	T3
International Prostatic Symptom Score (IPSS)	0-8	9-19	> 20
Prostate volume (g)	< 40	40-60	> 60
Qmax ml/sec	> 15	10-15	< 10
Residual volume (cm ³)			> 200
TURP			+

Table 13: Contraindications for prostate brachytherapy

Contraindication
• Life expectancy less than 5 years
• Metastatic disease
• Recent TURP ¹ with persisting prostatic defect
• Bleeding disorders
• Prostate gland volume > 50 cm ³ (46)

¹ TURP = transurethral resection of the prostate.

Brachytherapy is currently available as a curative treatment for localized CaP. However, this treatment modality requires further evaluation due to the insufficient follow-up of recent series and the absence of comparative studies (47-48).

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9. TREATMENT: HORMONAL THERAPY (EXCLUDING ANTIANDROGENS)

In 1941, Huggins et al. (1) in a seminal publication described the favourable effect of orchiectomy and oestrogen administration on the progress of metastatic CaP and, for the first time, demonstrated conclusively the responsiveness of CaP to androgen deprivation.

9.1 Basics of hormonal therapy for CaP

Although not tumourigenic, testosterone is essential to the perpetuation of CaP (2). The testes are the source of the vast majority of the androgenic substances that support CaP; approximately 5% of the circulating androgen derives from the adrenal secretion of androstenedione and dihydroepiandrosterone. Any treatment that affects the level of testosterone is called hormonal therapy (3). The early treatments used orchiectomy and/or DES to reduce the supply of testosterone to the prostate (1, 4, 5). Although hormone-based therapy is unable to cure CaP, it is able to diminish the size of the tumour and its metastases quite dramatically and to slow down its growth. Surgical or medical androgen deprivation results in a median progression-free survival of 12-33 months and a median overall survival of 23-37 months in CaP patients with bone metastases (6).

9.2 Major categories of hormonal therapy for CaP

9.2.1 Surgical castration

The gold standard against which other treatments must be compared is bilateral orchiectomy. A bilateral orchiectomy or surgical castration is a direct way of eliminating the circulating levels of testosterone, which is still the mainstay for metastatic CaP. It decreases serum levels of testosterone considerably, although a very low level of testosterone remains known as the castration level. After orchiectomy, the prostate atrophies, ceases to function and the androgen-dependent part of the CaP shrinks or even disappears. The surgical procedure is well-tolerated by nearly all patients and can easily be done under local anaesthesia. A favourable response can be expected in about 80% of patients treated, and the mean duration of effectiveness averages 2.5 years (7). Whereas some older studies have pointed out that the results of orchiectomy are slightly inferior to those of oestrogen therapy (8), such differences have not been confirmed in other studies and therefore bilateral orchiectomy is still regarded as the gold standard of treatment (9). However, it is important to remember that for some men castration is an unacceptable assault on their manhood and such sentiments must be respected.

Furthermore, the declining incidence of CaP in recent years, combined with a shift to earlier stages at diagnosis and the development of pharmacological approaches to hormonal manipulation, have led to a dramatic decline in the utilization of bilateral orchiectomy (10).

9.2.2 Oestrogens

Oestrogens act mainly by activating the feedback mechanism on the pituitary-gonadal axis. They mimic testosterone in the feedback mechanism, block the secretion of LH and follicle-stimulating hormone (FSH) and thereby the production of testosterone. As a result, testosterone levels decrease to castration levels. Direct effects of oestrogens on the testes may also contribute to depressed androgen synthesis.

The most commonly used oestrogen is DES. Utilizing oestrogen therapy at a dosage level of 5 mg/day produces cardiovascular morbidity (7, 11, 12). A dose of 1 mg/day limits the risks; however, plasma testosterone levels do not fall to levels seen in orchiectomized patients (13). Furthermore, the testosterone level frequently begins to rise after 6-12 month of treatment. A dose of 3 mg/day provides better efficacy, but with an

increased risk of side-effects. However, DES is not a satisfactory option due to the cardiovascular disease associated with an elderly population that has co-morbid medical conditions (14).

In randomized studies by the Veterans Administration Cooperative Urological Research Group (VACURG) (11, 7), the Leuprolide Study Group (12) and the EORTC Urological Group (15, 16) cardiovascular toxicities of DES have been compared to other hormonal treatments. The type and frequency of cardiovascular toxicity was greater when DES was used in comparison to other non-oestrogen therapies.

However, DES retains some of its appeal due to the low costs, decreased vasomotor hot flushes and its effectiveness. Thus, other agents have been added in order to neutralize the cardiovascular side-effects. The data on DES in combination with aspirin and low-dose warfarin are discouraging and still demonstrate a cardiovascular risk in about 10% of patients. Therefore, the present data do not support DES in combination with an anticoagulant as a standard of care as they still demonstrate a persistent level of thromboembolic risk (17).

In conclusion, DES is the classic form of hormonal therapy. Its effectiveness was demonstrated years ago and was recently confirmed in a meta-analysis of endocrinal therapy for CaP (18). The significant cardiovascular side-effects, even at lower doses, remain a concern. Because of these factors and the advent of LHRH agonists and oral antiandrogens, DES has been relegated to a minor role in the treatment of CaP.

9.2.3 *LHRH-analogues*

More recently, LHRH analogues (LHRHa) have been advocated for the treatment of metastatic CaP. LHRH-analogues, such as leuprolide, goserelin and buserelin, have been shown to be as effective as DES without the risk of serious cardiovascular side-effects. LHRH-analogues are chemically similar to LHRH released by the hypothalamus and interfere with the feedback mechanism that stimulates and controls testosterone production in the testes. They induce an initial rise in LH and FSH release from the pituitary with a resultant surge in testosterone production by the Leydig cells, which is transient (3 to 5 days). This LH and FSH release induces regulatory loss of gonadotropin receptors in the testes. By chronic administration, a down-regulation of pituitary receptors is achieved. This consequently suppresses the secretion of LH and FSH from the pituitary, and testosterone production in the Leydig cells decreases until castration levels are reached usually within 21 to 28 days (12, 19). However 5-13% of patients treated with an LHRH agonist fail to reach castration levels of testosterone (20).

In a recent meta-analysis, single-therapy androgen suppression in men with advanced CaP was performed. Survival after therapy with an LHRH agonist was equivalent to that after orchiectomy and there was no difference in effectiveness between the LHRH-agonists (18).

LHRH-agonists have become the preferred method of androgen ablation in patients with advanced CaP, as their use is more acceptable to many patients than orchiectomy. Furthermore, it lacks the potential cardiotoxicity associated with DES. However LHRH-agonists can produce some harmful effects as they cause a surge in testosterone levels during the first weeks of therapy prior to causing its suppression. This so-called 'flare-up' phenomenon appears in up to 10% of patients with CaP and bone metastases (21). In addition to bone pain, cord compression and bladder outlet obstruction, another potentially severe side-effect is cardiovascular risk arising from the associated hypercoagulability. Concomitant antiandrogen therapy reduces, but does not eliminate, the flare responses in patients at high risk for flare. However, from the risk-to-benefit ratio, concomitant antiandrogen therapy is recommended for the first month of LHRH-agonist treatment, especially in patients with symptomatic bone metastases. For patients at risk for cord compression, other means of ablating testosterone might be considered, such as orchiectomy or LHRH-antagonists (22).

9.2.4 *LHRH-antagonists*

LHRH-antagonists directly inhibit LHRH without any initial stimulation of the LHRH receptor. The physiological response is a direct and rapid decrease in LH, FSH, and testosterone without any flare (23, 24). Histamine-mediated side-effects have limited their clinical use. Depot formulae have been tested in clinical studies and the flare phenomenon seems to be avoided (25, 26). Further studies are needed before these substances will enter widespread clinical use (27).

9.2.5 *Early versus delayed hormonal therapy*

The timing of hormone therapy in patients with advanced CaP remains controversial (28). Although evidence from the VACURG data (7) indicated a potential benefit of immediate hormone treatment in terms of time to progression and disease-specific survival, it also supported the possibility of deferred treatment (29).

Patients presenting with metastatic CaP can be categorized into three groups. At present, most patients seen with metastases are those identified as having lymph-node disease when being assessed for curative therapy. The second group consists of patients with a high level of PSA, without symptoms, who are found incidentally to have asymptomatic bone metastases or metastases in soft tissue. The third group, who previously comprised about half of patients presenting with metastatic CaP, are those presenting with painful metastases (30). There can be little doubt regarding the treatment at the outset of the second and third group

of patients with hormone therapy. The question is whether the mere presence of lymph-node metastases or painless bony or soft-tissue metastases justifies the side-effects of long-term hormone therapy (31).

Data from the MRC (32, 33), the EORTC Urological Group (15, 34, 35) and the Eastern Cooperative Oncology Group (ECOG) (36) indicates that the survival and welfare of patients with advanced CaP could be considerably better with immediate hormone therapy rather than deferred treatment.

A number of studies have shown a benefit in progression-free survival in the treatment of patients with lymph-node disease. Only one study has shown an advantage in overall survival (37). All studies of hormone therapy in asymptomatic and symptomatic metastatic disease have shown that serious complications of the disease can be avoided by offering hormonal therapy when the diagnosis is established. With the new generation of antiandrogens, differentiation therapies, and possibly alpha-reductase inhibitors, hormone therapy causes many fewer side-effects than in the past and can be tolerated for longer periods of time. An aim of early hormonal therapy and its justification is a possible improvement in the quality of life of patients with metastatic CaP, whose quantity of life cannot be lengthened. However, patients should be strongly encouraged to enter clinical trials to answer this question (28).

9.2.6 Intermittent androgen blockade

Patients treated with permanent androgen blockade usually relapse and die secondary to the ability of CaP to progress to an androgen-independent state of growth. Based on experimental and preclinical studies, intermittent androgen blockade (IAB) with LHRH-analogues appears to be a potential alternative to permanent androgen blockade. Through the cycling of reversible androgen suppression, there appears to be recovery of apoptosis and subsequent slower progression to an androgen-independent state (38, 39). Phase II trials have demonstrated the feasibility of IAB but lack the statistical power to show its equivalence to continuous androgen blockade (40). Despite the lack of data, IAB is now widely used in patients with CaP. IAB might provide a more tolerable and more economical form of hormonal therapy for younger men who are likely to be receiving hormonal treatment for many years.

Given the lack of sufficient long-term data it is mandatory to explain to the patient that IAB is an investigational rather than a standard to androgen blockade, and to record the fact that the patient understands this distinction. Phase III trials to evaluate the comparative efficacy of IAB are now underway. However, until the results of these trials are available, this approach remains experimental (39, 41).

9.3 Other hormonal treatments

Other treatments have been used as first- and second-line therapy for patients with metastatic CaP. However, for first-line therapy they are not standard care.

9.3.1 Estramustine

Estramustine is a molecule that combines oestradiol and nitrogen mustard. The drug is both oestrogenic and cytotoxic. Its main indication is second- or third-line treatment in hormone-refractory CaP. Side-effects are mainly those of oestrogens (42). Furthermore, in hormone-refractory cancer of the prostate (HRCaP), the combination of estramustine and cytotoxic chemotherapy (e.g. vinblastine) has been found to be effective. Combination regimens incorporating new active agents (e.g. mitoxantrone, taxanes) have demonstrated significant activity in this setting, renewing interest in the use of chemotherapy to treat HRCaP (43, 44).

9.3.2 Gestogens

Gestogens have been used in the treatment of CaP as they inhibit the enzymes, dehydrogenase and isomerase, which are necessary for steroid metabolism. They have antigonadotropic properties, thus suppressing LH and FSH. Furthermore, they compete with testosterone in target cells as substrates for 5-alpha-reductase. Megestrol acetate and medroxyprogesterone acetate have been used in Phase III trials but have turned out to be less effective than DES or antiandrogens (16).

9.3.3 Ketoconazole

Ketoconazole is an antimycotic drug, which in larger doses interferes with androgen synthesis. It has been used in studies in patients with CaP, but side-effects are considerable and careful monitoring of adrenal and liver function is necessary (45).

9.3.4 Aminoglutethimide

Medical ablation of the adrenals can be achieved by the administration of aminoglutethimide. It blocks androgen synthesis by inhibiting desmolase activity and destroying cytochrome P450. Side-effects are serious and cortisol has to be added to inhibit adrenocorticotropin (ACTH) release induced by the feedback mechanism (46).

9.4 Side-effects of hormonal therapy

The major side-effects of any hormonal treatment that eliminates testosterone is loss of sexual desire and impotence. Hot flushes, altered and diminished body hair, and breast tenderness occur to varying degrees with these therapies. Hot flushes occur more commonly in patients receiving an LHRH-agonist or with bilateral orchiectomy. Side-effects are listed in Table 14.

For patients who have hydronephrosis or bone metastases, it is important to know that there is often a transient worsening of the metastases when beginning treatment with an LHRH-agonist. Thus, combination therapy with an antiandrogen is advisable to avoid this effect.

Table 14: Complications of CaP treatments. Adapted from Catalona (47)

Treatment	Complication (incidence)	Comment
Orchiectomy	Hot flushes Decreased libido and sexual potency Gynaecomastia Wound infection (1-3%)	Hot flushes treated with clonidine or megestrol acetate
DES	Gynaecomastia Thromboembolism Fluid retention Gastrointestinal upset Decreased libido and potency	Prevention by pre-treatment breast irradiation
LHRH-analogues	Decreased libido and sexual potency	Initial flare-up (5-10%) blocked by an antiandrogen
Gestogens	Fluid retention Shortness of breath Gynaecomastia Thromboembolism	Cardiovascular side-effects less severe than those associated with oestrogens
Ketoconazole	Nausea	Inhibits adrenal steroidogenesis:
Aminoglutethimide	Hepatotoxicity	cortisone must be substituted
Estramustine	Gynaecomastia (8-10%) Gastrointestinal upset	Affects mitotic spindle function

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10. TREATMENT: HORMONAL THERAPY WITH ANTIANDROGENS

Suppression of androgen stimulation of the prostate gland remains the cornerstone of the management of locally advanced or metastatic CaP. 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 androgens at the cellular level using compounds known as antiandrogens. Alternatively, these two treatment modalities can be combined in order to achieve what is commonly known as maximal androgen blockade (MAB) or complete androgen blockade (CAB).

Antiandrogens are classified according to their chemical structure as either steroidal antiandrogens (e.g. cuprotene acetate [CPA] or medroxyprogesterone acetate) or non-steroidal antiandrogens (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 also have progestational properties, with central actions on the pituitary gland (1). The practical consequences of these differences are that non-steroidal antiandrogens do not lower serum testosterone but tend to increase it, whereas steroidal antiandrogens significantly lower the levels of both serum testosterone and LH, which might reduce libido and sexual potency. Due to the effects of non-steroidal antiandrogens on serum androgens, uro-oncologists have been reluctant to use these agents outside the CAB setting, fearing that persistently normal or supranormal levels of circulating androgens may ultimately overcome the available antiandrogens and have a stimulatory effect on the tumour (1). It should be emphasized, however, that this hypothesis has never been proven from clinical or experimental data (2).

10.1 Non-steroidal antiandrogens

Three non-steroidal antiandrogens are currently available:

- Nilutamide: 150-300 mg/day
- Flutamide: 250 mg three times daily (due to a shorter half-life)
- Bicalutamide: 150 mg/day (the monotherapy regimen is not yet clearly defined, but this agent has a half-life longer than flutamide [3]).

Antiandrogen monotherapy has been suggested to be an effective tool for the management of advanced CaP as a first-line therapy in selected cases, i.e. in younger patients with locally advanced or low-volume metastatic disease (PSA level < 100 ng/mL), for whom quality of life and preservation of sexual function are important (4).

10.1.1 Experience with nilutamide

Nilutamide is not recommended by the manufacturer for use as monotherapy. Experience with nilutamide in this setting is limited to a single study in which 26 previously untreated patients with metastatic CaP were treated with nilutamide, 100 mg three times daily. The results showed that 38.5% of patients experienced a partial response; the median progression-free survival time was 9 months, with an observed median survival time of 23 months. A total of 50% of patients remained sexually potent. The most frequently reported side-effects were visual disturbances, alcohol intolerance, respiratory disturbances (which may be related to interstitial pneumopathy) and hepatic dysfunction (5). The clinical utility of this agent as monotherapy would appear to be limited by a high incidence of drug-related side-effects (6). However, a recent report by Desai et al. suggested that nilutamide may show some activity in patients who progressed with prior antiandrogen therapy (7).

10.1.2 Experience with flutamide

Flutamide was the first antiandrogen to become available and has been studied as monotherapy for more than 20 years. Early, relatively short, Phase II monotherapy studies showed flutamide to be effective in the treatment of locally advanced or metastatic CaP, although the reported response rates are difficult to correlate with currently used endpoints. The main advantage of the drug in these early studies was undoubtedly the preservation of sexual function, seen in up to 80% of patients who were potent prior to initiation of therapy (8-13).

Phase III studies with flutamide are often difficult to evaluate because of certain drawbacks, such as the use of suboptimal comparators and inadequate endpoints, limited follow-up and insufficient power to detect a significant difference in outcome. No differences were found between flutamide, 750 mg/day or 1500 mg/day, and DES, 1 mg/day (14) or 3 mg/day (15), in terms of time to progression or progression-free survival rates in early, small studies. When comparing estramustine phosphate, 280 mg twice daily, with flutamide, 250 mg three times daily, flutamide-treated patients had a higher rate of relapse but there was no difference in mortality (16). Three recent, randomized, Phase III trials have compared flutamide with DES, orchiectomy or MAB (17-19).

Chang et al. randomized 92 patients between DES, 1 mg three times daily, and flutamide, 250 mg three

times daily, and found DES to be superior to flutamide in terms of both time to progression and overall survival (17). Boccon-Gibod et al. randomized 104 patients to receive flutamide, 250 mg three times daily, or orchiectomy, and found no difference in progression-free survival or overall survival time between the two groups (18). Pavone-Macaluso found equal effect in patients randomized to receive either flutamide or MAB (19).

The main side-effects of flutamide are breast tenderness, hepatic dysfunction and diarrhoea.

10.1.3 Experience with bicalutamide

Bicalutamide is a highly selective, non-steroidal, antiandrogen with limited ability to cross the blood-brain barrier. This means that bicalutamide has little effect on serum LH and testosterone levels, at least in the animal model. However, the elevation of LH and serum testosterone levels has been documented in treated patients (20).

The effect of bicalutamide, 50 mg/day, 100 mg/day and 150 mg/day, has been compared with medical or surgical castration in several studies. An overview analysis of more than 1000 patients showed a significant difference in favour of castration compared with bicalutamide, 50 mg/day, in terms of time to progression and median survival (21). Bicalutamide, 150 mg/day, was as effective as castration in M0 patients, producing significant improvement in sexual interest and physical capacity; in M1 patients, bicalutamide, 150 mg/day, was not as effective as castration (22).

The side-effects of bicalutamide are more common after monotherapy (i.e. gynaecomastia in 25-49% of patients and breast pain in 34-40%) than when given in combination with LHRH analogue (LHRHa). The elevation of liver enzymes has also been reported (22).

To date, bicalutamide appears to have some advantage over flutamide and nilutamide in terms of tolerability (23).

Iversen et al. updated Tyrrell's study, which compared bicalutamide monotherapy with castration in patients with non-metastatic locally advanced CaP: after a median follow-up of 6.3 years, no significant difference in overall survival and time to progression between the two groups was found. On the contrary, significant benefits in sexual interest and physical capacity were reported. Gynaecomastia (49.4%) and breast pain (40%) were the most evident side-effects of treatment with bicalutamide (24).

The effect of bicalutamide monotherapy has been compared with placebo in 8113 patients with localized or locally advanced CaP: a significant decrease in the risk of disease progression was reported after a median follow-up of 2.6 years (25).

10.2 Steroidal antiandrogens (CPA)

Cyproterone acetate (CPA) is a potent steroidal antiandrogen and has gestogenic properties leading to the suppression of LH and testosterone production. It was established as a therapy for CaP in a number of early studies, including EORTC protocol 30761, which compared CPA, 250 mg/day, with DES, 3 mg/day. In both M0 and M1 patients, there was no difference with respect to time to cancer progression or overall survival (26). The final analysis with regard to the main endpoints, time to progression and survival, are still pending for EORTC protocol 30892, which compared flutamide monotherapy with CPA monotherapy in untreated metastatic CaP (27). Final results related to the evaluation of sexual functioning, prior to and during treatment, indicate that gynaecomastia, diarrhoea, nausea and liver function deterioration occurred more frequently with flutamide, while thrombotic events were seen more frequently with CPA (28). The advantage of flutamide in preservation of sexual function is statistically not significant and must be balanced against the side-effects of flutamide and other pure antiandrogens, which may exceed those of CPA, especially with respect to gynaecomastia. Hepatic toxicity may limit the long-term use of both drugs (28).

10.3 Combination therapies

10.3.1 Combined androgen blockade

Despite the plethora of studies evaluating CAB in which LHRHa or surgical orchiectomy is supplemented by adding an antiandrogen, there seems to be a lack of consensus as to its value in the management of CaP. Out of 22 papers on CAB, only three were able to demonstrate a statistically significant longer time to disease progression and longer average survival time (3-6 months) in CAB groups compared with surgical or medical hormone ablation alone (29-31). However, a meta-analysis including almost all trials, published and unpublished, showed no significant advantage in terms of efficacy for CAB compared with castration alone (32). In agreement with this, a large randomized trial comparing orchiectomy, with or without flutamide, could find no survival benefit in the combination arm, not even in the subgroup of patients with minimal metastatic disease (33).

However, a recent paper re-examined the design and results of three trials. According to the authors, most studies were planned to detect an over-optimistic difference in survival; immature data were published, and the survival curves showed that statistical assumptions were not fulfilled (34).

10.3.2 Minimal androgen blockade

A combination of finasteride plus low-dose non-steroidal antiandrogen has been compared with castration in advanced CaP. No difference in efficacy after 24 months follow-up between these two therapies was reported. It was concluded that in sexually active patients with small volume, localized disease, minimal androgen blockade might well be a reasonable therapy to start with (35).

10.3.3 The antiandrogen withdrawal phenomenon

Patients with metastatic CaP receiving androgen suppression usually experience a rise in PSA level at a median of 2 years after starting treatment. Once a patient has relapsed, second-line endocrine therapy may produce a brief clinical response in 20-40% of cases, but all cancers will progress to become androgen independent and hormone insensitive (HRCaP). The median survival time for these patients is less than 1 year. It was demonstrated that discontinuation of flutamide in patients who relapsed on CAB could result in significant clinical benefit for 4-6 months in one-third of cases. This phenomenon, known as 'androgen withdrawal syndrome', has also been described with bicalutamide and other antiandrogens, and represents the first-line of treatment after failure of hormonal manipulation (36). The molecular basis for this syndrome is not completely understood, but data suggest that mutations in the androgen-receptor gene or gene amplification of the androgen receptor may be responsible for the paradoxical effect observed (37-39).

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11. 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
	Radical prostatectomy	Optional in young patients with a long life expectancy, especially for poorly differentiated tumours
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation
	Hormonal	Not an option
	Combination	Not an option
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
	Radical prostatectomy	Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with a 5-10 year life expectancy and poorly differentiated tumours (combination therapy is recommended; see below)
	Hormonal	Symptomatic patients unfit for curative treatment
	Combination	NHT + radical prostatectomy: no proven benefit NHT + radiotherapy: better local control. No proven survival benefit Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumours
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumours, and a life expectancy < 10 years
	Radical prostatectomy	Optional for selected patients with T3a and a life expectancy > 10 years
	Radiotherapy	T3 (N0) with > 5-10 years of life expectancy. Dose escalation 70 Gy seems to be of some benefit. If this is not available, a combination with hormonal therapy could be recommended (see below)
	Hormonal	Symptomatic patients, extensive T3-T4, high prostate-specific antigen level (> 25 ng/mL), unfit patients
	Combination	Radiotherapy + hormonal seems better than radiotherapy alone NHT + radical prostatectomy: no proven benefit
N+, M0	Watchful waiting	Asymptomatic patients. Driven by the patient
	Radical prostatectomy	No standard option
	Radiotherapy	No standard option
	Hormonal	Standard therapy
	Combination	No standard option. Patient driven
M+	Watchful waiting	No standard option
	Radical prostatectomy	Not an option
	Radiotherapy	Not an option (given for cure)
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment
	Combination	Not an option

12. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

12.1 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 cryosurgical ablation of the prostate (CSAP), high-intensity focused ultrasound (HIFU) or radiofrequency interstitial tumour ablation (RITA), are outside the scope of these guidelines.

12.2 Why follow-up?

The first question to be answered is: 'If failure after curative treatment is so common, are follow-up efforts worthwhile?' The number of patients who will have a detectable PSA level after radical prostatectomy varies between published series. The Johns Hopkins group reported 16%, 26% and 34% biochemical progression after 5, 10 and 15 years, respectively. At the Cleveland Clinic, the 5-year biochemical progression rate was as high as 39% in stage T1-T2 CaP (1, 2). Similar data have been presented by European centres (3). It has also been shown that the risk of relapse after radical prostatectomy can persist even after 5 years, suggesting that follow-up should be continued for a longer time period (1, 4).

After radiotherapy, there is a similar course of events. A considerable proportion of patients will have a rising PSA level, and disease recurrences will continue to become obvious, even after 15 years of follow-up (5-7). 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.

The second question to be answered is: 'What is the reason for follow-up?' Reasons may vary depending on the treatment given, patient age, co-morbidity 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.

Please refer to Section 14 for discussion about treatment options.

12.3 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. In conjunction, 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.

12.3.1 PSA monitoring

The measurement of PSA level is a cornerstone of 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, 8-10). It is recommended that the finding of a single, elevated, serum PSA level should be re-confirmed before treatment is altered.

It is worth pointing out that the use of hormonal therapy before, during, or after curative treatment may make PSA unreliable as a tumour marker for follow-up. It has been shown that a 3-month course of LHRHa treatment prior to radical prostatectomy can delay PSA progression by approximately 1 year, without obvious impact on later progression-free survival (11). A 3-year course of LHRHa, as advocated for bulky localized CaP treated with radiotherapy, may well have an even larger influence on PSA level as a follow-up tool (12, 13).

12.3.2 Definition of PSA progression

The level of PSA at which to define treatment failure differs between radical prostatectomy cases and radiation-treated cases. Following RRP, two consecutive values of 0.2 ng/ml or greater appear to represent an international consensus defining recurrent cancer (14, 15). Following radiation therapy, a reasonable definition of biochemical relapse is three consecutive increases according to the recommendation of the ASTRO (16).

12.3.3 PSA monitoring after radical prostatectomy

PSA is expected to be undetectable within 3 weeks after a successful radical prostatectomy (17). 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 (18, 19). 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) (20, 21). This means that in patients with 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. The PSA cut-off point recommended should be no lower than 0.2 ng/mL. 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 (22). Furthermore, no adjuvant treatment given at an even earlier stage has proved to be beneficial to patients with PSA relapse. Therefore, the use of an ultrasensitive PSA assay is not justified for routine follow-up after radical prostatectomy. If ongoing randomized trials show that early adjuvant treatment after radical prostatectomy improves survival, this issue should be reconsidered.

12.3.4 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 1 ng/mL seems to be associated with a favourable outcome, at least within the 3-5 year perspective (23). Lately, however, it has been suggested that this nadir level should be reduced to less than 0.5 ng/mL. This is because only 4% of treated patients with a nadir of less than 0.5 ng/mL failed therapy after 40 months of follow-up compared with 26% of those with a nadir of 0.6-1.0 ng/mL (24). The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. 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 (7).

There is a consensus that a rising PSA level is an early sign of treatment failure. This has led the ASTRO to define failure after radiation therapy as three consecutive rises in PSA level, irrespective of the nadir value (16). It is important to realize that this definition may cause outcomes that are difficult to interpret in certain situations. Pending on timing of the PSA measurements, the time before a biochemical progression is ultimately recognized may be delayed by several years. Also, these criteria are hard to use after adjuvant/neoadjuvant hormonal therapy, commonly used together with radiotherapy.

12.3.5 Digital rectal examination (DRE)

Digital rectal examination 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 (20, 21). 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.

12.3.5 Transrectal ultrasonography and biopsy

Transrectal ultrasonography and biopsy have no place in the routine follow-up of asymptomatic patients. Transrectal ultrasonography cannot stand alone as a diagnostic tool, but must be combined with biopsy to establish the presence of local disease recurrence. The purpose of the investigation is to confirm a diagnosis of local disease recurrence. It is only warranted if the finding of a local recurrence affects the treatment decision. Please see Section 14 for a more detailed discussion.

12.3.6 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 (20, 21).

12.3.7 Computed tomography or magnetic resonance imaging

Computed tomography or MRI have no place in the routine follow-up of asymptomatic patients. They may be used selectively in the evaluation after biochemical failure (see Section 14).

12.4 When to follow-up?

Most patients who fail treatment for CaP do so early, even if failure only becomes clinically obvious after years (1-7). The patient should therefore be followed-up more closely during the first years after treatment when the risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at the following intervals: 3, 6 and 12 months post-operatively, every 6 months thereafter until 3 years, and then annually. The purpose of the first clinic visit is mainly to detect treatment-related complications and to assist patients in coping with the new situation. Tumour or patient characteristics may allow alterations to this schedule; for example, patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimen-confined tumour. Obviously, advanced age or associated co-morbidity may make further follow-up in asymptomatic patients superfluous.

12.5 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.
2. After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL is mostly associated with residual or recurrent disease.
3. After radiation therapy, a rising PSA level, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.
4. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.
5. Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the plan of treatment. In most cases, this is not necessary.
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 subject is sparse.
7. Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If the patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.

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13. FOLLOW-UP: AFTER HORMONAL TREATMENT

13.1 Introduction

A large proportion of the 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.

Another group of patients are those with biochemical failure only after treatments with curative intent. These patients may in, general, have a more protracted course.

13.2 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 and 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 excess 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. Currently, the issue of early versus late initiation of non-hormonal treatment in HRCaP 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.

13.3 How to follow-up?

13.3.1 PSA monitoring

Prostate-specific antigen is a good marker with which to follow the course of metastatic CaP and is more reliable than PAP. Many authors have studied 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 (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 to predict the duration of response to treatment (3).

Treatment response may be assessed utilizing the change in serum PSA level as a surrogate endpoint

after hormonal treatment has been initiated. The PSA decrease can be evaluated in terms of the absolute PSA level at 3 months or 6 months, the nadir PSA during treatment, or the rate at which PSA decreases (2, 4, 5). The PSA value after 3 and/or 6 months of hormonal treatment has been reported as being related to prognosis (3, 5-7). However, this criterion has no absolute value in any individual patient (5, 8). The subgroup of patients with a normal or undetectable PSA level at 3 and 6 months corresponds to the group with the highest probability of long-lasting response to endocrine treatment.

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 (1, 9, 10). 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 with normal PSA levels has been reported to occur in 15-34% of cases (9, 11).

Two mechanisms could explain the occurrence of tumour progression despite a normal PSA level in the context of androgen suppression. Firstly, antiandrogen activity and the fall in PSA level during endocrine treatment are not always proportional to the reduction in tumour volume (10, 12-16). Secondly, the proportion of poorly differentiated cells in the tumour, which secrete less PSA, increases during endocrine treatment (17-20).

13.3.2 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 (21).

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 (22). In this scenario, the determination of bone specific alkaline phosphatase might be helpful.

13.3.3 PAP monitoring, bone scan, ultrasound and chest X-ray

The monitoring of PAP levels no longer has any value since the introduction of PSA measurement (9). 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 (23-25). 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.

13.4 When to follow-up?

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

13.4.1 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.

13.4.2 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.

13.4.3 Hormone-refractory patients

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

13.5 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.
2. Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.
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.
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.
5. When disease progression occurs or if the patient does not respond to the treatment given, the follow-up needs to be individualized.
6. Routine imaging in stable patients is not recommended.

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14. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENTS WITH CURATIVE INTENT

14.1 Rising PSA following curative treatment

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 25% of all patients undergoing radiation therapy or radical prostatectomy will develop local or distant recurrences within 3-5 years after initial therapy (1-4).

Treatment failure has been redefined during the last decade. Earlier, treatment failure was defined as a clinical recurrence on DRE or the development of metastatic disease. Presently, treatment failure is defined as a rising PSA level. Pound et al. demonstrated that no patient followed for more than 5 years developed any recurrence without a concomitant PSA rise (5).

14.1.1 Definition of PSA progression

The level of PSA at which to define treatment failure differs between radical prostatectomy cases and radiation-treated cases. Following RRP, two consecutive values of 0.2 ng/ml or greater appear to represent an international consensus defining recurrent cancer (6, 7). Following radiation therapy, a reasonable definition of biochemical relapse is three consecutive increases according to the recommendation of the ASTRO (8).

14.1.2 Incidence of PSA recurrence

Depending on the patient selection, approximately 25% of the patients treated either by radical prostatectomy or radiation therapy will develop PSA recurrence within 3-5 years following primary therapy (1-4, 7).

14.1.3 Local or systemic relapse

With regard to further management, once PSA relapse has been diagnosed, it is of major importance to find out whether the recurrence has developed at local or distant sites. About 50% of the patients having undergone RRP will have local disease and the remainder will have either distant disease alone, or distant and local disease (9).

Timing of PSA increases after surgery, PSA velocity and PSA doubling time are important parameters helping to differentiate between local or distant relapse. PSA elevations developing within the first 2 years following surgery are associated with distant recurrences (9). It was shown that a median PSA doubling time of 4.3 months is associated with distant relapse, whereas a median PSA doubling time of 11.7 months predicts local failure (10). According to one study (11), 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.

It is well worth looking back at the patient's pathology report when a biochemical failure has been noticed. Patients with adverse pathology (stage pT3b, stage N1, poorly differentiated tumours) usually have both local and distant or distant failure.

14.1.4 Evaluation of PSA progression

In recent years, most patients with PSA progression following initial curative therapy have undergone radiographic studies or biopsies of the prostatic fossa and the vesicourethral anastomosis to confirm disease 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. (11) that biochemical failure precedes clinical disease by 6-48 months.

Traditionally, bone scans and abdominal CT scans have been applied to evaluate PSA elevations following primary treatment. However, both imaging studies 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. (12) studied 144 bone scans in 93 patients with PSA recurrence after RRP. 122 patients had undergone RRP without any hormonal treatment, whereas 22 patients received either neoadjuvant or adjuvant androgen deprivation. 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. However, there might be a slight difference between patients after RRP compared to patients after radiation therapy, as demonstrated by Johnstone et al. (13), with 5% and 30% of the bone scans being positive, respectively.

Data are sparse on the results of abdominal and pelvic CT for PSA-only recurrence after definitive therapy. One small study indicated that patients with a PSA of > 4 ng/ml may have a detection rate of nodal enlargement as high as 50%. Others have concluded that CT scans are of very limited value if the PSA is < 30 -40 ng/ml or rapidly rising (> 20 ng/ml/year) (14).

Immunoscintigraphy using a radio-labelled monoclonal antibody based on PSMA called $^{111}\text{indium}$ capromab pentetide 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 RRP (15-16). Independent of the PSA serum concentration, the capromab pentetide scan shows a diagnostic yield of 60-80% and it might help to stratify therapy according to the location of positive sites. However, clinical experiences are still too limited to recommend routine diagnostic application of this imaging study.

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 RRP 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% (17-20). Only in the presence of a palpable lesion or a hypoechoic lesion on TRUS can the diagnostic yield of the biopsy be improved to approximately 80%. Furthermore, there is a strong correlation between the positive biopsy rate and PSA serum concentrations (17-20). 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. Based on these findings, routine anastomotic biopsy is not indicated and the use of PSA and PSA doubling time 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, unless salvage radical prostatectomy or other salvage procedures are being considered (21).

14.2 Treatment of PSA-only recurrences

14.2.1 PSA-only recurrence after RRP

After RRP, therapeutic options include: observation; radiation therapy to the prostatic bed; (complete) androgen blockade; intermittent androgen deprivation; combination of antiandrogens with 5-alpha-reductase inhibitors; and even early chemohormonal approaches. The same therapeutic options might be applied for PSA recurrences following radiation therapy; in addition, salvage prostatectomy, cryotherapy and brachytherapy might be indicated in carefully selected patients.

14.2.2 Radiation therapy for PSA-only recurrence

Considering the numerous studies on the use of radiation therapy for PSA-only recurrence following RRP, there is a growing body of parameters predicting outcome that might be helpful to stratify between observation, radiation and hormonal therapy.

As confirmed by various studies, the pre-radiation PSA appears to be of critical importance in order to obtain optimal treatment results (22-30). Applying a pre-radiation cut-off of ≤ 2.5 ng/ml, Wu et al. (22) and Schild et al. (23) 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. (24) demonstrated a disease-free survival rate of 83% versus 33% in patients with a PSA-only recurrence of less than or greater than 2.0 ng/ml, respectively. Nudell et al. (25) reported a progression-free survival rate of 58% and 21% in patients who had undergone radiation of the prostate bed if their PSA serum levels were below or greater than 1.0 ng/ml, respectively. Based on these data, the ASTRO has published a consensus paper recommending a dose of at least 64 Gy when the PSA level is < 1.5 ng/ml after RRP (21). However, there is still a lack of data of prospective randomized trials and all studies being performed lack long-term follow-up so that the impact on survival is unknown.

In patients with a high pre-radical prostatectomy PSA > 20 ng/ml, a Gleason score ≥ 7 , an extensive positive surgical margin and extensive extraprostatic tumour growth (pT3b, pT_xpN1), immediate hormonal therapy might be a better alternative (26-30). These recommendations are corroborated by a recent study (27) demonstrating that none of the patients with a Gleason score 8, pT3b or pT_xpN1 CaP remained disease-free

following radiation therapy for PSA-only recurrence after radical prostatectomy. Similarly, other groups have reported disappointing disease-free survival rates after salvage radiotherapy (28-30).

14.2.3 Hormonal therapy

Hormonal therapy might be considered as an immediate therapeutic approach for patients who have unfavourable prognostic factors after radical prostatectomy indicating systemic disease, such as pre-radical prostatectomy PSA of > 20 ng/ml, pT3b, pTxN1, and extensive positive surgical margins.

Recommendations for optimal therapeutic management of PSA-only recurrences following RRP or radiation therapy are difficult to make since we cannot rely on prospective randomized trials. There are only very few studies analyzing the clinical utility of early androgen deprivation in locally advanced (M0) and metastatic CaP (31, 32). If it is true that the M0 category of patients with pTxN1 disease having undergone RRP reflects PSA-only recurrences, then 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 (33, 34). 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 (35). Furthermore, the risk of objective progression of the disease was significantly reduced in patients receiving bicalutamide, 150 mg (36). Antiandrogens might represent a viable alternative to other modes of androgen deprivation for the management of PSA-only recurrences, especially in young and otherwise healthy men.

Hormonal therapy might be considered as an immediate therapeutic approach for patients with unfavourable prognostic factors after RRP indicating systemic disease, such as a pre-radical prostatectomy PSA > 20 ng/ml, pT3b, pTxN1 and extensive positive surgical margins.

Non-traditional ways of hormonal therapy for PSA-only recurrence include intermittent androgen deprivation (IAD) and oral therapies combining antiandrogens with 5-alpha-reductase inhibitors (37-44).

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 the routine clinical application of IAD, despite potential benefits. Summarizing the series in which PSA-only recurrences were treated by IAD (37-41), PSA threshold levels at study entry varied significantly as did the PSA level at discontinuation of hormonal therapy. However, 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 intra-prostatic conversion of testosterone to dihydrotestosterone (DHT) and blocking the intracytoplasmic DHT receptor (42-44). In the latest report (44) 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.

14.3 Observation

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

14.4 Management of PSA failures after radiation therapy

Besides hormonal therapy or observation-selected cases might undergo salvage prostatectomy or salvage cryosurgery for radiation failures (45-50). Salvage RRP, however, has not gained widespread acceptance due to its associated morbidity (i.e. incontinence, local recurrences and rectal injuries). However, in well-selected patients, salvage RRP might result in long-term disease-free survival. One has to consider that most series reporting on salvage RRP included patients who were treated in the pre-PSA era without modern radiotherapeutic techniques and local recurrences 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 RRP had to undergo anterior or total extirpation for locally extensive disease associated with a high rate of local recurrences and a mean time to progression of only 1.3 years (45-48).

Current reports describe more optimistic outcomes after salvage RRP. In the series of Gheiler et al. (50), 40 patients with a mean PSA of 14 ng/ml underwent salvage RRP. 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 Wajzman (49), 24 patients underwent radical cystoprostatectomy or radical prostatectomy with neoadjuvant androgen deprivation. Neoadjuvant androgen deprivation was associated with a lower rate of positive surgical margins (21%). 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 (51) demonstrated a low complication rate, good post-operative continence and only one biochemical recurrence 36 months after salvage RRP.

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

14.4.1 Salvage cryosurgery 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. (52) reported on 150 patients who had undergone salvage cryotherapy for PSA recurrences following radiotherapy ($n = 110$) or other extensive pre-treatments ($n = 40$). After a mean follow-up of 13.5 months, 58% of the patients exhibited biochemical failure and only 31% demonstrated undetectable PSA serum levels. The complications associated with salvage cryotherapy were significant and occurred in basically all patients. Urinary incontinence (73%), obstructive symptoms (67%), impotence (72%) and severe perineal pain (8%) represented the main complications. After a 1-year follow-up, incontinence resolved in the majority of patients with a persistent significant incontinence in 28% of the patients (53). Unfortunately, there are no data available on the long-term biochemical failure rate.

14.4.2 Salvage brachytherapy for radiation failures

The experience with salvage brachytherapy for radiation failures is very limited and there is only one study available, including a representative number of patients and a mean follow-up of 64 months (54-56).

Grado et al. (56) treated 49 patients with transperineal transrectal ultrasound guided brachytherapy and reported 3- and 5-year disease-free survival rates of 48% and 43%, respectively. Since the frequency of associated complications was much lower than for salvage radical prostatectomy and cryosurgery, salvage brachytherapy deserves more attention in further studies.

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15. TREATMENT: SECOND-LINE TREATMENT OF CAP AFTER HORMONAL THERAPY

15.1 Background and definition

Preventing the growth and progression of cancer that has progressed despite initial androgen ablation therapy remains a significant challenge to clinicians. No major therapeutic strategies with an impact equal to that of androgen ablation have been devised. Hormone-refractory cancer of the prostate is a very heterogeneous disease that includes a variety of different patient cohorts with significant different median survival times. Many different terms have been used to describe cancers that relapse after initial hormonal ablation therapy, including HRCaP, androgen-independent cancers and hormone-independent cancers (1). The precise definition of recurrent or relapsed CaP remains controversial. Recently, the PSA working group has published practical recommendations that should be adhered to when defining HRCaP (2). Hormone-sensitive CaP has to be differentiated from true HRCaP 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.

For clinical purposes, HRCaP should be considered in the following circumstances:

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. Progression of osseous or soft tissue lesions (3).

15.2 Mechanisms of androgen independence

CaP is a heterogeneous disease and our understanding of the mechanism of androgen independence remains incomplete (3, 4). Androgen ablation provides a selective advantage to androgen-independent cells that grow and eventually comprise the majority of the tumour (5). 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 (6-8). 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.

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 regulation of microtubule integrity (9-11). The fact that the most active chemotherapeutics in HRCaP 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 has been shown to predict an aggressive clinical course (12-16).

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 (17, 18).

15.3 Assessing outcome of treatment in androgen-independent CaP

Between 80% and 90% of patients do not have bidimensionally measurable disease. Patients who have cancers with primarily soft tissue disease frequently have a different prognosis to those who have only osseous metastases. Osteoblastic bone metastases remain difficult to quantify accurately. There remains no general agreement regarding the methodology of measuring response (19-22). Determination of the cause of death in CaP patients is often unreliable, suggesting that overall, rather than disease-specific, survival rate may be a more valid endpoint (23).

Many contemporary studies use PSA as a marker of response, although there is no general consensus on what should be the magnitude and duration of decline in PSA level. In this context, the greatest use of PSA 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. Thus, knowledge of the effects of a drug on PSA expression is a key to interpreting PSA response data, which must be considered together with other clinical data (23-31). Despite these considerations, it has been reproducibly shown that a $\geq 50\%$ PSA decline in pre-treatment PSA following therapy is associated with a significant survival advantage (32). Molecular markers are just starting to be evaluated. In a promising study, positive RT-PCR findings were correlated with a poor survival (33); 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 assessing therapeutic response (34).

Growing numbers of investigators advocate subjective endpoints. Since a significant survival benefit from chemotherapy in HRCaP has not yet been demonstrated, the success of treatment may rely on redefining the goals of therapy (2, 23). Currently, investigators should rely on clearly defined endpoints in trials that 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 quality of life endpoints in symptomatic patients.

15.4 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 should be determined at initial relapse on hormonal therapy (35, 36). The overall effect of continued testicular androgen suppression in HRCaP 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. (37), which demonstrated significantly lower survival rates in patients without continuous androgen blockade. However, two recently published trials challenge these data by showing only a marginal survival benefit for patients staying on LHRH-analogues during second and third-line therapies (37, 38). 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 (38, 39).

15.5 Antiandrogen withdrawal syndrome

In 1993, Kelly and Scher 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 (40, 41). Approximately one-third of patients will respond to antiandrogen withdrawal as indicated by a $\geq 50\%$ PSA decrease with a median duration of response of approximately 4 months. Antiandrogen withdrawal responses have also been reported after treatment with bicalutamide and megestrol acetate (42, 43). 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, observation remains a viable choice for symptomatic patients.

15.6 Secondary 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 (44). Bicalutamide is a non-steroidal antiandrogen that demonstrates a dose response; thus, 200 mg of bicalutamide normalizes PSA more effectively than 50 mg of bicalutamide in patients with androgen-dependent CaP (45-48). Megestrol acetate is a steroidal antiandrogen with progestational activity. It has limited antitumour activity in androgen-independent CaP and should not be routinely used for this indication (49-51). At low doses (20 mg twice daily), it is effective in suppressing hot flashes in 70% of men receiving first-line hormonal ablation. At higher doses (160-320 mg/day), the antiandrogen can stimulate appetite in patients with cancer and could have a multidimensional role in selected symptomatic patients with advanced CaP (52, 53). 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 because a clinical response can be induced by a further decrease in circulating androgen levels by bilateral adrenalectomy or drugs that inhibit adrenal steroidogenesis. Aminoglutethimide, ketoconazole and corticosteroid act primarily via this mechanism (54-60), resulting in a PSA response in about 25% of patients lasting for about 4 months.

CaP normally express 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% (61, 62). In contrary, high-dose oestrogens have been reported to have salvage objective responses. The mechanism for the effect has been postulated to be the mitotic arrest of direct cytotoxic effects on the cells, perhaps through an apoptotic mechanism (63, 64). Recently, DES has been evaluated in two studies (65, 66), including 21 and 32 patients, respectively. 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.

15.7 Non-hormonal therapy (cytotoxic agents)

Lack of representative randomized Phase III trials and efficacy that is still unknown in terms of long-term outcome are the major problems associated with all studies being reported.

Renewed enthusiasm for the role of non-hormonal therapy in HRCaP is emerging. Underlying this optimism are several factors. Newer measures of response, including PSA level and quality of life measures, suggest activity with some older drugs that were previously thought to be inactive. New combinations of drugs appear to have synergistic activity of clinical relevance. Better supportive care measures, such as the use of antiemetics and haematological growth factors, are allowing chemotherapy to be administered more safely and with less toxicity. Newer agents with novel mechanisms of action are also becoming available.

An anthracenedione, mitoxantrone, structurally related to anthracycline is less toxic than doxorubicin. Several pilot studies have suggested the activity of mitoxantrone with corticosteroids (28, 29) primarily in patients with symptomatic osseous lesions. Although none of the studies demonstrated any survival benefit for the patients, quality of life was improved significantly due to pain reduction. The synergy observed for estramustine in combination with other drugs that target microtubule action has generated promising results in several clinical trials. 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 (27, 67, 68). Although time to progression and frequency of $\geq 50\%$ PSA decrease were significantly higher in the combination arm, median survival did not differ significantly between the estramustine and the estramustine plus vinblastine arms. Estramustine plus paclitaxel or docetaxel was investigated, despite the inactivity of paclitaxel as a single agent, because preclinical evidence suggested synergistic antimetabolic effects (69). Taxanes are believed to interfere with the polymerization and depolymerization process of the microtubuli inhibiting the formation of an intact spindle apparatus. Preclinical studies suggest that taxanes phosphorylate and inactivate bcl-2, thereby

allowing cancer cells to undergo apoptosis again (70). Based on these pre-clinical findings, taxanes appear to represent one of the most promising new cytotoxic drugs for the management of HRCaP. A variety of clinical Phase II studies have been performed combining estramustine with paclitaxel or docetaxel. Overall, combination therapy results in a PSA response of 60% to 80% with a mean duration of response of 7 to 13 months (paclitaxel) and 23 months (docetaxel). Docetaxel is associated with significantly less cardiotoxic and neurotoxic side-effects than paclitaxel. Currently, 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% (71-81). Estramustine plus oral etoposide also showed synergy (26).

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 (82, 83). A study of the combination of oral cyclophosphamide and oral etoposide in 20 patients was similarly encouraging (84). Ciplastin 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 HRCaP. A combination of estramustine, etoposide and paclitaxel has also recently been reported to produce high response rates (85, 86).

15.8 Other treatments

The majority of patients with HRCaP 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). 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). Recently, the use of bisphosphonates has demonstrated a significant reduction or even complete pain relief in 70-90% of the patients with symptomatic osseous lesions (34, 88). The high efficacy of 80% and the extremely low frequency of side-effects make bisphosphonates an ideal medication for palliative therapy of advanced HRCaP. Bisphosphonates should be considered early in the management of symptomatic HRCaP. Currently, a prospective randomized clinical Phase III trial compares the efficacy of ibandronate versus mitoxantrone in HRCaP with symptomatic skeletal lesions.

Hormone-refractory prostate cancer 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 (89).

15.9 Future developments

As we begin to understand the complex biological interactions underlying progression to androgen-independent CaP, our ability to target areas for rational drug development is improving. Since the survival time of patients with symptomatic HRCaP is, and will be limited, today and in the future, it appears to be necessary to identify novel treatment strategies in asymptomatic progression of CaP in order to prolong time to progression and ultimately to extend survival. New biological and cytotoxic agents, as well as novel combinations of therapy, are allowing these hypotheses to be tested.

Suramin activity against HRCaP 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 HRCaP is still undetermined, recent results renew some of this agent's initial promise (90-92). Other growth factor inhibitors have shown some promise in pre-clinical testing while trials to evaluate the efficacy of new differentiating agents in advanced CaP are ongoing. Flavopiridol potently inhibits cell cycle progression in the G1 or G2 phase and decreases proliferation of LNCaP cells *in vitro*. A Phase II study is currently underway (93). In addition, paclitaxel induces *bcl-2* phosphorylation and apoptosis in androgen-independent CaP (94). Currently, a Phase II trial has been initiated assessing the clinical efficacy of the combination of docetaxel and mitoxantrone in advanced HRCaP.

Bisphosphonates have been shown to exert significant inhibitory effects on prostate cancer cell proliferation, invasion and the capability to metastasize in pre-clinical trials. Recently, a prospective randomized trial on zoledronate in patients with asymptomatic skeletal lesions has demonstrated a significant prolongation of time to first skeletal event and even prolongation of survival (95). Since animal studies have indicated a synergistic effect of bisphosphonates and taxanes, a Phase II trial is currently underway evaluating the combination of zoledronate and docetaxel in asymptomatic HRCaP.

With regard to growth factors, it has been shown that the expression of Her-2/neu is increased in HRCaP as compared to control groups. Future clinical trials have to demonstrate the clinical efficacy of the anti-Her-2/neu antibody in the management of HRCaP (96), and a pilot trial is currently underway.

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ABBREVIATIONS

ACTH	Adrenocorticotropin
ASTRO	American Society of Therapeutic Radiology and Oncology
BFFF	biochemical freedom from failure
CAB	complete androgen blockade
CaP	cancer of the prostate
CI	confidence interval
CPA	cyproterone acetate
3D-CRT	three-dimensional conformal radiation therapy
CSAP	cryosurgical ablation of the prostate
CT	computed tomography
DES	Diethylstilboestrol
DHT	Dihydrotestosterone
DRE	digital rectal examination
EORTC	European Organization for Research and Treatment of Cancer
FSH	follicle-stimulating hormone
HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HRCaP	hormone-refractory prostate cancer
IAD	intermittent androgen deprivation
IPSA	initial prostate-specific antigen
I-125	iodine-125
Ir-92	iridium-92
LDR	low-dose rate
LHRH	luteinizing hormone releasing hormone
LHRHa	luteinizing hormone releasing hormone analogue
LNCaP	human prostatic carcinoma cell line
LTAD	long-term androgen deprivation
MAB	maximal androgen blockade
MRC	Medical Research Council
MRI	magnetic resonance imaging
NED	no evidence of disease
NHT	neoadjuvant hormonal therapy
PAP	prostatic acid phosphatase
Pd-103	palladium-103
PEP	polyestradiol phosphate
PIN	prostatic intraepithelial neoplasia
PNI	perineural invasion
PSA	prostate-specific antigen
PSMA mRNA	prostate specific membrane antigen for messenger RNA
RITA	radiofrequency interstitial tumour ablation
RRP	radical retropubic prostatectomy
RRPSA	relapsing or rising prostate-specific antigen
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)
TNM	Tumour Node Metastasis
TRUS	transrectal ultrasonography
TURP	transurethral resection of the prostate
VACURG	Veterans Administration Cooperative Urological Research Group
WW	watchful waiting (deferred treatment)

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