eau

European Association of Urology

GUIDELINES ON PROSTATE CANCER*

G. Aus, C.C. Abbou, D. Pacik, H-P. Schmid, H. van Poppel,

J.M. Wolff, F. Zattoni

TABLE OF CONTENTS   page

1. BACKGROUND

Cancer of the prostate (CaP) is now recognized as one of the principal medical problems facing the male population. In the European Union, an estimated 85,000 new cases of CaP are diagnosed each year, accounting for 9% of all cancer deaths among men (1,2). However, the discrepancy between clinical incidence and pathological prevalence remains an unresolved issue. By the time of diagnosis only 50% of tumours are clinically localized, and half of these are found to be extracapsular at pathological staging (3,4).

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 nodes[3]**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	**Distant metastasis[4]**
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

[1] Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
[2] Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as T3, but as T2.
[3] 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.

3. RISK FACTORS

The factors that determine the risk of developing clinical CaP are not well-known; however, a few have been identified. The most important risk factor seems to be heredity - if one first-line relative (brother or father) has the disease, the risk is doubled. If two or more first-line relatives are affected the risk increases to 5-11-fold (5,6). 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 (before age 55 years) (7).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (8). 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 (9,10). However, if Japanese men move from Japan to Hawaii their risk of CaP increases, and if they move further on to California their risk approaches that of American men (11).

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. Other factors include low intakes of vitamin E, lignans and iso-flavonoids (12). 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, i.e. sunlight may be protective against CaP (13).

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, vegetables and red wine) in order to decrease the risk. There is some evidence for this, and this information should 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) (14). Diagnosis demands the presence of adenocarcinoma in 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 hypoechoic zones (15-17).

4.1   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 presence of an abnormality on DRE signifies cancer in 15-40% of cases, depending on the experience of the examiner. If DRE is used to detect unsuspected CaP in asymptomatic men it will identify carcinoma in 0.1-4% of those examined (18,19).

4.2   PSA
The determination of PSA level has revolutionized the diagnosis of CaP (4). 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 cancer-specific, and serum levels may be elevated in the presence of benign prostatic hypertrophy, prostatitis and other non-malignant conditions. The role of PSA in the diagnosis and staging of CaP is increasing. PSA level as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS (20,21).

Currently, many different commercial test kits for the measurement of PSA are available, but no common international standard exists (22,23). 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 (24). A threshold level of PSA that indicates the highest risk of CaP needs to be defined (25, 26). The positive predictive value of PSA is approximately 25-35% for levels between 4 and 10 ng/mL (using monoclonal antibody assays) and 50-80% for those above 10 ng/mL, depending on findings at DRE (27).

For the detection of non-palpable CaP, it is generally agreed that prostate biopsies should be performed when the PSA level is over 10 ng/mL and probably when it is above 4 ng/mL. Although recent studies showed the number of organ-confined cancers to be particularly high for values between 4 and 10 ng/mL, the majority of patients within this range will have benign disease (20). 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 (28).

One important issue associated with lowering the PSA level threshold is the avoidance of detection of insignificant cancers whose natural history is unlikely to be life threatening. 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 that may improve the specificity of PSA in the early detection of CaP have been described:
•   PSA density (29-33)
•   PSA density of the transition zone (34)
•   Age-specific reference ranges (35-37)

- PSA molecular forms (21,38-42)
- PSA velocity (43-46)
- PSA doubling time (46)

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.

The more widespread use of PSA level for the early detection of CaP has led to the introduction of a new clinical stage (T1c). This 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 indicates that between 11 and 26% of cases are insignificant cancers but between 18 and 49% represent locally advanced disease (47).

4.3   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 (48). Small tumours often appear as hypoechoic lesions, whereas larger tumours appear with a mixed pattern consisting of hypo- and hyperechoic areas (49). However, 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 (17).
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 (50,51). 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 (17,51,52). Colour Doppler sonography is still under evaluation and its routine use has not yet been shown to improve detection rate or staging (49,53).

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% (14,50,51). 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 biopsy allows the diagnosis and cytological grading of the tumour with a minimal risk of complications (54). 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 (55,56).

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 (57). Sextant biopsies, as described by Hodge *et al.*, have been used in this situation (15). Lately, the standard way of obtaining sextant biopsies has been replaced by laterally directed sextant biopsies in order to optimize the CaP detection rate (58). Biopsy cores obtained in this way include the posterolateral aspect of the peripheral zone, the most common location for early CaP.

If the first set of biopsies is negative, repeated biopsies can be recommended. In the second set of biopsies a detection rate of about 20% has been reported in cases with 'persistent indication' and a negative first set of biopsies (59,60). In cases where high-grade prostatic intraepithelial neoplasia (PIN) is present, as many as 50-100% of prostates harbour a concomitant cancer and immediate rebiopsy is indicated (61,62).

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 a study a positive correlation between DRE and pathological tumour stage was found in fewer than 50% of tumours (63). 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 (64-66). 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 (67).

TRUS may reveal unsuspected extracapsular invasion, 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 (68). The differentiation between T2 and T3 tumours should not be based on TRUS alone (49,69).

Biopsies of the seminal vesicles may be used to increase the accuracy of pre-operative staging. 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 over 10 ng/mL are candidates for seminal vesicle biopsies (70,71). Patients with any of the basal biopsies positive for cancer are more likely to have positive seminal vesicle biopsies (72).

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 (73-75).

CT 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 (76-79). 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 (49). 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 treatments with curative intent are planned. High PSA values, stage T2b-T3 disease, poor tumour differentiation and perineural tumour invasion have been associated with a higher risk of the presence of nodal metastases (67,81,82). 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 (24). 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 (67,81,82).

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 treatment with curative intent (67).

The gold standard for N-staging is operative lymphadenectomy, by either open or laparoscopic techniques. Both CT and MRI are considered of limited use due to their low sensitivity, which varies from 0 to 70% (76,83,84), although CT accuracy increases when fine-needle aspiration biopsies are applied to virtually all visible and asymmetric lymph nodes (85). 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 (86).

5.3 M-staging

The axial skeleton is involved in 85% of patients dying from CaP (87). 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 (88). 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 (89,90). Technetium diphosphonates are the optimum radiopharmaceuticals currently available due to their extremely high bone-to-soft-tissue ratio (91). A semi-quantitative grading system based upon the extent of disease observed on the bone scan was found to correlate with survival (92).

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 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% (93). On the other hand, on very rare occasions patients with a low serum PSA concentration have been found to harbour detectable skeletal metastases. The negative predictive value of serum PSA levels less than 20 ng/mL was found to be about 99% (4). The correlation between serum PSA and bone scintigraphy in patients with newly diagnosed untreated CaP has been investigated (93-97). Results suggest that a staging bone scan may be superfluous if the serum PSA concentration is less than 10 ng/mL in asymptomatic patients with well or moderately differentiated tumours.

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 indicated if they do not 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 treatment with curative intent is planned. Accurate lymph node staging can only be determined by bilateral pelvic lymphadenectomy; CT/MRI are of limited value due to low sensitivity. However, in patients with a high risk of node metastases, CT/MRI may be useful in recognizing enlarged lymph nodes and in guiding aspiration biopsy, thus avoiding an operative procedure.
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 10 ng/mL in the presence of well or moderately differentiated tumours.

5.5 REFERENCES

1. **Jensen OM, Esteve J, Moller H, Renard H.**
   Cancer in the European Community and its member states. Eur J Cancer 1990; 26: 1167-1256.
2. **Black RJ, Bray F, Ferlay J, Parkin DM.**
   Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997; 33: 1075-1107.
3. **Catalona WJ, Stein AJ.**
   Staging errors in clinically localized prostate cancer. J Urol 1982; 127: 452-454.
4. **Oesterling JE.**
   Prostate-specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol 1991; 145: 907-923.
5. **Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC.**
   Family history and the risk of prostate cancer. Prostate 1990; 17: 337-347.
6. **Grönberg H, Damber L, Damber JE.**
   Familial prostate cancer in Sweden. A nation-wide register cohort study. Cancer 1996; 77: 138-143.
7. **Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC.**
   Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 1992; 89: 3367-3371.
8. **Breslow N, Chan CW, Dhom G, Drury RAB, Franks LM, Gellei B, Lee YS, Lundberg S, Sparke B, Stenby NH, Tulinius H.**
   Latent carcinoma of prostate at autopsy in seven areas. Int J Cancer 1977; 20: 680-688.

9.   **Zaridze DG, Boyle P.**
      Cancer of the prostate: epidemiology and aetiology. Br J Urol 1987; 59: 493-502.
10.   **Carter HB, Piantadosi S, Isaacs JT.**
      Clinical evidence for and implications of the multistep development of prostate cancer.
      J Urol 1990; 143: 742-746.
11.   **Zaridze DG, Boyle P, Smans M.**
      International trends in prostatic cancer. Int J Cancer 1984; 33: 223-230.
12.   **Denis L, Morton MS, Griffiths K.**
      Diet and its preventive role in prostatic disease. Eur Urol 1999; 35: 377-387.
13.   **Hanchette CL, Schwartz GG.**
      Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation.
      Cancer 1992; 70: 2861-2869.
14.   **Gerber GS, Chodak GW.**
      Routine screening for cancer of the prostate. J Natl Cancer Inst 1991; 83: 329-335.
15.   **Hodge KK, McNeal JE, Terris MK, Stamey TA.**
      Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate.
      J Urol 1989; 142: 71-75.
16.   **Brawer MK, Nagle RB.**
      Transrectal ultrasound guided prostate biopsy following negative digitally guided biopsy.
      J Urol 1989; 141: 278A.
17.   **Ellis WJ, Chetner MP, Preston SD, Brawer MK.**
      Diagnosis of prostatic carcinoma: the yield of serum prostate specific antigen, digital rectal examination
      and transrectal ultrasonography. J Urol 1994; 152: 1520-1525.
18.   **Chodak GW.**
      Early detection and screening for prostatic cancer. Urology 1989; 34 (Suppl 4): 10-12.
19.   **Pedersen KV, Carlsson P, Varenhorst E, Lofman O, Berglund K.**
      Screening for carcinoma of the prostate by digital rectal examination in a randomly selected population.
      BMJ 1990; 300: 1041-1044.
20.   **Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff
      TL, Kavoussi LR, Dalkin BL, Waters WB, MacFarlane MT, Southwick PC.**
      Comparison of digital rectal examination and serum prostate specific antigen (PSA) in the early detection
      of prostate cancer: results of a multicenter clinical trial of 6630 men. J Urol 1994; 151: 1283-1290.
21.   **Elgamal AA, Petrovich Z, van Poppel H, Baert L.**
      The role of prostate specific antigen in the management of prostate cancer. In: Carcinoma of the
      Prostate. Innovations in Management. Petrovich Z, Baert L and Brady LW et al. (eds). Springer
      Verlag:Berlin, 1996; 179-196.
22.   **Semjonow A, Brandt BF, Roth S, Hertle L.**
      Discordance of assay methods creates pitfalls for the interpretation of prostate-specific antigen values.
      Prostate 1996; 7 (Suppl): 3-16.
23.   **Semjonow A, Oberpenning F, Brandt B, Zechel C, Brandau W, Hertle L**.
      Impact of free prostate-specific antigen on discordant measurement results of assays for total prostate-
      specific antigen. Urology 1996; 48 (Suppl): 10-15.
24.   **Wirth MP, Frohmuller HG.**
      Prostate-specific antigen and acid phosphatase in the detection of early prostate cancer and the
      prediction of regional lymph node metastases. Eur Urol 1992; 22: 27-32.
25.   **Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, Petros JA, Andriole GL.**
      Measurement of prostate-specific antigen in serum as a screening test for prostate cancer.
      N Engl J Med 1991; 324: 1156-1161.
26.   **Brawer MK, Chetner MP, Beatie J, Buchner DM, Vessella RL, Lange PH.**
      Screening for prostatic carcinoma with prostate specific antigen. J Urol 1992; 147: 841-845.
27.   **Haas GP, Montie JE, Pontes JE.**
      The state of prostate cancer screening in the United States. Eur Urol 1993; 23: 337-347.
28.   **Lodding P, Aus G, Bergdahl S, Frosing R, Lilja H, Pihl CG, Hugosson J.**
      Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng/mL
      prostate specific antigen. J Urol 1998; 159: 899-903.
29.   **Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, Cooner WH.**
      Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate
      cancer. J Urol 1992; 147: 815-816.
30.   **Benson MC, Olsson CA.**
      Prostate specific antigen density - roles in patient evaluation and management. Cancer 1994; 74: 1667-1673.

31. **Schmid H-P, Ravery V, Billebaud T, Toublanc M, Boccon-Gibod LA, Hermieu JF, Delmas V, Boccon-Gibod L.**
Early detection of prostate cancer in men with prostatism and intermediate prostate-specific antigen levels. Urology 1996; 47: 699-703.

32. **Paul R, Breul J, Hartung R.**
Prostate-specific antigen density and age-specific prostate specific antigen values: the solution of prostate cancer screening? Eur Urol 1995; 27: 286-291.

33. **Wolff JM, Boeckmann W, Effert PJ, Handt S, Jakse G.**
Evaluation of patients with diseases of the prostate using prostate-specific antigen density.
Br J Urol 1995; 76: 41-46.

34. **Zlotta AR, Djavan B, Marberger M, Schulman CC.**
Prostate specific antigen of the transition zone: a new parameter for prostate cancer prediction.
J Urol 1997; 157: 1315-1321.

35. **Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM.**
Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993; 270: 860-864.

36. **Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL, Waters WB, MacFarlane MT, Southwick PC.**
Effect of patient age on early detection of prostate cancer with serum prostate specific antigen and digital rectal examination. Urology 1993; 42: 365-374.

37. **Partin AW, Criley SR, Subong EN, Zincke H, Walsh PC, Oesterling JE.**
Standard versus age-specific prostate specific antigen reference ranges among men with clinically localized prostate cancer: a pathological analysis. J Urol 1996; 155: 1336-1339.

38. **Catalona WC, Smith DS, Wolfert RL, Wang TJ, Rittenhouse HG, Ratliff TL, Nadler RB.**
Evaluation of percentage of free serum prostate specific antigen to improve specificity of prostate cancer screening. JAMA 1995; 274: 1214-1220.

39. **Luderer AA, Chen Y, Soriano TF, Kramp WJ, Carlson G, Cuny C, Sharp T, Smith W, Petteway J, Brawer MK, Thiel R.**
Measurement of the proportion of free to total prostatic-specific antigen improves diagnostic performance of prostate-specific antigen in the gray zone of total prostate-specific antigen. Urology 1995; 46: 187-194.

40. **Huber PR, Schmid H-P, Mattarelli G, Strittmatter B, van Steenbrugge GJ, Maurer A.**
Serum free prostate specific antigen: isoenzymes in benign hyperplasia and cancer of the prostate.
Prostate 1995; 27: 212-219.

41. **Demura T, Shinohara N, Tanaka M, Enami N, Chiba H, Togashi M, Ohashi N, Nonomura K, Koyanagi T.**
The proportion of free to total prostate specific antigen - a method of detecting prostate carcinoma.
Cancer 1996; 77: 1137-1143.

42. **Wolff JM, Borchers H, Effert PJ, Habib FK, Jakse G.**
Free-to-total prostate specific antigen concentrations in patients with prostate cancer and benign prostatic hyperplasia. Br J Urol 1996; 78: 409-413.

43. **Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, Fozard JL, Walsh PC.**
Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease.
JAMA 1992; 267: 2215-2220.

44. **Oesterling JE, Chute CG, Jacobsen SJ, Brant LJ, Chan DW, Andres R, Fozard JL, Walsh PC.**
Longitudinal changes in serum PSA (PSA velocity) in a community-based cohort of men.
J Urol 1993; 149: 412A.

45. **Catalona WJ, Smith DS, Ratliff TL.**
Value of measurements of the rate of change of serum PSA levels in prostate cancer screening.
J Urol 1993; 149: 300A.

46. **Schmid H-P, McNeal JE, Stamey TA.**
Observations on the doubling time of prostate cancer: the use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer 1993; 71: 2031-2040.

47. **Elgamal AA, van Poppel HP, van de Voorde JA, Oven RH, Baert LV.**
Impalpable, invisible stage T1c prostate cancer: characteristics and clinical relevance in 100 radical prostatectomy specimens - a different view. J Urol 1997; 157: 244-250.

48. **Lee F, Torp-Pedersen ST, Siders DB, Littrup PJ, McLeary RD.**
Transrectal ultrasound in the diagnosis and staging of prostate cancer. Radiology 1989; 170: 609-615.

49. **Oyen RH.** Imaging modalities in diagnosis and staging of carcinoma of the prostate. In: Carcinoma of the Prostate. Innovations in Management. Petrovich Z, Baert L and Brady LW et al. (eds). Springer Verlag Berlin 1996; 65-96.

50. **Gustavsson O, Norming U, Almgård L-E, Fredriksson A, Gustavsson G, Harvig B, Nyman CR.**
Diagnostic methods in the detection of prostate cancer: a study of a randomly selected population of 2400 men. J Urol 1992; 148: 1827-1831.

51. **Mettlin C, Murphy GP, Babaian RJ, Chesley A, Kane RA, Littrup PJ, Mostofi FK, Ray PS, Shanberg AM, Toi A.**
The results of a five-year early prostate cancer detection intervention. Cancer 1996; 77: 150-159.

52. **Jones WT, Resnick MI.**
Prostate ultrasound in screening, diagnosis and staging of prostate cancer. Probl Urol 1990; 4: 343-357.

53. **Patel U, Richards D.**
The diagnostic value of colour Doppler flow in the peripheral zone of the prostate, with histological correlation. Br J Urol 1994; 74: 590-595.

54. **Esposti PL, Elman A, Norlén H.**
Complications of transrectal aspiration biopsy of the prostate. Scand J Urol Nephrol 1975; 9: 208-213.

55. **Aus G, Ahlgren G, Bergdahl S, Hugosson J.**
Infection after transrectal core biopsies of the prostate - risk factors and antibiotic prophylaxis.
Br J Urol 1996; 77: 851-855.

56. **Collins GN, Lloyd SN, Hekir M, McKelive GB.**
Multiple transrectal ultrasound-guided biopsies - true morbidity and patient acceptance.
Br J Urol 1997; 79: 460-463.

57. **Aus G, Ahlgren G, Hugosson J, Pedersen K, Rensfeldt K, Soderberg R.**
Diagnosis of prostate cancer: optimal number of prostate biopsies related to serum PSA and findings on digital rectal examination. Scand J Urol Nephrol 1997; 131: 541-544.

58. **Stamey TA.**
Making the most out of six systemic sextant biopsies. Urology 1995; 45: 2-12.

59. **Keetch DW, Catalona WJ, Smith DS.**
Serial prostate biopsies in men with persistently elevated serum prostate specific antigen levels.
J Urol 1994; 151: 1571-1574.

60. **Roerhborn CG, Pickers GJ, Sanders JS.**
Diagnostic yield of repeated ultrasound guided biopsies stratified by specific histopathologic diagnosis and prostate specific antigen levels. Urology 1996; 47: 347-352.

61. **Zlotta AR, Raviv G, Schulman CC.**
Clinical prognostic criteria for later diagnosis of prostate carcinoma in patients with isolated prostatic intraepithelial neoplasia. Eur Urol 1996; 30: 249-255.

62. **Haggman MJ, Macoska JA, Wojno KJ, Oesterling JE.**
The relationship between prostatic intraepithelial neoplasia and prostate cancer: critical issues.
J Urol 1997; 158: 12-22.

63. **Spigelman SS, McNeal JE, Freiha FS, Stamey TA.**
Rectal examination in the volume determination of carcinoma of the prostate: clinical and anatomical correlations. J Urol 1986; 136: 1228-1230.

64. **Hudson MA, Bahnson RR, Catalona WJ.**
Clinical use of prostate-specific antigen in patients with prostate cancer. J Urol 1989; 142: 1011-1017.

65. **Lange PH, Ercole CJ, Lightner DJ, Fraley EE, Vessella R.**
The value of serum prostate-specific antigen in the determinations before and after radical prostatectomy. J Urol 1989; 141: 873-879.

66. **Partin AW, Carter HB, Chan DW, Epstein JI, Oesterling JE, Rock RC, Weber JP, Walsh PC.**
Prostate-specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. J Urol 1990; 143: 747-753.

67. **Partin AW, Yoo J, Pearson JD, Chan DW, Epstein JI, Walsh PC.**
The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol 1993; 150: 110-114.

68. **Enlund A, Pedersen K, Boeryd B, Varenhorst E.**
Transrectal ultrasonography compared to histological assessment for local staging of prostatic carcinoma. Acta Radiol 1990; 31: 597-600.

69. **Rorvik J, Halvorsen OJ, Servoll E, Haukaas S.**
Transrectal ultrasonography to assess local extent of prostatic cancer before radical prostatectomy.
Br J Urol 1993; 73: 65-69.

70. **Stone NN, Stock RG, Unger P.**
Indications for seminal vesicle biopsy and laparoscopic pelvic lymph node dissection in men with localized carcinoma of the prostate. J Urol 1995; 154: 1392-1396.

71. **Allepuz Losa CA, Sans Velez JI, Gil Sanz MJ, Plaza Mas L, Rioja Sanz LA.**
Seminal vesicle biopsy in prostate cancer staging. J Urol 1995; 154: 1407-1411.

72. **Guillonneau B, Debras B, Veillon B, Bougaran J, Chambon E, Vallancien G.**
Indications for preoperative vesicle biopsies in staging of clinically localized prostatic cancer.
Eur Urol 1997; 32: 160-165.

73. **Ackermann DA, Barry JA, Wicklund RA, Olson N, Lowe BAl.**
Analysis of risk factors associated with prostate cancer extension to the surgical margin and pelvic lymph node metastasis at radical prostatectomy. J Urol 1993; 150: 1845-1850.

74. **Hammerer P, Huland H, Sparenberg A.**
Digital rectal examination, imaging, and systematic-sextant biopsy in identifying operable lymph node-negative prostatic carcinoma. Eur Urol 1992; 22: 281-287.

75. **Ravery V, Schmid H-P, Toublanc M, Boccon-Gibod L.**
Is the percentage of cancer in biopsy cores predictive of extra capsular disease in T1--T2 prostate cancer? Cancer 1996; 78: 1079-1084.

76. **Bezzi M, Kressel HY, Allen KS, Schiebler ML, Altman HG, Wein AJ, Pollack HM.**
Prostatic carcinoma: Staging with MR imaging at 1.5T. Radiology 1988; 169: 339-346.

77. **Platt JF, Bree RL, Schwab RE.**
The accuracy of CT in the staging of carcinoma of the prostate. Am J Roentgenol 1987; 149: 315-318.

78. **Rifkin MD, Zerhouni EA, Gatsonis CA, Quint LE, Paushter DM, Epstein JI, Hamper U, Walsh PC, McNeil BJ.**
Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer.
N Engl J Med 1990; 323: 621-626.

79. **Schiebler ML, McSherry S, Keefe B, Mittelstaedt CA, Mohler JL, Dent GA, McCartney WH.**
Comparison of digital rectal examination, endorectal ultrasound, and body coil magnetic resonance imaging in the staging of adenocarcinoma of the prostate. Urol Radiol 1991; 13: 110-118.

80. **Schnall MD, Imai Y, Tomaszewski J, Pollack H, Lenkinski RE, Kressel HY.**
Prostate cancer: local staging with endorectal surface coil MR imaging. Radiology 1991; 178: 797-802.

81. **Stone NN, Stock RG, Parikh D, Yeghiayan P, Unger P.**
Perineural invasion and seminal vesicle involvement predict pelvic lymph node metastasis in men with localized carcinoma of the prostate. J Urol 1998; 160: 1722-1736.

82. **Pisansky TM, Zincke H, Suman VJ, Bostwick DG, Earle JD, Oesterling JE.**
Correlation of pretherapy prostate cancer characteristics with histologic findings from pelvic lymphadenectomy specimens. Int J Radiat Oncol Biol Phys 1996; 34: 33-39.

83. **Golimbu M, Morales P, Al-Askari S, Schulman Y.**
CAT scanning and staging of prostate cancer: Urology 1981; 23: 505-508.

84. **Hricak H, Dooms GC, Jeffrey RB, Avallone A, Jacobs D, Benton WK, Narayan P, Tanagho EA.**
Prostatic carcinoma: staging by clinical assessment, CT and MR imaging. Radiology 1987; 162: 331-336.

85. **Van Poppel H, Ameye F, Oyen R, Van de Voorde WM, Baert L.**
Accuracy of combined computer tomography and fine needle aspiration cytology in lymph node staging of localized prostate carcinoma. J Urol 1994; 151: 1310-1314.

86. **Wolf JS Jr, Cher M, Dall'era M, Presti JC, Hricak H, Carroll PR.**
The use and accuracy of cross sectional imaging and fine needle aspiration cytology for detection of pelvic lymph node metastases before radical prostatectomy. J Urol 1995; 153: 993-999.

87. **Whitmore WF Jr.**
Natural history and staging of prostate cancer. Urol Clin North Am 1984; 11: 209-220.

88. **Wolff JM, Ittel TH, Borchers H, Boekels O, Jakse G.**
Metastatic workup of patients with prostate cancer employing alkaline phosphatase and skeletal alkaline phosphatase. Anticancer Res 1999; 19(4A): 2653-2655.

89. **McGregor B, Tulloch AGS, Quinlan MF, Lovegrove F.**
The role of bone scanning in the assessment of prostatic carcinoma. Br J Urol 1978; 50: 178-181.

90. **O'Donoghue EPN, Constable AR, Sherwood T, Stevenson JJ, Chisholm GD.**
Bone scanning and plasma phosphatases in carcinoma of the prostate. Br J Urol 1978; 50: 172-178.

91. **Buell U, Kleinhans E, Zorn-Bopp E, Reuschel W, Muenzing W, Moser EA, Seiderer M.**
A comparison of bone imaging with Tc-99m DPD and Tc-99m MDP: concise communication.
J Nucl Med 1982; 23: 214-217.

92. **Soloway MS, Hardemann SW, Hickey D, Raymond J, Todd B, Soloway S, Moinuddin M.**
Stratification of patients with metastatic prostate cancer based on the extent of disease on initial bone scan. Cancer 1988; 61: 195-202.

93. **Rana A, Karamanis K, Lucal MG, Chisholm GD.**
Identification of metastatic disease by T category, Gleason score and serum PSA level in patients with

carcinoma of the prostate. Br J Urol 1992; 69: 277-281.

94. **Chybowski FM, Keller JJ, Bergstrahl EJ, Oesterling JE.** Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other parameters. J Urol 1991; 145: 313-318.

95. **Oesterling JE, Martin SK, Bergstralh EJ, Lowe FC.** The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. JAMA 1993; 269: 57-60.

96. **O'Donoghue JM, Rogers E, Grimes H, McCarthy P, Corcoran M, Bredin H, Given HF.** A reappraisal of serial isotope scans in prostate cancer. Br J Radiol 1993; 66: 672-676.

97. **Wolff JM, Bares R, Jung PK, Buell U, Jakse G.** Prostatic specific antigen as a marker of bone metastasis in patients with prostate cancer. Urol Int 1996; 56: 169-173.

6. TREATMENT: DEFERRED TREATMENT (WATCHFUL WAITING; WW)

6.1 Summary

Definition

The term deferred treatment or WW is used to describe a treatment strategy that includes an active standpoint to postpone treatment until it is required. This does not by necessity mean that treatments, such as palliative or hormonal, are withdrawn until symptomatic progression occurs (local or systemic). It may also in rare, selected cases include younger patients with localized disease where treatment with curative intent is withheld until indications for tumour activity (i.e. rising serum PSA level) occurs. Patients who are offered WW must be followed up carefully. It is worth mentioning that patients' worry is also a symptom that might warrant active treatment.

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.

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 analyse 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 of this pooled analysis 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 SEER database (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 have been advocated, especially in younger males with a long life expectancy (17).

The impact of grade on the risk of tumour progression and ultimately death from CaP is further described in a paper by Albertsen and co-workers (18). They re-evaluated all biopsy specimens using the more widely accepted Gleason grading system and showed that the risk of CaP death was very high in Gleason 7-10 tumours, intermediate in Gleason 6, 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 has 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 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.

The data above indicate a high risk of tumour progression after conservative treatment for 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 (20-22).

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 (23).

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. No randomized studies comparing more aggressive treatments, such as radiation therapy or surgery, eventually in combination with hormones, exist. 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 stating that this 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 (24,25). 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 (26), comparable with the results of Lundgren *et al.* mentioned earlier (23).

Fifty selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 CaP were followed up for 169 months (27). 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 watchful waiting (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 (26,28). If a deferred treatment policy is chosen for the patient with advanced CaP, there must be a possibility of close follow-up.

6.5   REFERENCES

1.   **Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, Chisholm GD, Moskovitz B, Livne PM, Warner J.**
Results of conservative management of clinically localized prostate cancer.
N Engl J Med 1994; 330: 242-248.
2.   **Middleton RG, Thompson IM, Austenfeld MS, Cooner WH, Correa RJ, Gibbons RP, Miller HC, Oesterling JE, Resnick MI, Smalley SR, Wasson JH.**
Prostate cancer clinical guidelines panel summary report on the management of clinically localized prostate cancer. The American Urological Association. J Urol 1995; 154: 2144-2148.
3.   **Thompson IM.**
Observation alone in the management of localized prostate cancer: the natural history of untreated disease. Urology 1994; 43: 41-46.
4.   **Schelhammer PF.**
Contemporary expectant therapy series: a viewpoint. Urology 1994; 44: 47-52.
5.   **Steinberg GD, Bales GT, Brendler CB.**
An analysis of watchful waiting for clinically localized prostate cancer. J Urol 1998; 159: 1431-1436.
6.   **Adolfsson J, Steineck G, Whitmore WF Jr.**
Recent results on management of palpable clinically localized prostate cancer.
Cancer 1993; 72: 310-322.
7.   **Moskovitz B, Nitecki A, Richter Levin D.**
Cancer of the prostate: is there a need for aggressive treatment? Urol Int 1987; 42: 49-52.
8.   **Goodman CM, Busuttil A, Chisholm GD.**
Age, and size and grade of tumour predict prognosis in incidentally diagnosed carcinoma of the prostate. Br J Urol 1988; 62: 1091-1096.
9.   **Jones GW.**
Prospective, conservative management of localized prostate cancer. Cancer 1992; 70 (Suppl): 307-310.
10.   **Whitmore WF Jr, Warner JA, Thompson IM.**
Expectant management of localized prostate cancer.: Cancer 1991; 67: 1091-1096.
11.   **Adolfsson J, Carstensen J, Lowhagen T.**
Deferred treatment in clinically localised prostatic carcinoma. Br J Urol 1992; 69: 183-187.
12.   **Johansson JE, Adami HO, Andersson SO, Bergstrom R, Krusemo UB, Kranz W.**
Natural history of localized prostate; A population-based study in 223 untreated patients.
Lancet 1989; 1: 799-803.

13. **Johansson JE, Adami HO, Andersson SO, Bergström R, Holmberg L, Krusemo UB.**
High 10-year survival rate in patients with early, untreated prostatic cancer. JAMA 1992; 267: 2191-2196.
14. **Lu-Yao GL, Yao S-L.**
Population-based study of long-term survival in patients with clinically localised prostate cancer.
Lancet 1997; 349: 906-910.
15. **Lowe BA.**
Management of stage T1a prostate cancer. Semin Urol Oncol 1996; 14: 178-182.
16. **Loughlin KR, Renshaw AA, Kumar S.**
Expectant management of stage A-1 (T1a) prostate cancer utilizing serum PSA levels: a preliminary
report. J Surg Oncol 1999; 70: 49-53.
17. **Griebling TL, Williams RD.**
Staging of incidentally detected prostate cancer: role of repeat resection, prostate-specific antigen,
needle biopsy, and imaging. Semin Urol Oncol 1996; 14: 156-164.
18. **Albertsen PC, Hanley JA, Gleason DF, Barry MJ.**
Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically
localized prostate cancer. JAMA 1998; 280: 975-980.
19. **Albertsen P, Hanley JA, Murphy-Setzko M.**
Statistical considerations when assessing outcomes following treatment for prostate cancer.
J Urol 1999; 162: 439-444.
20. **Aus G, Hugosson J, Norlén L.**
Long-term survival and mortality in prostate cancer treated with noncurative intent.
J Urol 1995; 154: 460-465.
21. **Hugosson J, Aus G, Bergdahl C, Bergdahl S.**
Prostate cancer mortality in patients surviving more than 10 years after diagnosis.
J Urol 1995; 154: 2115-2117.
22. **Brasso K, Friis S, Juel K, Jorgensen T, Iversen P.**
Mortality of patients with clinically localised prostate cancer treated with observation for 10 years or
longer: a population based study. J Urol 1999; 161: 524-528.
23. **Lundgren R, Nordle O, Josefsson K, The South Sweden Prostate Cancer Study Group.**
Immediate estrogen or estramustine phosphate therapy versus deferred endocrine treatment in
nonmetastatic prostate cancer: a randomized multicenter study with 15 years of follow-up.
J Urol 1995; 153: 1580-1586.
24. **Rana A, Chisholm GD, Khan M, Rashwan HM, Elton RA.**
Conservative management with symptomatic treatment and delayed hormonal manipulation is justified
in men with locally advanced carcinoma of the prostate. Br J Urol 1994; 74: 637-641.
25. **Parker MC, Cook A, Riddle PR, Fryatt I, O'Sullivan J, Shearer RJ.**
Is delayed treatment justified in carcinoma of the prostate? Br J Urol 1985; 57: 724-728.
26. **The Medical Research Council Prostate Cancer Working Party Investigators Group.**
Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical
Research Council trial. Br J Urol 1997; 79: 235-246.
27. **Adolfsson J, Steineck G, Hedlund PO.**
Deferred treatment of locally advanced nonmetastatic prostate cancer: a long-term follow-up.
J Urol 1999; 161: 505-508.
28. **Walsh PC, The Medical Research Council Prostate Cancer Working Party Investigators Group.**
Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical
Research Council trial. J Urol 1997; 158: 1623-1624.

7. TREATMENT: RADICAL PROSTATECTOMY

7.1   Summary

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.

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.

Options
- Stage T3 when there is limited extracapsular extension, a Gleason score below 8 and a PSA level below 20 ng/mL.

Contraindications
When no survival benefit is expected:
- Life expectancy of less than 10 years
- Stage T1a disease with limited survival expectancy and a Gleason score of 7 or less.

When there is a low probability of cure:
- Stage T3 disease with extensive extracapsular extension, high PSA level or poor differentiation.

7.2 General considerations

Although it has been suggested that early CaP can be followed up without treatment, patients with clinically localized CaP have a substantial risk of dying from the disease (1). 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 (2) who used a perineal approach, while Memmelaar and Millin performed retropubic radical prostatectomy for the first time (3). Radical prostatectomy was rather unpopular because of its associated morbidity. The high degree of blood loss, frequency of urinary incontinence and unavoidable erectile impotence were considered too high a price to pay for the cure of a disease that often has a protracted course. In 1982, Walsh and Donker published 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 (4).

At the present time, many experts consider radical prostatectomy to be the first choice of treatment to achieve local eradication of early CaP (5). 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 more often result in positive surgical margins than the retropubic approach (6,7), 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.

The post-operative complications of radical prostatectomy are listed in Table 4. The mortality rate is 0-1.5% (8), urinary fistulas are seen in 1.2-4% of patients (9) and urinary incontinence that persists after 1 year in 7.7% (10). Erectile dysfunction used to occur in nearly all patients, but nerve-sparing techniques can be applied in early-stage disease (11). 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 intraoperatively palpable tumour are not suitable candidates for a nerve-sparing approach (12).

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 the eradication of the disease (13). WW can be advocated in patients with a shorter life expectancy with low-stage and low-grade tumours, but it is not acceptable in younger men at high risk of tumour progression (14). Primary hormonal treatment may be given to patients with clinically localized CaP when they are not suitable candidates for curative treatment. In fact, there is no age limit for radical prostatectomy and a patient should not be denied this procedure on the grounds of age alone (15).

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. Although the risk of disease progression of untreated T1a CaP after 5 years is only 5%, these cancers can progress in about 50% after 10-13 years (16). In younger patients who are expected to survive for 15 years or more, therefore, 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 (16). Consequently, it is very important to distinguish between T1a and T1b tumours. 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 (17). In these cases, radiotherapy could be proposed as an alternative treatment with curative intent.

Stage T1c CaP

The clinically inapparent tumour identified by needle biopsy because of an aberrant PSA level is becoming increasingly common. 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 (18). The proportion of insignificant tumours detected because of PSA elevation varies between 11% and 16% (19,20). 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. Nevertheless, without proof of an invasive carcinoma, radical prostatectomy cannot be advised.

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. It was recently shown that for well-differentiated tumours that only invade three or fewer of the six biopsy cores, with invasion limited to less than 50% of the core and a free-to-total PSA ratio of 0.15 or greater, the positive predictive value that the tumour could be insignificant was 94% (21,22). It might be reasonable to follow up some patients whose tumours are highly 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.

Stage T2 CaP

When the tumour 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 as, after 5 years, 35-55% of them will have disease progression if not treated (23). 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 after radical prostatectomy if the diagnosis is made early enough, when the tumour is confined to the prostate based on pathological examination (24,25).

A WW policy has been proposed for T2 tumours (26). If WW is proposed for low-grade T2 cancer, it should be borne in mind that pre-operative assessment of tumour grade by needle biopsy is frequently unreliable (27). Alternatively, it has been clearly shown that most poorly differentiated tumours extend outside of the prostate. Patients with high-grade tumours that are confined to the prostate still have a good prognosis (28).

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 (29). 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 (30-38).

Surgical treatment of clinical stage T3 CaP is traditionally discouraged (39), mainly because patients have an increased risk of both lymph node metastases and local or distal relapse (40). Combination treatment with hormonal and radiation therapy is gaining popularity (39,41).

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 considered when defining 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) (30,32). Patients who were overstaged obviously did very well, while most of those with pT3b cancer showed early disease progression. For clinical T3 cancer as a whole the overall PSA-free survival rate is about 20% after 5 years. It is difficult, however, to refuse to give radical prostatectomy to all clinical T3 CaP patients as at least a selected group of them can be cured with radical prostatectomy alone. 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. The Gleason score of the tumour has a definite impact on progression (28), 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 (21,30,37). Others have shown that the clinical T3a cancer patient with a PSA concentration below 10 ng/mL can achieve a 5-year PSA-free survival rate exceeding 60% (38).

Surgery can still be considered a therapeutic option for patients with clinical T3a CaP who have a PSA level lower than 10 or 25 ng/mL. 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 (22). Also, 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 the patients who would not benefit from a surgical approach.

Embarking on radical prostatectomy for clinical T3 cancer necessitates sufficient surgical expertise in order to keep the morbidity level acceptable. Increased overall surgical experience has certainly contributed to the decreased operative morbidity rate from radical prostatectomy for clinical T3 cancer (34).

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 if followed up for a sufficient period. Nevertheless, the combination of radical prostatectomy and simultaneous hormonal treatment has shown a 10-year cancer-specific survival rate of 80% (42). 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 the radical prostatectomy if a frozen section shows lymph node invasion. It should be noted that the definitive pathological examination after radical prostatectomy can show microscopic lymph node invasion. The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only. 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 should be advocated, although no randomized study has, to date, shown any survival advantage of early versus delayed treatment in these patients.

Results of radical prostatectomy
The results achieved in a number of studies involving radical prostatectomy are shown in Table 5 (43-47).

Table 5: Results of radical prostatectomy

Study	No. of patients	Mean follow-up (months)	5-year prostate-specific antigen-free survival (%)	10-year prostate-specific antigen-free survival (%)
Partin *et al.*, 1993 (43)	894	53	87	77
Catalona and Smith, 1994 (44)	925	28	78	65
Ohori *et al.*, 1994 (45)	500	36	76	73
Trapasso *et al.*, 1994 (46)	601	34	69	47
Zincke *et al.*, 1994 (47)	3170	60	70	52

7.4 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 this treatment. Surgery alone cures the majority of men with organ-confined disease or with well to moderately well differentiated tumours who have perforated the prostate capsule to an extent where it is still possible to obtain clear surgical margins. The role of radical prostatectomy in margin-positive disease and in poorly differentiated extracapsular tumours remains doubtful. Furthermore, the use of combination treatments with hormonal manipulation and/or radiotherapy in a neoadjuvant or adjuvant setting is still under investigation. 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. 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. Adjuvant radiotherapy may be beneficial in margin-positive patients, and hormonal treatment can be useful in pN+ patients or those with seminal vesicle involvement. 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 extensive local resection and avoidance of surgical complications.

7.5 REFERENCES

1. **Lerner SP, Seale-Hawkins C, Carlton CE, Scardino PT.**
   The risk of dying of prostate cancer in patients with clinically localized disease. J Urol 1991; 146: 1040-1045.
2. **Young H.**
   Radical perineal prostatectomy. Johns Hopkins Hosp Bull 1905; 16: 315-321.
3. **Memmelaar J, Millin T**.
   Total prostatovesiculectomy; retropubic approach. J Urol 1949; 62: 340-348.
4. **Walsh PC, Donker PJ.**
   Impotence following radical prostatectomy: insight into etiology and prevention. J Urol 1982; 128: 492-497.
5. **Van Poppel H, De Ridder D, Goethuys HH, Elgamal AA, Baert L.**
   Surgical treatment of carcinoma of the prostate. In: Carcinoma of the Prostate. Innovations in Management Petrovich Z, Baert L, Brady LW (eds). Petrovich Z et al. (eds). Springer Verlag:Berlin, 1996; 105-124.
6. **Boccon-Gibod L, Ravery V, Vortos D, Toublanc M, Delmasse V.**
   Radical prostatectomy for prostate cancer: the perineal approach increases the risk of surgically induced positive margins and capsular incisions. J Urol 1998; 160: 1383-1385.
7. **Weldon VE, Tavel FR, Neuwirth H, Cohen R.**
   Patterns of positive specimen margins and detectable prostate specific antigen after radical perineal prostatectomy. J Urol 1995; 153: 1565-1568.
8. **Davidson PJ, Van den Ouden D, Schroeder FH.**
   Radical prostatectomy: prospective assessment of mortality and morbidity. Eur Urol 1996; 29: 168-173.

9.   **Hautmann RE, Sauter TW, Wenderoth UK.**
      Radical retropubic prostatectomy: morbidity and urinary continence in 418 consecutive cases.
      Urology 1994; 43: 47-51.
10.   **Murphy GP, Mettlin C, Menck H, Winchester DP, Davidson AM.**
      National patterns of prostate cancer treatment by radical prostatectomy: results of a survey by the
      American College of Surgeons Commission on Cancer. J Urol 1994; 152: 1817-1819.
11.   **Walsh PC, Partin AW, Epstein JI.**
      Cancer control and quality of life following anatomical radical retropubic prostatectomy. Results at 10
      years. J Urol 1994; 152: 1831-1836.
12.   **Huland H, Hübner D, Henke RP**.
      Systemic biopsies and digital rectal examination to identify the nerve-sparing side for radical
      prostatectomy without risk of positive margin in patients with clinical stage T1, T2, N0 prostatic
      carcinoma. Urology 1994; 44: 211-214.
13.   **Huland H.**
      Treatment of localized disease: treatment of clinically localized prostate cancer (T1/T2). In: Proceedings
      of the First International Consultation on Prostate Cancer. Murphy G, Denis L, Chatelain C, Griffiths K,
      Khoury S, Cockett AT. (eds). Scientific Communication International Ltd., Jersey, Channel Islands, 1997,
      227-257.
14.   **Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, Chisholm GD,
      Moskovitz B, Livne PM, Warner J.**
      Results of conservative management of clinically localized prostate cancer.
      N Engl J Med 1994; 330: 242-248.
15.   **Corral DA, Bahnson RR**.
      Survival of men with clinically localized prostate cancer detected in the eighth decade of life.
      J Urol 1994; 151: 1326-1329.
16.   **Lowe BA, Listrom MB.**
      Incidental carcinoma of the prostate: an analysis of the predictors of progression. J Urol 1988; 140:
      1340-1344.
17.   **Van Poppel H, Ameye F, Van de Voorde WM, Baert L.**
      Radical prostatectomy for localized prostate cancer. Eur J Surg Oncol 1992; 18: 456-462.
18.   **Elgamal AA, Van Poppel HP, Van de Voorde WM, Van Dorpe JA, Oyen RH, Baert LV.**
      Impalpable invisible stage T1 prostate cancer: characteristics and clinical relevance in 100 radical
      prostatectomy specimens. J Urol 1997; 157: 244-250.
19.   **Oesterling JE, Suman VJ, Zincke H, Bostwick DG.**
      PSA detected (clinical stage T1c or B0) prostate cancer: pathologically significant tumors.
      Urol Clin North Am 1993; 20: 687-693.
20.   **Epstein JI, Walsh PC, Brendler CB.** Radical prostatectomy for impalpable prostate cancer.
      J Urol 1994; 152: 1721-1729.
21.   **Epstein JI, Chan DW, Sokoll LJ, Walsh PC, Cox JL, Rittenhouse H, Wolfert R, Carter HB.**
      Nonpalpable stage T1c prostate cancer: prediction of insignificant disease using free/total PSA levels
      and needle biopsy findings. J Urol 1998; 160: 2407-2411.
22.   **Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, Scardino PT, Pearson J.**
      Combination of prostate-specific antigen, clinical stage and Gleason score to predict pathological stage
      of localized prostate cancer. A multi-institutional update. JAMA 1997; 277: 1445-1451.
23.   **Graverson PH, Nielsson KT, Gasser TC, Corle DK, Madsen PO.**
      Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A 15 year
      follow-up. Urology 1990; 36: 493-498.
24.   **Gibbons RP.**
      Total prostatectomy for clinically localized prostatic cancer: long-term surgical results and current
      morbidity. NCI Monogr 1988; 7: 123-126.
25.   **Pound CR, Partin AW, Epstein JI, Walsh PC.**
      Prostate-specific antigen after anatomic radical retropubic prostatectomy.
      Urol Clin North Am 1997; 24: 395-406.
26.   **Johansson JE, Andersson SO.**
      Deferred treatment in localized prostatic cancer. Acta Oncol 1991; 30: 221-223.
27.   **Epstein JI, Steinberg GD.**
      The significance of low grade prostate cancer on needle biopsy. Cancer 1990; 66: 1927-1932.
28.   **Ohori M, Goad JR, Wheeler TM, Eastham JA, Thompson TC, Scardino PT.**
      Can radical prostatectomy alter the progression of poorly differentiated prostate cancer?
      J Urol 1994; 152: 1843-1849.

29. **Schröder FH, Van den Ouden D, Davidson P.**
The role of surgery in the cure of prostatic carcinoma. Eur Urol Update Series 1992; 1: 18-23.
30. **Morgan WR, Bergstralh EJ, Zincke H.**
Long-term evaluation of radical prostatectomy as treatment for clinical stage C (T3) prostate cancer. Urology 1993; 41: 113-120.
31. **Van den Ouden D, Davidson PJT, Hop W, Schröder FH.**
Radical prostatectomy as monotherapy for locally advanced (stage T3) prostate cancer.
J Urol 1994; 151: 646-651.
32. **Lerner SE, Blute ML, Zincke H.**
Extended experience with radical prostatectomy for clinical stage T3 prostate cancer: outcome and contemporary morbidity. J Urol 1995; 154: 1447-1452.
33. **Di Silverio F, D'Eramo G, Buscarini M.**
Gleason score, pathological stage and serum PSA levels as predictors of disease free survival in C-D1 prostate cancer patients submitted to radical prostatectomy. Eur Urol 1996; 30: 316-321.
34. **Blute ML, Lerner SE, Bergstralh EJ, Eickholt JT, Zincke H.**
Extended experience with radical prostatectomy for clinical stage T3 prostate cancer: outcome and contemporary morbidity. J Urol 1995; 153: 313A.
35. **Gerber GS, Thisted RA, Chodak GW, Schroder FH, Frohmuller HG, Scardino PT, Paulson DF, Middleton AW, Rukstalis DB, Smith JA, Ohori M, Theiss M, Schellhammer PF.**
Results of radical prostatectomy in men with locally advanced prostate cancer: multi-institutional pooled analysis. Eur Urol 1997; 32: 385-390.
36. **Theiss M, Langer W, Hofmockel G, Frohmüller H.**
Radikale Prostatektomie als primäre Monotherapie bei kapselüberschreitendem Prostatakarzinom, 15-Jahres-Ergebnisse. Urologe A 1997; 36: 343-347.
37. **Van den Ouden D, Hop W, Schröder FH.**
Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. J Urol 1998; 160: 1392-1397.
38. **Van Poppel H, Goethuys H, Callewaert P, Vanuytsel L, Van de Voorde WM, Baert L.**
Radical prostatectomy can provide cure for well-selected clinical stage T3 prostate cancer.
Eur Urol 2000; 38: 372-379.
39. **Hodgson D, Warde P, Gospodarowicz M.**
The management of locally advanced prostate cancer. Urol Oncol 1998; 4: 3-12.
40. **Fallon B, Williams RD.**
Current options in the management of clinical stage C prostatic carcinoma.
Urol Clin North Am 1990; 17: 853-866.
41. **Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M.**
Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997; 337: 295-300.
42. **Zincke H.**
Extended experience with surgical treatment of stage D1 adenocarcinoma of prostate. Significant influences of immediate adjuvant hormonal treatment (orchiectomy) on outcome. Urology 1989; 33: 27-36.
43. **Partin AW, Pound CR, Clemens JQ, Epstein JL, Walsh PC.**
Prostate-specific antigen after anatomic radical prostatectomy: the Johns Hopkins experience after 10 years. Urol Clin North Am 1993; 20: 713-725.
44. **Catalona WJ, Smith DJ.**
Five-year tumor recurrence rates after anatomic radical retropubic prostatectomy for prostate cancer.
J Urol 1994; 152: 1837-1842.
45. **Ohori M, Goad JR, Wheeler TM, Easten JA, Thompson TC, Scardino PT.**
Can radical prostatectomy alter the progression of poorly differentiated prostate cancer?
J Urol 1994; 152; 1843-1849.
46. **Trapasso JG, DeKernion JB, Smith RB, Dorey F.**
The incidence and significance of detectable levels of serum PSA after radical prostatectomy.
J Urol 1994; 152: 1821-1825.
47. **Zincke H, Oesterling JE, Blute ML, Bergstalh EJ, Myers RP, Barett DM.**
Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol 1994; 152: 1850-1857.

8. TREATMENT: DEFINITIVE RADIATION THERAPY

8.1   Conventional external beam radiation therapy

Clinically localized CaP (T1-T2, Nx-N0 N0/X)
Radiation therapy may produce treatment results comparable to those achieved by radical prostatectomy. 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 analysing 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, 1995 (6)	16 112 373	A1 A2 B	100% 10 year 69% 10 year 57% 10 year	
Kuban *et al.*, 1995 (7)	27 60 246	A2 B1 B2	66% 10 year 57% 10 year 48% 10 year	83% 10 year 93% 10 year 78% 10 year
Hahn *et al.*, 1996 (8)	16 135 77 269	T1a T1b T2a T2b	100% 10 year 98% 10 year 88% 10 year 63% 10 year	
Zagars *et al.*, 1997 (9)	643	T1-T2	66% 6 year	
Pollack and Zagars, 1998 (10)	643	T1-T2	> 67 Gy: 87% 4 year freedom from failure < 67 Gy: 67% 4 year freedom	

In addition to survival, the endpoint that can make radiotherapy nearly, but not fully, comparable with radical prostatectomy is the number of patients who can be defined as free from biochemical (PSA) failure. However, no randomized studies have compared the outcome between radical prostatectomy and radiotherapy so comparisons are difficult to make. 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)]. Moreover, 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). Table 7 summarizes selected series expressing and comparing survivals and biochemical control (4,5,7,9,16,17).

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 et al., 1997 (9)	643	66% 6 year DFS and bFFF (< 2 ng/mL, after nadir)		
Horwitz et al., 1998 (16)	568	99%[1] 5 year 64%[1] 5 year	98% 5 year 89% 5 year	bFFF ASTRO criteria Failed ASTRO criteria
Kupelian et al., 2000 (17)	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, 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. analysed 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	Prostate-specific antigen ≤ 4 (ng/mL)	Prostate specific antigen 4-10 (ng/mL)	Prostate specific antigen 10-20 (ng/mL)	Prostate-specific antigen > 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

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	Prostate-specific	At 6 years after radiotherapy		
			Relapse or rising prostate-specific antigen	Local failure	Metastases
I	2-6	≤ 4	6%	3%	0%
II	7-10 2-7	≤ 4 4-10	30%	24%	1%
III	8-10 2-7	4-10 10-20	40%	26%	4%
IV (unfavourable)	8-10 2-10	10-20 > 20	88%	43%	12%

Therapeutic approaches suggested for prostate carcinoma T1-T2 are:
- Category I: excellent prognosis: WW (?).
- Categories II-III: outcome 6 years after radiotherapy seems comparable to recently reported results following radical prostatectomy, making it a viable treatment option, especially for patients with a life expectancy of 10-15 years.
- Category IV: patients with T1-T2 fare poorly, with a prognosis similar to T3-T4; such patients are candidates for radiotherapy with adjuvant androgen deprivation, and/or to experimental therapeutic approaches.

Locally advanced CaP (T3-T4, N0/XNx-N0)
Historical selected series with locally advanced tumours involving radiotherapy alone as the initial treatment without hormonal blockade are summarized in Table 10 (5, 7-9,18-20). Currently, it is almost universally accepted that the addition of hormonal manipulation to radiation therapy is one of the most promising prospects for improving treatment results when external beam radiation is used in patients with locally advanced CaP. Support for this can be found in both experimental (capacity of inducing apoptosis, synergistic interactions in a mouse model) and clinical (reduction of extracapsular extension or positive margins in randomized surgical trials) observations.

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 (18): T3	64%	35%	18%	46%	28%	23%
Perez *et al.*, 1993 (19): T3	65%	42%		58%	38%	
Arcangeli *et al.*, 1995 (20): 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%	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 (21) reported the advantages of diethylstilbocestrol (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 seen in patients receiving oestrogen.

In a prospective, randomized study, Laverdière *et al.* reported a 2-year positive biopsy rate of 65% with radiotherapy alone (22). 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).

In a paper presented at the 41st Annual Meeting of ASTRO, Horwitz et al. reported on the long-term results of RTOG (Radiation Therapy Oncology Group) trials 85-31 and 86-10 (575 patients T3N0M0 and 418 patients T2b-T4N0M0) (23). Patients randomized to receive long-term hormonal therapy in RTOG 85-31 received goserelin starting in the last week of radiotherapy and continued indefinitely. Patients treated with short-term hormones in RTOG 86-10 received goserelin and flutamide 2 months prior to and during radiotherapy. Endpoints included rates of 8-year overall survival, cause-specific failure, distant metastases failure and 5-year biochemical disease-free survival, defined as a post-treatment PSA level less than 1.5 ng/mL at more than 1 year post-randomization. Statistically significant differences in outcome were observed between the radiotherapy alone and radiotherapy plus hormones groups for biochemical disease-free survival rate and distant metastases failure rate. Borderline statistically significant differences were observed between the groups for cause-specific failure rate and overall survival rate. Comparing patients receiving long- or short-term hormonal therapy, statistically significant differences were observed for rates of cause-specific failure, distant metastases failure and 5-year biochemical disease-free survival. In patients receiving long-term hormonal therapy, the benefit in the rates of biochemical disease-free survival (p = 0.0002), distant metastases failure (p = 0.05) and cause-specific failure (p = 0.02) was limited to Gleason 7 and 8-10 tumours. The authors concluded

that patients with locally advanced CaP show improved rates of biochemical disease-free survival and distant metastases failure when treated with adjuvant hormones and radiotherapy. Adjuvant long-term blockade was shown to be superior to short-term hormonal therapy.

At the same ASTRO meeting, Bolla et al. updated the results of Phase III European Organization for Research and Treatment of Cancer (EORTC) trial 22863 (415 patients T1-T2G3/T3-T4Nx-N0N0-X; radiotherapy ± goserelin for a period of 3 years + cyproterone acetate [CPA] for 1 month) (24). The results were summarized by the author as follows:

- Outcomes for the radiotherapy/hormone group were statistically significantly better than those for the radiotherapy alone group.
- Five-year local control was achieved in 79% of the radiotherapy alone group versus 97% of the combined group (p < 0.001).
- The clinical disease-free survival rate was improved from 40% to 75% (p < 0.001).
- Five-year overall survival was favoured in the combined group (78% vs. 62% for the radiotherapy alone group; p < 0.001).
- There was no difference in acute or late toxicity, with the exception of hot flushes that occurred in 33% of the hormone plus radiotherapy group and 1% of the radiotherapy alone group.
- Based on the long-term results of this study, patients with locally advanced, high-risk adenocarcinoma of the prostate should be strongly considered for combined treatment with hormones plus radiotherapy.
- Promising results for this same population of patients have recently been reported with conformal dose-escalation radiotherapy alone.
- Future investigations comparing these two treatment approaches may be beneficial.

8.2   Three-dimensional conformal radiation therapy (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 thereby minimize the risk of morbidity from high-dose radiotherapy (25). Table 11 summarizes recent series of 3D-CRT (13,25,26).

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 IPSA 4-10 ng/mL IPSA 10-20 ng/mL IPSA > 20 ng/mL	 90% 4 year 60% 4 year 35% 4 year 30% 4 year
Zelefsky *et al.*, 1998 (25)	213 T1-T2 (leuprolide and flutamide given 3 months before 3D-CRT) IPSA ≤ 10 ng/mL IPSA > 10 ≤ 20 ng/mL IPSA > 20 ng/mL	 93% 5 year 60% 5 year 40% 5 year
Anderson *et al.*, 1998 (26)	172 T1-T2a,b; Gleason score 2-6; no PNI° 94 T2c-T3 or Gleason score 7-10 or PNI°	91%* 5 year 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).

In their large series, Zelefsky et al. (27) 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. (28), also reporting on a dose-escalation study, concluded that patients with pre-treatment PSA levels less than 10 ng/mL do 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 benefit from dose escalation beyond 70 Gy, but doses beyond 75 Gy result in more than 10% serious morbidity. Horwitz et al. (29), in a series of 160 patients with T1c tumours (non-palpable PSA detected), reported a 86% 5-year biochemical disease-free survival rate (ASTRO criteria), with 4% (6/160) having toxicities grade 3-4. Nevertheless, randomized trials will be required to prove that higher irradiation doses are more effective and as safe as normal doses, and to assess the true cost benefit.

8.3   Post-operative radiotherapy

In some series, as many as 50% of all patients undergoing surgery are found to have pathological stage pT3 cancer (extension of tumour beyond the prostatic capsule; evidence of cancer at the inked surgical margin; presence of cancer in the seminal vesicles). Among them the local failure rate has been estimated to be 25-68% (30). Post-operative radiotherapy appears to reduce both local recurrence rates and PSA levels (30,31), even with a moderate dose (48 Gy) (32); however, the impact on survival remains unproven. Valicenti and co-workers (33) 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.

Although post-operative radiation therapy seems to affect the risk of PSA relapse, its impact on survival has not been proven in the published literature.

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 means that the radiation source is left within the prostate for a very short time to deliver its radiation. The most commonly used isotope is iridium-92 (Ir-92). HDR is most commonly used in combination with external beam therapy to boost the dose. For patients this means first a few weeks of external beam therapy, 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 (34). The results seem comparable to those of surgery and better than those of conventional external beam therapy, but only short-term results are available (34,35). 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 (36).

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 outpatient procedure. The long-term side-effect profile seems advantageous, with < 1-2% of patients reporting urinary incontinence and 1-2% experiencing proctitis (37). It must, however, 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 may be age dependent (38). A biochemical control rate of 83.5% at 9 years was achieved by Pd-103 monotherapy in patients with stage T1-T2 CaP (39). For patients with stage T1c-T2a disease, a Gleason score less than 3 + 4 and a PSA level less than 10 ng/mL, seed implant as single treatment may be recommended (40).

To conclude, brachytherapy can rightfully be considered 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 (41).

8.5 REFERENCES

1. **Leibel SA, Hanks GE, Kramer S.**
   Patterns of care outcome studies: results of the national practice in adenocarcinoma of the prostate.
   Int J Radiat Oncol Biol Phys 1984; 10: 401-409.

2. **Hanks GE, Martz KL, Diamond JJ.**
   The effect of dose on local control of prostate cancer. Int J Radiat Oncol Biol Phys 1988; 15: 1299-1305.

3. **Hanks GE, Hanlon A, Schultheiss T, Corn B, Shipley WU, Lee WR.**
   Early prostate cancer: the national results of radiation treatment from the Patterns of Care and Radiation Therapy Oncology Group studies with prospects for improvement with conformal radiation and adjuvant androgen deprivation. J Urol 1994; 152: 1775-1780.

4. **Fowler JE, Braswell NT, Pandey P, Seaver L.**
   Experience with radical prostatectomy and radiation therapy for localized prostate cancer at a Veterans Affairs medical center. J Urol 1995; 153: 1026-1031.

5. **Zietman AL, Coen JJ, Dallow KC, Shipley WU.**
   The treatment of prostate cancer by conventional radiation therapy: an analysis of long-term outcome.
   Int J Radiat Oncol Biol Phys 1995; 32: 287-292.

6. **Perez CA.** Carcinoma of the prostate: a model for management under impending health care system reform. Radiology 1995; 196: 309-322.

7. **Kuban DA, El-Mahdi AM, Schellhammer PF.**
   Prostate-specific antigen for pretreatment prediction and posttreatment evaluation of outcome after definitive irradiation for prostate cancer. Int J Radiat Oncol Biol Phys 1995; 23: 307-316.

8. **Hahn P, Baral E, Cheang M, Math M, Kostyra J, Roelss R.**
   Long-term outcome of radical radiation therapy for prostatic carcinoma: 1967-1987.
   Int J Radiat Oncol Biol Phys 1996; 34: 41-47.

9. **Zagars GK, Pollack A, von Eschenbach AC.**
   Prognostic factors for clinically localized prostate carcinoma. Cancer 1997; 79: 1370-1380.

10. **Pollack A, Zagars GK.** External beam radiotherapy for stage T1/T2 prostate cancer: how does it stack up? Urology 1998; 51: 258-264.

11. **Ritter MA, Messing EM, Shanahan TG, Potts S, Chappell RJ, Kinsella TJ.**
    Prostate-specific antigen as a predictor of radiotherapy response and patterns of failure in localized prostate cancer. J Clin Oncol 1992; 10: 1208-1217.

12. **D'Amico AV, Whittington R, Malkowicz SB, Schultz D.**
    A method for determining a prostate-specific antigen cure after radiation therapy for clinically localized prostatic cancer. Int J Radiat Oncol Biol Phys 1995; 32: 473-477.

13. **Roach M III, Burton E, Kroll S, Bevins S, Ryu JK, Holland JM, Hunter DC, Rosenthal S, Margolis LW, Phillips TL.**
    501 men irradiated for clinically localized prostate cancer (1987-1995): preliminary analysis of the experience at UCSF and affiliated facilities [abstract]. Int J Radiat Oncol Biol Phys 1996; 36: 248.

14. **Zagars GK.**
    The prognostic significance of a single serum prostate-specific antigen value beyond six months after radiation therapy. Int J Radiat Oncol Biol Phys 1993; 27: 39-44.

15. **Kavadi VS, Zagars GK, Pollack A.**
    Serum prostate-specific antigen after radiation therapy for clinically localized prostate cancer: prognostic implications. Int J Radiat Oncol Biol Phys 1994; 30: 279-287.

16. **Horwitz EM, Vicini FA, Ziaja EL, Dmuchowski CF, Stromberg JS, Martinez AA.**
    The correlation between the ASTRO Consensus Panel definition of biochemical failure and clinical outcome for patients with prostate cancer treated with external beam irradiation. American Society of Therapeutic Radiology and Oncology. Int J Radiat Oncol Biol Phys 1998; 41: 267-272.

17. **Kupelian PA, Mohan DS, Lyons J, Klein EA, Reddy CA.**
    Higher than standard radiation doses (> or = 72 Gy) with or without androgen deprivation in the treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys 2000; 46: 567-574.

18. **Bagshaw MA, Cox RS, Ray GR.**
    Status of radiation therapy of prostate cancer at Stanford University. Monogr Natl Cancer Inst 1988; 7: 47-60.

19. **Perez CA, Hanks GE, Leibel SA, Zietman AL, Fuks Z, Lee WR.**
    Localized carcinoma of the prostate (stages T1B, T1C, T2, and T3). Review of management with external beam radiation therapy. Cancer 1993; 72: 3156-3173.

20. **Arcangeli G, Micheli A, Verna L, Saracino B, Arcangeli G, Giovinazzo G, D'Angelo L, Pansadoro V, Sternberg CN.** Prognostic impact of transurethral resection on patients irradiated for localized prostate cancer. Radiother Oncol 1995; 35: 123-128.

21. **Zagars GK, Johnson DE, von Eschenbach AC, Hussey DH.**
Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate. Long-term results of a prospective randomized study. Int J Radiat Oncol Biol Phys 1988; 14: 1085-1091.

22. **Laverdière J, Gomez JL, Cusan L, Suburu ER, Diamond P, Lemay M, Candas B, Fortin A, Labrie F.**
Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37: 247-252.

23. **Horwitz EM, Winter K, Hanks GE, Byhardt RW, Russell AH, Machtay M, Pilepich MV.**
Long-term outcome for patients with locally advanced non-metastatic prostate cancer treated with adjuvant hormones and radiation therapy versus radiation therapy alone: subset analysis of RTOG 85-31 and 86-10. Int J Radiat Oncol Biol Phys 1999; 45 (Suppl): 220-221.

24. **Bolla M, Collette L, Gonzalez D, Warde P, Dubois JB, Mirimanoff R, Storme G, Bernier J, Kuten A, Pierart M.**
Long term results of immediate adjuvant hormonal therapy with goserelin in patients with locally advanced prostate cancer treated with radiotherapy (phase III EORTC study).
Int J Radiat Oncol Biol Phys 1999; 45: 147.

25. **Zelefsky MJ, Lyass O, Fuks Z, Wolfe T, Burman C, Ling CC, Leibel SA.**
Predictors of improved outcome for patients with localized prostate cancer treated with neoadjuvant androgen ablation therapy and three-dimensional conformal radiotherapy.
J Clin Oncol 1998; 16: 3380-3385.

26. **Anderson PR, Hanlon AL, Patchefsky A, Al-Saleem T, Hanks G.**
Perineural invasion and Gleason 7-10 tumors predict increased failure in prostate cancer patients with pre-treatment PSA < 10 ng/mL treated with conformal external beam radiation therapy.
Int J Radiat Oncol Biol Phys 1998; 41: 1087-1092.

27. **Zelefsky MJ, Leibel SA, Graudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, Reuter VE, Fair WR, Ling CC, Fuks Z.**
Dose escalation with three dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998; 41: 491-500.

28. **Hanks GE, Schultheiss TE, Hanlon AL, Hunt M, Lee WR, Epstein BE, Coia LR.**
Optimization of conformal radiation treatment of prostate cancer: report of a dose escalation study.
Int J Radiat Oncol Biol Phys 1997; 37: 543-550.

29. **Horwitz EM, Hanlon AL, Pinover WH, Hanks GE.**
The treatment of nonpalpable PSA-detected adenocarcinoma of the prostate with 3-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 1998; 41: 519-523.

30. **Zietman AL.**
Locally advanced or recurrent prostate cancer. In: Comprehensive Textbook of Genitourinary Oncology. Vogelzang NJ and Miles BJ et al. (eds). Williams & Wilkins:Baltimore, 1996, pp. 782-790.

31. **Anscher MS, Robertson CN, Prosnitz LR.**
Adjuvant radiotherapy for pathologic stage T3/4 adenocarcinoma of the prostate: ten-year update.
Int J Radiat Oncol Biol Phys 1995; 33: 37-43.

32. **Petrovich Z, Lieskovsky G, Langholz B, Formenti S, Baert L, Streeter O, Skinner DG.**
Radical prostatectomy and postoperative irradiation in patients with pathological stage C (T3) carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1998; 40: 139-147.

33. **Valicenti RK, Gomella LG, Ismail M, Strup SE, Mulholland SG, Dicker AP, Petersen RO, Newschaffer CJ.**
The efficacy of early adjuvant radiation therapy for pT3N0 prostate cancer: a matched-pair analysis.
Int J Radiat Oncol Biol Phys 1999; 45: 53-58.

34. **Borghede G, Hedelin H, Holmäng S, Johansson KA, Aldenborg F, Pettersson S, Sernbo G, Wallgren A, Mercke C.**
Combined treatment with temporary short-term high dose rate ^{192}Ir brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. Radiother Oncol 1997; 44: 237-244.

35. **Khan K, Thompson W, Bush S, Stidley C.**
Transperineal percutaneous ^{192}Ir interstitial template implant of the prostate: results and complications in 321 patients. Int J Radiat Oncol Biol Phys 1992; 22: 935-939.

36. **Kovacs G, Galalae R, Loch T, Bertermann H, Kohr P, Schneider R, Kimming B.**
Prostate preservation by combined external beam and HDR brachytherapy in nodal negative prostate cancer. Strahlenther Onkol 1999; 175 (Suppl 2): 87-88.

37. **Blasko J, Ragde H, Luse RW, Sylvester JE, Cavanagh W, Grimm PD.**
Should brachytherapy be considered a therapeutic option in localized prostate cancer?
Urol Clin North Am 1996; 23: 633-650.

38. **Ragde H, Blasko JC, Grimm PD, Kenny GM, Sylvester JE, Hoak DC, Landin K, Cavanagh W.** Interstitial ^{125}I radiation without adjuvant therapy in the treatment of clinically localized prostate carcinoma. Cancer 1997; 80: 442-453.
39. **Blasko JC, Grimm PD, Sylvester JE, Badiozamani KR, Hoak D, Cavanagh W.** Palladium-103 brachytherapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 2000; 46: 839-850.
40. **Nag S, Beyer D, Friedland J, Grimm P, Nath R.** American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys 1999; 44: 789-799.
41. **Peneau M.** Radiotherapie interstitielle et cancer prostatique. Analyse de la literature. Sous-Comite Cancer de Prostate du CCAFU. Prog Urol 1999; 9: 440-451.

9. TREATMENT: HORMONAL (EXCLUDING ANTIANDROGENS)

9.1 Summary

Definition
As testosterone is essential to the perpetuation of CaP, any treatment that reduces the level of testosterone either in serum or at the prostate level is called hormonal therapy. Major categories of hormonal therapy include surgical castration, oestrogens, Luteinizing Hormone Releasing Hormone analogues (LHRHa) and antiandrogens.

Indications
Hormonal therapy is indicated in patients with locally advanced or metastatic disease.

Options
Hormonal therapy is optional in symptomatic patients with localized CaP, who are not fit for curative treatment. The following options are applicable to the different disease stages:
•   T1a: no option
•   T1b-T2: symptomatic patients unfit for curative treatment
•   T3-T4: symptomatic patients with advanced disease
•   N+/M+: standard therapy.

9.2 Hormonal treatment for CaP

In 1941, Huggins et al. and Hodges (1) 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. Although at that time the mechanism of endocrine dependence of CaP was not fully understood, a new era had begun in the management of patients with CaP. Since that time, endocrine manipulation by androgen ablation has been the mainstay of the management of metastatic CaP.

Basics of hormonal therapy for CaP
Although testosterone is not tumorigenic, it is essential to the perpetuation of CaP (2). The testes are the source of the vast majority of androgenic substances that support CaP; approximately 5% of circulating androgens are derived from the adrenal secretion of androstenedione and dihydroepiandrosterone. Any treatment that reduces the level of testosterone is called 'hormonal therapy' (3). These treatments may use hormones or drugs that mimic hormones to interfere with the cycle of testosterone production or not involve hormones at all. The early treatments used orchiectomy, diethylstilboestrol (DES) or a combination of both to reduce the supply of testosterone to the prostate (1,4,5). Although hormone-based therapy is not able to cure CaP, it can diminish the size of the tumour and its metastases quite dramatically as well as slow down its growth. Surgical or medical androgen deprivation results in a median progression-free survival time of 12-33 months and a median overall survival time of 23-37 months in CaP patients with bone metastases (6).

In time, however, most CaPs become resistant to hormonal treatment, although the mechanism for development of hormonal resistance is not completely understood. A CaP cell colony consists of androgen-sensitive (requiring dihydrotestosterone [DHT] for growth and continued viability) and androgen-insensitive (not requiring DHT for viability) cells. Hormonal treatment suppresses androgen-sensitive cells, but, over time, androgen-independent cells continue to grow and to resist programmed cell death until they predominate.

Recent evidence suggests that mutations in the androgen receptor are associated with the development of hormone-refractory CaP. As this development appears to be inevitable in patients with advanced CaP, hormonal therapy is considered 'palliative' rather than curative. However, these concepts are continuously being refined. One of these is intermittent androgen deprivation, which aims to maintain the androgen responsiveness of tumour cells using regular cycles of treatment cessation (and tumour growth) to enable a given PSA level to be reached before therapy is reinitiated. Preliminary data suggest that intermittent androgen deprivation is feasible and may improve quality of life in patients with hormone-sensitive tumours. Randomized clinical trials are underway to address the impact of this approach on survival (7).

Major categories of hormonal therapy for CaP
Although hormonal therapy has long been established as the standard treatment for metastatic CaP, uncertainties and controversies still exist. For example:
•   When should treatment be instituted?
•   Which type of therapy should be used and why?

There is, however, evolving evidence that early treatment might be superior to delayed treatment in patients with metastatic disease (8-10).

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 circulating levels of testosterone. It decreases serum levels of testosterone considerably. Nevertheless, a very low level of testosterone remains - the castration level. After orchiectomy, the prostate atrophies and 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 carried out 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 (11). Although some older studies pointed out that the results of orchiectomy are slightly inferior to those of oestrogen therapy (12), more recent studies do not establish a difference between the success rates of these two modalities of androgen deprivation. Bilateral orchiectomy is therefore regarded as the gold standard (13). It must be borne in mind that for some men castration is an unacceptable assault on their manhood and that such sentiments must be respected.

Oestrogens
Oestrogens mainly act by activating the feedback mechanism on the pituitary-gonadal axis. They mimic testosterone in the feedback mechanism and block the secretion of luteinizing hormone (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 (11,14,15). A dose of 1 mg/day limits the risk but plasma testosterone levels do not fall to levels seen in orchiectomized patients (16). Furthermore, the testosterone level frequently begins to rise after 6-12 months of treatment. A dose of 3 mg/day provides better efficacy, though with an increased risk of side-effects compared with the 1 mg dose. However, DES is not a satisfactory option due to the cardiovascular disease associated with an elderly population with comorbid medical conditions (17). In theory, DES platelet aggregating effects can be counteracted by the daily use of acetylsalicylic acid. However, there are no studies to support this practice.
        In randomized studies by the Veterans Administration Cooperative Urological Research Group (VACURG) (11,14), the Leuprolide Study Group (15) and the EORTC Urological Group (18,19), cardiovascular toxicities of DES have been compared with other hormonal treatments. The type and frequency of cardiovascular toxicity was greater when DES was used compared with other non-oestrogen therapies. A comprehensive review of oestrogen-induced toxicities has been published (20).
        Recently, parenteral oestrogens have been investigated in order to minimize cardiovascular side-effects. The Finnprostate Group evaluated the clinical efficacy and cardiovascular complications of orchiectomy and polyestradiol phosphate (PEP) in the treatment of advanced CaP. Parenteral PEP was found to be as efficient as orchiectomy; however, more cardiovascular complications were seen in patients given PEP (21). In contrast, a group at the Swedish Karolinska Institute compared PEP and orchiectomy but found no increased cardiovascular morbidity (22). Therefore, the addition of daily low-dose acetylsalicylic acid to prevent cardiovascular complications is under discussion. This view is supported by the results reported by the Antiplatelet Trialists' Collaboration (23-25), who reported a marked decrease in the incidence of heart attack, stroke, venous thrombosis and pulmonary embolism in patients treated with acetylsalicylic acid. Furthermore,

oestrogens, but not orchiectomy or LHRH agonists, seem to protect patients with CaP from osteoporosis. Further studies are necessary to establish the future role of oestrogens in the treatment of advanced or metastatic CaP (26).

LHRH -analogues
More recently, luteinizing hormone releasing hormone analogue (LHRHa) have been advocated for the treatment of metastatic CaP. LHRHa, such as leuprolide, goserelin and buserelin, have been shown to be as effective as DES, but are without the risk of serious cardiovascular side-effects (17). LHRHa are chemically similar. LHRH is released by the hypothalamus and interferes with the feedback mechanism that stimulates and controls testosterone production in the testes. It induces an initial rise in LH and FSH release from the pituitary, with a resultant surge in testosterone production by Leydig cells, which is transient (3-5 days). LH and FSH release induces regulatory loss of gonadotrophin receptors in the testes. Through chronic administration, a down-regulation of pituitary receptors is achieved. This consequently suppresses the secretion of LH and FSH from the pituitary. Testosterone production in Leydig cells decreases until castration levels are reached, which is usually within 21-28 days (15,27).

LHRHa can cause deleterious effects, however, due to their ability to stimulate testosterone prior to causing its suppression. This so-called 'flare phenomenon' should be prevented by the administration of an antiandrogen prior to and during the first weeks of therapy with LHRHa.

The use of LHRH antagonists is a novel way of suppressing testosterone that is currently under development. These agents are direct antagonists of the LHRH receptor and shut off gonadotrophin secretion immediately. Several LHRH antagonists are currently under investigation. They have the advantage of overcoming the flare phenomenon.

A summary of the prospective randomized studies comparing different endocrine treatments is shown in Table 12 (28-31).

Table 12: Prospective, randomized studies comparing endocrine treatment options

Design	No. of patients	Follow-up (median)	Progression-free survival (median)	Survival
Orchiectomy versus goserelin (28)	144 148	24 months	40 weeks 27 weeks Not significant	104 weeks 115 weeks Not significant
Orchiectomy versus oestrogens (29)	76 74	96 months	49% 64% at 5 years p = 0.04	47% 51% Not significant
Orchiectomy versus oestrogens (30)	131 146	> 60 months	54% 68% at 5 years p = 0.06	34% 31% Not significant
Goserelin versus diethylstilboesterol (31)	124 126	43 months	14.5 months 11.4 months p = 0.06	27.4 months 27.7 months Not significant

Other hormonal treatments
Other hormonal treatments have been used as second-line and occasionally first-line therapy for patients with metastatic CaP.

Gestogens: These have been used in the treatment of CaP as they inhibit the steroid metabolism. They have antigonadotrophic properties, thus suppressing LH and FSH. Furthermore, they compete with testosterone in target cells as substrates for 5-a reductase. Megestrol acetate and medroxyprogesterone acetate have been used in Phase III trials, but appeared to be less effective than DES or antiandrogens (19).

Estramustine: This drug is both oestrogenic and cytotoxic. It has been examined as an adjuvant therapy to orchiectomy with some possible benefits in younger patients with bone metastasis (32). Its main indication is second- or third-line treatment in hormone-refractory CaP. Furthermore, in hormone-refractory disease, the

combination of estramustine and cytotoxic chemotherapy (e.g. vinblastine) has been found to have some effect (33). Its side-effects are mainly the same as those of oestrogens and the risk of cardiovascular morbidity is substantial (34).

Ketoconazole: This is an antimycotic drug, which, in larger doses, interferes with androgen synthesis. It has been used in studies in patients with CaP (35), but the side-effects are considerable and careful monitoring of adrenal and liver function is necessary (36). In practice, it can only be administered with hydrocortisone to compensate for adrenal insufficiency.

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. The side-effects are serious and cortisol has to be added to inhibit adrenocorticotrophic hormone release induced by the feedback mechanism (37).

Side-effects of hormonal therapy
The major side-effects of any hormonal treatment that eliminates testosterone are loss of libido and impotence. Hot flushes, altered and diminished body hair and tenderness in the breasts occur to varying degrees with these therapies. Hot flushes occur more commonly in patients receiving an LHRHa or after bilateral orchiectomy.

For patients with hydronephrosis or bone metastases, it is important to be aware that there is often a transient elevation of serum testosterone which might result in worsening of symptoms from metastases when beginning treatment with an LHRHa. Therefore, 1 month of combination therapy with an antiandrogen, starting 1 week prior to the first injection of the LHRHa, is advisable to avoid this effect.

Owing to the high response rate and frequency of profound remissions induced by continuous androgen blockade, there has been little incentive to examine the less obvious physiological changes that accompany androgen ablation and affect sense of well-being. In addition to loss of libido and potency, the long-term adverse effects on bone (osteoporosis), muscle (atrophy), breast (gynaecomastia), blood (anaemia), lipids (high-density lipoprotein) and mood (depression) remain a source of distressing clinical symptoms (38-44). A summary of the side-effects of hormonal therapy is shown in Table 13 (45).

Table 13: Complications of hormonal therapy for cancer of the prostate. Adapted from Catalona, 1994 (45)

Treatment	Complication (incidence)	Comment
Orchiectomy	Hot flushes, decreased libido and erectile potency, gynaecomastia, wound infection (1-3%)	Hot flushes treated with clonidine, megestrol acetate, cyproterone acetate or low-dose diethylstilboesterol
Diethylstilboesterol	Gynaecomastia, thromboembolism, fluid retention, gastrointestinal upset. Decreased libido and erectile potency	Prevention of gynaecomastia possible by pre-treatment breast irradiation
Luteinizing hormone releasing hormone analogues	Hot flushes, decreased libido and erectile potency, gynaecomastia	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 Aminoglutethimide	Nausea Hepatotoxicity	Inhibits adrenal steroidogenesis; cortisone must be substituted
Estramustine	Gynaecomastia, gastrointestinal side-effects	Prevention of gynaecomastia possible by pre-treatment breast irradiation

When should hormonal therapy be initiated?
Although earlier studies found that the effects of delayed and immediate endocrine therapy were equivalent, any apparent benefit of immediate therapy may have been obscured by cardiovascular side-effects (26). However, a more recent randomized, controlled study of patients with locally advanced disease compared

radiation therapy plus 3 years of adjuvant hormonal therapy with radiation therapy initially plus hormonal therapy only at disease recurrence. A significantly better 5-year overall survival rate was reported in the first group (46). Furthermore, the results of the MRC study comparing early and delayed endocrine treatment in patients with advanced CaP also supported the use of immediate therapy (10).

There is accumulating evidence to support the belief that initiation of hormonal therapy as soon as locally advanced, recurrent or metastatic CaP is diagnosed may have some survival benefits. However, for the individual patient, this should be balanced against the side-effects of the treatment mentioned earlier.

9.3   REFERENCES

1.   **Huggins C, Hodges CV.**
      Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1941; 1: 293-297.
2.   **McConnell JD.**
      Physiologic basis of endocrine therapy for prostatic cancer. Urol Clin North Am 1991; 18: 1-13.
3.   **Garnick MB.**
      Prostate cancer: screening, diagnosis and measurement. Ann Int Med 1993; 118: 804-818.
4.   **Huggins C, Stevens RE Jr, Hodges CV.**
      Studies on prostatic cancer. II. The effect of castration on advanced carcinoma of the prostate gland. Arch Surg 1941; 43: 209-223.
5.   **Huggins C, Scott WW, Hodges CV.**
      Studies on prostatic cancer. III. The effect of fever, of desoxycortisone and of estrogen on clinical patients with metastatic carcinoma of the prostate. J Urol 1941; 46: 997-1006.
6.   **Denis L, Murphy GP**.
      Overview of phase III trials on combined androgen treatment in patients with metastatic prostate cancer. Cancer 1993; 72: 3888-3895.
7.   **Rambeaud JJ.**
      Intermittent complete androgen blockade in metastatic prostate cancer. Eur Urol 1999; 35: 32-37.
8.   **Sarosdy MF**. Do we have a rational treatment plan for stage D1 carcinoma of the prostate?
      World J Urol 1990; 8: 27-33.
9.   **Kozlowski JM, Ellis WJ, Grayhack JT.**
      Advanced prostatic carcinoma. Early versus late endocrine therapy. Urol Clin North Am 1991; 18: 15-21.
10.   **The Medical Research Council Prostate Cancer Working Party Investigators Group.**
      Immediate versus deferred treatment for advanced prostatic cancer: the initial results of the Medical Research Council trial. Br J Urol 1997; 79: 235-246.
11.   **Veterans Administration Cooperative Urological Research Group.**
      Treatment and survival of patients with cancer of the prostate.
      Surg Gynecol Obstet 1967; 124: 1011-1017.
12.   **Emmett LF, Greene LF, Papantoniou A.**
      Endocrine therapy in carcinoma of the prostate gland: 10 year survival studies. J Urol 1960; 83: 471-484.
13.   **Murphy GP, Beckley S, Brady MF, Chu TM, deKernion JB, Dhabuwala C, Gaeta JF, Gibbons RP, Loening SA, McKiel CF, McLeod DG, Pontes JE, Prout GR, Scardino PT, Schlegel JU, Schmidt JD, Scott WW, Slack NH, Soloway MS.**
      Treatment of newly diagnosed metastatic prostate cancer patients with chemotherapy agents in combination with hormones versus hormones alone. Cancer 1983; 51: 1264-1272.
14.   **Byar DP, Corle DK.**
      Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. Natl Cancer Inst Monogr 1988; 7: 165-170.
15.   **Garnick MB, Glode LM for the Leuprolide Study Group.**
      Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1986; 311: 1281-1286.
16.   **Shearer RJ, Hendry WF, Sommerville IF, Fergusson JD.**
      Plasma testosterone: an accurate monitor of hormonal treatment in prostatic cancer.
      Br J Urol 1973; 45: 668-677.
17.   **Blithe B, McRae CU, Espiner EA, Nicholls MG, Conaglen JV, Gilchrist N.**
      Effect of stilbestrol on sodium balance, cardiac state and renin-angiotensin-aldosterone activity in prostatic carcinoma: BMJ 1985; 291: 1461-1464.
18.   **De Vooght HJ, Smith PH, Pavone-Macaluso M, dePauw M, Suciu S and members of the EORTC-GU group.**
      Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate and estramustine phosphate used for the treatment of advanced prostatic cancer: results from EORTC trials 30761 and 30762. J Urol 1986; 135: 303-307.

19. **Pavone-Macaluso M, de Vooght HJ, Viggiano G, Barasolo E, Lardennois B, de Pauw M, Sylvester R.**
Comparison of diethylstilbestrol, cyproterone acetate and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomized phase III trial of the EORTC-GU group. J Urol 1986; 136: 624-631.

20. **Cox RL, Crawford ED.**
Estrogens in the treatment of prostate cancer. J Urol 1995; 154: 1991-1998.

21. **Mikkola AK, Ruutu ML, Aro JL, Rannikko SA, Salo JO.**
Parenteral polyestradiol phosphate vs orchidectomy in the treatment of advanced prostatic cancer. Efficacy and cardiovascular complications: a 2-year follow-up report of a national, prospective prostatic cancer study. Finnprostate Group. Br J Urol 1998; 82: 63-68.

22. **Henriksson P, Carlstrom K, Pousette A, Gunnarsson PO, Johansson CJ, Eriksson B, Altersgard-Brorsson AK, Nordle O, Stege R.**
Time for revival of estrogens in the treatment of advanced prostatic carcinoma? Pharmacokinetics, and endocrine and clinical effects, of a parenteral estrogen regimen. Prostate 1999; 40: 76-82.

23. **Antiplatelet Trialists' Collaboration.**
Collaborative overview of randomized trials of antiplatelet therapy I. BMJ 1994; 308: 81-106.

24. **Antiplatelet Trialists' Collaboration.**
Collaborative overview of randomized trials of antiplatelet therapy II. BMJ 1994; 308: 159-168.

25. **Antiplatelet Trialists' Collaboration.**
Collaborative overview of randomized trials of antiplatelet therapy III. BMJ 1994; 308: 235-246.

26. **Iversen P.**
Orchidectomy and estrogen therapy revisited. Eur Urol 1998; 34: 7-11.

27. **Kuhn JM, Billebaud T, Navratil H, Moulonguet A, Fiet J, Grise P, Louis JF, Costa P, Husson JM, Dahan R, Bertagna C, Edelstein R.**
Prevention of the transient adverse effects of a gonadotropin-releasing hormone analogue (buserelin) in metastatic prostatic carcinoma by administration of an antiandrogen (nilutamide).
N Engl J Med 1989; 321: 413-418.

28. **Peeling WB.**
Phase III studies to compare goserelin with orchidectomy and with diethylstilboestrol in treatment of prostatic carcinoma. Urology 1989; 33 (Suppl 5): 45-52.

29. **Johansson JE, Andersson SO, Holmberg L, Bergström R.**
Primary orchidectomy versus oestrogen therapy in advanced prostatic cancer - a randomized study: results after 7-10 years of follow- up. J Urol 1991; 145: 519-523.

30. **Haapiainen R, Ranniko S, Ruutu M.**
Orchiectomy versus oestrogen in the treatment of advanced prostate cancer. Br J Urol 1991; 67: 184-187.

31. **Waymont B, Lynch TH, Dunn JA, Emtage LA, Arkell DG, Wallace DM, Blackledge GR.**
Phase III randomized study of Zoladex versus stilbestrol in the treatment of advanced prostate cancer. Br J Urol 1992; 69: 614-620.

32. **Janknegt RA, Boon TA, van de Beek C, Grob P, The Dutch Estracyt Study Group.**
Combined hormono/chemotherapy as primary treatment for metastatic prostate cancer: a randomised, multicenter study of orchiectomy alone versus orchiectomy plus estramustine phosphate.
Urology 1997; 49: 411-420.

33. **Seidman AD, Scher HI, Petrylak D, Dershaw DD, Curley T.**
Estramustine and vinblastine: use of prostate-specific antigen as a clinical trial end point for hormone refractory prostate cancer. J Urol 1992; 147: 931-934.

34. **Newling DDW, Fossa SD, Tunn UW, Kurth KH, de Pauw M, Sylvester R.**
Mitomycin C versus estramustine in the treatment of hormone resistant metastatic prostate cancer: the final analysis of the EORTC-GU group prospective randomized phase II study (30865). J Urol 1993; 150: 1840-1844.

35. **Trachtenberg J, Halpern N, Pont A.**
Ketoconazole: a novel and rapid treatment for advanced prostatic cancer. J Urol 1983; 130: 152-153.

36. **Pont A.**
Long-term experience with high dose ketoconazole therapy in patients with D2 prostate carcinoma.
J Urol 1987; 137: 902-904.

37. **Harnett DR, Raghavan D, Caterson I.**
Aminoglutethimide in advanced prostate carcinoma. Br J Urol 1987; 59: 323-327.

38. **Da Silva FC, Fossa SD, Aaronson NK, Serbouti S, Denis L, Casselman J, Whelan P, Hetherington J, Fava C, Richards B, Robinson MR.**
The quality of life of patients with newly diagnosed M1 prostate cancer: experience with EORTC clinical trial 30853. Eur J Cancer 1996; 32A: 72-77.

39. **Daniell HW.**
    Osteoporosis after orchiectomy for prostate cancer. J Urol 1997; 157: 439-444.
40. **Herman SM, Robinson JT, McCredie RJ, Adams MR, Boyer MJ, Celermajer DS.**
    Androgen deprivation is associated with enhanced endothelium-dependent dilatation in adult men.
    Arterioscler Thromb Vasc Biol 1997; 17: 2004-2009.
41. **Strum SB, McDermed JE, Scholz MC, Johnson H, Tisman G.**
    Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined
    hormone blockade. Br J Urol 1997; 79: 933-941.
42. **Diamond T, Campbell J, Bryant C, Lynch W.**
    The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated
    for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy.
    Cancer 1998; 83: 1561-1566.
43. **Mahler C, Verhelst J, Denis L.**
    Clinical pharmacokinetics of the antiandrogens and their efficacy in prostate cancer.
    Clin Pharmacokinet 1998; 34: 405-417.
44. **Wie JT, Gross M, Jaffe CA, Gravlin K, Lahaie M, Faerber GJ, Cooney KA.**
    Androgen deprivation therapy for prostate cancer results in a significant loss of bone density. Urology
    1999; 54: 607-611.
45. **Catalona WJ.**
    Management of cancer of the prostate. N Engl J Med 1994; 331: 996-1004.
46. **Bolla M, Gonzales D, Warde P, Dubois JB, Mirimanoff RO, Storne G, Bernier J, Kuten A, Sternberg
    C, Gil T, Collette L, Pierart M.**
    Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and
    goserelin. N Engl J Med 1997; 337: 295-300.

10. TREATMENT: HORMONAL TREATMENT 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. cyproterone 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 stimulatory effects 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), when quality of life and preservation of sexual function are important (4).

Experience with nilutamide

Nilutamide is not recommended by the manufacturer for use as monotherapy. Experience with this compound is limited to a single study in which 26 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).

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 (6-11).

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 (12) or 3 mg/day (13), 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 (14). Three recent, randomized, Phase III trials have compared flutamide with DES, orchiectomy or MAB (15-17).

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 (15). Boccon-Gibod et al. randomized 104 patients to receive either flutamide, 250 mg three times daily, or orchiectomy and found no difference in progression-free survival or overall survival time between the two groups (16). Pavone-Macaluso found equal effect in patients randomized to receive either flutamide or MAB (17).

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

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, elevation of LH and serum testosterone levels has been documented in treated patients (18).

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 (19). 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 (20).

The side-effects of bicalutamide are more common after monotherapy (gynaecomastia 25-49% of patients and breast pain 34-40%) than when given in combination with LHRHa. Elevation of liver enzymes has also been reported (20).

10.2   Steroidal antiandrogens

CPA

CPA is a potent steroidal antiandrogen and has gestogenic properties leading to 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 (21). The results are still pending for EORTC protocol 30892, which compared flutamide monotherapy with CPA monotherapy in untreated metastatic CaP. Preliminary results indicate that gynaecomastia, diarrhoea, nausea and liver function deterioration occurred more frequently with flutamide, and thrombotic events were seen more frequently with CPA (22).

CAB

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 in CAB groups compared with surgical or medical hormone ablation alone (23-25). However, a meta-analysis including almost all trials, published and not published,

showed no significant advantage in terms of efficacy for CAB compared with castration alone (26). 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 (27).

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 initiation of therapy. Once patients relapse, 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 (hormone-refractory CaP). 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. The molecular basis for this syndrome is not completely understood, but data suggest that mutations in the androgen receptor may be responsible for the paradoxical effect observed (28).

10.3   REFERENCES

1.   **Soloway MS, Matzkin H.**
      Antiandrogenic agents as monotherapy in advanced prostatic carcinoma. Cancer 1993; 71: 1083-1088.
2.   **Schroeder FH.**
      Pure antiandrogens as monotherapy in prospective studies of prostatic carcinoma. In: Treatment of Prostatic Cancer - Facts and Controversies. EORTC Genitourinary Group Monograph 8, 1990; 93-103.
3.   **Blackledge GR.**
      Clinical progress with a new antiandrogen, Casodex (bicalutamide). Eur Urol 1996; 29: 96-104.
4.   **Kaisary AV.**
      Antiandrogen monotherapy in the management of advanced prostate cancer.
      Eur Urol 1997; 31 (Suppl 2): 14-19.
5.   **Decensi AU, Boccardo F, Guarneri D.**
      Monotherapy with nilutamide, a pure nonsteroidal antiandrogen, in untreated patients with metastatic carcinoma of the prostate. J Urol 1991; 146: 377-381.
6.   **Sogani PC, Vagaiwala MR, Whitmore WF.**
      Experience with flutamide in patients with advanced prostatic cancer without prior endocrine therapy. Cancer 1984; 54: 744-750.
7.   **Lundgren R.**
      Flutamide as primary treatment for metastatic prostatic cancer. Br J Urol 1987; 59: 156-158.
8.   **Prout GR, Keating MA, Griffin PP, Schiff SF.**
      Long term experience with flutamide in patients with prostatic carcinoma. Urology 1989; 34 (Suppl): 37-45.
9.   **Pavone-Macaluso M, Pavone C, Serretta Y, Daricello G.**
      Antiandrogens alone or in combination for treatment of prostate cancer: the European experience.
      Urology 1989; 34: 27-36.
10.   **Delaere KPJ, Van Thillo EL.**
      Flutamide monotherapy as primary treatment in advanced prostatic carcinoma.
      Semin Oncol 1991; 18: 13-18.
11.   **Narayana AS, Loening SA, Culp DA.**
      Flutamide in the treatment of metastatic carcinoma of the prostate. Br J Urol 1981; 53: 152-153.
12.   **Jacobo E, Schmidt JD, Weinstein SH, Flocks RH.**
      Comparison of flutamide and diethylstilbestrol in untreated advanced prostatic cancer.
      Urology 1976; 8: 231-233.
13.   **Lund F, Rasmussen F.**
      Flutamide versus stilboestrol in the management of advanced prostatic cancer. A controlled prospective study. Br J Urol 1988; 61: 140-142.
14.   **Johansson JE, Andersson SO, Beckman Lingardh G, Zador G.**
      Clinical evaluation of flutamide and estramustine as initial treatment of metastatic carcinoma of prostate. Urology 1987; 24: 55-59.
15.   **Chang A, Yeap B, Davis T, Blum R, Hahn R, Khanna O, Fisher H, Rosenthal J, Witte R, Schinella R, Trump D.**
      Double blind randomized study of primary hormonal treatment of stage D2 prostate carcinoma: flutamide versus diethylstilbestrol. J Clin Oncol 1996; 14: 2250-2257.
16.   **Boccon-Gibod L, Fournier G, Bottet P, Marechal JM, Guiter J, Rischman P, Hubert J, Soret JY,**

Mangin P, Mallo C, Fraysse CE.
Flutamide versus orchidectomy in the treatment of patients with metastatic prostate carcinoma.
Eur Urol 1997; 32: 391-395.

17. Pavone-Macaluso M.
Flutamide monotherapy versus combined androgen blockade in advanced prostate cancer. Interim report of an Italian multicenter, randomized study. Societé International d'Urologie (SIU) 23rd Congress 1994; abstract 354: 170.

18. Furr BJA.
The development of Casodex (bicalutamide): preclinical studies. Eur Urol 1996; 29: 83-95.

19. Bales GT, Chodak GW.
A controlled trial of bicalutamide versus castration in patients with advanced prostate cancer.
Urology 1996; 47: 38-43.

20. Tyrrell CJ, Kaisary AV, Iversen P, Anderson JB, Baert L, Tammela T, Chamberlain M, Webster A, Blackledge G.
A randomised comparison of Casodex (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998; 33: 447-456.

21. Pavone-Macaluso M, de Voogt HJ, Viggiano G, Barasolo E, Lardennois B, de Pauw M, Sylvester R.
Comparison of DES, CPA and MAP in the treatment of advance prostatic cancer: final analysis of a randomised phase III trial of the EORTC. J Urol 1986; 136: 624-631.

22. Schroeder FH, Whelan P, Kurth KH, Sylvester R, Depauw M.
Antiandrogens as monotherapy for metastatic prostate cancer: a preliminary report on EORTC protocol 30892. In: Recent Advances in Prostate Cancer and BPH. Schroeder FH (ed.). Parthenon:London, 1997, pp. 141-146.

23. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, Blumenstein BA, Davis MA, Goodman PJ.
A controlled trial of leuprolide with and without flutamide in prostatic carcinoma.
N Engl J Med 1989; 321: 419-424.

24. Denis LJ, Carnelro de Moura JC, Bono A, Sylvester R, Whelan P, Newling D, Depauw M.
Goserelin acetate flutamide versus bilateral orchiectomy. A phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. Urology 1993; 42: 119-129.

25. Dijkman GA, Janknegt RA, De Reijke TM, Debruyne FM.
Long term efficacy and safety of nilutamide plus castration in advanced prostate cancer and the significance of early PSA normalization. J Urol 1997; 158: 160-163.

26. Prostate Cancer Trialists' Collaborative Group.
Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Lancet 1995; 346: 265-269.

27. Eisenberger MA, Blumenstein BA, Crawford ED, Miller G, McLeod DG, Loehrer PJ, Wilding G, Sears K, Culkin DJ, Thompson IM, Bueschen AJ, Lowe BA.
Bilateral orchiectomy with or without flutamide for metastatic prostate cancer.
N Engl J Med 1998; 339: 1036-1042.

28. Kelly WK.
Endocrine withdrawal syndrome and its relevance to the management of hormone refractory prostate cancer. Eur Urol 1998; 34 (Suppl 3): 18-23.

11. TREATMENT: NEOADJUVANT HORMONAL THERAPY (NHT) PRIOR TO CURATIVE TREATMENT (SURGERY OR RADIATION)

11.1 Principles of neoadjuvant therapy

Neoadjuvant or up-front therapy in general is defined as therapy given prior to definitive local treatment with curative intent (surgery, radiation, brachytherapy). As CaP is an androgen-dependent tumour, neoadjuvant hormonal therapy (NHT) is an appealing concept. Proliferation of both normal and cancerous cells is suppressed and apoptosis is activated when androgens are withdrawn (1). Attempts to decrease the size of the prostate before radical prostatectomy were first reported by Vallett as early as 1944 (2). However, it was more than 40 years later before the possibility of reversible androgen withdrawal and the steeply increasing number

of radical prostatectomies performed rekindled interest in combination therapy (3).

Despite improvements in diagnosing prostatic carcinoma, the pathological understaging of apparently localized cancer remains a major clinical problem (4). Possible rationales for NHT include, firstly, induction of early regression of the primary tumour (reducing tumour bulk). With radical prostatectomy this could result in less frequent positive surgical margins, and consequently increased rates of organ-confined cancer. With external beam irradiation, decreasing the volume of tissue that needs to be irradiated may reduce the acute and long-term side-effects of radiation and the number of clonogens that have to be targeted. Furthermore, NHT may remove tumour cells from the active cycling phase into the resting phase and may potentiate radiation effects on apoptosis (5). Secondly, micrometastatic disease may also be treated together with the primary lesion. Finally, patients who respond to NHT can be identified and therefore may be candidates for adjuvant systemic therapy after surgery or radiation.

Drawbacks of NHT include delay of definitive local treatment resulting in possible disease progression during hormonal pre-treatment, increased overall incidence of side-effects and cost of therapy. In addition, resistant clones may develop with the early use of hormones, and pathological staging could be more difficult due to scarring and fibrosis, with subsequent uncertainty in prognosis.

11.2   NHT and radical prostatectomy

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 (6,7). However, those trials were not randomized, there was no standard treatment protocol and the lengths of NHT varied considerably.

Until now, only five prospective, randomized studies with a sufficiently large number of patients to be evaluable have been published (Table 14) (8-12). Evaluation of radical prostatectomy specimens showed a comparable number of involved seminal vesicles in one study (15% with NHT versus. 22% with surgery alone) (11) and a disadvantage of NHT in another (28% in NHT group vs. 14% in control group) (12). In both studies, there was no difference in the incidence of regional lymph node metastases between the two treatment arms. The most striking pathological feature in all five trials was the significantly lower number of positive surgical margins in the NHT group. However, when follow-up was considered, this favourable finding did not translate into reduced PSA failure rates (Table 14). Only in the Swedish study, a follow-up article showed that the interval to biochemical failure was longer for NHT (24 months vs. 13 months in controls) (13). Using PSA as a surrogate endpoint, there was no significant difference between the failure rates in the two treatment arms at 6 months and 24 months (9,14,15). 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 (11), but that the duration of radical prostatectomy, blood loss and number of transfusions were similar in NHT-treated patients and controls (10,11).

Table 14: Randomized trials of neoadjuvant hormonal therapy (NHT) in radical prostatectomy-treated patients

Study	No. of patients	Clinical stage[1]	Hormonal therapy	Follow-up reports (PSA failure)[1]
Labrie et al., 1994 (8)	161	B-C	LHRHa: 3 months Antiandrogen: 3 months	Not reported
Van Poppel et al., 1995 (9)	130	T2b-T3	Estramustine: 6 weeks	At 6 months: 14% in NHT, 15% in control
Hugosson et al., 1996 (10)	126	T1b-T3a	LHRHa: 3 months CPA: 3 weeks	Interval to failure: 24 months in NHT, 13 months in control
Soloway et al., 1995 (11)	303	T2b	LHRHa: 3 months Antiandrogen: 3 months	At 24 months: 21% in NHT and control
Goldenberg et al., 1996 (12)	213	T1b-T2c	CPA: 3 months	At 24 months: 28% in NHT, 20% in control

PSA = prostate-specific antigen; LHRHa = luteinizing hormone releasing hormone analogues; NHT = neoadjuvant hormonal therapy; CPA = cyproterone acetate.

[1]   As defined in study.

11.3   NHT and radiation therapy

Studies in nude mice have shown some degree of synergistic interaction of hormonal treatment followed by irradiation (16). Retrospective analysis and Phase II trials have suggested some benefit for combined therapy (17,18). Recently, preliminary data from two prospective trials of NHT followed by radiotherapy have been reported (Table 15) (19,20). In the first study, patients with clinical T2-T4 CaP were randomized to receive either radiation alone or radiation in combination with MAB (LHRHa plus antiandrogen) 2 months before and during radiation therapy (19). At a median follow-up of 4.5 years, local control and progression-free survival rates were significantly in favour of the NHT group. However, a recent update could not demonstrate improved overall survival (21). In another study, patients with clinical T2b-T3 tumours were randomized into one of three groups: (1), radiation therapy only; (2), NHT for 3 months before irradiation; and (3), NHT for 3 months before, during and 6 months after irradiation (20). Two years after radiotherapy, the positive biopsy rate was 69% in group 1, 29% in group 2 and 6% in group 3, but the interpretation of these results is not yet clear and the follow-up period is too short to draw meaningful conclusions from these data.

It is worth pointing out that no randomized studies have evaluated monotherapy with non-steroidal antiandrogens prior to curative treatment. Several issues have to be considered in NHT and radiation therapy. Future studies should include a treatment arm of hormonal therapy alone (i.e. without radiation). In addition, the duration and timing of NHT are not yet clearly defined. The combination of NHT and adjuvant hormonal therapy has to be evaluated; results of studies of the latter have already been reported with favourable outcome for the adjuvant arm in patients with poorly differentiated or locally advanced CaP (22).

Table 15: Randomized trials of neoadjuvant hormonal therapy in radiation-treated patients

Study	No. of patients	Clinical stage1	Hormonal therapy	Local progression[1]	Distant metastases
Pilepich *et al.*, 1995 (19)	471	T2-T4	Maximum androgen blockade 2 months before and during radiotherapy	At median 4.5 years: 46% in neoadjuvant hormonal therapy, 71% in control (p < 0.001)	At 5 years: 34% in neoadjuvant hormonal therapy, 41% in control (p = 0.09)
Laverdière *et al.*, 1997 (20)	120	T2b-T3	(a) Maximum androgen blockade 3 months before radiotherapy (b) Maximum androgen blockade 3 months before, during, and 6 months after radiotherapy	Biopsy positive at 2 years: 69% in control and 29% in (a) and 6% in (b)	

[1] As defined in study

11.4 REFERENCES

1. **Kyprianou N, English HF, Isaacs JT**.
   Programmed cell death during regression of PC-82 human prostate cancer following androgen ablation.
   Cancer Res 1990; 50: 3748-3753.
2. **Vallett BS**.
   Radical perineal prostatectomy subsequent to bilateral orchiectomy. Delaware Med J 1944; 16: 19-20.
3. **Monfette G, Dupont A, Labrie F**.
   Temporary combination therapy with flutamide and tryptex as adjuvant to radical prostatectomy for the treatment of early stage prostate cancer. Early Stage Prostate Cancer: Diagnosis and Choice of Therapy. Labrie F, Lee F, Dupont A et al. (eds). Elsevier:New York, 1989, pp. 41-51.
4. **Schmid H-P, Oberpenning F, Pummer K**.
   Diagnosis and staging of prostatic carcinoma: what is really necessary? Urol Int 1999; 63: 57--61.
5. **Widmark A, Damber JE, Bergh A, Henriksson R**.
   Estramustine potentiates the effects of irradiation on the Dunning (R3327) rat prostatic adenocarcinoma. Prostate 1994; 24: 79-83.
6. **Fair WR, Aprikian A, Sogani P, Reuter V, Whitmore WF**.
   The role of neoadjuvant hormonal manipulation in localized prostatic cancer.
   Cancer 1993; 71(Suppl): 1031-1038.
7. **Oesterling JE, Andrews PE, Suman VJ, Zincke H, Myers RP**.
   Preoperative androgen deprivation therapy: artificial lowering of serum prostate specific antigen without downstaging the tumor. J Urol 1993; 149: 779-782.
8. **Labrie F, Cusan L, Gomez J-L, Diamond P, Suburu R, Lemay M, Tetu B, Fradet Y, Candas B**.
   Down-staging of early stage prostate cancer before radical prostatectomy: the first randomized trial of neoadjuvant combination therapy with flutamide and a luteinizing hormone-releasing hormone agonist. Urology 1994; 44 (Symposium suppl): 29-37.
9. **Van Poppel H, De Ridder D, Elgamal AA, Van de Voorde W, Werbrouck P, Ackaert K, Oyen R, Pittomvils G, Baert L, The Belgian Uro-Oncological Study Group**.
   Neoadjuvant hormonal therapy before radical prostatectomy decreases the number of positive surgical margins in stage T2 prostate cancer: interim results of a prospective randomized trial.
   J Urol 1995; 154: 429-434.
10. **Hugosson J, Abrahamsson PA, Ahlgren G, Aus G, Lundberg S, Schelin S, Schain M, Pedersen K**.
    The risk of malignancy in the surgical margin at radical prostatectomy reduced almost three-fold in patients given neo-adjuvant hormone treatment. Eur Urol 1996; 29: 413-419.
11. **Soloway MS, Sharifi R, Wajsman Z, McLeod D, Wood DP, Puras-Baez A, The Lupron Depot Neoadjuvant Prostate Cancer Study Group**.
    Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. J Urol 1995; 154: 424-428.

12. **Goldenberg SL, Klotz LH, Srigley J, Jewett MA, Mador D, Fradet Y, Barkin J, Chin J, Paquin JM, Bullock MJ, Laplante S, The Canadian Urologic Oncology Group.**
Randomized, prospective, controlled study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. J Urol 1996; 156: 873-877.
13. **Aus G, Abrahamsson P-A, Ahlgren G, Hugosson J, Lundberg S, Schain M, Schelin S, Pedersen K.**
Hormonal treatment before radical prostatectomy: a 3-year follow-up. J Urol 1998; 159: 2013-2017.
14. **Soloway M, Sharifi R, Wajsman Z, McLeod D, Wood D, Puras-Baez A.**
Radical prostatectomy alone vs radical prostatectomy preceded by androgen blockade in cT2b prostate cancer - 24 month results (abstract). J Urol 1997; 157 (Suppl): 160.
15. **Goldenberg SL, Klotz L, Jewett M, Barkin J, Chenter M, Fradet Y, Chin J.**
A randomized trial of neoadjuvant androgen withdrawal therapy prior to radical prostatectomy: 24 month post-treatment PSA results (abstract). J Urol 1997; 157 (Suppl): 92.
16. **Zietman AL, Nakfoor BM, Prince EA, Gerweck LE.**
The effect of androgen deprivation and radiation therapy on an androgen-sensitive murine tumor: an in vitro and in vivo study. Cancer J Sci Am 1997; 3: 31-36.
17. **Pilepich MV, Krall JM, Sause WT, Johnson RJ, Russ HH, Hanks GE, Perez CA, Zinninger M, Martz KL.**
Prognostic factors in carcinoma of the prostate - analysis of RTOG study 75-06.
Int J Radiat Oncol Biol Phys 1987; 13: 339-349.
18. **Pollack A, Zagars GK, Kopplin S.**
Radiotherapy and androgen ablation for clinically localized high-risk prostate cancer.
Int J Radiat Oncol Biol Phys 1995; 32: 13-20.
19. **Pilepich MV, Krall JM, Al-Sarraf M, John MJ, Doggett RL, Sause WT, Lawton CA, Abrams RA, Rotman M, Rubin P, Shipley WU, Grignon D, Caplan R, Cox JD, Radiation Therapy Oncology Group.**
Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of Urology 1995; 45: 616-623.
20. **Laverdière J, Gomez JL, Cusan L, Suburu ER, Diamond P, Lemay M, Candas B, Fortin A, Labrie F.**
Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37: 247-252.
21. **Pilepich MV, Winter K, Roach M, Russell AH, Sause W, Rubin P, Byhardt R, Machtay M, Grignon D.**
Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation before and during radiotherapy in locally advanced carcinoma of the prostate (abstract).
Proc Am Soc Clin Oncol 1998; 17: 308a.
22. **Bolla M, Gonzales D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M.**
Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997; 337: 295-300.

12. TREATMENT: SECOND-LINE TREATMENT OF CaP

12.1 Background

Preventing the growth and progression of cancer, despite initial androgen ablation therapy and management of this hormone-refractory stage of CaP, remains a significant challenge to clinicians. No major therapeutic strategies with an impact equal to that of androgen ablation have been devised. A better understanding of the biology of the hormone-refractory state, the development of new classes of drugs and re-examination of older drugs all support the contention that important moves are being made towards improving care of the patient with hormone-refractory CaP. Many different terms have been used to describe cancers that relapse after initial hormonal ablation therapy, including hormone-refractory CaP, androgen-independent cancers and hormone-independent cancers (1). The precise definition of recurrent or relapsed CaP remains controversial. A reasonable criterion proposed involves serial PSA tests carried out at least 2 weeks apart resulting in two 50% increases over the nadir value (2).

12.2 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 abundance 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 CaPs 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 hormone-refractory CaP 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 CaPs. Overexpression of bcl-2 and p53 in prostatectomy specimens have been shown to predict an aggressive clinical course (12-15).

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 (16,17).

12.3   Assessing outcome of treatment in androgen-independent CaP

From 80 to 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 (18-21). 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 (22).

Many contemporary studies use PSA as a marker of response, although there is no general consensus on what the magnitude and duration of decline in PSA level should be. The greatest use of PSA in this context is as a rapid screening tool to test new agents for activity. However, conflicting evidence is emerging regarding the role of PSA as a marker for response, and wide fluctuations have been seen in PSA values, indicating a transient effect of drugs on PSA production. Therefore, knowledge of the effects of a drug on PSA expression is key to interpreting PSA response data, which must be viewed in conjunction with other clinical data (23-30).

Growing numbers of investigators advocate subjective endpoints. Since a significant survival benefit from chemotherapy in hormone-refractory CaP has not yet been demonstrated, the success of treatment may rely on redefining the goals of therapy (2,22). 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 in conjunction with other clinical parameters of response and consider quality of life endpoints in symptomatic patients.

12.4   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 (31). The overall effect of continued testicular androgen suppression in hormone-refractory CaP is minimal at best. 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 (32,33).

12.5   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 (34,35). Antiandrogen withdrawal responses have also been reported after treatment with bicalutamide and megestrol acetate (36,37). 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 of clinical trials. However, observation remains a viable choice for symptomatic patients.

12.6   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 (38). Bicalutamide is a non-steroidal antiandrogen that demonstrates a dose response, so, 200 mg of bicalutamide normalizes PSA more effectively than 50 mg of bicalutamide in patients with androgen-dependent CaP (39-42). 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 (43-45). At low doses (20 mg twice daily), it is effective in suppressing hot flushes in 70% of men receiving first-line hormonal ablation. At higher doses (160-320 mg/day), the antiandrogen can stimulate appetite in cancer patients and could have a multidimensional role in

selected symptomatic patients with advanced CaP (46,47). Approximately 10% of circulating androgen in humans is secreted by the adrenal glands.

In androgen-independent states, some tumour cells must retain sensitivity to androgens, as a further decrease in circulating androgen levels by bilateral adrenalectomy or drugs that inhibit adrenal steroidogenesis can induce a clinical response. Aminoglutethimide, ketoconazole and corticosteroid act primarily via this mechanism (48-54).

CaPs 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 CaPs. Antioestrogens in CaP have been reported to have measurable response rates of only 0-10% (55,56). Alternatively, high-dose oestrogens have been reported to have salvage objective responses. The mechanism for the effect has been postulated to be from mitotic arrest of direct cytotoxic effects on the cells, perhaps through an apoptotic mechanism (57,58).

12.7   Non-hormonal therapy

Renewed enthusiasm for the role of non-hormonal therapy in hormone-refractory CaP 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 are 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 (27,28). 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, significant PSA and measurable responses have been reported in three separate studies (26,59,60). Estramustine plus paclitaxel was investigated, despite the inactivity of paclitaxel as a single agent, because preclinical evidence suggested synergistic antimitotic effects (61). Estramustine has also been combined with docetaxel in patients with androgen-independent and hormone-independent CaPs. Overall PSA responses and measurable responses were similarly promising (62,63). Estramustine plus oral etoposide also showed synergy (25).

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 (64,65). A study of the combination of oral cyclophosphamide and oral etoposide in 20 patients was similarly encouraging (66). 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, hormone-refractory CaPs. A combination of estramustine, etoposide and paclitaxel has also recently been reported to produce high response rates (67,68).

12.8   Other treatments

The majority of patients with hormone-refractory CaP have painful bone metastases. The two b-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 (69). 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). A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses and social workers (70).

12.9   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. New biological and cytotoxic agents as well as novel combinations of therapy are allowing these hypotheses to be tested.

Suramin activity against hormone-refractory CaP is likely to be mediated through the inhibition of binding of growth factors, such as transforming growth factor b, to their receptors. Although the ultimate role of suramin in the treatment of hormone-refractory CaP is still undetermined, recent results renew some of this agent's initial promise (71-73). Other growth factor inhibitors have shown some promise in preclinical testing, and 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 (74). In addition, paclitaxel induces bcl-2 phosphorylation and apoptosis in androgen-independent CaP (75).

12.10 REFERENCES

1. **Oh WK, Kantoff PW**.
   Management of hormone refractory prostate cancer: current standards and future prospects.
   J Urol 1998; 160: 1220-1229.
2. **Waselenko JK, Dawson NA.**
   Management of progressive metastatic prostate cancer. Oncology 1997; 11: 1551-1560.
3. **Logothetis CJ, Hoosein NM, Hsieh J-T.**
   The clinical and biological study of androgen independent prostate cancer (AI PC).
   Semin Oncol 1994; 21: 620-629.
4. **Isaacs JT, Coffey DS.**
   Adaptation versus selection as the mechanism responsible for the relapse of prostatic cancer to androgen ablation therapy as studied in the Dunning R-3327-H adenocarcinoma. Cancer Res 1981; 41: 5070-5075.
5. **Horoszewicz JS, Leong SS, Kawinski E, Karr JP, Rosenthal H, Chu TM, Mirand EA, Murphy GP.**
   LNCaP model of human prostatic carcinoma. Cancer Res 1983; 43: 1809-1818.
6. **Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP.**
   Mutation of the androgen-receptor gene in metastatic androgen independent prostate cancer.
   N Engl J Med 1995; 332: 1393-1398.
7. **Elo JP, Kvist L, Leinonen K, Isomaa V, Henttu P, Lukkarinen O, Vihko P.**
   Mutated human androgen receptor gene detected in a prostatic cancer patient is also activated by estradiol. J Clin Endocr Metab 1995; 80: 3494-3500.
8. **Visakorpi T, Hyytinen E, Kovisto P, Tanner M, Palmberg C, Keinänen R, Tammela T, Isola J, Kalloniemi OP.**
   Amplification of the androgen receptor gene is common in recurrent prostate cancer from patients treated with androgen withdrawal. J Urol 1995; 153: 379A (abstract 603).
9. **Furuya Y, Krajewski S, Epstein JI, Reed JC, Isaacs TJ.**
   Expression of bcl-2 and progression of human and rodent prostate cancers. Clin Cancer Res 1996; 2: 389-398.
10. **Haldar S, Basu A, Crose CM.**
    bcl-2 is the guardian of microtubule integrity. Cancer Res 1997; 57: 229-233.
11. **Navone NM, Troncoso P, Pisters LL, Goodrow TL, Palmer JL, Nichols WW, von Eschenbach AC, Conti CJ.**
    p53 protein accumulation and gene mutation in the progression of human prostate carcinoma.
    J Nat Cancer Inst 1993; 85: 1657-1669.
12. **Stapleton AMF, Timme TL, Gousse AE, Li QF, Tobon AA, Kattan MW, Slawin KM, Wheeler TM, Scardino PT, Thompson TC.**
    Primary human prostate cancer cells harboring p53 mutations are clonally expanded in metastases.
    Clin Cancer Res 1997; 3: 1389-1397.
13. **Bauer JJ, Sesterhenn IA, Mostofi FK, McLeod DG, Srivastava S, Moul JW.**
    Elevated levels of apoptosis regulator proteins p53 and bcl-2 are independent prognostic biomarkers in surgically treated clinically localized prostate cancer. J Urol 1996; 156: 1511-1516.
14. **Theodorescu D, Broder SR, Boyd JC, Mills SE, Frierson HF Jr.**
    p53, bcl-2 and retinoblastoma proteins as long-term prognostic markers in localized carcinoma of the prostate. J Urol 1997; 158: 131-137.
15. **MacGrogan D, Bookstein R.**
    Tumor suppressor genes in prostate cancer. Semin Cancer Biol 1997; 8: 11-19.
16. **Kim IY, Ahn HJ, Zelner DJ, Shaw JW, Lang S, Kato M, Oefelein MG, Miyazono K, Nemeth JA, Kozlowski JM, Lee C.** Loss of expression of transforming growth factor 3 type I and type II receptors correlates with tumor grade in human prostate cancer tissues. Clin Cancer Res 1996; 2: 1255-1261.
17. **Figg WD, Ammermann K, Patronas N, Steinberg SM, Walls RG, Dawson N, Reed E, Sartor O.** Lack of correlation between prostate-specific antigen and the presence of measurable soft tissue metastases in hormone refractory prostate cancer. Cancer Invest 1996; 14: 513-517.
18. **Di Sant'Agnese PA.** Neuroendocrine differentiation in carcinoma of the prostate. Diagnostic, prognostic, and therapeutic implications. Cancer 1992; 70: 254-268.
19. **Smith PH, Bono A, Calais da Silva F, Debruyne F, Denis L, Robinson P, Sylvester R, Armitage TG.**
    Some limitations of the radioisotope bone scan in patients with metastatic prostate cancer. A subanalysis of EORTC trial 30853. The EORTC Urological Group. Cancer 1990; 66: 1009-1016.
20. **Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S, Moinuddin M.**
    Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer 1988; 61: 195-202.
21. **Scher HI, Mazundar M, Kelly WK.**
    Clinical trials in relapsed prostate cancer: defining the target. J Natl Cancer Inst 1996; 88: 1623-1634.

22. **Dawson NA, McLeod DG.**
The assessment of treatment outcomes in metastatic prostate cancer: changing endpoints.
Eur J Cancer 1997; 33: 560-565.

23. **Kelly WK, Scher HI, Mazurndar M, Vlamis V, Schwartz M, Fossa SD.**
Prostate-specific antigen as a measure of disease outcome in metastatic hormone refractory prostate cancer. J Clin Oncol 1993; 11: 607-615.

24. **Sella A, Kilbourn R, Amato R, Bui C, Zukiwski AA, Ellerhorst J, Logothetis CJ.**
Phase B study of ketoconazole combined with weekly doxorubicin in patients with androgen-independent prostate cancer. J Clin Oncol 1994; 12: 683-688.

25. **Pienta KJ, Redman B, Hussein M, Cummings G, Esper PS, Appel C, Flaherty LE.**
Phase II evaluation of oral estramustine and oral etoposide in hormone-refractory adenocarcinorna of the prostate. J Clin Oncol 1994; 12: 2005-2012.

26. **Hudes GR, Greenberg R, Krigel RL, Fox S, Scher R, Litwin S, Watts P, Speicher L, Tew K, Comis R.**
Phase II study of estramustine and vinblastine, two microtubule inhibitors, in hormone-refractory prostate cancer. J Clin Oncol 1992; 10: 1754-1761.

27. **Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, Armitage GR, Wilson JJ, Venner PM, Coppin CM, Murphy KC.**
Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996; 14: 1756-1764.

28. **George DJ, Kantoff PW.**
Prognostic indicators in hormone refractory prostate cancer. Urol Clin North Am 1999; 26: 303--310.

29. **Scher HI, Curley T, Geller N, Engstrom C, Dershaw DD, Lin SY, Fitzpatrick K, Nisselbaum J, Schwartz M, Bezirdjian L, Eisenberger M.**
Trimetrexate in prostatic cancer: preliminary observations on the use of prostate-specific antigen and acid phosphatase as a marker in measurable hormone-refractory disease. J Clin Oncol 1990; 8: 1830-1838.

30. **Thalmann GN, Sikes RA, Chang SM, Johnston DA, von Eschenbach AC, Chung LW.**
Suramin-induced decrease in prostate-specific antigen expression with no effect on tumor growth in the LNCaP model of human prostate cancer. J Natl Cancer Inst 1996; 88: 794-801.

31. **Klugo RC, Farah RN, Cerny JC.**
Bilateral orchiectomy for carcinoma of the prostate: response of serum testosterone and clinical response to estrogen therapy. Urology 1981; 17: 49-50.

32. **Taylor CD, Elson P, Trump DL.**
Importance of continued testicular suppression in hormone-refractory prostate cancer.
J Clin Oncol 1993; 11: 2167-2172.

33. **Hussein M, Wolf M, Marshall E, Crawford ED, Eisengerger M.**
Effects of continued androgen-deprivation therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group report. J Clin Oncol 1994; 12: 1868-1875.

34. **Kelly WK, Scher HI.**
Prostate specific antigen decline after antiandrogen withdrawal syndrome. J Urol 1993; 149: 607-609.

35. **Scher HI, Kelly WK.**
Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer.
J Clin Oncol 1993; 11: 1566-1572.

36. **Small EJ, Carroll PR.**
Prostate-specific antigen decline after Casodex withdrawal: evidence for an antiandrogen withdrawal syndrome. Urology 1994; 43: 408-410.

37. **Dawson NA, McLeod DG.**
Dramatic prostate specific antigen decline in response to discontinuation of megestrol acetate in advanced prostate cancer: expansion of the antiandrogen withdrawal syndrome. J Urol 1995; 153: 1946-1947.

38. **Small EJ, Vogelzong NJ.**
Second-line hormonal therapy for advanced prostate cancer: a shifting paradigm.
J Clin Oncol 1997; 15: 382-388.

39. **Blackledge GRP, Lowery K.**
Role of prostate-specific antigen as a predictor of outcome in prostate cancer. Prostate 1994; 5: 34-38.

40. **Scher HI, Liebertz C, Kelly WK, Mazumdar M, Brett C, Schwartz L, Kolvenbag G, Shapiro L, Schwartz M.**
Bicalutamide for advanced prostate cancer: the natural versus treated history of disease.
J Clin Oncol 1997; 15: 2928-2938.

41. **Joyce R, Fenton MA, Rode P, Constantine M, Gaynes L, Kolvenbag G, DeWolf W, Balk S, Taplin ME, Bubley GJ.**

High dose bicalutamide for androgen independent prostate cancer: effect of prior hormonal therapy.
J Urol 1998; 159: 149-153.

42. **Kucuk O, Blumenstein B, Moinpour C et al.**
Phase II trial of Casodex in advanced prostate cancer (CaP) patients who failed conventional hormonal manipulations: a Southwest Oncology Group study (SWOG 9235). Proc Am Soc Clin Oncol (ASCO) 1996; 15: 245.

43. **McLeod DG.**
Antiandrogenic drugs. Cancer 1992; 71: 1046-1049.

44. **Dawson NA, Small EJ, Conaway M et al.**
Megestrol acetate in men with hormone-refractory prostate cancer: prostate specific antigen (PSA) response and antiandrogen withdrawal (AAWD): CALGB 9181. Proc Am Soc Clin Oncol (ASTRO) 1996; 15: 241.

45. **Osborn JL, Smith DC, Trump DL.**
Megestrol acetate in the treatment of hormone refractory prostate cancer.
Am J Clin Oncol 1997; 20: 308-310.

46. **Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE, Bate WW, Rospond RM, Oesterling JE.**
Megestrol acetate for the prevention of hot flashes. N Engl J Med 1994; 331: 347-352.

47. **Gebbia V, Tesa A, Gebbia N.**
Prospective randomized trial of two dose levels of megestrol acetate in the management of anorexia-cachexia syndrome in patients with metastatic cancer. Br J Cancer 1996; 73: 1576-1580.

48. **Wilding G.**
Endocrine control of prostate cancer. Cancer Surv 1995; 23: 43-62.

49. **Dawson NA.**
Treatment of progressive metastatic prostate cancer. Oncology 1993; 7: 17-24.

50. **Sartor O, Cooper M, Weinberger M, Headlee D, Thibault A, Tompkins A, Steinberg S, Figg WD, Linehan WM, Myers CE.**
Surprising activity of flutamide withdrawal when combined with aminoglutethimide, in treatment of 'hormone refractory' prostate cancer. J Natl Cancer Inst 1994; 86: 222-227.

51. **Dupont A, Gomez JL, Cusan L, Koutsilieris M, Labrie F.**
Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol 1993; 150: 908-913.

52. **Rochlitz CF, Damon LE, Russi MB, Geddes A, Cadman EC.**
Cytotoxicity of ketoconazole in malignant cell lines. Cancer Chemother Pharmacol 1988; 21: 319-322.

53. **Mahler C, Verhelst J, Denis L.**
Ketoconazole and liazorole in the treatment of advanced prostatic cancer. Cancer 1993; 71: 1068-1073.

54. **Small EJ, Egan B, Apodace D, Fippin L.**
Ketoconazole retains significant activity in patients with advanced prostate cancer who have progressed despite flutamide withdrawal. Proc Am Soc Clin Oncol (ASCO) 1996; 15: 255.

55. **Horton J, Rosenbaum C, Cummings FJ.**
Tamoxifen in advanced prostate cancer: an ECOG pilot study. Prostate 1988; 12: 173-177.

56. **Bergan RC, Blagosklony M, Dawson NA.**
Significant activity by high dose tamoxifen in hormone refractory prostate cancer. Proc Am Soc Clin Oncol (ASCO) 1995; 14: A637.

57. **Ferro MA, Gillatt D, Symes MO, Smith PJ.**
High dose intravenous estrogen therapy in advanced prostatic carcinoma. Use of serum prostate-specific antigen to monitor response. Urology 1989; 34: 134-138.

58. **Robertson CN, Roberson KM, Padilla GM, O'Brien ET, Cook JM, Kim CS, Fine RL.**
nduction of apoptosis by diethylstilbestrol in hormone-insensitive prostate cancer cells. J Natl Cancer Inst 1996; 88: 908-917.

59. **Ellerhorst JA, Tu SM, Amato RJ, Finn L, Millikan RE, Pagliaro LC, Jackson A, Logothetis CJ.**
Phase II trial of alternating weekly chemohormonal therapy for patients with androgen-independent prostate cancer. Clin Cancer Res 1997; 3: 2371--2376.

60. **Seidman AD, Scher HI, Petrylak D, Dershaw DD, Curley T.**
Estramustine and vinblastine: use of prostate specific antigen as a clinical trial end point for hormone refractory prostate cancer. J Urol 1992; 147: 931-934.

61. **Hudes GR, Nathan FE, Khater C, Greenberg R, Gomella L, Stern C, McAleer C.**
Paclitaxel plus estramustine in metastatic hormone-refractory prostate cancer. Semin Oncol 1995; 22: 41-45.

62. **Petrylak DP, Shelton G, Judge T, O'Connor M, MacArthur RB.**
Phase I trial of docetaxel (D) and estramustine (E) in androgen-insensitive prostate cancer.
Proc Am Soc Clin Oncol (ASCO) 1997; 16: 310A.

63. **Kreis W, Budman DR, Fetten J, Behr J.**
Phase VII study of the combination of estramustine phosphate (Emcyt) plus docetaxel (Taxotere) in patients with hormonerefractory prostate cancer. Proc Am Soc Clin Oncol 1997; 16: 337A.

64. **Raghavan D, Cox K, Pearson BS, Coorey GJ, Rogers J, Watt WH, Coates AS, McNeil E, Grygiel JJ.**
Oral cyclophosphamide for the management of hormone-refractory prostate cancer.
Br J Urol 1993; 72: 625-628.

65. **Abell FL, Wilkes JD, Divers L.**
Oral cyclophosphamide (CTX) for hormone refractory prostate cancer (HRPC).
Proc Am Soc Clin Oncol (ASCO) 1995; 14: 646.

66. **Meulard-Durdux C, Dufour B, Hennequin C, Chrétinen Y, Delamian S, Housset M.**
Phase II study of the oral cyclophosphamide and oral etoposide combination in hormone-refractory prostate carcinoma patients. Cancer 1996; 77: 1144-1148.

67. **Frank SJ, Amsterdam A, Kelly WK et al.**
Platinum-based chemotherapy for patients with poorly differentiated hormone-refractory prostate cancers (HRPC): response and pathologic correlations. Proc Am Soc Clin Oncol (ASCO)1996; 15: 232.

68. **Smith DC, Esper PS, Todd RF, Pienta KJ.**
Paclitaxel, estramustine and etoposide in patients with hormone refractory prostate cancer (HRPC): a phase II trial. Proc Am Soc Clin Oncol (ASCO) 1997; 16: 310A.

69. **Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, Sathyanarayana JR, Yakemchuk VN, Thomas GM, Erlich LE, Crook J, Gulenchyn KY, Hong KE, Wesolowski C, Yardlye J.**
Results of a randomized phase III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer.
Int J Radiat Oncol Biol Phys 1993; 25: 805-813.

70. **Esper PS, Pienta KJ.**
Supportive care in the patient with hormone refractory prostate cancer. Semin Urol Oncol 1997; 15: 56-64.

71. **Dawson NA, Cooper MR, Figg WD, Headlee DJ, Thibault A, Bergan RC, Steinberg SM, Sausville EA, Myers CE, Sartor O.**
Antitumor activity of suramin in hormone-refractory prostate cancer controlling for hydrocortisone treatment and flutamide withdrawal as potentially confounding variables. Cancer 1995; 76: 453-462.

72. **Kelly WK, Curley T, Liebreertz C, Dnistrian A, Schwartz M, Scher Hl.**
Prospective evaluation of hydrocortisone and suramin in patients with androgen-independent prostate cancer. J Clin Oncol 1995; 13: 2208-2213.

73. **Small EJ, Marshall ME, Reyno L et al.**
Superiority of suramin + hydrocortisone over placebo + hydrocortisone: results of a multi-center double-blind phase III study in patients with hormone refractory prostate cancer.
Proc Am Soc Clin Oncol (ASCO) 1996; 17: 308A.

74. **Sendorowicz AM.**
Flavopiridol: the first cyclin-dependent kinase inhibitor in human clinical trials. Invest New Drugs. 1999; 17: 313-320.

75. **Haldar S, Chintapalli J, Crose CM.**
Taxol induces bcl-2 phosphorylation and death of prostate cancer cells.
Cancer Res 1996; 56: 1253-1255.

13 GUIDELINES ON TREATMENT OF CANCER OF THE PROSTATE

Stage	Treatment	Comment
T1a	Watchful waiting	Standard treatment for well and moderately differentiated tumours and a < 10-year life expectancy. In patients with > 10-year life expectancy, a restaging with transrectal ultrasonography 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 transurethral resection of the prostate, 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	Patients with life expectancy > 10 years who accept treatment-related complications.
	Radiotherapy	Patients with a life expectancy > 10 years who prefer radiation treatment and accept treatment-related complications. Patients with contrain-dications for surgery. Unfit patients with a 5-10 year life expectancy and poorly differentiated tumours.
	Hormonal	Symptomatic patients unfit for curative treatment.
	Combination	Neoadjuvant hormonal therapy + radical prostatectomy: no better. Neoadjuvant hormonal therapy + 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 and moderately differentiated tumours and a life expectancy < 10 years.
	Radical prostatectomy	Optional for selected patients with 'small T3', prostate-specific antigen < 20 ng/mL, Gleason score < 8 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.
	Hormonal	Symptomatic patients, extensive T3-T4, high prostate-specific antigen level (> 25 ng/mL), unfit patients.
	Combination	Radiotherapy + hormonal seems better than radiotherapy alone. Neoadjuvant hormonal therapy + 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 (requires asymptomatic, informed patient, good compliance and good access to health care).
	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.

hormonal = all forms of hormonal therapy; combination = hormonal therapy given prior to and/or after radical prostatectomy or radiotherapy; TURP = transurethral resection of the prostate;

14. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

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.

14.1 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 30% PSA progression within 10 years, while 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 was also 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 (3,4).

After radiotherapy there is a similar course of events. A considerable proportion of patients will have a rising PSA level or positive biopsy, 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, comorbidity and the patient's own will. In general, patients who receive curative therapy may be followed up for any of the following reasons:
- Good responsible patient care
- Possibility of second-line treatment with curative intent
- Possibility of early hormonal therapy after failure
- As part of a study protocol.

Responsible patient care
A certain percentage of patients who receive curative treatment will experience treatment-related complications, such as strictures, urinary incontinence, impotence, bowel or bladder disturbances (1,8-13). These complications may result in further regular clinic visits for patient reassurance and to discuss whether or not any treatment is warranted. Moreover, most patients treated for cancer feel more comfortable with regular visits to a physician.

Second-line treatment with curative intent
Additional curative treatment is a possibility for patients who fail first-line curative treatment and who are presumed still to have a local failure only. To be candidates for such salvage treatments, patients must have a life expectancy of more than 10 years. This is particularly true as the (salvage) curative treatment is associated with higher morbidity than first-line therapy. For patients suffering documented or presumed local treatment failure after radical prostatectomy, external beam radiation is an option (14,15). Some patients, with local disease recurrence after radiation therapy, could benefit from either radical prostatectomy or cryotherapy as a salvage procedure (16,17).

Early hormonal therapy after failure
It has been extensively debated as to whether or not giving early hormonal treatment is of any benefit compared with delayed treatment applied only when symptomatic progression occurs. Early endocrine therapy has been shown to be effective in achieving an undetectable PSA value in patients found to have advanced disease at the time of radical prostatectomy (18). The question of whether or not a patient with a rising PSA level after curative therapy should be recommended to undergo early androgen deprivation therapy has to be studied in clinical trials.

As part of study protocol
Patients who are undergoing treatment in the setting of clinical trials will be followed up according to the protocol.

14.2 How 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. Techniques such

as immunoscintigraphy, polymerase chain reaction and positron emission tomography are not yet used routinely and will not be discussed. In asymptomatic patients, 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 that may be used for the evaluation of treatment-related complications must be individualized and are beyond the scope of these guidelines. Examinations used most often for cancer-related follow-up after curative surgery or radiation treatment are discussed below.

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 (1,5,18-20). It is recommended that the finding of a single elevated serum PSA level should be reconfirmed 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 progression-free survival (21). 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 (22,23).

PSA monitoring after radical prostatectomy

PSA is expected to be undetectable within 3 weeks after after a successful radical prostatectomy (24). 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 (25,26). 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) (27,28). 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 and 0.2 ng/mL after radical prostatectomy had neither clinical nor biochemical disease progression (29). 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.

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 (30). Lately, however, it has been suggested that this nadir level 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 (31). Thus, the goal for the PSA nadir after radiation therapy given with intent to cure should be less than 0.5 ng/mL. The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more.

There is a consensus that a rising PSA level is an early sign of treatment failure (7,19,31). This has led ASTRO to define failure after radiation therapy as three consecutive rises in PSA level, irrespective of the nadir value (32). Patients with local treatment failure only have been shown to have a PSA doubling time of 13 months compared with 3 months for patients with both local and distant disease recurrence (7).

DRE

DRE is performed to assess whether or not there is any sign of local disease recurrence. It is very difficult to interpret the findings of DRE after curative therapy, especially after radiotherapy. A newly detected nodule should raise the suspicion of local disease recurrence. Further investigations with TRUS and biopsy may be warranted when a pathologically proven local recurrence may have therapeutic implications.

As mentioned previously, a local disease recurrence after curative treatment is possible without a concomitant rise in PSA level (27,28). However, this has only been proven in patients with unfavourable

pathology, i.e. those with undifferentiated tumours. Therefore, 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.

TRUS and biopsy
TRUS 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 the diagnosis of local disease recurrence. It is only warranted if the finding of a local recurrence affects the treatment decision. The examination is recommended for the confirmation of local recurrence prior to deciding upon second-line curative treatment.

TRUS and biopsy after radical prostatectomy
Patients who have a suspicious DRE or a rising PSA level after radical prostatectomy may be subjected to transrectal biopsy. This can be taken from visible lesions or otherwise at the level of the urethro-vesical anastomosis. In a study, more than one set of biopsies was shown to be necessary in one-third of cases to establish the diagnosis of local disease recurrence (33). A negative biopsy does not rule out the presence of local recurrence. The search for local disease recurrence must be balanced against the fact that salvage radiation therapy might be most effective if given early, before the PSA level reaches 1 ng/mL (15).

TRUS and biopsy after radiotherapy
The use of prostatic biopsies after radiotherapy is highly controversial. A positive biopsy at least 18 months after radiotherapy is associated with a higher clinical failure rate (31). This does not, however, warrant the routine use of TRUS and biopsy in all patients (6,34). A biopsy can be omitted if the PSA level remains low and stable and the results on DRE remain unchanged. It may be most useful in the (few) cases where salvage second-line curative therapy is considered, e.g. in patients with a PSA level less than 10 ng/mL and a clinically and ultrasonographically prostate-confined recurrence.

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 (27,28). When there is only a modest rise in PSA level in asymptomatic patients with favourable initial pathology, the bone scan can be delayed for some time as it is nearly always negative in patients with low PSA values. In fact, evidence suggests that it is rare to see a positive bone scan in patients not receiving adjuvant hormonal therapy before the serum PSA level is over 40 ng/mL (35). There is no consensus concerning the PSA level at which a bone scan should be performed, but recently a delay was recommended until the serum PSA reached 20 ng/mL, provided that the patient was asymptomatic (36). Nevertheless, the examination is recommended in patients where second-line curative therapy is planned, irrespective of the PSA level.

CT/MRI
The main purpose of CT/MRI is to detect the presence of nodal metastases, but this is not part of routine follow-up. Most studies performed on patients prior to lymph node dissection have shown that the sensitivity of CT/MRI for detecting node metastasis is low (37-39). Others have claimed high sensitivity rates when a CT scan was combined with a fine-needle aspiration biopsy (40).
No reliable data are available on the specificity or sensitivity of CT scanning after treatment with curative intent. However, a recent report indicated that CT may be helpful in detecting the presence of node metastasis in patients with a negative bone scan and a PSA level above 4 ng/mL (41). Another application of these examinations is for dose planning before radiation treatment of local disease recurrence after radical prostatectomy.

14.3   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 comorbidity may make further follow-up in asymptomatic patients superfluous.

14.4 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 recommended if it will affect the plan of treatment, i.e. second-line treatment with curative intent.
6. Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be delayed until the serum PSA level exceeds 4 ng/mL or 20 ng/mL, respectively.
7. If the patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.

14.5 REFERENCES
1. **Walsh PC, Partin AW, Epstein JI.**
   Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. J Urol 1994; 152: 1831-1836.
2. **Kupelian P, Katcher J, Levin H, Zippe C, Klein E.**
   Correlation of clinical and pathologic factors with rising prostate-specific antigen profiles after radical prostatectomy alone for clinical localized prostate cancer. Urology 1996; 48: 249-260.
3. **Van den Ouden D, Hop WCJ, Kranse R, Schröder FH.**
   Tumour control according to pathological variables in patients treated by radical prostatectomy for clinically localized carcinoma of the prostate. Br J Urol 1997; 79: 203-211.
4. **Blute ML, Seay TM, Bergstralh EJ, Zincke H.**
   Long-term hazard of progression with clinically localized prostate cancer (PC) treated with radical prostatectomy (RP): continued risk of failure after 5 years. J Urol 1996; 155: 649A.
5. **Schellhammer PF, El-Mahdi AM, Wright GL Jr , Kolm P, Ragle R.**
   Prostate-specific antigen to determine progression-free survival after radiation therapy for localized carcinoma of prostate. Urology 1993; 42: 13-20.
6. **Zagars GK, von Eschenbach AC, Ayala AG, Schultheiss TE, Sherman NE.**
   The influence of local control on metastatic dissemination of prostate cancer treated by external beam megavoltage radiation therapy. Cancer 1991; 68: 2370-2377.
7. **Hancock SL, Cox RS, Bagshaw MA.**
   Prostate specific antigen after radiotherapy for prostate cancer: a reevaluation of long-term biochemical control and the kinetics of recurrence in patients treated at Stanford University.
   J Urol 1995; 154: 1412-1417.
8. **Catalona WJ, Basler JW.**
   Return of erections and urinary continence following nerve sparing radical retropubic prostatectomy.
   J Urol 1993, 150: 905-907.
9. **Zincke H, Bergstralh EJ, Blute ML, Myers RP, Barrett DM, Lieber MM, Martin SK, Oesterling JE.**
   Radical prostatectomy for clinically localized prostate cancer: long-term results of 1143 patients from a single institution. J Clin Oncol 1994; 12: 2254-2263.
10. **Lawton CA, Won M, Pilepich MV, Asbell SO, Shipley WU, Hanks GE, Cox JD, Perez CA, Sause WT, Doggett SR, Rubin P.**
    Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 1991; 21: 935-939.
11. **Mettlin CJ, Murphy GP, Sylvester J, McKee RF, Morrow M, Winchester DP.**
    Results of hospital cancer registry surveys by the American College of Surgeons.
    Cancer 1997; 80: 1875-1881.
12. **Pedersen K, Herder A.**
    Radical retropubic prostatectomy for localised prostatic carcinoma: a clinical and pathological study of 201 cases. Scand J Urol Nephrol 1993; 27: 219-224.

13. **Baert L, Elgamal AA, van Poppel H.**
Complications of radical prostatectomy. In: Carcinoma of the Prostate. Innovations in Management. Petrovich Z, Baert L and Brady LW et al. (eds). Springer Verlag:Berlin, 1996: 139-156.

14. **Coetzee LJ, Hars V, Paulson DF.**
Postoperative prostate-specific antigen as a prognostic indicator in patients with margin-positive prostate cancer, undergoing adjuvant radiotherapy after radical prostatectomy. Urology 1996; 47: 232-235.

15. **van der Kooy MJ, Pisansky TM, Cha SS, Blute ML.**
Irradiation for locally recurrent carcinoma of the prostate following radical prostatectomy.
Urology 1997; 49: 65-70.

16. **Pontes JE.**
Role of surgery in managing local recurrence following external beam radiation therapy.
Urol Clin North Am 1994; 21: 701-706.

17. **Miller RJ, Cohen JK, Schuman BA, Merlotti L.**
Percutaneous transperineal cryoablation of the prostate as salvage therapy for post-radiation recurrence of adenocarcinoma. Cancer 1996; 77: 1510-1514.

18. **Morgan WR, Zincke H, Rainwater LM, Myers RP, Klee GG.**
Prostate specific antigen values after radical retropubic prostatectomy for adenocarcinoma of the prostate: impact of adjuvant treatment (hormonal and radiation). J Urol 1991; 145: 319-323.

19. **Kaplan ID, Cox RS, Bagshaw MA.**
Prostate specific antigen after external beam radiotherapy for prostatic cancer: follow-up.
J Urol 1993; 149: 519-522.

20. **Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M, Schelin S, Pedersen K.**
Hormonal treatment before radical prostatectomy: a 3-year follow-up. J Urol 1998; 159: 2013-2017.

21. **Frazier HA, Robertson JE, Humphrey PA, Paulson DF.**
Is prostate specific antigen of clinical importance in evaluating outcome after radical prostatectomy.
J Urol 1993; 149: 516-518.

22. **Bolla M, Gonzalezs D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M.**
Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997; 337: 297-300.

23. **Pilepich MV, Caplan R, Byhardt RW, Lawton CA, Gallagher MJ, Mesic JB, Hanks GE, Coughlin CT, Porter A, Shipley WU, Grignon D.**
Phase III trial of androgen suppression using goserelin in unfavourable-prognosis carcinoma of prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-61.
J Clin Oncol 1997; 15: 1013-1021.

24. **Stamey TA, Kabalin JN, McNeal JE, Johnstone IM, Freiha F, Redwine EA, Yang N.**
Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol 1989; 141: 1076-1083.

25. **Partin AW, Pearson JD, Landis PK, Carter HB, Pound CR, Clemens JQ, Epstein JI, Walsh PC.**
Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology 1994; 43: 649-659.

26. **Trapasso JG, deKernion JB, Smith RB, Dorey F.**
The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. J Urol 1994; 152: 1821-1825.

27. **Oefelein MG, Smith N, Carter M, Dalton D, Schaeffer A.**
The incidence of prostate cancer progression with undetectable serum prostate specific antigen in a series of 394 radical prostatectomies. J Urol 1995; 154: 2128-2131.

28. **Leibman BD, Dilliouglugil Ö, Wheeler TM, Scardino PT.**
Distant metastases after radical prostatectomy in patients without an elevated serum prostate specific antigen level. Cancer 1995; 76: 2530-2534.

29. **Schild SE, Wong WW, Novicki DE, Ferrigni RG, Swanson SK.**
Detection of residual prostate cancer after radical prostatectomy with the Abbott Imx IMx PSA assay.
Urology 1996; 47: 878-881.

30. **Lee WR, Hanlon AL, Hanks GE.**
Prostate-specific antigen nadir following external beam radiation therapy for clinically localized prostate cancer: the relation between nadir level and disease free survival. J Urol 1996; 156: 450-453.

31. **Crook JM, Bahadur YA, Bociek RG, Perry GA, Robertson SJ, Esche BA.**
Radiotherapy for localized prostate carcinoma. The correlation of pretpre-treatment prostate specific antigen and nadir prostate specific antigen with outcome as assessed by systematic biopsy and serum prostate specific antigen. Cancer 1997; 79: 328-336.

32. **American Society of Therapeutic Radiology and Oncology Consensus Panel.**
    Consensus statement: guidelines for PSA following radiation therapy.
    Int J Radiat Oncol Biol Phys 1997; 37: 1035-1041.
33. **Connolly JA, Shinohara K, Preszti JC Jr, Carroll PR.**
    Local recurrence after radical prostatectomy: characteristics in size, location, and relationship to
    prostate-specific antigen and surgical margins. Urology 1996; 47: 225-231.
34. **Scardino PT.**
    The prognostic significance of biopsies after radiotherapy for prostatic cancer. Semin Urol 1983; 1: 243-251.
35. **Cher ML, Bianco FJ, Lam JS, Davis LP, Grignon DJ, Sakr WA, Banerjee M, Pontes JE, Wood DP.**
    Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after
    radical prostatectomy. J Urol 1998; 160: 1387-1391.
36. **Van Poppel H, Elgamal AA, Goethuys H, de Ridder D, Van de Voorde WM, Oyen RH, Baert L.**
    Patterns of failure in surgically treated patients. In: Carcinoma of the Prostate: Innovations in
    Management. Petrovich Z, Baert L and Brady LWet al. (eds). Springer Verlag:Berlin, 1996, 125-137.
37. **Hricak H, Dooms GC, Jeffrey RB, Avallone A, Jakobs D.**
    Prostatic carcinoma: staging by clinical assessment, CT and MR imaging. Radiology 1987; 162: 331-336.
38. **Platt JF, Bree RL, Schwab RE.**
    The accuracy of CT in staging of carcinoma of the prostate. Am J Roentgenol 1987; 149: 315-318.
39. **Rifkin MD, Zerhouni EA, Gatsonis CA, Quint LE, Paushter DM, Epstein JI, Hamper U, Walsh PC,
    McNeil BJ.**
    Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer.
    Results of a multi-institutional cooperative trial. N Engl J Med 1990; 323: 621-626.
40. **Van Poppel H, Ameye F, Oyen R, Van de Voorde WM, Baert L.**
    Accuracy of combined computerized tomography and fine needle aspiration cytology in lymph node
    staging of localized prostatic carcinoma. J Urol 1994; 151: 1310-1314.
41. **Seltzer M, Barbaric Z, Belldegrun A, Naitoh J, Dorey F, Phelps ME, Gambhir SS, Hoh CK.**
    Comparison of helical computerized tomography, positron emission tomography and monoclonal
    antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen
    relapse after treatment for localized prostate cancer. J Urol 1999; 162: 1322-1328.

15. FOLLOW-UP: AFTER HORMONAL TREATMENT

CaP is associated with a high incidence of metastases, as bone metastases are present in 25% of cases at the time of diagnosis and more than 50% of clinically localized cancers actually present with locally advanced disease or lymph node metastases.

15.1 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.

15.2 How to follow up

PSA monitoring

PSA 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 this parameter 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 to be related to prognosis (3,5-7). However, this criterion has no absolute value in a given 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, as clinical disease progression with normal PSA levels was 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 is 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).

Creatinine, haemoglobin and liver function monitoring
Creatinine monitoring has some value as 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).

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.

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 (21-23). 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 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.

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

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.

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.

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

15.4 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 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. This follow-up should minimally 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.

15.5 REFERENCES

1. **Ercole CJ, Lange PH, Mathisen M, Chiou RK, Reddy PK, Vessella RL.**
   Prostatic specific antigen and acid phosphatase in the monitoring and staging of patients with prostatic cancer. J Urol 1987; 138: 1181-1184.
2. **Mecz Y, Barak M, Lurie A et al.**
   Prognostic importance of the rate of decrease in prostatic specific antigen (PSA) levels after treatment of patients with carcinoma of prostate. J Tumor Marker Oncol 1989; 4: 323-328.
3. **Petros JA, Andriole GL.**
   Serum PSA after antiandrogen therapy. Urol Clin North Am 1993; 20: 749-756.
4. **Arai Y, Yoshiki T, Yoshida O.**
   Prognostic significance of prostate specific antigen in endocrine treatment for prostatic cancer. J Urol 1990; 144: 1415-1418.
5. **Matzkin H, Eber P, Tood B, van der Zwaag R, Soloway MS.**
   Prognostic significance of changes in prostate-specific markers after endocrine treatment of stage D2 prognostic cancer. Cancer 1992; 70: 2302-2308.
6. **Smith JA Jr, Lange PH, Janknegt RA, Abbou CC, deGery A.**
   Serum markers as a predictor of response duration and patients survival after hormonal therapy for metastatic carcinoma of the prostate. J Urol 1997; 157: 1329-1334.
7. **Stamey TA, Kabalin, Ferrari M, Yang N.**
   Prostate specific antigen in the diagnosis and treatment on adenocarcinoma of the prostate. IV., Anti-androgen treated patients. J Urol 1989; 141: 1088-1090.
8. **Blackledge GRP, Lowery K.**
   Role of prostate-specific antigen as a predictor of outcome in prostate cancer. Prostate 1994; 5: 34-38.
9. **Dupont A, Cusan L, Gomez JL, Thibeault MM, Tremblay M.**
   Prostate specific antigen and prostatic acid phosphatase for monitoring therapy of carcinoma of the prostate. J Urol 1991; 146: 1064-1068.
10. **Leo ME, Bilhartz DL, Bergstralh EJ, Oesterling JE.**
    Prostate specific antigen in hormonally treated stage D2 prostate cancer: is it always an accurate indicator of disease status? J Urol 1991; 145: 802-806.
11. **Fossa SD, Waehre H, Pause E.**
    The prognostic significance of prostate cancer. Br J Cancer 1992; 66: 181-184.
12. **Csapo Z, Brand K, Walther R, Fokas K.**
    Comparative experimental study of the serum prostate specific antigen and prostatic acid phosphatase in serially transplantable human prostatic carcinoma lines in nude mice. J Urol 1988; 140: 1032-1038.
13. **Gleave ME, Hsieh JT, Wu HC, von Eschenbach AC, Chung LW.**
    Serum prostate specific antigen levels in mice bearing human prostate LNCaP tumors are determined by tumour volume and endocrine and growth factors. Cancer Res 1992; 52: 1598-1605.
14. **Grignon D, Troster M.**
    Changes in ilmmunohisto-chemical staging in prostatic adenocarcinoma following diethystilbestrol therapy. Prostate 1985; 7: 195-202.
15. **Henttu P, Liao S, Vihko P.**

Androgens up-regulate the acid human prostate specific antigen messenger ribonucleic acid (mRNA) but downregulate the prostatic acid phosphatase mRNA in the LNCaP cell line.
Endocrinology 1992; 130: 766-772.

16. **Young CY, Montgomery BT, Andrew SPE, Qui SD, Bilhartz DL, Tindall DJ.**
Hormonal regulation of prostate specific antigen messenger RNA in human prostatic adenocarcinoma cell line LNCaP. Cancer Res 1991; 31: 3748-3752.

17. **Keillor JS, Aterman K.**
The response of poorly differentiated prostatic tumors to staining for prostate specific antigen and prostatic acid phosphatase. A comparative study. J Urol 1987; 137: 894-896.

18. **Partin AW, Carter HB, Chan DW, Epstein JI, Oesterling JE, Rock RC, Weber JP, Walsh PC.**
Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. J Urol 1990; 143: 747-752.

19. **Stege R, Tribukait B, Lundh B, Carlstrom K, Pousette A, Hasenson M.**
Quantitative estimation of tissue prostate specific antigen deoxyribonucleic acid ploidy and cytological grade in fine needle aspiration biopsies for prognosis of hormonally treated prostatic carcinoma.
J Urol 1992; 148: 833-837.

20. **Montgomery BT, Young CY, Bilhartz DL.**
Hormonal regulation of prostate specific antigen (PSA), glycoprotein in the human prostatic adenocarcinoma cell line LNCaP. Prostate 1992; 21; 63-73.

21. **Miller PD, Eardley I, Kirby RS.**
Prostate specific antigen and bone scan correlation in the staging and monitoring of patients with prostatic cancer. Br J Urol 1992; 70: 295-298.

22. **Oesterling JE.**
Prostate specific antigen: a critical assessment of the most useful tumor maker for adenocarcinoma of the prostate. J Urol 1991; 145: 907-920.

23. **Sissons GR, Clements MA, Peeling WB, Penney MD.**
Can serum prostate-specific antigen replace bone scintigraphy in the follow-up of metastatic prostatic cancer? Br J Radiol 1992; 65: 861-864.

ACKNOWLEDGEMENTS

ABBREVIATIONS USED IN THE TEXT

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
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
MAB: maximal androgen blockade
MRC: Medical Research Council
MRI: magnetic resonance imaging
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
RITA: radiofrequency interstitial tumour ablation
RRPSA: relapsing or rising prostate-specific antigen
RTOG: Radiation Therapy Oncology Group
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)