GUIDELINES ON PROSTATE CANCER

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BACKGROUND</td>
<td>5</td>
</tr>
<tr>
<td>2. CLASSIFICATION</td>
<td>5</td>
</tr>
<tr>
<td>3. RISK FACTORS</td>
<td>5</td>
</tr>
<tr>
<td>4. DIAGNOSIS</td>
<td>6</td>
</tr>
<tr>
<td>4.1 DRE</td>
<td>6</td>
</tr>
<tr>
<td>4.2 PSA</td>
<td>6</td>
</tr>
<tr>
<td>4.3 TRUS</td>
<td>7</td>
</tr>
<tr>
<td>4.4 Relationship between DRE, TRUS and CaP</td>
<td>7</td>
</tr>
<tr>
<td>4.5 Prostate biopsies</td>
<td>7</td>
</tr>
<tr>
<td>5. STAGING</td>
<td>8</td>
</tr>
<tr>
<td>5.1 T-staging</td>
<td>8</td>
</tr>
<tr>
<td>5.2 N-staging</td>
<td>8</td>
</tr>
<tr>
<td>5.3 M-staging</td>
<td>9</td>
</tr>
<tr>
<td>5.4 Guidelines on diagnosis and staging</td>
<td>9</td>
</tr>
<tr>
<td>5.5 References</td>
<td>9</td>
</tr>
<tr>
<td>6. TREATMENT: DEFERRED TREATMENT (WATCHFUL WAITING; WW)</td>
<td>14</td>
</tr>
<tr>
<td>6.1 Summary</td>
<td>14</td>
</tr>
<tr>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td></td>
</tr>
<tr>
<td>Options</td>
<td></td>
</tr>
<tr>
<td>6.2 Deferred treatment of localized CaP (stage T1–T2, Nx–N0, M0)</td>
<td>14</td>
</tr>
<tr>
<td>6.3 Deferred treatment for locally advanced CaP (Stage T3–T4, Nx–N0, M0)</td>
<td>16</td>
</tr>
<tr>
<td>6.4 Deferred treatment for metastatic CaP (stage M1)</td>
<td>16</td>
</tr>
<tr>
<td>6.5 References</td>
<td>16</td>
</tr>
<tr>
<td>7. TREATMENT: RADICAL PROSTATECTOMY</td>
<td>17</td>
</tr>
<tr>
<td>7.1 Summary</td>
<td>17</td>
</tr>
<tr>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td></td>
</tr>
<tr>
<td>Options</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td></td>
</tr>
<tr>
<td>7.2 General considerations</td>
<td>18</td>
</tr>
<tr>
<td>7.3 Indications for radical prostatectomy</td>
<td>19</td>
</tr>
<tr>
<td>Stage T1–T1b CaP</td>
<td></td>
</tr>
<tr>
<td>Stage T1c CaP</td>
<td></td>
</tr>
<tr>
<td>Stage T2 CaP</td>
<td></td>
</tr>
<tr>
<td>Stage T3 CaP</td>
<td></td>
</tr>
<tr>
<td>Nodal disease</td>
<td></td>
</tr>
<tr>
<td>Results of radical prostatectomy</td>
<td></td>
</tr>
<tr>
<td>7.4 Conclusions</td>
<td>21</td>
</tr>
<tr>
<td>7.5 References</td>
<td>21</td>
</tr>
<tr>
<td>8. TREATMENT: DEFINITIVE RADIATION THERAPY</td>
<td>24</td>
</tr>
<tr>
<td>8.1 Conventional external beam radiation therapy</td>
<td>24</td>
</tr>
<tr>
<td>Clinically localized CaP (T1–T2, Nx–N0)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced CaP (T3–T4, Nx–N0)</td>
<td></td>
</tr>
<tr>
<td>8.2 Three-dimensional conformal radiation therapy (3D-CRT)</td>
<td>28</td>
</tr>
<tr>
<td>8.3 Post-operative radiotherapy</td>
<td>29</td>
</tr>
<tr>
<td>8.4 Interstitial radiotherapy (brachytherapy)</td>
<td>29</td>
</tr>
<tr>
<td>8.5 References</td>
<td>30</td>
</tr>
</tbody>
</table>
9. TREATMENT: HORMONAL (EXCLUDING ANTIANDROGENS) 32
   9.1 Summary 32
      Definition
      Indications
      Options
   9.2 Hormonal treatment for CaP 32
      Basics of hormonal therapy for CaP
      Major categories of hormonal therapy for CaP
      Surgical castration
      Oestrogens
      LHRH analogues
      Other hormonal treatments
      Side-effects of hormonal therapy
      When should hormonal therapy be initiated?
   9.3 References 36

10. TREATMENT: HORMONAL TREATMENT WITH ANTIANDROGENS 38
   10.1 Non-steroidal antiandrogens 38
      Experience with nilutamide
      Experience with flutamide
      Experience with bicalutamide
   10.2 Steroidal antiandrogens 39
      CPA
      CAB
      The antiandrogen withdrawal phenomenon
   10.3 References 40

11. TREATMENT: NEONADJUVANT HORMONAL THERAPY (NHT) PRIOR TO CURATIVE TREATMENT (SURGERY OR RADIATION) 41
   11.1 Principles of neoadjuvant therapy 41
   11.2 NHT and radical prostatectomy 42
   11.3 NHT and radiation therapy 43
   11.4 References 44

12. TREATMENT: SECOND-LINE TREATMENT OF CaP 45
   12.1 Background 45
   12.2 Mechanisms of androgen independence 45
   12.3 Assessing outcome of treatment in androgen-independent CaP 46
   12.4 Androgen deprivation in androgen-independent CaP 46
   12.5 Antiandrogen withdrawal syndrome 46
   12.6 Secondary hormonal therapy 46
   12.7 Non-hormonal therapy 47
   12.8 Other treatments 47
   12.9 Future developments 47
   12.10 References 48


14. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT 53
   14.1 Why follow up? 53
      Responsible patient care
      Second-line treatment with curative intent
      Early hormonal therapy after failure
      As part of study protocol
   14.2 How to follow up 53
      PSA monitoring
      PSA monitoring after radical prostatectomy
      PSA monitoring after radiation therapy
      DRE
      TRUS and biopsy

   4
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

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumour not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen level)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within the prostate¹</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostatic capsule²</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator ani and/or pelvic wall</td>
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<table>
<thead>
<tr>
<th>N</th>
<th>Regional lymph nodes³</th>
</tr>
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<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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<table>
<thead>
<tr>
<th>M</th>
<th>Distant metastasis⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s)</td>
</tr>
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</table>

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.

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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)

<table>
<thead>
<tr>
<th></th>
<th>Percentage of patients (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Disease-specific survival</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>98 (96-99)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>97 (93-98)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>67 (51-79)</td>
</tr>
<tr>
<td><strong>Metastasis-free survival</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>93 (90-95)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>84 (79-89)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>51 (36-64)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Risk of cancer death</th>
<th>Cancer-specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>4-7%</td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td>6-11%</td>
<td>14%</td>
</tr>
<tr>
<td>6</td>
<td>18-30%</td>
<td>44%</td>
</tr>
<tr>
<td>7</td>
<td>42-70%</td>
<td>76%</td>
</tr>
<tr>
<td>8-10</td>
<td>60-87%</td>
<td>93%</td>
</tr>
</tbody>
</table>

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 orchietomy 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

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 prostatectomy. 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

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

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

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.

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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

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

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

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of patients</th>
<th>Disease-free survival</th>
<th>Cause-specific survival</th>
<th>PSA bFFF criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler et al., 1995 (4)</td>
<td>138</td>
<td>43% 10 year</td>
<td>67% 10 year</td>
<td>34% PSA &lt;1 ng/mL after 10 year nadir</td>
</tr>
<tr>
<td>Zietman et al., 1995 (5)</td>
<td>504</td>
<td>65% 10 year</td>
<td></td>
<td>52% PSA &lt;4 ng/mL 10 year</td>
</tr>
<tr>
<td>Kuban et al., 1995 (7)</td>
<td></td>
<td></td>
<td></td>
<td>40% PSA &lt;1 ng/mL 10 year</td>
</tr>
<tr>
<td></td>
<td>27 (A2)</td>
<td>66% 10 year</td>
<td>83% 10 year</td>
<td>35% PSA &lt;4 ng/mL 10 year</td>
</tr>
<tr>
<td></td>
<td>60 (B1)</td>
<td>57% 10 year</td>
<td>93% 10 year</td>
<td>18% PSA &lt;4 ng/mL 10 year</td>
</tr>
<tr>
<td></td>
<td>246 (B2)</td>
<td>48% 10 year</td>
<td>78% 10 year</td>
<td>21% PSA &lt;4 ng/mL 10 year</td>
</tr>
<tr>
<td>Zagars et al., 1997 (9)</td>
<td>643</td>
<td>66% 6 year DFS and bFFF (&lt;2 ng/mL after nadir)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horwitz et al., 1998 (16)</td>
<td>568</td>
<td>99% 5 year</td>
<td>98% 5 year</td>
<td>bFFF ASTRO criteria Failed ASTRO criteria</td>
</tr>
<tr>
<td>Kupelian et al., 2000 (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>509</td>
<td>64% 5 year</td>
<td>89% 5 year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>222</td>
<td>51% bFFF ASTRO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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)

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Prostate-specific antigen ≤ 4 (ng/mL)</th>
<th>Prostate specific antigen 4-10 (ng/mL)</th>
<th>Prostate specific antigen 10-20 (ng/mL)</th>
<th>Prostate-specific antigen &gt; 20 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>1</td>
<td>2. 7</td>
<td>4. 3</td>
<td>11. 1</td>
</tr>
<tr>
<td>7</td>
<td>1. 3</td>
<td>3. 5</td>
<td>5. 7</td>
<td>14. 5</td>
</tr>
<tr>
<td>8-10</td>
<td>2</td>
<td>5. 3</td>
<td>8. 6</td>
<td>22</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Category</th>
<th>Gleason score</th>
<th>Prostate-specific</th>
<th>At 6 years after radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relapse or rising prostate-specific antigen</td>
</tr>
<tr>
<td>I</td>
<td>2-6</td>
<td>≤ 4</td>
<td>6%</td>
</tr>
<tr>
<td>II</td>
<td>7-10 2-7</td>
<td>≤ 4 4-10</td>
<td>30%</td>
</tr>
<tr>
<td>III</td>
<td>8-10 2-7</td>
<td>4-10 10-20</td>
<td>40%</td>
</tr>
<tr>
<td>IV (unfavourable)</td>
<td>8-10 2-10</td>
<td>10-20 &gt; 20</td>
<td>88%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Series</th>
<th>Overall survival (years)</th>
<th>Disease-free survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Bagshaw et al., 1988 (18): T3</td>
<td>64%</td>
<td>35%</td>
</tr>
<tr>
<td>Perez et al., 1993 (19): T3</td>
<td>65%</td>
<td>42%</td>
</tr>
<tr>
<td>Arcangeli et al., 1995 (20): T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zietman et al., 1995 (5): T3-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuban et al., 1995 (7): T3-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hahn et al., 1996 (8): T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zagars et al., 1997 (9): T3-4</td>
<td>IPSA &lt; 10 ng/mL</td>
<td>46% 6-year RRPSA</td>
</tr>
<tr>
<td></td>
<td>IPSA 10-20 ng/mL and Gleason score &lt; 8</td>
<td>57% 6-year RRPSA</td>
</tr>
<tr>
<td></td>
<td>IPSA &gt; 20 ng/mL or Gleason score 8-10</td>
<td>88% 6-year RRPSA</td>
</tr>
</tbody>
</table>

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

In 1988, Zagars and co-workers (21) reported the advantages of diethylstilboestrol (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-N0X; 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

<table>
<thead>
<tr>
<th>Series</th>
<th>Patients</th>
<th>Biochemical freedom from failure (Prostate-specific antigen &lt; 1 ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roach et al., 1996 (13)</td>
<td>501 T1-T2&lt;br&gt;IPSA &lt; 4 ng/mL&lt;br&gt;IPSA 4-10 ng/mL&lt;br&gt;IPSA 10-20 ng/mL&lt;br&gt;IPSA &gt; 20 ng/mL</td>
<td>90% 4 year&lt;br&gt;60% 4 year&lt;br&gt;35% 4 year&lt;br&gt;30% 4 year</td>
</tr>
<tr>
<td>Zelefsky et al., 1998 (25)</td>
<td>213 T1-T2 (leuprolide and flutamide given 3 months before 3D-CRT)&lt;br&gt;IPSA ≤ 10 ng/mL&lt;br&gt;IPSA &gt; 10 ≤ 20 ng/mL&lt;br&gt;IPSA &gt; 20 ng/mL</td>
<td>93% 5 year&lt;br&gt;60% 5 year&lt;br&gt;40% 5 year</td>
</tr>
<tr>
<td>Anderson et al., 1998 (26)</td>
<td>172 T1-T2a,b; Gleason score 2-6; no PNi*&lt;br&gt;94 T2c-T3 or Gleason score 7-10 or PNi*&lt;br&gt;IPSA &gt; 20 ng/mL</td>
<td>91%* 5 year&lt;br&gt;74%* 5 year</td>
</tr>
</tbody>
</table>

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).
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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 (L,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 buserein, 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

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

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 antgonadotrophic 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)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complication (incidence)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orchiectomy</td>
<td>Hot flushes, decreased libido and erectile potency, gynaecomastia, wound infection (1-3%)</td>
<td>Hot flushes treated with clonidine, megestrol acetate, cyproterone acetate or low-dose diethylstilboesterol</td>
</tr>
<tr>
<td>Diethylstilboesterol</td>
<td>Gynaecomastia, thromboembolism, fluid retention, gastrointestinal upset, Decreased libido and erectile potency</td>
<td>Prevention of gynaecomastia possible by pre-treatment breast irradiation</td>
</tr>
<tr>
<td>Luteinizing hormone analogues</td>
<td>Hot flushes, decreased libido and erectile potency, gynaecomastia</td>
<td>Initial flare-up (5-10%) blocked by an antiandrogen</td>
</tr>
<tr>
<td>Gestogens</td>
<td>Fluid retention, shortness of breath, gynaecomastia</td>
<td>Cardiovascular side-effects less severe than those associated with oestrogens</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nausea, Hepatotoxicity</td>
<td>Inhibits adrenal steroidogenesis; cortisone must be substituted</td>
</tr>
<tr>
<td>Aminoglutethimide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estramustine</td>
<td>Gynaecomastia, gastrointestinal side-effects</td>
<td>Prevention of gynaecomastia possible by pre-treatment breast irradiation</td>
</tr>
</tbody>
</table>

**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.

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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 progesterational 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).

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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

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

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

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

1 As defined in study

### 11.4 REFERENCES


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 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 data (23-30).

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. Anti-oestrogens 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 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).
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<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Watchful waiting</td>
<td>Standard treatment for well and moderately differentiated tumours and a &lt; 10-year life expectancy. In patients with &gt; 10-year life expectancy, a restaging with transrectal ultrasonography and biopsy is advised.</td>
</tr>
<tr>
<td></td>
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<td>Radical prostatectomy: Optional in young patients with a long life expectancy, especially for poorly differentiated tumours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hormonal: Not an option.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination: Not an option.</td>
</tr>
<tr>
<td>T1b-T2b</td>
<td>Watchful waiting</td>
<td>Asymptomatic patients with well and moderately differentiated tumours and a life expectancy &lt; 10 years. Patients who do not accept treatment-related complications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radical prostatectomy: Patients with life expectancy &gt; 10 years who accept treatment-related complications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiotherapy: Patients with a life expectancy &gt; 10 years who prefer radiation treatment and accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with a 5-10 year life expectancy and poorly differentiated tumours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination: Neoadjuvant hormonal therapy + radical prostatectomy: no better. Neoadjuvant hormonal therapy + radiotherapy: better local control. No proven survival benefit.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoadjuvant hormonal therapy + radiotherapy: better than radiotherapy in poorly differentiated tumours.</td>
</tr>
<tr>
<td>T3-T4</td>
<td>Watchful waiting</td>
<td>Option in asymptomatic patients with T3, well and moderately differentiated tumours and a life expectancy &lt; 10 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radical prostatectomy: Optional for selected patients with ‘small T3’, prostate-specific antigen &lt; 20 ng/mL, Gleason score &lt; 8 and a life expectancy &gt; 10 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiotherapy: T3 (N0) with &gt; 5-10 years of life expectancy. Dose escalation &gt;70 gy seems to be of some benefit.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hormonal: Symptomatic patients, extensive T3-T4, high prostate-specific antigen level (&gt; 25 ng/mL), unfit patients.</td>
</tr>
<tr>
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<td>Combination: Radiotherapy + hormonal seems better than radiotherapy alone. Neoadjuvant hormonal therapy + radical prostatectomy: no proven benefit.</td>
</tr>
<tr>
<td>N+, M0</td>
<td>Watchful waiting</td>
<td>Asymptomatic patients. Driven by the patient.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radical prostatectomy: No standard option.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiotherapy: No standard option.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hormonal: Standard therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination: No standard option. Patient driven.</td>
</tr>
<tr>
<td>M+</td>
<td>Watchful waiting</td>
<td>No standard option (requires asymptomatic, informed patient, good compliance and good access to health care).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radical prostatectomy: Not an option.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiotherapy: Not an option (given for cure).</td>
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<tr>
<td></td>
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<td>Combination: Not an option.</td>
</tr>
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</table>

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 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


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.

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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)