1. Hermanek P, Sobin LH. *TNM Classification of Malignant Tumours*, International Union Against Cancer, 4th ed. Heidelberg, Springer, 1987.
2. Soloway MS. Selecting initial therapy for bladder cancer. *Cancer 60* (Suppl.), 1987, 502–513.
3. Morrison DA, Murphy WM, Ford KS, Soloway MS. Surveillance of stage 0, grade I bladder cancer by cytology alone: is it acceptable? *J Urol* 1984, **132**, 672–674.
4. Jakse G, Hofstater F, Leitner G, *et al.* Karzinoma *in situ* der Harnblase: eine diagnostische und therapeutische Herausforderung. *Urologe* 1980, **19**, 93–99.
5. Anderstrom C, Johansson S, Nilsson S. The significance of lamina propria invasion on the prognosis of patients with bladder tumours. *J Urol* 1980, **124**, 23–26.
6. Lutzeyer W, Rubben H, Dahm H. Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. *J Urol* 1982, **127**, 250–253.
10. Soloway MS, Ford KS. Thiotepa induced myelosuppression: review of 670 bladder instillations. *J Urol* 1983, **130**, 889–891.
11. Prout GR, *et al.* Long term fate of 90 patients with superficial bladder cancer randomly assigned to receive or not to receive thiotepa. *J Urol* 1983, **130**, 677–690.
12. Crawford ED, *et al.* Adverse reactions to the intravesical administration of doxorubicin hydrochloride: a report of six cases. *J Urol* 1986, **136**, 668–669.
13. Witjes JA, vd Meijden APM, Debruyne FMJ. Use of intravesical Bacillus Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder: an overview. *Urol Int* 1990, **45**, 129–136.
14. Soloway MS. Introduction and overview of intravesical therapy for superficial bladder cancer. *Urology* 1988, **31**(Suppl.) 5–16.
14. Kurth KH, Schroeder FH, Tunn U, *et al.* Adjuvant chemotherapy of superficial transitional cell bladder carcinoma: preliminary results of a European Organization for Research on Treatment of Cancer randomized trial comparing doxorubicin hydrochloride, ethoglucid and transurethral resection alone. *J Urol* 1984, **132**, 258–262.
15. Debruyne FMJ, vd Meijden APM, Witjes JA, *et al.* Bacillus Calmette-Guerin versus mitomycin-C intravesical therapy in superficial bladder cancer. Results of a randomized trial after 21 months of follow up. *J Urol* (in press).
16. Huland H, Otto U, Droese M, Kloeppel G. Long-term mitomycin C instillation after resection of superficial bladder carcinoma: influence on recurrence, progression, and survival. *J Urol* 1984, **132**, 27–29.
17. Huland H, Kloeppel G, Feddersen I, *et al.* Comparison of different schedules of cytostatic intravesical instillations in patients with superficial bladder carcinoma: final evaluation of a prospective multicenter study with 419 patients. *J Urol* 1990, **144**, 68–72.
18. Chodak GW. Intravesical interferon treatment of superficial bladder cancer. *Urology* 1989, **34**, 84–96.
19. Hillyard RW, Jr Ladaga L, Schellhammer PF. Superficial transitional cell carcinoma of the bladder with mucosal involvement of the prostatic urethra: results of treatment with intravesical bacillus Calmette-Guerin. *J Urol* 1988, **139**, 290–293.
20. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumours. *J Urol* 1976, **116**, 180–183.
21. Lamm DL, *et al.* Complications of bacillus Calmette-Guerin immunotherapy: review of 2602 patients and comparison of chemotherapy complications. In: Debruyne FMJ, Denis L, vd Meijden APM eds. *EORTC Genito-Urinary Group Monograph 6: BCG in Superficial Bladder Cancer*. New York, Alan R. Liss, 1989, 335–355.
22. Lamm DL, Stogdill VD, Stogdill BJ, *et al.* Complications of bacillus Calmette-Guerin immunotherapy in 1278 patients with bladder cancer. *J Urol* 1986, **135**, 272–274.
23. Studer U, *et al.* Percutaneous bacillus Calmette-Guerin perfusion of the upper urinary tract for carcinoma *in situ*. *J Urol* 1989, **142**, 975–977.
24. Glashan RW. A randomized controlled study of intravesical a-2b-interferon in carcinoma *in situ* of the bladder. *J Urol* 1990, **144**, 658–661.
25. Bretton PR, *et al.* Intravesical bacillus Calmette-Guerin therapy for *in situ* transitional cell carcinoma involving the prostatic urethra. *J Urol* 1989, **141**, 853–856.

Eur J Cancer, Vol. 27, No. 3, pp. 333–341, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Controversies in the Management of Localised and Metastatic Prostatic Cancer

L.J. Denis

INTRODUCTION

CLINICAL PROSTATIC cancer in its natural course is a single biological process with a usually slow but constant growth. This growth can be temporarily arrested by endocrine treatment offering palliation but never cure in the majority of patients with extraprostatic disease. The clinical stage and grade of the tumour as well as a number of prognostic factors define the outcome of the disease independent of a given treatment. This state of affairs is apt to create controversies in the management of the disease, leading to errors in treatment by commission or by omission. The lack of a clear consensus on grade and classification, the absence of a reliable indicator of metastatic potential and competing causes of death at the age of the peak incidence contribute to the chaos.

There is consensus that localised disease may be curable while metastatic disease is incurable. A renewed interest in radical prostatectomy has not solved the controversy on treatment but has brought new insight into the pathogenesis and biological aspects of the disease, while the development of a safe medical castration opened new avenues to improved quality of life as an end point in metastatic disease. The bottom line is that at this moment we cannot agree on a perfect treatment for any individual patient but we can improve management by improved detection and diagnosis. We review some basic concepts and the management of localised, metastatic and relapsed disease.

BASIC CONCEPTS

Any man in the industrialised nations of Western Europe has a one in ten chance to develop prostatic cancer. It is now the

Correspondence to L.J. Denis, Department of Urology, AZ Middelheim, Antwerp, Belgium.
Received 21 Nov. 1990; accepted 28 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.

second most frequent cancer in men. The relative increase in incidence is small but real, and about half of these men will die from prostatic cancer [1].

Classification

Adenocarcinoma of the prostate originates from the prostatic epithelium. There is consensus on the terminology for early prostatic cancer, as presented in Table 1. The suspected precursor lesion is the atypical, epithelial proliferation termed prostate intraepithelial neoplasia (PIN). The strong association between PIN grade 3 and focal carcinoma is so clear that a second biopsy is indicated whenever the first biopsy is negative for cancer and positive for PIN [2]. A focal cancer is of microscopic size and involves less than 3 chips of tissue removed or less than 5% of the surgical specimen [3]. These cancers are prevalent in men after the fifth decade and may be diagnosed in over 75% of men over 70 years by serial step sections of the prostate. Specimen focal cancer is evenly diagnosed in both oriental and caucasian races and it is clear that other factors such as lifestyle promote the development into a clinical carcinoma, as shown by geographical variations [4].

Discovered at the time of surgery, in the absence of a prior diagnosis of malignancy, these focal cancers are labelled incidental cancer which creates an immediate practical problem of attaching a pathological or a clinical label to this lesion. The lesions are called latent when discovered at autopsy or occult when diagnosed in the presence of clinical metastatic disease. The management of incidental cancer is the first controversy in the management of localised disease. The vast majority of the incidental carcinomas are well differentiated but it has been demonstrated on studies of radical prostatectomy specimen that the tumour volume correlates with dedifferentiation and increased metastatic potential [5].

Poor differentiation of tumour cells is accepted as a prime factor in aggressive malignant behaviour. However, the wide range of histological differentiation directs our research to other expressions of biological aggression such as ploidy. For the moment there is agreement that the Gleason grading system is the most popular grading system in clinical use. Its practical value is the ability to derive a simple score by adding a primary and a secondary pattern of histological differentiation [6]. The combined degree of differentiation and tumour volume allow prediction of prognosis in the early, moderate and late stages of the disease. The extent of nodal disease and patterns of progression as well as the extent of metastatic disease and survival confirm this general concept [7, 8].

Course

There is consensus that prostatic cancer follows a steady course to death, the duration of which is determined by the extent and differentiation of the disease at the time of diagnosis. Androgen withdrawal is able to delay this course depending on the percentage of hormone dependent cells present at the time of diagnosis. The median survival for localised disease may extend over 10 years, for node positive disease over five years, for metastatic disease over three years, while median survival in patients with hormone refractory disease after previous remissions is merely six to nine months, usually with poor quality of life. These figures call for restraint in treating the elderly population and for aggressive therapy in younger men.

Table 1. Terminology for early prostatic cancer

Prostate intra-epithelial neoplasia (PIN) (precursor)
Focal carcinoma (microscopic)
Incidental carcinoma
Latent carcinoma
Occult carcinoma

Diagnosis

The diagnosis of prostate cancer in our daily practice is based on a routine rectal examination feeling for induration and/or asymmetry of the gland. Subsequent blind biopsy may be positive in roughly half of the cases. On other occasions one is confronted with elevated prostate cancer markers in the serum, osteoblastic bone lesions on radiography or suggestive histology in biopsy specimens taken from tumour masses elsewhere. Advanced prostatic cancer with urinary symptoms is not easily missed by the index finger and the rule is that this stage of the disease is incurable unless the symptoms are caused by concomitant prostatic pathology such as benign prostatic hyperplasia. Encouragement of the surgical pathologist to increase the number of sections of transurethral resected specimens results in a growing number of pathological diagnosis of early disease [9].

The clinical situation is considerably improved by the introduction of transrectal ultrasound imaging in the routine urological clinic. This examination produces not only a reliable, reproducible document of the size, shape and symmetry of the prostate gland against the surrounding fatty tissues but it also provides a detailed view of the internal echoes outlining the intraprostatic anatomy and pathology [10, 11].

The 1990 stand of the Executive Board of the American Urological Association is representative of expert opinion. The recommended policy recognises the clinical value of transrectal prostate ultrasonography when used as a diagnostic procedure in the evaluation and management of malignant diseases of the prostate. It is most effectively utilised by physicians who are trained in its application and who understand its limitations to cancer detection, including its specificity and sensitivity.

The value of transrectal prostate ultrasonography as an independent screening procedure for the diagnosis of prostate cancer has not been established.

Several screening attempts to detect unsuspected early prostate cancer in asymptomatic males have failed for a variety of reasons mostly in the organisation of the screening and its epidemiological methodology. At this moment several studies are in development or in progress e.g. the National Prostate Cancer Detection Project (NPCDP) coordinated by F. Lee, a prostate disease screening study coordinated by L. Denis for the Flemish Advisory Commission of Cancer Prevention (VACK), and a collaborative cancer screening project for colon and prostate cancer by the National Cancer Institute, Bethesda.

More than 50% of prostatic cancers are first diagnosed in transurethral resection specimens as a direct result of improved awareness and methodology of surgical pathology [12]. The availability of transrectal ultrasound and the utilisation of ultrasound directed biopsies will hopefully change this trend to increased detection by means of a biopsy. Prostatic biopsy is carried out by the transperineal or transrectal route producing a core of tissue. Guidance by transrectal palpation is markedly improved by ultrasound guidance. The biopsy gun is now widely used and allows for an improved local staging by taking biopsies of selected sites such as the apex, the capsule and the seminal vesicles. The added advantage is aspiration cytology introduced

Table 2. Biological markers studied in relation to prostatic cancer

Prostate-specific antigen (PSA)
Prostatic acid phosphatases (PAP)
Alkaline phosphatases and their fractions
Carcino-embryonic antigen (CEA)
Alpha fetoprotein (AFP)
Human chorionic gonadotrophin (HCG)
Creatine kinase isoenzyme (CK-BB)
Lactate dehydrogencise (LDH) isoenzymes
Spermine and spermidine
Gamma seminoprotein
DNA content
Oncogene products
Cancer associated antigens: Ca 549, 15-3, 19-9, 125
Cytokeratins
Tissular growth factors
Antimitogenic protein (growth inhibitor)
Zinc

Table 3. UICC prostate cancer TNM categorisation and grading

Classification	
T1	Incidental finding
T1a	≤ 3 foci
T1b	> 3 foci
T2	Present clinically or grossly, limited to gland
T2a	≤ 1.5 cm
T2b	> 1.5 cm/one lobe
T3	Invades prostatic apex/beyond capsule/bladder neck/seminal vesicle/not fixed
T4	Fixed or invades other adjacent structures
N1	Single ≤ 2 cm
N2	Single > 2 cm ≤ 5 cm, multiple ≤ 5 cm
N3	> 5 cm
Grade	
GX	Grade cannot be assessed
G1	Well differentiated, slight anaplasia
G2	Moderately differentiated, moderate anaplasia
G3–4	Poorly differentiated or undifferentiated marked anaplasia

by Franzen in 1960 [13]. Again expert surgical pathology is needed to obtain optimal results. These techniques permit outpatient diagnosis and local staging by multiple, prostate biopsy specimen with low morbidity and high patient acceptance. Our experience to date has shown that transrectal ultrasound examination by high resolution biplanar examination in expert hands has doubled the diagnostic yield of early prostate cancer by simple digital rectal examination [14]. Transrectal ultrasound also provides information on the volume of the tumour and hyperplastic tissue.

Biological markers (Table 2)

Additional cases of prostate cancer are detected by the elevation of prostatic specific antigen (PSA) levels in the serum in patients with an otherwise normal rectal examination and even negative ultrasound images.

A decade of experience with PSA as an independent marker of prostate cancer brought consensus on its superiority to prostatic acid phosphatase (PAP) to detect prostate cancer [15]. However, as with all the other biological markers studied to diagnose prostate cancer it lacks the specificity/sensitivity to be effective as an independent screening marker. Its application is based on a gross relationship between the tumour volume and PSA serum levels. Elevated levels above 40 mg/ml have consistently been associated with extra prostatic disease. The clinical value of PSA to monitor response to treatment or predict prognosis is generally accepted [16]. Improved prognostic index on progression and survival may be obtained by measuring the tumour DNA content. Preliminary reports suggest that cell ploidy may become the prostate cancer marker of the next decade to predict response to treatment as well as survival.

Staging

Once the histological/cytological grade is confirmed, the clinical extent of the disease needs to be assessed. A number of staging systems have been utilised but the UICC TNM staging system, as presented in Table 3, has been accepted as the universal staging system [17]. This system united the staging systems into a single, simple TNM system. Simplicity was obtained by following a single approach to all tumours in order to achieve simple categories, and this involved a focus on tumour volume in nodal disease. Considerable criticism came from various urological groups including the urological group of the EORTC [18].

The criticism centred mainly on changes in the T category and the stage grouping. Subsequent workshops re-established consensus by utilising telescopic ramification of several T categories and the reservation for the stage grouping in future publications. One of the criticisms focused on the minimal requirements to categorise the tumour. A consensus proposal to assess the primary tumour was discussed during the last meeting of the EORTC urological group in Hull 1989. This proposal is presented in Table 4 [18].

The clinical routine staging procedures are presented in Table

Table 4. Consensus proposal to assess primary tumour, EORTC Urological Group

1.	TNM system 1987 needs adaption/interpretation
2.	Categories are more reliable than stage divisions
3.	Grading is included in the evaluation
4.	Biopsy is preferable to transurethral resection (TUR) for diagnosis
5.	Rectal examinations on a diagram
6.	Rectal examination serves in T1/T4 category
7.	Ultrasound is better in T2/T3 category
8.	Computed tomography (CT) does not contribute essentially to assessment
9.	Nuclear magnetic resonance (NMR) is still at the stage of clinical investigation

Table 5. Routine staging procedures

Primary tumour	PSA, PAP*
	Digital rectal examination (DRE)
	Transrectal ultrasound (TRUS)
	Intravenous pyelography (IVP)
	Biopsy procedures
	NMR*
	Cystoscopy*
Nodes	CT
	Nodal aspiration*
	Diagnostic lymphadenectomy*
Metastatic disease	Bone scan. X-ray confirmation*
	Chest X-ray
	Liver ultrasound
	CT*

*Optional.

Table 6. Prognostic factors for duration of survival based on data of early EORTC Genitourinary Group studies [25]

Highly significant ($P \leq 0.0001$)	General parameters
	Performance status
	Haemoglobin
	Specific parameters
	Pain
	TM classification
	PAP
	ALP
Significant ($P \leq 0.05$)	General parameters
	Age
	Chronic diseases
	Serum tetosterone
	Specific parameters
	Histology ($P = 0.0004$)
	Tumour size
Marginally significant ($P \leq 0.10$)	Treatment

5. The presence or absence of metastatic disease is the most important criterion. Severe urological symptoms, back pain and poor performance status are all clinical indications of metastatic disease. The suspicion will be acute in the presence of elevated alkaline phosphatase and high PSA serum levels. The diagnostic confirmation is obtained with the bone scan. The reported hot spots are controlled by radiographic imaging. The lack of accuracy in the skull, the cervical vertebrae and the shoulder joints has to be recognised, but it is the undisputed first clinical test in the initial diagnosis of metastatic disease or in the detection of new lesions. Quantitative bone scans have been advocated but quality control in randomised trials question the validity of serial bone scans in the patients enjoying remission after first line therapy [19, 20].

The confirmed presence of metastatic disease excludes further local or nodal staging procedures. The diagnostic procedures act also as a staging procedure of the primary tumour. Understaging and overstaging were the general rule but the updated biopsy procedures are more reliable. The diagnostic lymph node dissection is universally accepted as a first step to radical surgery. There is still controversy if microscopic lymph node invasion leaves an opportunity for cure, but long term survival is to be expected in these patients.

Intravenous pyelography is the first step in patients with obstruction of the lower urinary tract and hydronephrosis is regarded as a poor prognostic factor. Transurethral resection should not be regarded as a diagnostic procedure and should only be performed in the face of obstructive disease. Suspicions of cancer spread by this procedure have not been supported by subsequent data and the overall decreased survival of these patients should be attributed to the poor prognosis of locally extensive disease.

A series of prospective EORTC studies established the different pathways of disease progression in patients with both measurable local disease only and patients with measurable metastatic disease [21].

Prognostic factors

Last but not least one should evaluate the prognostic factors which should dictate conservative or aggressive treatment in patients with good or poor prognostic factors.

Usually patients with good prognostic factors will do well while patients with poor prognostic factors will die within a 24 month period [22]. As shown in Table 6, based on more than 1000 patients in EORTC trials, one can evaluate performance status (PS), absence or presence of pain, extent of primary tumour, or metastatic disease (M), excessive elevations of PAP, alkaline phosphatase (AP), and PSA, as well as serum testosterone (T) levels at initial diagnosis to predict prognosis. From this table it is clear that prognostic factors at initial diagnosis or during treatment (intermittent prognostic factors) have more impact on survival than any form of treatment. The importance of metastatic extent of disease as well as elevated PSA has been confirmed in our latest EORTC studies [16, 19] or other studies [23].

Variations in prognostic factors and differences in response criteria make sensible comparisons between therapeutic trials impossible unless these aspects have been thoroughly investigated [24].

MANAGEMENT OF LOCALISED DISEASE

Treatment of localised disease is curative in intent. Both surgery and radiotherapy achieve similar 10 year survival rates according to a Consensus Development Conference organised by the National Institutes of Health of the USA in 1987 [26].

Surgery

Surgery involves total prostatectomy by the perineal or retropubic route. The term of radical prostatectomy is reserved for the total prostatectomy removing the prostate, part of the bladder neck and the seminal vesicles, and a pelvic lymph node dissection. This approach has been utilised over the last fifty years but became popular in the last decade with the introduction of newer techniques to preserve continence and potency by nerve sparing [27]. Many urologists now believe that radical prostatectomy via the retropubic route after the pelvic staging lymphadenectomy is the preferred choice of treatment in patients with an expected 10 year survival. We know from the survival series of Jewett that the ideal candidate for this treatment is the patient with a localised nodule (categorisation T2a) in whom capsule penetration and seminal vesicle involvement are rare

[28]. The survival and disease free survival of these patients were better than for the diffuse, high graded T1b disease.

The indications for surgery extended towards the lower stages. Here overtreatment is common in T1a disease which is now regularly diagnosed after transurethral resection by improved pathological sampling, and undertreatment is common in T1b disease with high grade where lymph node involvement is present in 50% of the cases. The solution to this problem is to focus our diagnosis on extent of disease by improved pathological techniques or multiple sampling biopsies to reserve watchful waiting for the true incidental carcinomas and plan therapy for more extensive disease in the younger (50–60) age group. The survival of these patients is close to the theoretical life expectancy with low local recurrence rates. These results are obtained with ease in recent series where pelvic lymph node dissection allows the proper patient selection [29]. The indication for surgery are also extended to the higher categories of T2b and T3 disease. Only one-third of these patients seem to profit from the treatment by a recurrent free survival.

Radiotherapy

Radiotherapy given by external beam irradiation or by brachytherapy, usually by implantation of iodine-125 seed implants, is the other treatment of choice in the same group of patients [31]. There is consensus that X-ray beams from high energy linear accelerators are the preferred form of treatment and that treatment results in preservation of potency in 50% of the treated patients as well as low rates of other forms of morbidity. Controversy exists on the indication for pelvic nodal radiotherapy. We believe that positive lymph nodes are indicative of systemic spread of disease and exactly as in surgery the pelvic lymph node dissection informs the treating physician of the proper stage of the disease.

This eliminates the need for whole pelvis radiotherapy with a reduction of the incidence of complications. The added advantage of pelvic lymph node dissection is the number of patients that can be adequately compared in comparative series, in terms of survival and/or time to progression.

In contrast to the elective irradiation of the involved pelvic lymphatics there may be an indication for a therapeutic irradiation just as therapeutic irradiation of positive margins after total prostatectomy has been advocated. The reverse is also advocated that positive biopsies after proper irradiation are treated by total prostatectomy.

Conclusions

Long term follow-up is needed to evaluate these dual strategies but one may state that local recurrence rates are higher after radiotherapy as compared to surgery.

When there is a choice of treatment to be made there is consensus that the patient should be properly informed on the probability of cure, mortality and morbidity, especially incontinence and impotence, and the psychological and economical consequences of each form of treatment. The age and the overall physical condition of the patient will play a role in the choice of treatment. The addition of systemic hormonal treatment given before or after both surgery or radiotherapy is apt to improve the first five year survival results as reported in T3 lesions [31]. Analysis of these studies however will require extended ten year evaluation. A scheme of treatment choice according to stage and grade is presented in Table 7. Several prospective randomised studies are open to elucidate some aspects of this treatent choice as immediate or deferred adjunctive hormonal therapy.

Table 7. Scheme of treatment choice of prostate cancer

Stage/grade	Prognostic factors	Primary therapy
T1aG1NxMo T2aG1NxMo	Age Chronic disease Performance status	Wait and see
T1bG2-3NxMo T2bG2-3NxMo		Total prostatectomy Radiation
T3G1-3NxMo	Tumour stage Pain PSA	Palliative hormonal therapy
T3G1-3N1-3Mo T1-4G1-3N1-3Mo T1-4G1-3NxM1	Extent of metastases Plasma testosterone	

MANAGEMENT OF METASTATIC DISEASE

There is consensus that metastatic prostatic cancer is an incurable disease. The fact that 50% of these patients, however, die with their cancer instead of from their cancer is only due to competing fatal diseases at the age of 70 years. The greying of the population with an increased mean survival and the increase in relative incidence and mortality will pose an enormous challenge to the medical profession to prevent or eradicate these fatal results.

There is also consensus that first line treatment usually involving some type of androgen withdrawal or blocking treatment brings subjective relief in 60–80% of the patients while objective remissions are achieved in 40–60% of cases, according to response criteria. Complete responses are rare but even objective responders ultimately progress to disease refractory to hormonal therapy.

The patient's quality of life is the first goal of any palliative treatment. The option is open that asymptomatic patients with prostate cancer with good prognostic factors in contrast to poor general health could benefit from no treatment or essentially deferred treatment. This option is indicated in the patients over 70 years with early prostate cancer or with tumours with low biological aggression. Three randomised clinical trials, two from the EORTC Genitourinary Group and one from the Medical Research Council of the UK (coordinators: Schröder, Studer and Kirk), currently aim to provide an answer to this aspect of treatment choice by offering immediate or deferred treatment to patients who are, respectively, pelvic node positive after surgical lymphadenectomy, have M0 or have advanced asymptomatic disease with M0 or M1 category. The opposite side of the spectrum involves patients with advanced disease with poor prognostic factors. Here the EORTC GU Group initiated trial 30893 (coordinator: Keuppens) comparing bilateral orchiectomy with or without mitomycin chemotherapy. We hope to improve survival by combining hormonal and cytotoxic therapy at the time of initial diagnosis.

The current treatment philosophy suggests a tailored treatment based on initial and intermittent prognostic factors from tumour and patient that can be adopted in the course of the disease. Progression of disease usually associated with symptoms indicates a change in treatment.

Table 8. First line endocrine treatment options

Androgen deprivation	
1. Surgical castration	Bilateral orchiectomy Subcapsular bilateral orchiectomy
2. Medical castration	
Oestrogens	Diethylstilbestrol 1 mg Polyestradiol phosphate 160 mg i.m. intramuscularly
LHRH agonists	Depot preparations
Androgen blockade	
3. Steriod anti-androgens	Cyproterone-acetate 300 mg/day
4. Pure anti-androgens	Flutamide 3 × 250 mg/day Nilutamide 2 × 150 mg/day Casodex 50 mg/day
Combination treatment	
5. Maximal androgen withdrawal	LHRH A depot and anti-androgens Bilateral orchitectomy and anti-androgens
6. Combinations endocrine/ chemotherapy	Estramustine phosphate 560–840 mg/day

A wide range of endocrine treatment options has been introduced in clinical oncology since the work of Huggins and Hodges [33] established the hormone dependence of prostate cancer. A selection of these treatment options is presented in Table 8. They aim to achieve a reduction of circulating testosterone levels by surgical or medical castration or by blocking the androgen activity of dihydrotest osterone (DHT) in the prostatic cancer cell. No superior first line endocrine treatment has been established as regards increased survival or progression free disease with the exception of the widely publicised combination treatments. Surgical castration is still for most urologists the gold standard against which the results of any new treatment should be compared [34]. The recently introduced concept of combination treatment aiming to block the effect of the adrenal androgens by adding an anti-androgen to surgical or medical castration has blurred the lines between classical first line and second line hormonal treatment [35]. The hypothesis already proposed by Huggins looks attractive, but definitive confirmation of its clinical superiority depends on the outcome of a series of randomised trials comparing monotherapy to combination treatment and a subsequent meta-analysis [36]. The following are the most popular first line treatments.

Bilateral orchiectomy

The removal of the testicles, which are the main source of serum testosterone, will produce a rapid and immediate fall to castrate levels of this hormone. It is an easy and cheap procedure that will require no follow-up on castrate levels. It is of course a definitive procedure in face of the fact that up to 40% of patients have no benefit from first line endocrine treatment. The surgical mutilation and its psychological impact have some problems for most patients. Subcapsular orchiectomy leaving the tunica or a testicular prothesis prevents this psychological trauma. The side-effects are minimal and consist mainly of hot flushes which occur in 30–40% of the patients.

Oestrogens

The effects of oestrogenic drugs are mainly due to their inhibiting effect on the hypothalamo-pituitary-gonadal axis, reducing LH secretion and subsequently testosterone testicular synthesis. They raise SHGB (sex hormone binding globulin) levels, lowering the amount of free active testosterone [37]. Several steroidal (polyoestradiol phosphate, ethinyloestradiol) and non-steroidal synthetic compounds (diethylstilbestrol [DES], fosfestrol) have been extensively used in the treatment of advanced prostatic cancer.

DES has been investigated at therapeutic doses of 5, 3 and 1 mg/day. Although VACURG and EORTC studies confirmed its efficacy as to regard of orchiectomy, all those studies revealed a significant cardiovascular toxicity and associated mortality. Other side-effects include feminising symptoms, such as frequent painful gynaecomastia [38].

For these reasons most clinicians today believe that oestrogens should no longer be considered as a first line therapy in advanced prostatic cancer. High dose oestrogens (fosfestrol) might however be useful in some patients in relapse after a first line hormonal manipulation.

Another compound, estramustine phosphate, an association of oestradiol with nitrogen mustard, exerts simultaneously an antigonadotropin and cytotoxic effect by binding to specific microtubule associated proteins. Estramustine is recommended in poorly differentiated and hormone unresponsive cancer. An average response rate of about 35% is to be expected in these conditions [39].

LHRH analogues

The ability of LHRH analogues or superagonists to down regulate LHRH receptors on pituitary gonadotrophs and to desensitise these cells, inducing a medical castration by lowering LH and FSH secretion and subsequent T biosynthesis when given in high and sutained doses, was first put to profit in hormone dependent tumours.

Several phase II and phase III studies with different LHRH analogues comparing them to oestrogens and to orchiectomy showed identical but not superior response rates in the treatment of advanced prostatic cancer, but devoid of the side-effects of oestrogens and orchitectomy [40]. Except for the possible "flare-up" phenomenon at the start of treatment, no LHRH A associated toxicity has been reported. Side-effects are those related to the testosterone deprivation with decrease of libido and potency. Hot flushes are present in about 40% of patients.

The "flare-up" phenomenon due to the initial stimulating effect on LH and testosterone has been reported, with conflicting incidence rates by several groups. Clinical complications, such as pain exacerbation, occur in less than 5% of all cases. Biochemical aggravation (rise in PSA or PAP) has been reported in up to 10% of patients. Concomitant administration of DES or an anti-androgen started before or at the same time as the LHRH A treatment and, given during the 2 to 4 first weeks of treatment, prevents this possible complication [41].

The use of LHRH A has also been suggested in order to test the hormone dependency of the tumour in a given patient by judging the response of therapy after 3 months [42]. The slow release depot preparations (1–3 mo) lower testosterone values to castration levels within the first 4 weeks. Long term follow-up studies for up to five years reveal no significant changes in the major hormonal serum profiles [43].

Anti-androgens

Anti-androgens block the androgen receptors in the presence of normal or even increased levels of dihydrotestosterone (DHT). There are two types of antiandrogens: the steroidal and non-steroidal agents. The steroidal compounds, with cyproterone acetate (CPA) as the foremost example, not only block the cellular nuclear receptor but also have some progestational antigonadotrophic activity. The non-steroidal compounds displace the androgens from the receptors, activating at the hypothalamic pituitary level a compensatory increase of LH, resulting in increased serum testosterone levels. It is probably this unwanted side-effect that limits the potency of treatment in a number of patients. Both compounds have been used in combination treatment to achieve maximal androgen withdrawal in several randomised trials. CPA has also been used as monotherapy in randomised EORTC trials showing comparable treatment results but also cardiovascular toxicity [44]. Monotherapy with the pure antiandrogens such as flutamide, nilutamide or casodex, are still in the realm of clinical investigation. The side-effects for the former two include gastrointestinal problems, liver toxicity, hot flushes and gynecomastia. Haemeralopia is a reported recurring problem in the nilutamide treatment. Casodex so far has shown minimal side-effects in the phase II studies [45].

Maximal androgen withdrawal

There is some evidence that the prostatic cell is able to convert the weak adrenal androgens into DHT, the bioactive hormone that is required to maintain prostatic cell metabolism and growth. As the adrenals are the main source of these weak androgens, medical or surgical castration fails to eliminate this potential source of DHT precursors. According to Labrie and his coworkers, these androgens are able to stimulate the prostatic tumour cells which are not, as is commonly thought, hormone insensitive, but rather hypersensitive to androgens [46]. This might explain the remissions that have been reported after surgical or medical adrenal suppression. The concept, however, remains controversial. Nevertheless, Labrie and coworkers claimed very impressive results in patients treated with a combination of surgical or medical castration and pure anti-androgens. Recently Crawford *et al.* [47] reported in a randomised study improved survival (7 mo) for those patients that were treated by combination therapy as to those treated by monotherapy.

These results are confirmed by a few studies, but unfortunately not confirmed by the majority of seventeen randomised trials analysed in a workshop in Paris in June, 1990, to examine the feasibility of a meta-analysis [48]. There is still a possibility that combination treatment offers treatment advantage to subsets of patients but the overall clinical impact of the treatment will be small. The maturation of a few phase III studies and especially the meta-analysis may provide a correct answer in the near future.

Second line endocrine treatent has no good rationale if one accepts the concept of endocrine resistant clones of cancer cells. Still, it is difficult to call these progressions hormonally independent since the majority of these tumours show immediate aggravation by the administration of exogenous testosterone. On the other hand responses have been noted by high doses of fosfestrol, medroxyprogesterone acetate, anti-androgens and especially blockers of adrenal androgen biosynthesis such as aminoglutethimide and imidazole derivatives. Responses to second line endocrine agents are minimal and short-lived. Many urologists still perform a bilateral orchiectomy when medical castration fails to achieve a castrate reduction in serum testosterone, the only chance for a response, or when the tumour goes into relapse [49].

Aminoglutethimide (AG)

This compound blocks the transformation of cholesterol to pregnenolone and is also an effective aromatase inhibitor. As monotherapy it can suppress adrenal function requiring cortisone substitution. Objective responses are rare but subjective responses and increased survival have been reported in a few studies [50]. Some of the beneficial effects have been attributed to the substitution therapy. Side-effects of doses above 500 mg/day are frequent and limit the use of this drug.

Ketoconazole high dose (KHD)

Ketoconazole, a known antimycotic imidazole derivative, blocks by interfering with the cytochrome P450 dependent testicular and adrenal enzymatic systems, the biosynthesis of sex steroids, when given at doses of 800–1200 mg/day. We have shown that with 1200 mg/day, castration testosterone values are reached within hours. Unfortunately synthesis of other steroids might also be partially or completely inhibited leading to potentially lethal Addisonian crises [51].

Thus KHD may achieve complete androgen blockade but it still fails to achieve better responses as compared with other first line therapeutic modalities. Its side-effects, mainly gastrointestinal disturbances, weakness, and asthenia limit its use. Its pain relieving effect in relapsing patients however can be put to good use in selected patients.

R 75251

R 75251, another imidazole derivative, was shown in animals and healthy volunteers to inhibit selectively androgen biosynthesis. Our own experience with this new drug, however, in relapsing castrated patients did not show adrenal androgen synthesis inhibition, although objective partial responses and subjective responses were seen in nearly 50% of patients. This molecule seems to act as a chemotherapeuticum, devoid of the side-effects that are generally associated with chemotherapy. The exact mechanism by which this drug exerts its beneficial effects are not yet elucidated, but might be partially related to accumulation of retinoic acid in epithelial tissues [52].

The clinical availability of growth hormone analogues and growth factor blockers introduced a new class of endocrine related compounds in the clinical investigation of failed hormonal treatment in prostate cancer.

Somatostatin analogues

Experimental evidence for the involvement of growth factors and their cellular receptors in the growth control of prostatic tumours has led researchers to explore the possibility to inhibit or to antagonise the effects of the different growth polypeptides and factors. Schally [53] and others have shown in experimental Dunning PCA models a growth inhibiting effect of somatostatin super analogues. Several clinical studies at present are evaluating the effects of some of those analogues in the treatment of PCA.

Suramin

Recently suramin, a drug used for more than 50 years for the treatment of African trypanosomiasis and onchocerciasis, was shown to inhibit, by specific binding to their cellular receptors, different membrane-associated growth factors such as platelet derived growth factor (PDGF), epidermal growth factor (EGF),

Table 9. Single agents with reasonable response rates in men with relapsed prostate cancer

Epirubicin	Estramustine
Cyclophosphamide	Mitomycin
Cisplatin	Vinblastin

fibroblast growth factor (FGF) and transforming growth factor beta. There is also experimental evidence that suramin can counteract the stimulating effects of androgens on the growth of LNLAP cells.

Winnan *et al.* reported the beneficial effects of suramin in patients with relapsing metastatic prostatic cancer [54]. We were able to confirm their results but considerable toxicity is a limiting factor in the use of this old drug [55]. Side-effects included rash, fever, fatigue, gastrointestinal disturbances, liver and corticoadrenal toxicity, polyneuritis and coagulation disorders.

MANAGEMENT OF RELAPSED DISEASE

Here the cancer cells unresponsive to first and second line endocrine treatment dominate the clinical picture. These patients go through an asymptomatic phase of a median six months where rising serum values of PSA and new hot spots on the bone scan herald impending disaster. Many clinicians employ no therapy or known therapy in these cases with minimal side-effects, to preserve quality of life as long as possible. Clinical research groups await measurable disease to institute chemotherapy, hoping to find the single or combination of agents that may bring objective or subjective remissions. Extensive efforts led by the National Prostatic Cancer Project of the USA to identify effective chemotherapeutic agents have failed so far to select first choices over estramustine phosphate. The survival curves of all single agents in a composite graph of all curves, which we call the spaghetti curves, gives an immediate appreciation of the lack of success of this search [56]. The currently used single drugs which have shown a minimum of 20% of responses in some studies are presented in Table 9. At this moment there is consensus that a combination of agents is not better than the use of single agents. Some have been reported to be effective in low repetitive doses to avoid excessive toxicity. It also would be wise to start phase II or even phase III studies in patients that have not been heavily pretreated and avoid far advanced disease with heavy tumour burden. Both of these factors limit effective therapy or even effective palliation. The introduction of elevated PSA as a meaningful measurable tumour marker for prostate cancer will open new avenues for clinical research to find effective agents in the early stages of relapsed disease.

CONCLUSIONS

Controversies in the management of prostate cancer are numerous and due to several factors.

1. Our lack of consensus on universal staging and grading systems, response criteria and calculation of initial and intermittent prognostic factors.
2. Our failure to evaluate the biological metastatic potential of the cancer cells.
3. Our ignorance of the survival risks of chronic concomitant disease.
4. Our lack of communication, leading to a failure to conduct our phase II and phase III randomised trials in a coordinated pattern.

Table 10. The selection of primary endocrine treatment

Conceptions of patient	Possible treatment choice
Indifferent to sexual status	Bilateral orchiectomy Oestrogens LHRH agonists Progestational antiandrogens
Fears stigma of mutilation/ gynaecomastia	Subcapsular orchitectomy LHRH agonists
Cardiovascular risk	Bilateral orchiectomy LHRH agonists
Preserve sexuality	Pure anti-androgens Trial period of LHRH agonists
Fears lack of treatment efficacy	Trial period of LHRH agonists Combination treatment

5. Our lack of modesty to evaluate errors of commission or omissions in early prostate cancer.
6. Our lack of understanding that endocrine treatment has to be considered as palliative treatment with emphasis on palliation and quality of life.

Some of these controversies could be solved in the near future by increased collaboration by the different clinical research groups and institutions on a worldwide scale. It will be fairly easy and ethical to appreciate patients' concepts and choice in treatment with similar efficacy. Some of these concepts are presented in Table 10. Our common goal is to improve the quality and quantity of life for our patients. We all realise that progress in treatment comes with small steps at the time but we pledge with confidence that each decade will bring better insight in the management of this complex heterogeneous tumour.

1. Schröder FH. Carcinoma of the prostate. In: Veronesi U, Arnesjö B, Burn I, Denis L, Masseo F, eds. *Surgical Oncology—A European Handbook*. Heidelberg, Springer, 1989, 720–745.
2. Bostwick DG, Srigley JR. Premalignant lesions of the prostate. In: Bostwick DG, ed. *Pathology of the Prostate*. New York, Churchill Livingstone (in press).
3. Eble JN, Epstein JI. Stage A carcinoma of the prostate. In: Bostwick DG, ed. *Contemporary Issues in Surgical Pathology*. New York, Churchill Livingstone, 1990, 61–82.
4. Yamabe H, ten Kate FJW, Gallee MPW, *et al.* Stage A prostatic cancer: a comparative study in Japan and the Netherlands. *World J Urol* 1986, **4**, 136–140.
5. McNeal JE. The prostate gland: morphology and pathobiology. In: Stamey TA, ed. *Monographs in Urology: Prostate*. Princeton, Custom Publishing, 1988, 36–54.
6. Gleason DF. Histologic grading of prostatic carcinoma. In: Bostwick DG, ed. *Contemporary Issues in Surgical Pathology*. New York, Churchill Livingstone, 1990, 83–93.
7. Gervasi LA, Mata J, Easley JD, *et al.* Prognostic significance of lymph nodal metastases in prostate cancer. *J Urol* 1989, **142**, 332–336.
8. Soloway MS, Hardeman SW, Hickey D, *et al.* Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer* 1988, **61**, 195–202.
9. Murphy GP, Natarajan N, Pontes JE, Schmitz RL, Schmidt JD, Mettlin C. The national survey of prostate cancer in the United States by the American College of Surgeons. *J Urol* 1982, **127**, 928–934.

10. Braeckman J, Denis L. The practice and pitfalls of ultrasonography in the lower urinary tract. *Eur Urol* 1983, **9**, 193–201.
11. Lee F, Torp-Pedersen ST, Siders DB, Kumasaka GH, McHugh TA. The use of transrectal ultrasound in the study of normal and abnormal anatomy of the prostate gland. In: Labrie F, Lee F, Dupont A, eds. *Diagnosis and Choice of Therapy: Early Stage Prostate Cancer*. Amsterdam, Elsevier, 1989, 23–26.
12. Schmidt JD, Mettlin CJ, Natarajan N, *et al.* Trends in patterns of care for prostatic cancer, 1974–1983: Results of surveys by the American College of Surgeons. *J Urol* 1986, **136**, 416.
13. Franzen S, Giertz G, Zajicek J. Cytological diagnosis of prostatic tumours by transrectal aspiration biopsy: a preliminary report. *Br J Urol* 1960, **32**, 193–196.
14. Lee F, Torp-Pedersen ST, Siders DB. The role of transrectal ultrasound in the early detection of prostate cancer. *CA* 1989, **39**, 337–360.
15. Wang KW, Papsidero LD, Kuriyama M, Valenzula LA, Murphy GP, Chu TM. Prostatic antigen: a new potential marker for prostatic cancer. *Prostate* 1981, **2**, 89–96.
16. Cooper EH, Armitage TH, Robinson MRG, *et al.* Prostatic specific antigen and the prediction of prognosis in metastatic prostatic cancer. *Cancer* 1990, **66** (Suppl.), 1025–1028.
17. Hermanek P, Sobin LH. *TNM Classification of Malignant Tumours*. Fourth edition. Geneva, International Union against Cancer, 1987.
18. Schröder FH, Cooper EH, Debruyne FMJ, *et al.* TNM classification of genito urinary tumours 1987—position of the EORTC Genitorurinary Group. *Br J Urol* 1988, **62**, 502–510.
19. Smith PH, Bono A, Calais da Silva F, *et al.* Some limitations of the radioisotope bone scan in patients with metastatic prosttaic cancer: A sub-analysis of EORTC trial 30853. *Cancer* 1990, **66** (Suppl.), 1009–1016.
20. Dann J, Castronovo FP, McKusick K, Griffin PP, Strauss HW, Prout GR Jr. Total bone uptake in management of metastatic carcinoma of the prostate. *J Urol* 1987, **137**, 444–448.
21. Jones WG, Bono A, Verbaeys A, *et al.* Can the primary tumour be used as the sole parameter for response in phase II chemotherapy studies in metastatic prostate cancer? An EORTC Genito-Urinary Group Report. *World J Urol* 1986, **4**, 176–181.
22. de Voogt HJ, Suciu S, Sylvester R, *et al.* Multi-variate analysis of prognostic factors in patient with advanced prostatic cancer: results from 2 European organisations for research and treatment of cancer trials. *J Urol* 1989, **141**, 883–888.
23. Soloway MS. The importance of prognostic factors in advanced prostate cancer. *Cancer* 1990, **66** (Suppl.), 1017–1021.
24. Newling DWW. Criteria of response to treatment in advanced prostatic cancer. In: Furr BJA, Denis L, eds. *Clinical Oncology: International Practice and Research. Prostatic Cancer*. London, Ballière, 1988, 505–519.
25. de Voogt HJ. Prognostic factors. In: Furr BJA, Denis L, eds. *Clinical Oncology: International Practice and Research. Prostatic Cancer*. London, Baillière, 1988, 521–526.
26. Office of Medical Applications of Research, National Institutes of Health, Bethesda. The management of clinically, localised prostate cancer. *JAMA* 1987, **258**, 2727–2730.
27. Walsh PC. The role of radical prostatectomy in the management of prostatic cancer. *Cancer* 1987, **60**, 526–537.
28. Jewett HJ. The present status of radical prostatectomy for stages A and B prostatic cancer. *Urol Clin North Am* 1975, **2**, 105–119.
29. Gibbons RP, Correa RJ, Brannen GE, Mason JT. Total prostatectomy for localised prostatic cancer. *J Urol* 1984, **131**, 73–76.
30. Plowman PN. The case for radiotherapy. In: Furr BJA, Denis L, eds. *Clinical Oncology: International Practice and Research. Prostatic Cancer*. London, Ballière, 659–673.
31. Zincke H, Utz DC, Taylor WF. Bilateral pelvic lymphadenectomy and radical prostatectomy for clinical stage C prostatic cancer: role of adjuvant treatment for residual cancer and in disease progression. *J Urol* 1986, **135**, 1199–1205.
32. Kirk D. Trial and tribulations in prostate cancer. *Br J Urol* 1987, **59**, 375–379.
33. Huggins C, Hodges CV. Studies in prostate cancer. I. The effects of castration, of estrogens and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941, **1**, 293–297.
34. Seftel AD, Resnick MI. Rationale for surgical castration. In: Furr BJA, Denis L, eds. *Clinical Oncology: International Practice and Research. Prostatic Cancer*. London, Ballière, 1988, 527–534.
35. Labrie F, DuPont A, Bélanger A. Complete androgen blockade for the treatment of prostate cancer. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Important Advances in Oncology*. Philadelphia, JB Lippincott, 1985, 193–217.
36. Denis L, Mettlin C. Conclusions. *Cancer* 1990, **66** (Suppl.), 1086–1089.
37. Altwein J. Estrogens in the treatment of prostatic cancer. In: Pavone-Macaluso M, Smith PH, eds. *Cancer of the Prostate and Kidney*. New York, Plenum Press, 1983, 317–328.
38. Byar DP. Proceedings: The Veteran's Administration Cooperative Urological Research Group's studies of cancer of the prostate. *Cancer* 1973, **32**, 1126–1130.
39. Ekman P. Oestrogens and estracyt in human prostate cancer. In: Denis L, ed. *Medical Management of Prostate Cancer*. Heidelberg, Springer, 1991 (in press).
40. Namer M. Rationale for medical castration. In: Furr BJA, Denis L, eds. *Clinical Oncology: International Practice and Research. Prostatic Cancer*. London, Ballière, 1988, 535–546.
41. Mahler C, Denis L. Simultaneous administration of a luteinizing hormone releasing hormone agonist and diethylstilbestrol in the initial treatment of prostatic cancer. *Am J Clin Oncol* 1988, **11** (Suppl 2), S127–128.
42. Newling DWW. The value of reversible androgen suppression as a diagnostic value. In: Murphy GP, Khoury S, Küss R, Chatelain C, Denis L, eds. *Prostate Cancer. Part A: Research, Endocrine Treatment, and Histopathology*. New York, AR Liss, 1987, 261–265.
43. Mahler C, Verhelst J, Chaban M, Denis L. Prolactin and pituitary gonadotropin values and responses to acute LHRH challenge in patients under longterm treatment with a depot LHRH analogue. *Cancer* 1991, **67**, (in press).
44. Pavone-Macaluso M, de Voogt HJ, Viggiano G, *et al.* Comparison of diethylstilbestrol, cyproterone acetate and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomised phase III trial of the European Organisation for Research and Treatment of Cancer Urological Group. *J Urol* 1986, **136**, 624–631.
45. Schröder F. Anti-androgens. In: Denis L, ed. *Medical Management of Prostate Cancer*. Heidelberg, Springer, 1990 (in press).
46. Labrie F, Dupont A, Bélanger A. The importance of combination therapy with flutamide and castration (LHRH agonist or orchiectomy) in previously untreated as well as previously treated patients with advanced prostate cancer. In: Klijn JGM, Paridaens R, Foekens JA, eds. *Hormonal Manipulation of Cancer: Peptides, Growth Factors and (Anti)-Steroidal Agents*. New York, Raven Press, 1986.
47. Crawford DE, Eisenberger MA, McLeod D, *et al.* Controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989, **321**, 419–424.
48. Denis L, Mettlin C. Conclusions from the workshop. *Cancer* 1990, **66**, (Suppl. 1), 1086–1089.
49. Denis L, Nowé P. Bilateral orchiectomy in patients with progressive advanced prostatic cancer. *Acta Urol Belg* 1980, **48**, 113–116.
50. Murray R, Pitt P. Aminoglutethimide in the treatment of advanced prostatic cancer. In: Murphy GP, Khoury S, Küss R, Chatelain C, Denis L, eds. *Prostate Cancer. Part A: Research, Endocrine Treatment, and Histopathology*. New York, AR Liss, 1987, 275–282.
51. Mahler C, Denis L, De Coster R. The endocrine effect of ketoconazole high doses (KHD). In: Murphy GP, Khoury S, Küss R, Chatelain C, Denis L, eds. *Prostate Cancer. Part A: Research, Endocrine Treatment, and Histopathology*. New York, AR Liss, 1987, 291–297.
52. Mahler C, Denis L, De Coster R. The effect of a new imidazole derivative in advanced prostatic cancer. A preliminary report. In: Murphy GP, Khoury S, eds. *Therapeutic Progress in Urological Cancer*. New York, AR Liss, 1989, 205–209.
53. Schally AV, Redding TW. Somatostatin analogs as adjuncts to agonists of LHRH in the treatment of experimental prostate cancer. *Proc Natl Acad Sci USA* 1987, **84**, 7275–7279.
54. Winnan Ewing M, Larocca RV, Stein CA, Myers CE, Linehan WM. Effect of suramin on proliferation of human prostate carcinoma. *Proc AACR* 1989, **30**, 310.
55. van Oosterom AT, De Smedt EA, Denis LJ, *et al.* Suramin for prostate cancer: A phase I/II study in advanced extensively pretreated disease. *Eur J Cancer* 1990, **26**, 422.
56. Eisenberger M. Chemotherapy for advanced prostatic cancer. In: Denis L, ed. *Medical Management of Prostate Cancer*. Heidelberg, Springer, (in press).