Linköping University Medical Dissertation No.1073

Prediction of survival in prostate cancer

aspects on localised, locally advanced and metastatic disease

David Robinson

Division of Surgery and Clinical Oncology
Department of Clinical and Experimental Medicine
Faculty of Health Sciences
Linköping University, Sweden

Linköping 2008

Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2008

ISBN 978-91-7393-829-7
ISSN 0345-0082

There is no substitute for hard work
Thomas Alva Edison

CONTENTS

ABSTRACT

Background and aims: The clinical course of prostate cancer is highly variable and difficult to predict. Stage at presentation, grade and PSA at diagnosis are traditionally used to predict outcome. The aim of this thesis was to identify strategies for improved survival prediction in men with prostate cancer. The way in which prostate cancer affects a population based-cohort and how routinely measured variables can be used to predict survival in an intermediate to long follow-up period were explored. From this large cohort we separately evaluated how survival can be predicted in men with incidental carcinoma (T1a and b) and locally advanced disease (lymph node- positive). Immunohistochemistry was added to routinely measured variables in the subgroup of men with incidental carcinoma. Furthermore, we assessed how the outcome of metastatic disease may be predicted from information available at diagnosis, and during the first six months after treatment. Finally we predicted survival for men with metastatic hormone-refractory prostate cancer (HRPC).

Material and methods: From the Swedish South-East Region Prostate Cancer Register data on 8887 men were studied and the impact of tumour grade, serum PSA concentration, TNM classification and treatment was studied in relation to survival.

Furthermore, an evaluation of the disease-specific mortality of conservatively managed incidental carcinoma in relation to T-category, Gleason score, p53, Ki-67, Chromogranin A and serotonin was made. From the same register we studied whether common predictive factors such as serum-PSA, T-category and biopsy tumour grade could be used to better assess the prognosis of men with node-positive prostate cancer. Using data from the clinical trial SPCG-5 we studied the possibility of serial measurements of PSA and ALP being to predict survival early in the course of hormone-treated metastatic prostate cancer. From the same trial, we also assessed the value of PSA kinetics in predicting survival and related this to baseline variables in men with metastatic HRPC.

Results: In the South –East Region, where screening was seldom done the median age at diagnosis and death was 75 and 80 years respectively, and 12% were diagnosed before the age of 65 years. High tumour grade, high serum PSA and high T category were associated with poor outcome. The projected 15-year disease-specific survival rate was 44% for the whole population. In total, 18% of patients had metastases at diagnosis and their median survival was 2.5 years.

In the cohort of men with incidental carcinoma, 17% died of prostate cancer. Of 86 patients with Gleason score ≤5, three died of prostate cancer. Independent predictors of disease-specific mortality in multivariate analysis were category T1b prostate cancer, Gleason score >5 and high immunoreactivity of Ki-67. Men with lymph-node positive disease have a median cancer-specific survival of 8 years. Preoperatively known factors such as PSA, T-category, age, mode of treatment, failed to predict outcome, but there was a weak, not statistically significant difference in cancer-specific survival in relation to tumour grade.

Initial ALP, and ALP and PSA after 6 months of treatment were the serum markers that provided the best prognostic information about the long-term outcome of metastatic prostate cancer. In men with HRPC, PSA velocity alone gave a better prediction of survival than all other PSA kinetic variables.

Conclusion: In an almost unscreened population, prostate cancer is the elderly mans disease but the mortality is high. Ki-67 may be of value in addition to stage and Gleason score for predicting the prognosis in men with incidental carcinoma.

The impact of lymph node metastases on survival overrides all other commonly used prognostic factors.

By following ALP and PSA for 6 months it is possible to predict outcome in metastatic prostate cancer. This gives a much better prediction than baseline PSA and helps to select men with a poor prognosis. By combining PSAV with the variables available at baseline, a better ground for treatment decision-making in men with HRPC is achieved.

LIST OF PAPERS

I Aus G, Robinson D, Rosell J, Sandblom G and Varenhorst E: Survival in prostate carcinoma-outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up: results from three counties in the population-based National Prostate Cancer Register of Sweden. Cancer. 103: 943-51, 2005.

II Robinson D, Aus G, Bak J, Gorecki T, Herder A, Rosell J and Varenhorst E: Long-term follow-up of conservatively managed incidental carcinoma of the prostate: a multivariate analysis of prognostic factors. Scand J Urol Nephrol. 41: 103-9, 2007.

III Aus G, Nordenskjold K, Robinson D, Rosell J and Varenhorst E: Prognostic factors and survival in node-positive (N1) prostate cancer-a prospective study based on data from a Swedish population-based cohort. Eur Urol. 43: 627-31, 2003.

IV Robinson D, Sandblom G, Johansson R, Garmo H, Stattin P, Mommsen S and Varenhorst E: Prediction of survival of metastatic prostate cancer based on early serial measurements of prostate specific antigen and alkaline phosphatase. J Urol. 179: 117-22; discussion 122-3, 2008.

V Robinson D, Sandblom G. Johansson R, Garmo H, Aus G, Hedlund PO, Varenhorst E. PSA kinetics provide improved prediction of survival in metastatic hormone-refractory prostate cancer. Urology. 2008 Jul 16. [Epub ahead of print]

ABBREVIATIONS

ADT	androgen deprivation therapy
ALP	alkaline phosphatase
AS	active surveillance
AUC	area under the curve
BPH	benign prostatic hyperplasia
CT	computed tomography
DES	diethylstilboestrol
DHT	dihydrotestosterone
DRE	digital rectal examination
ECE	extracapsular extention
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EOD	extent of disease
EORTC	European Organisation for Research and Treatment of Cancer
FSH	follicle-stimulating hormone
HDR	High dose rate
HRPC	hormone-refractory prostate cancer
LH	luteinising hormone
LHRH	luteinising hormone-releasing hormone
LND	lymph node dissection
MRI	magnetic resonance imaging
NCR	National Cancer Register
NE	neuroendocrine
NRI	net reclassification improvement
PEP	polyoestradiol phosphate
PET	positron emission tomography
PNR	personal registration number (PRN)
PPLR	positive predictive likelihood ratio
PSA	prostate-specific antigen
PSAV	prostate-specific antigen velocity
PSADT	prostate-specific antigen doubling time
ROC	receiver operating characteristics curve
SD	standard deviation
TAB	total androgen blockade
TNM	Tumour Node Metastasis (classification)
TRUS	transrectal ultrasonography
TURP	transurethral resection of the prostate
WHO	World Health Organisation
WW	watchful waiting (deferred treatment)

BACKGROUND

Epidemiology

Prostate cancer is a common disease in Sweden today. The incidence of prostate cancer has risen in Sweden from approximately 4000 men in 1985 to 8930 cases in 2006.[1] But the mortality rate has remained unchanged the last decade with around 2500 deaths per year due to metastatic decease.[2] This increase is linked to a rising number of non-palpable tumours that have been diagnosed because prostate-specific antigen (PSA) testing has become more frequent. Prostate cancer is the most common cause of cancer death in Swedish men today. In Sweden, age at diagnosis is falling. In 2006 the median age was 69 years, which is 3 years lower than in 2002. The numbers of early prostate cancers are rising; more than 40% of the tumours are T1c cancers. This coincides with a fall in the numbers of locally advanced and metastatic tumours.[3]

In Europe, prostate cancer is estimated to have affected 345.900 men in 2006 and 87.400 of these will die of generalised disease.[4] The American Cancer Society estimates that 218.890 new cases were diagnosed in the United States during 2007 and that more than 27 000 men died of prostate cancer.[5]

Diagnosis

The main diagnostic tools used to search for evidence of prostate cancer include digital rectal examination[6] (DRE), serum concentration of PSA and transrectal ultrasonography (TRUS). Diagnosis depends on the presence of adenocarcinoma in prostate biopsy cores, operative specimens, or fine needle aspiration biopsy. Histopathology examination also allows grading of the tumour. Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is large enough. The risk for a positive DRE turning out to be cancer is highly dependent on the PSA value. With a PSA between 0-1(ng/mL) there is a 3-5% risk for having a prostate cancer. With a PSA of 1-2.5 the risk is 11-14%, if PSA is 2.5-4 the risk rises to 22-30 % and a PSA of 4-10 corresponds to a 40% risk for having a prostate cancer. If PSA is above 10 the risk becomes 70%. [7-9]

PSA as a diagnostic tool for prostate cancer

The measurement of PSA level has revolutionised the diagnosis of prostate cancer.[10] PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. For practical purposes, it is organ-specific but not cancer-specific, and serum levels may be elevated in the presence of benign prostatic hyperplasia (BPH), prostatitis and other non-malignant conditions. PSA level, as an

independent variable, is a better predictor of cancer than suspicious findings on DRE or TRUS.[9]
The detection of non-palpable prostate cancer is dependent on the serum level of PSA.[11] There is no universally accepted lower cut-off value, although > 4 ng/mL has been used in many studies. The finding that many men may harbour prostate cancer despite low serum PSA levels has been underscored by results from a US prevention study.[12]
The following modifications of serum PSA value, which may improve the specificity of PSA in the early detection of prostate cancer, have been described: PSA density[13]; PSA density of the transition zone[14]; age-specific reference ranges[15]; PSA molecular forms[16-18]; PSA velocity[19]; and PSA doubling time.[20]

TRUS and biopsy

The various forms of prostate cancer appear differently on TRUS. The classic picture of a hypo-echoic area in the peripheral zone of the prostate is not always seen. It must be stressed that many cancers are iso-echoic and only detectable by systemic biopsies. TRUS has two potential roles in the diagnosis of prostate cancer: 1. To identify lesions suspected of malignancy; and 2. To improve the accuracy of prostate biopsy. Thus, the main role of greyscale TRUS is to direct biopsies in order to obtain a systemic sampling of the gland. Ultrasound-guided transrectal 18G core biopsy has become the standard way to obtain material for histopathological examination. Multiple cores can be taken with a low risk for complications if antibiotic prophylaxis is used.[21, 22] The number of biopsies required for the optimal detection of prostate cancer is controversial. Several studies have examined the detection rate with higher numbers of biopsy cores at primary biopsy. Nearly all have shown a higher cancer detection rate compared to the standard sextant technique described by Hodge.[23] For example, Eskew and co-workers demonstrated that the five-region biopsy protocol with 13 to 18 cores increased the detection rate by 35% when compared to standard, mid-lobar sextant biopsies.[24] If the first set of biopsies is negative, repeated biopsies can be recommended. In the second set of biopsies, a detection rate of about 10-35% has been reported in cases with a negative first set of biopsies.[25-27]

Grading

WHO grading

The WHO (Mostofi) system, for grading prostate carcinoma is based on nuclear features as well as architectural patterns. Grade I: well-differentiated glands with nuclei that show slight nuclear anaplasia. Grade II: gland formation but the nuclei show moderate nuclear anaplasia. Grade III: Glands with marked nuclear anaplasia or tumours that are undifferentiated (do not form glands).[28]

Gleason grading

The most commonly used system for grading adenocarcinoma of the prostate is the Gleason score.[29] Biopsy material (core biopsy or operative specimens) is required to be able to assess the Gleason score; cytological preparations cannot be used. The Gleason score is based upon the degree of loss of the normal glandular tissue architecture (i.e. shape, size and differentiation of the glands).

The sum of the primary and secondary Gleason grades is shown as the Gleason score. The system traditionally describes a score between 2 and 10, with 2 being the least aggressive and 10 the most aggressive (Fig1). Since 2005 this has been modified whereby in core biopsy the most frequent grade is reported and then the worst grade. For prostatectomy specimens the primary Gleason and the secondary Gleason grades are reported; the secondary should be at least 5% of the pattern of the total cancer observed. A tertiary grade could be added if higher than the first and second grade.[30]

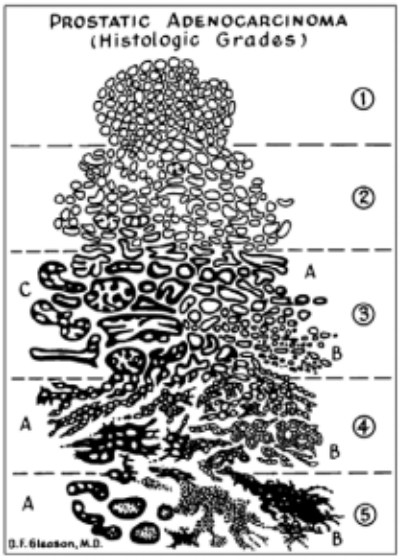


Figure 1. The original drawing of the 5 different Gleason grades.[29]

TNM

In the TNM system[31], the extent of the primary tumour (T-category), regional lymph node involvement (N-category) and distant metastases (M-category) are determined. The clinical TNM categories are usually assigned at presentation using observations from clinical examination, imaging modalities and laboratory testing. Pathological TNM (pTNM) refers to categories determined by pathological examination of a cancer resection specimen.

2002 Tumour Node Metastasis (TNM) classification of prostate cancer

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically unapparent tumour not palpable or visible by imaging
- T1a Tumour incidental histological finding in 5% or less of tissue resected
- T1b Tumour incidental histological finding in more than 5% of tissue resected
- T1c Tumour identified by needle biopsy (e.g., because of elevated PSA level)

T2 Tumour confined within the prostate
T3 Tumour extends through the prostatic capsule
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

T-category
The first level is the assessment of local tumour stage is done by DRE, 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. Category T1a and T1b prostate cancer are incidentally diagnosed at transurethral resection of the prostate (TURP) or open enucleation for what was perceived, prior to surgery, to be benign prostatic hyperplasia (BPH).
The most commonly used method for viewing the prostate is TRUS. However, only 60% of tumours are visible at TRUS and the remainder are not recognised due to their echogenicity. TRUS may reveal unsuspected extracapsular extension, but it does not determine tumour extent with sufficient accuracy to be recommended for routine use in staging. Magnetic resonance imaging (MRI) of the prostate appears to be the most accurate non-invasive way of identifying locally advanced disease.[32] However, its routine use for the pre-treatment staging of prostate cancer remains unclear and no definitive recommendations can be made.

N-category

N-staging is only performed when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatment is planned. The risk for having lymph node metastases is higher if the tumour is locally advanced, if PSA is high or if the Gleason grade is high. Each patient's individual risk could be predicted using Partin tables.[33] The best method for the patient to obtain the nodal status for the patient would be a non-invasive one, but today the gold standard for N-staging is operative lymphadenectomy. Computer tomography (CT) and MRI are not sensitive enough to diagnose regional lymph node disease. But there are new techniques that could detect small metastatic nodes such as MRI with ultra small superparamagnetic iron oxide as contrast.[34] The use of positron emission tomography (PET) has shown promising results[35], but there is not enough evidence to warrant the use of this method routinely.

Although it is generally accepted that lymph node dissection (LND) provides important information for prognosis (number of nodes involved, tumour volume, capsular perforation) that cannot be matched by any other current procedures, consensus has not been reached as to when LND is indicated and to what extent it should be performed.

M-category

Early detection of bone metastases will alert the clinician to the possible complications inherent in skeletal destruction. Bone scintigraphy has been the method of choice for detecting bone metastases, being superior in clinical evaluation, bone radiographs, or ALP measurement. [36, 37] But MRI seems to be superior in detecting involvement of the axial skeleton in patients with high-risk prostate cancer.[38]

Besides bone, prostate cancer may metastasise 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.

PSA and ALP as staging tools

PSA

The need for reliable serum markers to improve the pre-treatment staging of patients with prostate cancer has long been recognised. At present, PSA is the marker of choice. The stage of prostate cancer and the probability of a positive bone scan are strongly related to the serum PSA concentration.[39] Patients with a low serum PSA concentration have only rarely been found to harbour detectable skeletal metastases. The correlation between serum PSA and bone scintigraphy in patients with newly

diagnosed untreated prostate cancer has been further investigated. Results suggest that a staging bone scan may be unnecessary if the serum PSA concentration is less than 20 ng/mL in asymptomatic patients with a well-, or moderately differentiated tumour.[40] In contrast, a staging bone scan should be obtained in patients with poorly differentiated tumours and locally advanced disease, regardless of the serum PSA value.[41, 42]

ALP

ALP is a group of enzymes found primarily in the plasma membranes of osteoblasts and in the epithelium of the bile ducts. That is measured in the blood is the total amount of ALP released from these tissues into the blood. As the name implies, this enzyme works best at an alkaline pH and thus the enzyme itself is inactive in blood. ALP acts by splitting off phosphorus creating an alkaline pH. The primary importance of measuring ALP in men with prostate cancer is that elevated levels may indicate the presence of bony metastasis.[39]

Treatments with curative intent

Surgery

In organ-confined prostate cancer radical prostatectomy is shown to reduce overall mortality when compared to watchful waiting (WW).[43] Today this procedure can be done by a retropubic, transperineal, laparoscopic or robot-assisted laparoscopic approach. For men with clinical stage T1 to T2 the overall progression-free probability was 75% at 10 years postoperatively.[44] For men with pT2 and Gleason 6 or less the, 15-year PSA free-survival is as high as 98.7%.[45]

No randomized clinical trials comparing treatments have been performed on men with clinically T3 cancer. Only single or multicentre reports can be used to define the role of radical prostatectomy, so operative treatment is controversial. But it is becoming increasingly evident that surgery has a place in treating locally advanced disease.[46, 47]

Radiation therapy

There are three ways to deliver radiation to the prostate: 1. External beam radiotherapy (EBRT); 2. High dose rate with temporary brachytherapy Ir-192 as radiation boost to EBRT; 3. Low dose rate brachytherapy with permanent transperineal seed implantation.

There are no randomised studies comparing the outcome of surgery with either external beam radiotherapy or brachytherapy for patients with clinically localised prostate cancer. However, there is substantial documentation from large single-centre and multi-centre series on patients with this disease category showing that the outcome of external beam radiotherapy and brachytherapy is similar to that of surgery.[48] In locally advanced prostate cancer high dose rate has been tried with some success.[49]

Active surveillance (AS)
The concept of AS is to identify those patients who are not likely to experience significant progression, while offering radical therapy to those who are at risk. The approach to low-risk prostate cancer uses estimation of PSA-DT and repeat biopsy to stratify patients according to the risk for progression. Those patients who have a PSA-DT of ≤3 years (based on a minimum of 3 determinations over 6 months) or a worse Gleason score at biopsy are offered radical intervention. The remaining patients are closely monitored with serial PSA and periodic prostate repeat biopsy at 1, 4, 7, and 10 years. So by following men with low-risk cancer, defined as a Gleason score of ≤6, PSA <10, and T1c-T2a[50], it was possible to keep 65% of the patients treatment-free at 8 years. The cancer-specific survival was 99.3%.[51]

Non-curative treatments

Watchful waiting (WW)
During watchful waiting, no medical treatment is provided – by that is meant medications, radiation and surgery – avoiding the risks and side-effects associated with those management options. Watchful waiting can be recommended if the cancer does not cause signs and symptoms, is expected to grow very slowly, and is at an early stage. Watchful waiting is particularly appropriate in older men, in men with poor health, or both. Many such men may live out their normal life span without problems from their disease.[52] If there is any progression of the disease androgen deprivation therapy (ADT) should be initiated. The term ADT refers to any treatment ultimately resulting in the suppression of androgen activity.

Hormonal treatment
In 1941, Huggins and Hodges assessed the favourable effect of surgical castration and oestrogen administration on the progression of metastatic prostate cancer, demonstrating for the first time the responsiveness of prostate cancer to ADT.[53] Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. The hypothalamic luteinising hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the Leydig cells of the testes to secrete testosterone. If prostate cells are deprived of androgenic stimulation, they undergo apoptosis.[54] ADT can be achieved either by suppressing the secretion of testicular androgens by means of surgical (bilateral orchiectomy) or medical (LHRH-agonists or parenteral oestrogen) castration, or by inhibiting the action of the circulating androgens at the level of their receptor in prostate cells using competing antiandrogens that could be steroidal or non-steroidal.

Bilateral orchiectomy
Surgical castration is still considered the gold standard for ADT with which all other treatments are compared.[55] By removing the testicular source of androgens, a considerable decline in testosterone concentrations is induced.

Luteinising hormone-releasing hormone (LHRH) agonists
These are synthetic analogues of LHRH which interfere with the hypothalamic-pituitary-gonadal axis. They initially stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release and consequently elevate testosterone production. This initial rise in testosterone could cause a flare of symptoms. Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors, with subsequent suppression of pituitary LH and FSH secretion and testosterone production. The level of testosterone usually decreases to castration levels within 2 to 4 weeks.

Oestrogens
The mechanism of action is manyfold: down-regulation of LHRH secretion; androgen inactivation; direct suppression of Leydig cell function; and direct cytotoxicity to the prostate epithelium (in-vitro evidence only). [56] Oral oestrogens are associated with high cardiovascular morbidity and mortality due to first-pass hepatic metabolism and the formation of thrombogenic metabolites. By using the parenteral route of administration, which avoids hepatic first-pass metabolism it is possible to reduce the cardiovascular mortality.
The final analysis of the Scandinavian Prostatic Cancer Group Study No 5 (a prospective randomised trial of more than 900 men with metastatic prostate cancer that compared parenteral estrogen therapy (polyoestradiol phosphate) with TAB (orchiectomy or LHRH-agonist plus flutamide) showed neither significant difference in disease-specific and OS between the treatment arms, nor significant increase in cardiovascular mortality in the oestrogen arm, although the occurrence of non-fatal cardiovascular adverse events was considerably higher in this group. [57]

Antiandrogens
Antiandrogens compete with testosterone and DHT for binding sites on their receptors in the prostate cell nucleus, thus promoting apoptosis and inhibiting prostate cancer growth.[58] These orally administered compounds are classified according to their chemical structure as steroidal or non-steroidal. Both classes act as competitors of androgens at the receptor level, but while this is the sole action of non-steroidal antiandrogens, steroidal antiandrogens also have progestational properties with central inhibition of the pituitary gland. As a consequence, non-steroidal antiandrogens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

If the patient has undergone surgical or medical castration and the PSA starts to rise an antiandrogen may be added with PSA decease of 50% or more in more than 50% of patients. [59]

Total androgen blockade (TAB)

Although serum testosterone levels are reduced by up to 95% by castration, the intraprostatic androgen stimulus is sustained by the conversion of circulating androgens of adrenal origin into DHT within the prostate cells. The action of these adrenal androgens is blocked by the addition of an antiandrogen to either surgical or pharmacological castration, a concept known as total androgen blockade. TAB produces a modest increase in overall and cancer-specific survival at 5 years but is associated with increased adverse events and reduced quality of life. [60] When PSA starts to rise after TAB treatment, it is possible to develop an antiandrogen withdrawal syndrome when stopping the antiandrogen.[61, 62]

Timing of hormonal treatment

The Cochrane Library review extracted four good-quality randomised controlled trials [63-66] which were all conducted in the pre-PSA era and included patients with advanced prostate cancer who received early versus deferred ADT. The conclusion was that early ADT does not improve cancer-specific survival and provides a relatively small benefit in overall survival with an absolute risk reduction of 5.5%, which does not become evident until after 10 years.[67]

Deferred hormonal treatment for men with advanced disease until they become symptomatic may increase the risk for spinal cord compression, ureteric stasis and development of extra-skeletal metastases.[66] Early ADT benefits patients with nodal metastases who have undergone prostatectomy and lymphadenectomy, compared with those who receive deferred treatment.[68]

Chemotherapy

Evolving data on chemotherapy in hormone-refractory prostate cancer (HRPC) over recent years suggest that this modality of treatment is likely to become an important component in the overall treatment of prostate cancer. Until recently, the role of chemotherapy was limited to palliation, based on the results of randomised clinical trials that found a modest improvement in symptoms associated with mitoxantrone-based therapy. [69 70] However, results of recent clinical trials have renewed enthusiasm for the development of effective treatments for this disease. Docetaxel can now be considered the standard of care for the treatment of men with HRPC. [71-73] Despite these encouraging results, the time-point at which to initiate a cytotoxic regime in patients with HRPC remains controversial. Since the prolongation of survival is modest and there is significant toxicity associated with the treatment, a more reliable prediction of survival in order to enable better risk group stratification would be of great value. By identifying these groups it may be possible to predict which patients can expect the greatest treatment benefit.

Hormone-refractory prostate cancer

Most patients with metastatic disease are primarily hormone-sensitive where tumours that proliferate at physiologic levels of testosterone undergo apoptosis in response to androgen ablation. Later they become androgen-independent and hormone-sensitive which implies a tumour that proliferates in a castrate environment but undergoes apoptosis when exposed to secondary hormonal manipulation. And finally they are, hormone-insensitive and androgen-independent which implies tumours that proliferates in a castrate environment and fails to respond to subsequent hormonal manipulation.[74] This last step could be considered true HRPC.

The definition of hormone-refractory disease is not standard.[75] One definition of HRPC is three consecutive PSA increases above the nadir, occurring at least 2 weeks apart in a confirmed castrated man who stopped any non-steroidal antiandrogen therapy at least 4–6 weeks previously. The increasing PSA must be at least 50% more than the nadir level.[76] Other authors use a similar definition but only two consecutive PSA increases above nadir and a PSA level of at least 5ng/ml. [77] A serum testosterone level < 20 to 50 ng/mL should be documented at initial clinical relapse on hormonal therapy.[77]

For the patient with progressive disease despite androgen deprivation, multiple therapeutic options are available. These include addition of antiandrogens, withdrawal of antiandrogen, oestrogenic compounds or corticosteroids.[78] Further hormonal manipulation with diethylstilboestrol had been tried with some effect on PSA response.[79]

The natural course of early prostate cancer

Without an understanding of the natural history of prostate cancer, patient counselling and clinical management is difficult. In the case of early prostate cancer, the challenge is to maximise the possibility of survival without extensive overtreatment. There are two studies on early prostate cancer with follow-up exceeding 20 years. These studies are from the pre-PSA era. In the Swedish population-based, cohort study, 223 patients with early-stage (T0-T2 NX M0) prostate cancer were followed for a mean observation period of 21 years. [80] All men were without initial treatment, if tumour progression occurred they were given ADT. Johansson et al concluded that most cancers had an indolent course during the first 10-15 years. Further follow-up from 15 until 20 years, however, revealed a substantial decrease in cumulative progression-free survival. Tumour grade was a very strong predictor for survival.

In the study by Albertsen, 767 men with a median observation period of 24 years were followed. These men were a case mix of M0 and MX and T0-T3 tumours. The tumours were diagnosed at transurethral resection of the prostate, adenoma

enucleation or needle biopsy. Their conclusions were that there is small risk for death due to metastatic disease after 20 years in men with localised, low-grade prostate cancer. In the Albertsen study, 29% of the patients died due to prostate cancer compared to 16% in the study by Johansson. When this is compared with the mortality of 14% after a median of 8.2 years in the very well documented cohort of the 348 men assigned to WW in the study undertaken by the Scandinavian Prostate Cancer Group-4 (SPCG-4), the conclusion must be that our understanding of the natural course of early prostate cancer is highly dependent on which patients are studied. There are several older studies on incidental carcinoma and they all conclude that most men do well without any additional treatment but that some will progress in their disease and some will eventually die due to metastatic disease.[81-85]

The natural course of lymph node-positive prostate cancer

For obvious reasons there no studies on totally untreated lymph node-positive prostate cancer, but Davidson et al evaluated 61 patients from the European Organisation for Research and Treatment of Cancer (EORTC) protocol 30846 with node-positive disease who received no treatment until progression. The median time to progression was only 18 months without treatment, underlining the fact that N1 disease at times is an aggressive disease.[86]

Zagars reported on a series of 179 patients treated with early ADT and with a median follow-up of 43 months. They noted a five-year survival rate of 85% but thereafter a relatively rapid decline and after 8 years the survival rate was 57%. [87]

The natural course of metastatic prostate cancer

When referring to the natural course of distant metastatic disease this often implies the natural course of hormonally treated metastatic disease. The 5-year overall survival rate by life table analysis reported by Ryan et al was 61%.[88] When this is compared to approximately 20% alive at 5-years in the Kaplan–Meier estimates of overall survival by Hedlund et al it is clear that metastatic disease is a very diverse disease. [89] Most patients that receive ADT in metastatic prostate cancer experience relief from their symptoms and an initial decline in their PSA but their median survival is still only 2 to 3 years.[90, 91] [63, 92, 93]

Population-based studies on all stages of prostate cancer

There are few unselected studies on prostate cancer; most reports dealing with specific tasks. However there are some population-based studies with intermediate- to long-term follow-up of how prostate cancer affects a whole population. Grönberg reported on 6514 men diagnosed between 1971 and 1987 in northern Sweden. Very few of these men received treatment with curative intent. They saw that prostate cancer-specific survival was 55% and that age and tumour grade were

strong predictors of prostate cancer deaths. T-category could not be studied. Patients younger than 60 years at diagnosis had 80% risk for dying of prostate cancer. [94]
There is one Danish study on 719 men diagnosed without any screening programmes and treated without curative intent. 31% of all patients had organ-confined disease (T1a-T2, NX, M0) and 62% of the patients died primarily of prostate carcinoma. The median age at diagnosis was 75 years. A multivariate analysis showed a statistically significant relationship between disease-specific death and T-category and tumour differentiation.[95] From Iceland there is a population-based study of stage, Gleason score, treatment and long-term survival on men diagnosed between 1983 and 1987. The mean age at diagnosis was 74.4 years and after a median follow-up of 6.15 years 50% had died of prostate cancer. A Cox multivariate analysis showed age, stage and Gleason score to be independent predictors of prostate cancer death.[96]
Finally Sandblom repored the survival of 813 men in a population-based cohort with a mean age at diagnosis of 73 years. After 10 years the prostate cancer-specific survival was 53.7% and as suspected higher grade and higher stage were associated with a worse outcome. [97] So to summarise these four studies: in unscreened populations prostate cancer affects older men and the prostate cancer-specific mortality is high; large population-basedstudies are few; and very large population based studies with TNM, grade/Gleason score and treatment are lacking.

Prognostic factors of incidental carcinoma

The incidence of incidental carcinoma has decreased since the introduction of PSA testing[98, 99], this is especially true for T1b tumours.[100] But even with a PSA within age-specific reference levels and a normal digital rectal examination incidental carcinoma could be diagnosed after TURP.[101]
T1a tumours have a very good prognosis even without treatment.[102, 103]
To advise these men on further treatment is still a balance between overtreatment and the risk for losing the chance of cure for a potentially lethal disease. So prognostic factors are of interest when to advising these men what to do. But prognostic factors of incidental carcinoma are also interesting since there are tumour data available with long-term follow-up where the outcomes of the untreated and palliative treated patients are known.
Immunohistochemistry can be added to the standard variables Gleason score and TNM category to see if there is any extra information that can be retrieved, but this has been used sparsely in incidental carcinoma. [104]

Ki-67

Expression of the human Ki-67 protein is strictly associated with cell proliferation. During interphase, the antigen can be exclusively detected within the nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. The fact that the Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent from resting cells (G0), makes it

an excellent marker for determining the so-called growth fraction of a given cell population.[105]
In the population-based cohort from Örebro, 240 men with incidental carcinoma were followed for 20 years. They found that higher Gleason grade, higher nuclear grade and larger tumour volume were independent predictors of death in prostate cancer. Their analysis included Ki-67 but this gave no additional information. [104]
Ki-67 was also studied by Feneley et al and in their settings there was no independent information in the Ki-67 index to be found when added to grade and stage in T1 disease.[106]
Josefsson et al studied Ki-67 to se if it could add prognostic information in prostate cancer diagnosed at TURP (all tumour stages). It did not give any extra information when added to Gleason score or tumour volume.[107] Two earlier studies with basically the same setting showed that Ki-67 index remained an independent predictive factor in a Cox multiple regression analysis.[108, 109] So it is unclear if Ki-67 has any prognostic value in incidental carcinoma.

p53

Mutations in the p53 tumour suppressor gene, found on the short arm of chromosome 17, can be detected by immunohistochemical staining for its protein product. Antibodies to p53 protein bind both normal (wild type) and mutant forms, but the mutant protein has a much longer half-life and is not affected by formalin fixation. Hence, detecting the p53 protein immunohistochemically on formalin-fixed paraffin tissue has been shown to correlate with alterations at the genetic level. Wild type p53 protein normally inhibits the advancement of cells from the Gl to the S phase of the cell cycle. When DNA is damaged, the cell signals for an increase in p53 production, which then arrests the cycle, allowing for repair of the DNA. Once DNA repair is complete, p53 production returns to normal levels and the cell is allowed to continue through the cycle. Loss of this regulation due to a damaged (mutated) or deleted p53 gene allows for unregulated growth of abnormal cells and has been implicated in the pathogenesis of numerous human malignancies.[110, 111]
p53 was studied in 44 men with T1a prostate cancer and there was no evidence that p53 could add prognostic information on survival or progression in a multivariate setting.[112] Gleason score was the only significant predictor of progression. 102 patients with T1a tumor were followed at the Mayo Clinic with a mean follow-up of 9.5 years and their conclusion was that Gleason score did not predicted outcome. The only variable that predicted outcome was the weight of the TURP material.[113]

Chromogranin A

A substantial proportion of primary prostate cancer cases contain a subpopulation of highly specialised malignant cells expressing a neuroendocrine (NE) phenotype. NE cells are characterised by the synthesis and secretion of a variety of neuropeptides and hormones, such as chromogranin A and neuron-specific enolase, which are considered to play a significant role in prostatic growth and differentiation, as well as in the regulation of the secretory process of the mature gland, by way of endocrine, lumencrine, or neurocrine mechanisms.[114] There is a study from Greece that suggests

that chromogranin A could be of importance for progression in well- and moderately differentiated incidental carcinoma of the prostate.[115]

Prognostic factors in lymph node-positive prostate cancer

Davidsson evaluated 61 patients from the EORTC protocol 30846 with node-positive disease who received no treatment until progression. After a median follow-up of 41 months, tumour grade was predictive of progression. A higher initial T-category was also associated with an increased risk for progression, with clinically extracapsular disease having a greater risk for progression than organ-confined disease. Patient age, change in T-category during the study, and the degree of nodal involvement were shown not to correlate with risk for progression.[86] Zagars reported that pre-operative PSA or T-category or grade did not give any prognostic information about survival, but tumour grade and T-category affected progression.[87] So the value of T-category and grade when predicting survival is unclear.

Prognostic variables in hormone naïve metastatic prostate cancer

The Soloway score

In 1988 Mark Soloway presented his study on 166 men with untreated metastatic disease. By using a semiquantitative grading system based upon the extent of disease (EOD) observed on the bone-scan, he showed that the EOD on the scan correlated with survival. EOD grades are as follows: I, number of bony metastasis less than six, each of which is less than 50% the size of a vertebral body; II, number of bone metastases between six and 20; III, number of metastases more than 20 but less than superscan; IV, superscan or its equivalent, i.e. more than 75% of the ribs, vertebrae and pelvic bones involved. One lesion about the size of a vertebral body would be counted as two lesions. The 2-year survival rates for EOD I to IV were 94%, 74%, 68%, and 40%, respectively. The survival of patients in categories EOD I and IV significantly differed from the other categories.[116]

PSA

PSA has been used as a marker of total tumour burden in metastatic disease but the prognostic role of pretreatment PSA level is controversial. In the study by Reynard et al based on 134 men with metastatic prostate cancer that were followed prospectively, it was found that pretreatment PSA levels were not related to survival in univariate analysis.[117] On the other hand in the study by Ernst et al on 162 men with metastatic disease, there was a trend toward a decrease in survival with increasing PSA values at diagnosis in univariate analysis. However, they concluded that the limited follow-up made it impossible to draw definite conclusions.[118] Two more studies on metastatic disease concluded that a high pretreatment PSA level was associated with worse outcome[119, 120] Figg could not find any value of pretreatment PSA values in predicting death.[121]

ALP

Nakashima et al found that a pretreatment ALP level higher than twice normal was significantly related to a worse outcome in univariate analysis.[122] The same definition of ALP at diagnosis was used by Smith et al in a study on 868 men, coming to the same conclusion.[123]

ALP flare

ALP flare, i.e. a transient increase in ALP following initiation of androgen deprivation treatment is an index of activity of osteoblasts during the initial month of treatment. This flare phenomenon is linked to a poor outcome. [122, 124]

Prognostic variables in metastatic hormone-refractory prostate cancer (HRPC)

The ability to provide prognostic information in men with HRPC is essential for randomised clinical trials where homogenous groups with similar survival data prior to onset of the trial are required. Furthermore if physicians are to recommend treatment to their patients they must have some idea of the individual patient's prognosis. Today nomograms are recommended and frequently used.[125] There are several nomograms that may be used to predict death in men with HRPC.[126-128] These protocols typically include baseline PSA, ALP, hemoglobin and performance status. The Karnofsky[129] score is an example of a performance status and it is an indicator of the general well-being of the patient and there are various other forms of performance status that correlate with survival in metastatic disease.[90, 130]

The weakness of the nomogram is that their concordance index is just below 0.70. This means that the model correctly predicts that the patient who dies first had a higher probability of death in less than 7 out of 10 times. 0.5 means no ability to discriminate and 1 indicates perfect discrimination.[131] A variable that make it possible to get a better concordance index would enable better discrimination.

PSA kinetics

PSA doubling time (PSA-DT) is calculated using logarithmic transformation of PSA values, and a slope is calculated by linear regression. The doubling time is determined by dividing the slope with log(2).[20] PSA-DT could be used as a proxy for increasing tumour volume.[77, 132] PSA-DT has been studied in med with HRPC and a PSA-DT of 70 days or less was a significant predictor for shorter survival in multivariate analyses.[133] There is one similar study from France that showed that a PSA-DT below 45 days prior to onset of chemotherapy in metastatic HRPC was associated with an increased risk for death from the cancer.[134]

PSA velocity is the rate at which PSA increases per time unit, it is presented as ng/ml and year. Rozhansky at al using multivariate Cox analysis showed that PSA velocity (PSAV) was associated with survival in men with HRPC treated with cytotoxic, cytostatic or combination therapy, PSA-DT was not tested in this study.[135]

AIMS

To describe how prostate cancer affects men in a population-based prospectively assembled cohort and to see how tumour grade, serum PSA concentration, TNM classification, and treatment are related to survival (Paper I)

To evaluate the disease-specific mortality of conservatively managed incidental carcinoma of the prostate (T1a and T1b) in relation to prognostic factors in a population-based cohort (Paper II)

To investigate whether common prognostic factors such as serum-PSA, T-category and biopsy tumour grade can be used to better assess the prognosis of the individual patient with locally advanced (T1–4, N1, M0) prostate cancer (Paper III)

To determined how serial measurements of PSA and ALP can be used to predict survival early on in the course of hormone-treated metastatic prostate cancer (Paper IV)

To assess the value of PSA kinetics in predicting survival and relate this to baseline variables in men with metastatic hormone-refractory prostate cancer (Paper V)

MATERIAL, METHODS AND STATISTICS

Sources of data Papers I-III

The South-East Region Prostate Cancer Register

Since 1987, the National Cancer Register (NCR) has expanded to include a separate register for prostate carcinoma in the South-East Region of Sweden. This extended registration includes the collection of data on tumour characteristics, treatment, and survival in order to track patterns of epidemiology, treatment, outcomes, and assessment of prognostic factors for mortality and quality of life. The South-East Region had a total population of 978,442 in 2003 and comprises of the counties of Östergötland, Jönköping and Kalmar. Whenever a patient is newly diagnosed with prostate carcinoma and a treatment decision is taken, the physician responsible for the patient submits a report, according to a standardised protocol, to the oncologic centre of the South-East Region for registration. This includes tumour classification according to the TNM system, serum PSA concentration, grade of malignancy, and treatment. Second and third protocols are submitted for patients who receive secondary therapy after expectant management, patients who receive hormone treatment after curative therapy, and/or patients who have died. The date and cause of death are recorded in the register when applicable. Causes of death are reported by the attending physician, who fills in a special form according to the register protocol. One problem with registers, when the registration continues for several years, is the gradually changing views on staging, diagnosis, and treatment of disease. The codes employed at the time when the register is initiated are often insufficient for adequate description of the tumour and treatment when new principles of management evolve. For this reason the South-East Region Prostate Cancer Register is updated continuously. Several new variables have been added or adapted, and new modes of treatment have been included. No variables have been removed, and the original codes have remained the same, which makes longitudinal comparisons possible. A local management programme is incorporated in the South-East Region Prostate Cancer Register to maintain common principles for diagnosis and treatment in the region. The register has been updated as shown in Table 1.
A validation study of the South-East Region Prostate Cancer Register showed high accuracy.[136] The National Cause of Death Register was checked for deaths that were not available in the regional register.

National Cancer Register

The National Cancer Register was founded in 1958 to enable continuous surveillance of the incidence of oncologic disease and to detect any regional or temporal variations occurring in the population. According to law, the NCR must be notified separately by the clinician responsible and by the pathologist or cytologist involved in the case for every diagnosis of primary cancer in residents in Sweden. The date of diagnosis, municipality, county of residence, and type of tumour are reported.

Personal registration number

The Scandinavian system of a personal 10-digit registration number (PRN) for each resident, which has been in use since 1947, enables efficient follow-up and linking between different registers. By using the PRN, every individual can be traced in different registers without drop-out. Data are primarily collected in regional oncologic centres. Sweden is divided into six health-care regions, each with a regional oncologic centre that is responsible for collecting data regarding cancer.

Table 1. Variables included in The South-East Region Prostate Cancer Register

Version	Year	Variables included
1	1987	TNM classification [UICC 1978] Tumour grade[WHO 1980] Base for diagnosis (cytology/histopathology) Primary therapy Date of death Autopsy performed (yes/no) First version of the management programme
2	1989	Management programme updated
3	1990	Gleason score added Date and type of secondary treatment following expectancy or radical treatment added.
4	1992	PSA value and date of sampling added Management programme updated
5	1994	TNM classification changed to the 1992 version [UICC 1992] Cause of death changed to four categories: 1. Prostate cancer 2. Other cause and prostate cancer as a contributing factor 3. Other cause, advanced prostate cancer present 4. Other cause 5. Unknown Management programme updated
6	1995	New treatment alternatives added (neoadjuvant therapy)
7	1998	New treatment alternatives added (brachytherapy) PSA value missing included as an alternative Autopsy performed unknown included as an alternative Secondary therapy unknown included as an alternative 'Management programme updated
8	2000	TNM classification changed to the 1997 version [UICC 1997] Adaptation to the National Prostate Cancer Register Free text alternatives excluded New form for registration of secondary therapy and cause of death Management programme updated
9	2004	TNM classification changed to the 2002 version [UICC 2002] Prostate cancer diagnosed due to LUTS added to the reasons of diagnosis

Methods specific for Paper I

A total of 8887 patients diagnosed with prostate carcinoma between 1987 and 1999 were registered. Follow-up data with regard to survival and cause of death were available up to December 31, 2002. TNM stage, tumour grade, PSA (available from 1992), primary treatment and time and cause of death were registered. The study endpoints were prostate carcinoma-specific survival, overall survival, and relative survival (the ratio between the observed survival and the expected survival of age-matched controls according to the Swedish population).

The life table method was used to estimate the projected disease-specific survival. A Cox proportional hazards model was used to examine the effects of tumour grade, serum PSA concentration, TNM classification, and treatment on disease-specific survival.

Methods specific for Paper II

All patients below 8o years-of-age, diagnosed with incidental prostate cancer between 1987 and 1991 at two departments of pathology were included in the study. 197 cases were managed with watchful waiting or with ADT when symptoms occurred. The median age at diagnosis was 75.2 years (range 55-79 years). The material in this study was assembled before PSA values were entered into the register. Follow-up was available until 31 October, 2004. Follow-up was possible for up to 17.5 years and the mean follow-up period was 7.8 years (median 6.8 years).

Gleason score and tumour involvement

The malignancy grading of the tumour material was performed according to the original description by Gleason and Mellinger.[29] The Gleason score was divided according to Egevad et al. into four groups, as follows: (I) 4-5; (II) 6; (III) 7; and (IV) 8-10. [137] The percentage of chips involved was determined by counting the proportion of carcinoma involved TUR chips. All material was embedded and examined. A chip was considered malignant regardless of the degree of involvement.

p53

Analysis was performed using Dako Monoclonal Anti- Human p53 protein. Antigen retrieval was performed by heating in 0.01M citrate buffer for 10 min at 100°C. Slides treated with primary antibody and secondary Envision antibody were incubated for 25 min at room temperature and consecutively developed with diaminobenzidine and nuclei staining using Harris haematoxylin.

Chromogranin A and serotonin

The polyclonal antibody against chromogranin A was purchased from Dako (A 430; lot 072). The antibody was diluted 1:100. For antigen retrieval, slides were treated in a microwave oven for 10 min while immersed in 0.01 M citrate buffer, pH 6.0. The serotonin monoclonal antibody (Dako; M 758; lot 120; clone 5 HT-H209) was diluted 1:10, and slides were trypsinated for 10 min.

Ki-67
The monoclonal antibody (Ki-67; Immunotech; lot 197; clone MIB-1) was diluted 1:25, and slides were treated in a microwave oven for 30 min in 0.01 M citrate buffer, pH 6.0. Negative controls were obtained from Dako: x0931 mouse IgG1 and X0903 Ig fraction. Quantitative and qualitative assessments of the histological and immunohistochemical parameters were performed using a standard optical microscope.
Microscope fields with the highest achieved immunohistochemically positive yield were chosen and five consecutive high-power fields (X/400) were randomly scrutinised and counted for positively stained cells.

The independent prognostic value of each variable determined at diagnosis was analysed by means of univariate analysis and multiple Cox regression analysis.[138] Cox regression was also used to test for a linear trend in the hazard ratio between the categories of a prognostic variable. Cancer-specific survival was calculated and presented using Kaplan-Meier curves and a survival difference was tested using the log-rank test.

Methods specific for Paper III
We selected all 181 patients with T1–T4, N1, M0 prostate cancer found in the South-East Region Prostate Cancer Register, diagnosed between January 1, 1987 and October 1, 2000. Follow-up was until December 31, 2001. TNM-category, tumour grade, PSA (available from 1992), primary treatment and time and cause of death were registered. To be categorised as M0, the patient must have had a negative bone scan and to be categorized as N1 and to have had an operative lymphadenectomy with histopathologically verified cancer growth in the lymph node specimens.
The cancer-specific and overall survival were calculated and presented with the Kaplan–Meier curves. The impact of different prognostic factors was tested with the log-rank test.

Sources of data Papers IV-V
Between December 1992 and June 1997, 915 men with hormone-naive, T1-4, Nx, M1, all Grades prostate cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 from 63 Nordic urological centres were randomised to receive treatment with either PEP or TAB. All patients had skeletal metastases as evaluated by bone scans supplemented with X-rays when needed. The primary tumour was staged by digital rectal examination according to the TNM classification of 1987, and graded according to the World Health Organisation (WHO) system, either on the base of fine-needle aspiration cytology or histologically from transurethral resection specimen and needle biopsies. The extent of bone disease was

calculated from pretreatment bone scans according to a modified Soloway score as follows: score 1, total area of hot spots is less than three bodies of a lumbar vertebra; score 2, the total area of hot spots is larger of that of score 1, but less than 75% of the total scan; and score 3, superscan.
Exclusion criteria were as follows: patients who had received previous systemic therapy for prostate cancer or other malignancy of any kind with the exception of basal cell carcinoma of the skin, patients who had suffered a myocardial infarction or cerebral infarction within 1 month prior to randomisation in the study, patients with current or previous liver disease with a bilirubin or alanine aminotransferase value above the upper limit of normal, and patients who it was felt would not be able to comply with the study protocol. The patients were given verbal and written information about the study and gave their verbal consent to participate. The patients were stratified according to country, with Iceland included in the Norwegian group, ECOG performance status 0-1 versus 2, an alkaline phosphatase under versus over 1.25 times the upper normal limit, and whether they had or not had a previous or current history of cardiovascular disease. PEP was given as i.m. injections of 240 mg twice a month for 2 months and thereafter once a month. TAB was given as flutamide 250 mg orally three times a day in combination with either intramuscular triptorelin 3.75 mg per month, or bilateral orchiectomy according to the choice of the patient and trialist. Flutamide was started 1 week before the first triptorelin injection. Irradiation of the breasts prior to therapy was optional. The patients were followed by visits to the trialist 1, 3 and 6 months after randomisation and thereafter every 6 months until clinical progression was clearly established. At every visit the patients were questioned and evaluated with regard to symptoms and signs of disease progression and adverse events. Blood pressure, body weight, performance status and pain and analgesic scores were noted, and levels of hemoglobin, creatinine, PSA and liver enzymes including ALP were measured. Digital rectal examination and bone scan or X-rays were done only if considered necessary for the evaluation of the disease status. Between the 6 monthly visits the PSA was measured so that the patients were monitored for PSA every 3 months. If required, the patients could attend for extra checks. When clinical progression was definitely established, treatment and follow-up of the patient were at the discretion of the individual trialist. Patients were usually given other forms of endocrine therapy, sometimes with known cardiovascular toxicity, or chemotherapy. Time and cause of death were recorded. Monitoring was done by research nurses or monitoring specialists by means of visits to the trialist at least once a year for the first 5 years. After this, monitoring was done only by means of telephone contacts or correspondence. To check compliance with medication the patients had to return empty vials of flutamide and charts were kept by the nurses of all injections of PEP or triptorelin. A statement by the trialist regarding compliance was included in the case report form.

Definition of endpoints: Time to biochemical progression was the time from randomisation to the time when the first rise of PSA from nadir was observed and followed by a continuous rise in consecutive measurements. Time to clinical progression was the time from randomisation to the first suspicion of clinical deterioration of the disease which could be supported by further clinical deterioration in consecutive evaluations. Overall survival was the time from randomisation to death from any cause. Analysis of disease-specific survival included all the typical deaths from prostatic cancer with progressive cachexia, etc., but also deaths from another disease with significant contribution from the prostatic malignancy meaning that clinical progression of the cancer was established. For patients who died of another disease and had no symptoms of their prostate cancer, the cause of death was counted as being independent of the prostatic malignancy. Patients found dead in their homes and where no examination had been made in the immediate period prior to death or where no post-mortem examination was done were classified as death of unknown cause.
There was no difference between the treatment groups in terms of biochemical or clinical progression-free survival or in overall or disease-specific survival. [139]

Methods specific for Paper IV
From the SPCG-5 study named above we had the serum concentrations of PSA and total ALP, these were determined by routine laboratory methods before the start of treatment, after month 1, after month 3 and every 3 months thereafter. There were 697 men still alive 6 months after starting treatment who had complete data on PSA and ALP for the first 6 months. The normal range for PSA was 0-3ng/ml, for ALP <4.6 μKat/l and for hemoglobin 134-170 g/l. The 6-month longitudinal course of PSA and ALP levels was used to define the 6 prognostic factors: 1) logPSA at baseline; 2) relative PSA velocity (during the period 0 to 6 months) defined as the slope from a linear regression of the logarithmic transformation of the PSA level at baseline, and 1, 3 and 6 months after start of treatment; 3) ALP at baseline; 4) ALP at 6 months (to adjust for minor variations during the 6-month period we extrapolated the ALP level at 6 months from a linear regression based on the logarithmic transformation of ALP levels measured at 1, 3 and 6 months); 5) ALP flare (The model is based on the increase in ALP 1 month after start of treatment, ie the ratio between ALP after 1 month and before treatment. ALP at 1 month was extrapolated from the linear regression in number 4); and 6) logPSA at 6 months taken from the regression model in number 2. The relative PSA velocity was calculated as described by Vollmer.[140]
The prognostic factors were initially studied using Cox's regression analysis with death from prostate cancer death as the main end point, censoring for deaths from other causes.[138] In a further analysis Cox's regression was adjusted for age, grade and tumour stage. In the case of a statistically or close to significant interaction between treatment and prognostic factor, analysis for that prognostic factor was performed for each treatment (PEP or TAB) separately. Our models were constructed on the information available after the initial 6-month treatment period. The prognostic

capability of the variables was studied by ROC curves. Whereas traditional ROC curves (ie plots of sensitivity vs 1-specitivity for various cut-off values) cannot depict the ability of the model for censored data during the follow-up period, this can be solved by using time-dependent ROC curves. In a time-dependent ROC curve the probability of prostate cancer death is replaced by an estimate originating from the survival function.[141] A span of λ_n=5% is the nearest neighbour estimator of the time-dependent ROC curves. We used the survival of 3 years as the cut-off for our time-dependent ROC curves.
Area under the curve was also calculated from the time-dependent ROC curves. On the ROC curve we chose a cut-off value where sensitivity and specificity was of the same magnitude. This value was used as cut-off point, dividing data into 2 groups. For each group we determined the cumulative incidence of lethal prostate cancer, with death from other causes considered as competing events, and the positive predictive likelihood ratio.[142]

Methods specific for Paper V

Of the original 915 patients in SPCG-5, 383 were excluded due to incomplete PSA follow-up. In 21 men the cancer was primarily hormone-insensitive and 10 had missing values at baseline. In 81 men the PSA at 6 months after nadir was lower than 3 months after nadir, and in 3 men no date of nadir was recorded. The remaining 417 constituted our study population. PSA, ALP and hemoglobin were determined by routine laboratory methods prior to start of treatment. Thereafter PSA was taken every third month. The tumour burden seen on bone scan was classified according to a modified Soloway score. Performance Status Pain Analgesic score (PSPA- score) was obtained by adding WHO performance status 0-5 points, pain 0-4 points and use of analgesic 0-5 points. This being a measure of how patients are clinically affected by the disease. These 5 variables (PSA, ALP, hemoglobin, Soloway- and PSPA- score) constituted the baseline model and benchmark against which the variables related to PSA kinetics were compared. In order to see which variable added most prognostic information compared to the baseline model, we included PSA nadir, PSAV, time to nadir, PSA-DT, PSA halving time, treatment and age when HRPC was confirmed. Definitions of the post-treatment covariates were as follows:

1. Time to nadir

Time from start of treatment until the lowest PSA value was recorded. If there were several identical values, the time to when the last one was recorded was used.

2. PSA halving time

Calculated from the PSA values taken from start until nadir. If the lowest value was repeated, the first one was used. Using logarithmic transformation of PSA values a slope was calculated by linear regression. The halving time was calculated by dividing the slope by -log(2).

3. PSA-DT
Calculated from the PSA values from nadir until HRPC was diagnosed. Using logarithmic transformation of PSA values a slope was calculated by linear regression. The doubling time was determined by dividing the slope with log(2).
4. PSA nadir
The lowest PSA value measured.
5. PSAV
The absolute increase in PSA (ng/ml/year) from nadir until HRPC was diagnosed.
6. HRPC age
Age when HRPC was diagnosed.
7. Treatment
Parenteral oestrogen treatment or total androgen blockade.

Our definition of HRPC was two consecutive rising PSA following nadir. Since PSA was taken every 3rd month it took 6 months after nadir before HRPC could be diagnosed. PSAV and PSA-DT were calculated from PSA values between nadir and 6 months thereafter.
The data were dichotomised into two groups; dead or alive 9 months after diagnosis of hormone-refractory disease. To begin with, a baseline covariate risk model was established by a backward elimination in a logistic regression analysis using, PSPA, hemoglobin, Soloway score, ALP and PSA as covariates. In the analysis of odds ratios, logarithmic transformation was performed to achieve symmetric distribution for the skewed variables PSA, PSAV and PSA nadir. Odds ratios were calculated by standardising for the standard deviation of the distribution of each covariate. In order to evaluate the predictive ability of the various covariates and models, we studied odds ratios, net reclassification improvement (NRI) proposed by Pencina et al[143], and area under the receiver operating characteristic (ROC) curve.
The predicted 9-month death probability gained from the baseline model gave three risk groups: the low-risk group with predicted probability less than 0.23 corresponding to the 30% percentile of predicted risk; the intermediate-risk group with predicted probability between 0.23 and 0.40, where 0.40 corresponds to the 70% percentile of predicted risk; and a high-risk group with a predicted probability above 0.40.
For each of the new prognostic markers a logistic regression model including the baseline covariates and the new prognostic marker were fitted and the predicted 9-month survival calculated. The cut-off probabilities 0.23 and 0.40 split the data into new risk categories and NRI were calculated. The prognostic ability of each prognostic marker was tested by z-statistics. AUC was calculated by means of the c-statistic[144], a nonparametric estimate of the area under the ROC curve.

RESULTS

PAPER I

The median patient age at diagnosis was 75 years (mean, 74.1 years; range, 40–96 years), with 1072 men (12.1%) age < 65 years, 4531 men (37.0%) ages 65–74 years, and 4531 men (51.0%) age ≥75 years. 5873 of the 8887 men (66.1%) had died. The median age at death was 80 years (mean, 79.6 years; range, 41–100 years). The causes of death were prostate carcinoma in 2595 men (44.2%). 2582 (44.0%) men died from unrelated causes and the cause of death was unknown in 146 men (2.5%). The overall survival, disease-specific survival, and relative survival for the entire cohort are presented in Figure 1. In addition, both the tumour grade (Fig. 2) serum PSA concentration (Fig. 3) and M-category (Fig 4) were clearly related to the disease-specific survival rate. The projected 15-year disease-specific survival rate was 44% for the whole population. In total, 18% of patients had metastases at diagnosis (M1), and their median survival was 2.5 years. Patients with non-metastatic T1–T3 prostate carcinoma (age<75 years at diagnosis; *n*=2098 patients) had a 15-year projected disease-specific survival rate of 66%.

Figure 1. Overall, disease-specific, and relative survival in the full cohort of 8887 men. Patients at risk were calculated for overall- and disease-specific survival.

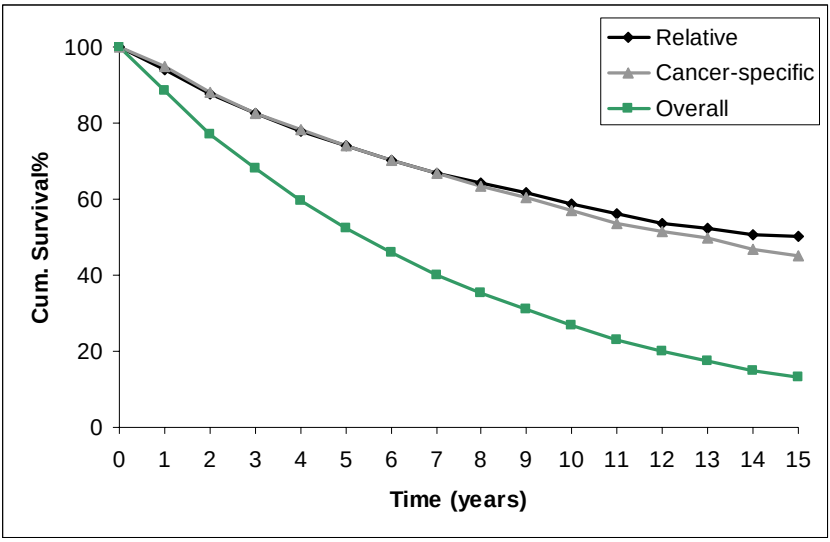


Figure 2. The impact of tumor grade on disease-specific survival for the full cohort (n = 8887 men). G1–G3: Grades 1–3.

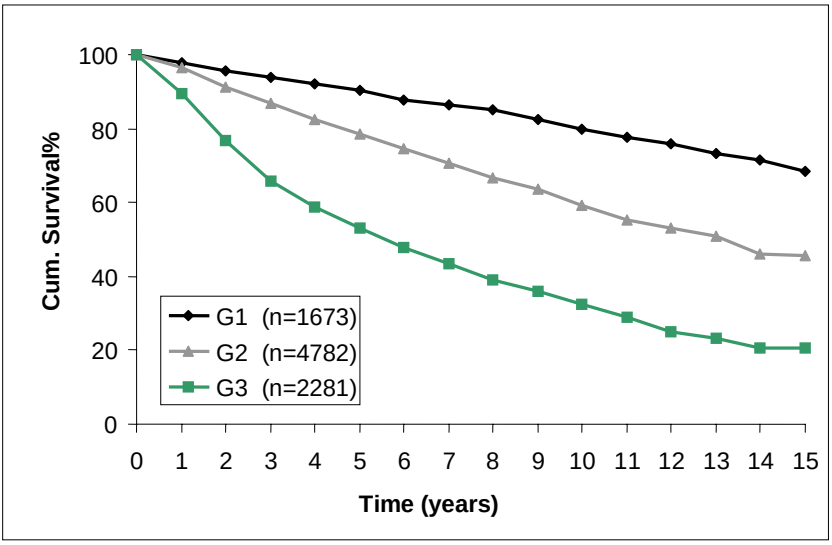


Figure 3. The impact of serum prostate-specific antigen (PSA) concentration (ng/mL) on disease-specific survival in patients who were diagnosed between 1992 and 1999 (n=4480 men).

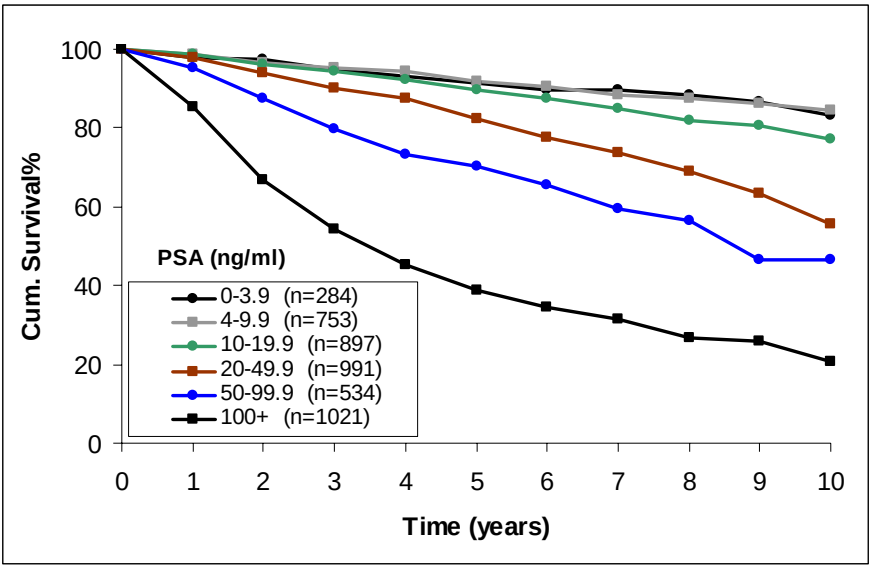
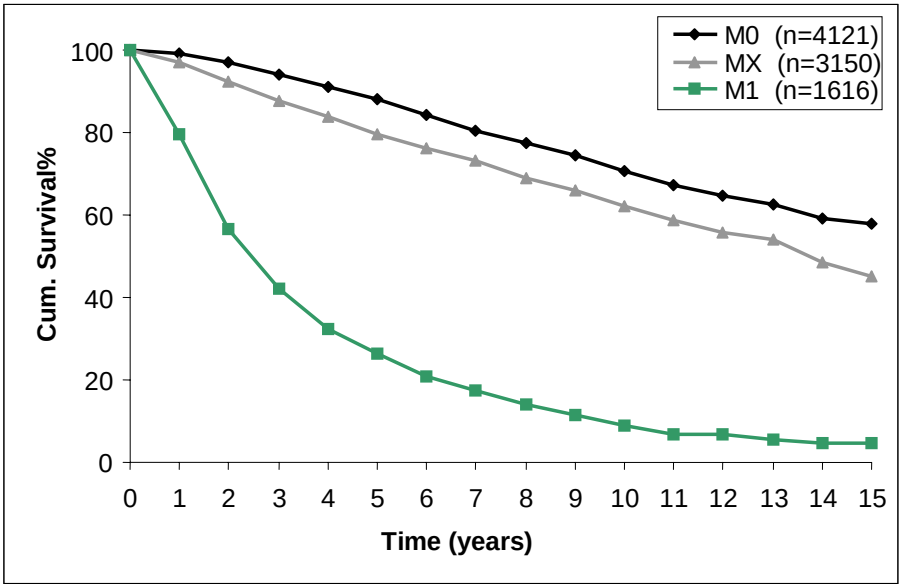


Figure 4. The impact of M-category on cancer-specific survival for the full cohort (n=8887).



A Cox multivariate analysis showed that T-classification, tumour grade, and type of treatment all had an independent impact on the disease-specific survival in this group of patients, who most likely had non-metastatic prostate carcinoma, Table 2.

Table 2. Disease-specific survival for patient's age < 75 years with no metastasized disease at diagnosis: Cox multivariate regression analysis

	No. of patients	**No. of events**	**HR**	***P* value**	**95% CI**
T-category					
T1	516	49	1.00	-	-
T2	1131	154	1.51	0.013	1.09-2.09
T3	440	149	2.77	< 0.00001	1.99-3.85
N-category					
NX	1305	251	1.00	-	-
N0	782	101	0.83	0.23	0.60-1.13
Tumour grade					
Grade 1	463	37	1.00	-	-
Grade 2	1285	208	2.47	< 0.00001	1.73-3.53
Grade 3	339	107	4.90	< 0.00001	3.33-7.22
PSA level (ng/mL)					
0 ≤PSA < 10	417	27	1.00	-	-
10 ≤PSA < 20	316	25	1.16	0.59	0.67-2.01
20 ≤PSA < 50	265	33	1.39	0.21	0.83-2.33
PSA missing	1089	267	1.90	0.0019	1.27-2.85
Treatment					
Expectancy or palliative treatments	1252	242	1.00	-	-
Radical prostatectomy	546	51	0.40	< 0.00001	0.27-0.59
Radiation therapy	289	59	1.01	0.98	0.72-1.41

PAPER II

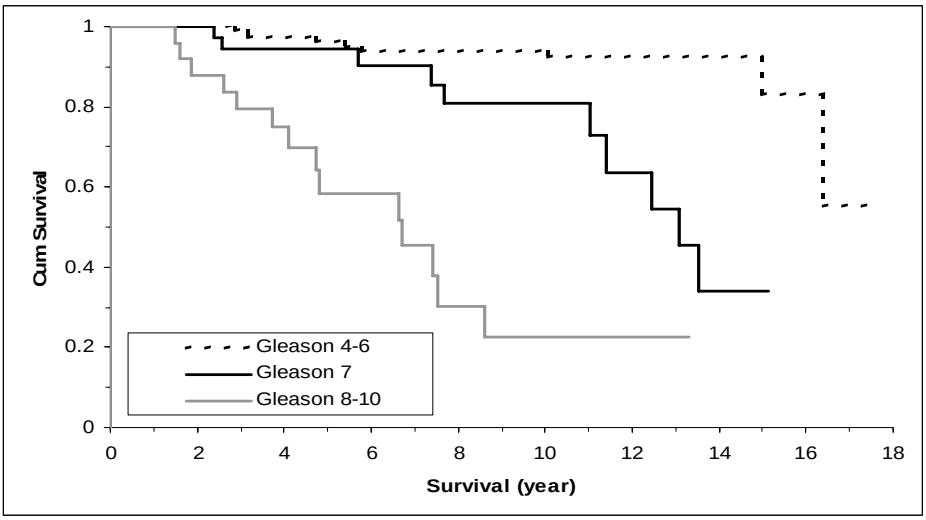
Age, TNM category and Gleason score for the study population are shown in Table 3. During follow-up, one (2.3%) of the 44 men in category T1a received treatment with curative intent and five (11.4%) received ADT. Of the 152 patients in category T1b, 52 (34%) received ADT and one (0.7%) treatment with curative intent. At the time of the last follow-up, therefore, 139 patients (70%) had not received treatment for their prostate cancer.

Table 3
Distribution of age, TNM categories and Gleason score

	Number (%)
Age (years)	
55-69	*40 (20.3)*
70-74	55 (27.9)
75-79	102 (51.8)
T-category	
T1a	44 (22.3)
T1b	152 (77.2)
Information missing	1 (0.5)
N-category	
NX	182 (92.4)
N0	10 (5.1)
N1	5 (2.5)
M-category	
MX	89 (45.2)
M0	107 (54.3)
M1	-
Information missing	1 (0.5)
Gleason score	
4-5	86 (43.7)
6	42 (21.3)
7	40 (20.3)
8-10	29 (14.7)

158/197 patients (80%) had died. Of these 158 patients, 33 (21%) died of prostate cancer, corresponding to 17% of the entire cohort. Only cases with prostate cancer as the underlying cause of death (n=33) were used in our evaluation of disease-specific survival.

Figure 5. Kaplan-Meier curves of prostate cancer-specific survival for men with different Gleason scores (n=197). Log-Rank: p<0.0001



Of the 86 patients with Gleason score 4-5 tumours, there were three deaths (3.5%) due to prostate cancer. Similarly, there was only one death due to prostate cancer amongst the 44 patients (2.3%) with category T1a disease. Of the 89 patients with MX disease, 13 (14.6%) died of prostate cancer and of the 107 M0 patients, 20 (18.7%) died of prostate cancer. Kaplan-Meier curves of prostate cancer-specific survival for men with different Gleason scores are shown in Figure 5.

In multiple Cox regression analysis, patients with category T1b disease showed a significant risk for dying of prostate cancer when analysed against Gleason score. Finally, we applied Cox multivariate analysis to the clinically used variables T1a and T1b and Gleason scores 4-5, 6, 7 and 8-10 to see if Ki-67, chromogranin or p53 provided any extra prognostic information in addition to that provided by T-category and Gleason score. We found that Ki-67 provided extra prognostic information, whereas none of the other variables did so when used in the same multivariate setting as shown in Table 4.

Table 4. Multiple Cox's regression analysis comparing T-category, Gleason score and Ki-67.

	n	No. of events	Hazard Ratio	95 % Confidence Interval	Statistical Significance (p value)
T1a	38	1	1.00	-	-
T1b	144	31	15.24	1.51-153.94	0.021
Gleason score 4-5	79	3	1.00	-	-
Gleason score 6	38	6	11.96	2.19-65.14	0.0041
Gleason score 7	37	10	17.87	3.41-93.64	0.00065
Gleason score 8-10	28	13	34.78	6.14-196.89	0.00006
Ki-67 1-50	97	8	1.00	-	-
Ki-67 51-100	54	10	1.59	0.56-4.47	0.38
Ki-67 > 100	31	14	2.87	1.03-7.98	0.043

Test for trend Ki-67: p=0.036

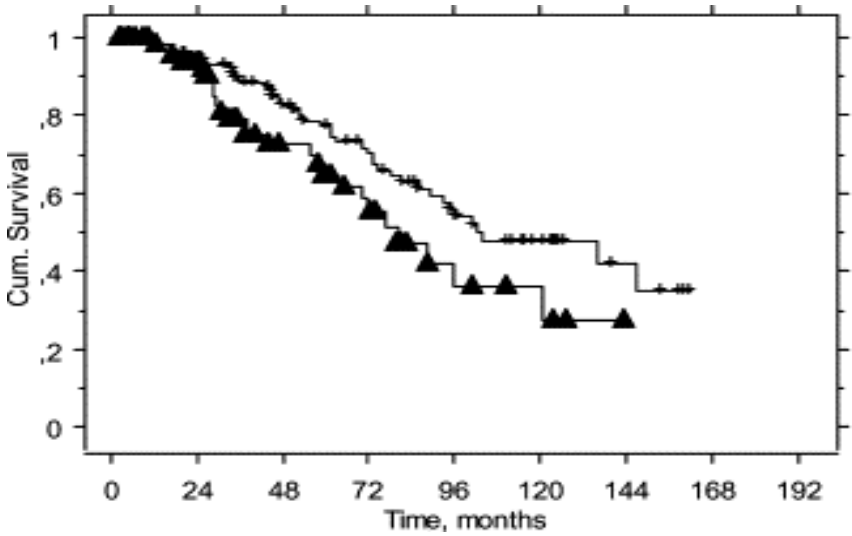
PAPER III

Characteristics of the tumours at diagnosis and primary treatments given are shown in Table 5. Median age at diagnosis was 65 years. Cancer-specific survival was highly variable with a 5-year survival of 72%, a median survival of 8 years and the projected 13-year figure being 31%. T-category, age, PSA or treatment did not affect the outcome while poorly differentiated tumours had a tendency towards lower cancer-specific survival (p = 0.0523) when compared to well- and moderately differentiated tumours, Figure 6.

Table 5. Characteristics of the tumours at diagnosis and primary treatments given.

	Number of patient (%)
T-category	
T1-T2	100 (55,2%)
T3-T4	81 (44,8%)
Tumour grade	
Well differentiated	13 (7,2%)
Moderately differentiated	87 (48,1%)
Poorly differentiated	77 (42,5%)
Unknown	4 (2,2%)
PSA (ng/ml)	
<10	13 (7,2%)
10-30	47 (26,0%)
30-100	45 (24,9%)
>100	16 (8,8%)
Not known	60 (33,1%)
Primary treatments	
Hormonal or expectancy	160 (88,4%)
Radiotherapy or prostatectomy	21 (11,6%)

Figure 6. Cancer-specific survival curve according to tumour differentiation. (A) Well and moderately differentiated, — cumulative survival, + censor times. (B) Poorly differentiated, — cumulative survival, ◎ censor times (p = 0.0523).



PAPER IV

PSA at baseline, relative PSA velocity, ALP at baseline, ALP at 6 months, ALP flare and PSA at 6 months were all significantly associated with death from prostate cancer within 3 years (Table 6). The 3 variables with the best ability to predict survival were ALP at 6 months (AUC 0.79 for PEP and 0.72 for TAB), ALP at baseline (AUC 0.70) and PSA at 6 months (AUC 0.70). The cumulative incidence of death from prostate cancer after 3 years is shown in Table 7. The 2 best predictive variables in the PEP group when the PPLR is calculated were ALP at 6 months <4 μKat/l compared to ALP≥4 μKat/l giving a ratio of 2.61 and a baseline ALP<6 μKat/l compared to ALP≥6 μKat/l giving a ratio of 1.77. The best predictive variables in the TAB group was a baseline ALP<6 μKat/l compared to ALP≥6 μKat/l giving a ratio of 1.88. The second best predictive variable was ALP at 6 months <4 μKat/l compared to ALP≥4 μKat/l giving a ratio of 1.84.

Table 6. Cox regression analysis with unadjusted and adjusted (age, grade and tumor stage) hazard ratios (HR) for the risk for death from metastatic prostate cancer in 697 patients treated with PEP or TAB and calculations with P-values showing if there is any interaction between the covariates and treatment. In the case of interactions, PEP and TAB are separated into different groups. P-value 1 refers to the hazard ratios and P-value 2 refers to the interaction test.

Model Characteristic	Treat-ment	HR (95% CI)	P-value 1	P-value 2	HR adj (95%CI)	P-value 1	P-value 2
logPSA level at baseline, per 1 unit increase	All	1.12 (1.05-1.19)	<0.001	0.33	1.11 (1.04-1.19)	0.001	0.19
Relative PSA velocity per 1 unit increase	All	4.83 (3.55-6.56)	<0.001	0.72	5.23 (3.82-7.18)	<0.001	0.66
ALP at baseline, per 10 unit increase	All	1.18 (1.14-1.22)	<0.001	0.016	1.17 (1.12-1.22)	<0.001	0.051
	PEP	1.16 (1.10-1.22)			1.14 (1.08-1.21)		
	TAB	1.30 (1.19-1.42)			1.29 (1.18-1.41)		
ALP at 6 month per 1 unit increase	All	1.033 (1.027-1.040)	<0.001	0.041	1.037 (1.030-1.044)	<0.001	0.065
	PEP	1.031 (1.023-1.039)			1.033 (1.025-1.042)		
	TAB	1.045 (1.032-1.058)			1.046 (1.032-1.060)		
ALP flare per 1 unit increase	All	1.038 (1.015-1.061)	0.001	0.30	1.039 (1.013-1.065)	0.003	0.83
logPSA at 6 month	All	1.34 (1.28-1.40)	<0.001	0.30	1.36 (1.30-1.43)	<0.001	0.33
per 1 unit increase	PEP	1.33 (1.24-1.42)			1.37 (1.27-1.47)		
	TAB	1.39 (1.30-1.48)			1.42 (1.32-1.52)		

Table 7. Cumulative incidence of lethal prostate cancer at 3 years among 697 patients with metastatic disease, stratified by value of baseline logPSA (ng/ml), relative PSA velocity (1/year), baseline ALP(μKat/l), ALP after 6 months (μKat/l), ALP flare(quotient) and logPSA after 6 months (ng/ml) treated with PEP or TAB and corresponding positive predictive likelihood ratio (PPLR).

	n (%)	**Cumulative incidence 3 years**	**Confidence interval 95%**	**Sensi-tivity**	**1-Speci-ficity**	**PPLR**
log (Baseline PSA)<5.3	315 (45.2)	0.40	(0.34 , 0.46)	0.60	0.51	1.19
log (Baseline PSA)≥5.3	382 (54.8)	0.49	(0.44 , 0.54)			
RelativePSA Velocity < -0.69	269 (38.8)	0.29	(0.23 , 0.35)	0.74	0.50	1.49
Relative PSA Velocity ≥ - 0.69	425 (61.2)	0.55	(0.50 , 0.60)			
Baseline ALP<6 for PEP	185 (53.2)	0.30	(0.23 , 0.36)	0.63	0.36	1.77
Baseline ALP≥6 for PEP	163 (46.8)	0.57	(0.49 , 0.65)			
Baseline ALP<6 for TAB	187 (53.6)	0.34	(0.27 , 0.40)	0.62	0.33	1.88
Baseline ALP≥6 for TAB	162 (46.4)	0.64	(0.56 , 0.72)			
ALP6months<4PEP	198 (57.1)	0.24	(0.18 , 0.30)	0.68	0.26	2.61
ALP6months≥4PEP	149 (42.9)	0.66	(0.58 , 0.74)			
ALP6months<4 TAB	175 (50.3)	0.33	(0.26 , 0.40)	0.66	0.36	1.84
ALP6months≥4 TAB	173 (49.7)	0.63	(0.56 , 0.70)			
ALP flare<1.25	315 (45.3)	0.32	(0.26 , 0.38)	0.68	0.44	1.53
ALP flare≥1.25	380 (54.7)	0.56	(0.50 , 0.62)			
Log(PSA6months<1.1)	334 (48.1)	0.30	(0.25 , 0.35)	0.68	0.39	1.74
Log(PSA6months≥1.1)	360 (51.9)	0.59	(0.54 , 0.64)			

Paper V

Time to nadir, PSA-DT and PSAV were the variables with the highest odds ratios to predict death within 9 months. Log (PSA) at base line, PSA halving time, HRPC age and treatment had no predictive power (Table 8). ALP was excluded from the baseline model since it had no predictive power in the multivariate logistic regression model (data not shown). PSAV gave the highest NRI when added to the baseline model (NRI=0.35, AUC=0.81) followed by time to nadir (NRI=0.27, AUC=0.76) and PSA-DT (NRI=0.25, AUC = 0.76) (Table 9).When all the baseline variables were included in a multivariate model together with PSAV, time to nadir, PSA-DT, and HRPC age, the NRI was 0.39 with an AUC of 0.83 (Table 9). The NRI calculation for the baseline model plus PSAV is shown in Table 10.

Table 8. Univariate logistic regression with odds ratios (OR) and p-values for all variables studied to predict the risk for death within 9 months of diagnosis of hormone refractory-prostate cancer, sd=standard deviation

Model Characteristic	OR (95% CI)	p
Log(PSA) level at baseline, per 1 sd decrease	1.09 (0.89-1.34)	0.39
Soloway score , 1 =reference		
2	2.22 (1.36-3.62)	0.001
3	2.53 (1.24-5.15)	0.011
Hb at baseline per 1 sd decrease	1.60 (1.29-2.00)	<0.001
ALP at baseline per 1 sd increase	1.39 (1.13-1.70)	0.002
PSPA per 1 sd increase	1.45 (1.18-1.78)	<0.001
HRPC age, per 1 sd decrease	1.01 (0.82-1.24)	0.91
Treatment	1.30 (0.86-1.96)	0.22
Time to nadir, per 1 sd decrease	3.51 (2.35-5.24)	<0.001
PSA halving time, per 1 sd increase	1.03 (0.85-1.26)	0.76
PSA-DT, per 1 sd decrease	4.69 (2.59-8.47)	< 0.001
Log(PSA nadir), per 1 sd increase	1.51 (1.22-1.86)	<0.001
Log(PSAV), per 1 sd increase	3.05 (2.33-3.99)	<0.001

Table 9
Net reclassification improvement (NRI) for PSA kinetic variables, HRPC age and treatment when added to the baseline variables. The prognostic ability for each prognostic marker is shown by z-statistics with corresponding p-value and area under the ROC curve (AUC).

	NRI	Z-statistic	p	AUC
Baseline variables and	-	-	-	0.67
PSA nadir	0.09	1.51	0.13	0.70
PSAV	0.35	4.89	<0.001	0.81
Time to nadir	0.27	3.93	<0.001	0.76
Treatment	0.01	0.38	0.70	0.68
PSA halving time	0.00	-0.27	0.78	0.67
PSA-DT	0.25	3.73	<0.001	0.76
HRPC age	0.00	-0.22	0.83	0.67
Multivariate model with the baseline variables and PSAV, PSA-DT, time to nadir and HRPC age	0.39	5.05	<0.001	0.83
Baseline variables and	-	-	-	-
PSA nadir + PSAV	0.34	4.67	<0.001	0.81
PSA nadir + time to nadir	0.25	3.60	<0.001	0.76
PSA nadir + PSA-DT	0.30	4.43	<0.001	0.79
PSAV + time to nadir	0.35	4.76	<0.001	0.82
PSAV + PSA-DT	0.32	4.44	<0.001	0.81
Time to nadir + PSA-DT	0.35	4.84	<0.001	0.80

Table 10
Baseline model and baseline model including PSAV in a net reclassification improvement model. The NRI calculation is shown below the Table. Risk group 1= low risk. Risk group 2=intermediate risk. Risk group 3= high risk

	Baseline model		Baseline model plus PSAV			
			Risk group 1	Risk group 2	Risk group 3	Total
Alive at 9 months	Risk group	1	80	**18**	**6**	104
		2	**64**	28	**27**	119
		3	**19**	**19**	21	59
	Total		163	65	54	282
Dead within 9 months	Risk group	1	10	**3**	**5**	18
		2	**10**	20	**33**	63
		3	**3**	**5**	46	54
	Total		23	28	84	135

For men with no event a change from a lower to a risk higher group (**18+6+27**) when adding PSAV should be interpreted as unfavourable reclassification and a change from a higher to a lower risk group (**64+19+19)** as favourable reclassification.
For men with a recorded event, the interpretation is the opposite: a change from a lower to a higher risk group (**3+5+33**) implies a favourable reclassification and a change from a higher to a lower risk group (**10+3+5**) indicates unfavourable reclassification. The NRI is calculated:
NRI = ((**3+5+33**)/135-(**10+3+5**)/135)-((**18+6+27**)/282-(**64+19+19**)/282)=(**41**/135 - **18**/135) – (**51**/282-**102**/282) = 0.351

DISCUSSION

A newly diagnosed patient with prostate cancer wants to know what lies ahead; he wants to accurately predict his own future and he wants to know if a poor prognosis can be improved by treatment. An accurate prognosis is necessary when planning management of men with localised as well as node-positive and metastatic prostate tumours. Clinical outcome predictions are made by determining how the individual patient relates to other similar men who have been followed over time and whose prognostic factors and clinical outcomes are known. The characteristics of a historical population of men with prostate cancer are thus very important. The ideal is a populations-based cohort that is large enough, and followed up over a period enough to enable prediction of survival. When treatments are compared, the results from randomised controlled trials are superior to other study forms.[145] This thesis is based on data from the validated South-East Region Prostate Cancer Register[136] and from the randomised controlled trial SPCG-5.[139]

Prostate cancer and it's affect on an almost unscreened population

The results from this prospective, population-based study describe the outcomes of 8887 patients with prostate carcinoma in a defined geographic area from 1987 to 1999. Based on these results, it becomes apparent that, when no active screening policy is advocated, prostate carcinoma is a disease that appears to affect mostly elderly males, with >50% of men diagnosed after the age of 75 years, and only 12% of men being <65 years at the time of diagnosis. This may be compared with the results from early-detection programmes in which the average age at diagnosis is 63 years.[146] When the mean age at death is as high as 79.6 years it seems that early detection programmes do not significantly influence the overall survival for these men. They probably die at about the same mean age but of something else, hopefully something less painful than metastatic prostate cancer. The overall cumulative risk for dying from prostate carcinoma after 15 years of follow-up was 56% with the diagnostic and treatment strategy used during this period. The rates for both overall survival and disease-specific survival after 15 years were remarkably similar to those reported by Johansson et al. in their population-based study from Örebro, Sweden[147]. It is very clear that metastatic status, tumour grade, and serum PSA concentration at the time of diagnosis have a close relationship to the risk for dying from prostate cancer.

From this large cohort of 8887 patients we chose two stages of cancer which are not so common today. The best way to acquire enough patients to predict survival in these stages is through large prospective population-based material such as the South-East Region Prostate Cancer Register. We studied men with incidental carcinoma and men with metastasis to the lymph nodules and investigated if it was possible to predict outcome for these men in relation to the variables routinely registered. In the subgroup of men with incidental carcinoma immunohistochemistry was added.

Prediction of survival for men with incidental carcinoma

We examined the long-term outcome of patients with incidental carcinoma of the prostate without known distant metastases and managed conservatively. Our survival data show that only one of 44 patients died of a T1a tumour, which correlates well with the EAU guidelines and previous studies.[100, 113, 148]. In our study we found that there was a statistically significant difference between the Gleason groups regarding survival prediction. In our series, 3/86 patients died of a Gleason 4-5 tumour. This in line with a previous report.[137] Therefore, incidental carcinoma with a Gleason score of 4-5 seems to have a very indolent course and is suitable for watchful waiting. In our report immunohistochemical staining yielded significant prognostic information in univariate analysis, but only Ki-67 immunoreactivity retained the ability to provide independent prognostic information in multivariate analysis. Previous studies of Ki-67 in men with prostate cancer have yielded varying results but most indicated that there is prognostic information to be retrieved when Ki-67 is used in multivariate settings. [107-109] Paper II is however the first to show that Ki-67 provides extra prognostic information in a multivariate setting in incidental carcinoma.

When comparing our material with that of others[80] who studied the natural history of early, population-based, localised prostate cancer, we conclude that the mortality rate due to early prostate cancer in this relatively old population followed up without curative intent was 16-17%. However, when life expectancy is taken into account, as in the Kaplan- Meier analysis, even patients in the most favourable group (those with Gleason 4-6 score) may also have a substantial risk for dying from their disease if they live long enough. This is also clearly shown in the Örebro study. [80]

Prediction of survival for men with lymph node metastases

We describe the outcome for a consecutive, population-based group of patients found to have lymph node metastases at staging pelvic lymphadenectomy. The management was mainly without curative intent. The vast majority of patients who succumbed during the follow-up period did so due to prostate cancer indicating the aggressiveness of the disease. The cancer-specific survival for patients with nodal metastases is unpredictable with a projected 28% cancer-specific mortality at 5 years, a median survival of about 8 years and 31% still alive after 13 years. We failed to find any clinically significant relationship to ultimate outcome of preoperatively known factors such as serum PSA, T-category, age, mode of treatment but there was a weak, not statistically significant difference in cancer-specific survival in relation to tumour grade. It seems that when lymph node metastases are present, this overrides the common prognostic factors. These findings are in line with previous reports.[86, 87]

The prognosis of men with bone metastasis is generally poor, but as seen in Figure 4 there are a number of men living more than two years. We wanted to predict their survival after treatment start but this information is not possible to retrieve from the South-East Region Prostate Cancer Register, since the register does not record variables routinely measured at follow-up. For this purpose we used data from SPCG-5.

Prediction of survival of metastatic prostate cancer based on early serial measurements of PSA and ALP

We studied how serial measurements of PSA and ALP can be used to predict survival early in the course of hormone-treated metastatic prostate cancer. PSA[117-119, 149, 150] has been used as a marker of total tumour burden and ALP[122-124, 151] as a marker of skeletal involvement. However, these studies have provided conflicting results. The early course of PSA and ALP may not only provide information on initial tumour burden and skeletal involvement, but also on the response to hormone treatment and predict long-term outcome. A high ALP flare is associated with a poor outcome.[124, 152, 153] By using ROC curves and the corresponding AUC we can determine the prognostic value of each variable. Our model provides the possibility of observing what happens to sensitivity and specificity at various cut-off points and emphasises the importance of PSA and ALP as prognostic factors in metastasising prostate cancer. The cut-off levels presented in our study have been chosen arbitrarily as examples of the trade-off between sensitivity and specificity. Some of the curves achieved can be used as strong predictors of survival, in particular baseline ALP, ALP and PSA 6 months after start of treatment. We also found that PSA and ALP levels 6 months after start of treatment give better prediction of survival than the baseline levels. The strong prognostic value of ALP after 6 months has not to our knowledge been described before. We recommend that the ALP level after 6 months of treatment is included in the follow-up of every patient where prognostic information is required. The interpretation of normalisation of ALP after 6 months is that treatment has been effective and that tumor activity in the skeleton is low which in turn implies longer survival. In recent years there have not only been different forms of androgen deprivation therapy but also new chemotherapy drugs such as docetaxel that could prolong survival in men with metastatic disease.[71-73] Unfortunately the general condition of the patient has often deteriorated too much when the question of chemotherapy is raised. As the men in our study were in good to fair performance status according to the WHO classification, they could be considered potential candidates for chemotherapy early on in the course of their disease. In a systematic review by Lucas et al. it was concluded that prognostic markers are important in the selection of patients with metastatic disease for early therapy.[154] However, aggressive chemotherapy should be avoided in men with long survival on hormone treatment alone to avoid the side-effects of chemotherapy. By assessing these markers according to the principles presented in this study, we believe it is possible to select patients with poor prognosis after 6 months of

treatment. However, the optimal timing of treatment is an issue that still lacks a reliable evidence base.

PSA kinetics provide improved prediction of survival in metastatic HRPC

We assessed the value of PSA kinetics in predicting survival and related this to baseline variables in men with metastatic HRPC. Several nomograms have been developed to predict prostate cancer-related outcomes and have proved to be of great use in treatment decision-making.[125] There are two nomograms for prediction of survival in men with metastatic HRPC, both using pretreatment variables only. [126, 127]

When introducing a new prognostic marker the predictive ability of the markers that are already established in clinical practice should be considered as benchmarks for comparison. By quantifying any improvement using NRI the clinical value of the new marker can be determined. The AUC in the previous studies were 0.71 and 0.69. Our results showed the baseline model to provide prognostic information with an AUC of 0.67, but when PSAV was added to the model the NRI was 0.35 and the AUC became 0.81. This implies that PSAV gives a reliable prediction of survival in men with HRPC. When all combinations of PSA kinetic variables were tested the maximum NRI was found to be 0.39 and the corresponding AUC 0.83 in the multivariate model. Since PSAV alone gave almost the same increase as all other variables put together, this variable may be considered a major predictor of disease course in clinical practice as well as in research.

Conclusions Paper I
In an almost unscreened population the median patient age at diagnosis and death is 75 and 80 years respectively, 12% of patients were diagnosed before the age of 65. The projected 15-year disease-specific survival rate was 44% for the whole population. In total, 18% of patients had metastases at diagnosis, and their median survival was 2.5 years. A high tumour grade, a high serum PSA and a poor T-classification predicted a worse outcome.

Conclusions Paper II
Elderly men with category T1a and/or Gleason score 4-5 prostate cancer have a favourable prognosis with conservative management. Immunohistochemical staining with Ki-67 may be of help in situations where further prognostic information is required.

Conclusions Paper III
This population-based cohort of prostate cancer patients with pelvic lymph node involvement treated principally with non-curative intent had a median cancer-specific survival of 8 years. We failed to find any clinically significant relationship to ultimate outcome of preoperatively known factors such as serum PSA, T-category, age, and mode of treatment, but there was a weak, not statistically significant difference in cancer-specific survival in relation to tumour grade. It seems that when lymph node metastases are present, this overrides the common prognostic factors.

Conclusions Paper IV
Initial ALP and ALP and PSA after 6 months of treatment are serum markers that provide prognostic information about the probable long-term outcome of metastatic prostate cancer. They give a much better prediction than baseline PSA, for example, and help to select men with a poor prognosis.

Conclusions Paper V
PSAV alone has a better prediction of survival value than all other PSA kinetics variables. By combining PSAV with the variables available at baseline, a better foundation for treatment decision-making in men with HRPC is achieved. Together with other variables available prior to start of treatment, PSAV may be helpful in clinical decision-making as well as stratification in clinical studies.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all those who have contributed to the completion of this thesis. In particular I would like to acknowledge:

Eberhard Varenhorst, for being an excellent tutor, for guiding me through this project and for his never failing enthusiasm regarding prostate cancer research.

Gunnar Aus for introducing me to research and for always being positive and willing to share his huge knowledge in the field of prostate cancer. Thank you for all your friendly support!

Gabriel Sandblom for always taking time to read what I have written and to make clear suggestions on how to improve our work.

Johan Rosell for helping me with the statistical sections and always having time to explain when I pondered over our results.

Hans Garmo for sharing his excellent statistical knowledge and his willingness to explain things when I could not understand how our results were derived.

Robert Johansson for never saying no to endless calculations and for helping me to interpret our results.

Julia Bak, Thomasz Gorecki and **Anders Herder** for the histopathology interpretations.

Pelle Larsson for being the nice chap he is and a magician with boring but necessary papers.

Staffan Jahnsson and **Kurt Borch** for helping me when the bureaucracy became hard to handle.

All present and previous members of the South-East Region Prostate Cancer Committee.

All members of the Scandinavian Prostate Cancer Group nr 5.

P-O Hedlund for letting us use the material from SPCG-5.

Per-Olof Nostell for introducing me into the world of hunting, retrievers and urology.

Carsten Berg, Eibert Einarsson, Karsten Offenbartl, Hans Ravn and **Göran Simert** for teaching me surgery.

Carl-Gustav Hermansson, **Bruno Larsson**, and **Peter Ströberg** for teaching me how to do a proper prostatectomy and always having time for debriefing afterwards.

Axel Ros for never asking if it was necessary for me to be elsewhere doing research and for pointing me towards Futurum and their ability to finance this project.

Peter Cox for fast and skilful language improvement.

To all the staff at Ryhov medical library for always helping me with the right papers at the right time.

This work has been supported by grants from **Futurum, Jönköpings läns landsting** and from the **Health Research Council of South-East of Sweden**.

Funding of SPCG-5 study was provided by Ferring AB, Malmö, Sweden; Pharmacia AB, Sweden; and Schering-Plough AB, Stockholm, Sweden.

Kristina Lindkvist for helping me with the computer whenever it did new and wicked things, and for never complaining while I was preparing this thesis.

Alva and Kerstin for being marvellous daughters reminding me that there are greater things in life than preparing a thesis.

REFERENCES

1. The national prostate cancer register (NPCR) in Sweden 2006: www.roc.se/prostata/rapport/rapport_02_06.pdf, 2007

2. The national board of health and welfare. Causes of death 1996-2005.: http://192.137.163.40/epcfs/DorRes.asp, 2007

3. Stattin, P., Berglund, A., Bratt, O., Adolfsson, J.: Trendbrott:Antalet nya fall av prostatacancer går ner i Sverige. http://www.roc.se/prostata/nyhetsbrev/nr_5.pdf, 2008

4. Ferlay, J., Autier, P., Boniol, M., Heanue, M., Colombet, M., Boyle, P.: Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol, **18:** 581-592, 2007

5. Jemal, A., Siegel, R., Ward, E., Murray, T., Xu, J., Thun, M. J.: Cancer statistics, 2007. CA Cancer J Clin, **57:** 43-66, 2007

6. Houtappel, H. C.: Carcinoma of the prostate. Arch Chir Neerl, **2:** 246-260, 1950

7. Carvalhal, G. F., Smith, D. S., Mager, D. E., Ramos, C., Catalona, W. J.: Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng/ml. or less. J Urol, **161:** 835-839, 1999

8. Eastham, J. A., May, R., Robertson, J. L., Sartor, O., Kattan, M. W.: Development of a nomogram that predicts the probability of a positive prostate biopsy in men with an abnormal digital rectal examination and a prostate-specific antigen between 0 and 4 ng/mL. Urology, **54:** 709-713, 1999

9. Catalona, W. J., Richie, J. P., deKernion, J. B., Ahmann, F. R., Ratliff, T. L., Dalkin, B. L., Kavoussi, L. R., MacFarlane, M. T., Southwick, P. C.: Comparison of prostate specific antigen concentration versus prostate specific antigen density in the early detection of prostate cancer: receiver operating characteristic curves. J Urol, **152:** 2031-2036, 1994

10. Stamey, T. A., Yang, N., Hay, A. R., McNeal, J. E., Freiha, F. S., Redwine, E.: Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med, **317:** 909-916, 1987

11. Aus, G., Becker, C., Franzen, S., Lilja, H., Lodding, P., Hugosson, J.: Cumulative prostate cancer risk assessment with the aid of the free-to-total prostate specific antigen ratio. Eur Urol, **45:** 160-165, 2004

12. Thompson, I. M., Pauler, D. K., Goodman, P. J., Tangen, C. M., Lucia, M. S., Parnes, H. L., Minasian, L. M., Ford, L. G., Lippman, S. M., Crawford, E. D., Crowley, J. J., Coltman, C. A., Jr.: Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med, **350:** 2239-2246, 2004

13. Benson, M. C., Whang, I. S., Pantuck, A., Ring, K., Kaplan, S. A., Olsson, C. A., Cooner, W. H.: Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol, **147:** 815-816, 1992

14. Zlotta, A. R., Djavan, B., Marberger, M., Schulman, C. C.: Prostate specific antigen density of the transition zone: a new effective parameter for prostate cancer prediction. J Urol, **157:** 1315-1321, 1997

15. Oesterling, J. E., Jacobsen, S. J., Chute, C. G., Guess, H. A., Girman, C. J., Panser, L. A., Lieber, M. M.: Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. Jama, **270:** 860-864, 1993

16. Catalona, W. J., Smith, D. S., Wolfert, R. L., Wang, T. J., Rittenhouse, H. G., Ratliff, T. L., Nadler, R. B.: Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. Jama, **274:** 1214-1220, 1995

17. Okihara, K., Cheli, C. D., Partin, A. W., Fritche, H. A., Chan, D. W., Sokoll, L. J., Brawer, M. K., Schwartz, M. K., Vessella, R. L., Loughlin, K. R., Johnston, D. A., Babaian, R. J.: Comparative analysis of complexed prostate specific antigen, free prostate specific antigen and their ratio in detecting prostate cancer. J Urol, **167:** 2017-2023; discussion 2023-2014, 2002

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

19. Carter, H. B., Pearson, J. D., Metter, E. J., Brant, L. J., Chan, D. W., Andres, R., Fozard, J. L., Walsh, P. C.: Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. Jama, **267:** 2215-2220, 1992

20. Schmid, H. P., McNeal, J. E., Stamey, T. A.: Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer, **71:** 2031-2040, 1993

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

22. Collins, G. N., Lloyd, S. N., Hehir, M., McKelvie, G. B.: Multiple transrectal ultrasound-guided prostatic biopsies--true morbidity and patient acceptance. Br J Urol, **71:** 460-463, 1993

23. Hodge, K. K., McNeal, J. E., Terris, M. K., Stamey, T. A.: Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol, **142:** 71-74; discussion 74-75, 1989

24. Eskew, L. A., Bare, R. L., McCullough, D. L.: Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol, **157:** 199-202; discussion 202-193, 1997

25. Applewhite, J. C., Matlaga, B. R., McCullough, D. L.: Results of the 5 region prostate biopsy method: the repeat biopsy population. J Urol, **168:** 500-503, 2002

26. Roehrborn, C. G., Pickens, G. J., Sanders, J. S.: Diagnostic yield of repeated transrectal ultrasound-guided biopsies stratified by specific histopathologic diagnoses and prostate specific antigen levels. Urology, **47:** 347-352, 1996

27. Djavan, B., Ravery, V., Zlotta, A., Dobronski, P., Dobrovits, M., Fakhari, M., Seitz, C., Susani, M., Borkowski, A., Boccon-Gibod, L., Schulman, C. C., Marberger, M.: Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? J Urol, **166:** 1679-1683, 2001

28. Mostofi, F. K.: Grading of prostatic carcinoma. Cancer Chemother Rep, **59:** 111-117, 1975

29. Gleason, D. F., Mellinger, G. T.: Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol, **111:** 58-64, 1974

30. Epstein, J. I., Allsbrook, W. C., Jr., Amin, M. B., Egevad, L. L.: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol, **29:** 1228-1242, 2005

31. UICC (Union internationale Contre le Cancer). TNM Classification of Malignant Tumours., 6th ed. Geneva (Switzerland): International Union Against Cancer, 2002

32. Heenan, S. D.: Magnetic resonance imaging in prostate cancer. Prostate Cancer Prostatic Dis, **7:** 282-288, 2004

33. Partin, A. W., Mangold, L. A., Lamm, D. M., Walsh, P. C., Epstein, J. I., Pearson, J. D.: Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology, **58:** 843-848, 2001

34. Heesakkers, R. A., Futterer, J. J., Hovels, A. M., van den Bosch, H. C., Scheenen, T. W., Hoogeveen, Y. L., Barentsz, J. O.: Prostate cancer evaluated with ferumoxtran-10-enhanced T2*-weighted MR Imaging at 1.5 and 3.0 T: early experience. Radiology, **239:** 481-487, 2006

35. de Jong, I. J., Pruim, J., Elsinga, P. H., Vaalburg, W., Mensink, H. J.: Preoperative staging of pelvic lymph nodes in prostate cancer by 11C-choline PET. J Nucl Med, **44:** 331-335, 2003

36. McGregor, B., Tulloch, A. G., Quinlan, M. F., Lovegrove, F.: The role of bone scanning in the assessment of prostatic carcinoma. Br J Urol, **50:** 178-181, 1978

37. O'Donoghue, E. P., Constable, A. R., Sherwood, T., Stevenson, J. J., Chisholm, G. D.: Bone scanning and plasma phosphatases in carcinoma of the prostate. Br J Urol, **50:** 172-177, 1978

38. Lecouvet, F. E., Geukens, D., Stainier, A., Jamar, F., Jamart, J., d'Othee, B. J., Therasse, P., Vande Berg, B., Tombal, B.: Magnetic resonance imaging of the axial skeleton for detecting bone metastases in patients with high-risk prostate cancer: diagnostic and cost-effectiveness and comparison with current detection strategies. J Clin Oncol, **25:** 3281-3287, 2007

39. Stenman, U. H., Abrahamsson, P. A., Aus, G., Lilja, H., Bangma, C., Hamdy, F. C., Boccon-Gibod, L., Ekman, P.: Prognostic value of serum markers for prostate cancer. Scand J Urol Nephrol Suppl**:** 64-81, 2005

40. Sandblom, G., Holmberg, L., Damber, J. E., Hugosson, J., Johansson, J. E., Lundgren, R., Mattsson, E., Nilsson, J., Varenhorst, E.: Prostate-specific antigen for prostate cancer staging in a population-based register. Scand J Urol Nephrol, **36:** 99-105, 2002

41. Bruwer, G., Heyns, C. F., Allen, F. J.: Influence of local tumour stage and grade on reliability of serum prostate-specific antigen in predicting skeletal metastases in patients with adenocarcinoma of the prostate. Eur Urol, **35:** 223-227, 1999

42. Wolff, J. M., Zimny, M., Borchers, H., Wildberger, J., Buell, U., Jakse, G.: Is prostate-specific antigen a reliable marker of bone metastasis in patients with newly diagnosed cancer of the prostate? Eur Urol, **33:** 376-381, 1998

43. Bill-Axelson, A., Holmberg, L., Ruutu, M., Haggman, M., Andersson, S. O., Bratell, S., Spangberg, A., Busch, C., Nordling, S., Garmo, H., Palmgren, J., Adami, H. O., Norlen, B. J., Johansson, J. E.: Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med, **352:** 1977-1984, 2005

44. Hull, G. W., Rabbani, F., Abbas, F., Wheeler, T. M., Kattan, M. W., Scardino, P. T.: Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol, **167:** 528-534, 2002

45. Hernandez, D. J., Nielsen, M. E., Han, M., Trock, B. J., Partin, A. W., Walsh, P. C., Epstein, J. I.: Natural history of pathologically organ-confined (pT2), Gleason score 6 or less, prostate cancer after radical prostatectomy. Urology, **72:** 172-176, 2008

46. Ward, J. F., Slezak, J. M., Blute, M. L., Bergstralh, E. J., Zincke, H.: Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int, **95:** 751-756, 2005

47. Hsu, C. Y., Joniau, S., Oyen, R., Roskams, T., Van Poppel, H.: Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol, **51:** 121-128; discussion 128-129, 2007

48. Nilsson, S., Norlen, B. J., Widmark, A.: A systematic overview of radiation therapy effects in prostate cancer. Acta Oncol, **43:** 316-381, 2004

49. Deger, S., Boehmer, D., Turk, I., Roigas, J., Wernecke, K. D., Wiegel, T., Hinkelbein, W., Dinges, S., Budach, V., Loening, S. A.: High dose rate brachytherapy of localized prostate cancer. Eur Urol, **41:** 420-426, 2002

50. Klotz, L.: Active surveillance with selective delayed intervention for favorable risk prostate cancer. Urol Oncol, **24:** 46-50, 2006

51. Klotz, L.: Active surveillance with selective delayed intervention: using natural history to guide treatment in good risk prostate cancer. J Urol, **172:** S48-50; discussion S50-41, 2004

52. Chodak, G. W., Thisted, R. A., Gerber, G. S., Johansson, J. E., Adolfsson, J., Jones, G. W., Chisholm, G. D., Moskovitz, B., Livne, P. M., Warner, J.: Results of conservative management of clinically localized prostate cancer. N Engl J Med, **330:** 242-248, 1994

53. Huggins, C., Hodges, C.: Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res, **1:** 293-297, 1941

54. Denmeade, S. R., Lin, X. S., Isaacs, J. T.: Role of programmed (apoptotic) cell death during the progression and therapy for prostate cancer. Prostate, **28:** 251-265, 1996

55. Heidenreich, A., Aus, G., Bolla, M., Joniau, S., Matveev, V. B., Schmid, H. P., Zattoni, F.: EAU Guidelines on Prostate Cancer. http://www.uroweb.org/fileadmin/tx_eauguidelines/Prostate%20Cancer.pdf, 2007

56. Oh, W. K.: The evolving role of estrogen therapy in prostate cancer. Clin Prostate Cancer, **1:** 81-89, 2002

57. Hedlund, P. O., Damber, J. E., Hagerman, I., Haukaas, S., Henriksson, P., Iversen, P., Johansson, R., Klarskov, P., Lundbeck, F., Rasmussen, F., Varenhorst, E., Viitanen, J.: Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. Scand J Urol Nephrol, **42:** 220-229, 2008

58. Anderson, J.: The role of antiandrogen monotherapy in the treatment of prostate cancer. BJU Int, **91:** 455-461, 2003

59. Fowler, J. E., Jr., Pandey, P., Seaver, L. E., Feliz, T. P.: Prostate specific antigen after gonadal androgen withdrawal and deferred flutamide treatment. J Urol, **154:** 448-453, 1995

60. Schmitt, B., Bennett, C., Seidenfeld, J., Samson, D., Wilt, T.: Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev**:** CD001526, 2000

61. Kelly, W. K., Scher, H. I.: Prostate specific antigen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome. J Urol, **149:** 607-609, 1993

62. Small, E. J., Carroll, P. R.: Prostate-specific antigen decline after casodex withdrawal: evidence for an antiandrogen withdrawal syndrome. Urology, **43:** 408-410, 1994

63. Jordan, W. P., Jr., Blackard, C. E., Byar, D. P.: Reconsideration of orchiectomy in the treatment of advanced prostatic carcinoma. South Med J, **70:** 1411-1413, 1977

64. Byar, D. P.: Proceedings: The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. Cancer, **32:** 1126-1130, 1973

65. Messing, E. M., Manola, J., Sarosdy, M., Wilding, G., Crawford, E. D., Trump, D.: Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med, **341:** 1781-1788, 1999

66. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol, **79:** 235-246, 1997

67. Nair, B., Wilt, T., MacDonald, R., Rutks, I.: Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev**:** CD003506, 2002

68. Messing, E. M., Manola, J., Yao, J., Kiernan, M., Crawford, D., Wilding, G., di'SantAgnese, P. A., Trump, D.: Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol, **7:** 472-479, 2006

69. Kantoff, P. W., Halabi, S., Conaway, M., Picus, J., Kirshner, J., Hars, V., Trump, D., Winer, E. P., Vogelzang, N. J.: Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol, **17:** 2506-2513, 1999

70. Tannock, I. F., Osoba, D., Stockler, M. R., Ernst, D. S., Neville, A. J., Moore, M. J., Armitage, G. R., Wilson, J. J., Venner, P. M., Coppin, C. M., Murphy, K. C.: Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol, **14:** 1756-1764, 1996

71. Fossa, S. D., Jacobsen, A. B., Ginman, C., Jacobsen, I. N., Overn, S., Iversen, J. R., Urnes, T., Dahl, A. A., Veenstra, M., Sandstad, B.: Weekly Docetaxel and Prednisolone versus Prednisolone Alone in Androgen-Independent Prostate Cancer: A Randomized Phase II Study. Eur Urol, 2007

72. Tannock, I. F., de Wit, R., Berry, W. R., Horti, J., Pluzanska, A., Chi, K. N., Oudard, S., Theodore, C., James, N. D., Turesson, I., Rosenthal, M. A., Eisenberger, M. A.: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med, **351:** 1502-1512, 2004

73. Petrylak, D. P., Tangen, C. M., Hussain, M. H., Lara, P. N., Jr., Jones, J. A., Taplin, M. E., Burch, P. A., Berry, D., Moinpour, C., Kohli, M., Benson, M. C., Small, E. J., Raghavan, D., Crawford, E. D.: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med, **351:** 1513-1520, 2004

74. Scher, H. I., Steineck, G., Kelly, W. K.: Hormone-refractory (D3) prostate cancer: refining the concept. Urology, **46:** 142-148, 1995

75. Mike, S., Harrison, C., Coles, B., Staffurth, J., Wilt, T. J., Mason, M. D.: Chemotherapy for hormone-refractory prostate cancer. Cochrane Database Syst Rev**:** CD005247, 2006

76. Scher, H. I., Mazumdar, M., Kelly, W. K.: Clinical trials in relapsed prostate cancer: defining the target. J Natl Cancer Inst, **88:** 1623-1634, 1996

77. Bubley, G. J., Carducci, M., Dahut, W., Dawson, N., Daliani, D., Eisenberger, M., Figg, W. D., Freidlin, B., Halabi, S., Hudes, G., Hussain, M., Kaplan, R., Myers, C., Oh, W., Petrylak, D. P., Reed, E., Roth, B., Sartor, O., Scher, H., Simons, J., Sinibaldi, V., Small, E. J., Smith, M. R., Trump, D. L., Wilding, G., et al.: Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol, **17:** 3461-3467, 1999

78. Ryan, C. J., Small, E. J.: Role of secondary hormonal therapy in the management of recurrent prostate cancer. Urology, **62 Suppl 1:** 87-94, 2003

79. Smith, D. C., Redman, B. G., Flaherty, L. E., Li, L., Strawderman, M., Pienta, K. J.: A phase II trial of oral diethylstilbesterol as a second-line hormonal agent in advanced prostate cancer. Urology, **52:** 257-260, 1998

80. Johansson, J. E., Andren, O., Andersson, S. O., Dickman, P. W., Holmberg, L., Magnuson, A., Adami, H. O.: Natural history of early, localized prostate cancer. Jama, **291:** 2713-2719, 2004

81. Epstein, J. I., Paull, G., Eggleston, J. C., Walsh, P. C.: Prognosis of untreated stage A1 prostatic carcinoma: a study of 94 cases with extended followup. J Urol, **136:** 837-839, 1986

82. Blute, M. L., Zincke, H., Farrow, G. M.: Long-term followup of young patients with stage A adenocarcinoma of the prostate. J Urol, **136:** 840-843, 1986

83. Zhang, G., Wasserman, N. F., Sidi, A. A., Reinberg, Y., Reddy, P. K.: Long-term followup results after expectant management of stage A1 prostatic cancer. J Urol, **146:** 99-102; discussion 102-103, 1991

84. Roy, C. R., 2nd, Horne, D., Raife, M., Pienkos, E.: Incidental carcinoma of prostate, Long-term follow-up. Urology, **36:** 210-213, 1990

85. Thompson, I. M., Zeidman, E. J.: Extended follow-up of stage A1 carcinoma of prostate. Urology, **33:** 455-458, 1989

86. Davidson, P. J., Hop, W., Kurth, K. H., Fossa, S. D., Waehre, H., Schroder, F. H.: Progression in untreated carcinoma of the prostate metastatic to regional lymph nodes (stage t0 to 4,N1 to 3.M0,D1). European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol, **154:** 2118-2122, 1995

87. Zagars, G. K., Sands, M. E., Pollack, A., von Eschenbach, A. C.: Early androgen ablation for stage D1 (N1 to N3, M0) prostate cancer: prognostic variables and outcome. J Urol, **151:** 1330-1333, 1994

88. Ryan, C. J., Elkin, E. P., Cowan, J., Carroll, P. R.: Initial treatment patterns and outcome of contemporary prostate cancer patients with bone metastases at initial presentation: data from CaPSURE. Cancer, **110:** 81-86, 2007

89. Hedlund, P. O., Ala-Opas, M., Brekkan, E., Damber, J. E., Damber, L., Hagerman, I., Haukaas, S., Henriksson, P., Iversen, P., Pousette, A., Rasmussen, F., Salo, J., Vaage, S., Varenhorst, E.: Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer -- Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. Scand J Urol Nephrol, **36:** 405-413, 2002

90. de Voogt, H. J., Studer, U., Schroder, F. H., Klijn, J. G., de Pauw, M., Sylvester, R.: Maximum androgen blockade using LHRH agonist buserelin in combination with short-term (two weeks) or long-term (continuous) cyproterone acetate is not superior to standard androgen deprivation in the treatment of advanced prostate cancer. Final analysis of EORTC GU Group Trial 30843. European Organization for Research and Treatment of Cancer (EROTC) Genito-Urinary Tract Cancer Cooperative Group. Eur Urol, **33:** 152-158, 1998

91. Denis, L. J., Keuppens, F., Smith, P. H., Whelan, P., de Moura, J. L., Newling, D., Bono, A., Sylvester, R.: Maximal androgen blockade: final analysis of EORTC phase III trial 30853. EORTC Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center. Eur Urol, **33:** 144-151, 1998

92. Glass, T. R., Tangen, C. M., Crawford, E. D., Thompson, I.: Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol, **169:** 164-169, 2003

93. Collette, L., de Reijke, T. M., Schroder, F. H.: Prostate specific antigen: a prognostic marker of survival in good prognosis metastatic prostate cancer? (EORTC 30892). Eur Urol, **44:** 182-189; discussion 189, 2003

94. Gronberg, H., Damber, L., Jonson, H., Damber, J. E.: Prostate cancer mortality in northern Sweden, with special reference to tumor grade and patient age. Urology, **49:** 374-378, 1997

95. Borre, M., Nerstrom, B., Overgaard, J.: The natural history of prostate carcinoma based on a Danish population treated with no intent to cure. Cancer, **80:** 917-928, 1997

96. Jonsson, E., Sigbjarnarson, H. P., Tomasson, J., Benediktsdottir, K. R., Tryggvadottir, L., Hrafnkelsson, J., Olafsdottir, E. J., Tulinius, H., Jonasson, J. G.: Adenocarcinoma of the prostate in Iceland: a population-based study of stage, Gleason grade, treatment and long-term survival in males diagnosed between 1983 and 1987. Scand J Urol Nephrol, **40:** 265-271, 2006

97. Sandblom, G., Dufmats, M., Varenhorst, E.: Long-term survival in a Swedish population-based cohort of men with prostate cancer. Urology, **56:** 442-447, 2000

98. Fowler, J. E., Jr., Pandey, P., Bigler, S. A., Yee, D. T., Kolski, J. M.: Trends in diagnosis of stage T1a-b prostate cancer. J Urol, **158:** 1849-1852, 1997

99. Soh, S., Kattan, M. W., Berkman, S., Wheeler, T. M., Scardino, P. T.: Has there been a recent shift in the pathological features and prognosis of patients treated with radical prostatectomy? J Urol, **157:** 2212-2218, 1997

100. Tombal, B., De Visccher, L., Cosyns, J. P., Lorge, F., Opsomer, R., Wese, F. X., Van Cangh, P. J.: Assessing the risk of unsuspected prostate cancer in patients with benign prostatic hypertrophy: a 13-year retrospective study of the incidence and natural history of T1a-T1b prostate cancers. BJU Int, **84:** 1015-1020, 1999

101. Zigeuner, R. E., Lipsky, K., Riedler, I., Auprich, M., Schips, L., Salfellner, M., Pummer, K., Hubmer, G.: Did the rate of incidental prostate cancer change in the era of PSA testing? A retrospective study of 1127 patients. Urology, **62:** 451-455, 2003

102. Lowe, B. A.: Management of stage T1a prostate cancer. Semin Urol Oncol, **14:** 178-182, 1996

103. Loughlin, K. R., Renshaw, A. A., Kumar, S.: Expectant management of stage A-1 (T1a) prostate cancer utilizing serum PSA levels: a preliminary report. J Surg Oncol, **70:** 49-53, 1999

104. Andren, O., Fall, K., Franzen, L., Andersson, S. O., Johansson, J. E., Rubin, M. A.: How well does the Gleason score predict prostate cancer death? A 20-year followup of a population based cohort in Sweden. J Urol, **175:** 1337-1340, 2006

105. Scholzen, T., Gerdes, J.: The Ki-67 protein: from the known and the unknown. J Cell Physiol, **182:** 311-322, 2000

106. Feneley, M. R., Young, M. P., Chinyama, C., Kirby, R. S., Parkinson, M. C.: Ki-67 expression in early prostate cancer and associated pathological lesions. J Clin Pathol, **49:** 741-748, 1996

107. Josefsson, A., Wikstrom, P., Granfors, T., Egevad, L., Karlberg, L., Stattin, P., Bergh, A.: Tumor size, vascular density and proliferation as prognostic markers in GS 6 and GS 7 prostate tumors in patients with long follow-up and non-curative treatment. Eur Urol, **48:** 577-583, 2005

108. Stattin, P., Damber, J. E., Karlberg, L., Bergh, A.: Cell proliferation assessed by Ki-67 immunoreactivity on formalin fixed tissues is a predictive factor for survival in prostate cancer. J Urol, **157:** 219-222, 1997

109. Aaltomaa, S., Lipponen, P., Vesalainen, S., Ala-Opas, M., Eskelinen, M., Syrjanen, K.: Value of Ki-67 immunolabelling as a prognostic factor in prostate cancer. Eur Urol, **32:** 410-415, 1997

110. Levine, A. J., Momand, J., Finlay, C. A.: The p53 tumour suppressor gene. Nature, **351:** 453-456, 1991

111. Hollstein, M., Sidransky, D., Vogelstein, B., Harris, C. C.: p53 mutations in human cancers. Science, **253:** 49-53, 1991

112. Abaza, R., Diaz, L. K., Jr., Laskin, W. B., Pins, M. R.: Prognostic value of DNA ploidy, bcl-2 and p53 in localized prostate adenocarcinoma incidentally discovered at transurethral prostatectomy. J Urol, **176:** 2701-2705, 2006

113. Cheng, L., Bergstralh, E. J., Scherer, B. G., Neumann, R. M., Blute, M. L., Zincke, H., Bostwick, D. G.: Predictors of cancer progression in T1a prostate adenocarcinoma. Cancer, **85:** 1300-1304, 1999

114. di Sant'Agnese, P. A.: Neuroendocrine differentiation in carcinoma of the prostate. Diagnostic, prognostic, and therapeutic implications. Cancer, **70:** 254-268, 1992

115. Theodoropoulos, V. E., Tsigka, A., Mihalopoulou, A., Tsoukala, V., Lazaris, A. C., Patsouris, E., Ghikonti, I.: Evaluation of neuroendocrine staining and androgen receptor expression in incidental prostatic adenocarcinoma: prognostic implications. Urology, **66:** 897-902, 2005

116. Soloway, M. S., Hardeman, S. W., Hickey, D., Raymond, J., Todd, B., Soloway, S., Moinuddin, M.: Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer, **61:** 195-202, 1988

117. Reynard, J. M., Peters, T. J., Gillatt, D.: Prostate-specific antigen and prognosis in patients with metastatic prostate cancer--a multivariable analysis of prostate cancer mortality. Br J Urol, **75:** 507-515, 1995

118. Ernst, D. S., Hanson, J., Venner, P. M.: Analysis of prognostic factors in men with metastatic prostate cancer. Uro-Oncology Group of Northern Alberta. J Urol, **146:** 372-376, 1991

119. Furuya, Y., Akakura, K., Tobe, T., Ichikawa, T., Igarashi, T., Ito, H.: Prognostic significance of changes in prostate-specific antigen in patients with metastasis prostate cancer after endocrine treatment. Int Urol Nephrol, **32:** 659-663, 2001

120. Cooper, E. H., Armitage, T. G., Robinson, M. R., Newling, D. W., Richards, B. R., Smith, P. H., Denis, L., Sylvester, R.: Prostatic specific antigen and the prediction of prognosis in metastatic prostatic cancer. Cancer, **66:** 1025-1028, 1990

121. Figg, W. D., Franks, M. E., Venzon, D., Duray, P., Cox, M. C., Linehan, W. M., Van Bingham, W., Eastham, J. A., Reed, E., Sartor, O.: Gleason score and pretreatment prostate-specific antigen in survival among patients with stage D2 prostate cancer. World J Urol, **22:** 425-430, 2004

122. Nakashima, J., Ozu, C., Nishiyama, T., Oya, M., Ohigashi, T., Asakura, H., Tachibana, M., Murai, M.: Prognostic value of alkaline phosphatase flare in patients with metastatic prostate cancer treated with endocrine therapy. Urology, **56:** 843-847, 2000

123. Smith, J. A., Jr., Lange, P. H., Janknegt, R. A., Abbou, C. C., deGery, A.: Serum markers as a predictor of response duration and patient survival after hormonal therapy for metastatic carcinoma of the prostate. J Urol, **157:** 1329-1334, 1997

124. Pelger, R. C., Lycklama, A. N. G. A., Zwinderman, A. H., Papapoulos, S. E., Hamdy, N. A.: The flare in serum alkaline phosphatase activity after orchiectomy: a valuable negative prognostic index for progression-free survival in prostatic carcinoma. J Urol, **156:** 122-126, 1996

125. Chun, F. K., Karakiewicz, P. I., Huland, H., Graefen, M.: Role of nomograms for prostate cancer in 2007. World J Urol, **25:** 131-142, 2007

126. Smaletz, O., Scher, H. I., Small, E. J., Verbel, D. A., McMillan, A., Regan, K., Kelly, W. K., Kattan, M. W.: Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. J Clin Oncol, **20:** 3972-3982, 2002

127. Halabi, S., Small, E. J., Kantoff, P. W., Kattan, M. W., Kaplan, E. B., Dawson, N. A., Levine, E. G., Blumenstein, B. A., Vogelzang, N. J.: Prognostic model for predicting

survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol, **21:** 1232-1237, 2003

128. Armstrong, A. J., Garrett-Mayer, E. S., Yang, Y. C., de Wit, R., Tannock, I. F., Eisenberger, M.: A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res, **13:** 6396-6403, 2007

129. Karnofsky, D., Burchenal, J.: The Clinical Evaluation of Chemotherapeutic Agents in Cancer., *Evaluation of Chemotherapeutic Agents*. Columbia Univ Press, p. 196, 1949

130. Mulders, P. F., Dijkman, G. A., Fernandez del Moral, P., Theeuwes, A. G., Debruyne, F. M.: Analysis of prognostic factors in disseminated prostatic cancer. An update. Dutch Southeastern Urological Cooperative Group. Cancer, **65:** 2758-2761, 1990

131. Justice, A. C., Covinsky, K. E., Berlin, J. A.: Assessing the generalizability of prognostic information. Ann Intern Med, **130:** 515-524, 1999

132. Schmid, H. P., McNeal, J. E., Stamey, T. A.: Clinical observations on the doubling time of prostate cancer. Eur Urol, **23 Suppl 2:** 60-63, 1993

133. Semeniuk, R. C., Venner, P. M., North, S.: Prostate-specific antigen doubling time is associated with survival in men with hormone-refractory prostate cancer. Urology, **68:** 565-569, 2006

134. Oudard, S., Banu, E., Scotte, F., Banu, A., Medioni, J., Beuzeboc, P., Joly, F., Ferrero, J. M., Goldwasser, F., Andrieu, J. M.: Prostate-specific antigen doubling time before onset of chemotherapy as a predictor of survival for hormone-refractory prostate cancer patients. Ann Oncol, **18:** 1828-1833, 2007

135. Rozhansky, F., Chen, M. H., Cox, M. C., Dahut, W., Figg, W. D., D'Amico, A. V.: Prostate-specific antigen velocity and survival for patients with hormone-refractory metastatic prostate carcinoma. Cancer, **106:** 63-67, 2006

136. Sandblom, G., Dufmats, M., Olsson, M., Varenhorst, E.: Validity of a population-based cancer register in Sweden--an assessment of data reproducibility in the South-East Region Prostate Cancer Register. Scand J Urol Nephrol, **37:** 112-119, 2003

137. Egevad, L., Granfors, T., Karlberg, L., Bergh, A., Stattin, P.: Prognostic value of the Gleason score in prostate cancer. BJU Int, **89:** 538-542, 2002

138. Cox, D. R.: Regression models and life-tables. J R Stat Soc B, **34:** 187-220, 1972

139. Hedlund, P. O., Damber, J. E., Hagerman, I., Haukaas, S., Henriksson, P., Iversen, P., Johansson, R., Klarskov, P., Lundbeck, F., Rasmussen, F., Varenhorst, E., Viitanen, J.,

Spcg, T., Group, S.: Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: Part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. Scand J Urol Nephrol, **42:** 220-229, 2008

140. Vollmer, R. T., Egawa, S., Kuwao, S., Baba, S.: The dynamics of prostate specific antigen during watchful waiting of prostate carcinoma: a study of 94 Japanese men. Cancer, **94:** 1692-1698, 2002

141. Heagerty, P. J., Lumley, T., Pepe, M. S.: Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics, **56:** 337-344, 2000

142. Kalbfleisch, D. L., Prentice, R. L.: The statistical analysis of failure time data. New York: John Wiley, pp. 252-258, 2002

143. Pencina, M. J., D' Agostino RB, S., D' Agostino RB, J., Vasan, R. S.: Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med, **27:** 157-172, 2008

144. Hosmer DW, L. S.: Applied Logistic Regression, 2nd Edition ed. New York: John Wiley and Sons, pp. 160-164, 2000

145. http://www.cebm.net/index.aspx?o=1025.

146. Hugosson, J., Aus, G., Lilja, H., Lodding, P., Pihl, C. G.: Results of a randomized, population-based study of biennial screening using serum prostate-specific antigen measurement to detect prostate carcinoma. Cancer, **100:** 1397-1405, 2004

147. Johansson, J. E., Holmberg, L., Johansson, S., Bergstrom, R., Adami, H. O.: Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. Jama, **277:** 467-471, 1997

148. Aus, G., Abbou, C. C., Bolla, M., Heidenreich, A., Schmid, H. P., van Poppel, H., Wolff, J., Zattoni, F.: EAU guidelines on prostate cancer. Eur Urol, **48:** 546-551, 2005

149. Kwak, C., Jeong, S. J., Park, M. S., Lee, E., Lee, S. E.: Prognostic significance of the nadir prostate specific antigen level after hormone therapy for prostate cancer. J Urol, **168:** 995-1000, 2002

150. Sim, H. G., Lau, W. K., Cheng, C. W.: Predictors of androgen independence in metastatic prostate cancer. BJU Int, **93:** 1221-1224, 2004

151. Cook, R. J., Coleman, R., Brown, J., Lipton, A., Major, P., Hei, Y. J., Saad, F., Smith, M. R.: Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res, **12:** 3361-3367, 2006

152. Mackintosh, J., Simes, J., Raghavan, D., Pearson, B.: Prostatic cancer with bone metastases: serum alkaline phosphatase (SAP) as a predictor of response and the significance of the SAP "flare". Br J Urol, **66:** 88-93, 1990

153. Berruti, A., Cerutti, S., Fasolis, G., Sperone, P., Tarabuzzi, R., Bertetto, O., Pagani, G., Zolfanelli, R., Pallotti, S., Bumma, C., Fontana, D., Rosseti, S. R., Dogliotti, L., Angeli, A.: Osteoblastic flare assessed by serum alkaline phosphatase activity is an index of short duration of response in prostate cancer patients with bone metastases submitted to systemic therapy.Gruppo Onco Urologico Piemontese (G.O.U.P). Anticancer Res, **17:** 4697-4702, 1997

154. Lucas, A., Petrylak, D. P.: The case for early chemotherapy for the treatment of metastatic disease. J Urol, **176:** S72-75, 2006