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Disease-Specific Survival in Prostate Cancer Patients

**Results from the Scandinavian Prostate Cancer Group (SPCG) Trial No. 5
and Regional Cancer Register Data**

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Cover designed by Rami Klaff. The symbol represent the male gender and awareness of prostate cancer (moustache).

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To: Rohida, Christian, Sebastian and Lucian

*“There are no incurable diseases-only the lack of will. There are no
worthless herbs-only the lack of knowledge”*

“Width of life is more important than length of life”

“Avicenna (980-1037)”

Disease-Specific Survival in Prostate Cancer Patients

Results from the Scandinavian Prostate Cancer Group (SPCG) Trial No. 5 and Regional Cancer Register Data

THESIS FOR DOCTORAL DEGREE (PhD)

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ABSTRACT

Introduction

Prostate cancer (PCa) is the most common cancer among men in Sweden. The clinical course varies considerably, which makes it difficult to predict the prognosis in the individual case. In order to explore the early as well as the late course of the disease, large study groups and population-based cohorts are necessary.

Aims

- To explore factors that influence the long-term outcome of men with low-risk tumours in a population-based register, to predict the long-term course, and to assess the mortality rate for men with prostate cancer (Paper I)
- To analyse long-term outcome and to investigate factors associated with long-term survival in patients with metastases to the skeleton (Paper II)
- To analyse early androgen deprivation treatment (ADT) failure and to define clinical predictors associated with short survival due to early ADT failure in prostate cancer patients with bone metastases (Paper III)
- To analyse the prognostic significance of the extent of bone metastases in relation to other pretreatment variables in prostate cancer patients, and to explore the impact of bone metastases on quality-of-life (Paper IV)

Material and methods

The study groups were assembled from The South East Region Prostate Cancer Register (SERPCR), and The Scandinavian Prostate Cancer Group (SPCG) Trial No. 5. In the first study, prognostic factors and long-term disease-specific mortality rates of low-risk prostate cancer patients from the early PSA era were analysed. In the second study, patient-related factors, quality-of-life (QoL) and long-term survival in 915 PCa patients with bone metastases (M1b) under ADT, were analysed. In Study III factors predicting primary failure to respond to ADT

were identified. Study IV explored the impact of the extent of bone metastases on survival and QoL for these men.

Result and conclusions

The long-term disease-specific mortality of low-risk localised PCa is low, but the annual mortality rate gradually increases. This indicates that some tumours slowly develop into lethal cancer, particularly in men 70 years or older and with a PSA level ≥ 4 $\mu\text{g/L}$. From the SPCG Trial No. 5, a subgroup of patients with M1b disease and favourable set of predictive factors survived more than 10 years under ADT with an acceptable QoL. Independent predictors of long-term survival were identified as performance status (PS) < 2 , limited extent of bone metastases, and a PSA level < 231 $\mu\text{g/L}$ at the time of enrolment in the trial. However, four independent clinical predictors of early ADT failure could be defined. Men exhibiting these features should be considered for an alternative treatment. Patient grouping based on three categories of extent of bone metastases related to PS, haemoglobin, and QoL at presentation, as independent predictors of mortality, may provide improved accuracy of prognosis.

Keywords: androgen deprivation treatment; bone metastases; early failure; extent of disease; hormone-naïve; long-term disease-specific survival; low-risk; mortality; quality-of-life; predictors of survival; prostate cancer.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Prostatacancer är den vanligaste cancerformen bland män i Sverige. Det kliniska förloppet för män med prostatacancer varierar kraftigt, vilket gör det svårt att avgöra värdet av behandlingsinsatser. Denna heterogena grupp av patienter har varierande långtidsöverlevnad och sjukdomsförlopp. För att förstå hela sjukdomsförloppet är därför en lång observationstid nödvändig.

I denna avhandling utvärderas efter mer än två årtionden av observation, sex prognostiska faktorer för män med lokaliserad låg-risk prostatacancer (studie I) och fjorton prognostiska faktorer för män med avancerad, spridd prostatacancer (studie II-IV). Dessa studier syftar till att utforska de sjukdomsspecifika egenskaperna och överlevnaden hos män med prostatacancer, i synnerhet män med låg-risk tumörer och män med avancerade tumör stadier med spridning till skelettet.

I våra dagar handläggs patienter med en låg-risk tumör, utan tecken till spridning till andra delar i kroppen, med så kallad aktiv övervakning. Detta innebär att ingen behandling ges från början men att förloppet följs upp med upprepade blodprover (PSA = Prostata Specifik Antigen) och vävnadsprover från prostatan för att kunna sätta in en botande behandling om tumören skulle visa tendens till att bli elakartad. Det slutgiltiga målet med avhandlingen är att utvärdera de förutsättningar för de väl etablerade metoder som finns idag, vilket i sin tur skulle kunna bana vägen för nya behandlingsstrategier och leda till en ökad överlevnad. Första arbete i denna avhandling bygger på Sydöstra Regionens Prostatacancerregistret. Detta register var det första registret med fullständig geografisk täckning av män med prostatacancer i Skandinavien. Nästan 9000 män diagnostiserade med prostatacancer i tre län (Östergötland, Kalmar, Jönköping) från 1992 till 2003 har följts från diagnostillfället och framåt. Från detta register identifierades män med låg-risk tumörer för analys av långtidsöverlevnad. De tre efterföljande arbeten är baserade på ”Scandinavian Prostate Cancer Group (SPCG) Studie No. 5”, som är en av de största randomiserade studierna för män med en spridd prostatacancer till skelettet under hormonbehandling som finns i litteraturen. Mer än 900 patienter med tidigare obehandlad spridd prostatacancer rekryterades från 61 centra i Danmark, Finland, Island, Norge och Sverige mellan december 1992 och juni 1997. I denna studie jämfördes östrogen som intramuskulär injektion med total

blockering av det manliga könshormonet (total androgenblockad), vilka visade sig vara likvärdiga. Långsiktig överlevnad definierades som patienter som har en total överlevnad mer än 10 år. Logistiska regressionsmodeller konstruerades för att analysera prediktorer för överlevnaden. Livskvaliteten (QoL = Quality-of-Life) under uppföljningen bedömdes med hjälp av EORTC-30 (European Organisation for Research and Treatment of Cancer-30).

Resultatet från arbete I, där en analys av de prognostiska faktorerna, långtids- och den årliga sjukdomsspecifika dödligheten hos prostatacancerpatienter med låg-risk tumör, visade att den sjukdomsspecifika dödligheten var bara 7%. Dödligheten ökade dock gradvis över tid vilket tyder på att vissa cancrar långsamt utvecklades till en dödlig sjukdom. Detta gällde speciellt för patienter som primärt handlades utan någon terapi, var äldre än 70 år och hade ett PSA värde $\geq 4 \mu\text{g/L}$.

Arbete II beskriver egenskaperna och livskvaliteten, samt faktorer som är förknippade med långtidsöverlevnad i en undergrupp av prostatacancer patienter med spridd sjukdom till skelettet. Fyrtio (4,4%) av de 915 män överlevde längre än 10 år med en spridd prostatacancer. Faktorer som var förknippade med långtidsöverlevnaden var: avsaknad av cancerrelaterad smärta; gott allmäntillstånd (PS = Performance status mindre än 2); låg konsumtion av smärtstillande mediciner; lokalt begränsad primärtumör; PSA mindre än 231 $\mu\text{g/L}$; och begränsad spridning av tumören till skelettet enligt skelettscintigrafi.

Arbete III syftar till att undersöka vilka män med spridd prostatacancer som inte svarar på hormonbehandlingen initialt. Nittiofyra (10,3%) män som avled inom ett år identifierades. Lågt PS, hög konsumtion av smärtstillande mediciner, lågt hemoglobin och ökad spridning av cancern till skelettet var kopplat till risk för utebliven behandlingseffekt. Män med dåligt PS eller hög konsumtion av smärtstillande mediciner hade en trefaldig risk för terapivikt.

Effekterna av skelettmetastaser på överlevnaden och livskvaliteten hos män med prostatacancer, är tidigare inte helt klarlagda. Arbete IV visar en försämrad livskvalitet med ökande grad av tumörspridning till skelett. Det genomsnittliga allmänna hälsotillståndet var också nedsatt. Efter en statistisk justering för allmäntillståndet, konsumtion av smärtstillande behandling, grad av cancern, PSA och hemoglobin, så hade allt mera ökad tumör spridning till skelettet, en ökad cancer dödlighet i jämförelse med den minsta omfattningen av skelettspridningen.

Sammanfattningsvis: Prognosen för patienter med låg-risk tumörer och patienter med spridd cancer kan nu enligt våra resultat förutsägas med förbättrad säkerhet. Denna avhandling visar att den långsiktiga sjukdomsspecifika dödligheten för män med låg-risk lokaliserad prostatacancer är låg, men att den årliga dödligheten från prostatacancer gradvis ökar på lång sikt. Risken att dö i prostatacancer kan i framtiden kanske minskas om lämpliga molekylärbiologiska prover används och utvärderas fortlöpande. Även om prognosen överlag är dålig, förekommer tioårsöverlevnad med acceptabel livskvalitet hos män med cancerspridning till skelettet under hormonell behandling. För patienter som inte svarar på hormonell behandlingen initialt och avlider av sin cancer inom ett år, kan flera oberoende kliniska prediktorer tidigt identifieras. En alternativ behandling bör övervägas för denna patient grupp. Omfattningen av cancerspridning till skelett vid diagnos påverkar tydligt överlevnaden. Det finns anledning att anta att riskbedömning och därmed terapival kan förbättras genom mer omfattande utredning av cancerspridningen.

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LIST OF ORIGINAL PAPERS

This Thesis is based on the following original articles:

- I. **Klafl R**, Rosell J, Varenhorst E, Sandblom G. **The Long-Term Disease-Specific Mortality of Low-Risk Localized Prostate Cancer: a Prospective Population-Based Register Study Over Two Decades.** Urology. 2016 Feb 12. Pii: S0090-4295(16)00126-6. Doi: 10.1016/j.urology.2016.01.033.
- II. **Klafl R**, Berglund A, Varenhorst E, Hedlund PO, Jónler M, Sandblom G; Scandinavian Prostate Cancer Group (SPCG) Study No. 5. **Clinical characteristics and quality-of-life in patients surviving a decade of prostate cancer with bone metastases.** BJU International. 2015 Jun 1. Doi: 10.1111/bju.13190.
- III. Varenhorst E, **Klafl R**, Berglund A, Hedlund PO, Sandblom G; Scandinavian Prostate Cancer Group (SPCG) Trial No. 5. **Predictors of early androgen deprivation treatment failure in prostate cancer with bone metastases.** Cancer Medicine. 2016 Jan 14. Doi: 10.1002/cam4.594.
- IV. **Klafl R**, Varenhorst E, Berglund A, Hedlund PO, Sjöberg F, Sandblom G; Scandinavian Prostate Cancer Group (SPCG) Study No. 5. **Clinical presentation and predictors of survival related to extent of bone metastasis in 900 prostate cancer patients.** Scand J Urol. 2016 Oct; 50(5):352-9. doi: 10.1080 /21681805 .2016. 1209689. Epub 2016 Aug 9.

LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Treatment
ALP	Alkaline Phosphatase
AS	Active Surveillance
BPH	Benign Prostate Hypertrophy
CI	Confidence Interval
COD	National Cause of Death Register
CR	National Cancer Register
CSS	Cause-Specific Survival
CT	Computed Tomography
DRE	Digital Rectal Examination
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EOD	Extent of Disease
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GS	Gleason Score
ICD-10	International Statistical Classification of Diseases and Related Health Problems –10 th Revision
LHRH	Luteinising Hormone-Releasing Hormone
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MRI	Magnetic Resonance Imaging
MRT	Magnetic Resonance Tomography
mSS	Modified Soloway Score
NCCN	National Comprehensive Cancer Network
NNT	Number Needed to Treat
NPCR	Swedish National Prostate Cancer Register
OR	Odds Ratio
OS	Overall Survival
PCa	Prostate cancer
PIVOT	Prostate Cancer Intervention versus Observation Trial
PS	Performance Status
PSA	Prostate-Specific Antigen
PSAD	Prostate-Specific Antigen Density
PSPA	Performance Status, Pain and Analgesic
QoL	Quality-of-Life

RCT	Randomised Controlled Trial
SDR	Swedish Death Register
SEER	Surveillance Epidemiology and End-Results
SHBG	Sex Hormone-Binding Globulin
SERPCR	South East Region Prostate Cancer Register
SNPCG	Swedish National Prostate Cancer Guidelines
SPCG	Scandinavian Prostate Cancer Group
TAB	Total Androgen Blockade
TNM	Tumour Node Metastasis (Classification)
TRUS	TransRectal UltraSound
UICC	Union Internationale Contre le Cancer
WHO	World Health Organisation
WW	Watchful Waiting

1. INTRODUCTION

Predicting disease-specific survival in Prostate cancer (PCa) is fundamental in deciding on treatment for men with newly diagnosed disease. Since treatment may result in both cure of the cancer as well as complications and side-effects that decrease quality-of-life, it is crucial to make the right management decision on an individual basis, taking estimated survival into account. Disease-specific survival is defined by the proportion of the population that die from a disease during a defined period of time. Overall survival, on the other hand, includes all causes of death including those in the estimation of disease-specific survival.

Many studies have described several aspects of the natural history and long-term survival in prostate cancer, in both observational and randomised controlled trials (RCT) [1-3]. Continual evaluation and analyses of PCa survival is vital if we are to ensure that effectiveness in management of the disease is maintained and improved as far as possible. The failure of management in a population of PCa patients should be seen as being caused by a lack of knowledge. The purpose of his thesis was to analyse and describe disease-specific survival in men with PCa, in particular men with low-risk disease and men with an advanced stage tumour and to define a basis upon which new strategies for improving survival may be assessed.

1.1. Background

Prostate cancer is a major public health concern and one of the five most common causes of death in men worldwide and the second most common cancer in men in the world according to GLOBOCAN 2012 (**Figure 1**). In Europe it is the third most common cause of death due to cancer, and in the United States it is the second. Among men, it is the most common cause of cancer death in the United States as well as in Europe. The estimated incidence and mortality of 27 major cancers and all cancers combined for 2012 are available in the GLOBOCAN series of the International Agency for Research on Cancer [4].

Taking both genders into account prostate cancer is the fourth most common cancer in the world. Almost 1.1 million cases of prostate cancer were diagnosed

globally in 2012, and correspondingly there are an estimated 307,000 deaths from PCa, representing 6.6% of the total male cancer mortality and about 15% of cancer cases in men. Age-standardised prostate cancer mortality rate is high in the Caribbean and Africa, and very low in Asia [4].

The incidence of PCa in Europe 2012 was estimated at 400,000 cases, with approximately 92,000 PCa deaths. The increase in incidence in Europe over the last decade is probably due to the widespread use of PSA screening for early detection of PCa, and because of the aging population [5, 6]. In the USA, the incidence was 180,890 cases and about 26,120 men died of the disease in 2016. PCa accounts for 10.7% of all new cancer cases and 4.4 of all cancer deaths. The ≥ 5 -year survival rate for PCa patients was 98.9% between 2006 and 2012, according to SEER [7].

Figure 1. The ten most common forms of cancer and cancer death worldwide among men in 2012. Incidence- and mortality rates (world/Sweden) per 100,000, GLOBOCAN 2012.

In western and some northern countries such as Sweden, however, the incidence of prostate cancer has stagnated and has even decreased slightly in recent years [8]. In Sweden the incidence of prostate cancer increased 1998-2009 from 6,121 to 10,505 cases and the proportion of cases in the low-risk group from 13.6% to

28.4% [9]. This progress has levelled off, with 9,663 and 9,678 new cases being reported by the Swedish Cancer Register in 2012 and 2013 respectively. In 2014 there were 10,985 males diagnosed with the disease corresponding to 226 cases per 100,000 and a third of all male cancers [10] (**Figure 2**).

PCa is the most common cause of cancer death among men in Sweden and constitutes a third of all cancers in men. Just over 5% of Swedish men die of PCa and half of these are over 80 years old. A total of 2,382 PCa deaths during 2010 and 2014 were reported in NORDCAN, which accounts for 20.5% of all deaths, regardless of cause [11].

Figure 2. Age-standardised incidence and mortality rate for prostate cancer per 100,000 men in Sweden, crude rate. Source: National Board of Health and Welfare, www.socialstyrelsen.se (Incidence) and NORDCAN (Mortality), www.ancr.nu.

1.2. Register studies vs. randomised controlled trials

In Sweden there are several patient registers. Although the patient register has proved to be an effective tool in the improvement of health care, it is important to ensure that patients benefit from a register, otherwise they may consume an enormous amount of resources, and intrude into patient integrity without providing data that is useful in day-to-day medical care. Gorgio Gandaglia et al evaluated existing prostate cancer registers, describing their strengths and limitations, and the potential role they may have in outcome research [12]. The conclusion of this review was that large registers play an increasingly important role in advancing PCa research and care compared to randomised controlled trials, although those, in their opinion, still provide the highest level of evidence.

As opposed to an observational register study, an RCT enables testing of the hypothesis under circumstances where the impact of all factors except the single intervention is reduced through randomisation. A register study, on the other hand, reflects the effectiveness of the intervention in normal medical practice ("treatment outcome outside centres of excellence"), and is hypothesis-generating rather than hypothesis-testing. Register studies may not provide a definitive answer to all questions, but they may constitute a very important step in the scientific process. A properly planned RCT provides more unbiased data than a register study. In other words, a RCT provides more sustainable conclusions than a register study when two interventions are compared. Because of the inclusion criteria of a RCT, the external validity is often limited to selected patients. Therefore, the results from a RCT cannot always be generalised to all patients with the same disease. If information on the recruitment criteria in a RCT is lacking, it is impossible to ascertain whether or not the outcome can be generalised to the general population. A register study can give a rough indication of how "the results tend to be". In that sense, register data depict reality more accurately than an RCT. Some forms of evidence may be difficult to achieve from register data, but observations from register studies may provide the basis for hypotheses that may be evaluated in RCTs of various designs. In other words, register studies and RCTs complement each other [13-15].

2. PREDICTION OF SURVIVAL

In most cases prostate cancer is a hormone-dependent adenocarcinoma. Spread of the cancer varies in extent, and has a major impact on prognosis. The mortality rate of prostate cancer is low if the tumour is confined to the prostate (low-risk) and high in the case of disseminated disease (high-risk). Yet it is impossible to predict if or when a patient will die of the disease. The reason for this uncertainty is the fact that the cancer appears to be multifocal within the prostate and may even be heterogeneous at the time of diagnosis. Other factors are tumour instability and that the course of the disease may extend over decades.

2.1. The course of localised prostate cancer

To predict the prognosis once PCa is diagnosed and for safe and effective management of the disease, knowledge of the natural course of the disease is necessary. Long observation and follow-up times are needed if we are to increase our knowledge about this disease. In general, localised tumours are associated with a favourable prognosis, even though they may become aggressive and metastasise if followed long enough. With an improved understanding of the natural course, overtreatment may be avoided. In a Swedish population-based cohort study by Johansson et al 1997, a group of 642 patients with PCa consecutively diagnosed between 1977 and 1984 were followed until 1994 [16]. PSA level was not in clinical use at that time. Two hundred patients with initially untreated, early detected PCa (T0-T2, NX, M0) were observed for up to 15 years. Tumour grade had a high predictive value for survival; well differentiated tumours had a 6% disease-specific mortality rate, whereas intermediate and poorly differentiated PCa had 11% and 56% PCa-specific mortality rates, respectively. However, in 2013 Popiolek et al presented a report with even longer follow-up. They showed that well-differentiated tumours (T0-T1 and WHO Grade 1) also continue to progress and PCa-specific mortality increased over a 25 year follow-up period [2]. Based on a large cohort similar to that of Johansson, Albertson et al analysed long-term disease-specific survival. They showed that among 767 men diagnosed with PCa 1971-1984 at the age 55-74 years (T0-T3 and M0-MX), the PCa-specific mortality rate was

42-70% for Gleason Score (GS) 7 and 60-87% for GS 8-10 after a 15-year follow-up period. However, men with low-grade localised PCa had a small but not negligible risk of dying of metastatic disease over a 20-year follow-up period [17].

2.2. The course of metastatic prostate cancer

The outcome of prostate cancer is mainly determined by the presence or not of distant metastases. Metastases most frequently (90%) involve the skeleton [18]. To some extent, it is possible to determine the natural course of untreated prostate cancer with skeletal metastases from the pre-ADT era. In a study from the Mayo Clinic 1925, the presence of bone metastases at diagnosis was associated with a 9-month mortality rate of 66% [19]. In a series of 260 patients with bone metastases, overall survival ranged from one month to 176 months. The longest survival was seen in an untreated man who had metastases in the spine and pelvis at the time of diagnosis, who survived nearly 15 years [20]. Because of variations in the clinical background, survival following standard androgen deprivation treatment (ADT) varies greatly [21]. ADT has been the standard management of prostate cancer with distant metastases for more than half a century. ADT was originally achieved by surgical castration or oestrogen treatment. In the 1980s medical castration by means of LHRH agonists with the addition of antiandrogens was introduced. A substantial proportion of prostate cancers are still detected at an advanced stage, having distant metastases at diagnosis. In Sweden 1,228 (12%) of 10,452 men diagnosed in 2014 [22] had metastases at the time of diagnosis. Once distant metastases are present, the disease is incurable, albeit many men live for several years with generalised prostate cancer [23].

Since that time, monotherapy with castration, oestrogen or antiandrogen has been compared to combination treatment, i.e. total androgen blockade (TAB), castration and antiandrogen, in clinical trials [24, 25]. Approximately 15% of men fail to respond to ADT initially [26].

2.3. Castration-resistant metastatic prostate cancer

Not only did Huggins and co-workers describe a significant improvement in the clinical condition of patients with metastatic prostate cancer subjected to ADT, they also defined a new disease state of primarily castration-resistant metastatic prostate cancer, i.e. early primary ADT failure [27]. In their series of 21 consecutive patients “a noticeable improvement occurred in the clinical status of all but three patients”. The response to ADT varies, with approximately 15% of men with metastatic disease primarily failing to respond to ADT [25, 26, 28-35].

With time PCa ceases to respond to ADT, becomes castration-resistant, and the patient eventually dies of cancer progression unless death for other reasons occurs. The refractoriness of metastatic prostate cancer after long-term ADT has received increasing attention over the last two decades as new hormonal and chemotherapeutic therapies have been introduced, and the mechanisms leading to the development of castration resistance through different pathways of cell de-differentiation has been extensively explored [26, 36-38]. So far there have been no adequate methods to predict which men benefit from ADT. Previous studies on the clinical significance of androgen receptors in prostate cancer have been questioned [29, 39]. Theories at present include both androgen receptor-dependent and androgen receptor-independent mechanisms [40, 41].

Biochemical and histochemical assays have failed to predict primary response to ADT [42-44]. Previously much focus has been on serum testosterone and other sex hormone levels and their relationship to prostate cancer, but results have been inconclusive [45-47]. Multiple studies have identified recurrent somatic mutations, copy number alterations, and oncogenic structural DNA rearrangements in primary prostate cancer [38]. Although certain primary prostate cancer alterations or signatures have prognostic clinical significance, the impact of addressing primary prostate cancer genomic events in clinical practice has yet to be explored [38, 48-50]. Few studies have been undertaken to elucidate the non-responsivity of PCa to ADT, even though it continues to be mentioned in the uro-oncologic literature [25, 26, 28-31, 34, 51, 52]. A state of castration resistance usually develops after long-term ADT. Improving the results of metastatic castration-resistant prostate cancer (mCRPC) treatment is currently regarded as one of the most critical goals in the management of the disease [35, 53-55]. A better understanding of the mechanisms behind secondary resistance following long-term ADT may eventually result in a better

understanding of early ADT failure. However, mCRPC following long-term ADT is probably a much more heterogeneous condition than metastatic prostate cancer primarily failing to respond to ADT [38].

3. DIAGNOSTIC TOOLS

3.1. Digital rectal examination

The digital rectal examination (DRE) was one of the earliest methods for early detection of PCa. However, when PSA was introduced into clinical practice, low-risk non-palpable tumours, could be detected. With DRE, tumour localized in the posterior and lateral zones of the prostate may easily be recognized by the experienced physician, but it is observer-dependent and may be normal, even in men with advanced disease. Previous studies have aimed to determine the value of DRE in the detection of PCa [56-59]. In a meta-analysis of the diagnostic value of DRE in primary care screening for prostate cancer, sensitivity was found to be 59% and specificity 94%. The positive predictive value of an abnormal DRE for the presence of PCa was estimated to be 28% [60].

Furthermore, an abnormal DRE was associated with an increased risk for PCa with GS > 7 [61]. DRE is included in the urologic work-up following discovery of an elevated PSA level, and may be useful in differentiating between other conditions of the prostate such as inflammation or infection, calculi and benign hypertrophy (BPH).

3.2. Prostate-specific antigen

Since the beginning of the prostate-specific antigen (PSA) era, with the increase in the routine use of PSA in clinical practice during the 1990s, the incidence rate of PCa increased in most parts of the world. PSA has revolutionised the diagnosis of PCa, and is the most effective clinical test for early PCa detection. In the lower range, PSA has acceptable sensitivity even for localised tumours, but a low specificity [62]; in other words, PSA is organ-specific but not specific for prostate cancer.

PSA was discovered when antigens of the semen and prostate were explored by several researcher groups during the 1960s and 1970s [63]. PSA is a kallikrein-like serine protease produced by the epithelial cells of the prostate. It is expressed by the prostatic luminal epithelial cells and released into seminal fluid, helping in liquefying the semen following ejaculation. PSA was purified

from prostatic tissue by Wang in 1979 [64]. Very small amounts of PSA can be detected in serum. Elevated levels can be measured in such conditions as prostate cancer, infection, inflammation, trauma and BPH. PSA that enters the circulation is bound to alpha-1 anti-chymotrypsin but a fraction is inactivated in serum and circulates as free PSA [65]. Prostatic acid phosphatase had previously been used for the detection of prostate cancer. Stamey showed that PSA is a better tumour marker for men with the disease [66], and in 1994 PSA was accepted as a tool for the detection of PCa in men by the Food and Drug Administration (FDA) in the United States. DRE and PSA in conjunction may be used to maximise sensitivity in detecting prostate cancer. This combination has been evaluated in several studies [67, 68]. PSA doubling time, PSA velocity, PSA isomer, PSA with age-specific ranges, and PSA density have also been shown to improve accuracy and specificity in the early detection of PCa [69-75]. According to the Swedish National Prostate Cancer guidelines, however, screening for prostate cancer using PSA is not recommended on the basis of the results of a population-based randomised screening trial [76, 77].

3.3. Biopsy of the prostate after diagnostic imaging

Sixten Franzén introduced fine needle aspiration biopsy of the prostate in 1960. *Ad modum* Franzén implied that the physician performed prostate biopsy through the perineum or transrectally under digital control [78]. In 1989, Hodge introduced the sextant biopsy using transrectal ultrasound of the prostate (TRUS) providing 18G core biopsy samples [79]. In 1995 Thomas Stamey showed that sextant biopsies guided with TRUS using a lateral approach gave better coverage of the anterior aspect of the peripheral zone [80]. Later on, 10-12 core biopsies were recommended to achieve a sufficient cancer detection rate in the peripheral zone [81]. Today this is the gold standard for histopathologic examination of the prostate gland [82]. Tumours in the anterior zone of the prostate account for approximately 20% of all prostate cancers. TRUS-guided anterior biopsy is a second-line method used when standard dorsal biopsy does not detect PCa [83]. Further development includes the cognitive biopsy of suspect lesions detected by MRI (Imaging-Reporting and Data System, PI-RADS) and the new role of MRI fusion-guided biopsy in PCa. **Table 1** shows PCa detection rates by MRI. Potential roles of TRUS are: the visualisation of lesions suspected of being malignant; improvement in the accuracy of prostate

biopsy; and the measurement of prostate volume, helping in the determination of PSA density as a tool for risk calculation in prostate cancer.

Table 1. PCa detection rates (%) by MRI by tumour volume and Gleason Score [84].

Gleason Score (GS)	Tumour volume (mL)		
	< 0.5 mL	0.5-2 mL	> 2mL
6	21-29%	43-54%	67-75%
7	63%	82-88%	97%
> 7	80%	93%	100%

3.4. Staging and the TNM system

It is crucial to determine the severity of PCa, staging the tumour by calculating the size and extent of local growth and whether or not it has spread to lymph nodes or to distant organs. The TNM system (Tumour Node Metastasis) was accepted in Sweden for staging prostate cancer in 1992 [85]. The extent of the primary tumour (T-category) is defined by combining DRE performed by the physician, TRUS, and histopathologic examination. Regional lymph node involvement, defined as PCa metastases limited to lymph nodes below the bifurcation of the common iliac arteries as detected by imaging or by exploration of suspect lymph nodes, determines the N-category. The M-category is determined by PCa spread beyond regional lymph nodes, to the skeleton and to other sites in the body. These can be detected by various imaging modalities and scintigraphy. The TNM system has gradually been updated in recent years

Table 2.

3.5. Grading and the Gleason Score

Before the Gleason grading system was used, Mostofi, in 1975, introduced the three-grade categorisation of PCa based on the cytologic pattern of the aspiration biopsy taken with a fine needle [86]. This was accepted by the World Health Organisation (WHO) in 1980 as a standard cytologic grading system.

The WHO cytologic grading system was used at the beginning of the SERPCR, and the Gleason Score based on histopathologic examination was added in 1990.

Determination of the differentiation of prostate cancer cells by histopathologic examination of TRUS-guided biopsy samples of the prostate or surgical specimens is crucial in treatment decision-making. The Gleason grading system was initially presented in 1966 by Donald Gleason (**Figure 3**) [87]. Gleason described how glandular tissue and cancer cells appear in shape, size and differentiation. The individual assessment by the pathologist when examining a specimen is important and much depends on experience. The Gleason Score is obtained from two sub-scores, the primary (predominant) and secondary (second most prevalent) Gleason grades. The sum of these two indicates severity of the disease (**Table 3**). The lowest score is 3 and the highest 5, the highest grade being the most poorly differentiated (Gleason Scores 6, 7 and 8-10). The International Society of Urological Pathology (ISUP) organised a consensus conference to update the Gleason grading system. This led to the standardisation of both interpretation of histological patterns and the reporting of grades. This has since become the standard for the histopathologic grading of PCa [88].

Table 3. SNPCG risk groups for localised and locally advanced prostate cancer.

	T-category	Gleason Score	PSA (µg/L)
Low-risk	T1-T2a	≤ 6	< 10
Intermediate-risk	T2b	7	10-19.9
High-risk	T2c-T3	8-10	≥ 20

Table 2. TNM classifications from 1978 [UICC 1978], 1992 [UICC 1992], 2002 [UICC 2002] and 2009 [UICC 2009].

	TNM classification 1978	TNM classification 1992	TNM classification 2002	TNM classification 2009
Primary tumour -No evidence of primary tumour -Incidentally detected tumours, focal growth. -Incidentally detected tumours, diffuse growth. -Incidentally detected non-palpable tumours, diagnosed after PSA needle biopsy	T0a (≤ 3 tumour foci) T0b (> 3 tumour foci)	T1a ($\leq 5\%$ of tissue resected) T1b ($> 5\%$ of tissue resected) T1c	T0 T1a T1b T1c	T0 T1a T1b T1c
-Intracapsular tumour -Tumour involving one half of one lobe or less -Tumour involving more than half of one lobe, but not both lobes	T1	T2	T2	T2 T2a T2b
-Tumour involves both lobes -Tumour confined to the gland. Smooth nodule deforming contour but lateral sulci and seminal vesicles not involved.	T2	T2		T2c
-Tumour extending through the capsule. -Extracapsular extension, including microscopic bladder neck involvement -Tumour invading seminal vesicle(s)	T3	T3	T3	T3 T3a T3b
-Tumour fixed or infiltrating neighbouring structures. -Primary tumour cannot be assessed	T4	T4	T4 TX	T4 TX
Regional lymph nodes -No regional lymph node involvement shown by pelvic lymph node exploration	N0	N0	N0	N0
-Regional lymph node metastases confirmed	N1-3	N1-3	N1	N1
-Presence of regional metastases cannot be assessed (pelvic lymph node exploration not performed)	NX	NX	NX	NX
Distant metastases -No evidence of distant metastases	M0	M0	M0	M0
-Evidence of distant metastases	M1	M1	M1	M1
-Non-regional lymph nodes(s)				M1a
-Bone(s)				M1b
-Other site(s)				M1c
-Presence of distant metastases cannot be assessed (bone scan not performed)	MX	MX	MX	MX

Figure 3. The original drawing of the 5 different Gleason grades. *Source: Human Pathology, www.humpath.com*

3.6. Risk stratification

Because of the heterogeneity of prostate cancer, risk stratification is important when deciding on treatment. Patient stratification is based on prognostic factors. Depending on the risk group, different treatment options are available. A literature search undertaken 2008 by Shariat et al generated 109 published prediction tools, including only 68 that had undergone validation [89]. A validated and widely used system is the one developed by D’Amico [90]. Prostate cancer is stratified into low-, intermediate-, and high-risk cancer based on PSA level, GS and T stage (**Table 4**). However, when taking into account multiple risk factors such as cancer extent and volume, the D’Amico classification has its limitations.

Table 4. D’Amico risk group [91].

Low-risk	Intermediate-risk	High-risk
PSA ≤ 10 µg/L, and GS 6, and T1c-T2a	PSA > 10 - ≤ 20 µg/L, or GS 7, or T2b	PSA > 20 µg/L, or GS ≥ 8, or T2c, or N1/M1

Other risk classifications suitable for active surveillance are described in Study I (**Table 5**). Nomograms and other calculating tools have been developed for risk

assessment, incorporating multiple variables into mathematical models to predict PCa outcome. Several validated online options are available for clinical use, although some of them have limitations [89]. Recently, the STHLM3 study showed that the STHLM3 model performed significantly better than PSA alone in the detection of cancer with a Gleason Score of at least 7. The area under the curve in a Receiver Operating Curve (ROC) was 0.56 (95% CI 0.55–0.60) with PSA alone, and 0.74 (95% CI 0.72–0.75) using the STHLM3 model [92]. Grönberg et al suggest that the use of the STHLM3 model should reduce the number of biopsies necessary by 32% (95% CI 24–39) and avoid biopsy in benign cases by 44% (35–54). By reducing the number of unnecessary biopsies, the risk for complications such as septicaemia may be avoided.

Table 5. Criteria for defining T-category at diagnosis in low-risk prostate cancer (Gleason Scores 2-6, PSA ≤ 10) in selected clinical practice guidelines and selected series managed with active surveillance.

Year of publication	Organisation / First Author (Reference)	T-category	Extent of cancer in biopsy cores	Other criteria
2014	SNPCG [76]	T1-T2	-	PSAD $< 0.15 \mu\text{g/L/cm}^3$
2014	NCCN [93]	T1-T2a	< 3 biopsy cores, and $\leq 50\%$ in any core	PSAD $< 0.15 \mu\text{g/L/cm}^3$
2014	EAU[94]	T1c	$< 5 \text{ mm}$ or $< 50\%$ in a single core	-
2005	Klotz L.[95]	T1c –T2a	< 3 cores involved, $< 50\%$ of any one core	-
2007	Soloway MS [96]	T1-T2a	≤ 2 biopsy, $\leq 20\%$ of any core	-
2009	van den Berg RC [97]	T1c-T2	< 3 biopsy cores	PSAD $< 0.2 \mu\text{g/L/cm}^3$
2011	Tosoian JJ [98]	T1	≤ 2 biopsy, $\leq 50\%$ of any core	PSAD $\leq 0.15 \mu\text{g/L/cm}^3$
2013	Godtman RA [99]	T1	< 3 biopsy cores, and $\leq 50\%$ in any core	PSAD $< 0.15 \mu\text{g/L/cm}^3$
2014	Schröder FH [100]	T1-2	≤ 2 biopsy cores	PSAD $\leq 0.2 \mu\text{g/L/cm}^3$

SNPCG: Swedish National Prostate Cancer Guidelines. NCCN: National Comprehensive Cancer Network. EAU: European Association of Urology. PSAD: PSA-Density. GS: Gleason Score.

3.7. The Soloway Score

In 1988, Mark Soloway studied men with prostate cancer bone metastases [101]. In this study, one hundred and sixty-six men with prostate cancer were treated with androgen deprivation when metastases to the bone had been confirmed by bone scintigraphy. The Extent of Disease (EOD) was compared with long-term survival of those prostate cancer patients.

A semi-quantitative grading system based upon the extent of skeletal metastases observed on the bone-scan, was used. Mark Soloway showed that survival was significantly correlated to EOD. Extent of skeletal metastases grades were defined as follows: 0 = normal or abnormal due to benign bone disease; 1 = less than six bony metastases, each of which is less than 50% the size of a vertebral body (one lesion about the size of a vertebral body would be counted as two lesions); 2 = between six and 20 bone metastases, the size of lesions as described above; 3 = more than 20 metastases but less than a “superscan”; and 4 = “superscan” or its equivalent, i.e. more than 75% of the ribs, vertebrae. and pelvic bones [101].

The 2-year survival rates for EOD Grades I to IV were 94%, 74%, 68% and 40%, respectively. Survival differed significantly between EODs I, IV and II and III. There was, however, no significant difference between II and III. Since EODs II and III did not differ in the Soloway study, a modified Soloway Score (mSS) was used in the SPCG5 trial with the following scores: 1 = the total area of hot spots is less than three bodies of a lumbar vertebra; 2 = the total area of hot spots is larger than of score 1, but $< 75\%$ of the total scan; and $3 \geq 75\%$ of the total scan i.e. “super scan” [102, 103].

Traditionally, radionuclide imaging of the skeleton with measurement of bone uptake is used to diagnose metastatic bone involvement [104]. By quantifying the extent of bone metastases, a better prediction of survival may be achieved than when using undifferentiated M1b–categorisation.

4. MANAGEMENT

Prostate cancer is a heterogeneous disease and the choice of treatment depends on the patient as well as the nature of the disease. When deciding on treatment, age, comorbidity and life expectancy should be taken into consideration. However, the stage and the aggressiveness of the disease as well as localisation of the tumour and potential treatment side-effects all have a crucial impact on treatment outcome.

4.1. Watchful waiting

In the pre-PSA era, i.e. prior to 1990, the “watchful waiting” (WW) strategy was commonly practised. WW was also known as symptom-guided treatment. Men with PCa and an estimated survival less than 10 years and with several comorbidities may benefit from this management strategy. In other words, WW may be an option for patients with limited life expectancy or elderly men with less aggressive disease. WW implies a conservative form of management until the development of local or systemic progression and disease-related complications. When symptoms appear, treatment focused on specific symptoms is initiated, e.g. ADT, palliative TUR-P if there is urinary tract obstruction or, if necessary, palliative radiotherapy of metastatic lesions when pain or neurological symptoms develop. WW is a non-curative option, in contrast to active surveillance (AS), as described below [105, 106]. Patients with PCa managed with a WW strategy are expected to have a slowly growing tumour. Men with PCa managed with WW may live a normal life span without any deterioration in their QoL.

Sandblom et al described the course of PCa in a population-based study. The disease-specific survival rate of men with PCa managed with WW was 79.7 ± 6.3 after 10 years follow-up [107]. Other studies of WW have included men with PCa and follow-up times up to 25 years reporting disease-specific survival rates of 82%-87% after 10 years [105, 108].

4.2. Active surveillance

EAU guidelines defined AS as follows:” *Active surveillance aims to achieve correct timing for curative treatment, rather than delayed application of palliative treatment. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, while considering individual life expectancy*” [94].

In contrast to watchful waiting, AS implies that the patient is followed and curative treatment is given as soon as the tumour shows signs of progression. In Sweden, the proportion of men managed with AS has increased from 55% in 2009 to 85% in 2013 [10]. Men with localised, low-risk PCa with life expectancy of more than ten years without serious comorbidity contraindicating curative treatment may preferably be managed with the AS strategy [109]. By the application of surveillance instead of immediate curative treatment, side-effects and impaired quality of life caused by overtreatment may be avoided. Patients should be monitored carefully during AS, and the physician prepared to intervene when the tumour shows sign of progress. The Study on Active Monitoring in Sweden (SAMS) is currently being conducted with the aim of assessing the outcome of AS [110]. Studies that evaluate outcome after AS are scarce. In a systematic review by Dell’Era et al, focusing on disease-specific mortality after AS with follow-up times ranging from 1.8-6.8 years, prostate cancer-specific mortality was found to be very low ($\leq 1\%$). Further long-term observational studies providing better evaluation and better strategies for AS are needed [111].

Wilt et al and Bill-Axelsson, in a study on mortality in patients with PCa randomised between observation and radical prostatectomy, with a median follow-up of 10 years, showed that the curative option had no significant impact on survival compared to observation. Risk reduction from all causes of death after surgery was 10%, while the risk of dying due to surgery was 4%. The number needed to treat (NNT) to save one life was 8 [112, 113]. If men with tumours detected at an early stage are followed long enough, it is possible that the NNT will gradually decrease. In a previous report from the South-East Region of Sweden, time trends in incidence rates and the choice of treatment for prostate cancer were analysed in a prospective, population-based register study [114]. A 15-year follow-up of the same database has also been performed [115]. In a study by Klotz et al, it was possible to maintain 65% of patients, treatment-

free at 8 years with selective delayed intervention. The cancer-specific survival was 99.3% [116].

The treatment of men with low-risk tumour remains controversial. In an observational study undertaken since the introduction of PSA testing, high long-term survival rates among men managed with expectancy was seen [117].

Previous register-based studies [117, 118] have been inconclusive, to some extent due to the fact that PSA and Gleason Score were not included until the beginning of the 1990s. However, long-term follow-up studies suggest that even low-risk tumours with an initially indolent course may become aggressive and eventually turn into more lethal tumours [1]. According to the Scandinavian Prostate Cancer Group Trial No. 4, untreated men aged > 65 years had a 12-year prostate cancer-specific survival of 88% with no significant difference from men who underwent radical prostatectomy [119]. Ross et al, in a large American study, showed that PCa tumours with $GS \leq 6$ have very little potential to metastasise to lymph nodes [120].

4.3. Curative treatment

4.3.1. Radical prostatectomy

In the middle of the 19th century, Billroth introduced a model for prostatectomy. The aim of this procedure was to eliminate an urinary tract obstruction [121]. In 1904 the first radical perineal prostatectomy was performed by Hugh Young [122]. In 1945 Millin performed the first radical retropubic prostatectomy in London [123]. This procedure was adapted and brought to the USA by Bacon, one of Millin's students. In 1982, Patrick Walsh refined the technique at Johns Hopkins Hospital, resulting in the nerve-sparing procedure. By preserving nerves, erectile function improved in PCa patients after surgical treatment [124]. Laparoscopic radical prostatectomy was first performed in 1999 and further refinement with robot-assisted radical prostatectomy in 2000 [125]. This approach has gained increasing popularity worldwide, not least in Sweden, with minimal blood loss and shorter hospital stay [126]. However, evidence for its superiority in radicality and functionality is still lacking [127-129].

To evaluate the benefit of the radical prostatectomy on PCa mortality and survival, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) study included 731 men with PCa randomised to radical prostatectomy or observation. The men were recruited between 1994 and 2002. There was no statistically significant difference in overall survival between the two groups after a follow-up period of 10 years (47% vs 49.9%; $p = 0.22$) nor in disease-specific mortality (5.8% vs. 8.4%; $p = 0.09$) [130]. Patients with intermediate- and high-risk prostate cancer seemed to gain more benefit from radical prostatectomy than those with low-risk tumours [112]. On the other hand, in the Scandinavian Prostate Cancer Group, Trial No. 4 (SPCG-4), 695 PCa patients with T1-T2 tumour were randomised to radical prostatectomy or WW between 1989 and 1999, i.e. before the PSA-era. After 23-years of follow-up there was some evidence for reduction in overall mortality in the operated group compared to the WW group (RR 0.71; 95% CI = 0.59-0.86; $p < 0.001$) as well as disease-specific mortality (RR 0.56; 95 CI = 0.41-0.77; $p = 0.001$). However, the advantage of surgical treatment was more pronounced in men < 65 years-of-age [113, 131, 132]. Since the study was carried out before PSA testing was established in clinical practice, there were only 12% with low-risk PCa (T1c). The SPCG-4 as well as the PIVOT study favoured surgical treatment for intermediate- and high-risk PCa.

In a study based on the Swedish National Prostate Cancer Register (NPCR), Berglund et al showed an estimated survival rate for PCa patient with various stages stratified by the Charlson Comorbidity Index. Those with a high index had lower overall survival compared to patients without comorbidity, and the risk of dying of other causes was greater [133]. Men with an expected survival of more than ten years may be offered curative treatment, bearing in mind the side-effects caused by treatment.

The risk of dying from PCa for patients with low-risk tumours is low. These men may preferably be managed with AS or WW [118]. Hull showed that the overall progression-free survival for PCa patients with tumour Stages T1-T2 was 75% after 10 years postoperative follow-up [134]. For T3 tumours there is more evidence in support of treatment with intention-to-cure [135, 136]. Stattin et al have recently presented data on treatment of very high-risk PCa (T4 and PSA 50-200 $\mu\text{g/L}$) providing evidence for a substantially lower mortality in patients undergoing surgery and/or radiation [137]. Ongoing RCT, as LIDONET and SPCG15 (Scandinavian Prostate Cancer Group Trial No. 15), have been started with the aim of evaluating the increase in survival of PCa patients with locally

advanced (SPCG15) or metastatic disease (LIDONET). Patients are treated with surgery or radiation therapy combined with ADT (SPCG15), and surgery of the primary tumour and lymph nodes combined with ADT vs. ADT alone (LIDONET) [138-140].

4.3.2. Radiation therapy

In 1896 X-rays were discovered by the German physicist Roentgen. Three years later, radiation was used for cancer diagnosis and treatment. In the early 20th century, the discovery that radiation may cause and even be used to cure cancer was made. Bagshaw developed external beam radiation in 1956 and in 1961 he treated *mycosis fungoides* with electron beam therapy [141]. In 1954 Flocks treated PCa by interstitial radiation with radioactive gold, which marked the beginning of brachytherapy [142].

Later on radiotherapy was developed and refined to external beam radiotherapy, high dose radiation boost radiotherapy, and seed implantation with low dose brachytherapy. These techniques are also used in combination whereas seed implantation alone is recommended for localised, low-risk tumours [143].

In a multicentre comparative analysis, Kishan analysed the clinical outcomes of 487 PCa patients with a Gleason Score 9-10 treated with either radiotherapy or prostatectomy between 2000 and 2013. Median follow-up was 4.6 years. The cancer-specific survival and overall survival did not differ between the treatment groups. However, extreme dose-escalated radiotherapy with ADT did provide improved systemic control [144]. Widmark, in 2009, reported a RCT undertaken at 47 centres in Scandinavia (SPCG 7). The study assessed the efficacy of treatment with ADT in combination with radiotherapy in high-risk PCa. Results suggested that this combination should be the new standard of treatment [145]. A follow-up study by Fosså in 2016, evaluated the ten- and fifteen-year prostate cancer-specific mortality rates. Endocrine therapy in combination with radiation therapy reduced the absolute risk of dying from PCa by 17% when compared with endocrine therapy alone. The prostate cancer-specific mortality rate after 15 years was halved from 34% to 17% [146].

Radiation therapy and radical prostatectomy are associated with negative side-effects; incontinence and impotence being the most common. Following external radiotherapy, the patient may suffer from symptoms from the rectum and the bladder. Incontinence was more pronounced after prostatectomy [147].

In a large meta-analysis, Wallis et al evaluated several studies reporting the risk for a second malignancy after radiotherapy for PCa [148]. They found an increased relative risk for bladder cancer (hazard ratio (HR) 1.7) and for colorectal cancer (HR 1.8). The increased risks were associated with external radiation, but not with brachytherapy. Nevertheless, the overall incidence of secondary cancer was very low 5-10 years after radiation. Younger men probably face a greater risk. Long-term studies are needed to evaluate this question [149].

4.4. Androgen deprivation treatment

Androgen deprivation treatment (ADT) has been the gold standard in treatment of prostate cancer with distant metastases for more than half a century [27, 150]. For men with metastatic or symptomatic PCa, at the stage when cure is no longer an alternative, endocrine therapy is the treatment of choice. However, endocrine therapy is also used as neo-adjuvant and/or adjuvant therapy in addition to curative intent treatment to prevent recurrence.

Huggins et al demonstrated in 1941 the effect of surgical castration and oestrogen administration on the progression of metastatic PCa. They were the first to demonstrate the responsiveness of prostate cancer to ADT. ADT can be achieved by surgical (bilateral orchiectomy) or medical castration (LHRH-agonists or parenteral oestrogen) by suppressing the secretion of testicular androgens, or by competing antiandrogens inhibiting the effect of circulating androgens at the level of their receptor in the prostate. ADT has since then been the standard care of prostate cancer with distant metastases. Originally it was achieved by surgical castration and oestrogens. In the 1980s medical castration by means of LHRH agonists and addition of antiandrogens was introduced. After the introduction of ADT, monotherapy (castration or oestrogen or antiandrogen) has been compared with combination treatment, (total androgen blockade (TAB) castration and antiandrogen), in clinical trials [23, 151, 152]. In most cases, however, treatment is followed by an initial response in terms of symptomatic relief, radiographic regression of skeletal metastases and decline in PSA, as well as decreased serum testosterone levels, but the disease is not cured [153].

The proportion of men with distant metastases at diagnosis decreased from 50% in the 1970s to currently less than 10%. However, even if most tumours are diagnosed at an earlier stage nowadays, all men with prostate cancer face the risk of tumour progress unless curative treatment is given. Although the benefits from ADT are widely recognised, little is known about which men benefit the most from this therapy since the response to treatment is inconsistent; approximately 15% of men fail to respond. According to the latest meta-analysis, TAB with non-steroidal antiandrogens provides a small survival advantage compared to medical castration, with median survival times of 30 to 36 months [151]. In a SWOG phase III trial by Tangen, the median survival times for men treated with TAB were 30 to 49 months for M1 patients in both the pre-PSA and PSA eras, they also showed that survival times were somewhat better for black American men in the PSA-era than before testing began [21]. Because of the rather short survival of these high-risk patients, however, long-term data on M1 patients are limited. In most studies, patients who die more than 5 years after diagnosis are excluded from analysis.

Hedlund et al compared the effect of parenteral oestrogen with TAB (orchiectomy or medical castration) as treatment for advanced PCa. This phase III study recruited 915 patients with hormone-naïve metastatic prostate cancer from 61 centres in Denmark, Finland, Iceland, Norway and Sweden between December 1992 and June 1997 [103, 154]. This study group also constitutes the study groups in Papers II-IV of the present thesis. There were no differences in anticancer efficacy or cardiovascular events. The author concluded that it is feasible to use estradurin, especially in patients with osteoporosis and low cardiovascular risk. Antiandrogens are currently used with nonsteroidal entities in monotherapy for the treatment of advanced PCa [155]. When monotherapy with antiandrogen blockade is not sufficient, and PSA-levels increase, the addition of LHRH is necessary to obtain TAB. Cancer-specific and overall survival rates are increased slightly with TAB over a 5-year period, but there is an increase in the incidence of side-effects and a lower QoL [156]. Intermittent ADT is sometimes given to men with a slowly progressing tumour, although data are insufficient to determine whether intermittent treatment avoids the long-term complications of ADT [24].

4.5. Chemotherapy and new therapy alternatives

Patients with hormone-refractory, castration-resistant disease are candidates for cytotoxic chemotherapy and other agents. Previous studies have shown that treatment with docetaxel and prednisolone increases survival by 2-3 months with no reduction in QoL [157, 158]. James et al presented data from the STAMPEDE trial in which there were 917 patients in the control arm, showing the survival outcomes and prognostic factors for PCa [159]. Since prolongation of survival is modest and because of the toxicity associated with treatment, there is a need for a reliable predictor of survival in order to decide on optimal management of the right treatment for the patient. Docetaxel administered by intravenous infusion every three weeks, combined with prednisolone, may be suitable for younger men without serious comorbidity. Cabazitaxel has been shown to be effective in reducing progression after treatment with docetaxel. There are new hormonally-acting agents under evaluation such as abiraterone (enzyme blocker of testosterone synthesis), enzalutamid (an androgen receptor blocker that is given orally and has very mild side-effects), radionuclides such as samarium-153 and strontium 89, and Radium-223 (for the treatment of metastatic bone pain).

5. QUALITY-OF-LIFE

In the early 1970s quality-of-life as outcome measure gained increasing attention in clinical studies. Over the last decade, consideration of quality-of-life (QoL) of men with prostate cancer, when deciding on management, is now an obvious factor. Previously, the main goal in prostate cancer care was to prolong life. With new management strategies, new drugs and increased survival after diagnosis and treatment, the interest in quality-of-life has increased even more. Nowadays, new therapeutic agents may provide control of the tumour for several years, even in the absence of radical cure. The tumour status as well as the treatment itself can influence the patient's well-being in many ways, in particular regarding urinary continence and erectile function. In metastatic disease, pain and fatigue may be reduced by palliative radiotherapy and analgesic therapy, that may increase both physical and emotional function [160]. However, QoL is often affected for many years due to the cancer itself and its treatment [161]. To be able to study QoL in the long-term, an observation time of the same order as expected survival in the background population is required.

For most malignant diseases, distant metastases are associated with a very poor prognosis with substantial deterioration in health-related quality-of-life. Prostate cancer, however, differs from most other malignant diseases in that generalisation does not inevitably imply the same rapid decline in health-related quality-of-life, at least not if the tumour responds to ADT. When deciding on treatment for men with skeletal metastases, QoL should therefore be a major consideration.

The European Organisation for Research and Treatment of Cancer (EORTC) developed and validated a patient questionnaire to assess the QoL of patients suffering from different types of cancer, including prostate cancer. The questionnaire was designed to be cancer-specific and has been utilised in several international clinical trials [162, 163]. It is available in Danish, Swedish, Norwegian and Finnish translations. The questionnaire is appropriate for self-administration and consists of 30 items, including nine multi-item scales, five functional scales, three symptom scales and a global health status scale and single items, adding up to a total of 15 ratings. The raw scores from the questionnaire are transformed into a standardised 0-100 scale score. Morbidity, urinary and sexual function, self-care, social relationships and humour are

covered [164], with special focus on items on pain and how pain interferes with sleep, and daily functions such as physical activity.

The EORTC includes specific questions regarding symptoms in the previous week based on a mixture of dichotomous yes/no response categories and a four-point response scale ranging from "not at all" to "very much". Global health status is calculated from answers to two questions asking patients to rate their overall health and QoL on a seven-point scale ranging from "1" (very poor) to "7" (excellent).

6. AIMS OF THIS THESIS

Disease-specific survival varies greatly in men with prostate cancer. Men with localised high-grade tumours face little risk of dying of their disease, while men with distant metastatic (spread) tumours have a very high risk of impaired quality-of-life and death due to rapidly progressing cancer. Many observational studies attempting to describe the course of the disease have been undertaken [2, 9, 165]. The treatment outcomes of PCa vary markedly, which makes it difficult to decide on optimal treatment for the individual patient.

Men are increasingly being diagnosed with a low-risk tumour that may have little or no impact on survival [166]. Slow tumour progress makes the decision on management complicated. The treatment of low-risk tumour remains controversial and depends on the effectiveness of treatment and the harm associated with treatment. For men with metastatic disease, scintigraphy (bone scan) is the standard imaging technique for assessing tumour spread.

Scintigraphy not only determines whether or not there are skeletal metastases, but also the tumour burden of the bone metastases. The Soloways Score was established for risk stratification in clinical trials on disseminated prostate cancer in the late 1980s [101, 102]. The prognostic significance of the rate of proliferation of bone metastases is well described in the literature [102, 167]. The degree of metastases in combination with other prognostic factors, however, has so far not been prospectively explored over long observation periods in large numbers of men. Furthermore, there is no detailed information available on patient populations with bone metastases as regards clinical characteristics and quality-of-life, and what clinical factors affect survival and interact with the degree of tumour spread to the bone.

The aim of the studies in the present thesis was to describe disease-specific survival in low-risk and metastatic prostate cancer and to evaluate the clinical characteristics of the cancer and how it affects quality-of-life. Armed with this information, we may provide a better basis for management decision-making and improve our knowledge on the quality-of-life and long-term survival among men with prostate cancer.

Specific aims

- To identify factors that influence the long-term outcome of men with a low-risk tumour in a population-based register, to predict the long-term course, and to assess whether or not mortality rate is increased in men with prostate cancer (Paper I).
- To analyse long-term outcome and to investigate factors associated with long-term survival in patients with metastases to the skeleton (Paper II).
- To analyse early androgen deprivation treatment (ADT) failure and to define clinical predictors associated with poor survival in the case of early ADT failure in prostate cancer patients with bone metastases (Paper III).
- To investigate the prognostic significance of the extent of bone metastases in relation to other pretreatment variables in prostate cancer patients, and to explore the impact of bone metastases on quality-of-life (Paper IV).

7. MATERIAL AND METHODS

7.1. The South East Region Prostate Cancer Register (Paper I)

7.1.1 Participants (Paper I)

The South-East Region Prostate Cancer Register (SERPCR), which covers of the counties of Östergötland, Jönköping and Kalmar, was started in 1987 [168]. All patients with newly diagnosed prostate cancer are included in the register. When a decision on treatment is made, the physician responsible for the patient submits a report, based on a standardised protocol, to the oncologic centre for registration. The register includes data on tumour characteristics, PSA, Gleason Score, management, date of diagnosis, and date and cause of death [85], [TNM-classification (ed. 6 New York: Wiley-Liss; 2002)] (**Table 2**).

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. Causes of death are reported by the attending physician who fills in a special form according to the register protocol. At the same time, causes of death are registered in the Swedish Death Register (SDR). Registrations in the SDR are systematically compared with registrations in the SERPCR. With the high coverage and accurately recorded data, the validity of SERPCR is guaranteed. The SERPCR relies on the National Cancer Register as a basic source of data, thereby ensuring a high coverage of the corresponding geographic area. To assess the reproducibility of the data recorded, a random sample of cases are reviewed a second time and registration compared to the original. The register has been updated as shown in **Table 6**. The validity of the SERPCR and the reliability of death certificates have been evaluated in previous studies [168, 169].

One limitation with the SERPCR, as with many other registers, is the change in routines applied during the follow-up period. Since the start of the register, staging, diagnosis, and treatment of prostate cancer have all been gradually changed. New codes have been included as tumour characterisation and new principles of management have evolved. The SERPCR has been updated continuously in order to adjust for these changes in cancer evaluation and treatment approaches. The original codes have been preserved in parallel with

the inclusion of new variables and categories, which makes longitudinal comparisons possible. A local management programme was incorporated in the SERPCR to maintain common principles for diagnosis and treatment in the region.

The SERPCR may be considered an extension of the National Cancer Register, with more detailed information added to the basic data included in the NCR.

7.1.2 Material and methods (Paper I)

In Study I, we analysed a population-based cohort of men with prostate cancer in the three counties of the South East Healthcare Region in Sweden, a region with a total population of 952 000 in 1990. Altogether 8921 patients diagnosed with prostate cancer were registered in SERPCR 1992-2003 with PSA and date of sampling included in the register. By using the National Registration Number, an identification number assigned to all Swedish residents, the SERPCR was cross-checked with both the Swedish Death Register and the National Cancer Register to ensure high coverage. The completeness of the register has increased progressively from 97.4% in 1987 to 99.1% in 1996, reaching > 99% completeness in 1999 [169].

7.1.3. Study design (Paper I)

A subgroup of 1300 men with a low-risk, clinically localised, tumour was identified based on the following criteria: T-category 1-2; PSA level ≤ 10 $\mu\text{g/L}$; and Gleason Score 2-4. In cases where the Gleason Score was not registered, grade of malignancy 1 [170] was considered equivalent. Survival was evaluated with Kaplan-Meier, and multivariate Cox proportional hazard analyses. Risk factors, including T-category (T1 vs. T2), serum PSA level (< 4 $\mu\text{g/L}$ vs. 4-10 $\mu\text{g/L}$) and primary management (curative treatment vs. watchful waiting or palliative treatment) were analysed as prognostic factors. Survival was followed until December 31st 2013.

Table 6. 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 (neo-adjuvant 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 for diagnosis

7.1.4. Statistics (Paper I)

Data are presented as median, mean and range. Kaplan-Meier curves of cancer-specific survival were calculated. Cox multivariate regression model was used to evaluate factors predicting survival. Age, TNM-classification, PSA and primary therapy were included as covariates, with overall survival as endpoint. $P < 0.05$ was considered statistically significant.

Prostate cancer-specific death was defined as death where prostate cancer was registered as the primary cause on the death certificate. For all Swedish residents, causes of death are routinely reported to the SDR and registered according to the ICD-10. Information on date and cause of death are routinely reported as well. All other causes of death, including those with prostate cancer as a contributing cause, were considered not to be prostate cancer-specific [171].

7.2. The Scandinavian Prostate Cancer Group Trial No. 5 (Papers II-IV)

7.2.1. Participants and clinical characteristics (Papers II-IV)

Between December 1992 and June 1997, the Scandinavian Prostate Cancer Group (SPCG) Trial No. 5, phase III study recruited 915 patients with hormone-naïve metastatic prostate cancer from 61 centres in Denmark, Finland, Iceland, Norway and Sweden [103, 154]. Inclusion criteria were skeletal metastases (M1b) and Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, where 0 denotes fully active, 1, restricted in strenuous activity but ambulatory, and 2, ambulatory and capable of self-care but unable to work. The primary objective of the trial was to determine whether survival was shorter with high-dose parenteral oestrogen compared to TAB. The secondary objective was to provide information about cardiovascular side-effects and about quality-of-life before and during ADT. The extent of the primary tumour was determined by means of digital rectal examination according to the TNM classification of 1987 [172] and cytological or histological specimens with grading according to the World Health Organization (WHO) system [173]. Levels of PSA, ALP, and haemoglobin were determined by routine laboratory methods before the start of treatment. A PSPA score (the

sum of Performance status, Pain and Analgesic score) was determined by adding cancer-related pain 0-4 points, and use of analgesic 0-5 points to the WHO performance status 0-5 points.

Skeletal involvement was quantified from bone scans. The bone uptake of ^{99m}technetium methylene diphosphonate (MPD) was assessed in all patients according to the local standard algorithms at each participating centre. Bone scans with multiple disseminated areas of increased activity were considered as diagnostic of multiple metastases. In case of equivocal bone scans, targeted radiography was performed to distinguish benign (fracture, degenerative joint disease, etc.) from lesions of metastatic origin. The extent of skeletal metastases was calculated according to a modified Soloway Score: 1 = the total area of hot spots less than three bodies of a lumbar vertebra; 2 = the total area of hot spots larger than of Score 1, but < 75% of the total scan; and 3 ≥ 75% of the total scan or “super scan” [101]. The presence of non-regional lymph-nodes (M1a) and soft tissue (M1c) metastases were not routinely investigated with CT or MRT scan. The European Organization for Research and Treatment of Cancer’s Quality-of-Life Questionnaire-C30 version 1 (EORTC-30) was used to evaluate quality-of-life (QoL). Health-related quality-of-life can be defined as “an individual’s perceived physical, mental and social health status affected by cancer diagnosis or treatment” [174]. The EORTC questionnaire is appropriate for self-administration and consists of 30 items, including nine multi-item scales, five functional scales, three symptom scales and a global health status scale and single items, a sum total 15 ratings [162].

7.2.1.1. Treatment

Patients were randomised to TAB or treatment with polyestradiol phosphate (240 mg) given as an intramuscular injection every two weeks for 8 weeks and monthly thereafter. TAB consisted of orchiectomy or medical castration, according to the preference of the clinician and patient, combined with 250 mg flutamide orally three times daily. In 298 patients orchiectomy was chosen and 159 men received medical castration by a monthly injection of the LHRH-analogue, triptorelin.

7.2.1.2. Follow-up

The patients were followed 1, 3 and 6 months after start of the study and thereafter every 6 months. The primary endpoints were overall and disease-specific survival, and secondary endpoints were time to progression, cardiovascular and other adverse events, and quality-of-life. When clinical progression of the cancer was confirmed, further therapy was at the discretion of the clinician together with the patient. All patients were followed until death. The cause of death was recorded by the clinician responsible for the study at each unit. After median follow-ups of 2.3 years and 11.7 years, there were no significant differences between the two treatment groups in terms of biochemical or clinical progression-free survival or in overall or disease-specific survival. However, the incidence of side-effects differed between the two treatment groups. There was a significant increase in non-fatal cardiovascular events during treatment with polyestradiol phosphate, and a significant increase in skeletal events and hot flushes in patients receiving TAB [175, 176]. ALP at start and ALP and PSA after 6 months of ADT predicted prostate cancer-specific death within 3 years [177]. PSA kinetics were studied during the hormone-refractory phase of the disease. Of the variables available before the start of treatment, PSA velocity was the single most reliable predictor of survival. For hormone-refractory cases with skeletal metastases, median survival in the groups varied between 6.2 and 26.4 months [178]. Determination of serum oestrogen and SHBG was optional.

7.2.2. Statistical methods (Paper II)

In Study II, short-, medium- and long-term survival were analysed based on the 915 patients in the study group. Differences in overall survival were tested using the Chi-square test, based on the predictors being assessed. Univariate logistic regression models, with OR and 95% CI were used to estimate the likelihood of long-term survival for each variable. Multivariate logistic regression models were constructed using all variables that were statistically significant in the univariate analyses. A smoothing-splines mixed-effects model was tested as a function of follow-up and plotted the fitted mean values of QoL against follow-up time, for each variable.

7.2.3. Statistical methods (Paper III)

In Study III, primary ADT failure was defined as patients dying of prostate cancer within 12 months after start of treatment. The cohort of the 915 patients was divided into two groups; cases that were defined as having primary ADT failure, and the group remaining (**Figure 4**). Differences in the characteristics of the early ADT failure group and those in the remaining cohort were tested using the Chi-square test. A univariate logistic regression model with OR and corresponding 95% CI was used to estimate the likelihood of early ADT failure for each variable. In order to identify independent predictors of early ADT failure, a multivariate logistic regression model was then constructed using all variables that were statistically significant in the univariate analyses. Three different criteria for early ADT failure were applied.

7.2.4. Statistical methods (Paper IV)

Study IV was based on a cohort of 900 patients in the SPCG-5 study. The extent of bone metastases was graded according to the modified Soloway Score (mSS 1, 2 and 3). Descriptive statistics were used for the clinical characteristics according to the mSS. The mean values of EORTC-30 ratings at baseline, according to the extent of bone metastases, were tested by ANOVA. Cumulative overall survival according to the extent of bone metastases was assessed using the Kaplan-Meier method. A univariate Cox regression model was performed to assess the risk of death according to mSS. In a subsequent step, the mSS and all other clinical variables were included in a stepwise Cox regression proportional hazards analysis. The clinical variables that had a major impact on the mSS and mortality were included in the final multivariate Cox regression model. In order to identify independent predictors in cases with various grades of bone metastases, a multivariate Cox regression model was constructed, using all variables that were statistically significant in the univariate analyses and stratified by mSS. In the sensitivity analyses, mSSs 2 and 3 were aggregated into one group and the univariate and the multivariate analyses repeated. In a subsequent step, we repeated all survival analyses including cancer-specific death only.

Figure 4. Flow chart showing study group assembly and follow-up of the Scandinavian Prostate Cancer Group (SPCG) No. 5 Trial on androgen deprivation treatment (ADT) in men with prostate cancer and bone metastases. Early ADT failure was defined as disease-specific death within 12 months after start of treatment.

8. RESULTS AND COMMENTS

8.1. Results (Paper I)

8.1.1. Factors that influence the long-term outcome of prostate cancer

The study presented in Paper I revealed several factors that influence the long-term outcome in men with low-risk PCa. These factors include age > 70 years and PSA level $\geq 4 \mu\text{g/L}$ at diagnosis. Watchful waiting as initial management was significantly associated with increased disease-specific mortality. A statistically significant difference was found between men who were treated with curative intent (radical prostatectomy or radiation therapy) and those who were managed with watchful waiting (expectancy) (**Figure 5**).

Figure 5. Kaplan-Meier curves for cumulative prostate cancer-specific survival (T2 and PSA ≥ 4).

Median age at diagnosis was 70 years (range 41-94 years) with 49% diagnosed before the age of 70 years, 42% between 70 and 80, and 9% in those 80 years or older. Of these 1300 tumours 779 (60%) were categorised as T1. There were 749 (58%) men primarily managed with watchful waiting, 411 (31%) received curative treatment, and 140 (11%) palliative therapy. Palliative therapy consisted of LHRH agonists, antiandrogens or orchiectomy on optional basis. Patients were followed up to 21.8 years (mean 10.6 years, median 11.0 years).

8.1.2. Increased mortality rate

During follow-up 1075, 833, 226 and 34 men were still alive 5, 10, 15, and 20 years after diagnosis. Ninety-three men (7%) died of prostate cancer. Cancer-specific survival was 0.98 (95% confidence interval (CI) 0.97-0.99), 0.95 (CI 0.93-0.96), 0.89 (CI 0.86-0.91) and 0.84 (CI 0.80-0.88) 5, 10, 15 and 20 years after diagnosis (**Figure 6**).

Figure 6. Kaplan-Meier curves for cumulative prostate cancer-specific and overall survival of 1300 patients with low-risk prostate cancer in the entire cohort. Patients at risk and cumulative survival with 95% confidence intervals are given at 5, 10, 15, 20 years after time of diagnosis.

The mean prostate cancer-specific mortality increased by 50.6% during the four follow-up periods.

Corresponding figures were seen when the data of the 779 T1 cases were analysed separately. Of all 779 patients with T1 tumours 48 (6%) died of prostate cancer. The cancer-specific survival of T1 cases was 0.98 (95% confidence interval (CI) 0.97-0.99), 0.95 (CI 0.94-0.97), 0.91 (CI 0.88-0.94) and 0.85 (CI 0.80-0.91) at 5, 10, 15 and 20 years after diagnosis (**Figure 7**).

Figure 7. Kaplan-Meier curves for cumulative prostate cancer-specific and overall survival (n = 446) **T1-tumours**. Patients at risk and cumulative survival with 95% confidence intervals are given at 5, 10, 15 and 20 years from date of diagnosis.

8.1.3. Prediction of long-term outcome

The hazard ratio for dying in prostate cancer was 1.69 for men with PSA ≥ 4 and T2 tumours when compared with the cohort remaining **Figure 8**).

Figure 8. Prostate cancer-specific mortality (T2 tumours).
Hazard ratio and 95% CI: Adjusted for age, N-category, M-category and management.

8.2. Results (Paper II)

8.2.1. Long-term outcome

Forty prostate cancer patients with metastatic disease at diagnosis (4.4%) in Study II, survived longer than 10 years. Altogether 167 died between 5 and 10 years, and 708 less than five years after enrolment into the study. The majority of the patients were older than 65 years at enrolment, had cancer-related pain and a performance score of at least 1. Four of five patients had a locally advanced tumour (T3-T4), 85% had WHO Grades 2-3, and 65% of the cases had a mSS of 2 or 3. Median PSA was 231 $\mu\text{g/L}$.

There were no statistically significant differences in age between the three survival groups. There were, however, differences in the proportion of patients

with cancer-related pain, performance status, and analgesic consumption between the three survival groups, where the majority of the long-term survivors had no sign of cancer-related pain, a high performance status, and did not require analgesics. There were differences with regard to WHO grade, PSA level, mSS and haemoglobin level between the survival groups. One in four of the long-term survivors had a mSS of 1, but there were no differences in distribution between T-category, absence of cardiovascular events, and men undergoing orchiectomy or not, between the three survival groups.

8.2.2. Factors associated with long-term survival

Prognostic factors associated with long-term survival were evaluated using univariate and multivariate logistic regression analyses. Factors significantly associated with long-term survival in the univariate analyses were: absence of cancer-related pain; performance status < 2 ; negligible analgesic consumption; localised tumour (T0-T2); PSA $< 231 \mu\text{g/L}$; and mSS 1. In the multivariate logistic regression analyses, performance status < 2 , PSA level $< 231 \mu\text{g/L}$, and mSS 1 were all independent predictors of long-term survival. For example, patients with a mSS 1 or a PSA level $< 231 \mu\text{g/L}$ had a threefold increased likelihood of long-term survival compared to men with a mSS 2-3 or PSA level $> 231 \mu\text{g/L}$.

Of men surviving at least ten years, 98% had at least one, 85% at least two and 45% all three favourable prognostics factors. The overall and cause-specific survival in relation to the number of favourable prognostics factors are shown in **Figures 9a and 9b**.

8.2.3. How does prostate cancer affect quality-of-life?

The EORTC-30 ratings are expressed as mean values. A wide range of mean values were obtained, and 7 out of 15 EORTC-30 ratings were significantly different between the survival groups ($p < 0.001$). The mean estimates of the global health status were 62.8, 69.7 and 72.6 for the short-, medium- and long-term survivors, respectively. There was a small decrease in the global health rating and functional ratings with time, a change that was most pronounced for physical function ratings. Among the long-term survivors, problems with fatigue

and dyspnoea were reported to increase during follow-up, from baseline mean values of 22 and 17 to 32 and 29 respectively at the ten-year follow-up.

Figure 9a. Cause-specific survival and **Figure 9b.** Overall survival of 915 patients with at least one, at least two, three or none of the favourable prognostics factors.

Figure 10. QoL overtime (mean) in prostate cancer patient (Paper II).

Data on QoL at the time of enrolment of the patient in the present study have been published in a previous study [179]. The overall mean QoL score was found to be 56.7, i.e. lower than that in a reference population of normal Swedish and Norwegian men, which emphasises the general clinical significance of prostate cancer with bone metastases as a serious disease (**Figure 10**).

8.3. Results (Paper III)

8.3.1. Early ADT failure

Data analyses from 915 patients with bone metastasis in Study III, showed that 94 patients (10.4%) died of progressive metastatic prostate cancer within 12 months after start of ADT, suggesting early ADT failure. The early ADT failure group had a significantly higher burden of cancer-related pain, poorer performance status, more analgesic consumption, and a higher mSS compared to the remaining cohort. There were also statistically significant differences with regards to level of haemoglobin and testosterone levels at the time of enrolment between the two groups. Factors without statistically significant differences related to early ADT failure were: age; treatment; cardiovascular comorbidity; T-category; grade of malignancy; serum oestrogen level; and SHBG at enrolment (**Table 7**).

8.3.2. Clinical predictors associated with early ADT failure

To identify factors associated with early ADT failure, univariate and multivariate logistic regression analyses were performed. Factors significantly associated with early ADT failure in the univariate analyses were: cancer-related pain; poor ECOG performance status; high analgesic consumption; high mSS; and a low level of haemoglobin at enrolment. In the multivariate logistic regression analyses, poor ECOG performance status, analgesic consumption, high mSS, and low level of haemoglobin were all independent predictors of early ADT failure. For example patients with an ECOG performance status of 1 or higher had a threefold increased likelihood of early ADT failure compared to patients with performance status of 0. The results of the 3 scenario analyses did not differ from the base case analyses (the 94 patients who died of progressive metastatic prostate cancer within 12 months), where a poor ECOG performance status, analgesic consumption, a high mSS, and low levels of haemoglobin were all independent predictors of early ADT failure (**Table 8**).

8.4. Results (Paper IV)

8.4.1. Prognostic significance in relation to other pretreatment variables

In Paper IV, 900 men were grouped according to the extent of bone metastasis (modified Soloway Score). The majority had a score of 2 at inclusion (53.7%). The median follow-up was 75.6 months (39.2–139.3 months), during which 841 men died. Median follow-up was shorter for patients with a higher mSS. Cancer-related pain, analgesic consumption, T-category, ALP, PSA, and haemoglobin all differed significantly between the mSS groups.

Overall survival was higher among patients with mSS 1 at inclusion (5-year 39%, 95% CI 34-45%) compared to those with Scores 2 (5-year 17%, 95% CI 14-21%) and 3 (5-year 9%, 95% CI 5-17%), respectively. This was also confirmed in a univariate Cox Regression model (**Figure 11a**). When adjusting for performance status, analgesic consumption, grade of malignancy, ALP, PSA, haemoglobin and global health status, mSS 2 and 3 had a 47% (HR 1.47, 95% CI 1.21-1.80) and 78% (HR 1.78, 95% CI 1.32-2.42) increased mortality compared to a score of 1, respectively (**Figure 11a**). The same pattern was observed when limiting to cancer-specific mortality (mSS 2 - HR 1.75, 95% CI 1.39-2.20; Score 3 - HR 1.96, 95% CI 1.39-2.72) (**Figure 11b**).

Table 7. Demographic and clinical characteristics of the primary ADT failure group and the remaining cohort.

	Primary ADT failure		Remaining cohort		Total		
	n	(%)	n	(%)	p-value	n	(%)
All cases	94	(100.0)	821	(100.0)	-	915	(100.0)
Age, years							
< 65	10	(10.6)	123	(15.0)		133	(14.5)
65-74	41	(43.6)	393	(47.9)		434	(47.4)
≥ 75	43	(45.7)	305	(37.1)	0.217	348	(38.0)
Initial Treatment							
Polyestradiol phosphate	44	(46.8)	414	(50.4)		458	(50.1)
TAB	50	(53.2)	407	(49.6)	0.579	457	(49.9)
Cardiovascular comorbidity							
None	80	(86.0)	731	(90.0)		811	(89.6)
Present	13	(14.0)	81	(10.0)	0.354	94	(10.4)
Missing	1	-	9	-		10	-
Cancer-related pain							
No pain	21	(22.3)	356	(43.6)		377	(41.4)
Pain	73	(77.7)	460	(56.4)	<0.001	533	(58.6)
Missing	-	-	5	-		5	-
ECOG performance status							
0	16	(17.0)	389	(47.7)		405	(44.5)
1	50	(53.2)	305	(37.4)		355	(39.0)
2-3	28	(29.8)	122	(15.0)	<0.001	150	(16.5)
Missing	-	-	5	-		5	-
Analgesic consumption							
Negligible	21	(22.3)	414	(50.7)		435	(47.8)
≥ 1	73	(77.7)	402	(49.3)	<0.001	475	(52.2)
Missing	-	-	5	-		5	-
Grade of malignancy							
WHO 1	12	(13.3)	124	(15.5)		136	(15.3)

WHO 2	34	(37.8)	380	(47.5)	414	(46.5)
WHO 3	44	(48.9)	296	(37.0)	340	(38.2)
Missing	4	-	21	-	25	-
T-category						
T0-T2	12	(13.0)	177	(21.9)	189	(21.0)
T3-T4	80	(87.0)	633	(78.1)	713	(79.0)
Missing	2	-	11	-	13	-
PSA, µg/L						
PSA < 100	24	(25.5)	223	(27.3)	247	(27.1)
PSA 100-500	39	(41.5)	353	(43.3)	392	(43.1)
PSA > 500	31	(33.0)	240	(29.4)	271	(29.8)
Missing	-	-	5	-	5	-
mSS						
1	14	(15.1)	305	(37.8)	319	(35.4)
2-3	79	(84.9)	502	(62.2)	581	(64.6)
Missing	1	-	14	-	15	-
Haemoglobin, g/L						
median, (q1-q3)	108.5	(11.3-129.0)	125.0	(11.6-141.0)	124.0	(11.6-140.0)
Missing	0	-	12	-	12	-
SHBG						
median, (q1-q3)	47.5	(39.8-53.3)	39.5	(28.0-57.8)	42.0	(29.3-57.0)
Missing	78	-	711	-	789	-
Estradiol						
median, (q1-q3)	64.0	(0.1-82.0)	65.0	(0.2-98.0)	64.5	(0.1-96.0)
Missing	79	-	712	-	791	-
Testosterone						
median, (q1-q3)	12.0	(8.3-16.6)	13.2	(10.0-17.4)	13.0	(9.8-17.2)
Missing	11	-	79	-	90	-

Table 8. Multivariate logistic regression for primary ADT Failure.						
	Scenario 1			Scenario 2		
	Multivariate			Multivariate		
	OR	CI 95%		OR	CI 95%	
Age, years						
< 65	-	-	-	-	-	-
65-74	-	-	-	-	-	-
≥ 75	-	-	-	-	-	-
Initial Treatment						
Polyestradiol phosphate	-	-	-	-	-	-
TAB	-	-	-	-	-	-
Cardiovascular comorbidity						
None	-	-	-	-	-	-
Present	-	-	-	-	-	-
Cancer-related pain						
No pain	1.00	ref.	1.00	1.00	ref.	1.00
Pain	0,5	0.20-1.21	0,55	0.22-1.31	0.22-1.26	0,53
ECOG Performance status						
0	1.00	ref.	1.00	1.00	ref.	1.00
1	3,31	1.76-6.54	3,32	1.75-6.60	1.65-6.09	3,09
2-3	4,07	1.95-8.77	3,84	1.82-8.37	1.67-7.44	3,47
Analgesic consumption						
Negligible	1.00	ref.	1.00	1.00	ref.	1.00
≥ 1	3,08	1.30-7.27	2,69	1.15-6.71	1.25-7.22	2,92
Grade of malignancy						
WHO 1	-	-	-	-	-	-
WHO 2	-	-	-	-	-	-
WHO 3	-	-	-	-	-	-

T-category									
T0-T2		1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
T3-T4		1.76	0.93-3.65	1.67	0.87-3.48	1.8	0.95-3.73		
PSA, µg/L									
PSA < 100		-	-	-	-	-	-	-	-
PSA 100-500		-	-	-	-	-	-	-	-
PSA > 500		-	-	-	-	-	-	-	-
mSS									
1		1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
2-3		2.11	1.17-4.04	1.67	0.91-3.25	2.22	1.24-4.25		
Haemoglobin, g/L									
High		1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Low		1.74	1.09-2.86	1.68	1.04-2.78	1.65	1.03-2.69		
SHBG									
Low		-	-	-	-	-	-	-	-
High		-	-	-	-	-	-	-	-
Estradiol									
Low		-	-	-	-	-	-	-	-
High		-	-	-	-	-	-	-	-
Testosterone									
Low		-	-	-	-	-	-	-	-
High		-	-	-	-	-	-	-	-

Figure 11a, 11b. Kaplan-Meier overall and disease-specific survival curves.

Independent prognostic factors associated with overall mortality risk according to extent of metastases were analysed in multivariate Cox regression analysis. Poor performance status, high analgesic consumption, high grade of malignancy and high level of PSA were all independent risk factors for mortality in patients with mSS 1. On the contrary, a normal haemoglobin and good global health status were both associated with lower mortality in patients with mSS 1. In patients with mSS 2, poor performance status, high grade of malignancy and elevated ALP were independent risk factors, while normal haemoglobin and good global health status were independent factors for lower mortality. In the mSS 3 group, only level of haemoglobin had a significant impact on mortality.

In the sensitivity analyses (mSS 2 and 3 aggregated); performance status, ALP, haemoglobin, and global health status were all independent prognostic factors of overall mortality **Table 9**.

In an analysis of cancer-specific mortality, grade of malignancy and PSA level were found to be independent predictive factors for mSS 1. Baseline demographic and disease characteristics were similar between the treatment groups. No significant differences in overall or disease-specific survival were observed and thus, treatment was not included in the multivariate models. Data on quality-of-life prior to start of endocrine treatment and during treatment were obtained from all patients but not analysed according to the different forms of treatment [179]. In an analysis limited to cancer-specific mortality, grade of malignancy and level of PSA were independent factors among patients with mSS 1. Performance status, grade of malignancy, ALP, and global health status were independent predictive factors for the mSS 2 group, whereas in the Score 3 group haemoglobin level was the only predictive factor (**Table 10**).

Table 9. Adjusted model (modified Soloway Score 2+3).

	mSS 2-3	
	aHR	95% CI
Age, years		
< 65	-	-
65-74	-	-
≥ 75	-	-
Cancer-related pain		
No pain	1	ref.
Pain	1,05	0.81-1.36
ECOG performance status		
0	1	ref.
1-3	1,29	1.02-1.63
Analgesic consumption		
Negligible	1	ref.
≥ 1	0,96	0.73-1.25
Grade of malignancy		
WHO 1	1	ref.
WHO 2	0,98	0.73-1.32
WHO 3	1,41	1.04-1.91
T-category		
T0-T2	-	-
T3-T4	-	-
Cardiovascular comorbidity		
None	-	-
Present	-	-
Alkaline phosphatase		
< 1.25	1	ref.

≥ 1.25	1,27	1.02-1.58
PSA, µg/L		
< median (< 233)	-	-
≥ median (≥ 233)	-	-
Haemoglobin, g/L		
< median (< 124)	1	ref.
≥ median (≥ 124)	0,73	0.59-0.89
Estradiol		
< median (< 65)	-	-
≥ median (≥ 65)	-	-
Testosterone		
< median (< 13)	-	-
≥ median (≥ 13)	-	-
SHBG		
< median (< 42)	-	-
≥ median (≥ 42)	-	-
Global Health status		
< mean (< 56.8)	1	ref.
≥ mean (≥ 56.8)	0,78	0.63-0.97
Physical Functioning		
< mean (< 76.5)	1	ref.
≥ mean (≥ 76.5)	1,03	0.83-1.27
Role Functioning		
< mean (< 91.6)	1	ref.
≥ mean (≥ 91.6)	0,87	0.69-1.09

Table 10. 5-year survival estimates and the log rank test between Kaplan-Meier curves according to modified Soloway Score

	mSS 1				mSS 2				mSS 3			
	Survival		Log rank test		Survival		Log rank test		Survival		Log rank test	
	5-year	95% CI	p-value		5-year	95% CI	p-value		5-year	95% CI	p-value	
All patients	39	34.0-44.9	-		16,9	13.9-20.7	-		9,2	4.9-17.1	-	
Initial treatment												
Polyestradiol phosphate	39,7	32.6-48.4	ref.		15,7	11.7-21.0	ref.		8,2	3.2-20.9	ref.	
TAB	38,4	31.5-46.8	0,796		18,3	13.9-24.0	0,884		10,2	4.5-23.4	0,743	
Age, years												
< 65	37,2	25.2-54.9	ref.		11,8	6.4-21.9	ref.		8,3	1.3-54.4	ref.	
65-74	36,1	29.0-45.0	0,555		19,6	15.0-25.5	0,169		12,2	5.8-25.9	0,825	
≥ 75	42,8	35.0-52.4	0,588		15,8	11.2-22.3	0,819		5,4	1.4-20.8	0,631	
Cancer-related pain												
No pain	44,4	38.4-51.2	ref.		19,7	15.5-24.9	ref.		11,7	5.8-23.4	ref.	
Pain	23,5	15.3-36.1	0,002		13,3	8.9-19.8	<0.001		6,3	1.6-23.9	0,869	
ECOG performance status												
0	46,9	40.4-54.4	ref.		21,1	16.6-26.8	ref.		11,3	5.3-24.1	ref.	
1-3	25,1	17.9-35.1	<0.001		11,4	7.7-17.1	<0.001		7,7	2.6-22.8	0,508	
Analgesic consumption												
Negligible	44,4	38.6-51.1	ref.		19,7	15.4-25.0	ref.		9,5	4.5-20.4	ref.	
≥ 1	18,2	10.4-31.9	<0.001		13,7	9.4-20.0	<0.001		10,3	3.5-30.2	0,715	
Grade of malignancy												
WHO 1	51,9	40.0-67.4	ref.		32,4	22.6-46.5	ref.		5,6	0.8-37.3	ref.	
WHO 2	47,7	40.1-56.8	0,681		19,7	15.1-25.7	0,17		10,8	4.3-27.3	0,374	
WHO 3	22,9	16.2-32.2	0,01		7,9	4.7-13.0	<0.001		7,9	2.7-23.4	0,438	

T-category										
T0-T2		41,6	31.9-54.3	ref.	22,6	15.1-33.9	ref.	8,7	2.3-32.7	ref.
T3-T4		37,9	32.2-44.7	0.916	12,7	12.7-20.1	0.243	9,5	4.7-19.1	0.139
Cardiovascular comorbidity										
None		40,2	34.7-46.5	ref.	17,6	14.3-21.7	ref.	8,7	4.5-16.9	ref.
Present		31,8	20.1-50.3	0.141	11,3	4.9-25.7	0.164	16,7	2.8-99.7	0.617
Alkaline phosphatase										
< 1.25		42	36.5-48.4	ref.	23,1	17.4-30.8	ref.	13,3	3.7-48.5	ref.
≥ 1.25		20,1	10.8-37.1	<0.001	13,9	10.5-18.4	<0.001	8,4	4.2-17.1	0.192
PSA, µg/L										
< median (< 233)		42,9	36.7-50.2	ref.	18	13.4-24.2	ref.	16,1	7.2-36.0	ref.
≥ median (≥ 233)		31	23.2-41.5	0.006	16,1	12.3-21.2	0.572	6	2.3-15.4	0.534
Haemoglobin, g/L										
< median (< 124)		33,8	26.1-43.7	ref.	12,4	8.9-17.2	ref.	6,2	2.4-15.9	ref.
≥ median (≥ 124)		42,6	36.1-50.1	0.038	22,1	17.1-28.5	0.003	15,2	6.8-34.0	0.012
Testosterone										
< median (< 13)		38,6	31.3-47.8	ref.	17	12.7-22.9	ref.	11,4	5.0-25.9	ref.
≥ median (≥ 13)		40,1	33.2-48.6	0.861	15,5	11.3-21.4	0.682	9,5	3.8-24.2	0.719
Global Health status										
< mean (< 56.8)		23,3	16.1-33.8	ref.	12,6	8.9-18.0	ref.	4,4	1.1-16.9	ref.
≥ mean (≥ 56.8)		47,5	40.9-55.3	<0.001	21,2	16.1-28.0	<0.001	14,3	6.4-32.2	0.086
Physical Functioning										
< mean (< 76.5)		35,1	27.5-44.8	ref.	13,4	9.4-19.0	ref.	10,6	4.7-24.4	ref.
≥ mean (≥ 76.5)		43,3	36.3-51.7	0.076	19,9	15.2-26.1	0.049	7,3	2.5-21.8	0.343
Role Functioning										
< mean (< 91.6)		27,2	18.7-39.5	ref.	11,8	7.9-17.7	ref.	2,6	0.4-18.2	ref.
≥ mean (≥ 91.6)		43,6	37.4-50.9	0.004	20,9	16.4-26.7	<0.001	14,3	7.2-28.4	0.095

8.4.2. Impact of bone metastases on quality-of-life

The mean global health status was 64.4 and 50.5 for mSS 1 and 3. Four of five functioning scales showed decreased rating with increased mSS; mean physical functioning was 81.4 for Score 1 and 65.7 for Score 3. Most symptoms, including fatigue, pain, and insomnia was significantly more pronounced in patients with a higher mSS (**Table 11**).

Table 11. Baseline EORTC-30 ratings for the 900 study patients according to modified Soloway Score.

EORTC-30 ratings	mSS 1		mSS 2		mSS 3		p-value
	mean	sd	mean	sd	mean	sd	
Global Health status	64,4	21,7	52,6	24	50,5	25,1	<0.001
Functional scales							
Physical Functioning	81,4	22,8	72	28	65,7	30,4	<0.001
Role Functioning	94,1	10,7	90,3	12,8	89,3	13,4	<0.001
Emotional Functioning	79,6	19,8	75,2	22,2	72,4	23,4	0,005
Cognitive Functioning	85,2	18,3	83	21,1	82,4	21,8	0,287
Social Functioning	90,7	16	82,2	25	79,3	26,7	<0.001
Symptom scales							
Fatigue	27,6	22,7	41	27,2	49,5	25,2	<0.001
Dyspnoea	19,5	23,7	20,8	25,3	22,7	27,5	0,557
Nausea / vomiting	4,3	12,7	9,3	17,7	13,6	19,8	<0.001
Pain	21,8	25,7	41,5	31,3	45,5	32,9	<0.001
Insomnia	20,6	28,3	27,8	30,7	32,2	31,5	0,001
Appetite loss	11,7	25	25,8	33,5	34,5	35,4	<0.001
Constipation	16,1	25,3	22,5	30,4	29,5	31,9	0,001
Diarrhoea	7,4	16,7	6,2	16,7	9,8	21,7	0,195
Financial problems	4,2	16,1	6,5	18,6	3,9	13	0,156

9. GENERAL DISCUSSION

In the studies of this thesis, disease-specific survival in prostate cancer patients has been explored in two large study groups. The data were gathered from a register cohort from the SERPCR and from a cohort in a randomised clinical trial (SPCG5). Low-risk tumours as well as metastatic cancers were included in the studies. We identified factors that influence the long-term outcome of men with low-risk tumours in a population-based register, and explored mortality rate for men with low-risk PCa. In a population-based prospectively assembled cohort, factors associated with long-term survival in patients with metastases in the skeleton were investigated, as well as how PCa affects the quality of life of men with prostate cancer. We also analysed early ADT failure and defined predictors associated with short survival due to early ADT failure in M1b PCa patients. We investigated the prognostic significance of the extent of bone metastases in relation to other pretreatment variables, and explored the impact of bone metastases on QoL in those patients.

There is lack of consensus in the medical literature regarding criteria used to define a low-risk tumour; we used the criteria of the NPCR and MSKCC [180]. In some studies, T2 tumours and all T2 subgroups are considered low-risk tumours. Other studies have been based on criteria totally excluding T2 tumours from the low-risk group. Furthermore, the extent of tumour volume and size of tumour growth in the biopsies of T2 tumours also vary. In the SEER database at prostatectomy, 9.7% of cases were up-staged and 44% up-graded when comparing postoperative specimens with preoperative biopsies and clinical assessment [181]. Hopefully, as improved technology and methods develop, new approaches will more accurately characterise the disease [182]. In the SERPCR cohort the tumour had a very indolent course during the first years after diagnosis, but showed a gradual progression into more lethal cancer over the 20-year period. Studies with shorter follow-up may overestimate survival prognosis for these men if simple extrapolation is used. There are still insufficient morphologic or molecular biologic explanations for the instability and clinical progress of PCa over time [183-185].

For the more advanced forms of PCa, distant metastases are found either at the time of diagnosis or develop later during follow-up after initial management of the localised disease. At present it is not possible to predict whether or not a

tumour will develop metastases from onset. Death due to malignant disease is almost invariably the result of failure to control metastatic disease. In prostate cancer the skeleton is the most common site of metastases [18]. Skeletal metastases contribute significantly to disease-specific mortality and morbidity. Pain, pathological fractures, nerve compression syndromes and hypercalcaemia are manifestations of bone metastases. However, despite the poor prognosis once the tumour has spread to a distant location, generalised prostate cancer differs from other malignant diseases in several respects. A small, but not negligible, minority of men with metastasising disease may live a decade without substantial reduction in QoL. Although it may be difficult to predict which men will live that long, the detection of skeletal metastases does not inevitably rule out the possibility of living several years with an acceptable QoL. On the other hand there is a subgroup of men that do not primarily responded to ADT. Few studies have been undertaken to elucidate this phenomenon even though it continues to be mentioned in the uro-oncologic literature [25, 26, 28-31, 34, 51, 52]. A state of castration resistance usually develops after long-term ADT. Improving the results of mCRPC treatment is currently regarded as one of the most critical goals in the management of the disease [35, 53-55]. In the pre-ADT era, prostate cancer with bone metastases had a very short survival expectation, with a nine-month mortality rate of 66%. However, long-term survival was sometimes seen even in the pre-ADT era [19]. A better understanding of the mechanisms behind secondary resistance following long-term ADT may result in a better understanding of early ADT failure. However, mCRPC following long-term ADT is probably a much more heterogeneous condition than metastatic prostate cancer primarily failing to respond to ADT [38]. In 1992, a prognostic grouping was advocated by dividing metastatic spread (M1) into three different groups depending on site; M1a = non-regional lymph nodes, M1b = bone, and M1c = other sites i.e. soft tissue. The site of distant metastases is sometimes recorded in the literature, but the prognostic value of this classification is not clear. In a recent validation of the prognostic grouping of M1 disease, a considerable variation in five-year overall survival was found [186]. The extent of bone metastases, according to the mSS, has a crucial impact on expected quality-of-life and survival. The subgroups of men with widespread metastases and performance status deterioration are probably those that benefit the most from a combination of endocrine treatment and chemotherapy.

9.1. Strengths and Limitations

9.1.1. Paper I

The strength of Study I is that it is a population-based register study. The SERPCR was the first prostate cancer register in Scandinavia in which tumour characteristics and primary treatment of virtually all prostate cancer patients were registered. This register was also the first that included PSA as a staging and prognostic tool (from January 1st, 1992). The PSA levels were measured at three laboratories in the healthcare region and the laboratories were operating under standardised conditions (with a method calibrated against the Stanford 90:10 PSA standard [187]). A pathology re-review of Gleason scoring in this register was also performed and high immune reactivity of Ki-67 was suggested as independent adverse predictor of disease-specific mortality in patients after initial watchful waiting [188]. A further strength of the study is that the SERPCR has a high validity regarding cause of death based on comparison of registration in the SERPCR and that in the national Cause of Death Register. The SERPCR has achieved a coverage of > 98%.

At the time of our study the strategy of active surveillance had not yet been introduced into clinical practice. It is also unclear whether or not the low-risk group in the present cohort corresponds to patients that presently meet the criteria for active surveillance [109]. Although treatment has not radically changed, diagnostic methods have improved and characterisation of the low-risk group probably represents lower disease severity since patients are now diagnosed at an earlier stage. In 2005, the Gleason prostate cancer grading system underwent a major revision, which resulted in a relative upgrading of tumours [189]. Certain tumours in our study diagnosed before 2005 and graded as Gleason Score 6 would probably now be graded as Gleason Score 7 and thereby excluded from our study. Comparison between the initial and modified Gleason grading was not performed in the present study. This implies that the prognosis for men with tumours assigned the initial Gleason score appeared relatively poor. In this study based on data from the SERPCR, we were not able to analyse any change in treatment received once the first treatment decision was made, since this was not recorded in our database. Consequently we were unable to determine what impact any change in treatment had on survival.

9.1.2. Papers II-IV

From the SPCG5 study group we analysed the long-term outcome of a selected group with metastatic spread to the bone. Our prognostic models were based on a large dataset from a relatively homogeneous patient population with a long follow-up period and with sufficient rate of events to analyse the most important predictors. To our knowledge this is the first study where M1b disease has been divided into three groups based on the extent of bone metastases, enabling analyses of overall and disease-specific survival. We routinely used clinically relevant measurable variables including QoL.

We included men from a group taking part in the SPCG5 trial; a randomised controlled trial. This limits the external validity of our study since only men who fulfilled all criteria and were in a mental state to give consent to the trial were eligible for inclusion. Furthermore, the treatment of prostate cancer has progressed since the time of the start of that trial. Nowadays, ADT is no longer the only treatment alternative for men with metastasising prostate cancer [190].

A high PSA level at start of treatment indicates a large tumour burden.

However, PSA does not always correlate with tumour burden, especially in men with PSA levels $< 50 \mu\text{g/L}$. In another study on men with prostate cancer and distant metastases, the median PSA value was only $132 \mu\text{g/L}$. A PSA $< 65 \mu\text{g/L}$ was associated with a favourable outcome [191]. We did not have access to data on the location of bone metastases and we therefore could not say whether they were axial (pelvic bones and spine) or appendicular (long bones, skull), which has been a discriminating factor between risk groups in other trials [192-194].

At inclusion, no distinction between men with *de novo* metastatic disease and patients progressing from localised disease to metastatic disease was made. It is most likely that the population of the patients in this trial included a high proportion of men with *de novo* metastatic disease, which is not typical for men diagnosed with prostate cancer nowadays. Visceral and non-regional lymph node metastases were not evaluated at inclusion in this study. However, according to most studies, visceral metastases (M1c) have a low prevalence. The prevalence of metastases in the lungs in men with M1 disease ranges from 2% to 11%, and in the liver from 0.4% to 3% [192, 194]. The negative predictive value is not clear. No attempt has been made to classify or quantify metastases in sites other than bone.

10. CONCLUSIONS

- The long-term disease-specific mortality for men with low-risk localised prostate cancer is low, but the annual mortality rate from prostate cancer gradually increases. This indicates that some tumours slowly develop into lethal cancer, particularly in patients 70 years or older with a PSA level ≥ 4 $\mu\text{g/L}$.
- A subgroup of prostate cancer patients with M1b disease and certain characteristics showed a positive long-term response to ADT with an acceptable QoL over a decade or more. Independent predictors of long-term survival were identified as performance status < 2 , limited extent of bone metastases (mSS 1), and a PSA level < 231 $\mu\text{g/L}$ at the time of enrolment.
- Four independent clinical predictors of early ADT failure could be defined. Men with these features should be considered for an alternative treatment in parallel with ADT.
- Patient grouping into three categories based on extent of bone metastases showed in relation to performance status, haemoglobin, and global health status at presentation to be independent predictors of mortality. This information may provide us with a tool enabling improved and accurate prediction of prognosis.

Active surveillance provides an opportunity to identify markers of prostate cancer behaviour, and to test novel therapeutic strategies. Our data from clinical practice may be used to estimate changes in stage-specific incidence and disease-specific survival of low-risk prostate cancer for comparison with current low-risk prostate cancer groups. For men with a life expectancy shorter than twenty years, it appears that the risk for overtreatment is great.

A subgroup of M1b patients with PCa and certain characteristics have a long-term positive response to ADT. This group of men survived longer than a decade with an acceptable QoL. Independent predictors of long-term survival

were: good performance status; limited extent of bone metastases; and a low PSA level at the time of enrolment. On the other hand, there were men in this group that showed early treatment failure. Using multivariate analyses, poor ECOG performance status, analgesic consumption, high mSS, and low haemoglobin were found to be predictive of early ADT failure. We have shown that different subgroups of M1b disease have different prognoses depending on the extent of bone metastases.

The results of the studies in this thesis have provided vital information that should be taken into consideration when deciding on treatment for men with low-risk and those with metastasising prostate cancer. Men with above-mentioned characteristics should be considered for expectancy or alternative treatment. Application of predictive factors according to the results of this thesis may be used in future prospective trials evaluating individualised treatment strategies for men with prostate cancer.

11. FUTURE RESEARCH

Prostate cancer is a heterogeneous, complex disease with many clinical and molecular expressions. At present, digital rectal examination and PSA - screening are the most common ways to diagnose prostate cancer before symptoms develop. These diagnostic tools, however, have their limitations. Since PCa is increasingly being diagnosed at an early stage, we need to find better diagnostic tools to reduce unnecessary repeated testing in men with an elevated PSA value but with no sign of cancer. We must also find markers to predict prognosis of men managed with AS. Because the diagnostic tools of today are not accurate we need to improve them and find strategies to reduce the risk for men with advanced disease or those who face the risk of developing advanced disease, without missing the possibility to cure men harbouring lethal cancer.

With modern diagnostic biomarkers and knowledge about the function and division of cancer cells, we now have the ability to test new agents on prostate cancer samples, to differentiate low-risk tumours from intermediate- and high-risk prostate cancer.

The European Randomised Study of Screening for Prostate Cancer (ERSPC), recently found overdiagnosis to be between 27 and 56 per cent [195]. This is a particularly important issue, as treatment for prostate cancer is often associated with significant side-effects such as incontinence, bowel and sexual dysfunction. Prostate cancer grows slowly and rarely threatens the patient's life, making treatment unnecessary in many cases. Many men die *with* their prostate cancer not *of* it.

When low-risk prostate cancer is detected by screening, it is sometimes very difficult to determine whether or not there is more undetected advanced cancer before treatment or surveillance is started.

The hyperplastic prostate epithelium is composed of multiple differentiated cell types, including basal, luminal (secretory) and neuroendocrine cells. Moreover, there is an intermediate cell type that shares features with both luminal and basal cells described [196, 197]. Luminal secretory cells constitute the majority of the epithelial layer and because they express androgen receptors, they can respond directly to androgens by stimulating the production and secretion of prostate proteins such as PSA and prostatic acid phosphatase [198, 199]. Prostate basal

cells exist in one or two layers connected to the basement membrane in luminal cells [198, 200, 201] and can be distinguished from other prostatic cells by their morphology.

A hypothesis to be tested in future studies: immunohistochemical analysis of tissue from prostate needle biopsy samples may make it possible to identify the presence of prostate cancer even when normal biopsy microscopy does not reveal cancer cells.

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APPENDIX

Participants in the SPCG-5 trial

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