Living and dying with prostate cancer

Population-based register studies

MAGDALENA LYCKEN
Abstract

Tailored treatment with adequate timing is essential for the quality of prostate cancer care at all stages. Overtreatment should be avoided due to the side effects, but undertreatment may on the other hand lead to progression and death. This thesis aims to describe the patterns of use for non-curative treatments of prostate cancer, alongside the time trends of disease characteristics of men who die from prostate cancer. The work was based on the National Prostate Cancer Register of Sweden (NPCR).

The first study included 45 147 men. The cumulative incidence of castration was 11.6% at ten years after diagnosis, while it was 10.8% for antiandrogen monotherapy. Estimated median durations of castration ranged from four years in the deferred treatment high-risk group to seventeen years in the prostatectomy low-risk group. The second study included 114 cases and 1140 controls. Four men out of ten received androgen deprivation therapy although they had prostate-specific antigen doubling time ≥12 months and biopsy Gleason score ≤7, which was defined as non-adherence to the guidelines of the European Association of Urology. Most of these men had low-risk features at diagnosis. The third study included 8326 men. During the last year before death from prostate cancer, use of opioids increased from 30% to 72%. Men without close relatives and older men had lower probability to receive opioids. The fourth study included 45 850 men. During the study period of 1992 to 2012, the time trend showed a stage shift towards lower risk group at diagnosis, longer disease duration, and higher age at death among men who died from prostate cancer.

The first two studies indicate that overtreatment with androgen deprivation therapy is common after curative treatment, why interventions to improve adherence to guidelines are needed. The third study indicates that men without close relatives and older men are disadvantaged with respect to treatment of cancer pain, why they need closer attention from health care providers. The findings in the fourth study may reflect the synergistic effects of prolonged lead time, increased life expectancy, and improvements in the management of prostate cancer during the last two decades.

Keywords: Androgen deprivation therapy; Palliative medicine; Population-based study; Prostate cancer.

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<td>AGREE</td>
<td>Appraisal of Guidelines for Research and Evaluation</td>
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<td>CCI</td>
<td>Charlson comorbidity index</td>
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<td>CRPC</td>
<td>Castration-resistant prostate cancer</td>
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<td>EAU</td>
<td>European Association of Urology</td>
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<td>GnRH</td>
<td>Gonadotropin-releasing hormone</td>
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<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development, and Evaluation</td>
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<td>LISA</td>
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<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
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<td>NPCR</td>
<td>National Prostate Cancer Register of Sweden</td>
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<td>NSAID</td>
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<td>PSA</td>
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<td>PSADT</td>
<td>Prostate-specific antigen doubling time</td>
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<td>TNM</td>
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Introduction

This thesis comprises four clinical studies focusing on the patterns of use for non-curative treatments of prostate cancer, alongside the time trends of disease characteristics of men who die from prostate cancer. The work is based on the National Prostate Cancer Register of Sweden (NPCR).

The first paper describes the patterns of treatment with androgen deprivation therapy (ADT) for men initially diagnosed with localised prostate cancer. In the second paper the adherence to guidelines for ADT following radical prostatectomy is assessed. The third paper describes the use of palliative medications before death from prostate cancer. In the fourth paper the time trends of diagnostic criteria, disease duration, and age at death is described for men who died from prostate cancer between 1992 and 2012.

Background

The disease course of prostate cancer can take very different paths. Many tumours never show any symptoms during a lifetime, while others spread and become lethal. Overtreatment in the earlier stages of disease is a recognised problem, which can lead to prolonged time with severe side effects and decreased quality of life. Undertreatment, on the other hand, may lead to progression and death. Men with advanced prostate cancer often endure an extended period of life when the disease causes symptoms and complications. In this stage of the disease, symptoms like pain and mood disorders risk to be unnoticed and undertreated.

Tailored treatment to selected patients with adequate timing is therefore essential for the quality of prostate cancer care in all stages. However, there is much ongoing debate about the best choice of treatment, the best timing, and the right selection of patients along the whole disease trajectory. Several sets of guidelines exist to support treatment decisions, but their implementation into clinical practice remain a challenge. Individualised risk-based screening, evolving imaging techniques, and biological markers are promising tools to increase the specificity of screening tests and treatment decisions in the future.1–3
Epidemiology

Prostate cancer is the most common cancer in Sweden, with over 100 000 men living with the disease. Due to the introduction of prostate-specific antigen (PSA) testing, the incidence increased sharply during the 1990:s. The incidence has then reached a plateau at approximately 10 000 new cases per year, while the prevalence has increased fourfold since 1990 and continues to increase.4

Men live longer with prostate cancer today than two decades ago, as shown in Paper IV. Also, the population is aging, and old age is one of the most important risk factors for prostate cancer.5 We know from autopsies that 60 percent of the men over 80 years of age have a prostate tumour, often of no clinical importance due to slow progression.6

Even though competing causes of death are dominating, prostate cancer is still the single most common cause of cancer death among Swedish men.7 During the last decade, the crude prostate cancer mortality has remained stable, but the age-standardised prostate cancer mortality has decreased in Sweden and many other countries.4,8 This decrease is often referred to both earlier detection and improvements in disease management, but the relative effect by each on the age-standardised mortality is not yet understood.8
Symptoms of prostate cancer

The early stages of prostate cancer are often asymptomatic, since most symptoms originate either from local growth or from metastases. Local growth of the primary tumour into the surrounding urinary system might cause pain, obstruction, and haemorrhage and can eventually block the urine drainage.

The prime metastatic sites are the distant lymph nodes and the skeleton. In bone, the cancer cells induce increased osteolysis, which is crucial for the seeding of the cancer cells and the initial growth of the metastasis. During the subsequent phases of bone colonisation, the osteoblastic activity dominates which results in the typical osteosclerotic lesions seen in prostate cancer. However, the osteolytic activity persists and increases the risk of pathological fractures in the lesions.9,10 A feared complication of metastases is the spinal cord compression, a medical urgency that leads to paraplegia if left untreated. The damage to the spinal cord is done through both direct compression and secondary vascular damage, ultimately leading to spinal cord ischemia and infarction.11
The pain from bone metastases is a result of inflammatory, neuropathic and ischemic mechanisms. Both the cancer cells and the cells of the surrounding stroma release algogenic substances that stimulate nociceptors. They also release a number of growth factors and pro-inflammatory mediators that contribute to the ectopic sprouting and sensitisation of nerve fibres, which in turn leads to hyperexcitability and increased pain. An upregulation of the endogenous opioidergic system can mask the pain in the earlier stages of metastatic disease, but with heavier disease burden a constant pain accompanied by shorter intervals of severe flares of breakthrough pain may impair the quality of living. In late stages of disease, pain is often accompanied by fatigue, anxiety, depression, and sleep disorders.

The proportion of men with prostate cancer who suffer from different symptoms needs to be further explored. The prevalence of common mood disorders, such as depression and anxiety, is known to be higher among cancer patients with a considerable treatment gap. Among prostate cancer patients of mixed stages and treatments, the pooled prevalence has been assessed to 18% for both post-treatment depression and anxiety. The prevalence of pain in terminal prostate cancer has been evaluated in an Italian sample study, showing that 90% of the men who died of prostate cancer suffered from pain during the last three months of life, and 60% suffered from very distressing pain.
Non-curative treatments

Androgen deprivation therapy

Prostate cancer can be cured through radical prostatectomy or radiotherapy before systemic spread manifests. After the curative stage, the disease can still be effectively suppressed for many years through non-curative strategies. The main treatment in advanced disease is ADT. The rationale behind ADT is that androgen receptor signalling is essential for the survival and growth of the cancer cells. When deprived of androgens, the tumour burden shrinks, and PSA also dramatically decreases. Two approaches for androgen deprivation exists, castration and antiandrogen monotherapy.

Castration can be achieved surgically through bilateral orchidectomy or medically through gonadotropin-releasing hormone (GnRH) analogues, GnRH antagonists, or oestrogen therapy. It lowers testosterone levels in serum by affecting the hypothalamus. The use of castration is mandatory in symptomatic metastatic disease and it can be used intermittently. Castration is also recommended in asymptomatic metastatic disease, although the evidence is controversial. A meta-analysis of four randomised studies conducted in the pre-PSA era comparing early ADT to ADT deferred until symptoms of clinical progression for men with locally advanced disease or asymptomatic metastases concluded that the evidence is limited due to the heterogeneity of the studies. The pooled estimate of overall survival was improved with early ADT at ten years of follow-up, but prostate-cancer specific survival was not improved. Early use of castration in advanced disease is supported mainly to prolong the time to complications, such as pathological fractures, ureteric obstruction, and metastatic pain.

Antiandrogen monotherapy blocks the androgen receptor, while the testosterone levels in serum are preserved and even increased. The antiandrogen with the most favourable profile of side effects is bicalutamide. Randomised data has shown that bicalutamide as monotherapy improves survival for men with locally advanced disease compared to placebo. Furthermore, pooled data from two randomised studies has showed bicalutamide to be inferior to castration for men with metastatic disease in terms of survival, but this difference was not seen for non-metastatic disease. A post-hoc analysis of these studies indicated that bicalutamide is equivalent to castration in metastatic disease with a less heavy tumour burden.
Castration and antiandrogen monotherapy can be used concomitantly as a combined blockade, which also blocks the effects of the low levels of androgens released by the adrenal glands that are not impacted by castration. Combined blockade is used as protection for the initial flare symptoms of castration and has a small survival advantage over castration as monotherapy for men with advanced disease.\textsuperscript{18,27,28}

The timing of ADT in various settings has long been a focus of discussion, since the studies underlying the guidelines for treatment are heterogenous and the evidence is challenging to interpret. If ADT is initiated too early, the harms of the side-effects will surpass the benefits of the treatment.\textsuperscript{29}

In summary, randomised studies recommend the use of ADT for metastatic disease and for men with locally advanced disease not suitable for curative treatment, either as bicalutamide or as castration if PSA > 50 ng/ml and prostate-specific doubling time (PSADT) <12.\textsuperscript{22,24,30} Randomised studies also support the use of ADT as adjuvant to surgery for node-positive disease and as adjuvant to radiotherapy for intermediate-risk, high-risk, locally advanced, and node-positive disease.\textsuperscript{31} Furthermore, observational data also support early ADT for men with high-risk disease at relapse after curative treatment.\textsuperscript{32}

Adverse effects of ADT

The loss of testosterone induced by castration causes a wide range of adverse effects. Castration increases the risk of developing anaemia, fatigue, hot flushes, gynecomastia, and decreased sexual function.\textsuperscript{33} The dramatic decrease in testosterone and oestradiol induced by castration causes an increase in osteoclast activity which leads to osteoporosis and increased fracture risk.\textsuperscript{34,35} Moreover, both randomised and observational studies recognise side-effects similar to the metabolic syndrome, with negative impact on lipid metabolism, lean body mass, and insulin sensitivity.\textsuperscript{33,36–38}

Much concern is raised over the possible negative impact on cardiovascular health. Observational data links GnRH analogues to increased cardiovascular morbidity and mortality, although this correlation is yet not confirmed by randomised studies.\textsuperscript{39} The risk of cardiovascular events is shown to be significantly lower with GnRH antagonists compared to agonists, and higher with oestrogen therapy.\textsuperscript{40–42} The background for this remains to be explained in detail, however a general explanation is that the metabolic changes driven by castration are known to increase the risk for cardiovascular disease.\textsuperscript{39}

Treatment with antiandrogen monotherapy increases the serum levels of testosterone and oestradiol, why the side-effects differ from castration. In a randomised trial, bone mineral density was found to increase during bicalutamide treatment, compared to the decrease seen in castration.\textsuperscript{43} A recent observational study reported a decreased risk for cardiovascular disease for men.
treated with antiandrogen therapy, while the risk was increased for castration.\textsuperscript{44} The main side effects of antiandrogen monotherapy are breast pain and gynecomastia, which can be prevented by prophylactic breast irradiation.\textsuperscript{45,46}

Castration resistance
Within time, the cancer cells become resistant to castration and thus progression occurs despite castrate levels of testosterone. The androgen-depleted environment induces selective pressure promoting growth of cells with resistance to castration through various mechanisms, many of which affect the androgen receptor pathway. Some of these include amplification and hypersensitivity of the receptor, autocrine androgen synthesis, increased ligand-binding sensitivity to other steroid hormones such as oestrogens and cortisol, and mutations that convert receptor antagonists to agonists.\textsuperscript{47,48} The latter is the reason why disruption of the treatment with the anti-androgen during a combined blockade can result in a decline in PSA levels, known as the anti-androgen withdrawal effect.\textsuperscript{49}

Other treatment strategies in advanced disease

Novel therapies
Besides ADT, there are several other important non-curative treatments for late stage disease. Recently, results from two randomised studies showed that addition of the chemotherapeutic agent docetaxel in the beginning of castration resulted in significantly better cancer control and longer overall survival than castration alone.\textsuperscript{50,51}

Docetaxel was the only approved treatment shown to prolong survival in castration-resistant prostate cancer (CRPC) before 2010.\textsuperscript{52} Since then, five more therapies have come into clinical use. One is a second-line chemotherapeutic agent, two therapies target the altered androgen receptor pathway, one is a targeted alpha emitter, and one is an immunotherapeutic agent, all shown to improve median overall survival within a range of two to five months.\textsuperscript{53–59} Radium-223, the targeted alpha emitter, has also shown to prolong median time to first symptomatic skeletal event by nearly six months.\textsuperscript{60} The optimal sequencing of these agents still needs to be clarified, and the ongoing development of predictive biomarkers could hopefully make the treatment selection more precise.\textsuperscript{61}
Palliative treatments

A multimodal approach with a combination of palliative surgery, palliative radiotherapy and palliative medications can be used in synergy to treat symptoms from local growth and metastases. Meta-analyses on palliative radiotherapy for painful bone metastases show that the overall response rates for pain are approximately 60%, while complete response rates with pain scores reaching zero surpass 20%. 62 Pathological fractures are stabilised with surgery to reduce pain and regain function, often together with adjuvant radiotherapy to prevent recurrence. 63 For the spinal cord compression, randomised data has shown direct decompressive surgery combined with radiotherapy to be superior to radiotherapy alone, presuming that surgery is tolerated due to performance status. 64 The altered bone metabolism induced by both metastases and castration can be targeted by bisphosphonates, which inhibit osteoclast activity and have significant results in terms of decreased skeletal morbidity. 65 Denosumab, a monoclonal antibody, has shown to be more efficient compared to bisphosphonates in preventing skeletal-related events. 66,67

Palliative medications

In addition to the multimodal approach of treating the local symptoms and the metastases, medications aimed directly towards pain management is most often warranted in late stage prostate cancer. 68 According to the World Health Organization (WHO) three-step approach for analgesic treatment, non-opioids should be used for mild pain, with the addition of either weak opioids for moderate pain or strong opioids for severe pain. 69 Although non-opioids have proven efficient for mild cancer pain, there is not sufficient evidence for the additive effect of paracetamol to opioids in order to target moderate or severe cancer pain. 70 Nonsteroidal anti-inflammatory drugs (NSAID)s can reduce the required opioid dose, but they are not always tolerated due to renal toxicity and the risk of gastrointestinal bleeding. 71 The second step of weak opioids for moderate cancer pain has been suggested to be omitted and replaced by a lower dosage of strong opioids, which remain the cornerstone in the management of severe cancer pain. 68,72–74 Glucocorticoids have anti-inflammatory effects, and their use in late stage prostate cancer is associated with declines in pain scores, decreased opioid use, and improved overall well-being. 75 They are also used to counteract the toxic effects from chemotherapy and adrenal synthesis inhibitors. 76 Glucocorticoids have many side effects including hypertension, hyperglycaemia, osteoporosis, immune suppression, loss of muscle mass, insomnia, and gastritis, limiting the dosage and the duration of treatment. 77 During selective pressure, the androgen receptor can mutate and glucocorticoids may then start to act as agonists. However, this seems only to concern a subset of the men with CRPC, while the positive effects are recognised for the majority. 75
Implementation of guidelines

In late 2016, the National Board of Health and Welfare made a survey on the quality of the palliative care in Sweden. The survey showed that many patients are not reached by high-quality palliative care, although the trend is improving. Only half of all cancer patients had their pain measured with a validated pain assessment tool during the last week of life. Moreover, only one fourth of all cancer patients received measurement with a validated symptom assessment tool during the last week of life, suggesting that various symptoms are overlooked in the late stages of cancer. While it is obvious that more improvements are needed in the quality of care, the right method of accomplishment is not so clear.

Clinical guidelines play an essential role to overbridge the distance between current evidence and clinical practise, and several steps are identified in this process. The quality of the clinical guidelines is essential. Tools to assess the quality of guidelines have been developed, of which one of the most applied is the updated Appraisal of Guidelines for Research and Evaluation (AGREE-II) instrument. A recent assessment of five internationally available guidelines for CRPC using the AGREE-II tool showed considerable differences in how the guidelines translate evidence into clinical recommendations and suggested the introduction of a standardised quality mark system.

One specific challenge in the construction of guidelines is when there is a conflict of evidence, as when a systematic review and a large randomized control trial have non-consistent results. A systematic assessment of biases and grading of the quality of the evidence should always be performed, for which several tools are available such as the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The quality evaluation is preferably made by a working committee consisting of experts on the field, making agreements for the publications of the guidelines. International organisations such as the European Association of Urology (EAU) also perform their own systematic reviews to update the guidelines.

However, the existence of high-quality guidelines is of limited benefit to the patient if the implementation process cannot be assured. Barriers for implementation have been categorised as characteristics of guidelines, professionals, patients, and environment, with high complexity of the guidelines, lack of awareness and agreement among professionals, comorbidity, and insufficient time and support as examples of such barriers. Non-adherence can
also be intentional and thus attributable to a conscious decision. Common rea-
sons for intentional non-adherence has been identified as presence of contra-
indications or comorbidities, and patient preference. Several meta-reviews
have been performed on the subject, concluding that evidence of the efficacy
of strategies is limited and that systematic evaluation of the implementation
tools are needed to expand the knowledge. However, tailored interventions
and strategies with multiple components appear to be the most effective.
Aims of the studies

I To describe the patterns of use for ADT initiated after primary curative treatment. To assess the median duration of castration for men initially diagnosed with localised disease. To describe the differences in treatment with castration versus antiandrogen monotherapy due to primary treatment, age, educational level and comorbidity.

II To investigate the adherence to guidelines for ADT after radical prostatectomy. To answer the question remaining from Paper I regarding the possible overtreatment with androgen deprivation therapy after curative treatment.

III To describe the use of palliative medications during the three years prior to death from prostate cancer. To assess the proportion of men who received a prescription of androgen deprivation therapy, NSAID:s, paracetamol, opioids, glucocorticoids, antidepressants, anxiolytics, and sedative-hypnotics during the last three years of life. To analyse the differences in treatment with these medications related to age, time since diagnosis, educational level, family status and comorbidity.

IV To describe the time trends of diagnostic criteria, disease duration, and age at death for men who died from prostate cancer in Sweden between 1992 and 2012.
Material and methods

Categorisation

In the present studies we used a risk categorisation system based on the categorisation elaborated by National Comprehensive Cancer Network (NCCN). The cancer was classified as low risk, intermediate risk, high risk, regionally metastatic or distant metastatic based on the initial PSA, the Tumour, Node and Metastasis (TNM) staging, and the histo-pathological pattern, expressed as the Gleason sum (Figure 2).

Tumour stage (T-stage) is classified as T0-T4, depending on the growth and spread of the tumour. N-stage correlates to the spread to regional lymph nodes, assessed through radiological imaging or histological examination following surgery. M-stage classifies the tumour according to the spread to the distant lymph nodes, the skeleton, or other organs. For N and M, the classification is 0 for no spread, X for unknown spread, or 1 for spread disease. Gleason grading confers to the assessment of the histo-pathological pattern of the cancer cells, so that the higher the Gleason sum, the more aggressive is the tumour.

Comorbidity was classified through data retrieved from the National Patient Register according to the Charlson comorbidity index (CCI): 0 for none, 1 for mild, 2 for moderate, and 3+ for severe. Level of education was based on years of schooling according to the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) database. The men were divided according to years of schooling: low for ≤9 years, middle for 10–12 years, and high for ≥13 years.
Risk categorisation

**Localised disease:**

**Low-risk:**
Clinical stage T1-2, Gleason score 2-6 and PSA <10 ng/ml.

**Intermediate-risk:**
Clinical stage T1-2, Gleason score 7 and/or PSA 10-20 ng/ml.

**High-risk:**
- Clinical stage T1-2, Gleason score 8-10, and/or PSA 20-50 ng/ml.
- Clinical stage T3 and PSA <50 ng/ml. *(Locally advanced)*

**Regionally metastatic:**
Clinical stage T4 and/or N1 and/or PSA 50-100 μg/L, and M0/MX.

**Distant metastases:**
M1 and/or PSA ≥ 100 μg/L.

*Figure 2.* Risk categorisation used in NPCR.

Data collection

All studies used data from the NPCR. When a man is diagnosed with prostate cancer, information such as date of diagnosis, PSA level, TNM staging, Gleason grade, and primary treatment within six months from diagnosis is reported to the NPCR. It comprises 98% of all prostate cancer cases covered by the Swedish Cancer Registry, to which the reporting of prostate cancer is mandatory.92

Besides the NPCR, the studies of this thesis used several other population-based registries held at the National Board of Health and Welfare and Statistics Sweden, which were recordlinked to the NPCR through the unique personal identity number. These registers are the Swedish Cancer Registry, the Prescribed Drug Register, the National Patient Register, the Cause of Death Register, the Multi-Generation Register, the Register of the Total Population, and LISA.93 The second study was based on the database PSA Uppsala/Örebro, which covers data on PSA testing from the clinical laboratories in five counties in the region of Uppsala/Örebro and is recordlinked to the same national registers as above.
Paper I

Study design
The first study included men diagnosed with localised prostate cancer between 1997 and 2009. All men who received ADT as primary treatment, emigrated, or died before the start of the Prescribed Drug Register were excluded. The included men were categorised according to primary treatment, which comprised radical prostatectomy, radiotherapy and deferred treatment. Deferred treatment covered both active surveillance and watchful waiting, as these strategies were not separately registered in NPCR before 2007. Active surveillance denotes a strategy with close follow-up and curative treatment in case of progression, whereas in watchful waiting men with limited life expectancy are treated symptomatically when the disease progresses. Information on treatment with medical castration and antiandrogen monotherapy was gathered by searching the Prescribed Drug Register, while surgical castration was identified through the National Patient Register.

In this study, some challenges needed to be addressed in the study design to identify ADT as secondary treatment. For all men diagnosed before the start of the Prescribed Drug Register on July 1st, 2005 it was necessary to distinguish initiation of ADT from already ongoing treatment. This was done through a run-in period of six months beginning at this date. All men diagnosed before this were included only if they had been free of ADT during the run-in period. To achieve equivalence, all men treated with surgical castration before the start of the Prescribed Drug Register were likewise excluded.

However, men who had received intermittent treatment with medical castration before the start of the Prescribed Drug Register would not be identified through a run-in period. In order to assess how much this could distort the results, the occurrence of intermittent treatment in a subset of men with a follow-up of more than two years was assessed through calculating treatment adherence. An adherence of less than 50 per cent was regarded as intermittent treatment, and this was found in less than nine per cent of the subset.

Last, one more problem to be solved was how to separate ADT as a secondary treatment from adjuvant ADT. To achieve this, the first year following diagnosis was omitted in all calculations. Therefore, the proportions of ADT and death from any cause without prior ADT were based on one-year survival.

Statistical analysis
Start of treatment with ADT was analysed with period analysis, using left truncation. Initiation of antiandrogen monotherapy, initiation of castration, and death from any cause without previous treatment with ADT were analysed with cumulative incidence proportions and treated as competing risks.
The relative risk of receiving castration versus antiandrogen monotherapy was analysed with Cox proportional hazard models. Start of ADT was considered as an event, all other end points were censored, and left truncation was used. Differences in treatment were then compared depending on primary treatment, age, educational level and comorbidity.

The duration of castration was interpreted as the time from start of treatment until death. Cumulative incidence proportions of death from prostate cancer and death from other causes were investigated and considered as competing risks. To enable prediction beyond the end of the observation period, projected median durations of castration were analysed by using the Weibull distribution. The lower confidence limits of the median duration were calculated using the bootstrap confidence interval method.

Paper II

Study design

The second study included men diagnosed with localised and locally advanced prostate cancer who underwent radical prostatectomy as primary treatment between 1997 and 2012. One criteria for inclusion was that neither adjuvant nor salvage radiotherapy was received before the date of inclusion. The study design was chosen as a parallel to a case/control study to allow for assessment of both possible over- and undertreatment with ADT after radical prostatectomy.

Information on ADT treatment was gathered through the Prescribed Drug Register and the National Patient Register. The verification of treatments followed the elaborate rules presented in the Prostate Cancer data Base Sweden (PCBaSe)Traject, a project based on NPCR. Men treated with ADT were selected as cases, and the start of treatment was set as the inclusion date. For each case, ten men with no ADT at the inclusion date were selected as controls within four-year strata of time of radical prostatectomy.

PSADT was defined in agreement with the most wide-spread definition, which is the natural log of 2 divided by the slope of the linear regression line of the log of PSA over time. It was calculated for all cases with two or more measurements of PSA ≥0.2 ng/ml, which is the cut-off for biochemical recurrence in the Swedish guidelines.

All men with a PSADT <12 months and/or a biopsy Gleason score of 8-10 were considered to have an indication for ADT according to the EAU guidelines. The decision to treat with ADT was exclusively referred to the PSADT first and the Gleason score next, and if neither of these could explain the treatment decision a third category “non-adherent” was chosen.
Correspondingly, the indication for ADT according to the Swedish guidelines was interpreted as a PSADT <6 months, and/or a Gleason score 8-10, and/or a PSA \( \geq 5 \) ng/ml if PSADT \( \geq 6 \) months, with this order of priority in the analysis. If these criteria were fulfilled, the treatment was considered as non-adherent for the cases and adherent for the controls.

The adherent and non-adherent groups were described in terms of T-stage at diagnosis, biopsy Gleason score, expected remaining lifetime, and ADT category for the cases. Expected remaining lifetime was assessed as more or less than ten years through a defined set of combinations of age and comorbidity.

**Statistical analysis**

The statistical analysis was limited to the calculation of proportions.

**Paper III**

**Study design**

The third study included men registered in the Cause of Death Register between 2009 and 2012 with prostate cancer as the underlying cause of death. There is a small proportion of men in the Cause of Death Register who are not registered in the Swedish Cancer Registry nor in the NPCR before death from prostate cancer, and they were not included. This proportion has previously been found to comprise less than two per cent.

Collected prescriptions during the three years before death were identified through the Prescribed Drug Register, while surgical castration was identified through the National Patient Register. We assessed the proportion who collected a prescription of ADT, NSAIDs, paracetamol, opioids, glucocorticoids, antidepressants, anxiolytics, and sedative-hypnotics, alongside the differences in treatment related to age, time since diagnosis, educational level, close relatives, and comorbidity. Since GnRH-analogues can be prescribed for periods of six months, the search was performed for the preceding 180 days for androgen deprivation therapy and for the preceding 90 days for all other therapeutic groups.

**Statistical analysis**

The collection of prescriptions was analysed as a binary outcome, meaning that one single collected prescription during the interval was noted as positive. Multivariable logistic regression was used to calculate the odds ratios for the differences in treatment.
Paper IV

Study design
All men who died with prostate cancer as the underlying cause of death from 1992 to 2012 according to the Cause of Death Register who had previously been recorded in the Swedish Cancer Registry and/or the NPCR were included in the study. The main challenge to be met was the incomplete registration in NPCR for the men with an early date of diagnosis. Registration to NPCR started in 1987 and increased gradually over time until virtually complete registration was achieved in 1998. Information on missing data on risk groups for men with an early date of diagnosis was therefore imputed.

Imputation models
The method of chained equations was used for missing data on risk category, resulting in 10 imputation datasets. Due to the gradually increased completeness of data in the register we used three different imputation models for men diagnosed in 1970-1986, 1987-1995 and 1996-2012.

In the earliest period there were no clinical data present. Therefore, the imputation had to be based on complete data from a later calendar time. Men with known risk stage diagnosed between 1987 and 1991 were included when imputing data on men diagnosed in 1970-1986, due to the assumption of similar very low amount of opportunistic PSA screening.

For the second period of men diagnosed in 1987-1995, we had a limited number of complete cases. To increase this number, we also included complete cases diagnosed between 1996 and 2005 from low incident counties while excluding men with stage T1c, which covers nonpalpable cancers detected through PSA-testing and subsequent needle biopsies.

The imputation model for men diagnosed in the third period of 1996-2012 included TNM stages, Gleason score, WHO grade, serum PSA, risk category, age and year of diagnosis, civil status, county of residence, mode of detection, comorbidity, concomitant cancer, primary treatment, survival since diagnosis, and cause of death. All analyses were performed using R commander.

Methodological considerations
In general, the main strength of observational studies is that the populations studied can be large, often on a national basis, which reduces random error. National data from a tax-financed system with general health insurance also avoid the fallacy of studying selected patient groups whose experience may have only limited generalisability. Even though the level of evidence is lower
than from a randomised study, large observational studies can give information that would be too costly or even impossible to achieve by other study designs. Sometimes, practical circumstances and ethical considerations make an observational study the only suitable alternative to answer an important question. However, the quality and the capture rate of the registers determine the reliability of the result, as does the presence of systematic errors.

All the population-based registers used for this thesis has a high capture rate. NPCR has been validated for completeness, timeliness, comparability, and validity, with high quality of data overall. Only 2% of the men with prostate cancer in the Swedish Cancer Registry are not registered in the NPCR. These men are highly similar to the registered men in their characteristics, why the NPCR is generalisable as both nation-wide and population-based.

To ensure the quality of the results in observational studies, selection bias and confounding are among the most important systematic errors to deal with. Selection bias occurs when there is a systematic difference between the exposed and the non-exposed already at the start of the study, i.e. an error in the study base. Confounding happens when the study design or analysis cannot control for a disturbing factor associated with both the exposure and the effect.

Methods used to deal with systematic errors include Cox regression in the first study, multivariable logistic regression in the third study, and multiple imputation in the fourth study. In the second study, matching was performed through incidence density-based sampling due to the imbalanced population in terms of year of surgery, but matching was not performed for any other variables to reduce the risk of overmatching. Stratification and sensitivity analysis were performed throughout the thesis to reduce the risk of systematic errors.

Ethical considerations

The first and third study were approved by the Research Ethics Board at the Umeå University Hospital (2013-153-31M; 2015-218-32M). The second and fourth study were approved by the Regional Ethical Review Board at Uppsala University (2014-552; 2016-239).
Results

Paper I

In the first study, 45,147 men were included. Of these, 42% were treated with radical prostatectomy, 19% were treated with radiotherapy, and 39% received deferred treatment. At ten years, castration was received by 11.6% and antiandrogen monotherapy was received by 10.8%. The proportion treated with ADT increased with the higher risk group. Castration was the most used ADT category in the deferred treatment group, while antiandrogen monotherapy was most used among men treated with curative intent (Figure 3).

The probability of being treated with castration increased with age. In the deferred treatment group, the probability of castration increased with a higher comorbidity index and the probability of antiandrogen monotherapy was significantly decreased for men with low education.

Low-risk implied longer projected durations of castration. The estimated median durations of castration ranged from four years in the deferred treatment high-risk group to seventeen years in the prostatectomy low-risk group. Death from prostate cancer increased with the higher risk group, except for a decrease observed between the radiotherapy intermediate and high-risk groups. For men with primary curative treatment, prostate cancer death was more common than death from other causes. In the deferred treatment group, prostate cancer death was rather equivalent to death from other causes. A minority of the men died from prostate cancer within five years after the start of castration in all subgroups (Figure 4).
Figure 3. Cumulative incidence proportions of androgen deprivation therapy (ADT) and death from any cause without prior ADT over one to ten years from diagnosis. The analysis was based on the condition of one-year survival, since the first year following diagnosis was omitted in the calculations to distinguish secondary ADT from adjuvant ADT.
Figure 4. Proportion of death from prostate cancer and death from other causes. Time to death counted from the start of castration was interpreted as the treatment duration. Treatment during the first year following diagnosis was considered as adjuvant and omitted in the calculations. Median duration was evaluated through using parametric survival analysis to enable studies of events beyond the end of the observation period. Md = median; LCL = lower confidence limit; PC-death = prostate cancer death.
Paper II

In the second study, totally 114 cases and 1140 controls were included. The median PSA was 9 ng/ml at diagnosis and 3 ng/ml at inclusion date for the cases, compared to 7 ng/ml at diagnosis and 0.1 ng/ml at inclusion date for the controls. The cases had higher T-stage and Gleason score at diagnosis and a higher age at inclusion date. Educational level, marital status, and comorbidity index were similarly distributed. Among the cases 27% were treated with castration and 73% were treated with antiandrogen monotherapy (Table 1).

Adherence to the EAU guidelines was defined as ADT treatment for men with a PSADT <12 and/or a Gleason score of 8-10, which comprised 57% of the cases. The decision to treat with ADT could not be explained by these criteria for 39% (Figure 5). In the group without indication for ADT in terms of PSADT and Gleason score, 89% had T-stage 1-2 at diagnosis, 58% had a Gleason score 2-6, 98% had an expected remaining lifetime over ten years, 16% received castration, and 84% received antiandrogen monotherapy. Among the controls 5% fulfilled the criteria defined as indication for treatment, and 98% of these men had an expected remaining lifetime over ten years.

Adherence to the Swedish guidelines was defined as a PSADT <6 months, and/or a Gleason score of 8-10, and/or a PSA ≥5 ng/ml, which comprised 61% of the cases. The decision to treat with ADT could not be explained by these criteria for 36% (Figure 5). Among these men, 90% had T-stage 1-2 at diagnosis, 49% had a Gleason score 2-6, and 93% had an expected remaining lifetime over ten years, 12% received castration, and 88% received antiandrogen monotherapy.
Table 1. Characteristics of the study population. PSA = prostate-specific antigen; Q = quartile; T-stage = tumour stage; ADT = androgen deprivation therapy.

<table>
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<tr>
<th>Characteristics</th>
<th>Cases (n=114)</th>
<th>Controls (n=1140)</th>
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</thead>
<tbody>
<tr>
<td><strong>PSA level at diagnosis (Q1-Q3)</strong></td>
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<td></td>
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<tr>
<td>No.</td>
<td>(%)</td>
<td>No.</td>
</tr>
<tr>
<td>9</td>
<td>(6-15)</td>
<td>7</td>
</tr>
<tr>
<td><strong>T-stage at prostate cancer diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
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<td>692</td>
</tr>
<tr>
<td>T2</td>
<td>(54)</td>
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<td>25</td>
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<td>2</td>
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<tr>
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<td>7</td>
<td>(39)</td>
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<td>2010-2012</td>
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<td><strong>Educational level at inclusion date</strong></td>
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<tr>
<td>Antiandrogen</td>
<td>(73)</td>
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Figure 5. Adherence to the European Association of Urology (EAU) guidelines and the Swedish guidelines for androgen deprivation therapy following radical prostatectomy. PSA = prostate-specific antigen; PSADT = PSA doubling time; GS = biopsy Gleason score.
Paper III

In the third study, 8326 men who died from prostate cancer between 2009 and 2012 were included. The median time from diagnosis to death in the whole study population was approximately five and a half years, and one third had distant metastases at the time of diagnosis. One out of ten had received primary curative treatment and two thirds received primary ADT. Increasing age was associated with a longer median time since diagnosis, a lower proportion of distant metastases at diagnosis, and conservative treatment to be more common as primary treatment.

The proportion receiving ADT was constant at 89% during the last year of life, while the use of all other medications increased. Opioids increased from 30% to 72% during the last year of life, and 67% received a strong opioid at time of death. Antidepressants increased from 13% to 22%, anxiolytics from 9% to 27%, and sedative-hypnotics from 21% to 33% (Figure 6). NSAID:s and/or paracetamol were received concurrently with opioids by 57% of all men. No marked changes of these proportions were found among men who died from 2006 to 2012, with the exception that the use of NSAID decreased.

Older men had lower probability to receive ADT, opioids, and anxiolytics, while they had higher probability to receive paracetamol. Men with low education had higher probability to receive analgesics. Living without close relatives lowered the probability to receive opioids (Figure 7). Regional differences were seen for all groups of therapy.
Androgen Deprivation Therapy

No. at risk:
5702 6506 7484 8326

NSAID

No. at risk:
5702 6506 7484 8326

Glucocorticoids

No. at risk:
5702 6506 7484 8326

Antidepressants

No. at risk:
5702 6506 7484 8326
Figure 6. Proportions of men with prevalent prostate cancer who collected a prescription within the preceding 90 days (180 days for androgen deprivation therapy). The men were included at the date of diagnosis and those who were diagnosed less than 90 days before the date of death were excluded. Numbers at risk therefore varies according to the number of men who were diagnosed at each specific time point. Weak opioids refer to codeine, dextropropoxyphene, and tramadol, while strong opioids refer to all other opioids.
Androgen Deprivation Therapy

**Age**
- <70: 1.02 (Ref)
- 70-74: 1.06 (0.84-1.38)
- 75-80: 0.98 (0.78-1.26)
- 81-86: 0.86 (0.61-1.23)
- ≥85: 0.64 (0.33-1.26)

**Time since diagnosis (years)**
- <2: 1.02 (Ref)
- 2-5: 1.06 (0.80-1.43)
- 5-10: 0.95 (0.78-1.15)
- ≥10: 0.79 (0.57-1.10)

**Education**
- High: 1.00 (Ref)
- Middle: 0.90 (0.77-1.04)
- Low: 0.93 (0.80-1.08)

**Close relatives**
- Married, no children: 1.00 (Ref)
- Not married, with children: 0.79 (0.67-0.95)
- Not married, no children: 0.79 (0.66-0.96)

**CCI**
- 0: 1.00 (Ref)
- 1: 1.02 (0.85-1.21)
- 2: 1.05 (0.88-1.25)
- ≥3: 0.96 (0.38-2.54)

**NSAID**

**Glucocorticoids**

**Age**
- <70: 1.00 (Ref)
- 70-74: 0.99 (0.74-1.37)
- 75-80: 0.96 (0.70-1.35)
- 81-86: 0.98 (0.73-1.32)
- ≥85: 0.83 (0.52-1.36)

**Time since diagnosis (years)**
- <2: 1.00 (Ref)
- 2-5: 1.07 (0.84-1.36)
- 5-10: 1.07 (0.84-1.36)
- ≥10: 1.07 (0.84-1.36)

**Education**
- High: 1.00 (Ref)
- Middle: 1.14 (0.94-1.38)
- Low: 1.15 (1.07-1.24)

**Close relatives**
- Married, no children: 1.00 (Ref)
- Not married, with children: 0.80 (0.65-1.00)
- Not married, no children: 0.80 (0.65-1.00)

**CCI**
- 0: 1.00 (Ref)
- 1: 0.80 (0.71-0.90)
- 2: 0.75 (0.64-0.88)
- ≥3: 0.66 (0.37-1.21)

**Antidepressants**

**Age**
- <70: 1.00 (Ref)
- 70-74: 1.00 (0.80-1.25)
- 75-80: 1.00 (0.80-1.25)
- 81-86: 1.00 (0.80-1.25)
- ≥85: 1.00 (0.80-1.25)

**Time since diagnosis (years)**
- <2: 1.00 (Ref)
- 2-5: 1.01 (0.80-1.25)
- 5-10: 1.01 (0.80-1.25)
- ≥10: 1.01 (0.80-1.25)

**Education**
- High: 1.00 (Ref)
- Middle: 1.00 (0.80-1.25)
- Low: 1.00 (0.80-1.25)

**Close relatives**
- Married, no children: 1.00 (Ref)
- Not married, with children: 0.80 (0.65-1.00)
- Not married, no children: 0.80 (0.65-1.00)

**CCI**
- 0: 1.00 (Ref)
- 1: 0.80 (0.71-0.90)
- 2: 0.75 (0.64-0.88)
- ≥3: 0.66 (0.37-1.21)
**Figure 7.** Odds ratios of collected prescriptions during the last months of life. The time window was 180 days preceding death for androgen deprivation therapy and 90 days for all other medications. The result was analysed as a binary outcome. “Not married” included men who were never married, widowers, or divorced. NSAID = nonsteroidal anti-inflammatory drug; CCI = Charlson comorbidity index.
Paper IV

In the fourth study, totally 45,850 men were included. During the whole study period, the proportion of men aged over 85 years who died from prostate cancer increased from 10% to 13%. The proportion who lived with prostate cancer from eight to sixteen years before death from prostate cancer increased from 15% to 26%, and more than sixteen years from 2% to 5%.

During the study period of 1992-2012, the prevalence of prostate cancer increased from 26,576 to 87,956, the crude prostate-specific mortality was stable, and the age-standardised number of prostate cancer deaths decreased from 2547 to 2099 (Figure 1).

Among the men who died from prostate cancer the proportion of men with localised and locally advanced disease at diagnosis increased from 33% to 46% during the study period, while the proportion with regionally metastatic disease decreased from 14% to 12%, and the proportion with metastases decreased from 54% to 42% (Figure 8).

The median disease duration increased from 3.1 years in 1992 to 5.6 years in 2012. It remained in the lower half of the interquartile range during the study period (Figure 9).

The median age at death from prostate cancer increased from 78.3 years in 1992 to 81.9 years in 2012. During the study period, the proportion of metastases decreased in the first age quartile from 64% to 53%, while it decreased from 45% to 37% in the fourth age quartile (Figure 10).
Figure 8. Proportions of risk groups at date of diagnosis among men who died from prostate cancer by year of death.
Figure 9. Percentiles of prostate cancer duration by year of death. Duration of prostate cancer was defined as the time between the date of diagnosis and the date of death. P = Percentile; Median = P_{0.50}.
Figure 10. Percentiles of age at prostate cancer death by year of death and distribution of risk groups within quartiles of age. $P =$ Percentile; Median = $P_{0.50}$. 
Discussion

Paper I

The principal finding in the first study was that the proportion of ADT at ten years was 11.6% for castration and 10.8% for antiandrogen monotherapy. To assess whether this is high or low, it would be necessary to measure disease progression at the time for ADT initiation. However, this information is not available in NPCR. Since the main indication for castration is progression to metastatic disease, an alternative would be to compare the median time to prostate cancer death after start of ADT with median survival in metastatic disease. This was reported as five years in 1999, which is applicable to the study period. 98 Only a minority of the men receiving castration in our study died from prostate cancer within five years from the start of treatment, which implies that many men in our study might have been spared the burden of castration.

Castration was more common than antiandrogen monotherapy in the deferred treatment group. A possible explanation for this would be that progression to metastatic disease was more common among men on deferred treatment, but this was not supported by the prostate cancer mortality after start of castration. A possible explanation could be old age as a condition of choice for therapy, since men in the deferred treatment group were older than the other groups. This will be discussed further in the general discussion.

The projected median durations of castration were estimated as eleven to seventeen years in the radical prostatectomy low-risk and intermediate-risk group, and in the radiotherapy low-risk group. This implies prolonged time at risk for adverse effects with questionable benefit. Current guidelines state that only men with high-risk features may benefit from castration at biochemical relapse after curative treatment. 99,100 An important reason for the early initiation of castration is anxiety, which is shown to act as an independent predictor of early ADT for biochemical recurrence. 108
Paper II

The principal finding in the second study was that four men out of ten received ADT although they had PSADT $\geq 12$ months and biopsy Gleason score $\leq 7$, which was defined as non-adherence to the EAU guidelines. Nearly all of these men had an expected remaining lifetime over ten years, which fits the criteria of a long remaining life expectancy in the guidelines. However, the majority also had a Gleason score 2-6 and T-stage 1-2 at diagnosis. The natural history after biochemical recurrence is highly variable, with reported median time between biochemical recurrence and systemic progression ranging from one year to over fifteen years, depending on risk features. Therefore, many men with low-risk cancers never experience progression but die of other causes. For these men, treatment with ADT is likely to cause more harm than benefit and is non-adherent to the guidelines.

One possible barrier to adherence is the conflicting evidence of treatment with ADT after radical prostatectomy, which adds complexity to the guidelines and may cause uncertainty among clinicians. The importance of the physician is underscored in an observational study by Shahinian et al, which showed that the initiation of ADT depends more on the urologist than on tumour and patient characteristics. Interventions targeted towards urologists may therefore be effective to improve the adherence to guidelines for ADT. Prostate cancer anxiety and low health literacy among patients have also been identified as predictors for early use of ADT after curative treatment, why improved patient information may be of importance.

Among the controls five men out of hundred had PSADT <12 months and a biopsy Gleason score 8-10, and thereby fulfilled the defined indications for ADT. The majority of these men had a Gleason score of 8-10. Nearly all had an expected remaining lifetime over ten years, why this finding indicates undertreatment. This proportion is so small that it is unlikely that it represents a systematic misapplication of guidelines, but an explanation for the possible undertreatment can be intentional non-adherence. The EAU has a disclaimer for the guidelines, stressing that they are not meant to replace physician judgment in treating particular patients on a case-by-case basis. Given that ADT has a range of side-effects, patient reluctance towards the treatment could partly explain non-adherence.

Antiandrogen monotherapy was the most used form of ADT. In the Swedish guidelines, bicalutamide is recommended as the choice of ADT after radical prostatectomy for non-metastatic disease. The EAU guidelines state that antiandrogen monotherapy has not been shown to be inferior to castration for men with non-metastatic disease but gives no explicit recommendation. The consequences of overuse of ADT are probably more severe in countries where castration is more often used than antiandrogen monotherapy for non-metastatic disease.
Paper III

The principal finding in the third study was that unmarried men without children received less treatment with opioids, which points at the importance of having close relatives who recognise when pain increases and can encourage contact with the health care. This finding has not been reported before, although marital status alone reached significance in a population-based study from Norway. Older men also received less opioids, a finding which will be discussed in greater detail in the general discussion.

Opioids were prescribed to 72% of the men with a sharp increase during the last year, and 67% received a strong opioid. A meta-analysis from 2014 on treatment of pain from any cancer showed that 32% of the patients from a wide range of countries were undertreated. This was defined by a negative pain management index, which means that the perceived pain exceeded the strength of the pain medication. Our results also likely represent undertreatment, since over 90% of men with prostate cancer are reported to experience pain during the last three months of life.

The proportion of men receiving opioids in our study is comparable to population-based data from Denmark and Norway. When comparing the prescription patterns in different countries the variation in settings and whether only strong or all opioids are reported must be taken into account. A nationwide study of general practices from the Netherlands showed that 62% of the cancer patients received a strong opioid during the last three months of life, and similar results were observed in a multicentre study from Italy. However, a register study from a northern Italian region showed that only 21% of the cancer patients were prescribed opioids. Two studies from the United Kingdom showed that 44% and 48% of the patients with terminal cancer received treatment with strong opioids.

The variation between countries needs further exploration, although awareness among doctors, cultural differences, and patient attitudes have been identified as influencing factors. Contrary to the increase in opioid use reported from other European countries, we did not find any increase in collected prescriptions for men who died from 2006 to 2012.

Concurrent use of NSAID and/or paracetamol with opioids was seen in 57% of all men, indicating poor adherence to the WHO analgesic ladder for pain management. The reason may be interactions or contraindications, but it may also reflect that the addition of paracetamol to strong opioids is questioned due to weak evidence of efficacy for cancer pain.

Previous studies disagree on whether the prevalence of mood disorders increases as death approaches. We could not compare the proportions of men who received prescriptions of antidepressants, anxiolytics and sedative-hypnotics to the actual prevalence of symptoms in our study. In a meta-analysis of cancer patients in palliative care settings the pooled prevalence was
16% for depression and 10% for anxiety. This is in agreement with the increase of antidepressants from 13% to 22% and of anxiolytics from 9% to 27% during the last year of life in our estimates. Sleep disturbances have been reported for more than 60% of patients with advanced cancer, to be compared with the 33% who received sedative-hypnotics before death in our study. The previously mentioned survey made by the Swedish National Board of Health and Welfare found that only one fourth of all cancer patients in Sweden received measurement with a validated symptom assessment tool during the last week of life, which indicates that various symptoms are overlooked in the late stages of cancer.

The odds ratios to receive treatment with NSAID:s, paracetamol, and opioids were increased for men with low education compared to men with a high education. A Swedish observational study found that treatment with chemotherapy for castration resistant prostate cancer was more common among men with a high educational level, possibly reducing their need for analgesics. Also, a low educational level is reported to be a positive predictor of pain among cancer patients, why our finding could reflect a higher need for analgesics among men with low education.

Paper IV

The principal finding in the fourth study was that the proportion of men with localised and locally advanced disease at diagnosis increased during the study period, while regional and distant metastases decreased. In this study, the proportion of men with distant metastases at diagnosis decreased from 54% to 42%, compared to a decrease from 54% to 38% in a Danish nationwide population-based study of men who died from prostate cancer from 1995 to 2013. A similar shift in staging is recognised in prospective data from Sweden and other countries as a consequence of earlier detection by use of PSA testing. Additionally, stage migration towards more favourable tumour characteristics within each risk group is reported between 1998 and 2011 in the NPCR, such as an increasingly lower PSA levels within each Gleason score stratum. This implies that men who were diagnosed early in the study period have worse disease features than men with a later diagnosis in the same risk group, thus increasing the effect of stage migration seen in the study.

We found that the median disease duration increased from 3.1 years in 1992 to 5.6 years in 2012 among men who died from prostate cancer, which means a prolongation of the disease course by 2.5 years. In the previously mentioned Danish study, the time from diagnosis to death increased by 2.1 years, from 1.9 years in 1995 to 4.0 years in 2013. Thus, the men in the Danish study had a shorter disease duration by more than one year. Denmark differs from other Nordic countries by a lesser use of opportunistic PSA-screening, poorer differentiated tumours at diagnosis, less use of treatment with curative intent,
and higher mortality rates from prostate cancer. The increase in disease duration for men who died of prostate cancer can be explained by two different hypotheses, that may work together. One is that earlier diagnosis implies a longer lead time, defined as the time from diagnosis to clinical symptoms. A longer lead time is reported as a consequence of an increased use of PSA-testing. The other hypothesis is that improvements in treatment strategies during the two decades of our study period could have contributed to a prolonged disease duration before prostate cancer death, including more effective strategies in surgery and radiotherapy alongside the introduction of docetaxel for advanced disease. Abiraterone, the first of the novel treatments for castration-resistant metastatic disease was introduced in Sweden only in the very end of our study period and therefore none of these novel therapies could have had an impact on our results.

We found that the median age at prostate cancer death increased by 3.6 years during the study period, from 78.3 to 81.9 years. As background information, the life expectancy at birth in the whole male population in Sweden increased by 4.5 years during the same time period, from 75.6 to 80.1 years. This means that more men lived long enough for prostate cancer to spread and become lethal, while escaping death from other causes. Also, the age standardised mortality from prostate cancer has steadily decreased over the last two decades in Sweden and other countries with a wide-spread use of PSA-testing. Therefore, another interpretation of the increased median age at death from prostate cancer could be that progression and death from prostate cancer was postponed until later in life.

The proportion of metastases at diagnosis was highest among the youngest men who died from prostate cancer, with a decrease from 64% to 53% among the men among the first age quartile compared to a decrease from 45% to 37% in the fourth age quartile between 1992 and 2012. In the mentioned Danish study, the median age at diagnosis for men diagnosed with metastatic disease decreased from 74.8 years to 73.6 years between 1995 and 2013. These findings point out that among the men who dies from prostate cancer, the youngest men are most at risk for being diagnosed with incurable disease.

General discussion

Old age appeared to be applied as a condition of choice of therapy in both the first and the third study, which may be interpreted as ageism. Many old men in both studies had lived a long time with prostate cancer and were primarily treated with expectancy, which is a strategy with the aim to give symptomatic treatment only. This may result in longer intervals between controls, during which progression might be missed.

In the first study, the probability of receiving castration rather than anti-androgen monotherapy increased with age. Since the burden of comorbidity
grows with age, older men are more vulnerable to the adverse effects of castration. They might therefore benefit from antiandrogen monotherapy rather than castration when this treatment is indicated.

In the third study, not only opioids, but also androgen deprivation therapy, glucocorticoids, and anxiolytics were less often prescribed to older men. Older men are more sensitive to the adverse effects of opioids due to physiological changes, but this should be addressed by dose adjustment rather than opioid avoidance. Impaired efficacy of the endogenous analgesic systems and decreased tolerance make older men more unprotected to persisting pain. Even though ADT has a range of adverse effects, it must nevertheless be considered a mandatory treatment of symptomatic metastatic disease, independently of age. However, glucocorticoids may be contraindicated to frail older men.76 Anxiolytics can also be less suitable to older men, especially if there is a risk of drug interactions. Since a previous study have found a decrease of anxiety with older age among prostate cancer patients, our finding might also reflect a lower need for anxiolytics in the older age groups.

Conclusions
The first study indicates that the duration of castration can be decades when initiated early after curative treatment, why many men probably could be spared castration. The second study used PSA as a progress marker and shows that overtreatment with ADT in terms of castration or bicalutamide is common after radical prostatectomy, while undertreatment is unusual. Interventions to improve adherence to guidelines for ADT after curative treatment are needed to prevent unwarranted therapy that impairs long-term health.

The third study indicates that men without close relatives and older men are disadvantaged with respect to treatment of cancer pain, why they need closer attention from health care providers. It also highlights the importance to identify and reduce psychological distress in terminal prostate cancer.

The fourth study shows a stage shift at diagnosis, longer disease duration and higher age at death among men who died from prostate cancer during the study period, which may reflect the synergetic effects of prolonged lead time, increased life expectancy, and improvements in the management of prostate cancer during the last two decades.
Sammanfattning på svenska

Bakgrund


För att underlätta behandlingsbesluten finns olika versioner av riktlinjer som baseras på den befintliga vetenskapliga evidensen, som inte alltid är så självklar att tolka. I nästa steg ska riktlinjerna implementeras i den kliniska verkligheten. Denna process kan hindras av faktorer som till exempel oro för progress. För att minska såväl överbehandling som underbehandling är det viktigt med deskriptiva studier som beskriver hur olika behandlingar används.

Den här avhandlingen består av fyra kliniska studier som fokuserar på behandlingsmönster för icke-kurativa behandlingar vid avancerad eller recidiverande prostatacancer, samt tidstrender för olika karaktäristika hos män som dör i prostatacancer. Avhandlingen bygger på data från Nationella prostatacancerregistret (NPCR).

Sammanlagt inkluderades 45 147 män, varav 42% behandlats med radikal prostatektomi, 19% strålbehandlats, och 39% behandlats konservativt. Efter tio år hade 11,6% av männen fått kastrationsbehandling och 10,8% fått behandling med antiandrogener. För att bedöma om behandlingen sattes in på adekvat indikation skulle det behövas någon form av progressmarkör, vilket saknades i studien. Den främsta indikationen för kastrationsbehandling är progress till metastaser, och tidigare data har angett medianöverlevnaden vid metastaserad sjukdom till fem år.98 Att endast en minoritet av männen i vår studie dog inom fem år från insatt behandling indikerar därför att många fått kastrationsbehandling för tidigt i sin sjukdomsprocess.

Bland män med konservativ primärbehandling och bland äldre män var kastrationsbehandling vanligare än behandling med antiandrogener. Det verkar inte bero på att fler män med konservativ behandling fick metastaser, om man jämför med dödligheten i prostatacancer i samma grupp. Däremot var det fler äldre män i den gruppen. Kastrationsbehandling har betydligt fler biverkningar än behandling med antiandrogener, till exempel benskörhet och metabola förändringar.33 Eftersom äldre män har högre samsjuklighet kan det därför finnas anledning att erbjuda fler äldre män antiandrogener istället för kastration.

Behandlingslängden vid kastration uppskattades till mellan fyra och sjutton år, beroende på primärbehandling och riskgrupp. De längsta behandlingstiderna återfanns hos män med lågriskcancer som behandlats kurativt. Vid återfall av mätbart prostataspecifikt antigen (PSA) efter kurativ behandling kan hormonbehandling i och för sig vara indicerad även om det inte finns metastaser, men bara för högrisktumörer.99,100 Alltför tidigt insatt hormonbehandling verkar alltså kunna leda till mycket långa behandlingstider. Med tanke på hur många år dessa män får leva med biverkningar och sänkt livskvalitet är det angeläget att vid tidpunkten för att sätta in behandlingen vid rätt tidpunkt.
Arbete II


Indikationen för hormonbehandling enligt europeiska riktlinjer definierades i studien som dubbleringstid av prostataspecifikt antigen (PSADT) <12 månader och/eller Gleasonsumma 8-10. För svenska riktlinjer definierades indikationen som PSADT <6 månader, och/eller Gleasonsumma 8-10, och/eller PSA ≥5 ng/ml. Om dessa kriterier var uppfyllda klassades behandlingen som icke-indicerad för fallen och som indicerad för kontrollerna.

Totalt inkluderades 114 fall och 1140 kontroller. Så som behandlingsindikationen definierades i studien bedömde 39% av fallen ha behandlats i strid mot de europeiska riktlinjerna. Av dessa män hade 89% tumörstadium 1-2 vid diagnos, 58% hade Gleasonsumma 8-10, 98% hade en förväntad återstående livslängd på över tio år, 16% hade behandlats med kastration och 84% hade fått antiandrogener. Motsvarande andel som bedömdes ha fått behandling i strid mot de svenska riktlinjerna var 36%.


Bland kontrollerna var det 5% som inte fått någon behandling trots att de bedömdes uppfylla behandlingskriterierna. Eftersom andelen var så låg beror det antagligen inte på något systematiskt fel i tillämpningen av riktlinjerna, utan troligen på ett medvetet val att avstå från behandlingen. Tanken med riktlinjerna är inte att de ska följas slaviskt, utan att läkaren ska använda dem som underlag för att göra en individuell bedömning i varje enskilt fall. Man kan även tänka sig att vissa patienter tackar nej till behandlingen på grund av biverkningarna.

Antiandrogener användes betydligt mer än kastration vid hormonbehandling efter radikal prostatektomi. Eftersom kastration innebär fler biverkningar än antiandrogener, så är konsekvenserna av överbehandling troligen mycket allvarligare i länder där kastration används mer än i Sverige.
Arbete III

Syftet med den tredje studien var att beskriva behandlingsmönster för palliativa läkemedel under de tre sista åren före död i prostatacancer. Alla män som registrerats med prostatacancer som huvudsaklig dödsorsak i dödsorsakregistret mellan 2009 och 2012 inkluderades. De behandlingar som undersöcktes i studien var hormonbehandling, antiinflammatoriska (NSAID), paracetamol, opiater, kortison, antidepressiva, ångestdämpande, och sömnmedel. Skillnader i behandling med avseende på ålder, sjukdomsduration, utbildningsnivå, familjesituation och samsjuklighet undersöktes också.

I studien inkluderades sammanlagt 8326 män. Ogifta män utan barn behandlades i mindre utsträckning med opiater, vilket kan tyda på att närstående har en viktig roll i att uppmärksamma smärta och initiera kontakt med vården. Även äldre män fick opiater i mindre utsträckning. Hög ålder kan visserligen vara ett skäl att dosanpassa, men inte att undvika opiater helt.141 Tidigare forskning har dessutom visat att äldre är mer sårbara för långvarig smärta på grund av fysiologiska förändringar.142

Äldre män fick även hormonbehandling och ångestdämpande i mindre utsträckning än yngre. Många äldre män behandlades konservativt, och man kan fundera över om intervallerna mellan kontrollerna blir så långa att en eventuell sjukdomsprogress missas. Hormonbehandling är stommen i behandlingen av prostatacancer med fjärrmetastaser och ska inte undanhållas någon på grund av hög ålder.143 Ångestlindrande kan däremot vara kontraindicerade hos äldre, och en tidigare studie har visat att ångestnivån hos äldre män med prostatacancer ofta är lägre än hos yngre.144,145

Drygt två tredjedelar av alla män fick behandling med opiater före sin död. I en internationell metaanalys från 2014 såg man att cancersmärta underbehandlas hos cirka en tredjedel.115 En italiensk studie har funnit att cirka 90% av alla som dör i prostatacancer upplever smärta under sina sista tre månader, och mot bakgrund av det kan våra resultat tolkas som en underbehandling.17

Opiater användes samtidigt med icke-opiater hos 57%, vilket visar låg följksamhet till Världshälsoorganisationens (WHO):s smärttrappa. Det kan bero på läkemedelsinteraktioner och kontraindikationer, men skulle också kunna spegla att evidensen är svag för att paracetamol gör nytta som tillägg till starka opiater vid cancersmärta.70

Användningen av alla läkemedel ökade under det sista året utom för hormonbehandling, som låg stadigt på cirka 90%. Användningen av antidepressiva ökade från 13% till 22%, ångestdämpande från 9% till 27% och sönmmedel från 22% till 33% under det sista året, vilket tyder på att psykiska symptom ökar i sena sjukdomsstadijer.

Män med låg utbildning behandlades ofta med smärtlindrande än män med hög utbildningsnivå. En svensk observationsstudie har visat att män med högre utbildning ofta får behandling med cytostatika, vilket kan minska behovet av smärtlindring.127 Låg utbildning har också kunnat kopplas till högre
smärtnivåer hos cancerpatienter, vilket gör att fyndet kan spegla ett större behov av smärtlindring för män med lägre utbildningsnivå.\textsuperscript{128}

Arbete IV


Andelen med lokaliserad och lokalt avancerad cancer vid diagnos bland män som dog av prostatacancer ökade från 33\% till 46\% under studieperioden, medan andelen med lymfkörtelmetastaser minskade från 14\% till 12\% och andelen med fjärrmetastaser minskade från 54\% till 42\%. I en liknande dansk studie av män som dött i prostatacancer sjönk andelen män med fjärrmetastaser vid diagnos från 54\% till 38\% mellan 1995 och 2013.\textsuperscript{129} Liknande mönster med lägre riskgrupp vid diagnos ses även i prospektiva data från många länder och är en konsekvens av tidigare upptäckt på grund av ökad användning av PSA-test.\textsuperscript{130–133}

Mediantiden från diagnos till död i prostatacancer ökade från 3,1 år till 5,6 år mellan 1992 och 2012, vilket innebär att medianen för sjukdomsduration ökade med 2,5 år under perioden. Två olika hypoteser skulle kunna förklara att sjukdomsdurationen blivit längre. Antingen beror det på att tidigarelagd diagnos på grund av ökad förekomst av PSA-testning leder till längre ledtid, som är tiden från diagnos till kliniska symptom.\textsuperscript{136} Den andra hypotesen är att förbättringar i behandlingsmetoder inom operation, strålning och cytostatika under de senaste två decennierna gjort att man lever längre med prostatacancer.\textsuperscript{52,127,137–140} Det är också möjligt att båda hypoteserna tillsammans kan förklara förlängningen av sjukdomsdurationen.

Medianåldern vid död i prostatacancer ökade från 78,3 år till 81,9 år mellan 1992 och 2012. Under samma period ökade den förväntade levnadstiden vid födseln för män i Sverige med 4,5 år, från 75,6 år till 80,1 år.\textsuperscript{5} En ökad livslängd innebär längre tid för prostatacancern att sprida sig och till slut bli dödlig. Samtidigt har den åldersstandardiserade dödligheten i prostatacancer sjunkit, och den ökade medianåldern vid död kan därför tolkas som att sjukdomsprogressen skjuts upp till senare i livet.\textsuperscript{8}

För den yngsta gruppen minskade andelen fjärrmetastaser från 64\% till 53\% under studieperioden, jämfört med en minskning från 45\% till 37\% i den
äldsta åldersgruppen. I den danska studien sjönk medianåldern vid diagnos för män som diagnosticerats med fjärrmetastaser från 74,8 år till 73,6 år. Bland de män som dör av prostatacancer är det alltså de yngsta männen som löper störst risk att ha en obotlig sjukdom redan vid diagnos.

**Slutsatser**

Den första studien indikerar att kastrationsbehandling som sätts in tidigt efter radikal prostatektomi kan pågå i decennier, och att många män därför antagligen överbehandlas. I den andra studien visas att överbehandling med kastration eller antiandrogen är vanligt förekommande efter radikal prostatektomi, medan underbehandling är ovanligt. Följsamheten till riktlinjerna behöver därför förbättras, så att onödig behandling med nedsatt livskvalitet under många år kan undvikas.

Den tredje studien indikerar att män utan nära släktingar samt äldre män förskrivs opiater i mindre utsträckning, och därför är dessa män särskilt viktiga att uppmärksamma i den palliativa vården. Fynden understryker också vikten av att upptäcka och behandla psykiska symptom vid terminal prostatacancer.

Den fjärde studien påvisar ett skifte till lägre riskgrupp vid diagnos, längre sjukdomsduration, och högre ålder bland män som dör i prostatacancer, vilket antagligen speglar en samverkan av längre ledtid mellan diagnos och progress, längre förväntad livslängd samt förbättrad behandling av prostatacancer under de två senaste decennierna.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)