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LONG-TERM ONCOLOGICAL OUTCOME AND HEALTH-RELATED QUALITY OF LIFE AFTER CURATIVE TREATMENT OF PROSTATE CANCER WITH HDR-BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY

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Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN **978-91-8016-763-5**

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THESIS FOR THE DOCTORIAL DEGREE (Ph.D.)

The thesis will be defended in public at the Lecture Hall, CCK, Cancer Centrum Karolinska, Visionsgatan 56, Solna, Lecture hall.

Friday 18th of November 2022, at 09.00 am

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To my family

POPULAR SCIENCE SUMMARY OF THE THESIS

Prostatacancer är den vanligaste cancerformen bland män i Sverige. Antalet män som diagnostiseras med sjukdomen har dubblerats från 1990-talet. Årligen drabbas cirka 10000 män av prostatacancer och 2300 avlider i sjukdomen. Den ökade incidensen beror på flera faktorer. De viktigaste orsakerna är införandet av PSA-provtagning vid diagnostik och stigande ålder i befolkningen, samt en ökad medvetenhet om sjukdomen bland män.

Sjukdomsförloppet vid prostatacancer varierar från långsamt växande tumörer, med liten risk för spridning under mannens livstid, till snabbväxande tumörer med stor risk för spridning till andra organ redan vid diagnos. Sjukdomen ger sällan symtom i tidig fas och därför har PSA-prov blivit en viktig del av diagnostiken för tidig upptäckt. Dessvärre leder detta i många fall till överdiagnostik av latent prostatacancer, som med stor sannolikhet inte kommer ge symtom under mannens livstid. På senare tid har den diagnostiska proceduren förbättrats genom tillägg av magnetkameraundersökning av prostata och riktade biopsier mot misstänkta tumörhärdar, vilket minskar risken för över- och underdiagnostik.

Sjukdomen är botbar om den upptäcks i tidigt skede och är begränsad till prostatakörteln. Botande behandlingsalternativ vid prostatacancer utgörs av operation eller olika typer av strålbehandling. Aktiv uppföljning är en alternativ strategi vid s.k. låg-risk sjukdom. De olika behandlingsalternativen har specifika biverkningsprofiler. Få studier har gjorts där effekt, biverkningar och livskvalité direkt jämförts. Även om chansen till bot ofta är stor ställs patienten vid diagnos inte sällan inför svåra överväganden inför val av behandlingsstrategi. Förutom sjukdomens allvarlighetsgrad påverkas behandlingsrekommendationen även av ålder, samsjuklighet, biverkningsrisker på kort och lång sikt, och inte minst patientens egen inställning till behandling. Kunskap om biverkningar och hur dessa påverkar livskvalitet efter olika behandlingsmodaliteter är därför central för att erbjuda varje patient en personligt övervägd behandling.

Den här avhandlingen syftar till att närmare undersöka effektiviteten av strålbehandling, samt påverkan på livskvalitet av ett de botande behandlingsalternativen för lokaliserad prostatacancer; s.k. HDR-brachyterapi kombinerad med yttre strålbehandling mot prostata och en 6–9 månaders hormonbehandling. Metoden har använts sedan 1998 i Stockholm och totalt har över 7000 patienter behandlats fram till 2021. Kartläggning av långtidseffekter efter kombinerad strålbehandling har hittills varit begränsad.

Studie 1. Vi undersökte hälsorelaterad livskvalitet i genomsnitt sju år efter behandling av prostatacancer i en grupp män som genomgått antingen operation eller HDR-brachyterapi kombinerad med yttre strålbehandling under åren 1988–1997. Livskvalitet mättes med två frågeformulär, EORTC QLQ-C30 och det diagnosspecifika formuläret EORTC QLQ-PR25. De olika behandlingsgrupperna var jämförbara i ålder vid diagnos och beträffande andelen med högrisk prostatacancer. Vi fann att patienter efter genomgången behandling, oavsett behandlingsmodalitet, visade hög generell livskvalitet jämförbar med en svensk referenspopulation. Små skillnader mellan de olika behandlingstyperna rapporterades

gällande tarm- och urinvägsbesvär, till fördel för de patienter som opererats. Båda grupperna rapporterade samma nivå av påverkan på sexuell funktion.

I studierna 2–4 bestod studiepopulationen av olika definierade grupper av män behandlade med kombinationsstrålbehandling med HDR-brachyterapi under åren1998–2010 på Karolinska Universitetssjukhuset.

I studie 2 undersöktes hur total överlevnad och sjukdoms fri överlevnad efter behandling av prostatacancer påverkades av samsjuklighet jämfört med ålder och etablerade markörer för sjukdomens allvarlighetsgrad. Samsjuklighet mättes med ett index, s.k. Charlson comorbidity index. Ålder och samsjuklighet var de faktorer som hade störst inverkan på den totala överlevnaden efter behandling, medan den sjukdomsfria överlevnaden framför allt påverkades av markörer för tumörens allvarlighetsgrad, men även av samsjuklighet.

I Studie 3 undersöktes i hur hög grad män som genomgått kombinationsstrålbehandling botades från prostatacancern och hur stor risken var för återfall efter 10 års uppföljning. I studien ingick 2387 män som behandlats och följts upp i Stockholm mellan åren 1998 och 2010. Totalt avled 30% av patienterna under uppföljningstiden. Risken att avlida pga. av prostatacancer var 5% vid 10 års uppföljning och den totala överlevnaden var 77%. Risken för att återfå sjukdomen i prostata var låg och uppskattas till ca 1%. Vi studerade vidare behandlingsutfall i definierade prognostiska riskgrupper i enlighet med en etablerad klassifikation: Cambridge Prognostic Group classification. Våra resultat visar att riskgruppsindelningen ger kliniskt värdefull prognostisk information, både för risken att avlida i prostatacancer och för risken att återfå sjukdomen efter kombinationsstrålbehandling.

Studie 4. Vi undersökte hälsorelaterad livskvalitet fem år efter kombinationsstrålbehandling hos de män i studie 3 som behandlats under åren 2002 till 2008. Vi studerade även hur modern behandlingsteknik som infördes år 2001 påverkade den hälsorelaterade livskvalitén genom att jämföra mot en tidigare kohort behandlad vid vår enhet under åren 1998–2000. Den allmänna hälsorelaterade livskvalitén fem år efter genomgången behandling var hög och jämförbar med en svensk referenspopulation. Vidare rapporterade våra patienter låga nivåer av besvär från tarm och urinvägar. Sexuell funktion var mest påverkad av alla livskvalitetsområden. Sexuell aktivitet rapporterades av ca 40% av patienterna. Jämförelsen mellan patienter behandlade under 1998–2000 och den senare studiegruppen visade ingen skillnad i hälsorelaterad livskvalitet utom för frekvensen av nattlig vattenkastning, som var lägre i den senare gruppen.

Sammantaget visar våra studier att HDR-brachyterapi kombinerad med yttre strålbehandling och en kort hormonbehandling är en effektiv behandling av prostatacancer med hög lokal tumörkontroll och bot. Den generella livskvalitén är god 5 år efter behandling, som dock medför en risk för kvarstående måttliga urinvägsbesvär och impotens. Vid val av behandlingsstrategi är det viktigt att väga in både sjukdomens allvarlighetsgrad, ålder och samsjuklighet. I det sammanhanget kan riskgrupps indelning enligt Cambridge Prognostic Group vara ett värdefullt verktyg.

ABSTRACT

Prostate cancer (PC) is a major health problem among men in the western world. The prognosis of PC varies, with high mortality rates for high-risk disease in contrast to a mild course in low risk cancers with almost no risk of metastases. Radical treatment options for localized and locally advanced PC are surgery or different radiotherapy (RT) modalities. Randomized trials concerning the therapeutic effect of these treatment options are rare and have so far shown little difference in oncological outcome, but differences in patterns of side effects. Therefore, it is important to consider age, comorbidity and treatment induced effects on Health-Related Quality of Life (HRQoL) in the decision-making process pertaining to curative treatment of PC.

The primary aim of this thesis was to evaluate the long-term oncological outcome in terms of local control, PC specific and overall survival and HRQoL after curative treatment for PC with combined high dose-rate brachytherapy (HDRBT) and external beam radiotherapy (EBRT).

In a cohort study (**Study 1**), men treated with curatively intended radical prostatectomy (RP) or combined HDRBT and EBRT in Gothenburg from 1988-97 were investigated concerning long-term HRQoL measured by the EORTC QLQ-c30 and QLQ PR25 questionnaires. Patients reported high levels of general HRQoL comparable to a Swedish reference population. Small differences in the levels of bowel and urinary HRQoL were found in favour of the RP group.

The prognostic value of comorbidity for overall and disease-free survival measured by the Charlson comorbidity index (CCI) was investigated in 611 men with localized or locally advanced PC treated with dose-dense combined HDRBT and EBRT (**Study 2**). Comorbidity and age were found to be the only independent predictors of overall survival (OS) with hazard ratios (HR) of 1.44 and 1.73, respectively. In contrast, clinical factors; PSA, T-stage, Gleason score and comorbidity were prognostic of Disease-free survival (DFS).

Ten-year survival was retrospectively investigated in a cohort of men (n=2,387) treated with combined RT from 1998-2010 at the Karolinska University Hospital HDR-brachytherapy unit (**Study 3**). During a median follow-up of 10.2 years (Y) 30% of the patients died, of whom 6% from PC. The OS was 77% at ten Y and the cumulative incidence of prostate cancer specific death (PCSD) was 5%. The estimated risk of local recurrence was 1.2% in the whole cohort and the risk of prostate cancer specific failure (PCSF) was 68% at ten years. Competing risk regression was used to model the impact of risk group classification on PCSD and PCSF and was found to give prognostic information on PC specific death and failure for up to ten years.

In a cross-sectional study, five-year HRQoL was explored in a sub-cohort of men from study 3 treated between 2002 and 2008 (**Study 4**). The aim was to evaluate long-term effects of combined RT, using the EORTC QLQ-c30 and PR 25 questionnaires. Differences in HRQoL

in men treated before and after changes in the HDR-treatment procedure introduced in 2001 were also investigated using data from an earlier study at our institution. General HRQoL was high and, apart from small differences, comparable to normative data. A low level of problems was reported concerning bowel, urinary and hormone-related symptoms. However, urinary symptoms were reported more frequently than bowel problems. In the sexual domain substantial problems were present at five years. No difference in HRQoL was found between men treated before and after the introduction of the new HDR-technique, except for a reduced frequency of nocturia in favour of the present study group.

In summary, combined HDRBT and EBRT is an effective treatment that provides high disease-specific and overall survival with excellent local control in men with PC but involves a risk for development of long-term urinary and sexual problems.

LIST OF SCIENTIFIC PAPERS

I. **Hjälm-Eriksson M**, Lennernäs B, Ullén A, Johansson H, Hugosson J, Nilsson S, Brandberg Y. Long-term health-related quality of life after curative treatment for prostate cancer: A regional cross-sectional comparison of two standard treatment modalities. International Journal of Oncolology. 2015; 46: 381-388.
doi: 10.3892/ijo.2014.273

II. **Hjälm-Eriksson M**, Ullén A, Johansson H, Levitt S, Nilsson S, Kälkner KM. Comorbidity as a predictor of overall survival in prostate cancer patients treated with external beam radiotherapy combined with HDR brachytherapy boosts. Acta Oncologica. 2016; 56: 21-26.
doi: 10.1080/0284186X.2016.1253864

III. **Hjälm-Eriksson M**, Nilsson S, Brandberg Y, Johansson H, Lennernäs B, Lundell G, Castellanos E, Ullén A. High rate of local control and cure at 10 years after treatment of prostate cancer with external beam radiotherapy and high-dose-rate brachytherapy: a single centre experience. Acta Oncologica. 2021; 60: 1301-1307.
doi:10.1080/0284186X.2021.1953706

IV. **Hjälm-Eriksson M**, Ullén A, Castellanos E, Nilsson S, Brandberg Y. High levels of health-related quality of life five year after curative treatment of prostate cancer with HDR-brachytherapy and external beam radiation. Acta Oncologica. 2022; Sept 4:1-7. Online ahead of print.
doi: 10.1080/0284186X.2022.2115314.

CONTENTS

LIST OF ABBREVIATIONS

AD	Any death
ADT	Androgen deprivation therapy
AF	Any failure
AS	Active surveillance
BFS	Biochemical failure free survival
BT	Brachytherapy
CCI	Charlson Comorbidity Index
CFRT	Conventionally fractionated radiotherapy
CI	Confidence interval
CPG	Cambridge Prognostic Group classification
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical target volume
DFS	Disease-free survival
DRE	Digital rectal examination
EBERT	External beam radiotherapy
EORTC	European Organization of Research and Treatment of Cancer
EORTC QLQ C30	EORTC quality of life questionnarie C30
EORTC QLQ PR25	EORTC quality of life questionnarie PR25
GNRH	Gonadotropin-releasing hormone
GS	Gleason score
Gy	Gray
HDRBT	High dose-rate brachytherapy
HF	High-risk favourable
HRQoL	Health related quality of life
HFRT	Hypofractionated radiotherapy
HR	Hazard ratio
HU	High-risk unfavourable

IF	Intermediate-risk favourable
ISUP	International Society of Urological Pathology
IU	Intermediate-risk unfavourable
L	Low risk
LDRBT	Low dose-rate brachytherapy
LE	Life expectancy
LQ	Linear quadratic model
OS	Overall survival
MFS	Metastasis free survival
MRI	Magnetic resonance imaging
N	Number
NPCR	National Prostate Cancer Registry
PC	Prostate cancer
PCSD	Prostate cancer specific death
PCSF	Prostate cancer specific failure
PET-CT	Positron-emission tomography-computerized tomography
PIRADS	Prostate Imaging Reporting and Data System
PSA	Prostate specific antigen
PTV	Planning target volume
RCT	Randomized clinical trials
RWD	Real world data
RP	Radical prostatectomy
SD	Standard deviation
RT	Radiotherapy
RTOG	Radiation toxicity oncology group classification of toxicity
TNM	TNM Classification of Malignant Tumours
WHO	World health organization
Y	Year

LIST OF ABBREVIATIONS IN THE EORTC QLQ C30 AND PR25

PF	Physical functioning scale
RF	Role functioning scale
EF	Emotional functioning scale
SF	Social functioning scale
CF	Cognitive functioning scale
GH	Global health status scale
FA	Fatigue symptom scale
PA	Pain symptom scale
NV	Nausea vomiting symptom scale
DY	Dyspnea
AP	Loss of appetite
SL	Sleep disturbance
CO	Constipation
DI	Diarrhea
FI	Financial difficulties
PRURI	Urinary symptom-scale
PRBOW	Bowel symptom-scale
PRHT	Hormonal-treatment symptom-scale
PRSAC	Sexual activity functioning-scale
PRSFU	Sexual functioning-scale
PRAID	Incontinence Aid

1 INTRODUCTION

Prostate cancer (PC) is a major health problem. In high income countries, the incidence and prevalence of prostate cancer have increased dramatically during recent decades, mainly due to better diagnostic tools, an aging population and increased awareness of the disease. The prognosis of PC varies, with high mortality rates for high-risk disease in contrast to a mild course in low-risk cancers with almost no risk of metastases.

Radical treatment options for localized and locally advanced PC are surgery, external beam radiotherapy (EBRT), brachytherapy (BT) and combinations of these modalities. Randomized trials concerning the therapeutic effect of these treatment options are rare, and have so far shown little difference in oncological outcome, but differences in patterns of side effects. Therefore, it is important to consider age, comorbidity and treatment induced effects on Health-Related Quality of Life (HRQoL) in the decision-making process preceding curative treatment of PC. However, long-term patient reported outcomes concerning HRQoL after HDR-brachytherapy (HDRBT) are rare and often mix results from different BT modalities.

This dissertation aimed to deepen the knowledge about HDRBT combined with EBRT, an important treatment option for men with PC. Using real world data from a large cohort of consecutive patients, treatment efficacy at 10 years (Y) and patient reported HRQoL at five Y were assessed. Furthermore, the prognostic value of comorbidity and the Cambridge prognostic group risk-classification were assessed. In addition, long-term HRQoL after prostatectomy and combined HDRBT and EBRT was evaluated in a regional cohort study. Our results provide further knowledge regarding the long-term efficacy and effects on HRQoL of HDRBT combined with EBRT and can be useful for both physicians and patients in shared decision-making pertaining to curative treatment and in planning rehabilitation after treatment.

2 LITERATURE REVIEW

2.1 EPIDEMIOLOGY AND AETIOLOGY

Prostate cancer (PC) is the second most common cancer in men worldwide and a major health concern. In 2020, 1.4 million new cases were diagnosed and more than 375,000 men died from the disease. Age-standardised incidence and mortality rates were 31 per 100,000 and 7.7 per 100,000, respectively (1). The incidence varies substantially between countries, the highest being in Northern Europe, North America and the Caribbean, while the lowest is found in South-east and Central Asia. Each year about 10,000 men are diagnosed with PC in Sweden and approximately 2,300 men die from the disease (2). The PC mortality trend has gradually declined over the past 20 Y, except for men over 85 Y. In 2020, 124,700 men were living with the PC diagnosis (3). The estimated ten-year survival rate was 88% in 2016 (2). A majority of newly diagnosed men (80%) had localized or locally advanced disease with the potential for cure. The mean age at diagnosis was 69 Y.

The aetiology of prostate cancer is not fully understood and appears to be dependent on both genetic and environmental factors. Established risk factors are age, ethnicity, family history as well as inherited genetic aberrations and syndromes (e.g., mutations in BRCA 1/2 and other DNA repair genes, HOXB13 and Lynch syndrome) (4). Research results from studies of environmental factors are contradictory. Recent studies indicate that factors, such as smoking, obesity as well as a high intake of processed meat and dairy products, may influence the risk of PC (5,6,7).

2.2 CLINICAL PRESENTATION, SCREENING AND DIAGNOSIS

Men with early stage PC are usually asymptomatic, although urinary obstruction and retention sometimes occur in locally advanced cases. In metastatic disease, patients often present with fatigue, anorexia, bone pain or acute complications, such as medulla compression and bone fractures. Common metastatic disease sites in advanced PC are loco-regional lymph-nodes and bone, which affect a majority of patients. However, liver, lung, pleura, brain and adrenal glands metastasis is rare and found only in 1% to 10% of men with advanced disease (8).

2.2.1 Screening of prostate cancer

Screening is a way to diagnose localized prostate cancer in the early asymptomatic stage, when the disease is potentially curable. Current screening methods are based on blood tests with the prostate-specific antigen (PSA) biomarker. The sensitivity and specificity of the test vary depending on the PSA level set to trigger further investigations (9). Because PSA is an organ specific as opposed to a cancer-specific biomarker, PSA levels are influenced by other factors, such as age, surgical interventions and benign diseases of the gland. A meta-analysis of several large screening studies failed to show a reduction in PC death using PSA-screening (10). However, the European Randomized Study of Screening for Prostate cancer demonstrated a 20% reduction in PC specific mortality, but the number of screenings

necessary to save 1 life from PC death was high (1/570) (11). Thus, PSA screening results in overdiagnosis of latent PC, and authorities have argued against routine PSA screening (12-14). Guidelines currently endorse PSA testing on an individual basis after informed decision-making. At present, projects are ongoing in Sweden to implement structured PC testing programmes for men aged 50-75 Y. These programmes aim to offer informed PSA testing according to a pre-specified algorithm with continuous evaluation.

2.2.2 Diagnosis of prostate cancer

The current clinical routine for diagnosing PC comprises PSA measurements in blood or serum, digital rectal examination (DRE) of the tumour and core biopsies from the prostate for histopathological definitive diagnosis. In addition, Computerized Tomography (CT) of the thorax and abdomen, as well as, a bone-scan are performed, in high-risk patients to exclude metastatic disease. The addition of positron-emission tomography CT (PET-CT) using sodium fluoride or prostate cancer specific membrane-antigen as a tracer improves the chance of diagnosing de novo metastatic disease compared to a bone scan. However, earlier diagnosis of distant metastasis has so far not translated into improved survival time (15,16).

During the past decade the use of multi- and bi-parametric magnetic resonance imaging (MRI) has improved the diagnostic process of early PC due to its high sensitivity for detecting clinically significant prostate cancer, while the number of insignificant cancers is reduced (17). Areas with suspected tumours are classified from 1-5 by MRI in accordance with the Prostate Imaging Reporting and Data System v 2 (PI-RADS) (18). As a consequence of the use of MRI, the number of biopsies can be reduced by approximately 30% if restricted to PI-RADS ≥3, but with the risk of failure to detect about 10% of all significant PC cases (≥ISUP 2) (19). Nevertheless, in a Cochrane review, diagnostic work-up with “PSA, MRI and targeted or systematic biopsies” was found to outperform “PSA and systematic biopsies only”, especially in men with prior negative biopsies (19). Moreover, complementary tests and models using biomarkers from blood, urine or tissue have been proposed to enhance the selection of patients for MRI and prostate biopsy to reduce over- and underdiagnosis (20). However, guidelines have so far been hesitant to incorporate these tests in the diagnostic work, because of uncertainty about their predictive value and costs (12,14).

2.2.3 Histopathology

The histopathological diagnosis should always be performed on systematic or targeted biopsies from the prostate in candidates for curative treatment of PC. The dominant histological type is acinar adenocarcinoma, which constitutes 95% of all PC cases. The remainder consists of the following adenocarcinoma subtypes; ductal, mucinous, foamy gland and occasionally neuroendocrine and sarcomatous cancers.

From the early 1960s until the late 1990s prostate cancer in Sweden was diagnosed with fine needle aspiration biopsies and graded according to the WHO grading system (21). The classification categorizes tumours into 3 grades (G1-3); high, intermediate and low differentiated, based on the grade of nuclear atypia and glandular differentiation.

Table 1. ISUPgrade group and Gleason score.

ISUP grade	Gleason grade
ISUP 1	GS 2-6
ISUP 2	GS 3+4
ISUP 3	GS 4+3
ISUP 4	GS 8
ISUP 5	GS 9-10

The current standard for classification of primary tumours in the prostate was created by Gleason in 1966 and updated at the International Society of Urological Pathology (ISUP) consensus meetings (22,23). The classification from 1-5 is based on the architecture of the malignant glands. Grade 1 is defined as the most differentiated glands and Grade 5 the least differentiated. When biopsies are graded, a sum is created by adding the most common grade to the second most common grade, termed the Gleason score (GS). Regarding low grades, volumes less than 5% are not counted in the score, but for high grades even small volumes should be reported and included. At the ISUP 2005 conference, a major change in the classification growth patterns resulted in one third of tumours being upgraded from a GS 3 to a GS 4 pattern (24). In addition, it was proposed that the GS should be reported as ISUP grades or grade groups to better mirror the prognostic value of each grade and to overcome the problem with the GS 7 group, which includes tumours with both a favourable and an unfavourable prognosis (Table 1). The GS and the changes introduced in recent years are well validated and the GS is a strong predictor of the natural cause of the disease, as well as the outcome after curative treatment (24).

2.3 PROGNOSIS, CLINICAL STAGING AND RISK GROUP CLASSIFICATION

The prognosis of PC varies considerably from indolent cancer with a low risk of morbidity in 10 to 15 Y to highly aggressive tumours that rapidly progress to lethal disease. Studies of the natural history of PC have demonstrated that a majority of tumours are indolent and that when managed conservatively, men with high and to some extent intermediate differentiated tumours are at low risk of PC death (25,26). In contrast, about 30% of men with localized high-risk disease and about 40% of men with de novo regional metastases will die within 10 Y if not treated (27). Thus, it is a clinical challenge to select patients who will benefit from treatment. The PC risk stratification is therefore a cornerstone of the decision-making process in the choice of treatment for the individual patient. A number of pre-treatment risk stratification tools are available, all of which are based on the prognostic value of the T-stage as stated in the TNM Classification of Malignant Tumours (28), GS and PSA at diagnosis. One of the first risk classification tools proposed by D'Amico et al., stratified PC into three categories; low, intermediate and high-risk, based on the risk of biochemical failure after treatment with radical prostatectomy (RP) or radiotherapy (RT). This classification became a standard tool in clinical practice (29). Today, tools including more detailed histopathological information and additional strata are used. These tools also address different outcomes such as PCSD, OS and metastasis free survival (MFS). In a recent study, Zelic et al. compared

seven stratification tools for pre-treatment assessment of PC risk groups, one nomogram and one risk-score commonly employed in clinical practice, using a population-based cohort from the Swedish National Prostate Cancer Registry research (NPCR) database (30). The study demonstrated that the tools with more detailed information to discriminate between different risk groups outperformed the 3-tiered D'Amico-based tools. The Memorial Sloan Kettering Cancer Center nomogram, the Cancer of the Prostate Risk Assessment score and the Cambridge prognostic group (CPG) classification were the tools that performed best in the study (C-index 0.73-0.8) (31-33). The CPG classification (Table 2) is based on the D'Amico criteria but has been further developed to address death from PC and reflect the differences in prognosis in the intermediate and high-risk group. Furthermore, the CPG also includes stage T3 and T4 tumours (33). The National Swedish Prostate Cancer Guidelines currently recommend the use of a modified version of the CPG classification (14). Later in this review, the D'Amico based 3-tiered classification is used, unless otherwise specified, as most of the included studies employed this classification.

Table 2. Cambridge prognostic group (CPG) risk classification.

Risk group	Subgroup	Criteria
Low-risk	(L)	PSA <10 and Gleason score ≤ 6 and T stage cT1- cT2
Intermediate-risk	Favourable (IF)	Gleason score 3+4 or PSA 10-20 and T-stage cT1- cT2
	Unfavourable (UF)	PSA 10-20 and Gleason score 3+4 and T-stage cT1- cT2 or Gleason score 4+3 and T-stage cT1- cT2
High-risk	Favourable (HF)	PSA> 20 or Gleason score 8 or T-stage cT3
	Unfavourable (HU)	Minimum 2 factors; PSA> 20, Gleason score 8, T-stage cT3 or Gleason score ≥ 9 or T-stage cT4

2.4 PRIMARY TREATMENT OF LOCALIZED AND LOCALLY ADVANCED PROSTATE CANCER

In the clinical management of men with PC it is necessary to consider a number of variables in order to select the optimal treatment strategy and individualize the treatment for each patient. These variables include age, comorbidity, family history and risk group. In addition, MRI findings and histopathological features (i.e., cribriform and intraductal growth patterns, manifestation of ductal cancer, tumour burden) not accounted for in the risk classification should be considered. Furthermore, it is mandatory to involve the patient and consider his personal preferences in the decision-making process, as all treatment options have specific advantages/disadvantages and risk of side effects. In addition, there is always a risk of over- and undertreatment that can direct the decision towards either active treatment or surveillance.

Treatment options for localized PC and locally advanced disease include active surveillance (AS), radical prostatectomy (RP), EBRT, BT, deferred treatment and antiandrogen deprivation therapy (ADT) as well as combinations of these modalities. Randomized clinical studies (RCT) have shown that PC specific survival and OS benefits of RT and RP compared to symptom management and hormonal therapy in the intermediate and high-risk groups (34-37). In addition, recent results from the Stampede study revealed that intensified multimodal treatment including RT, of very high-risk or N1 PC reduces the risk of developing distant metastases and prolong biochemicalfree survival (BFS) at seven Y follow-up in the group with the highest risk of death from PC (38). In the landmark Protect-T study, AS, RP and RT were compared head-to-head in men with mainly low-risk or low-grade disease (Low risk 56%, PSA<10ng/l 90%, ISUP grade 77%) (39). Although a small reduction of the risk of metastasis at 10 Y was found in favour of RP and RT, no differences were seen in PC specific death or OS. This illustrates the risk of overtreatment in men with low and favourable intermediate-risk disease and strengthens the indication for an AS strategy in this group.

Which curative treatment option for localized disease is the most effective remains a subject of debate. During the past decade, several observational studies and meta-analyses have indicated the superiority of RP compared to RT (40-42). Despite advanced statistics, there were however, several potential confounding factors often not accounted for in those studies, such as differences in inclusion criteria, age, comorbidity and inconsistency in the treatment given both for the RP and the RT groups (43,44). So far, the Protect-T study is the only RCT to compare the efficacy of RP and RT in PC, but found no difference in PCSS or OS between the treatment options at 10 Y (39). Notably, in both arms, few deaths had occurred at the 10 Y follow-up, which per se reduces the chance of detecting a difference between the treatments. Currently, the Scandinavian PC group is conducting an RCT (SPCG-15) comparing RP with the addition of adjuvant or salvage RT with RT combined with ADT in a high-risk PC population, which will hopefully clarify the most effective treatment for the high-risk group.

2.4.1 Treatment options for localized and locally advanced prostate cancer

2.4.1.1 Active surveillance

AS is recommended as the primary treatment for low-risk and intermediate favourable-risk group patients because of the small likelihood of progress to a life-threatening disease during their lifetime (12,14). The aim is to avoid unnecessary treatment-related morbidity, and in the event of progression, to initiate curative treatment within the time frame during which the disease is still possible to cure. During AS, patients should be monitored according to pre-specified follow-up schedules, which include PSA tests, clinical examination, repeated biopsies and MRI. The optimal schedule has so far not been established. (45). The ten Y PC specific survival has been reported to be 96-100% during AS (39,46).

2.4.1.2 Deferred treatment

Deferred treatment, also called watchful waiting, refers to conservative management of patients with any stage of localized and locally advanced PC without metastasis, who are unsuitable for curative treatment. This treatment option is recommended for asymptomatic men with a life expectancy of less than 10 Y due to age or comorbidity. The aim is to carefully monitor signs of local or distant progression and initiate hormonal or local treatment early in the symptomatic phase to maintain HRQoL. As discussed above, men with low-risk PC have a low risk of death from PC when managed with deferred treatment (26,27). However, RCTs comparing RP and conservative management demonstrate a statistically significant reduction in cause-specific and overall mortality in favour of active treatment, but the absolute difference was small and only apparent after10 Y (34,37). Consequently, asymptomatic men with a life expectancy of less than 10 Y are more likely to benefit more from deferred than from active treatment (47).

2.4.1.3 Androgen deprivation therapy as primary treatment

Several RCTs have investigated the use of ADT (Gonadotropin releasing hormone agonists [GNRH] or antiandrogen) in localized and locally advanced PC. These studies showed little or no benefit of upfront hormonal therapy in men with slowly progressing localized disease. However, in men with rapidly progressing (i.e., PSA-DT < 1Y or PSA >50 µg/l) and locally advanced disease, early ADT was found to be beneficial leading to prolonged OS, longer time to first progression and reduced complications caused by metastasis (48,49). These studies also support the use of hormonal treatment administered as monotherapy with antiandrogen in this clinical setting to reduce the side effects compared to GNRH (50,51).

In summary, guidelines only recommend up-front hormonal treatment in men who are unsuitable for curative interventions, with rapidly progressing localized high-risk or locally advanced disease. Swedish guidelines recommend monotherapy with antiandrogen as the primary choice based on a superior side-effect profile compared to GNRH.

2.4.1.4 Radical prostatectomy

RP aims to remove the prostate gland and thereby the tumour using a nerve-sparing technique to save erectile function and urinary continence, where possible. RP can be performed with three standard techniques; open, laparoscopic or robot assisted prostatectomy. In Sweden, robotic RP is now the most commonly used technique. This approach has been shown to have less acute surgical complications, but randomized studies have failed to show superior oncological outcomes for any of the techniques (52). Regional lymph node dissection is often recommended when the risk of lymph node involvement indicated by nomograms exceeds 5-7%. It provides additional information on staging, but has so far not been shown to improve the oncological outcome (53,54). The most common long-term side effects after RP are loss of erectile function and incontinence, which to some extent can be prevented through the use of the nerve-sparing technique (55). RP is recommended for curative treatment of localized low, intermediate and high-risk PC with a life-expectancy over 10 Y.

2.4.1.5 Radiotherapy

Radiotherapy is a standard curative treatment option for PC in all risk groups. Several treatment modalities are available; EBRT, LDR and HDR brachytherapy and combinations of them. Modalities currently used in Sweden will be described below.

External beam radiotherapy

As a curative treatment for PC, external beam radiotherapy (EBRT) has improved immensely over recent decades, due to both technical advances and increased knowledge of PC tumour biology. Current practice is based on the knowledge that local control after RT is essential for achieving cure and that it will require doses in the range of 74-80 Gy (56-58). Several RCTs have shown that RT doses in the range of 74-80 Gy in standard (2Gy) fractions, with or without ADT, significantly reduce biochemical failure (BF) and PC specific death compared with conventional fractionation in total doses of 60-70 Gy (59-64). Therefore, dose-escalated RT with total doses of up to 80 Gy is considered standard care today and can be achieved with acceptable toxicity, especially using modern technology that enables the minimization of irradiated high dose regions in normal tissue (65,66).

In recent years, the development of hypofractionated RT (HFRT) has been in focus. This concept includes fewer but larger fractions to achieve the total dose, which could be more convenient for the patient as well as enabling better utilization of healthcare resources. The rationale for the use of hypofractionation in PC is based on radiobiological theory, which suggests that tumours with a slow proliferation rate and thereby a long cell cycle, such as PC, have a higher capacity for intracellular repair of radiation induced damage between fractions, potentially affecting the treatment result (67). Thus, standard (2Gy) fractionation could be suboptimal in PC, which instead may benefit from larger doses per fraction to achieve optimal tumour control (67,68). HFRT is defined as treatment with fractions from 2.5-10 Gy. Several RCTs have investigated moderate HFRT (2.5-3.4 Gy x 19-29) vs. conventional fractionated RT (CFRT), primarily in intermediate-risk PC with median follow-ups of around 5 Y. They showed that this technique is equally effective as, CFRT concerning BFS at 5 Y. However, the technique is also associated with higher acute bowel toxicity during the first year after treatment (69-73). Table 3 summarises HFRT studies using total doses comparable to the current standard.

Other authors have raised concerns about the long-term efficacy of HFRT because of the short follow-up (74). In a Cochrane analysis including ten RCTs, little or no difference in PC specific survival and comparable toxicity after a median follow-up of 7 Y was reported (75). However, the evidence level for some of the outcomes was reported as low. Studies of ultra-HFRT (5-10 Gy) treatment of PC with a long follow-up are rare, but early reports are promising (76). Furthermore, in a Scandinavian RCT, ultra-HFRT (6.1Gy x7) was compared to dose-escalated CFRT in a non-inferiority design (77). A majority of the study participants had intermediate-risk PC and ADT was not used. The study reported no difference in the 5 Y BFS rate but an increase in acute toxicity favouring the CFRT arm was found, which has

raised concerns regarding the use of ultra-HFRT. However, at five Y similar rates of late toxicity were reported in both study arms. Nevertheless, HFRT is controversial. European guidelines do not recommend ultra-HFRT and state that moderate HFRT should only be performed in accordance with the published Phase 3 protocols at institutions that have the latest technology and experienced teams (12). In contrast, the latest Swedish national guidelines recommend ultra-HFRT as the first choice of treatment for men with low to intermediate-risk PC and as a second choice in high-risk PC (14).

Table 3. Overview of randomized clinical HFRT studies using doses comparable to ≥74Gy in 2 Gy fractions,

Study	**n**	**Median FU,** mo	**Risk-group**	**Modality**	**Dose-schedule**	**BED** α/β= 1.5	**BFS 5Y**	**RTOG 5Y** GU ≥2	**RTOG 5Y** GI ≥2
Arcangeli[69]	168	70	HR	3D Con	2Gy*40	187Gy	79%	11% [a]	14% [a]
				ADT 100%	3.1Gy*22	209Gy	85%	16% [a]	17% [a]
Pollack[70]	303	NR	Inter	IMRT	2Gy*36	177Gy	21% [c]	similar at 5Y,	Similar at 5Y
Non-inferiority			HR 34%	ADT in IU and HR	2,7Gy*26	197Gy	23%[c]		
Dearnley[71]	3216	62.4	L 15%	IMRT	2Gy*37	173Gy	88,3%	9% [b]	14% [b]
Non-inferiority			Inter 73%	ADT 97%	3Gy*19	171Gy	85.9%		
					3Gy*20	180Gy	90.6%	12% [b]	14%[b]
			HR 12%						
Catton[72]	1206	72	Inter	3D-Con or	2Gy*39	182Gy	85%	22% [b]	14% [b]
Non-inferiority				IMRT	3Gy*20	180Gy	85%	22% [b]	9% [b]
				No ADT					
Innocenti[73]	804	60	Inter	IMRT 95%	2Gy*39	182Gy	77.1%	39% [a]	18% [a]
Superiority			HR 24%		3.4Gy*19	211Gy	80.5%	41% [a]	22% [a]
				ADT 67%					
Widmark[77]	1180	60	Inter	3D con or	2Gy*39	182Gy	84%	17% [b]	10% [b]
Non-inferiority			HR 11%	IMRT	6.1Gy*7	216Gy	84%	18% [b]	10% [b]
				No ADT					

BFS; biochemical-free survival, RTOG; Radiation oncology toxicity grading score, FU; follow-up, n; number, mo; month, BED; biologically equivalent dose, GI; gastro intestinal, GU; genitourinary. NR, not reported. [a] 3Y cumulative incidence. [b] 5 Y cumulative incidence . [c]BCDF, outcome measure defined as biochemical and, or clinical PC failure of PC.

Both intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) are techniques that allow dose planning and delivery with close adherence to the defined target volume, thus ensuring high quality dose-escalated CFRT or HFRT (60,78). Positioning is increasingly important both for tumour control and for reducing unintentional doses to

normal tissue when higher total doses and larger doses per fraction are used. To control organ movement, image guided RT (IGRT) is employed. This involves daily imaging before the start of treatment to establish the position of the target and organ movements and to correct the position in real time if necessary. Current knowledge suggests that IGRT further enhances the delivery of RT to the prostate and reduces side effects, especially those related to the bowel (79). Quality assurance routines are necessary to obtain the full potential of these technologies.

Brachytherapy

BT is defined as short-range radiation of tumours, with a radionuclide placed near the tumour during treatment. BT of the prostate can be performed with either low dose-rate permanent seed implantation or high dose-rate temporary source implants. The advantage of these modalities is that high doses can be delivered with minimal effect on surrounding tissue, as both options benefit from a rapid dose fall-off from the source.

Low dose rate brachytherapy

LDRBT is used as monotherapy for low risk to favourable intermediate-risk PC in patients with good urinary function or in combination with EBRT for more advanced risk groups. Typically, shielded sources of either Palladium-103 or Iodine-125 are implanted into the prostate using transrectal ultrasound guidance. The recommended total doses for Iodione-125 in mono-therapy and boost are 145Gy and 110Gy, respectively (80). Outcome data from single centre studies including clinically localized PC show BFS rates ranging from 65%-93% with 7-10 Y follow-up (81-85). Furthermore, an association between the implanted dose and BFS has been demonstrated (86). One RCT compared LDR and RP in low and intermediate-risk PC and found no difference in BFS at 5 Y (87). In addition, other studies have compared the efficacy of LDRBT, EBRT and surgery in low and intermediate-risk PC, in terms of PC specific mortality and disease-free survival (DFS). None of these studies showed any statistically significant differences between the treatments in low-risk PC (88,89). In high-risk PC, however, one of the studies found mono-LDRBT to perform worse than RP and EBRT in intermediate and high-risk PC (88). Recently, an RCT was published comparing dose escalated CFRT with LDRBT combined with CFRT and ADT in intermediate and high-risk PC. The results demonstrated a substantial improvement of BFS in the combined arm at 9 Y, but also an increase in urinary toxicity compared to the CFRT arm (90).

High dose rate brachytherapy

HDRBT as a monotherapy or combined with EBRT has been used in recent decades and found to be effective in all risk groups, thus is a recommended treatment option in guidelines (12,14,80,91). The combined technique was one of the first dose-escalated hypofractionated treatment options available and the total dose of the combined treatment exceeds 100 Gy in a biologically equivalent dose in 2Gy fractions. Due to the excellent conformity of the

treatment, which allows more advanced dose-planning and control of dose delivery, the high dose can be safely delivered to the prostate. Moreover, the prostate is fixed in position by the catheters, thus reducing the risk of target movement during treatment. The treatment technique uses transrectal ultrasound to define the target volume, guide the insertion of catheters to the prostate and control their position (92). The position of the catheters can also be controlled with CT or MRI. The source is then placed in position with an after-loading technique (93). To achieve a high dose-rate the Iridium-192 isotope is commonly used. It has physical characteristics that allow rapid dose delivery and has a greater range than the radionucleotides used in LDRBT, which is feasible when larger tumours are treated (80). There is no consensus on the optimal treatment schedule for combined HDRBT, and 1-4 fractions of 5-15 Gy have been used. In combination schedules both CFRT and moderate HFRT have been administered in doses up to 46-50 Gy in biologically equivalent 2 Gy doses. In the latest European brachytherapy guideline, one HDR fraction of 15 Gy is preferred to multiple HDR-fraction schedules in the combined treatment. The recommendation is based on the absence of evidence that multiple fractions are superior to single fractions in the combined setting, as well as, enabling more effective health resource utilization and convenience for patients (80, 94,95).

One RCT compared combined HDRBT and HFRT to HFRT alone with doses ≤70 Gy in the HFRT alone arm (96,97). Improvement of recurrence free survival was found in the combined arm at twelve Y, but no difference in OS. Furthermore, no statistically significant differences were found in bowel or urinary toxicity at 8 Y. In addition, data from an RCT investigating the effect of adjuvant ADT for 6 or 18 months in men treated with either combined HDRBT or three different CFRT schedules (total dose of 66, 70 or 74 Gy, respectively) and, demonstrated a significant reduction in distant metastases (primary endpoint) in the HDRBT group compared to CFRT alone regardless of total dose (98). Furthermore, several single centre studies report high rates of 10 Y BFS (62-79%) and PCSS (94-98%) in intermediate and high-risk PC after combined HDRBT with different treatment schedules, Table 4 (99-104).

So far, no RCT has been performed comparing dose escalated CFRT or HFRT alone with combined HDRBT. However, one single centre retrospective cohort study has investigated this, reporting in favour of the combined HDRBT arm (80% vs 71%), but with an increased risk of urinary strictures (105). Furthermore, observational data suggest that the combined approach may have advantages in terms of MFS in high-risk PC compared to other modalities (106). One cohort study investigating dose-escalated CFRT versus combined CFRT and BT (HDR/LDR not specified) and reported an OS benefit for the combined BT arm at the 7 Y follow-up (107). Interestingly, this cohort study showed that the difference between the groups disappeared, when the comparison was restricted to dose escalated RT using doses ≥79 Gy.

Table 4. RCT and Singel centre HDRBT combined with EBRT studies with long-term follow-up.

Study	**n**	**Median FU**, Y	**Risk-group**	**HDR dose**	**EBRT dose**	**BED** α/β= 1.5	**Outcome 10Y** BFS	**RTOG GU** ≥3	**RTOG GI** ≥3
Hoskin[96,97] (RCT)	218	12	L 7% IR 40% HR 53% ADT 77%	A, 8.5Gy*2	A, 2.7Gy *13 B, 2.75Gy *20	214Gy 156Gy	DFS 12Y 48% 27%	13%[a] 7%[c]	0% [a] 2%[c]
Galalae[99]	122	9.7	L 23% IR 33% HR 45% ADT 23%	9Gy*2	2Gy*20	219Gy	L to HR 67-74%	5%	2%
Demanes[100]	209	7.2	L 34% IR 44% HR 22%	5.5-6Gy *4	1.8Gy*20	182Gy/ 191Gy	L to HR 62-93%	7%	0%
Prada[101]	313	6	IR 5% HR 94% ADT 70%	11.5Gy *2	2Gy *23	306 Gy	84%	urethra-stricture 2%	0%
Martinez [102]	472	8.2	IR HR ADT 51%	A, 5.5-6.5 *3 or 8.25-8.75 *2 B, 9,5-11,5 *2	2Gy*23 WP	215Gy[c] 276Gy	A, 57% B, 81%	NR	NR
Yaxely[103]	507	10.3	IU 33% HR 67% ADT 100%	6.5Gy*3	2Gy*23	211Gy	IU to HR 64-85% VHR [e] 40-47%	Urethra stricture 13%	NR
Åström[104]	623	11	L 15% IR 32% HR42% VHR 11% ADT69%	10Gy *2	2Gy*25	270Gy	L to HR 67-100% VHR 35%	6% [b]	1% [b]
Single HDR fraction & EBRT							**BFS 5Y**	**CTCAE GU ≥3 5Y**	**CTCAE GI ≥3 5Y**
Martell[94]	518	5.2	IR ADT 16%	15Gy *1	2.5Gy*15	265Gy	All, 91%	4%	0%
Tharmalingam[95] (Cohort study)	812	4.7	IR 21% HR70% ADT 40%	15Gy *1	2.5Gy*15 or 2Gy*23 include WP	265Gy 272Gy	All, 81%	5%Y	0%

RTOG, Radiation toxicity oncology group classification, FU, follow-up, n Number, mo, month, BED, biologically equivalent dose, GI, gastro intestinal, GU, genitourinary, WP, whole pelvis. NR, not reported. BFS, biochemical-free survival, DSF disease-free survival include Biochemical failure, local failure or death of other cause. [a] Dische scale, prevalence 7Y, [b] CTCAE, Common terminology criteria for adverse events, [c] BED for the median HDR dose for the low (8.25 Gy) and high (10.5 Gy) dose schedule, respectively. [e] VHR, very high risk= 2 or 3 high risk criteria. For the Martini study, the HDR fractionation are shown per low (A) and the high (B) dose cohorts respectively. All numbers rounded to integers.

Mono HDR-brachytherapy

Mono-HDRBT has not been evaluated in comparison with other treatment modalities in RCT, but several larger single centre studies with a median follow-up of 5-7 Y report a high rate of 5 Y BFS and low toxicity rates primarily in the urinary tract (108-112). A recent review and meta-analysis reported a 5 Y BFS rate of 95% and grade 3 urinary toxicity of 2-3% and even lower rates of bowel toxicity (113). Mono-BT with one fraction has proved to be inferior to fractionated treatment (114). Swedish guidelines do not recommend mono-BT, as a standard treatment option but suggest that this strategy can be considered for selected patients when standard treatment options are unsuitable due to certain comorbidities. Figure 1 summarise curative treatment options for PC.

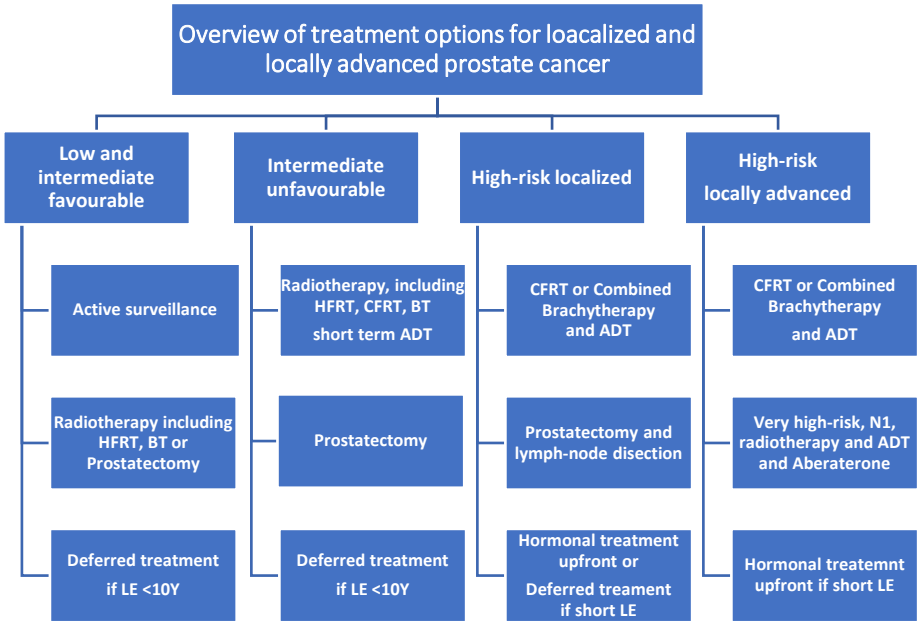


Figure 1. Summary of treatment of localized and locally advanced prostate cancer.

2.4.1.6 Pelvic lymph-node radiation

The radiation of pelvic lymph-nodes has been debated during the past decade. Until recently there was no proof of the benefit of whole pelvic radiation (115,116). However, a small RCT has now provided evidence in support of whole pelvic irradiation in high-risk PC. The RCT showed an increased PC specific survival and MFS at 5 Y in the group of men treated with whole pelvic RT, but also increased bowel toxicity (117). Because of increased bowel toxicity and other limitations of the study, pelvic lymph node treatment is still regarded as experimental in guidelines (12,14).

2.4.1.7 Neoadjuvant and adjuvant ADT in combination with RT

Endocrine treatment has since long been known to improve biochemical, PC specific survival and OS, when used in addition to curatively intended RT (118-121). Data from a review of two RCTs indicate that sequencing may be important and that adjuvant treatment might be

preferable (122). Current evidence supports the use of ADT combined with dose-escalated EBRT in unfavourable intermediate and high-risk PC (123-125). Moreover, results from the TROG 30.04 trial described above provide evidence for the use of ADT in intermediate and high-risk patients treated with combined HDRBT and EBRT (98). Swedish and European guidelines recommend short term ADT for the unfavourable intermediate risk-group and two to three Y of ADT in the high-risk group. In men with very high-risk M0 or N1 PC, the addition of GnRH for three Y combined with two Y of Abiraterone, a second-generation hormonal treatment, has recently been demonstrated to substantially increase both BFS and MFS rates (38). The addition of Abiraterone has rapidly been implemented in clinical practice and is now the new standard treatment for this patient group. An overview of curative treatment for PC including use of ADT is presented in Figure 1.

2.5 RADIATION INDUCED TOXICITY

Ionized radiation causes repairable and irreparable DNA damage and inflammation. Different responses occur depending on the normal tissue type but patient related factors, such as age, comorbidity and the genetic difference between individuals, will also affect the development of toxicity (126). These responses are divided into acute and late side effects.

Acute toxicity is defined as effects occurring within three months of the start of treatment and usually ending in the 3 months after the cessation of treatment. Early toxicity is primarily ascribed to rapidly proliferating normal tissues such as the rectal and bladder epithelium. Common symptoms that may occur during treatment irrespective of modality are urinary frequency, nocturia, urinary retention, haematuria, diarrhoea and proctitis. However, after dose-escalated CFRT, severe ≥grade 3 toxicity according to the Radiation Therapy Oncology Group (RTOG) scoring system (127) is low in the range of 2-13% and 0-4% for urinary and bowel symptoms, respectively (128-130). In comparison, reports from several HFRT studies demonstrate similar urinary toxicity, but more pronounced acute bowel morbidity than after CFRT (71,72,77), while low levels of ≥grade 3 toxicity have been observed. However, an RCT of dose-escalated CFRT vs LDRBT combined with CFRT demonstrated a double incidence of acute urinary grade 2 and 3 toxicity in the experimental arm, with similar bowel toxicity (90). One RCT compared HFRT and HDRBT combined with HFRT and found no statistically significant difference between the treatment groups concerning acute urinary and bowel morbidity and reported low levels of acute ≥ grade 3 toxicity (96). In a small randomized comparison of mono LDRBT and HDRBT, acute toxicity was more modest and recovery faster in the HDRBT arm (131).

Late side effects are defined as toxicity that occurs three months after termination of treatment or that continue after the acute phase. Furthermore, late effects are typically considered irreversible and caused by chronic radiation induced inflammation that leads to fibrosis and damage to the vascular bed (126). Late side effects after RT of PC include various degrees of urinary and bowel urgency, incontinence and bleeding, urethral stricture, fistulation and impaired sexual function. Several clinical risk factors for the development of late toxicity have been established: acute toxicity, irradiated volume of the rectum, patient-

related factors such as age and comorbid conditions, important factors being diabetes mellitus, inflammatory bowel disease, abdominal surgery and pre-treatment urinary function (132-136).

However, it is difficult to compare late toxicity rates between different studies, as there is no consensus on how to report toxicity and different classification systems are used. In a systematic review and meta-analysis of late toxicity in accordance with the RTOG classification, it was reported that after CFRT with 64-80 Gy, bowel toxicity ≥grade 3 was 2% (range 0-10%) and late urinary toxicity ≥grade 3 was 3% (range 0-13%) (66). Although a higher total dose seemed to increase the risk of late toxicities, results varied between studies reporting similar techniques and dose schedules. In the RCTs investigating HFRT vs CFRT, both late bowel and urinary toxicity were similar between the groups and severe late toxicity was relatively low, Table 3 (71,72,77). In one study however, urinary toxicity was reported to be higher in the experimental arm (73).

Both LDRBT and HDRBT combined with EBRT have been associated with a modest increased risk of late urinary bother but a low risk of late bowel morbidity compared to EBRT alone (99-100,104,137-139). However, randomized evidence from the Ascende-RT study showed a cumulative incidence of grade 3 toxicity at 6 Y of 18.2% in the LDRBT arm compared to 5.4% in the dose-escalated IMRT-arm, with a prevalence of 8.6% and 2.2%, respectively, at the same time-point (90). Urethra stricture was reported as the most common event (90). In the RCT investigating combined HDRBT vs CFRT, the rate of late toxicity was similar between the groups (96). However, 8% in the HDRBT group reported urinary stricture vs 2% in the CFRT group. In men treated with HDRBT, late grade 3 urinary toxicity has been reported to be from 0-13%, compared to 0-2% for late bowel toxicity, Table 4 (94, 99-103).

2.6 RADIOBIOLOGICAL ASPECTS

The relationship between the cell survival curve and the radiation dose is described by the linear quadratic model (68). Two parameters are of special interest; α indicating the sensitivity of a certain cell type to radiation and β describing the repair capacity of radiation damage that is not immediately lethal. The α/β ratio determines the sensitivity of a tumour or normal tissue to changes in fraction size. Slowly proliferating tumours, such as PC, are characterized by a low α/β ratio and thought to react favourably to large doses per fraction. In contrast, tumours with a high α/β ratio are expected to be insensitive to changes in fraction size. Generally, the α/β ratio is around 10 Gy in most tumours (68). In PC the α/β ratio has been calculated to be around 1.5 Gy, which supports the use of large doses per fraction as long as the α/β ratio for organs at risk is higher and does not overlap with the PC ratio (67,140). However, the α/β ratio for the rectum is estimated to be 2.5-5. In theory, this creates a window for the use of HFRT without increasing the risk of side effects to the rectum and bladder.

To compare the biological effect on normal tissue and tumours treated with different fractionation schedules, the biologically effective dose (BED) can be calculated using the α/β ratio, the number of fractions (n) and the dose per fraction (d) in Gy by applying the BED formula:

$$BED = nd\ (1 + d/\ \alpha/\beta)$$

This formula is often used to ensure an adequate total dose when new treatment schedules are investigated. The model is also applied in clinical practice to estimate total doses when for example patients are re-irradiated. In Table 3 and 4, the BED for each study is presented for comparison purposes.

2.7 HEALTH RELATED QUALITY OF LIFE.

2.7.1 The concept of HRQoL and the importance of HRQoL research

HRQoL is quality of life related to the problems, symptoms and treatments associated with a disease and is the term commonly used in clinical research and practice. There is no generally accepted definition of HRQoL, but most researchers agree that it is a multidimensional concept, including physical, emotional, cognitive and social functioning, as well as symptoms and problems related to a disease and its treatment (141,142).

It is generally accepted that HRQoL is a subjective experience that varies over time and should preferably be reported by the patients themselves. Further, several studies have found that there is poor correlation between healthcare professionals and patients when reporting patient outcomes (143).

HRQoL measurements are important in clinical research, as they are the only outcome measures evaluating the patient's perspective of how the disease and treatment affect her/his life. The use of patient reported outcome measurements can reveal unexpected aspects and issues that need to be considered to facilitate the treatment and patient care. Used together with other standard outcome measurements, such as tumour response and survival endpoints in clinical trials, HRQoL results have been shown to affect or modify the result and conclusion of RCTs (143). Knowledge of HRQoL is also important in clinical practice for improving communication and shared decision-making as well as in clinical follow-up for better understanding and managing treatment related side effects (144,145). HRQoL outcome measures have also been acknowledged as important in the new drug approval process and in the development of health policies (146,147).

In PC HRQoL is relevant from several perspectives. There is a risk of overtreatment in men diagnosed with low and favourable intermediate-risk PC and in many cases, it is difficult to determine which patient will benefit from curative therapy. In addition, patients are faced with a choice of treatment modalities considered to be equally effective, but with a risk of

inducing different modality-dependent life-long side effects. In this clinical situation, detailed knowledge of HRQoL outcomes associated with the various treatment options is important for healthcare professionals and for guiding and supporting the patient in the shared decision-making process. Moreover, the growing number of cancer survivors increases the need for information about long-term HRQoL in order to develop rehabilitation programmes to maintain or regain high HRQoL.

2.7.2 1.4.2 Instruments for measuring HRQoL

Several methods can be used to measure HRQoL, including questionnaires, structured interviews and focus groups. Questionnaires are most commonly used in clinical research, as they provide detailed structured information, are easy to handle in studies and in the clinic as well as being cost effective. There are several validated HRQoL questionnaires available. These are divided into three categories: general, disease specific and diagnosis specific (142). The first category is designed to measure a wide range of QoL aspects and compare HRQoL outcomes irrespective of the patient's diagnosis. One example is the Short form 36 health survey, where normative data from the Swedish population are also available (148).

Disease specific HRQoL instruments cover issues of interest for a specific group of diseases. The European Organization of Research and Treatment of cancer (EORTC QLQ c30) and The Functional Assessment of Cancer Therapy-general (FACT-G) are among the most commonly used questionnaires for cancer (149,150) and often employed in combination with questionnaires developed for a specific cancer diagnosis. The latter cover diagnosis specific functions, symptoms and treatment related side effects. Commonly used questionnaires in PC studies are The Expanded prostate cancer index composite (EPIC), FACT-Prostate and EORTC QLQ PR25 (151-153).

HRQoL instruments are usually organized in the form of scales that contain one or several items, which represent different areas of the HRQoL concept. Instruments used in clinical trials must be concise and practical to use as well as applicable to different cultural groups. In addition, the instrument needs to fulfil certain psychometric properties including validity, reliability, responsiveness and sensitivity, which are all interrelated (142).

Validity refers to how well an instrument assesses the properties it is designed to assess and if it is useful for the intended purpose. The validation process contains three different aspects; content validity, criterion validity and construct validity. Content validity relates to the accuracy of the content and whether the questions adequately describe and cover all necessary issues. Criterion validity involves measuring the performance of the instrument or scales compared to the "true value" it is intended to assess. This could be achieved by comparing the instrument to other validated questionnaires or to clinical tests and standards deemed to estimate the same properties. Construct validity is an important but complex part of the validation process. It evaluates how well the scales measure the properties they were designed to measure and if the results are stable over time and between different cultural and geographical populations.

Reliability consists of two different aspects; internal consistency and repeatability. The latter measures the extent to which the score of an instrument is consistent when repeated under the same circumstances in a patient over time or by different observers. Internal consistency relates to the homogeneity of a multi-item scale, e.g. how well all items in the scale measure the same variable. The most common statistical method used to measure the internal consistency of a multi-item scale is the Cronbach´s coefficient α (Cα), which should exceed 0.7 to be considered acceptable (154). However, this method is under debate, as it has been found that the assumptions required for the method often are violated, thus leading to biased estimates of the internal consistency (156).

Sensitivity refers to the ability of an instrument to detect clinically relevant differences between groups of patients. This includes discriminating between patients in different stages of a disease or patients in an RCT treated with different drugs. The sensitivity could be compromised by floor and ceiling effects, i.e., if a majority of patients respond in the maximum or minimum category, the instrument will not be sensitive to detecting changes (142). Sensitivity is best explored in cross-sectional studies.

Responsiveness is related to sensitivity but evaluates the ability of the instrument to detect changes in well-being within a patient over time. Responsiveness is also sensitive to floor and ceiling effects. The responsiveness of an instrument is investigated in longitudinal studies where change in health status is expected. These studies can also contribute to supporting the validity of the instrument, provided they show high responsiveness (142).

2.7.3 Long-Term HRQoL in prostate cancer state of the art.

The Prostate, lung, colorectal and ovarian cancer-screening study (PLCO) compared HRQoL in screened individuals diagnosed with cancer and screened individuals without cancer, at 5 and a 10 Y follow-up. It was concluded that cancer patients had clinically significantly lower urinary and sexual functioning after curative treatment irrespective of modality compared with the non-cancer group (156). In another large cohort study, HRQoL was reported at 2, 5 and 15 years after treatment for PC with RP, RT and BT. Increased incontinence and sexual problems after RP and bowel disturbances including urgency after RT were reported. In addition, the difference in urinary and bowel problems levelled out at 15 Y, but a decrease in functional levels for general HRQoL domains was noted at the same time point, probably influenced by the effects of aging (157). Most prospective longitudinal studies report a decrease in general HRQoL in the first 6-12 months after treatment, which improves over time to similar levels as the baseline data or HRQoL in a reference population. A number of disease and patient related factors, including old age, obesity, hormonal treatment and a high level of pre-treatment PSA, have all proved to have a negative association with HRQoL, regardless of treatment option (158).

In the Protect-T RCT discussed above, HRQoL was thoroughly investigated in men treated with AS, RP or CFRT (159). 6 Y HRQoL results revealed that men treated with RP had worse urinary and sexual functioning than RT and AS during the whole study period,

although a partial recovery was seen in the urinary domain. Furthermore, the RT group had worse urinary bother at six months compared to the other groups but recovered after that. Bowel functioning and bother, however, were more pronounced after RT, although these differences also levelled out during the study period.

Several of the RCTs conducted to explore HFRT vs CFRT have also studied the effects on HRQoL. In summary, they found an increase in the level of acute urinary and especially bowel problems in the HFRT arm (160-164). However, general and disease specific HRQoL reported at 5-6 Y were similar in both study arms. A deterioration in sexual functioning compared to baseline was noted in all patients, irrespective of the fractionation schedule.

After mono-LDRBT a reversible increase in urinary bother is typically seen, but the effect on sexual functioning is limited compared to the other treatment options (158,165,166). In the Ascende-RT study, combined LDRBT and CFRT with ADT was found to improve BFS, but also to increase early and late urinary toxicity compared to dose-escalated CFRT and ADT. This translated into worse urinary problems and lower physical functioning in the combined arm at 6 Y. No difference was seen between the arms concerning the bowel or sexual domain at the same time point, but sexual functioning was worse compared to baseline in both arms (167). Furthermore, a prospective cohort study explored disease specific HRQoL for up to 3 Y in a large cohort of men in the same setting and showed worse bowel problems at 12 months and worse urinary HRQoL at 3 Y in the combined arm (168).

In comparison, HDRBT combined with HFRT vs HFRT also showed increased BFS in an RCT and similar HRQoL results for all domains at the 10 Y follow-up (169), which may suggest that this treatment option can be of greater benefit than the LDRBT combination due to methodological advantages in dosimetry and dose delivery. Long-term HRQoL data from observational prospective and retrospective studies show high levels of general HRQoL comparable with reference data after HDRBT/CFRT combined treatment (170-173). In the disease specific domains, modest urinary and sexual problems are reported to remain, even in longer follow-ups. However, bowel related problems seem to be low (170-173).

Regarding mono-HDRBT, few HRQoL follow-ups are available, but several studies report high BFS and a low risk of toxicity after such treatment for up to 8 Y. A phase 2 single centre study reported the HRQoL (EPIC questionnaire) from 79 men over 48 months and showed an increase in bowel and urinary problems that abated within one Y. On the other hand, sexual functioning decreased after treatment and was not regained during follow-up (174). Another retrospective cohort study with prospectively collected HRQoL questionnaires from 74 men for up to 18 months showed similar results (175). However, a properly designed RCT and longer follow-up of both survival and HRQoL endpoints are needed to evaluate the value of mono-HDRBT in relation to other RT modalities.

In summary, long-term general HRQoL after radiotherapy is high irrespective of treatment modality. Concerning disease specific HRQoL, the above-mentioned studies indicate that severe urinary and bowel problems are relatively rare 5 Y after dose-escalated RT.

Nevertheless, modest urinary problems remain after combined HDRBT as well as after LDRBT combined with CFRT. However sexual HRQoL is more severely affected after treatment, with a more favourable outcome after mono LDRBT.

3 RESEARCH AIMS

The overall aim of this thesis was to investigate the long-term oncological outcome and health-related quality of life after curative treatment of PC with combined high dose-rate brachytherapy and external beam radiotherapy and concomitant androgen deprivation therapy.

The specific aims of the four studies were as follows:

Study I

- To compare long term HRQoL in men with localized prostate cancer treated with open retropubic prostatectomy or HDRBT combined with EBRT in Gothenburg from 1988 until 1997.

Study II

- To investigate the prognostic value of comorbidity in relation to other prognostic markers after curative treatment of PC with HDRBT combined with EBRT.

Study III

- Assessment of the curative effect of HDRBT combined with EBRT on overall death, prostate cancer specific death and failure, any failure and local control in a large consecutive PC patient cohort.
- To investigate the prognostic value of the Cambridge prognostic group (CPG) classification in men treated with HDRBT and EBRT.

Study IV

- To assess long term HRQoL in men with prostate cancer treated with HDRBT and EBRT at the Karolinska University Hospital compared with a reference population.
- To explore differences in long-term HRQoL in patients treated before and after modifications in the treatment technique introduced in 2001.

4 MATERIALS AND METHODS

Table 5 presents a summary of the study design, patients and methods of the four studies included in this thesis.

Table 5. Overview of study design and methods.

Study	**1**	**2**	**3**	**4**
Design	Cross-sectional cohort HRQoL study	Retrospective RWD	Retrospective RWD	Cross-sectional Observational HRQoL study
Primary endpoint	Long-term HRQoL in men with PC treated with curative intent	The prognostic value of comorbidity, age, PSA, T-stage and WHO-grade on OS	PC specific death	HRQoL 5Y after combined HDRBT and EBRT treatment from 2002-2008
Secondary endpoints	Differences in HRQoL between men treated with open retropubic prostatectomy and HDRBT+EBRT	The prognostic value of comorbidity, age, PSA, T-stage and WHO-grade on DFS	Any death, death from other cause, Any Failure, PC specific failure or death from other cause as first failure. To evaluate the prognostic value of CPG classification	Differences in HRQoL compared to a reference population and to men treated before 2001
Patient cohort	Men treated with curatively intended RP or HDRBT+EBRT in Gothenburg from 1988-1997. n=492	Men treated with HDRBT+ EBRT in Stockholm from 1998-2004. n=611	Men treated with HDRBT+ EBRT and followed up in Stockholm from 1998-2010. n=2,387	A subset of men from study 3 treated from 2002-2008 and still alive at 5 Y. n =1,495
HRQoL questionnaires	EORTC QLQ C30 EORTC QLQ PR25	NA	NA	EORTC QLQ C30 EORTC QLQ PR25
Statistical analysis	EORTC scoring-manual, Descriptive statistics, Fischer´s exact test, Linear regression, Wald's test	Descriptive statistics, Kaplan-Meier estimates, Log rank test, Cox proportional hazard regression model, Stepwise regression model, Kruskal Wallis test, Wald´s test, Chi-square test	Descriptive statistics Chi-square test, Cumulative incidence functions, Competing risk regression, Wald's test, Likelihood ratio test	EORTC scoring manual, Descriptive statistics, Chi-square test

RWD= real world data

4.1 PATIENTCOHORT

4.1.1 Study 1

The study cohort comprised all men with PC treated with open RP or HDRBT combined with EBRT in Gothenburg from 1st January 1988 until 31st December 1997 (n=495). Men still alive in October 2000 were asked to participate in the study (n=421).

Men diagnosed with localized PC, with a life expectancy of at least 10 Y and without any sign of metastases, were eligible for treatment. Clinical staging was performed according to the Union for International Cancer Control (UICC) TNM-classification system from 1992(176). To establish N- and M-stage, surgical lymph-node dissection and a bone-scan were mandatory in high-risk patients. Risk groups were defined as follows; Low-risk PSA ≤10, T1, WHO-grade 1 (corresponding to Gleason score ≤5); High-risk PSA ≥20 and/or ≥T3 and/or WHO-grade 3 (corresponding to Gleason score ≥4+3). The intermediate risk group comprised all men not defined as either low or high-risk. Biochemical failure was defined as PSA >0.2 ng/L and as PSA ≥2 ng/L above the nadir in RP and HDRBT/EBRT patients, respectively (177).

4.1.1.1 Treatment

In this cohort RP was conducted with an open robotic technique. Lymph-node dissection was performed in a majority of cases and a nerve sparing technique was used whenever possible. Two urological departments were involved in the study.

The radiotherapy was delivered during a 7-week period. The EBRT dose was 50 Gy in 2-Gy fractions delivered with high energy photons to the prostate and vesicles in a four-field box. The HDRBT was delivered in 2 fractions of 10 Gy to the prostate gland and the base of the vesicles using a similar technique as described below.

4.1.2 Studies 2-4

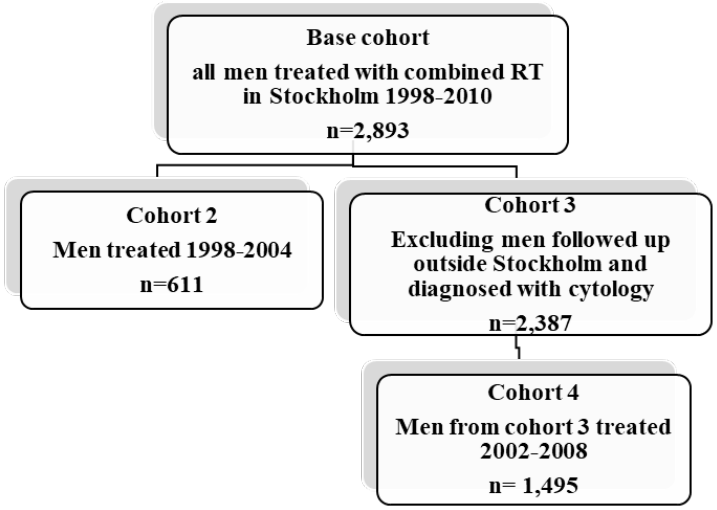


Figure 2, Overview patient cohort 2-4

A cohort of consecutive patients with PC treated with combined radiotherapy from 1998-2010 in the region of Stockholm formed the base for the patient cohorts in Studies 2-4, (Figure 2). The basic eligibility criteria for combined RT were the same for all patients (Table 6). However, some aspects of the diagnostic work changed over time, which affected the inclusion and exclusion criteria in each study cohort. Initially the basic diagnostic work included PSA, DRE and ultrasound guided cytology grading using the WHO classification (21). From the year 2000 men were diagnosed with core-biopsies and histopathological grading according to Gleason (22). The T-stage was classified according to the UICC TNM-classification 5th and 7th edition. Initially, all patients with PSA >10 ng/L underwent a surgical lymph-node dissection and bone-scan, but from July 2000 only men with high-risk PC, Gleason ≥4+3 and/or PSA >20 ng/L and from July 2007 those with T3-status were considered for these procedures. Biochemical failure was defined as PSA nadir + 2 ng/ml in accordance with to the Phoenix definition (177):

Table 6 Eligibility criteria patient cohort studies 2-4

Criteria	
Life-expectancy ≥10 years	
Adenocarcinoma of the prostate	Diagnosis with cytology or histology
T-stage ≤T3a	
N0	Surgical staging until Oct 2010
M0	Bone-scan

4.1.2.1 Hormonal treatment

A majority of patient (95%) received neoadjuvant and concomitant ADT for 6 months, including both an antiandrogen and GNRH-antagonist. Men with high-risk PC treated after November 2008, received additional adjuvant ADT for a total of nine months.

4.1.2.2 Radiotherapy

HDRBT combined with EBRT was introduced in 1998 at The Karolinska University Hospital and is still a standard treatment option for curative treatment of PC. The HDRBT dose was 20 Gy delivered in two 10 Gy fractions, two weeks apart. The dose plan was established using transrectal ultrasound and the PTV comprised the prostate gland and the base of the seminal vesicles with a 3 mm margin. The V100% was set to a minimum 90% of the prescribed dose to the clinical target volume. The dose constraints to the urethra and rectal wall were Dmax <11 Gy and Dmax <6 Gy, respectively. The HDRBT technique was further developed in 2001 when new equipment was installed (high visibility ultrasound and a modern dose planning system). The new system allowed the use of a higher number of needles to avoid hot spots in the prostate gland as well as contributing to improved visualization of the urethra to ensure accuracy of the delivered dose.

The EBRT was delivered in a 3D-conformal fashion using a CT-based dose planning system and a four-field box technique. The planning target volume (PTV) included the prostate gland and seminal vesicles with a margin of 2 cm, except for the dorsal where it was 1.5 cm. The

margin was reduced over time. The prescribed dose was 2 Gy in 25 fractions, delivered over five weeks, with the 95% iso-dose covering the PTV. The only restriction to organs at risk was to avoid doses of 50 Gy or more to the whole rectal circumference.

4.1.2.3 Charlson comorbidity index CCI

The CCI is a weighted comorbidity index, that assigns a score to each of 19 medical conditions (178). The assigned score is measured against the relative risk of death for each particular condition. The score is well validated and has been frequently used in studies on PC. In Studies 2-4 we applied the CCI to assess comorbidity retrospectively.

4.1.2.4 Study 2

Study 2 comprised 611 patients treated from 1998 to 2004, that fulfilled the inclusion criteria listed in Table 6. The patients were divided into three risk groups using modified D´Amico criteria. Definition of cause of death is described in Table 7.

Table 7, Definition of cause of death and disease-free survival in study 2.

Study 2	**Definition**
Death without PC	Biologically no evidience of disease at time of death, (death of other cause)
Death with PC	Death after relaps of PC with or without hormonal treatment, and no sign of progression under such treatment
Death of PC	Men with progression under hormonal treatment or metastatic disease at time of death
Overall survival	Time from HDRBT treatment 1, without death from any cause
Disease-free survival	Time from HDRBT treatment 1, without biochemicalfailure, distant failure or death of other cause

4.1.2.5 Study 3

The cohort in Study 3 included patients treated from May 1998 to December 2010, n=2,893. After applying exclusion criteria, 2,387 men remained for analysis. The following exclusion criteria were applied: men with their follow up outside Region Stockholm, men diagnosed with cytology, men treated with mono-brachytherapy and men with distant metastases. In this cohort the CPG risk classification was used to divide patients into five risk groups as described in Table 6 in the Introduction 2.3 (33). Cause of death were classified as described in, Table 7 and outcome variables are defined in Table 8 below.

4.1.2.6 Study 4

A sub-group of men (n=1,639) from the cohort in Study 3, treated from January 2002 to December 2008 and still alive and recurrence free at 5 Y after treatment constituted study Cohort A (n= 1,495). Men treated with the initial brachytherapy technique at Karolinska University Hospital from June 1998 until August 2000 and taking part in a 5 Y HRQoL study constituted Cohort B (n=158). Original data from this study were used to compare HRQoL in men treated before and after 2001 (171).

4.2 DATA COLLECTION

In all four studies clinical data were collected from patients' medical records including medical history, PSA, T-stage and histological grading, hormonal treatment, start and end of radiotherapy, biochemical recurrence and death. A specially trained nurse performed the comorbidity assessment according to the Charlson comorbidity Index (CCI) manual using both self-administered questionnaires distributed to the patient at the first visit and the physician's notes in the medical records from the same visit in Studies 2-4 (178). In Studies 1 and 4 self-administered questionnaires were used to collect HRQoL data. Data in Studies 2-4 were stored using the MEDLOG system (Information Analysis System, NV 89402, USA). The data collection procedure for Studies 1-4 is described in detail below:

Study 1.

In October 2000 men who were still alive were invited by mail to participate in a HRQoL study by answering a questionnaire and returning it in a prepaid envelope. One reminder was sent. The Regional Cancer Registry handled the questionnaires and managed the data base.

Study 2.

Clinical data were continuously collected from 2005 to the end of the study period in December 2014.

Study 3.

Data were continuously collected from medical records from 2005 until October 2019.

Study 4.

HRQoL questionnaires were distributed to the patients as part of the routine follow up, which they received together with the notification of the follow-up examination. Responses were used in the clinical evaluation and then collected and continuously entered into the study database. In the comparison of HRQoL between men treated before and after 2001, data from the early cohort were retrieved from the original article by Wahlgren et al. (171).

4.2.1 Questionnaires

4.2.1.1 EORTC QLQ C30

The European Organization of Research and Treatment of Cancer (EORTC) developed the Quality of Life Questionnaire (EORTC-QLQ C30) aimed at measuring HRQoL in cancer patients in clinical trials irrespective of type of cancer. The questionnaire was designed to be multi-dimensional, suitable for self-administration and relevant for use in different cultural settings (149). During recent decades the questionnaire has been evaluated in terms of validity, reliability and responsiveness and has to date been used in numerous oncological clinical trials. The current version consists of 30 items. Each item is scored from 1-4, defined as; 1 "Not at all", 2 "A little", 3 "Quite a bit" and 4 "Very much", with the exception of the

two Global health status scales, which range from 1 “Very poor” to 7 “Excellent”. The items are grouped into 5 multi-item functional scales (physical [PF], role [RF], emotional [EF], social [SF] and cognitive [CF]), three symptom scales (fatigue [FA], pain [PA], nausea and vomiting [NV]), a global health status (GH)/QoL scale and six single items (dyspnoea [DY], loss of appetite [AP], insomnia [SL], constipation [CO], diarrhoea [DI] and financial impact of the disease [FI]), covering the different aspects of the HRQoL concept. A high score reflects better function in the functioning scales and the GH/QoL scales, but more problems or symptoms in the symptom scales and single items.

4.2.1.2 EORTC-QLQ PR25

To further evaluate HRQoL the EORTC QLQ C30 core-questionnaire was complemented by a diagnose specific questionnaire directly addressing the specific functions and symptoms related to a particular disease and associated treatment side effects. The PC specific EORTC QLQ PR25 questionnaire consists of 25 items pertaining to urinary and bowel symptoms, sexual activity and function as well as hormonal treatment-related symptoms (153). The items are scored in the same manner as in the EORTC QLQ C30 and then clustered into three symptom scales: urinary (PRURI), bowel (PRBOW) and hormone related (PRHT); two functioning scales: sexual activity (PRSAC) and sexual functioning (PRSFU); and one single item: the bother of an incontinence aid (PRAID). The PRSFU scale is conditional on “being sexually active in the past month” and PRAID is conditional on using such aids. As in the EORTC QLQ C30, a high score indicates a high level of functioning in the functional scales and a high level of problems in the symptom scale.

4.3 ETHICAL APPROVAL AND CONSIDERATIONS

Ethical approvals were obtained from the Ethical Review Board, at the Medical faculty of University of Gothenburg (Study 1 no: R081-99) and the Regional Ethical Review Board in Stockholm (Studies 2-4, no:2006/620-31 and Study 4, no: 04-10253).

4.4 ANALYSIS AND STATISTICAL METHOD

4.4.1 Statistical method

An overview of the statistical methods used in this thesis is presented in Table 1. Descriptive statistics (means, Standard deviation [SD], confidence interval [CI] counts and percentages) were used to characterize the study cohorts. Differences between study groups and categorical variables were tested using Fisher’s exact test (Study 1) or the Chi-square test (Studies 2-4). Differences between study groups and continuous variables were tested using the Kruskal-Wallis test (Study 2) and the F-test from linear regression models (Studies 1-3). The level of statistical significance was set to ≤ 0.05, except in Study 1 where it was set to ≤ 0.01 due to multiple testing. The statistical analyses were conducted using the Stata software versions 11 and 16 (Stata Corp, College Station, TX, USA).

4.4.1.1 Survival analysis

In Study 2, the Kaplan-Meier method was applied to graphically illustrate the cumulative survival probability over time and the log-rank test was used to test differences in survival time between groups. Proportional hazard regression was performed to model the effect of clinical factors on time to death and failure. Factors that violated the proportional hazards assumption were included in the models as strata. The results were presented as HR with 95% CI and Wald's p-values. An additional stepwise regression model was used in an attempt to establish the strongest factor related to time to failure.

Table 8. Definition of outcome variables, Study3.

Study 3	**Definition of outcome variables**
Death	
Prostate cancer specific death, PCSD	Death of PC
Death of other cause, DOC	Death of other cause, including men with PSA failure and stable disease with or without ADT.
Any cause of death, AD	Death from PCSD or DOC
Failure	
PCSF	Biochemical or distant failure of PC as first failure
DOCF	Death from other cause as first failure
AF	Failure from PCSF or DOCF

In the survival analysis in Study 3 a competing risk approach was applied. Survival and failure times were calculated from first HDRBT to the date of event or last visit as defined in Table 8. Graphs of cumulative incidence functions were used to demonstrate cause specific risks over time. The prognostic value of clinical factors was explored using a competing risk regression model. The results were presented as sub-Hazard ratios (sHR) and a 95% CI. Within-group differences were established by means of Wald's test and the likelihood ratio test was used to test overall group effects.

4.4.2 HRQoL analysis

The HRQoL data in studies 1 and 4 were analysed according to the EORTC scoring-manual (REF), transforming the raw score into a linear scale ranging from 0 to 100 (179). For each summed scale, mean score and CI (Study 1, CI 99% and Study 4, CI 95%) were calculated for both the EORTC QLQ C30 and the QLQ PR 25. Using indirect standardization and Swedish norm data, expected mean scores were calculated for all EORTC QLQ C30 subscales in both Study 1 and Study 4. A linear regression model was used to compare differences in HRQoL between the two treatment modalities in Study 1. In the multivariate analysis in Study 1 the covariates of age, recurrent PC at time of completing the questionnaire and hormonal treatment were used. Results from the model were presented as mean differences together with a 99% CI and Wald's p-value. The significance level was set to 1%.

Missing data were not imputed. Our decision not to use the imputation methods described in the scoring manual was based on the assumption that, when using a self-assessment instrument, all answers given or not given by the patient, are considered equally relevant to that individual and should be acknowledged.

In a study by Osoba (180), a change in the EORTC QLQ C30 mean score of ten points or more was suggested to be clinically relevant. When interpreting our HRQoL results in Study 1, we applied the proposed score scale change: 5-10 denoted small, 10-20 moderate and > 20 large.

5 RESULTS

In this section a summary of the main results of Studies 1-4 is presented. Detailed information, tables and figures are available in the reprinted original articles.

5.1 STUDY 1

In this regional cross-sectional study, long-term general and disease specific HRQoL in men treated from 1988-1997 with curatively intended RP or HDRBT combined with EBRT was investigated. The response rate was 82% and the mean follow up 7 Y (range 4-16). Patient characteristics and number at risk are summarized in Table 9.

Table 9, Patient characteristics and number of respondents, Study1.

Variable	RP	HDRBT	Total sample
Initial cohort n	379	113	492
Dead before study n (%)	48 (13%)	23 (20%)	71 (14%)
Respondents n (%)	261 (79%)	86 (96%)	347 (82%)
Age Y, median (range)	70 (51 to 83)	70 (56 to 83)	
ADT %	51%	57%	52%
Relaps at time of questionaire %*	44%	9%	35%
PSA median (range)	9.2 (0.9 to 410)	9.6 (0,5 to 36)	9.4 (0,5 to 410)
T-stage % *			
T1	42%	29%	39%
T2	51%	57%	52%
T3	6%	13%	8%
T4	0%	1%	0%
missing	1%	0%	1%
WHO grade % *			
WHO1	41%	38%	41%
WHO2	43%	41%	43%
WHO3	12%	5%	10%
missing	3%	16%	6%
*% rounded to integers			

5.1.1 Main results of the EORTC QLQ C30

A comparison of the patient cohort with an age and gender matched Swedish reference population. We found that patients in our cohort reported similar HRQoL as the reference population in the functioning, as well as, in the symptom scale. However, a statistically significant difference in HRQoL mean score was found in PF, RF and pain in favour of the study cohort, while with regard to sleep disturbances, the difference was in favour of the reference population. Figures 3 and 4.

A comparison of general HRQoL between treatment modality groups. Taking account of age, PSA recurrence and neo-adjuvant hormonal treatment, only a statistically significant

difference concerning diarrhoea was found in favour of the RP group, p-values= 0.01 and 0.002, in the uni- and multivariate analysis respectively. A complementary analysis taking into account the risk group at diagnosis and time to questionnaire yielded the same result. Small clinically significant differences were found in the multivariate model for global health, physical function, fatigue, dyspnoea, insomnia and diarrhoea in favour of the RP group (range difference 5-7).

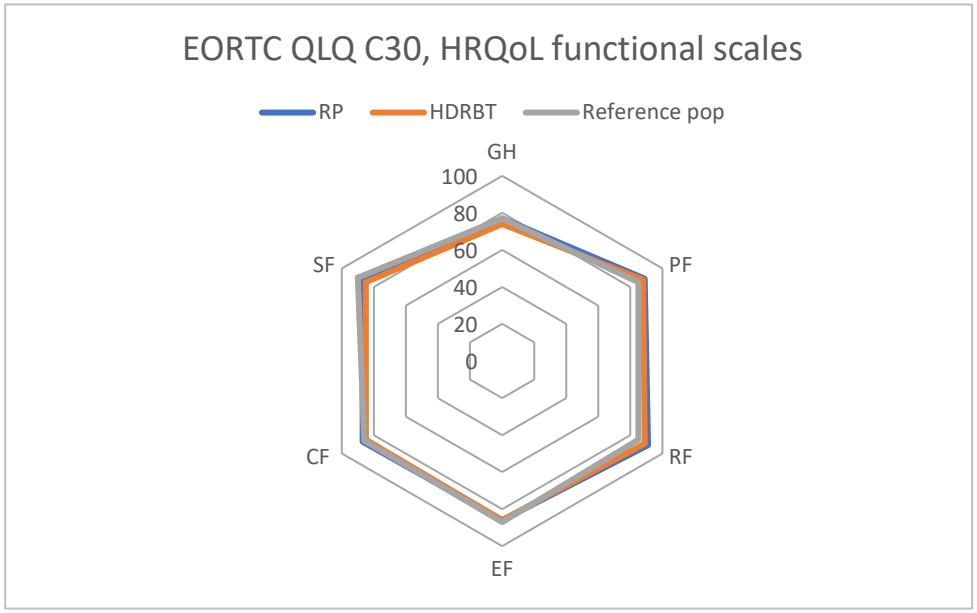


Figure 3. EORTC QLQ C30 HRQoL functional scales, RP;radical prostatectomi, HDRBT combined RT and the reference population. GH global health status; PF physical; RF Role; EF emotional; CF cognitive; SF social. high values indicate high levels of functioning and global heath

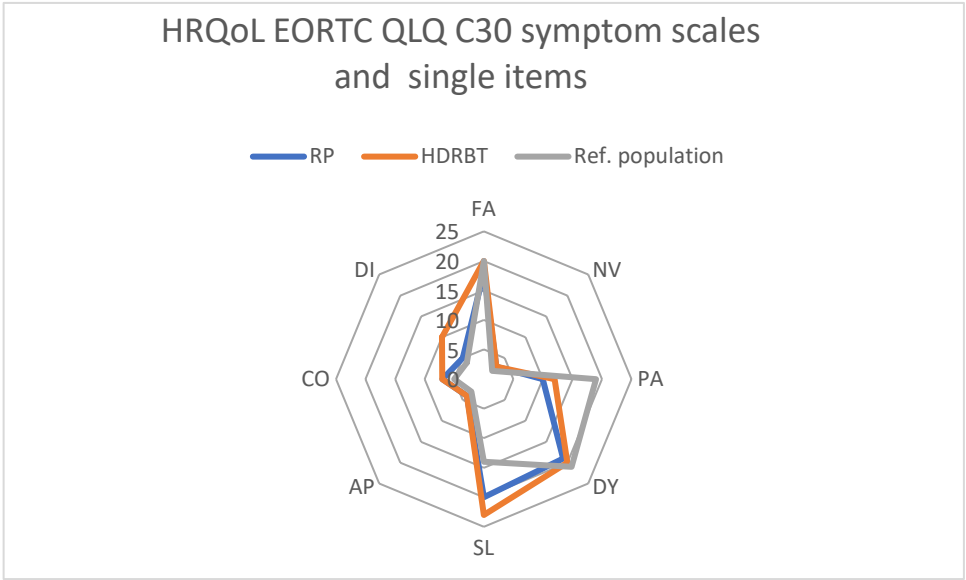


Figure 4. EORTC QLQ C30 symptom scales and single items, RP radical prostatectomi; HDRBT combined RT and the reference population. FA fatigue; NV nausea, vomiting; PA Pain; DY dyspnoea; SL sleep disturbances; AP loss of appetite; CO constipation, DI diarrhoe; high values indicate high levels of problems.

5.1.2 Main results of the EORTC QLQ PR25

A comparison of disease specific HRQoL between treatment modality groups. In the uni- and multivariate analyses of disease specific function and symptom scales based on the same variables as above, a statistically significant difference was found in both the urinary (p-values= 0.05 and 0.008) and the bowel scale (p-values= 0.003 and 0.001) in favour of the RP group. These differences also translated into a small clinically significant difference according to the scale proposed by Osoba (180). There were no statistically significant differences in sexual function or activity. Sexual activity was reported by 37% of men in both groups. Figure 5.

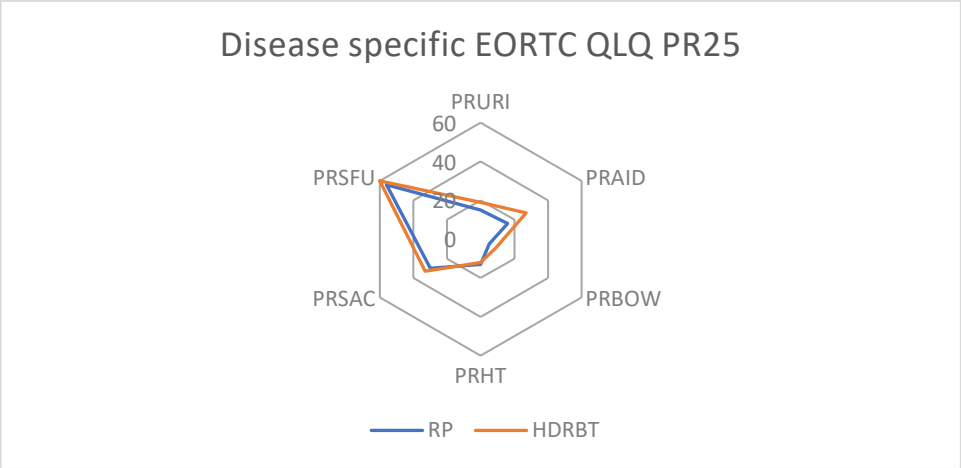


Figure 5. EORTC QLQ PR25 HRQoL, RP radical prostatectomi; and HDRBTcombined RT. PRURI urinary symptom;, PRAID use of incontinence aid; PRBOW bowel symptoms; PRHT hormone-related symptoms; PRSAC sexual activity; PRSFU sexual function. In functional scales high values indicate high levels of functioning and in symptom scales high values indicate high level problems

5.2 STUDY 2

In this retrospective single centre study, the importance of comorbidity as a prognostic factor for OS and DFS in relation to other significant clinical features was investigated. In total, 611 men were included, with a mean follow-up of 9.6 Y (range 0.3-15.3 Y). Comorbidity was present in approximately half of the patients, hypertension being the most common, followed by ischaemic heart disease and diabetes mellitus. The number of men with a large burden of comorbidity was small as a consequence of the inclusion criteria, i.e., men with an estimated life-expectancy of a minimum of 10 Y.

Table 10.Cause of death by Charlson comorbidity index.

Cause of death	**CCI 0**	**CCI 1-2**	**CCI ≥3**	**Total**
Number n	299	272	40	
Death from PC n (%)	18 (6%)	19 (7%)	0	37
Death with PC n (%)	10 (3.3%)	6 (2.2%)	1 (2.5%)	16
Death of other causes n (%)	39 (13%)	64 (23,5%)	15 (35%)	117
Total number of death n (%)	66 (22.4%)	89 (32.3%)	16 (37.5%)	171(100%)

Death classified by CCI is presented (no comorbidity or ≥1 comorbidity) in Table 10. The total number of deaths during follow-up was 171, 28% of the total cohort. The proportion of deaths increased in line with the number of comorbidities, p=0.009. In the group of men with no comorbidities, 13% died from "death of other cause" compared to 35% in the group with ≥3 comorbidities. No one in the latter group died due to "death from PC".

5.2.1 Overall survival

Figure 6 show OS according to comorbidity status. Using the Cox proportional hazard model, we demonstrated a relationship between the covariates of Age, Comorbidity, T-stage and OS

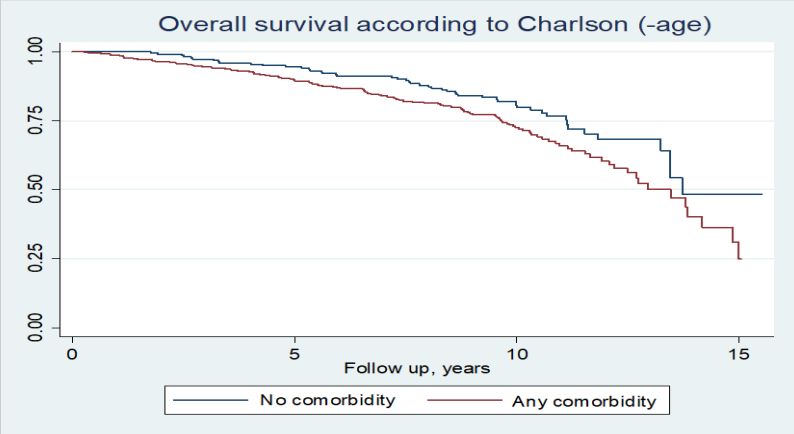


Figure 6. Overall survival according to Charlson index, No vs Any comorbidity, Study 2.

with HRs of 1.73, 1.46 and 1.24, respectively, in the multivariate analyses (p-values= 0.002, 0.0004 and 0.05). The value of each individual prognostic factor was further investigated in a stepwise regression model, where age and comorbidity were found to be the only predictors of OS with HRs of 1.8 and 1.5 (p-values= 0.002 and 0.004), respectively.

5.2.2 Disease free survival

Among living patients at the time of analysis (n=440), 89% were relapse free. The relationship between clinical parameters PSA at diagnosis, WHO grade, T-stage, comorbidity, age and DFS was evaluated using the above-mentioned model. With the exception of age, all parameters predicted DFS in both the uni- and the multivariate Cox model, as well as, in the stepwise regression model.

5.3 STUDY 3

In this retrospective real-world data study, we analysed the oncological 10 Y outcome of 2,387 men with localized PC consecutively treated with combined radiotherapy in Region Stockholm from 1998-2010 using a competing risk model. Patients were followed up for a median of 10.2 Y and 1,662 were still alive in October 2019 when the database closed. Patient characteristics comparing men treated before or after December 2005 were similar for the following clinical parameters; Age, PSA at diagnosis, T-stage and CPG risk group. However, men in the early period (1998-2005) had a greater proportion of Gleason grade 6

and a smaller proportion of Gleason grades 3+4 and 4+3 than the later cohort, reflecting changes in the Gleason grading system introduced in 2005.

5.3.1 Prostate cancer specific death and Any death

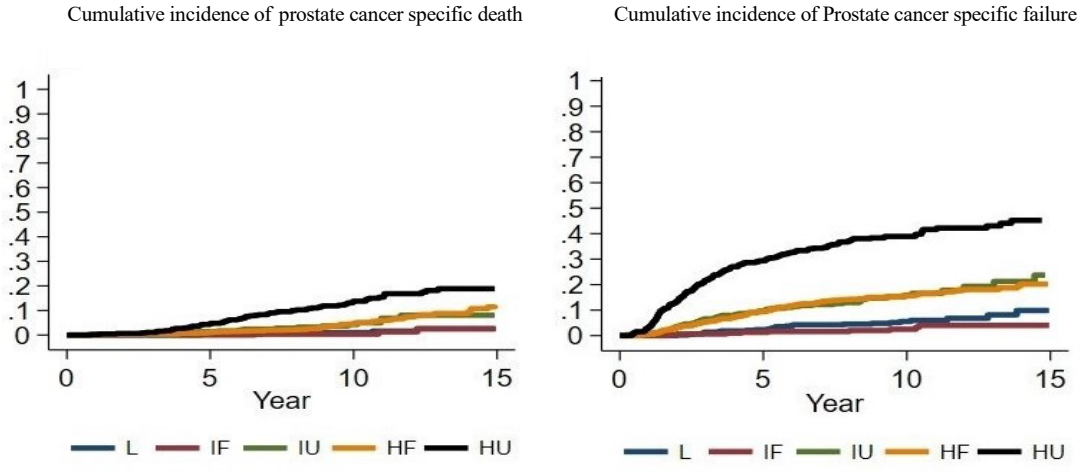
The number of deaths and failures by risk group is outlined in Table 11. The primary endpoint in this study, PCSD, showed a low risk of death due to PC at 5 and 10 Y, 1.5% (CI 95% [0.003, 0.01]) and 5% (CI 95% [0.005, 0.04]), respectively. The cumulative incidence of AD was 23%, translating into an OS of 77%. We found no difference in PCSD or AD when comparing the early and late treatment groups (p-values= 0.13 and 0.23, respectively).

Table 11. Survival and failure status according to risk group, Study 3.

Survival status	**Risk-group**					
	Low	**IF**	**UI**	**HF**	**UH**	**All**
n	319	415	310	853	454	2,387
Alive, n	241	337	228	593	263	1,662
PCSD/DOC, n	3/75	8/106	15/67	51/209	68/123	145/580
Failure status						
Failure-free	235	329	203	535	189	1,491
PCSF/DOCF	9/75	26/96	50/57	134/184	180/85	399/497

The cumulative incidence of PCSD according to risk group is shown in Figure 7. In the competing risk regression model, a statistically significant association between PCSD, AD and the CPG risk group was demonstrated (i.e., increased risk of death the higher the risk group). The association was confirmed in the adjusted model, stratifying for age, comorbidity, treatment period and hormonal treatment (p-values <0.0001 and <0.0001). Furthermore, when analysed with reference to time after RT, the CPG classification was found to have a prognostic value for PCSD and AD of up to 10 Y.

Figure 7. Cumulative incidence of prostate cancer specific death and failure, by risk group, Study 3.



5.3.2 Prostate cancer specific failure (PCSF) and Any failure (AF)

The cumulative incidence of PCSF and any failure (AF) at 10 Y was 16.5% (CI 95% [0.15-0.18]) and 32.3% (CI 95% [0.01–0.30]) respectively. Progression-free survival (PFS), the complement of AF was 68%. The cumulative incidence of PCSF according to risk group at 10 Y is shown in Figure 7. Furthermore, the competing risk regression analysis of PCSF and AF revealed an association between higher CPG risk group and risk of failure. Further analysis based on the length of time in the study confirmed the prognostic value of both parameters for up to 10 Y.

5.3.3 Local recurrence

In the group of 399 men with PCSF, 49% were investigated for local recurrence, which was found in 15% of them, translating into a 1.2% estimated risk of local failure in the whole cohort.

5.4 STUDY 4

In this cross-sectional study, general and disease specific HRQoL at 5 Y in a sub-cohort of men from Study 3 was investigated and compared to age and gender matched Swedish normative data. We also compared HRQoL in men treated before and after improvement of the HDRBT procedure introduced in 2001, to evaluate whether any measurable differences in HRQoL could be demonstrated as a possible effect of the novel technique. The response rate was 70% at a median follow up at 5.2 Y, range 4-5.9 Y.

5.4.1 Main results of the EORTC QLQ C30 analysis

In general, HRQoL was rated high, similar to normative data, Figures 8 and 9. However, a few statistically significant disparities were observed. The study cohort reported higher PF and RF, but lower SF and GH than the normative cohort. Concerning symptoms and single items, a higher level of constipation, diarrhoea and sleep disturbances was found in the patients when compared with the normative cohort, in contrast to lower levels of pain. Only pain and diarrhoea reached the level of a small clinically significant difference of 5-10 points as defined by Osoba (180).

5.4.2 Main results of The EORTC QLQ PR25

In terms of disease specific HRQoL, the men reported low levels of urinary, bowel and hormone related symptoms, but more tangible problems with sexual activity and functioning, Figure 10. However, 5 Y after treatment patients reported relatively more urinary tract discomfort than bowel symptoms, mainly concerning urgency and nocturia.

5.4.3 Results from the comparison of men treated before and after 2001

In summary, changes in the treatment procedure introduced in 2001 revealed no statistically significant difference between the treatment groups, except for the frequency of nocturia,

where men in the later cohort reported a smaller proportion of serious problems (22%) compared to the early cohort (31%), p=0.03.

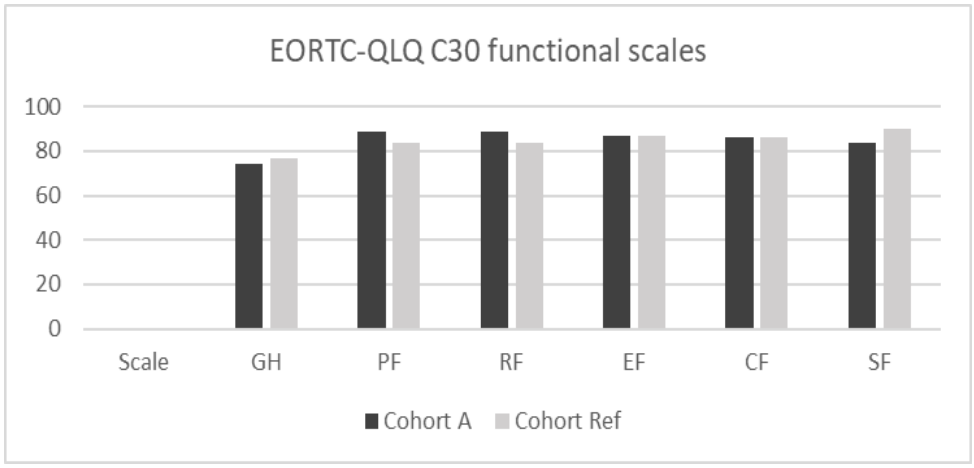


Figure 8. EORTC QLQ C30 functional scales. Cohort A and the reference population. GH global health status; PF physical; RF Role; EF emotional; CF cognitive; SF social. High values indicate high levels of functioning and global heath.

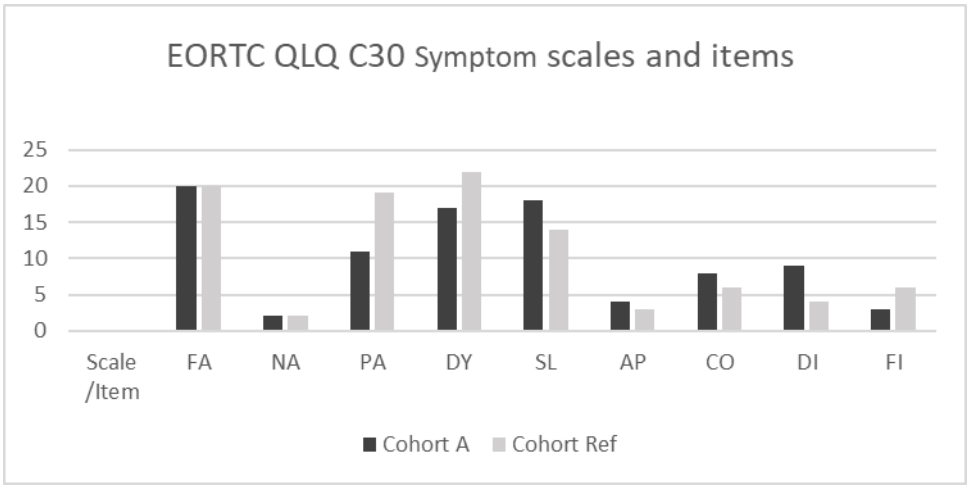


Figure 9 EORTC-QLQ C30 Symptom scale and Items. Cohort A and the reference population. FA fatigue; NV nausea vomiting; PA Pain; DY dyspnoea; SL sleep disturbances; AP loss of appetite; CO constipation; DI diahrroea. High values indicate high levels of problems.

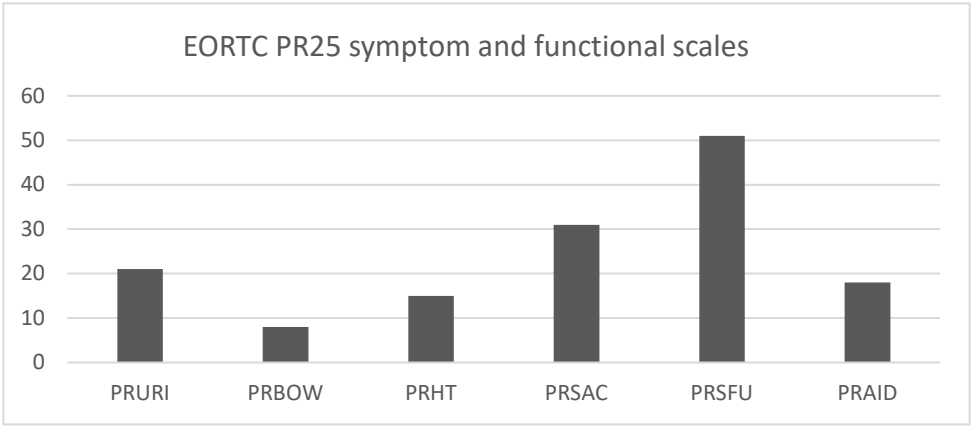


Figure 10. EORTC PR25 symptom and functional scales Cohort A, PRURI urinary symptoms; PRAID use of incontinence aid; PRBOW bowel symptoms; PRHT hormone-related symptoms; PRSAC sexual activity; PRSFU sexual function. High values indicate high levels of funtioning and and high levels of problems.

6 DISCUSSION

After decades of intensive research and development of various treatment methods to cure PC, there is little randomized evidence concerning the most effective treatment option and which individuals that really benefit from treatment. Thus, men are still subjected to choosing treatment with risk of harming side effects and for many a risk of over-treatment. The results of the studies in the present thesis contribute to further knowledge of the long-term effects of treatment of men with PC with HDRBT combined with CFRT. The results are discussed more comprehensively in relation to the literature.

6.1 SURVIVAL AND PROSTATE CANCER SPECIFIC FAILURE

The long-term outcome after PC treatment with HDRBT combined with EBRT shows excellent 10 Y results concerning prostate cancer specific mortality and failure. However, evidence from randomized trials is limited and only one out of two studies comparing HDRBT and EBRT versus EBRT alone has published 10 Y results, demonstrating a clear benefit of the combined arm in terms of biochemical free survival, but no overall survival benefit (96,97). In addition, several studies have reported 10 Y Biochemical free survival (BFS) rates for low, intermediate and high-risk patients in the range of 93-100%, 79-91% and 62-84%, respectively (99-104, 181, 182). Corresponding figures for PCSS in intermediate and high-risk cohorts are 94-98%. The results from our RWD, Study 3, confirm these findings in a large consecutive patient cohort, providing further support for the knowledge of combined HDRBT and EBRT as a valuable treatment option for PC in all risk groups.

Although the results of HDRBT and EBRT in the treatment of PC are excellent, there is a large variation in the risk of biochemical failure between studies, most prominent in the high-risk group. This could be explained by differences in the definition of biochemical failure and risk groups, use or non-use of ADT or technical differences. However, a comparison of the different fractionation schedules applied in these studies also reveals large differences in the dose administered, with BED varying from 206–306 Gy assuming an α/β of 1.5 Gy. Among these studies the one reporting the highest dose (BED 306 Gy) also demonstrated the highest BFS rate for men with high-risk disease, 79-88% (101). In comparison, our cohort treated with a dose corresponding to a BED of 270 Gy reported PCSF rates of 15.5 and 38.8% in the high-risk favourable (HF) and high-risk unfavourable (HU) groups, respectively (Study 3). The dose-response relationship has been further investigated in a prospective study by Martinez et al. (102). The authors observed a 25% difference in BFS at 10 Y between patients treated with HDRBT and EBRT, in favour of men treated with doses of BED over 268 Gy, assuming an α/β of 1.2 Gy. Other authors also found a higher rate of biochemical control (PSA< 0,2ng/L) after 5 Y in men treated with doses BED >260Gy, but with slightly more urinary toxicity (181). In addition, biopsy proven local control two years after treatment was found to be considerably higher in men treated with doses BED >200 Gy compared to BED <150 Gy in a cohort treated with mono LDRBT or combined LDRBT (183). These observations suggest that the total dose-level could be an important factor explaining some of the differences in outcome.

In Study 3, risk classification was performed using the CPG classification, a five-strata tool created to predict PC mortality and validated in two large population-based cohorts (33,184). Use of this tool only requires basic prognostic markers; PSA, Gleason grade and T stage to classify patients, all of which were available in 98% of the men in our cohort. The CPG was found to predict both PCSF and PCSD for up to 10 Y in our study. Notably, in our study the five CPG risk groups were rearranged into three new categories: The low and intermediate favourable groups clustered into a new low-risk group whereas, the intermediate unfavourable and high-risk favourable clustered into a new intermediate-risk group. Furthermore, the high-risk unfavourable group was defined as a new and distinct high-risk group. The long-term outcome of PCSF and PCSD was similar in the IU and HF groups. Furthermore, the HU group had a considerably worse outcome concerning both PCSD and PCSF. In a study by the Genito-Urinary Oncologists of Canada (GUROC) group, in which they redefined their risk score from three to five risk categories, similar long-term results for their IU, HF and HU risk groups concerning BFS were found (185).

Men in the HU group had a significantly higher risk of recurrence than the other risk groups, accounting for 45% of all relapses. The recurrence rate was highest up to 5 Y but then levelled off. Interestingly, the early recurrences manifested immediately after withdrawal of ADT. This, together with the low estimated risk of local recurrence in the whole cohort (1.2%), compared to the 16.5% risk of failure in all risk groups, indicates that these men presumably had disseminated disease at time of diagnosis and treatment. In order to improve the care of men with HU disease, better diagnostic tools and more intense multimodal treatment need to be developed, a process that is ongoing. During the past decade, PSMA-PET-CT and whole-body MRI have been developed and shown to improve the diagnostic work with higher sensitivity and specificity to detect metastatic disease but have so far not been found to increase OS in men with PC (16,186). In terms of the further development of treatment, studies exploring the addition of second-generation hormonal-therapy as adjuvant treatment for men with HU PC are ongoing. As mentioned above, published data from the multi-arm Stampede study show promising results with the addition of Abiraterone in an adjuvant setting in men with N1 or very high-risk disease (38).

6.2 COMORBIDITY

In the decision-making process concerning the treatment of men with newly diagnosed PC, it is essential to consider risk group classification, age, comorbidity and the patient's preference in order to support the individual patient in the choice of different treatment options. This is especially important, as current knowledge suggests that the treatment options available are equally effective. Moreover, men are at risk of both under and overtreatment depending on their clinical stage and age. At the time of Study 2, the role of comorbidity was established as an important prognostic factor of OS after RP (187-189). Nevertheless, there was uncertainty about the impact of comorbidity on outcome after dose-escalated RT. Our study and others have since confirmed comorbidity and age to independently predict OS in men treated with dose-escalated EBRT with or without BT (190,191).

The influence of age and comorbidity on treatment decision-making has been further explored in several studies over the past 20 Y. In summary, these studies revealed that the physician's treatment-decision was mainly based on chronological age and risk group classification (192,193). In a study based on the National Prostate Cancer Registry (NPCR) Sweden, the association between comorbidity and curative treatment was investigated, demonstrating that otherwise healthy men over the age of 70 Y with high-risk disease were at risk of undertreatment with a trend towards a larger proportion of men selected for curative treatment over time (194). In our material, the majority of deaths were due to other causes, although the aim was to treat men with an estimated life expectancy of 10 Y or more. In the group of men with a high burden of comorbidities, 38% died, all from causes other than PC, despite the fact that 25% had high-risk disease. However, the group with a high burden of comorbidity was small, constituting only 6.5% of the study cohort, indicating that comorbidity was considered in the decision-making process.

6.3 LONG-TERM HEALTH RELATED QUALITY OF LIFE

General HRQoL and disease specific HRQoL 5-7 Y after combined HDRBT and EBRT were evaluated in Studies 1 and 4 using the EORCT QLQ-c30 and QLQ-PR25 questionnaires. In Study 1, the HRQoL of men from the same region treated with RP during the same time period was compared. In Studies 1 and 4 normative data were used for comparison of the HRQoL outcome.

6.3.1 Long-term general HRQoL outcomes

In line with our results, the observations of long-term general HRQoL after treatment for PC in terms of the functional subscales seem to be limited and in agreement with aged-matched reference data or longitudinal studies reporting little or no difference between baseline and 5 Y outcomes, irrespective of RT treatment modality (160,166,169-171, 182). Regarding Physical and Role functioning and pain, our patients reported a more favourable score compared to the reference population, which has also been found in several other studies (170-172). This phenomenon has been referred to as a "response shift" and assumed to be an adaptation to major changes in health status, making the patient reconsider important QoL issues (195). In contrast, the patients reported poorer outcomes for social functioning, diarrhoea and sleep disturbances compared to the reference population, which could be due to remaining urinary, bowel and sexual problems after treatment. However, other studies have reported the same or even higher social functioning, despite similar levels of remaining treatment related problems (170,173). The higher level of sleep disturbances is probably related to nocturia, but the influence of disease related anxiety and ageing cannot be ruled. The occurrence of diarrhoea was low, but still more pronounced in the Study 4 patient cohort than in the reference population, where the difference was statistically significant and interpreted as a late radiation effect. This was not seen in Study 1, possibly due to combining the results of men treated with both RP and combined RT, as in the comparison between the treatment group, diarrhoea was demonstrated to be statistically and clinically significantly worse in men treated with RT. Notably, applying the Osoba scale to our results (Study 1),

clinically significant differences between the RP and HDRBT groups in the multivariate analysis for global health status, role functioning, fatigue, dyspnoea and sleep disturbances were found in favour of RP. However, these differences were small and their clinical value unclear. Furthermore, baseline comorbidity, another important factor associated with HRQoL, was not assessed in Study1 (196,197).

6.3.2 Long-term disease specific HRQoL

The analysis of the results from the QLQ-PR25 was hampered by the lack of baseline or reference data in Studies 1 and 4. In particular, the interpretation of data concerning the sexual domain was affected, as according to the literature, sexual HRQoL is known to be more affected at baseline than other function and symptom scales (198).

In our studies, we found various degrees of problems 5 Y after combined RT; low levels of bowel, moderate urinary and more substantial sexual problems. This pattern of HRQoL effects is in line with other long-term follow-up studies addressing HRQoL after combined BT (165,169-173,199). Several randomized non-inferiority studies comparing dose-escalated EBRT with hypofractionated EBRT regimes in similar biologically equivalent doses have reported long-term HRQoL outcomes (160-162). Compared to our results, these studies reported low levels of bowel and urinary problems and also more pronounced sexual problems after 5-6 Y irrespective of treatment schedule. The Ascende-RT trial comparing oncological and HRQoL outcomes in men treated with LDRBT combined with CFRT versus dose-escalated CFRT showed a higher cumulative incidence of Grade 3 urinary toxicity in the BT arm at 5Y, translating into worse HRQoL in the urinary domain. This finding suggests that the higher biological dose to the prostate achieved with the BT combination compared to EBRT alone might be important for the development of the higher rate of long-lasting urinary problems seen after combined BT. Further, a study investigating toxicity after combined HDRBT found an association between the Dmax 10% dose to the urethra and urinary function (199).

The modest levels of urinary problems reported after 5 Y in Studies 1 and 4, mainly consisted of urgency and nocturia. In Study 4, 25% and 22% of men reported ≥ "Quite a bit problems" concerning urgency and nocturia, respectively. In two earlier studies from our institution, early and long-term HRQoL outcomes were investigated in patients treated from 1998 to 2000 (171, 200). In these studies, an increase in urinary problems during the early years after treatment was found, which seemed to be followed by recovery at 5 Y.

Unexpectedly, men in Study 1 treated with HDRBT reported a considerably higher level of problems in the incontinence aid item than men in the RP group or men in Study 4. For the overall urinary scale, a statistically significant difference in mean score was also demonstrated in the multivariate analyses between the groups in Study 1. This observation is not consistent with the findings of earlier studies. Most authors report more urinary problems, especially incontinence, after RP compared to EBRT and BT, but others also report more urinary bother after BT (158, 201,202). However, these studies mainly included men treated

with mono-LDRBT, making a direct comparison with data in the present thesis difficult. The difference in the use of incontinence aids can partly be explained by how the incontinence aid question is formulated, as it is a conditioned question only to be answered by men using such aids. In our material 22% of men in the RP group compared to 11% in the HDRBT group answered the question, indicating that fewer men in the HDRBT group actually had an incontinence problem, but that those who used incontinence aids had worse problems than the men in the RP group.

Another possible explanation of the elevated urinary problems in this cohort could be related to the treatment procedure applied at that time. It involved the assumption of a centrally located urethra and the use of inferior ultrasound and dose-planning techniques compared to present day standards, which might have led to higher doses to the urethra than intended, causing an increase in chronic radiation induced symptoms. In Study 4, we explored this issue, as the procedure described above was previously used at Karolinska University Hospital. An early follow-up at our clinic had shown a higher level of urinary toxicity than expected in men treated before the introduction of the new technique, reported by the treating physician. However, Grade 3 and higher urinary toxicity were shown to be reduced by 50% in an evaluation of men treated after the procedure was changed (203). In the present study, the comparison of 5 Y patient reported general and disease-specific HRQoL between men treated before and after the introduction of the modern HDRBT technique could not confirm these findings. Despite our expectations, no differences in long-term HRQoL were found in men treated with the new technique, with the exception of a statistically significant difference in the frequency of nocturia. Moreover, several studies have revealed poor agreement between patient and physician reported side-effects, which might to some extent explain why there were no differences in HRQoL between the groups (204, 205).

In summary, modest irritative urinary symptoms were still present 5 Y after HDRBT, an indication of remaining late radiation induced toxicity.

The most prominent finding in our studies was the large proportion of men reporting a low level of sexual function and low sexual activity at 5 Y. The interpretation of these data is challenging, as no baseline assessment or reference population data were available for comparison. Longitudinal HRQoL studies report lower baseline levels of sexual function and activity compared to other HRQoL domains, which could explain our findings. The median age of our patients was 70 and 66 Y at time of treatment in Study 1 and Study 4, respectively, which might have influenced the sexual outcome. Fransson et al. (206) investigated long-term sexual function in men with prostate cancer treated with RT and compared them to age-matched controls. They found a correlation between age and erectile function in the control group, but not among treated patients, suggesting that age could influence sexual function at baseline, but probably has less impact on the 5 Y outcome. Interestingly, the shortcomings in the sexual domain did not seem to affect general HRQoL levels, which were high among the treated patients. A plausible explanation could be response shift, i.e. an adaptation to the cancer diagnosis and treatment related side-effects.

In our large HDRBT cohort, 46% of men who responded to the questions related to sexual functioning reported being sexually active. Of these, 40% reported “No” or “Small” problems with erectile dysfunction (ED). In the comparison between RP and HDRBT in Study 1, a similar level of sexual activity was reported and no difference was noted in sexual functioning between the groups. Persisting sexual problems after curative treatment of PC have been reported by a number of studies on different treatment modalities, showing moderate to pronounced deterioration of sexual function at various time points (158-162, 166,169). In general, these studies report more pronounced problems 5 Y after RP compared to moderate and low problems after EBRT and LDRBT monotherapy, respectively (158,159,165). However, few studies have explored long-term HRQoL after combined HDRBT and EBRT. The only study randomizing combined HDRBT and EBRT was that by Hoskin reporting 10 Y HRQoL (169). Concerning the sexual domain, no statistically significant difference was found between the groups, but lower erectile function was reported at follow up compared to baseline in both groups. However, this deterioration was only statistically significant in the HDRBT arm, indicating a worse outcome after HDRBT. The authors speculated that the deterioration could be related to trauma to the tissue during treatment or methodological issues concerning the HRQoL questionnaires. In comparison, the Ascende-RT trial, which investigated two dose-escalated regimes with the addition of ADT for 12 months, showed a deterioration of sexual function in both arms, but more substantial problems at 6 Y in the combined LDRBT group (167). Although, the reason for deterioration of erectile function is suggested to be multifactorial after RT, it is reasonable to assume that there is a correlation between the treatment dose and sexual function, as dose escalated RT and combined HDRBT and EBRT seem to have a higher risk of ED than EBRT and mono-BT. Pre-clinical data and small clinical studies have shown that increased BT doses to the proximal parts of the penile tissue could predict ED, thus it may be important to minimize the dose to both the penile bulb and corporal tissue to reduce the risk of ED (207). Furthermore, the use of hormonal treatment in addition to RT for PC, is another factor that might explain the different levels of sexual activity and functioning in the treated population. Several studies have previously reported of an association between accentuated sexual problems and the use of ADT after RT (166, 208). As, a majority of men in Study 4 were treated with ADT for 6-9 months this could also have affected the results in the sexual domain in our study.

6.4 METHODOLOGICAL CONSIDERATIONS

In recent decades, the interest in retrospective clinical studies based on real world data has developed as a complement to randomized clinical studies (RTC). Large observational studies offer an opportunity to further evaluate benefits and risks of a certain treatment or outcome in a broader patient population compared to a strictly randomized clinical trial cohort. The quality of a retrospective clinical study depends on the completeness and accuracy of the retrieved data and whether or not relevant parameters are available to adequately answer the research questions (209). Retrospective clinical trials raise specific methodological concerns, which are addressed in this section.

6.4.1 Internal validity, bias and confounding factors

Internal validity refers to the choice of study design, how well the included parameters are measured and whether or not they can answer the research question. High internal validity is characterized by the absence of systematic errors. Systematic errors are consistent regardless of sample size but can be controlled for at different levels in the study process. Such errors consist of bias and confounders. In contrast, random errors occur by chance and their influence on the result is reduced in large study cohorts. In our studies, selection bias, information/misclassification bias and confounders are of special interest to consider (210).

Selection bias

Selection bias refers to the problems that occur when there is a difference between the study participants and the population they are intended to represent in relation to the outcome of interest, and can thus affect the conclusions drawn from the results.

In the large cohort of consecutive men in Studies 2-4, all men selected for HDRBT treatment were included and only a small number were lost to follow up, thus minimizing the risk of selection bias. In Study 2, our aim was to investigate the prognostic impact of comorbidity on survival after HDRBT. Our observations revealed no statistically significant difference in comorbidity between the age groups, although one would expect increasing comorbidity with higher age. This suggests that either younger men with a higher burden of comorbidity or older men with a lower burden of comorbidity were selected. As our data show an overall low burden of comorbidity in the whole cohort, it is reasonable to assume that if a selection mechanism was present, it was mainly in the older age group.

Another form of selection bias is non-respondent bias, which often is recognized as a problem in long-term follow-up studies in HRQoL research. It refers to systematic differences that occur between patients who respond or do not respond to the complete questionnaire or to single items only. To send reminders is known to increase the numbers of respondents (211). In Study 1 the response rate was very high in both treatment groups, thus the risk of non-respondent bias was considered low. In Study 4, men completed the questionnaires, as part of their regular follow up and response rates were lower. The reason for not responding was not asked or recorded systematically in the medical chart and could therefore not be investigated or controlled for in the statistical analysis. However, the response rate was judged to be acceptable (70%), although non-respondent bias cannot be ruled out completely.

Information bias

Information bias refers to all forms of systematic distortions of data that occur during the collection, recall bias or handling of data in a study, including handling of missing data. Common information bias is misclassification, recall and reporting bias, all of which are possible limitations of retrospective studies.

To reduce the risk of information bias, specially trained nurses collected information from medical records in Studies 2-4. Furthermore, these studies were conducted at a single centre,

which reduced inter-individual differences in staging, treatment and follow-up, minimizing the risk of misclassification. However, the Gleason grading changed in 2005, leading to an up-grading of about 30% of tumours, but without any change in the distribution of risk groups between men in Studies 3 and 4 treated before and after 2005. Nevertheless, misclassification is likely to be present to some degree in our study cohorts, in terms of clinical T-stage and Gleason grading, as the classification of both of these variables is subject to inter-observer variations.

Recall bias refers to problems connected to the retrieval of correct information about variables in a retrospective setting. To avoid recall bias in the present HRQoL studies, all information collected in the questionnaires referred to the week before completing the instrument.

Confounders

A confounder is an unmeasured third factor that independently interacts with both the supposed exposure/risk factor and the outcome in a study, which may lead to an incorrect conclusion about causal associations. Common examples are age, comorbidity and ethnicity (210). The best way to manage confounders is through randomization of the study sample. In retrospective studies it is possible to control for known potential confounders with different statistical methods, e.g. regression analysis and stratification. As our studies are retrospective, it is possible that residual confounders are still present to some extent even after accurate adjustments, as relevant confounders might not be identified and controlled for. For example, when testing for equality in Study 1, no differences were found between treatment groups concerning clinical risk factors and age. However, data on comorbidity, a well-known confounder, were missing, which could have contributed to the differences in HRQoL in our study.

External validity

External validity refers to the extent to which the conclusions drawn from the study sample are also relevant in relation to other populations, i.e., generalization of results. Great caution is required when generalizing data from retrospective studies because of the risk of selection bias. However, considering the large study cohort including all men referred to the clinic with localized PC with a life expectancy of 10 Y, as well as the steps taken to enhance internal validity, make it reasonable to assume that our results are relevant in populations of men with PC who undergo curative treatment with combined HDRBT.

6.4.2 Competing risk

The Kaplan-Meier model (K-M) measures the cumulative failure probability over time (212). It considers time to the event of interest, and all other events that occur are deemed censored observations that do not affect the survival curve. The model assumes that censored events are independent and that the event of interest will eventually occur if enough time passes. In a situation where an event occur that hinders the event of interest the K-M estimate is biased

and the model should not be used. The event that prevents the outcome of interest occurring acts as a competing risk. In Study 2, our primary outcome of interest was time to death and time to any failure. As there was no competing risk, the standard K-M survival method was considered appropriate.

However, competing risk was a major concern in Study 3, as death from other causes is common among PC patients, and while our primary interest was to investigate PC specific death after combined HDRBT and EBRT treatment. In this setting the K-M method was considered inappropriate and instead the Cumulative incidence function model, that takes competing risk into account was used (213). This model considers all events that prevent or hinder the occurrence of the event of interest as a competing risk and treats them as dependent on each other. In the model the summed probability of failure of any type of event can be divided into the probabilities for each specific type of event. This means that the competing risks influence the cumulative incidence function. The probability of failure for any event is the equivalent of the 1-K-M survival estimate. The cumulative incidence function can be modelled using the sub hazard regression model (214), which makes it possible to study the impact of different variables on the risk of the failure of interest, taking competing risks into account.

6.4.3 HRQoL studies

In our HRQoL studies, the EORTC QLQ-c30 and PC specific questionnaire EORTC QLQ PR 25 were used. The general questionnaire has been used in numerous studies for over 30 years and its psychometric properties have been found satisfactory in different cultural settings. In addition, data from a Swedish reference population is available (215).

The current version of the EORTC QLQ PR25 was developed in the early 2000ies and was not fully validated at the start of our studies. Because there was limited access to a validated PC specific questionnaire at the time, and as the EORTC QLQ-C30 was used in our clinic, it was found reasonable to add the QLQ- PR25 to cover disease specific domains. In the validation process of QLQ PR25, the multi-item scale structure was established, but there were questions about the reliability of the bowel and hormonal scale, probably due to low score variation. However, the authors proposed that the scales still were relevant, but recommended that the results should be reported in more detail (mean score and frequency of intensity per item). Additional studies have validated the questionnaire in different geographical cohorts and in cancer survivors with similar results (216-218). In summary, it was found that these scales need additional development in future studies, which must be considered when interpreting our results in these domains.

6.4.3.1 Scoring procedure

The applied EORTC questionnaires use a mix of multi-item scales and single items. Multi-item scales are considered to improve the reliability and precision of each domain. In the scoring process, categorical data are transformed into linear continuous numerical data

ranging from 0-100, which are then analysed by means of standard statistical methods (219). HRQoL data in this thesis were analysed in accordance with the scoring manual.

Missing data is a matter of concern in HRQoL research and could be classified into two groups; missing questionnaires and missing items. In Study 1 the response rate was high and at an acceptable level in Study 4, hence missing questionnaires were not considered a major problem in our studies. The missing item rate in the general questionnaire was low in both of these studies in the PR25 for Study 4. However, in Study 1, missing items were more pronounced in the bowel domain, which might have affected our results in this domain.

6.4.3.2 Interpretation of the HRQoL results

The interpretation of the HRQoL outcomes and differences in HRQoL within and between groups is complex. There is consensus among researchers that both statistical and clinical significance are important and should be reported in clinical trials, as even small differences in score could prove statistically significant, especially in large cohorts but still be of little clinical relevance. Several authors have proposed that a change of 5-10 points on a 100-grade scale represents a clinically meaningful change in HRQoL (180). Furthermore, studies have revealed that patients might be more sensitive to perceived improvements than to deteriorations in QoL (220,221).

To put the HRQoL results from the EORTC QLQ-c30 into a clinically relevant context we used age and gender matched Swedish reference data from Michelson et al. (215) in both Study 1 and Study 4. In addition, we applied the suggested 5-10-point change in HRQoL score as a clinically meaningful difference in the comparison between men treated with surgery and with radiotherapy in Study 1.

7 CONCLUSIONS

- PC specific failure and death at 10 Y were low after HDRBT combined with EBRT, and in agreement with earlier reports.
- Men with high risk unfavourable PC accounted for 45% of all recurrences, which occurred within 5 Y of treatment in a majority of cases.
- Comorbidity is an important prognostic factor for overall survival in this clinical setting and should be evaluated and taken into account in the curative PC treatment desion-making process.
- The Cambridge prognostic group risk-classification give prognostic information on PC specific death and failure and death of any cause up to 10 Y after treatment and could be a useful tool in clinical practice.
- The long-term effects on general HRQoL appeared to be small and were comparable to a Swedish reference population.
- Moderate discomfort was still present in the urinary domain at 5Y, mainly concerning urgency and nocturia, indicating remaining radiation induced urethritis and cystitis.
- A negative effect on long-term sexual HRQoL was evident. However general bowel problems were at a low level at 5 Y, and severe problems with leakege or rectal bleeding were rare.

In summary, combined HDRBT and EBRT is an effective treatment and provides high long-term PC specific and overall survival with excellent local control in men with localized and locally advanced PC. Long-term general HRQoL was high but with moderate levels of urinary and more substantial sexual problems still present 5 Y after treatment.

8 FUTURE RESEARCH

In this thesis the focus was on evaluating long-term treatment efficacy, the impact of prognostic factors on the clinical results and HRQoL in men with PC treated with combined HDRBT and EBRT. For a long time, surgery and radiotherapy have been the main treatment options for curative treatment of localized and locally advanced PC. In the field of radiotherapy, the technical development over the past 30 Y has facilitated dose-escalation regimes, and a convincing body of evidence today supports the necessity of dose-escalation to cure PC. Another strategy explored in recent decades is the possible benefit of hypofractionation. The rationale relies on radiobiological studies, which have proved that PC has a low α/β and thus, prone to be sensitive to a higher dose per fraction. A large number of randomized studies have compared dose-escalated conventionally fractionated RT with different levels of hypo-fractionation schedules, demonstrating the benefit of shorter treatment time and non-inferiority concerning treatment results and long-term HRQoL. Few studies have compared LDR and HDR brachytherapy combined with EBRT and dose-escalated EBRT. However, several large cohort studies indicate that this combination seems to be more effective concerning BFS than either EBRT or surgery, especially in high-risk cohorts. It would be possible to conduct a randomized study in a Swedish setting to determine which treatment schedule is the most feasible from several perspectives; efficacy, toxicity, HRQoL and health economics. To facilitate such a study the new Individual Patient Overview (IPÖ) trial platform could be used. This trial unit has been developed on the national IT-platform INCA and is connected to the National Prostate Cancer Registry (NPCR) with the aim of providing an infrastructure for clinicians to conduct clinical research with small resources, using NPCR and IPÖ (Individual Patient Overview) data. In the future the platform can be used for both randomized and prospective studies of different kinds related to PC medical treatment and radiotherapy.

Selecting the right patients for curative treatment is still problematic in PC care, as over- and undertreatment continue to be an important health concern. In Study 2 comorbidity was established as a risk factor for OS. In the small group of men with high comorbidity, survival times differed significantly from 0.3 to 13.8 Y. An area of future research could be further evaluation of comorbidity and the impact of specific comorbidities on survival in a PC setting to construct tools that better predict the life expectancy of the individual patient. In such a study, data from the NPCR research data base could be used.

Today, HRQoL questionnaires are used in the clinic on an individual level to follow up on patients' well-being after treatment and to identify rehabilitation needs, in addition to their primary purpose of evaluating the effect of various forms of treatment on HRQoL on group level in clinical trials. Our studies left unanswered questions concerning sexual problems after HDRBT that require further attention as this is an important issue for patients. Possible implications for research could be to clarify the extent of the problem in a longitudinal HRQoL study and design an early intervention based on current knowledge of the

mechanisms involved in radiation induced damage to erectile structure in order to prevent loss of sexual function and activity.

9 ACKNOWLEDGEMENTS

Först ett varmt tack till alla patienter som genom åren passerat mottagningen och på olika sätt delat med sig av sin kunskap och erfarenhet av prostatacancersjukdomen. Utan er hade dessa studier inte kunnat genomföras. Dessutom vill jag tacka Prostatacancer förbundet som bidragit till att finansiera delar av forskningen. Många personer har bidragit till att det här doktorand projektet kunde slutföras efter många år, jag vill speciellt **Tacka**:

Sten Nilsson, min huvudhandledare fram till halvtid, nestor inom urologisk-onkologi i Sverige. Din stora kunskap, forskningserfarenhet och hjärta för patienterna har varit en stor inspirationskälla.

Anders Ullén, min huvudhandledare som med ett stort mått av kunnande, forskningserfarenhet och entusiasm styrt mej mot målet. Stort tack för goda råd, support och uppmuntran då det behövdes som bäst.

Yvonne Brandberg, min bihandledare som med lång forskningserfarenhet alltid bidrar med strategiska råd, struktur och glädje. Din kompetens som pedagog och handledare har varit ovärderlig.

Enrique Castellanos, min bihandledare och kollega. Tack för goda råd och givande samtal om prostatacancer, strålbehandling och i synnerhet HDR-brachyterapi.

Hemming Johansson, statistiker, som med stort tålamod förklarat och bollat statistiken genom åren.

Göran Lundell, Docent och vår databas manager, som lärt mej hur man hanterar data på ett effektivt och säkert sätt.

Carina Holmberg, sjuksköterska, som med minutiös noggrannhet, outtröttligt samlat in journaldata och beräknat Charlson score under många år.

Eva Gripenholm, forskningssekreterare, tack för administrativ support och många uppmuntrande samtal.

Erika Isaksson-Friman, Chef för Onkologsektionen Capio ST Görans sjukhus. Tack för att du i ditt ledarskap har förmåga att skapa en arbetsmiljö som möjliggör kliniskt arbete, forskning och även en vardag utanför arbetet.

Onkolog kollegorna på Capio ST: Göran, Karolinska och Södersjukhuset, för givande kunskapsutbyte, gott samarbete och kamratskap i den kliniska vardagen.

OA, Ost Akademin, mina goda vänner från studietiden, som alltid finns där för mej med omtanke och glada skratt.

Mina vänner, tack för support och omtanke.

Mina systrar Åse och Ann, för all värme, stöd och gemenskap**.**

Sist men inte minst, **min fina familj**, Roland, Martin, Gustav och numera också Sara och mitt barnbarn Ragna. Ni betyder allt. Ser framemot att vi får mer tid tillsammans.

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