Optimizing Postoperative Radiotherapy in Prostate Cancer:

focus on side effects, practical implementation and dose distribution

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“Sunflower, reaching for the sun” (Kapellagården Öland)
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To life, health and people I love

“It does not matter how slowly you
go as long as you do not stop”.

Confusius (551- 479 B.C)

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ABSTRACT

We analyzed side-effects, pre-treatment bladder preparations and dose distribution to the rectum in four different cohorts of patients, treated with postoperative radiotherapy (PRT) in prostate cancer.

Side-effects according to a self-reporting survey revealed rectal bleeding as a main result in a follow up time of 6.7 years in median, since PRT, compared to a control group of men only treated with surgery only. Side-effects from the urinary tract was less pronounced between the groups and no difference was found according to sexual function or global quality of life (**Paper I**). Further analysis of rectal bleeding and its relationship to rectal dose volume parameters was performed and compared to a new treatment technique in order to develop a risk assessment method. We identified dose response relationships between rectal dose distribution and reported rectal bleeding which could be applied to a newer treatment technique in order to better evaluate the dose volume parameters and calculated risk of rectal bleeding (**Paper II**).

A register based nationwide cohort study, of men prostatectomized between 1997 and 2016 was performed with focus on those men that had PRT added to the prior surgery. A comparison was made between the two groups focusing on severe side-effects that had been surgically handled. Interventions in the urinary and rectal tract were analyzed as were development of secondary malignancies and compared between the groups. Dominating were surgical interventions in the urinary tract in the PRT group with 3.66 higher risk per person year compared to the RP only group. The risk of development of bladder cancer was more than twice as big in the PRT group (**Paper III**). In a prospective clinical trial two different bladder preparation protocols were evaluated in men going through PRT. We could not detect any difference between the protocols according to bladder filling compliance or target localization (**Paper IV**).

Conclusion: this work has brought new insights on the development of late side effects in PRT and revealed areas of possible improvements in the practical work at the radio- therapy department.

Keywords: prostate cancer, postoperative radiation therapy, side-effects, practical preparations

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SAMMANFATTNING PÅ SVENSKA

Prostatacancer är den vanligaste cancerformen i Sverige med ca 10 500 nya fall 2019 och operation, radikal prostatektomi, RP, utfördes då på 2100 män. Postoperativ strålbehandling, PRT, ges då det finns tecken till återfall i sjukdomen med stigande prostata specifikt antigen, PSAvärde. Med syfte att förbättra PRT, som ges 35 gånger under en sju veckors period, ville vi studera förekomst av biverkningar, på längre sikt, och det praktiska genomförandet på strålavdelningen. Biverkningar efter PRT utvärderades och jämfördes med män som bara genomgått RP, dels via en självskattningsenkät (**artikel 1**) och dels via analyser från en rikstäckande databas, PCBaSe. Enkätsvaren visade att patienterna i PRT-gruppen i större utsträckning besvärades av blödning från ändtarmen jämfört kontrollgruppen som bara hade genomgått RP, vid en uppföljningstid på 6.7 år i median. Vi såg också i enkätsvaren att tillägg med PRT inte, i någon större utsträckning, påverkade kontinensen eller den sexuella funktionen jämfört med RP gruppen. Som följd av de rapporterade ändtarmsblödningarna gjorde vi en beräkning, via stråldosplaneringsdata, av relationen mellan blödning och hur stor stråldos som hamnat i ändtarmen (**artikel 2**). Vi kunde via denna analys skapa ett riskvärderingsverktyg för uppkomst av ändtarmsblödning att använda vid planering av kommande strålbehandling. PCBaSe är en patient-databas där flera register från hälso-och-sjukvården ingår förutom den registrering som görs av alla med prostatacancer i Sverige, Nationella Prostata Cancer Registret, NPCR. Med syfte att utvärdera hur behandlingen med PRT påverkar behovet av kirurgisk behandling, i ett långtidsperspektiv analyserades data från PCBaSe (**artikel 3**). Vi fann att risken att behöva genomgå operativt ingrepp i urinvägarna var större hos de i PRT gruppen än kontrollgruppen under en maximal uppföljningstid på 15 år. Vad gäller operationer i ändtarmsregionen kunde vi inte påvisa några egentliga skillnader mellan grupperna. Vi värderade också risken att utveckla sekundär cancer i urinblåsan och fann den ökad men inte cancer i ändtarmen, för PRT gruppen. Slutligen värderades dödsorsaker i grupperna; risken att avlida i prostatacancer var avsevärt ökad i PRT gruppen men risk att avlida av annan orsak var jämförbar i de båda grupperna.

Förberedelse för strålbehandling sker med rekommendationer om att urinblåsan ska vara lika fylld vid alla behandlingstillfällena. Vi jämförde två förberedelseregimer för att se om urinblåsan kunde bibehålla samma fyllnad inför behandlingarna under hela behandlingstiden. Vi kunde inte påvisa någon skillnad mellan de två grupperna; stora variationer i blåsfyllnad förelåg för enskilda patienter, mellan patienter och mellan grupperna då volymerna mättes (**artikel 4**).

Sammanfattningsvis har vi kartlagt förekomst av sena biverkningar, både patientrapporterade och via register, och funnit förbättringspotential vid genomförandet av strålbehandlingen för män som behandlas med PRT.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. *A comparison of side-effects and quality of life in patients operated for prostate cancer with and without salvage radiation therapy*
Karin Braide, Jon Kindblom, Ulrika Lindencrona, Marianne Månsson, Jonas Hugosson

Published on line 3 July 2020 in Scandinavian Journal of Urology

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II. *Salvage radiation therapy in prostate cancer: relationship between rectal dose and long-term, self-reported rectal bleeding*
Karin Braide, Jon Kindblom, Ulrika Lindencrona, Jonas Hugosson, Niclas Pettersson

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III. *Risk of severe complications after postoperative radiation therapy of prostate cancer: Results from a nationwide population based retrospective cohort study*

Karin Braide, Jon Kindblom, Pär Stattin, Jonas Hugosson, Marianne Månsson

In manuscript

IV. *The value of a bladder-filling protocol for patients with prostate cancer who receive post-operative radiation: results from a prospective clinical trial*

Karin Braide, Jon Kindblom, Ulrika Lindencrona, Marianne Månsson, Jonas Hugosson

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Prostate cancer

Clinical feasibility and positional stability of an implanted wired transmitter in a novel electromagnetic positioning system for prostate cancer radiotherapy

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ABSTRACT

Purpose: Three aspects of the RayPilot real-time tracking system were investigated: (1) feasibility of the transmitter with respect to implantation and explantation procedures, (2) user and patients' experiences and (3) quantification of the transmitter positional stability in relation to fiducial markers.

Methods and materials: Ten prostate cancer patients scheduled for radiotherapy received transmitter implantation in the prostate, concomitantly with fiducial markers. Transmitter and marker positions were assessed in 3D by orthogonal kV-imaging at daily treatment setup in eight patients.

Results: The transmitter was successfully implanted in all patients. Patients reported mild to moderate discomfort and impact on daily activities due to the implant but overall subjective tolerability was good. One patient had spontaneous explantation of the transmitter after four fractions. One patient had transmitter 3D shifts >9 mm, but also inter-marker shifts >6 mm. The mean inter-marker shift in the remaining patients was <1 mm. In four patients, maximum transmitter 3D shifts were 5–7 mm (mean >2 mm). In three patients, mean transmitter 3D shifts were <2 mm.

Conclusions: Implantation and explantation of the transmitter is generally feasible and safe. Patient tolerability is good overall. However, due to interfractional transmitter positional instability in this cohort, use of the system for real-time tracking should be combined with other daily setup techniques.

From Radiotherapy and Oncology 128 (2018) 336-34

CONTENT

ABBREVIATIONS 1
1 INTRODUCTION 3
The author's reflections 3
The patient's concerns 4
PROSTATE CANCER 5
Historical background 5
PSA 5
Diagnosis and risk groups 5
Diagnostic procedure 6
Risk classification 6
History of surgical treatment 8
Radical prostatectomy 9
Postoperative radiation therapy 10
Hormonal treatment 12
RADIOTHERAPY 13
History of radiotherapy 13
Target, dose planning, and treatment techniques 14
The target in general 14
Treatment planning 14
Treatment delivery 15
Treatment techniques 16
Dose prescription 17
Mechanism of action 18
Decision-making in SRT 19
Imaging to support decisions 21
Target in salvage radiation therapy 22
The target 22
Contouring guidelines 23
Preparing for radiotherapy 24
Preparing the bladder and rectum 24
REGISTRATION AND EVALUATION OF SIDE EFFECTS 26
NPCR and PCBaSe 27
Side effects and dose-volume considerations 29
The urinary tract 30
The gastrointestinal tract 32
Severe side effects, needing intervention 33
Erectile dysfunction 33

Secondary malignancies 34

2 AIM 35

3 METHODS AND METHODOLOGICAL CONSIDERATIONS
Paper I 36
Paper II 39
Paper III 41
Paper IV 44

Statistical methods 47

4 RESULTS
Paper I 50
Paper II 52
Paper III 53
Paper IV 55

5 GENERAL DISCUSSION and summary.....57

6 CONCLUSIONS 67

7 FUTURE PERSPECTIVES 68

ACKNOWLEDGEMENTS 70

REFERENCES 72

ABBREVIATIONS

ADT	androgen deprivation therapy
ART	adjuvant radiotherapy
CI	confidence interval
CT	computerized tomography
CTV	clinical target volume
CBCT	cone beam computerized tomography
DVH	dose volume histogram
EBRT	external beam radiotherapy
EORTC	European Organization for Research and Treatment of Cancer
FROGG	Faculty of Radiation Oncology Genito-Urinary Group
HDF	health declaration form
IGRT	image guided radiotherapy
IMRT	intensity modulated radiotherapy
IPSS	International Prostate Symptom Score
LAPPRO	Laparoscopic Prostatectomy Robot or Open Trial
MRT	magnetic resonance tomography
NPCR	National Prostate Cancer Register
OaR	organs at risk
PAD	pathoanatomical diagnosis
PAP	prostatic acid phosphatase

PC	prostate cancer
PCBaSe	Prostate Cancer data Base Sweden
PET	positron emission tomography
PMH	Princess Margaret Hospital
PROM	patient reported outcome measures
PRT	postoperative radiotherapy
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSMA	prostate-specific antigen membrane antigen
PTV	planning target volume
RALP	robot-assisted laparoscopic radical prostatectomy
RP	radical prostatectomy
RRP	retropubic prostatectomy
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SRT	salvage radiotherapy
TRUS	transrectal ultrasound
VMAT	volumetric modulated arch therapy
QoL.	Quality of life
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
3DCRT	three- dimensional conformal radio therapy

1 INTRODUCTION

The author's reflections

After many years of clinical work in the treatment of men suffering from different stages of prostate cancer (PC), introduction of postoperative radiotherapy (PRT) was a challenge for me. In short, it was necessary to change from dealing with surgery and often visible and touchable structures to performing image-based handling of patients with an "invisible" disease identified solely by an elevated level of prostate-specific antigen (PSA). In the clinical setting, this meant that informing a worried man and his partner about the possibility of a cure and potential side effects of treatment became a difficult task that could not always be based on reliable facts. The practical work in the radiation department involved knowing how to prepare for, perform, and follow the 7-week-long treatment, which would have an impact on both the possibility of cured and the development of side effects.

The questions regarding my uncertainties were many, and I am very grateful for having had the opportunity to conduct research of true clinical value. In short, I have addressed the following issues in my studies:
How can we prepare the organs that are close to and/or part of the treatment target, namely the urinary bladder and the rectum, which normally vary in volume and location?
What side effects can be expected to occur and to what extent in both the short and the long term in our own clinic?
In what manner can the treatment procedure be followed so as to ensure correct delivery?

These are some of the questions I considered in the work leading to this thesis, but there are many aspects that remain to be elucidated.

The patient's concerns

The patient's perspective is of great importance in the context of treatment information and decision-making, and this aspect should be in consensus with the patient himself. To achieve this, it is necessary to capture the doubts and anguish that a man in the relapse situation is experiencing, after initially believing that he has been cured by prostate surgery and later finding himself menaced by potentially life-threatening disease indicated by a rising PSA. In this situation, all possibilities to be cured appear to be the correct choice to make, even though the chance of cure is minimal [1]. The patient's longing for some new curative treatment option is strong, and this should be kept in mind by the doctor when discussing treatment options with the patient. The doctor's role is to provide balanced information on the planned procedure, which also includes considering whether to refrain from treatment. In 2017, Shakespeare et al. [2] reported that patients who were asked about their satisfaction after radical prostatectomy (RP) combined with PRT described a degree of regret that was not negligible. The main reason for the regret was the level of side effects, and it was expressed by about 17% of the patients in that study during a median follow-up period of 78 months, even though freedom from disease was 70% in that group. This observation stresses that it is important that the patient should be given information that is based on both scientific and experiential knowledge in relation to the patient's own situation, including good awareness of the potential side effects and the odds of cure.

PROSTATE CANCER

Historical background

PC was initially identified in the 19th century. George Langstaff (1780–1846) reported the first surgical case of macroscopic PC in 1817, and the first histologically confirmed case of such cancer was subsequently described by John Adams (1806–1877) in 1853 at the London Hospital [3].

PSA

PSA has been used in clinical practice as a biomarker for PC since the 1990s, both for detecting and monitoring the disease. Before PSA, prostatic acid phosphatase (PAP) was used to monitor progression in PC, and such testing had been done since the 1930s [4]. In 1987, Stamey et al. [5] showed that PSA was more sensitive than PAP for detection of PC, and use of the new marker PSA has subsequently been further developed. When monitoring patients after surgical treatment of PC, the desired PSA value is zero, or "immeasurable", and a value above that level is a sign of relapse of the disease.

Diagnosis and risk groups

The incidence of PC is increasing, probably mainly due to the use of PSA testing, but also as the result of an aging population. In Sweden (pop. approx. 10 million), about10,000 men were diagnosed with PC in 2018 according to the National Prostate Cancer Registry (NPCR, www.npcr.se). In more than 50% of those men, the diagnosis was based on an elevated PSA rather than on symptoms from the urinary tract. PSA testing in screening programs is a subject of continuous discussion worldwide, and numerous studies on this topic are in progress. Sweden does not yet have a screening program, although organized PSA testing will be performed in two regions in the country starting in 2020.

Diagnostic procedure

The PSA limits that are set vary with age and are considered to be elevated [6] when the following applies:

Age, years	**PSA ng/ml**
< 70	≥ 3
70–80	≥ 5
> 80	≥ 7

In addition to a PSA test, the diagnostic procedure includes rectal examination to judge the extent of the cancer; T staging, and transrectal ultrasound (TRUS) combined with core biopsies if deemed reasonable. Starting in 2020, the Swedish Prostate Care Program (www.cancercenrtrum.se) recommends that magnetic resonance tomography (MRT) should be performed before the TRUS examination and biopsies to reduce the number of biopsies necessary as much as possible and thereby avoid the risk of overdiagnosis and infection[7].

Risk classification is based on the histological findings from biopsies, together with TNM classification, which comprises the following: T, local tumor extension; N, regional nodal extension; and M, distant metastases. Complementary radiographic investigations are added in cases with high-risk parameters to be able to exclude the presence of nodal extension and metastases.

Risk classification

PC is divided into three risk categories designated low, intermediate, high and advanced disease, when there is supplementary information on finding of metastasis. This classification is based on PSA level, clinical palpation with T staging and pathoanatomical findings after biopsy, with Gleason grading [8].

Risk categories	PSA ng/ml	T stage	Gleason score
Low	< 10	T1–T2a	≥ 6
Intermediate	10–19.9 and/or	T2b and/or	≥ 7
High	> 20 and/or	T2c-T3 and/or	≥ 8

In short, the high-risk group is advocated treatment with curative intent, and the low-risk group should be followed with preparedness to treat curatively and active surveillance. In most cases, the intermediate group can be handled with expectancy or by treatment with curative intent, depending on the patient's preference and additional clinical factors. Men with metastasis are recommended hormonal treatment and in some cases complementary primary treatment, because novel results in the literature have shown improved survival when applying such an approach in these patients [9].

Treatment with curative intent can be achieved through surgery (RP) or through radiotherapy (RT) with or without hormonal treatment. Of the 10,000 men diagnosed with PC in Sweden in 2018, 50% were offered treatment with curative intent, and approximately 2,500 underwent RP. Complementary RT treatment after surgery has been developed to enable cure in the majority of men with PSA relapse of the disease. To irradiate the postoperative fossa, where the prostate was located before RP, has become a standard approach, although it has only been in practical use since 2000 at Sahlgrenska University Hospital. In 2018, about 650 men in Sweden received PRT.

History of surgical treatment

In 1867 in Vienna, Austria, Theodor Billroth apparently performed the first planned surgical removal of PC as a partial perineal excision. In 1904 in Baltimore, Maryland, in the United States, Hugh H. Young (1870–1945) carried out the first perineal RP and published a report on184 patients he had treated in that manner[10]. Early in the 1900s in France, Robert Proust, brother of the famous author Marcel Proust, was described as a promotor of the perineal approach in prostatectomy, which was consequently named "Proustatectomy" at that time. Proust's doctoral thesis entitled "*Prostatectomie perineale totale*" was published in 1900 (see *Figure 1*).

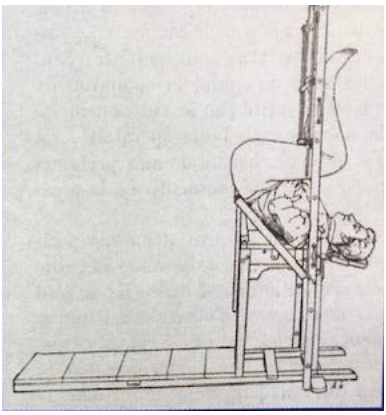


Figure 1 *An illustration of Robert Proust's surgical arrangement with perineal approach in prostatectomy from his thesis entitled "Prostatectomie perineale totale" published in 1900 (available from AbeBooks.com).*

Further development of surgical techniques was later achieved by Terence Millin [11], who published the first series of retropubic prostatectomies in 1945, and the sacroperineal approach was introduced by Thiermann in 1952. In 1991, another new era in prostate surgery began with the first laparoscopic prostatectomy, and further

development introduced the robotic approach first reported 2000. In 2011 Binder presented the laparoscopic DaVinci prostatectomy.

Figure 2 *The Da Vinci surgery system, around 2010*

Radical prostatectomy

The surgery for localized PC is RP, which can be performed either as an open procedure called retropubic prostatectomy (RRP) or as a laparoscopic event that is now often robot assisted (called robot-assisted radical prostatectomy [RALP] see *Figure 2*). Short term side effects in RRP are described as perioperative bleeding, infection and injuries to the intestine and in the long-term perspective incontinence, erectile dysfunction and development of anastomotic strictures. For short-term outcomes, advantages of RALP over RRP, for example, regarding blood loss and length of hospital stay, have been reported by the Swedish LAPPRO (Laparoscopic Prostatectomy Robot or Open Trial) group [12]. Functional outcomes with respect to side effects are primarily related to aspects of continence and erectile function, but can

also include strictures in the bladder neck[13]. The functional results of RP depend mainly on the extent of cancer in the prostate and the surgeon's experience [14,15]. Studies have provided divergent data on long-term functional outcomes. In a metanalysis published in 2012, Ficarra et al. found that, compared to RRP, RALP offered better urinary continence recovery at 12 months after the surgery. In 2018, Nyberg et al. [16] described better patient-reported outcome in erectile function with RALP than with RRP at 24-month follow-up, but no difference between the two approaches regarding continence. Further follow-up and analysis data are to be expected from the LAPPRO group. Oncological results have shown that 25–40% of men treated with RP develop a biochemical (i.e., PSA) relapse or are not cured initially [17,18]. In the relapse situation, complementary treatment is advocated, and the only possible curative treatment available today is PRT, which will be discussed below.

At Sahlgrenska University Hospital, RALP has become the method of choice, and, with very few exceptions, essentially all curative-intent surgeries for PC are performed with this approach. In most cases, the patient is admitted to the hospital the morning of the surgery and is discharged the following day if there are no complications. A catheter is placed in the bladder and removed 7 days later as an outpatient procedure. The PSA value is then monitored for 10 years with attempt to trace an increasing value.

Postoperative radiation therapy

RT as a treatment modality after surgical removal of a diseased organ, with curative intent, is practiced not only in PC but in many other forms of cancer as well, such as head and neck and breast cancer. In those cases, the RT is delivered in direct connection with the surgery that is performed, whereas in PC the RT can be administered at the time of PSA relapse. The era of PSA exploitation changed PRT in PC,

and, in the early 1990s, Ward et al. [19] referred to a detectable biochemical recurrence as a “paradigm”. Before that time, in the 1980s, when a positive margin or positive lymph nodes were found at surgical exploration RT could be delivered as a complement [20]. However, both the side effects and the results of that approach were unfavorable, and hence such treatment was abandoned.

With the advent of PSA sampling, it became possible to detect an early relapse of PC after the primary surgery and plan a supplementary treatment with curative intent de novo. Nonetheless, it was not until 2005 that reports and prospective data on this treatment were presented by the European Organization for Research and Treatment of Cancer (EORTC) study 22911 [21].

In Sweden in 2018, PRT was given to 650 patients according to guidelines and consensus, but this number is considered too low when taking the number of surgeries performed into account [22]. PRT is carried out as either adjuvant RT (ART) or salvage RT (SRT), the latter of which is applied when there is a biochemical relapse. As in other forms of cancer mentioned above, ART is a complementary treatment that is conducted after surgery when the postoperative histology findings are unfavorable, and it is often administered at a lower dose. The question of which treatment offers the best outcome according to oncological results, survival, and side effects has been focused on and studied prospectively for the last 15 years by prestigious expertise with somewhat varying results [23-25]. In a recent metanalysis of three randomized prospective studies comparing ART and SRT (RADICALS, GETUG-AFU 17, and RAVES) [26], it was suggested that these two RT treatment options offer similar outcomes of event-free survival. However, adopting SRT instead of ART can in many cases prevent unnecessary RT with associated side effects. In this treatment setting, to administer RT at the lowest level possible when there is an increase in PSA would result in a favorable outcome with regard to side effects and a 5-year PSA-progression-free probability of > 85%. SRT has already been the recommended strategy in Sweden over the last years.

Hormonal treatment

Hormonal treatment of PC was first used in the 1890s to reduce the symptoms of prostatic hypertrophy. C. B. Huggins performed experimental studies on prostate tissue and demonstrated the association between testosterone and secretion from prostatic cells and the reciprocal effect of estrogens, and, for these findings, Huggins was awarded the Nobel Prize in Physiology or Medicine in 1966. He later also proved that castration relieved pain from skeletal metastases in PC patients [27].

Hormonal therapy is an obvious strategy in PC and was long the only treatment offered to men with incurable or metastatic disease. Up until the 1990s, the hormonal treatment was achieved by surgical castration, that is, removal of the testicles. Today, the dominating hormonal approach is pharmacological in the form of androgen deprivation therapy (ADT), and this can be performed in two different ways: as a blockade of the androgen receptor; or as a pharmacological castration mediated via the pituitary hormones LH and FSH, which results in inhibition of the synthesis of testosterone. The side effects of such castration treatment can be numerous and severe, and, in addition to sexual dysfunction, include osteoporosis, metabolic syndrome, flushing and sweating, and weight gain [28].

RADIOTHERAPY

History of radiotherapy

The history of RT dates back to when Conrad Röntgen discovered x-rays in 1895, and when Henri Becquerel detected natural radiation from the element uranium in 1896. These two men won the Nobel Prize in Physics in 1901 and 1903, respectively. Marie Curie also studied radioactivity and won a Nobel Prize twice: first in physics in1903 together with Henri Becquerel and her husband Pierre Curie for studies on the phenomenon of radiation; and the second time in chemistry in 1911 on her own for discovering the elements radium (1898) and polonium. ("The Discovery of Radium" by Marie Curie is available as an E-book at www.project Gutenberg.de.) Radium has been used extensively in the development of RT, initially mainly as external applicators in skin cancer. Use of radiation energy in medicine was tailored to fit different scenarios [29]. For instance, local treatment of the prostate through a cystoscopic radium applicator was performed in the 1910s, and this probably represents the birth of brachytherapy for PC, a treatment option that is widely applied today[30]. External beam therapy for PC was not initiated until the 1960s, even though this treatment was performed for the first time in 1904. In the 1920s and 1930s, PRT was discussed pragmatically as a complement to unsuccessful surgical procedures for PC, but the outcome in that context was not particularly successful [19].

Target, treatment planning, and treatment techniques

The target in general

Delivery of RT requires careful treatment planning before initiating the treatment to indicate where and how the irradiation should be carried out. A target is outlined based on radiological images obtained by a planning computerized tomography, pCT and MRT. Of those two techniques, MRT is superior in visualizing the appearance of soft tissue, which constitutes the target in PRT. The MRT and CT examinations constitute the basis of the treatment planning and are performed a few weeks before treatment start. The target delineation is also based on the surgery specimen report, which provides information on tumor extension and surgical margins, and target guidelines developed from clinical experience that together result in a clinical target volume (CTV). Hence the CTV represents the volume where the cancer cells are, or are assumed to be, located. Furthermore, a margin is added to the CTV that is intended to guarantee the uncertainties that can occur when the patient is in the treatment position (e.g., internal movement and set-up errors), and this constitutes the planning target volume (PTV).

Treatment planning

Based on the CTV/PTV, a planning of radiation treatment is constructed by using a computerized treatment planning system that can visualize the distribution of the radiation dose. The radiation dose will be delivered to a volume in three dimensions, and it is possible to calculate the dose given to any specific point in the patient. The evaluation of the 3D dose distribution is usually carried out using a dose-volume histogram (DVH), which graphically summarizes the dose distribution in the CTV, PTV, and organs at risk (OaR) volumes (see *Figure 3*). Together with the DVH, treatment recommendations are provided concerning how percentages of the different volumes should be covered by the prescribed dose and to what limits the OaR can be exposed to the radiation. The goal of the treatment plan

optimization is to ensure that the CTV mean dose is 100% of the intended dose delivered to the target, and that the OaR are spared as much as possible.

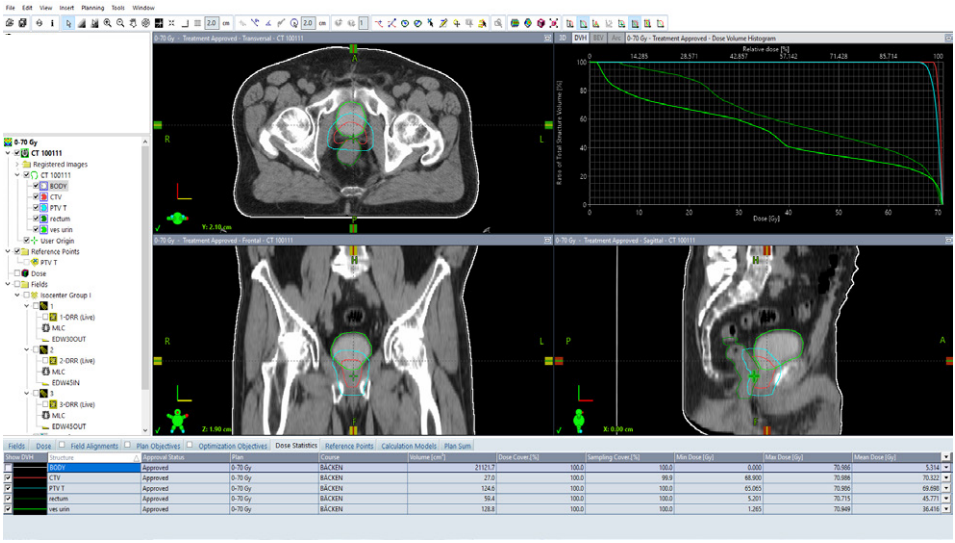


Figure 3 Figure 3 *An example of a DVH from a patient to be given SRT (created using an Eclipse™. treatment planning system). The target delineation is visualized in three projections: axial (upper left), frontal (lower left) and sagittal (lower right). At the upper right position a graph illustrates the dose distribution at different volumes for CTV (red), PTV (blue), rectum (dark green) and bladder (light green).*

Treatment delivery

As a standard approach, all treatment sessions are delivered according to a series of reference images created from the treatment planning procedure. In this approach, the treatment fractions will be delivered according to the set-up and by use of a matching procedure. The set-up meaning, in short, the position of the patient on the treatment table with help of skin and laser marking to gain a preliminary position. The following matching is achieved by applying some type of radiology method by evaluating radiographs obtained in connection directly before the daily treatment and compare with digitally reconstructed

radiographs (DRRs) created from the pCT in the treatment plan. The matching is accomplished towards skeletal structures since soft tissue, as the bladder and rectum, not are visible on a radiograph. Other examples of matching procedures are through a cone beam CT (CBCT), which represents a version of a CT (covering large volume with one single rotation about the patient) [31] and with this method soft tissue is visible and possible to match to in the PRT session.
In treatment of primary PC, the matching procedure is performed using markers, often consisting of gold, which are deposited in the prostate and can be reproduced in a radiograph/X-ray and thus make it possible to achieve a most acceptable fit. In the postoperative setting, there is no clear organ of choice in which markers can be placed, although the surgical clips that are inserted during the surgical procedure are used as markers in some cases [32] and a procedure to insert radiopaque tissue fiducial markers is described[33]. The urinary bladder and rectum can be implemented as matching structures, not by radiographs but by verifying their position in a CBCT, in which those organs can be visualized with respect to both volume and location [34]. The use of CBCT in the matching procedure for PRT is gaining ground as an obvious choice to achieve a better outcome.

Treatment techniques

In 2001, SRT was performed on a few patients at Sahlgrenska University Hospital, and this was initially done by three-dimensional conformal radiotherapy (3DCRT). Further development of the technology has resulted in improvements in the delivery of RT by what is called intensity-modulated RT (IMRT), and the rotation arc method designated volumetric modulated arc therapy (VMAT), which is now fully implemented at many radiation departments, including ours. With the VMAT technique, the radiation dose distribution can be better shaped according to the PTV and consequently has the potential to spare the OaR to a greater extent (see *Figure 4*). The duration of delivering the treatment is also shorter with VMAT, which is an

advantage to minimize organ motion, both in externa and internal respect.

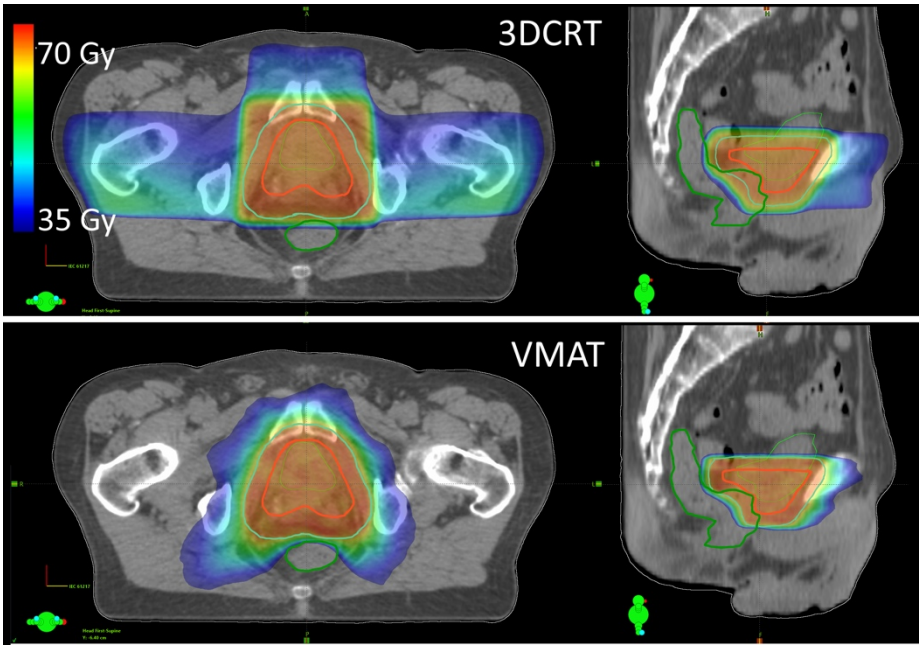


Figure 4 *A SRT patient's VMAT plan with dose distribution, "color wash" representing dose levels of 35 to 70Gy. This VMAT plan was made for PRT treatment and on the same patients images a 3DCRT plan was constructed.*

Dose prescription

The radiation dose to the postoperative area can vary, but the Swedish Care Program recommends a prescription dose of 70 Gray (Gy) in total for SRT, delivered at 2 Gy per treatment fraction, thus resulting in 35 days of treatment in a 5-days a week schedule. In ART, the prescribed dose is lower, often 66 Gy in 2-Gy fractions. Further development of SRT in the future will probably include evaluating the concept of hypofractionation, which entails a larger dose per fraction and consequently fewer treatment days. There are a few reports on this topic, and thus additional assessments are needed before hypofractionation can be implemented in the clinical setting [35,36].

Mechanism of action

The goal of cancer treatment is to kill, cancer cells by damaging their DNA, and that can be accomplished with ionizing radiation. This action is mediated through radiolysis of water, which is abundant in living cells, and it produces free radicals that impair the DNA. The ionizing rays are also deleterious to the normal tissue, but the cells in such tissue have the ability to repair DNA, and this is a fundamental difference compared to cancer cells. In short, this means that the radiation beams must be modulated in a balanced way so that cancer cells can be destroyed while normal cells stay intact, or at least suffer as little damage as possible. This is the background to the concept of fractionation in RT (see *Figure 5*). The normal tissues in the area receiving PRT are located predominantly in the urinary bladder, the rectum, and nerves involved in the erectile process, and the described side effects arise from those sites.

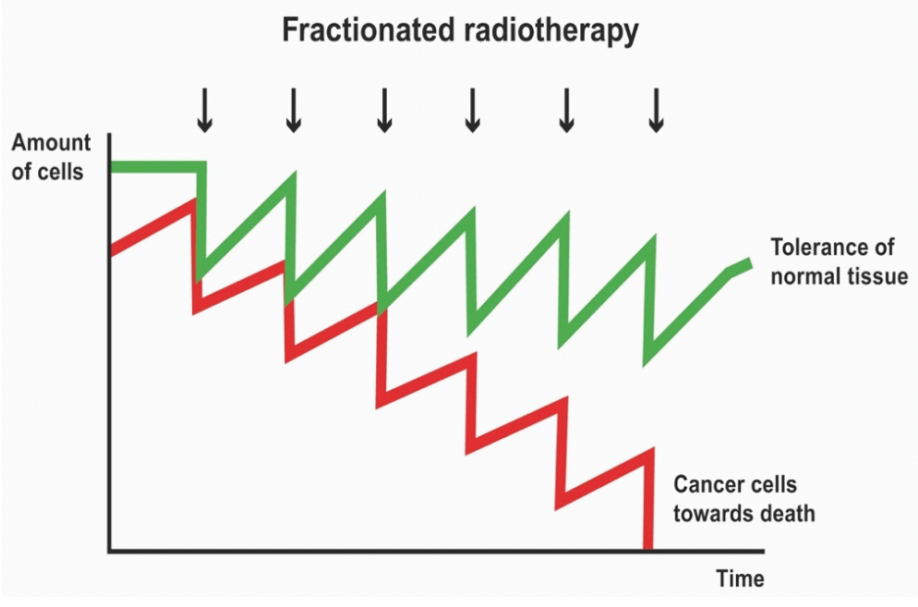
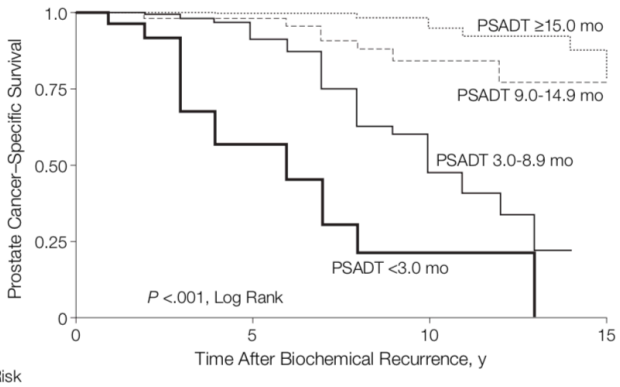


Figure 5 *Graph illustrating on fractionated radiotherapy with normal tissue tolerance and cancer cell death.*

DECISION-MAKING IN SRT

Offering a man SRT at PSA relapse means offering him a second chance to be cured. In many studies clinicians have found that the PSA limit of 0.2 ng/ml is optimal [18] and that a worse outcome can be expected at values above that level. However, values between 0.03 and 0.5 have also been described as optimal in the literature [37,38]. No other treatment known today can provide the possibility of cure. Therefore, the recommendation given to the patient must be derived from solid knowledge, experience, and research in this area, especially regarding expected side effects, which will be discussed further below. The possibility of refraining from radiation should also be considered. Based on histological findings as reported in 2009, Stephenson et al. [39] concluded that the probability of dying from PC after RP and PSA relapse is low, perhaps as low as a few percent within a period of 15 years following the surgery. According to results described by Freedland et al. and by Andersen et al. [40,41], the most important factor in assessment of the risk of death after RP for PC is the PSA-doubling time (PSADT), although other tumor characteristics can also provide valuable information in a risk evaluation. *Figure 6* presents PC-specific survival in relation to PSADT showing the differences between a short doubling time of 3 months and a longer such time of 15 months, with a very clear advantage in the latter group.

Figure 3. Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer–Specific Survival Curves by PSADT



No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Biochemical recurrence segregated by prostate-specific antigen doubling time among patients who experienced a biochemical recurrence. PSADT indicates prostate-specific antigen doubling time.

Figure 6 *From Freedland et al. 2005, JAMA; published with permission from the Editor.*

If the choice is to consider SRT, there are uncertainties in the decision-making, for example, regarding whether the PSA-producing cells are actually located in the area that can or is intended to be treated. It is obvious that the cancer cells that are generating the PSA value may be located in the local lymph nodes or, in the worst case, in distant metastases. However, as far as possible, this must be ruled out, because SRT will not cure a systematic, metastatic disease. According to some investigators [42-44], the most probable location of a local relapse after RP is in the vicinity of the anastomosis or in a retrovesical position. The surgical resection margins in each case must also be carefully considered. Still, there is currently no reliable way to visualize PSA-producing cells in patients with PSA values as low as 0.2–0.5 ng/ml. Therefore, various tools for probability judgement have been developed in relation to findings in the surgical specimen, which,

together with PSA kinetics, can support and guide the decision making. There are some "prediction tools" that rely on these findings and can deliver a prognosis for the SRT. An example of this is from Memorial Sloan Kettering Cancer Center, NewYork, NY, USA which makes use of PSA kinetics and pathological findings from the surgery for the individual and then presenting a prognosis on what to expect if the SRT is delivered. It is elaborated as an online tool so that the patients themselves can insert their own data. However, there is no prediction tool on what to expect if refraining the treatment which also could be a choice.

Imaging to support decisions

New diagnostic techniques based on visualization of PSA-producing cells are evolving, and the method Prostate-Specific antigen Membrane Antigen-Positron Emission Tomography, PSMA-PET, is appropriate. This approach uses the membrane antigen PSMA-11 marked with the radioactive isotope gallium-68, which has a half-life of 68 minutes and is therefore convenient for this imaging. The emission of positrons makes it possible to create three-dimensional PET scans that are further transformed in CT images and subsequently visualize the PSA-producing cells/areas. The reliability of this diagnostic procedure in patients with increasing PSA after prostatectomy depends on the level of the PSA. Hoffmann et al. [45] retrospectively analyzed 581 patients by use of PSMA-PET scans performed upon PSA relapse after RP and RT, and the results showed that, for RP, the optimal cut-off value for PSA was 1.24 ng/ml for predicting positive and negative scans. As mentioned above, the optimal PSA value for SRT is low, 0.2 [37,38] and, at that level, the PSMA-PET technique in its current form is not really applicable. Still, it is possible that the results of a PSMA-PET can help prevent inaccurate treatment of patients diagnosed with metastases, which is also highly important in the clinical perspective.

TARGET IN SALVAGE RADIOTHERAPY

The target

When RP is performed on a patient with PC, the whole prostate gland and the seminal vesicles are surgically removed. A new connection is created between the bladder neck and the external sphincter with the adjacent urethra, and this is achieved through downward displacement of the bladder (see *Figure 7*). Accordingly, the inferior (caudal) part of the bladder takes up the position formerly occupied by the prostate. The volume where the prostate had been located represents the target region [46], and the inferior part of the bladder is therefore unequivocally the midpoint of the radiation treatment. The bladder is an organ that constantly changes in size and, to some extent, also in location. The change in location is caused by increase in the bladder volume, and therefore substantial effort is made to standardize the volume during RT, which is discussed further below.

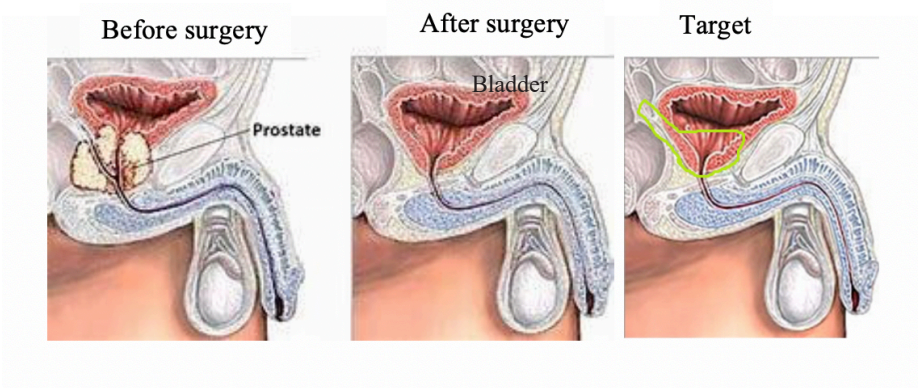


Figure 7. Sequence of images representing pre- and post-surgery in prostate cancer, and the target outlined in green (from http://studynursing.blogspot.com/).

Contouring guidelines

Contouring guidelines on how to define the postoperative PC treatment region (CTV/PTV) appeared at the beginning of this century and arose from international radiation associations such as the EORTC, the Radiation Therapy Oncology Group (RTOG), the Princess margaretHospital (PMH), and the Faculty of Radiation Oncology Genito-Urinary Group (FROGG) [47-50]. Development of these recommendations has been based on pragmatic discussions between urologists, radiation oncologists, and radiologists, which has resulted in guidelines that, to some extent differ from each other with varying definition of the CTV. As shown in *Figure 8* Malone et al. [51] have illustrated the effect of disparities in treatment volume when defining the CTV in the same patient but according to different guidelines.

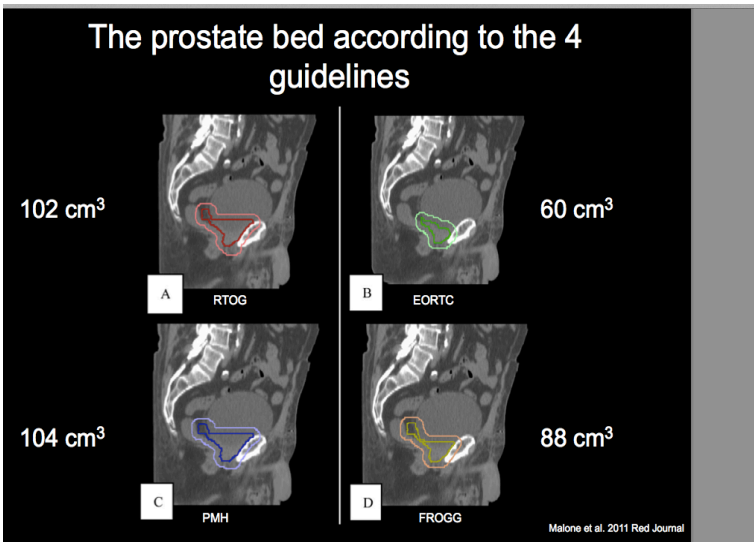


Figure 8. CTV/PTV determined by four different guidelines: RTOG, EORTC, PMH, FROGG.
Malone et al., 2012, Int J of Radiat Oncol Biol Phys; with permission from the Editor.

Thus, it can be concluded that there are disparities in the outlining of the CTV, and, in my opinion, this is one of the most uncertain factors when evaluating published studies. The occurrence of side effects should differ in relation to the extent of the CTV/PTV, and, reasonably, this will be seen as fewer side effects with a smaller irradiated volume. Unfortunately, reports in the literature seldom describe in what volume or according to what guideline the radiation energy has been delivered, which makes it more difficult to evaluate and compare the reported results of side effects. Not surprisingly, according to Cloak et al. [52], there are also differences between clinical colleagues regarding the extent of the target volume, even though the standard approach is to follow a specific guideline.

PREPARING FOR RADIOTHERAPY

Preparing the bladder and rectum

The above-mentioned contouring guidelines differ in bladder recommendations, to be kept full, partly full, comfortably full but all prescribe that it is desirable to achieve a reproducible bladder volume during the following treatment sessions. The bladder volume can be controlled by the use of bladder protocols [53] in which the patients are recommended particular modes of fluid intake and voiding. There are a number of such protocols [54] that describe different ways to handle the outcome, and they underline that it is important to control the results (i.e., ensure a constant bladder filling). Some protocols call for daily measurement of bladder volume by ultrasound examination, a time-consuming task with implications that the patient is either to empty the bladder to some extent or increase the intake of fluids [55] and continue controls.

Similarly, there are differences in the recommendations for preparing the rectum for RT. Daily emptying of the rectum, following a gut diet or even by use of a rectal rod or balloon during treatment are strategies that are known to provide control over the position and volume of the rectum [56,57]. An invasive procedure designated “SpaceOAR” has been shown to significantly reduce late toxicity of the rectum [58], but, thus far, this procedure is applied only in primary RT for PC and is not yet approved for PRT. In SpaceOAR, a hydrogel substance that acts as a spacer is injected into the region between the prostate and rectum that dissolves within 6 months. To accomplish control and reproducibility of the size and location of the rectum is an important but troublesome task. Bell et al. [48] have studied this topic and found that, if the rectum changes volume and location, it will result in a geographic miss in the upper part of the target that will have an impact on the distribution of the radiation energy [59,60]. This suggests that dislocation of the rectum can interfere with the dose distribution and thus have a negative effect on both the target and the OaRs. The optimal way to handle the influence of the rectum in the target area, during treatment, may be a standardized matching procedure with CBCT, as proposed by Ost et al. [31].

REGISTRATION AND EVALUATION OF SIDE EFFECTS

The registration of side effects can be achieved by use of different schedules in which health care staff judge the way a patient perceives his own symptoms, and the observations made are recorded according to pre-described values. One such approach is the Common Toxicity Criteria scale elaborated by the European Organization for Research and Treatment of Cancer (EORTC), which gives an objective view of radiation-related toxicity [61]. To register, descriptions of the subjective symptoms obtained directly from the patient, the use of patient-reported outcome measure (PROM) questionnaires can be recommended, because they clearly reveal the patient's own experience of troubles/symptoms and quality of life (QoL). One internationally frequently used PROM is the International Prostate Symptom Score (IPSS) which is used to evaluate urinary voiding symptoms, where the patient himself enters a chosen digit corresponding to his symptoms. Unfortunately, the PROM questionnaires are underutilized in published papers and studies, and there seem to be discrepancies between the ways that these instruments report side effects [62]. One example was presented by Sonn et al. [63], who found that there was physician patient disagreement in that the physician noted impairment in urinary and sexual function more often than pain and fatigue.

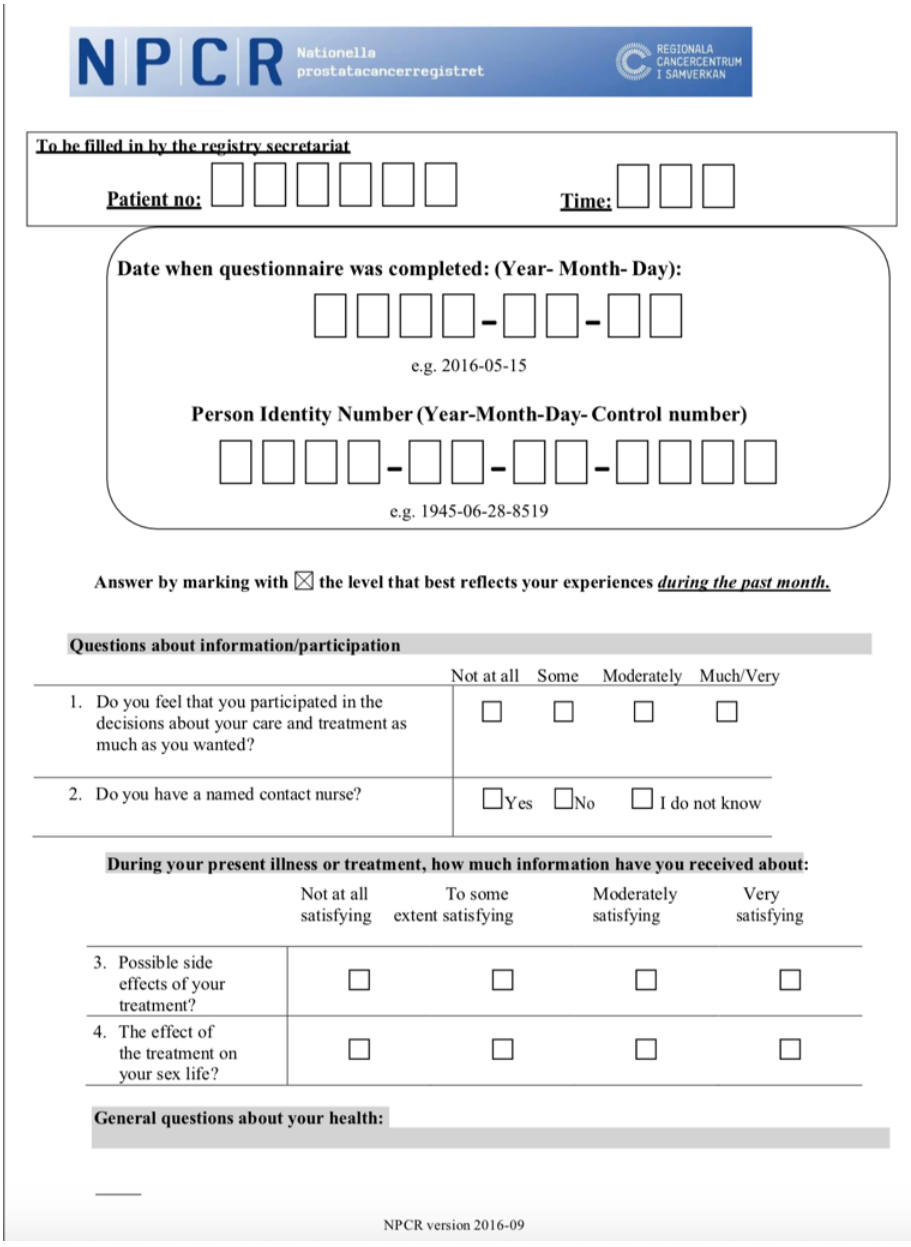
Further, the EORTC has developed the PROM QoL questionnaire QLQ-C30 (Core Quality of Life Questionnaire) for general application in cancer patients and in cancer trials. Questionnaires specific for PC patients also exist, for example, the EPIC 26 (Expanded Prostate Cancer Index Composite) [64] and the SWOG QoL (Southwest Oncology group Quality of Life) [65]. The QUFW94 (Questionnaire Umeå Fransson Widmark) is another questionnaire that is used in particular to study the side effects of RT in PC patients, and has been

developed to the “Prostate Cancer Symptom Scale” self-assessment questionnaire [66,67] that is frequently administered in Sweden via the NPCR (see *Figure 9*).

NPCR and Prostate Cancer data Base Sweden, PCBaSe

The NPCR was initiated to a limited extent in 1987 but includes all regions in Sweden since 1996, and the primary aim of this register is to present quality assurance work that is centrally administered and includes further reference back to the regional working groups. The NPCR database contains reports on diagnostic parameters, planned and executed primary treatment, treatment outcomes, and side effects. Since 2016, an interactive bulletin entitled “Ratten” is available online, which delivers updated reports from the NPCR on a daily basis [68].

A register-based resource for PC research known as PCBaSe was constructed in 2008 with the NPCR database as a hub. Development of that database has been achieved by use of the unique Swedish personal identity number, and various nationwide registers are linked to the NPCR, such as the following: the Cause of Death Register, the Swedish Cancer Register, the Prescribed Drug Register, and the National Patient Register. Thus, the NPCR serves as an important register-based resource and platform for PC research that is continuously up-dated and validated [69,70].



NPCR Nationella prostatacancerregistret

REGIONALA CANCERCENTRUM I SAMVERKAN

To be filled in by the registry secretariat

Patient no: ☐☐☐☐☐☐ Time: ☐☐☐

Date when questionnaire was completed: (Year- Month- Day):

☐☐☐☐-☐☐-☐☐

e.g. 2016-05-15

Person Identity Number (Year-Month-Day- Control number)

☐☐☐☐-☐☐-☐☐-☐☐☐☐

e.g. 1945-06-28-8519

Answer by marking with ☒ the level that best reflects your experiences *during the past month.*

Questions about information/participation

	Not at all	Some	Moderately	Much/Very
1. Do you feel that you participated in the decisions about your care and treatment as much as you wanted?	☐	☐	☐	☐

2. Do you have a named contact nurse?	☐Yes	☐No	☐ I do not know

During your present illness or treatment, how much information have you received about:

	Not at all satisfying	To some extent satisfying	Moderately satisfying	Very satisfying
3. Possible side effects of your treatment?	☐	☐	☐	☐
4. The effect of the treatment on your sex life?	☐	☐	☐	☐

General questions about your health:

NPCR version 2016-09

Figure 9. Cover sheet of the "Prostate Cancer Symptom Scale" self-assessment questionnaire. With permission from the Steering group in NPCR

SIDE EFFECTS AND DOSE-VOLUME CONSIDERATIONS

As mentioned above (see Figure 5), after RT delivered to any part of the body, it is necessary to take into account the balance between destruction of cancer cells and possible damage to remaining normal cells in the organs concerned. In PRT, the lower part of the bladder receives the total prescribed radiation dose and is most likely to suffer from side effects [71]. How pronounced these effects are is very individual, and the knowledge on this subject is poor, because data and reports often concern primary prostate RT in which a higher radiation dose is prescribed, and the urinary bladder is not in the center of the delivered radiation. Further, a method for reducing the risk of radiation to the bladder and rectum in primary prostate RT is the previously mentioned practice of IGRT with gold markers [72].

The rectum and the structures involved in sexual functioning are other areas that are to be affected by the radiation energy, the rectal wall, and for erectile structures also the preceding surgical procedure. The side effects currently observed after RT include symptoms in the urinary and gastrointestinal tracts and regarding sexual functioning, and in the short perspective also fatigue.

There is a distinction between early (acute) and late side effects, or toxicity, with the symptoms considered to be early occurring within the first 6 months after RT and those deemed late appearing during the time thereafter. Almost all published evaluations have indicated that late side effects after PRT are usually mild [22,73]. Also, an assessment considering a possible correlation between acute and late toxicity has suggested that acute toxicity is an independent predictor of late rectal toxicity [74].

Late toxicity is the topic further discussed below.

The urinary tract

The side effects observed most often after PRT are increased frequency and urge, and also dysuria, whereas leakage (incontinence) is more seldom reported. This is noted in most studies performing PROM surveys [75-77], which also describe the side effects as being well tolerated. Radiation scoring schemas outlined by the RTOG/EORTC are focused on grading and have indicated that urinary toxicity of grade 2, 3 is rare in most studies (see the scoring schema for grading presented in *Figure 10*). Nonetheless, it seems that side effects from the urinary tract increases over time. Cozzarini et al. [78] found that the 8-year risk of grade 2 or 3 side effects was nearly 24% and primarily represented hematuria and incontinence, with a median interval to onset of 20 months. Other investigators have reported similar findings, including the increase in symptoms over time [73,79]. The dose-volume relationship with proposed constraint levels is more uncertain, because the bladder is an organ that constantly changes in volume, which also results in different positions of the bladder both during and between treatment sessions. Consequently, the treatment plan with a dose distribution based on the pCT can most likely not illustrate the true dose distribution pattern during the course of the whole treatment period.

Considering the obvious difficulties in controlling the bladder volume, it has been suggested that some parts of the bladder are more sensitive to developing the side effects of radiation and therefore might be used as predictor sites. Cheung et al. [79] recently studied what they called a “hot-spot” model relating grade > 1 toxicity of the dose to the hottest 2.9% of the (full) bladder. Ghadjar et al. [80] further investigated the hot-spot theory in primary RT and found a significant association between high-dose spots in the trigone and relevant changes in IPSS. Hathcort et al. [81] proposed that the dose to the bladder neck in brachytherapy can be regarded as a strong predictor of developing acute and late toxicity.

In an organ-specific paper from the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group, Viswanathan et al. [71] stated that there is no convincing proof that a dose-response relationship actually exists, and they also proposed that the symptoms in the urinary tract may arise from the urethra or from a prostate gland that has not been removed. Clearly, further investigations are needed to address this issue.

RTOG/EORTC late radiation morbidity scoring schema

Organ	1	2	3	4	5
Bladder	Slight epithelial atrophy, minor telangiectasia (microscopic hematuria)	Moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria	Severe frequency and dysuria, severe generalized telangiectasia (often with petachiae), frequent hematuria, reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc), severe hemorrhagic cystitis	Death
Small/large intestine	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea and colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation, fistula	Death

Figure 10. The RTOG/EORTC scoring schema for late side effects in the bladder and small/large intestine (adapted from Ohri et al., 2012, Canadian Journal of Urology).

The gastrointestinal tract

Rectal inconveniences, toxicity, consists of especially bleeding, discharge of mucus and leakage of stools; though defecation urgency was the most prevalent in a PROM survey by Alsadius et al 2014, when investigating patients receiving different kinds of RT in prostate cancer[82,83]. Rectal bleeding has been described, according to RTOG grade 2, in a QUANTEC overview, occurring in about 5-20% in prostate cancer primary radiation series[83]. Such bleeding has been regarded as usually being self-limited, but in some patients it requires medication (e.g., suppositories), blood transfusion, or, in the worst case, surgical intervention such as a diversion (ostomy) [84].

The correlation between DVH parameters and development of rectal bleeding has been described in earlier studies, and the following dose-response constraint has been proposed [85,86]: > 60 Gy delivered to >35% of the rectal volume (representing about 90% if the prescribed dose is 70Gy in 2 Gy fractions) is significantly associated with late rectal toxicity. There are uncertainties in this context; Bruner et al. [87] compared the two techniques 3-DCRT and IMRT in primary PC treatment and found that despite of reduced treatment volumes and doses to the OaRs in the IMRT technique, the PROM questionnaire could not reveal any differences in the symptoms reported by the patients. Most analyses of dose-volume parameters have been performed on patients receiving RT in a primary setting, and it is not clear whether these findings also apply to the postoperative group. Hence, there are differences in the prescribed dose, with approximately 80 Gy delivered in 2 Gy fractions, given in the primary treatment and also in IGRT with gold markers, compared to IGRT in PRT with matching to skeletal structures, which has a negative impact in the PRT group. It has also been proposed that earlier abdominal surgery, as done after prostatectomy, makes the patient less tolerant to radiation [88].

Severe side effects, needing intervention

Adverse events and surgical interventions associated with late side effects of PRT have been studied to a somewhat lesser extent. Showalter et al. [89] conducted a large retrospective cohort investigation of long-term adverse events in nearly 10,000 men with PC. These authors used primary care and hospital database registers and focused specifically on adverse events in the following areas after treatment for PC: gastrointestinal and genitourinary problems, erectile dysfunction, and hip fractures. They compared RP and RP+RT over a 5-year follow-up period and found that the added exposure to RT after prostatectomy led to increased rates of gastrointestinal and non-incontinence urinary events but not urinary incontinence events or erectile dysfunction. In a 5-year follow-up cohort study including a total of 37,000 men, Wallis et al. [90] compared three groups of PC patients treated with RP, RT, and RP+RT, respectively, according to their need for in-patient care, interventions, or procedures in the urinary or rectal tract. The complication rate was highest in the RT-only group followed by the RP+RT group, and lowest in the RP-only group. However, it should be mentioned that that study had no information regarding possible use of ADT, which is often prescribed together with RT and can lead to a poorer result with respect to side effects.

Erectile dysfunction

The impact on erectile function when adding RT to a prostatectomized patient in the postoperative setting is difficult to evaluate, especially if there are no baseline data from before the RT. It has been proposed that the dose to the penile bulb can predict risk of erectile dysfunction, in primary RT, with a constraint level of 20 Gy [91]. Still, it is highly likely, in PRT, that the surgery itself additionally influences the erectile function. Reports on erectile dysfunction after PRT often show very little deterioration, if any at all [65,92].

Secondary malignancies

Development of secondary malignancies after RT for PC is particularly important to consider when handling younger patients. The aspects of dose response and time lag period, as well as age, seem to play a crucial role in the occurrence of secondary malignancy. Reports concerning primary radiation for PC predominantly deal with an increased risk of subsequent bladder and colorectal cancer [93], although lung cancer is also indicated. Brenner et al. [94] observed only a limited rise in the risk of secondary malignancies in the form of solid tumors, but this risk increased in long-term (> 10-year) survivors in primary radiated patients compared to operated men. Zelefsky et al. [95] compared primary RT (both EBRT and brachytherapy) with RP but, during a 10-year follow-up, found no significant difference between the two groups after adjusting for age and smoking habits.
A number of different treatment strategies (e.g., 3-DCRT, IMRT, VMAT, and protons) have been investigated with proposal on varying risks linked to the different methods [96,97]. Still, in a systematic review and meta-analysis, Wallis et al. [98] found that the absolute rates of secondary malignancies after RT for PC were low.
There are fewer reports on secondary malignancy in SRT. Aksnessæther et al. [99] conducted a register-based study in Norway to compare RP and different RTs, including PRT, with regard to secondary malignancies, and the results showed that only the risk of bladder cancer was increased in the PRT group compared to the RP group. In one of the previously mentioned investigations performed by Wallis et al. [90], both primary RT and PRT were compared with RP regarding the risk of secondary malignancy of any kind, and the increase in risk was found to be highest in the RT-only group followed by the PRT group, and lowest in the RP group. It is evident that further studies are needed to explore the impact of PRT on the risk of developing secondary malignancies, and such assessments should take the following parameters into account: treatment modality, radiation dose, patient age, and other as yet unidentified confounders.

2 AIM

The overall aim of the research leading to this thesis was to evaluate and improve the practical preparations for postoperative radiotherapy in prostate cancer and to assess the side effects in a long-term perspective.

Ethical approval was granted for each of the four studies, which have the following objectives:

PAPER I
To investigate post-radiation morbidity in a long-term perspective as outlined in a PROM survey, comparing to a matched control group of men treated only with RP.

PAPER II
To evaluate dose-response parameters related to patient reported rectal bleeding and assess the risk related to two different radiation treatment techniques.

PAPER III
To evaluate the presence of late, side-effects with need of surgical interventions, in a large unselected cohort by comparing men treated with RP exposed to RT with a matched control group non-exposed to RT. We also investigated the development of secondary malignancies and cause of death.

PAPER IV
To evaluate the impact on bladder-filling of two different bladder filling protocols and to evaluate how different levels of bladder filling affect the localization and probable coverage of the target.

3 Methods and methodological considerations

Paper I

All men who had undergone SRT after RP in the Western Region in Sweden during the period 2005-2010 were invited to participate in a mailed PROM survey. Men who had only undergone RP were selected from the NPCR database to serve as a matched control group, and those subjects were invited to complete the PROM survey in the same manner as the SRT group. The matching procedure was performed according to age, year of RP, and operating hospital. The SRT had been delivered as 2 Gy per fraction on 35 occasions to a total dose of 70 Gy, mainly with a 3DCRT technique (photon beam energy 15 MV) with a few exceptions (3% with IMRT technique).

We used the NPCR "Prostate Cancer Symptom Scale" self-assessment instrument, which is frequently administered within the field of PC in Sweden. Along with the survey document, a health declaration form (HDF) was attached that included questions on diseases, experienced symptoms, smoking habits, and pharmacological treatment. A reminder was sent if the survey was not returned within one month.

The self-assessment survey consists of 53 questions divided into different symptom areas. We selected 14 questions that represented symptoms that would most likely refer to RT in PC and divided them into four different groups according to the area they affected: (1) the urinary tract, including incontinence and other urinary symptoms; (2) the rectal tract, as leakage of stools and discharge of blood; (3) sexual function; (4) general health and QoL.

In addition, information on severe side effects was obtained from medical records for men who were deceased or did not participate in the survey.

Methodological considerations

The goal of this study was to provide a better understanding of what side effects patients experience in a long-term perspective after SRT. A PROM survey and an HDF were administered to the SRT group, which included patients who were registered in our treatment database system as having undergone SRT during the investigated time period. Patients to create a control group were chosen from the NPCR patient database to match the SRT group with regard to age, year of surgery, and hospital. It is possible that matching according to tumor characteristics would have resulted in a better comparison between the groups, but that was not possible due to lack of access to the complete pathoanatomical diagnosis data in the control group. Also, during the matching of the two patient groups, we did not consider potential bias from any conceivable future events (related to RT), and this might be considered a weakness of our study. Also, the actual oncological result, recorded as PSA values, was not known during the related follow-up, information that might have been useful even though the aim of our study was not to present oncological findings. We discussed what PROM survey would be most suitable, and this led to our choice of the instrument used nationally in Sweden: the NPCR "Prostate Cancer Symptom Scale" self-assessment. This instrument originated from the QUFW94 questionnaire, which was designed in 1994 and was further validated in 2001 and 2010. One reason for choosing the NPCR assessment was that it is widely used in Sweden for thousands of PC patients, and it has a system for handling the responses electronically. This survey has also been used in previously published studies. The HDF, which is applied on a daily basis at our department, could not be assessed automatically, and this led to considerable amounts of extra work such as the necessity of interpreting nearly illegible handwriting

and entering information in the database, tasks that entail, the risk of making mistakes related to the "human factor". Another challenge was having to search through medical records to find diagnoses and medical history of deceased and missing patients in order to avoid drawing misleading conclusions on possible side-effects.

Before actually applying the NPCR survey, we addressed the issue of how we would analyze the patients' responses by including questions that would not influence the answers that were given in a special direction. The response alternatives were dichotomized between "not at all" (1) and answers indicating any problem related to the specific question (2–4), although this differed for the items concerning leakage and QoL (see Appendix in Paper I). The collected data were analyzed by use of Poisson regression which gives relative risk estimates with corresponding confidence intervals (CIs). It seemed more appropriate to present the results as relative risks than as odds ratios of logistic regression, since we believe that relative risk is easier to assess.

Inasmuch as a major part of the results concerned patient-reported rectal bleeding, it is also appropriate to mention the related question in the survey (i.e., no. 28): "Do you have blood in your stools?" The response alternatives were "no", "a little", "to some extent", and "very much". This grading of the response can be compared with and commented on in relation to other PROM questionnaires, which provide more detailed descriptions of the quantity and duration of the bleeding. Still, the wording of the response to this item in our questionnaire makes it possible to differentiate between "no bleeding" and "any bleeding", which has served as the distinguishing feature in our model of evaluation: no bleeding = 0, and any bleeding = 1.

Paper II

Group 1 in this study consisted of the same SRT patients as included in the SRT group in our PROM survey (Paper I, see above), and these subjects were further analyzed for how the risk of rectal bleeding is affected by the rectal dose distribution. This investigation also included a second SRT group treated with VMAT at our department, here designated Group 2, which was retrospectively chosen to enable comparison with rectal DVH parameters in Group 1. Fifty-six (22%) of the patients in Group 1 had reported rectal bleeding to any extent in the PROM survey described in Paper I, which represented the main result of that survey.

Group 1 consisted of patients treated with 3DCRT in 2005–2010 at our hospital, and Group 2 was selected to include all patients treated with the VMAT technique in 2017–2018, at that time fully implemented in the department. In both groups, treatment and preparations for treatment were performed according to the standard protocols at the department, which did not include any specific rectal arrangement except instructions to empty the rectum prior to undergoing the planning CT. Target delineation varied over the study periods, with changes from a smaller toward a larger CTV according to existing guidelines (i.e., from EORTC to RTOG recommendations). Over time, CTV to PTV margins were gradually being reduced from 15 mm to 10 mm. However, the procedure for delineation of the rectum was identical in the two groups. With the treatment delivered as 2 Gy per fraction for 7 weeks to achieve a total dose of 70 Gy. A laser-based setup was followed by orthogonal kilovoltage or megavoltage positioning of bony anatomy with different time schedules: in Group 1, the average of the four first fractions was the base for setup, completed with weekly controls; in Group 2, daily orthogonal imaging was conducted. Using the self-reported data on rectal bleeding in Group 1, a dose-response analysis was performed to quantify the impact of rectal DVH parameters on the risk of rectal bleeding. The relative

rectal volume receiving at least 35Gy and 63Gy were separately investigated in univariable logistic regression using the maximum likelihood estimation method. The resulting dose response relationships between rectal V35Gy and V63Gy, called dose-response curves, were used to calculate the probability of rectal bleeding for each patient in both groups with purpose to investigate the potential benefits of treating patients with VMAT instead of 3DCRT.

Methodological considerations

The dose-response relationships considered in this study were those between the dose distribution in the rectum and reported rectal bleeding, and the data were extracted from the Eclipse treatment planning system where treatment-related data of interest are available. Rectal DVH parameters from both groups were included in the analysis. In Group 1, we had identified 56 of 255 men that reported rectal bleeding of any grade as compared to no rectal bleeding. In line with the above-mentioned goal, we performed a dose-response analysis to quantify the impact of rectal DVH parameters in the 3DCRT-treated Group 1. This relationship was then used to estimate the risk of rectal bleeding using the two rectal volume objectives applied at our department, V_{35Gy} (50% of prescribed total dose) and V_{63Gy} (90% of prescribed total dose). This resulted in two dose-response curves, which were then used to calculate the risk of rectal bleeding for each patient in both groups. Here we used PROM data including patients reports of any rectal bleeding, and we undertook risk assessment calculations that could subsequently be used in future development of evidence-based rectal dose constraint levels.

Paper III

All patients in Sweden that had been treated with RP in 1997–2016 were selected from the NPCR and investigated to choose a large cohort of men to be investigated according to: men who underwent RP and received RT postoperatively, called the exposed group; and men who underwent RP but had no postoperative RT, referred to as the non-exposed group. As the database for this study, we used the PCBaSe, which consists of the NPCR and its linkage to more than eight different national patient registers in Sweden, such as the following: the National Patient Registry, the Prescribed Drug Register, the Cancer Registry, and the Cause of Death Register.

After exclusions, a matching procedure was performed. The matching procedure was developed to avoid possible bias, in order to not be based on future information when considering date of RT as time zero. Prior to conducting this matching, censoring was performed if other malignancies, metastases, and symptoms and/or surgical procedures in the urinary or rectal tract had occurred before RT. Matching in the groups was done according to year of birth, year of surgery, and Charlson comorbidity index (CCI). A non-radiated man was given a fictive RT date that corresponded to the true RT date of a matched radiated man (see the matching algorithm in Appendix in Paper III). Differences between the two groups were investigated with regard to these outcome measures: surgical procedures in the urinary or rectal tract; development of secondary malignancies; mortality, considering deaths due to PC and all other causes. Kaplan-Meier survival analysis was performed on each outcome, and, to avoid overestimating the incidence associated with competing risk, incidence curves based on competing risk were constructed. Rate ratios between the two groups were calculated by Poisson regression analysis, and CIs were constructed based on profile likelihood.

Methodological considerations

The analysis of severe side effects after PRT reported in Paper III was based on data from different national registers linked to the NPCR, which make up the PCBaSe. The capture rate of the PCBaSe is known to be very good, described as 98% in the NPCR, and reporting is actually mandatory by law for some of these records, such as the Swedish Cancer Registry. The data on performed radiation therapies were updated with reliable information from 17 of 18 existing radiotherapy units in Sweden (compiled by RetroRad, 1998–2007), and this was necessary because the reporting of radiation data to the NPCR had not been initiated until 2008. Using the PCBaSe in our investigation was an obvious choice due to the reliability of this database and the large number of research papers that have emanated from it.

The data used as a basis for this study represented all men with PC who underwent RP in 1997–2016 in Sweden. From this cohort, all those who had also received RT as postoperative treatment were selected and designated as the exposed (RP+RT) group. Several of the patients were excluded before the matching procedure was performed. In short, subjects were excluded due to living in a region with missing PRT data, being lost to follow-up, and, most extensively, due to lack of information on timing of ADT. The matching strategy was developed to avoid "immortal time bias". In other words, the information on the groups we wanted to compare could not be based on unknown future information, which might have precluded the possibility of achieving comparable groups.

The matching procedure was time consuming and had to be redone more than once. For instance, data on surgical procedures and ICD-10 diagnoses became limited to us since *Socialstyrelsen, SoS* (in English: the National Board of Health and Welfare) implements restrictions on the availability of codes in the National Patient Registry in PCBaSe. This meant that we could not directly address our own selected codes

but had to relate to the prechosen codes given by *SoS*. Though, with the codes from *SoS* as first selection, other registered codes appeared, often the ones we had as a first choice and, as a whole, we considered that this did not, in any important way, influence the analysis. We investigated the cumulative incidence based on Kaplan-Meier estimation, and competing risk curves were constructed to ascertain whether censored events resulted in an overestimation of the cumulative incidence of the studied event.

Rate ratios were calculated by Poisson regression analysis. An alternative could have been to apply Cox regression analysis, but we found the relative risk and rate ratio easier to interpret. Furthermore, the hazard ratio from Cox analysis is often considered to be similar to the rate ratio, as we also found to be the case in the analysis of our data. Absolute risk calculations appeared as an additional analysis to perform, not yet completed but highly interesting in the evaluation. The sectioning in ART or SRT is also an additional analysis to perform, yet with some difficulties in the division between groups, possibly through the time since surgery information, since the ordinated radiation dose not is conclusive.

Paper IV

From the outpatient clinic, 32 patients with PSA relapse were invited and subsequently allocated to use of one of two different bladder filling protocols before a planned SRT treatment. This was done in a strictly time-dependent order, with every second patient assigned alternately to the two groups.

The two protocols stipulated the following:

Group 1 Voiding and drinking 300 ml of water 1 hour before the pCT and before each treatment occasion.
Group 2 No instructions other than to keep a comfortably full bladder before the pCT and before each treatment occasion.

The SRT was delivered as 2 Gy per fraction on 35 occasions to achieve a total of 70 Gy, thus requiring 7 weeks of treatment. A planning CT (pCT) followed by a CBCT performed weekly during the treatment period was registered to the pCT and further analyzed. Volumes of the bladder and CTV/PTV data were collected from the treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA, USA), and the bladder volumes from the CBCTs were delineated and measured. The difference in bladder extension between the pCT and CBCT was measured both cranially and caudally (see *Figure 11*).
The variation in the volume of the bladder covered with 95% of the dose ($V_{95\%,bladder}$) in the treatment positions was estimated based on the DVH and correlated with the corresponding bladder volume.
On a weekly basis, the patients were asked how well they had been able to follow the bladder protocol instructions, and the responses were registered by members of the clinical staff.

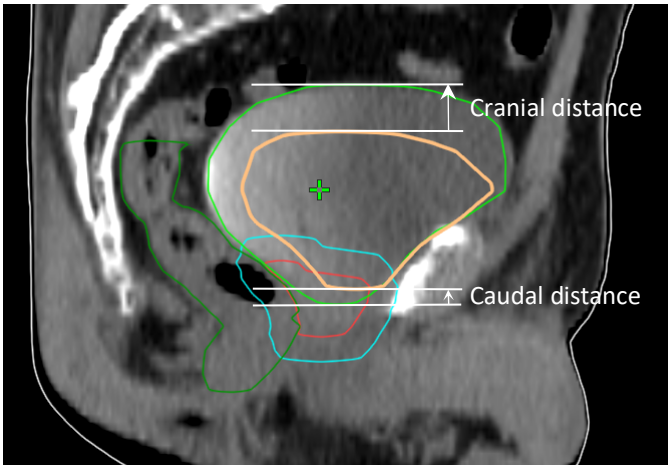


Figure 11. An example of pCT and CBCT images in a sagittal view matched and stored on top of each other. Colors indicate the following: bladder (green and orange), CTV (red), PTV (blue), Distance in the two-dimensional direction between different bladder volumes was measured cranially and caudally, arrow indicating positive (+) measurement.

Methodological considerations

In this study, our intention was to randomize patients to two separate groups with different bladder filling regimens, and a power calculation (assuming that the true mean difference between groups is 1.325 times the standard deviation, we had 80% power to detect this difference for a two-sided confidence level of 0.05) recommended that a total of 20 patients be included, 10 assigned to each group. The randomization was organized in a simple manner by allocating each patient to either protocol in the order in which they came to the outpatient ward. Later, after the manuscript had already been submitted for publication, we recognized that the rules for randomization had not been fulfilled; that is, the random sample selection should have been organized in a different way, possibly via a database selection.

The analysis was based on the planning CTs and CBCTs of each patient, the latter performed weekly. It was a challenge for the author to carry out all registrations between pCT and CBCTs and the delineations and measurements on the CT/CBCT images, but it was definitely an advantage that a single person was responsible for all

these tasks. There was no indication of which group each patient was associated with at the time of delineation.

The practical handling of the studied patients in the treatment ward differed very little from the routine practice at the department. Still, although the patients were questioned regarding how well they were able to follow the instructions on fluid intake and voiding given in the bladder protocol, their responses were not always registered. This can be explained by the fact that the department is not a research unit, and the recording of the results reflects the ordinary daily work at that facility.

Other potential approaches to achieve the same results for bladder volume measurements include ultrasound (US) measurements, as have been performed by other investigators. However, such measurements would have required introduction of a new and very user-dependent technique at the department, a strategy that was not realistic at that time. Furthermore, the US method would not have been appropriate for evaluating the effect of coverage of the target or made possible the measurements cranially and caudally.

The choice of $V_{95\%bladder}$ to evaluate the potential effect on increased irradiation of the bladder with increased bladder volume appeared as a possibility, and to relate to the finding of a stable localization of the distal part of the CTV. Though, conclusions could only be drawn when delineating the target according to EORTC which advocates smaller CTV.

Statistical methods used in the studies

The statistical analyses were performed using R Statistical Software Matlab (version 2019b; The MathWorks Inc., Natick, MA, USA) and SPSS.
Different statistical methods were applied in the four studies, because we analyzed different types of data on different topics. The statistical methods vary from quite basal, for example, considering medians and relative risks, to more advanced, such as analysis of survival and competing risk.

Paper I
In the analysis of the data from the PROM survey in the first study, we calculated the relative risks between the SRT and the reference group. To describe the margin of error, corresponding 95% CIs were calculated using Poisson regression with robust error variances. In the SRT group, the effects of age, PTV, and length of follow-up on the responses were investigated through dichotomization at median values. For each question in the survey, the proportion of missing answers was calculated based on available responses.

Paper II
In this study on rectal bleeding and dose-response relationships, we extracted radiation therapy data of interest from Eclipse using its capabilities for automatic data extraction. Dose-response data were investigated for patients in Group 1 (the PROM-reporting group), and they contributed with either 1 = any bleeding or 0 = no bleeding. The two dose-volume levels, V_{35Gy} and V_{63Gy}, were investigated separately in univariable logistic regression according to the maximum likelihood estimation method. The result is the s-shaped (logistic) curves that best described the risk of rectal bleeding as a function of either V35Gy or V63Gy.

Statistical significance for the models was assessed with the likelihood ratio test, and p-values of < 0.05 were considered statistically significant. Confidence intervals for the dose-response curves were estimated with bootstrapping, that is, random sampling with replacement using 5,000 bootstrap samples.

The dose-response relationships curves were used to calculate the probability of rectal bleeding for each patient in both groups. Welch's t-test was applied to assess differences between the two groups with regard to rectal V_{35Gy} and $V_{63\ Gy}$, and the corresponding calculated probabilities. A linear regression model was used to evaluate the relationship between PTV and rectal doses V_{35Gy} and V_{63Gy}.

Paper III

The follow-up time, with a maximum of 15 years, started at the true or fictive RT date. The collected data on the following events were censored at first date of occurrence: emigration, date of death, start of ADT or surgical castration, and, for the non-exposed men, also for undergoing RT. However, data on ADT or surgical castration were not censored from the analysis of secondary malignancies and PC or all-cause mortality.

Kaplan-Meier estimation served as the basis for the assessment of cumulative incidence, and competing risk analysis curves were constructed to address the risk of overestimation of incidence of the evaluated event. Comparison of the curves showed only negligible or small differences and no appreciable effect on the relationship between the curves. Poisson regression analysis was applied to calculate risk ratios and rate ratios between the two groups and the associated confidence intervals, based on profile likelihood.

Paper IV

In this study focused on variation in bladder filling, we calculated medians in bladder volume within individuals, within groups, and between groups to enable comparison of the observations. For this purpose, we used a linear mixed model that took into account the repeated measurements for each individual. To meet the assumption of normal distribution, the data were analyzed on a logarithmic scale. Pooled within-individual standard deviations were estimated.

Spearman correlations were calculated to measure the degree of association between bladder volume and, respectively, the cranial and caudal distances noted at each visit. Thereafter, weighted medians of the Spearman correlations were chosen as the measure of overall correlation, and the number of patients per visit served as weights. CIs were estimated by bootstrapping, with 10,000 bootstraps for each group.

A linear mixed model was used to investigate the increase in 95% dose to the bladder volume ($V_{95\%bladder}$) with increased total bladder volume. In this model, the result for each individual patient had its own slope and intercept with means depending on group. The mean slopes of $V_{95\%,bladder}$ versus bladder volume in the two groups were estimated and compared.

4 RESULTS

Paper I

In the SRT group 255 patients responded to the survey, 79% of invited and in reference group 485 responded ,74% of invited.
ADT was prescribed for 22% in the SRT group and 6% in the reference group. The median time from surgery to survey was 10 years in both groups, and the median time after radiation to the survey was 6.7 years.

Comparison of the two groups
The impact of SRT was most pronounced on rectal symptoms, with relative risk (=risk ratios=RR) of 1.7 to 6.5. The effect was more limited in the urinary symptom group, with RRs ranging from 1.2 to 1.4. For general health, QoL, and sexual symptoms, all the RRs were < 1.1. Also, the response rate for the question on sexual activeness (Q 38) was 30% in the SRT group and 32% in the reference group. Intensity of symptoms was investigated and plotted, which showed that having any rectal bleeding was reported by 22% in the SRT group compared to 3% in the reference group. Furthermore, fecal leakage of any extent was reported by 19% in the SRT group and 11% in the reference group, whereas intensity of other symptoms was generally low.

When comparing the two groups, the use of ADT did not seem to influence the answers to the survey. The presence of severe symptoms indicated by a response of 4/5 (worst grade) for at least one of several selected questions (i.e., nos. 13, 15, 18, 24, 26, and 28) was noted for 24% in the SRT group and 11% in the reference group. Dividing this into having at least one severe *urinary* symptom was reported by 16% in the SRT group and 9% in the reference group, and having at least one severe *rectal* symptom was reported by 8% and 2%, respectively.

SRT-only group

With older age, the risk was higher for the reporting of urinary leakage and sexual activity. With increasing time after radiation, higher RRs were seen for rectal symptoms such as leakage and bother, whereas rectal bleeding became less frequent over time. Increasing time between surgery and radiation led to a low RR of close to 0.9, indicating a positive effect on QoL and incontinence. Also, the size of PTV had an impact on the self-assessed general health and QoL, both of which were reported as worse with a larger PTV.

Non-responders and deceased

In all, 236 men did not respond to the survey: 69 in the SRT group and 167 in the reference group. Severe side effects such as bleeding requiring treatment and deviation surgery were found in four patients in the SRT group but none in the reference group. For the 46 deceased men in the SRT group, it was difficult to address the symptoms related to either the RT or malignancies other than PC. Four men had suffered urinary incontinence that required a surgical procedure (AMS 800), and one had fecal incontinence. Considering all 46 who died in the SRT group, death was due to PC in about half of the subjects, cardiovascular disease in four, and other malignancies in the remaining patients.

More detailed results are presented in Paper I.

Paper II

The analysis in this study covered data on 255 patients in Group 1 and 253 in Group 2. In Group 1, the treatment was delivered as 3DCRT to nearly all patients, although seven (3%) were treated with IMRT. In Group 2, all patients were treated with a VMAT technique.

When assessing the dose-response in rectal bleeding relative to V_{35Gy} and V_{63Gy}, significance was obtained for both parameters ($p = 0.005$ and $p = 0.003$, respectively; see estimated dose-response relationships and 95% CIs in Figure 2 in Paper II). The observed prevalence of rectal bleeding was 22% in Group1, whereas the average calculated risk of rectal bleeding was about 14% in Group 2 according to our estimated dose-response relationship. Also, according to relative average rectal volume, the V_{35Gy} was 17.9% larger (95% CI 15.6–19.7) in Group 1 than in Group 2, and V_{63Gy} was 12.3% larger (95% CI 11.0–13.5) in Group 1.

Our calculated dose-response model also indicated that the average risk of rectal bleeding with V_{35Gy} as parameter was 8% larger in Group 1 than in Group 2, and with V_{63Gy} as parameter it was 9.2% larger in Group 1. In Group 1 and Group 2, the values for average delineated rectal volume were 73.5 ± 26.6 and 72.6 ± 26.2 cm^3, and the average PTV values were 177 ± 53 and 221 ± 67 cm^3, respectively. Increasing PTV in Group 1 and Group 2 by 100 cm^3 increased the rectal V_{35Gy} by on average 4.8% and 3.1%, and the rectal $V_{63Gy\ by}$ 3.1% and 1.2%, respectively.

More detailed results are presented in Paper II.

Paper III

According to the NPCR and PCBaSe, 40,962 men were treated with RP in Sweden from 1 January 1997 to 31 December 2016. After exclusions, 37,848 men with RP were available for matching: 4,902 of those men had also had RT and hence were designated as exposed, and 32,946 did not have RT and were thus denoted non-exposed. The matching procedure resulted in a study cohort with 3494 exposed men and 6988 matched.

Median age at RT or fictive RT was 65 years (IQR 61–69 years), and the radiation dose was ≤ 66 Gy for 610 men (17.5%) and > 66 Gy for 2,884 men (82.5%). Median follow-up time after RT or fictive RT was 4.4 years (IQR 1.7–7.9 years) in the exposed group and 5.1 years (IQR 2.0–8.7 years) in the non-exposed group.

Differences between the exposed and the non-exposed group are presented as *rate ratios* (RR). Compared to the non-exposed group, in the exposed group the risk of any surgical intervention in the urinary tract was 3.66 times higher (95% CI 2.85–4.72), the risk of urinary diversion with or without cystectomy was 4.41 times higher (95% CI 2.25, 9.12), and the risk of endoscopic procedures in the urinary tract was 5.88 times higher (95% CI 4.15, 8.47). In addition, the risk of interventions of any kind in the rectal tract was 1.16 times higher (95% CI 0.86–1.57) in the exposed group, although this difference was not statistically significant.

Also, the risk of bladder cancer was 2.30 times higher (95% CI 1.54–3.45) and the risk of rectal cancer was about the same for the exposed subjects compared to non-exposed. Considering the men who had undergone cystectomy, three out of 20 (15%) in the exposed group had a diagnosis of bladder cancer before the intervention, and the corresponding number in the non-exposed

group was five out of seven (71%). For colostomy and/or rectal resection (amputation), four men out of 22 (18%) in the exposed group had a diagnosis of colorectal cancer before the surgical intervention, compared to 10 out of 34 (29%) in the non-exposed group.

Compared to the non-exposed group, in the exposed group the prostate cancer mortality was higher (RR 5.79, 95% CI 4.24–8.04), the non-prostate cancer mortality was about the same (RR 0.98, 95% CI 0.83–1.15), and the all-cause mortality was 1.5 times higher (RR 1.48 95% CI 1.30–1.70). According to age (at start of RT or fictive RT), non-prostate-associated mortality was not increased in men aged < 70 years (RR 1.04, 95% CI 0.85–1.26) or in men aged ≥ 70 years (RR 0.86, 95% CI 0.64–1.15) in the exposed group compared to the non-exposed group.

M*ore detailed results* are presented in Paper *III*.

Paper IV

The results of this study were based on 29 patients, 13 assigned to Group 1 and 16 to Group 2. Ninety-five CBCTs were performed in Group 1 and 119 in Group 2. Measured bladder volumes (median) per individual were 68–264 ml in Group 1 and 54–287 ml in Group 2, and medians per group were 120 ml (95% CI 93–154) in Group 1 and 123 ml (95% CI 98–155) in Group 2. The intraindividual variation in bladder volume presented as standard deviation was 64 ml in Group 1 and 61 ml in Group 2, suggesting a high level of intra-individual variation in both groups, with no clear difference between the groups.

With increasing volume, the bladder extended cranially; the larger the bladder volume, the greater was the extension, with correlations of 0.82 (95% CI 0.52–0.98) in Group 1 and 0.90 (95% CI 0.84–0.96) in Group 2. There was very little variation in caudal distance within each individual, and there was essentially no correlation with bladder volume 0.08 [95% CI 0.55–0.31] in Group 1 and 0.12 [95% CI 0.43–(-)0.33) in Group 2; see *Figure 12* below.

The results for $V_{95\%bladder}$ were similar in the two groups: medians per patient ranged from 13 to 39 ml in Group 1 and from 11 to 41 ml in Group 2. The difference between the groups regarding 100-ml increase in bladder volume was 0.2 ml (95% CI –0.11, 0.16).

Compliance with bladder filling instructions could be evaluated in 25 of the 29 patients (12 in Group 1 and 13 in Group 2). In Group 1, 5/12 patients (42%) had been able to prepare themselves according to the instructions on about 50% of the RT occasions. In Group 2, with free fluid intake and voiding, the mode of preparation varied, and, surprisingly, four patients (31%) had prepared for treatment in a manner similar to that applied in Group 1.

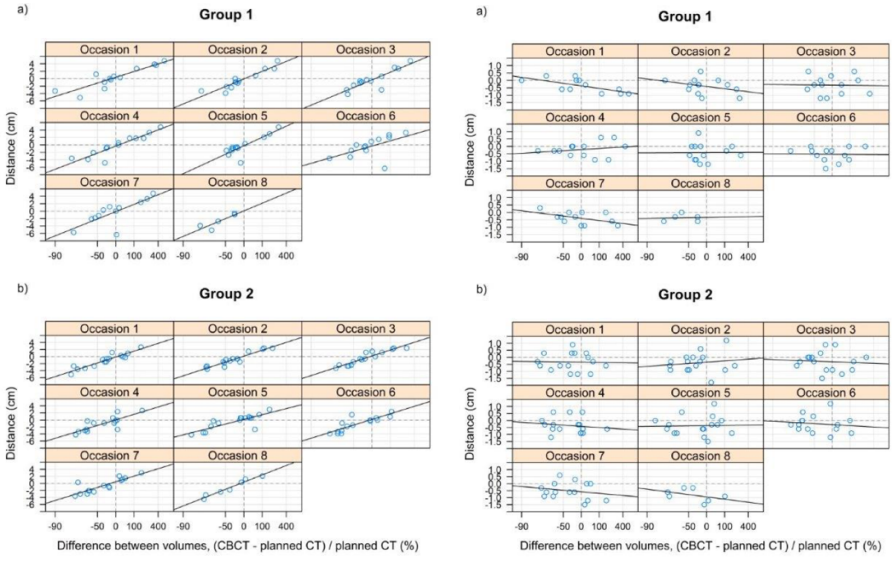


Figure 12. Correlation of bladder volume to measured distance on different treatment occasions in both groups. Cranial distance is shown to the left and caudal distance to the right.

More detailed results are presented in Paper IV.

5 GENERAL DISCUSSION

The present research has been in progress for almost 10 years, and during this time there have been many new findings, observations, and technical developments in the field of radiation that have influenced the concept of PRT after RP in PC patients. The results of a meta-analysis [26] presented at the meeting of the European Society for Medical Oncology (ESMO) held in September 2019 revealed that SRT can be preferable to ART, which is an awaited conclusion, because this can facilitate the difficult decision of when to propose the PRT. So now it is appropriate to focus on SRT and not ART. The diagnostic procedure PSMA-PET has been introduced, which offers the possibility to detect relapse of PC, but unfortunately it is not yet applicable at the low PSA value that supports the decision to perform PRT [45]. Using MRT images as support in establishing a target definition is now standard at our department and elsewhere. Other improvements in the field of RT that have been made during the last 10 years include the launching of advanced treatment methods such as VMAT and the continuing progress in finding better IGRT methods in the RT field. The studies assessing a hypo fractionated treatment regimen to reduce the number of fractions has provided results, and the research in this area continues [100]. Increasing utilization of PROM surveys, even as an online e-PROM, is now a reality for all patients in Sweden receiving curative treatment for PC, and this includes continued evaluation scheduled over time.

Thus, the above-mentioned aim of optimizing PRT is being addressed continuously, particularly with respect to evaluating the side effects. The findings of our PROM study (Paper I) revealed that, compared to the reference (RP only) group, the SRT group reported more side effects in the rectal tract and to some extent also in the urinary tract, whereas no differences were found between the two groups with regard to sexual function or global QoL. Rectal bleeding was the most obvious finding, reported as “any extent” by 22% of the men in the

SRT group but only 3% in the reference group; leakage of stools was reported by 19% in the SRT group and 11% in the reference group. Hence, some of the studied patients did have a problem with stool leakage, but the differences in reporting between the two groups were not as pronounced for this side effect as for rectal bleeding. Similar observations have also been described by other investigators. Alsadius et al. [82] used a PROM questionnaire to study a cohort comprising all categories of PC patients given RT and found that the most frequently reported symptoms from the rectal tract were leakage and defecation urgency. The assessment of side effects can be achieved with self-reported surveys, such as a PROM, or by clinical staff estimating the rates of symptoms in assessment scales [62,101]. We used a PROM questionnaire [66], which we believe illustrates symptoms in a clinically more relevant way compared to, for example, the objective RTOG/EORTC assessment scales [61]. The most relevant strategy for judging the symptoms is probably a combination of the two methods. Furthermore, it is necessary to bear in mind the possibility of other rectal disorders that can cause the bleeding [84] and undertake relevant examinations when such symptoms occur after RT.

Side effects can appear many years after RT, and therefore long-term follow-up is required [102]. The follow-up time in studies is commonly limited to a few years, often a median of up to 5 years, although with some exceptions [23,24]. The median follow-up time in our PROM study was 6.7 years after SRT and 10 years after RP, which are periods of reasonable length. The main observation in Paper I was an approximately six times higher level of rectal bleeding in the SRT group, although we also noted that the rectal bleeding diminished over time, which has been reported by other authors as well [103,104]. Nevertheless, Berlin et al. [105] found that the side effects of RT remained stable for at least 5 years.

In Paper I, urinary symptoms were frequently reported by both the SRT and the reference subjects, and differences between the two groups were most pronounced for the question about “problems in the urinary tract”, for which the relative risk was 1.4 (95% CI 1.2–1.7) for

the SRT group compared to the reference group. Severe symptoms in the urinary tract (i.e., a response of 4 or 5 [the maximum grade]) to at least one of the questions regarding urinary symptoms were reported by 16% in the SRT group and 9% in the reference group. Those levels are not negligible, and to some extent it is surprising that one in 10 of the men treated with RP only had such intense symptoms. The question concerning incontinence, an aspect that is very important to the patient, did not reveal any particular difference between the groups, which agrees with other studies [77,106]. The question about incontinence is also difficult to address if no pre-RT treatment evaluations have been performed [75], because the patients have undergone surgery that often affects the continence. The same objection about a lack of pretreatment symptom evaluation can be raised regarding sexual function. No results in our study indicated that SRT leads to deterioration of sexual function, but, inasmuch as all the investigated men had undergone RP, the evaluation would have to rely solely on the comparison of the two groups[65,76].

Raziee et al. [22] described the side-effects of PRT as tolerable and considered this treatment as underutilized based on the knowledge that side effects do not occur to an extent that would suggest not recommending PRT to the patient. There are fewer reports on severe symptoms after PRT that necessitate surgical interventions, with the exception of studies by Wallis et al. and Showalter et al. [89,90], and therefore we wanted to further investigate the incidence of serious side effects of such treatment in the long-term perspective in our own region/country. As outlined in Paper III, we conducted a register-based nationwide study to compare two matched groups of men, one treated with RP only (designated non-exposed) and the other with RP+RT (designated exposed), over a maximum follow-up period of 15 years after the RT. As our source of information, we used the PCBaSe, which is a highly reliable national database that has given rise to many studies[107-109]. Our analysis showed that the risk of having surgical interventions was increased in the urinary tract but not in the rectal tract in the exposed group as compared to the non-exposed group.

Interventions in the urinary tract were almost six times more frequently performed in the exposed group and was predominantly represented by bladder neck repair and urethrotomy. This observation agrees with the findings of Wallis et al. [90] showing that the complication rate following urinary tract procedures was higher for patients treated with RP+RT than for both those given RT only and those with RP only. We also found that the risk of undergoing interventions in the urinary tract steadily increased during the 15 years of follow-up time. The risk related to undergoing urinary diversion with or without cystectomy was four times more common in the exposed group, and we wanted to determine whether this intervention is related to the increased risk of bladder cancer (discussed further below). We found no such increased relationship between bladder cancer and cystectomy in the exposed group, in which only 15% had a bladder cancer diagnosis prior to cystectomy, whereas the corresponding rate in the non-exposed group was 71%. One conclusion that can be drawn from this finding is that the risk of undergoing urinary diversion after RP+RT is mainly increased by urinary tract complications after RT and not by the development of bladder cancer. Moreover, as described by other researchers as well [94,99], there is an increased risk of bladder cancer after RT, however based on our findings we believe that the bladder cancer mainly is of superficial origin since not necessarily treated with cystectomy, which would have been the fact if it had been muscle invasive.

In our study, there was no clear difference in incidence of rectal procedures between the groups, although there was an increased risk of rectal interventions during the first 10 years in the exposed group, with a peak at 4–7 years according to the Kaplan-Meier graph. These events might have remained undetected, if a follow-up time shorter than 5–7 years had been implemented. As reported by us and other investigators [84], rectal bleeding is a common side effect after RT for PC and is usually described as mild, and therefore the interventions we found probably represented more severe rectal bleeding (grade 3/4 according to RTOG/EORTC) that required local and presumably hemostatic

endoscopic treatment. This deduction is supported by our earlier finding that the rectal bleeding diminishes over time, as indicated by the observation that the incidence of surgical interventions in the rectal tract reached a peak in the RT group and then returned to about the same level as in the non-exposed group. Considering the overall cause of mortality, the higher rate in the exposed group in Paper III might be explained by more advanced PC in these patients. The PC mortality was nearly six times higher in the exposed group, but death due to non-prostate cancer was similar in the two groups and was not affected by age (i.e., being younger or older than 70 years). Bolla et al. [23] have described a relationship with higher overall mortality for men aged > 70 years at the time of RT, which could not be confirmed in our study. However, these two investigations differ in certain aspects, and thus it is necessary to be cautious about drawing conclusions. One disparity compared to our study is that Bolla and colleagues did not clarify to what extent ADT was administered to the patients they evaluated. ADT has severe side effects, such as metabolic syndrome and cardiovascular incidents [28,110], which can potentially influence mortality. In our assessment, censoring from the time of ADT start was possible, and the analysis could be performed both with and without censoring for ADT, but we found no differences in PC deaths between these two possibilities. Accordingly, our study provided no results to support the assumption that PRT has a detrimental effect on health that can lead to shorter survival.

We also investigated differences in development of secondary malignancies between the two groups in our study, and we found a more than twofold increase in the risk of developing bladder cancer in the exposed group. Such an elevated risk after PRT has also been described by other authors [99], although most reports have concerned primary RT and are therefore not directly applicable to PRT. In our study, the risk of bladder cancer in the exposed group increased steadily from 3 years after RT compared to the risk in the non-exposed group. However, the risk of rectal cancer did not differ between the exposed and the non-exposed group, and was actually almost identical

in the two groups after 15 years of follow-up. The development of secondary malignancies is probably influenced by dose-response factors, age, smoking habits, and length of follow-up, and needs to be further investigated, especially considering that younger men diagnosed with PC require treatment [111].

Part of the present research focused on the radiation treatment for PC and the concerns about the risk of side effects of treatment related to preparations, positioning, and matching procedures. Thus, in the second study (Paper II), we analyzed the dose distribution of SRT and the self-reported rectal bleeding of participants in the PROM survey (described in Paper I) who were, in majority, treated with the 3DCRT technique. We continued our evaluation by determining a possible relationship between the dose absorbed in the rectum and the PROM-reported rectal bleeding; a dose-response relationship. To our knowledge, this has not been done previously in the postoperative setting, although many studies have focused on quantifying a relationship between reported rectal bleeding and rectal dose relationships between the objective RTOG/EORTC scales [83,112]. In light of that, and considering the ongoing technical development in the field of RT, we decided to apply our dose-response relationship for the 3DCRT technique to estimate the risk for rectal bleeding for patients treated with VMAT. The observed prevalence of rectal bleeding to any extent was 22% in the 3DCRT group, and use of this estimated dose-response relationship resulted in an estimated risk of 14% in the VMAT group. Thus, theoretically, the VMAT approach has the potential to decrease the prevalence of rectal bleeding. When comparing the treatment implementation there were differences in treatment volumes between the 3DCRT and VMAT methods, since a new delineation guideline was introduced at our department around 2015, which resulted in larger target volumes in subsequent VMAT patients. Still, the rectal volume was essentially the same in the two treatment groups, and the calculated risk reduction remained, even though there were differences in target definition with larger PTV volumes in the VMAT group.

RT-induced rectal toxicity depends on the dose delivered, which in turn depends on the dose distribution technique, as well as the set-up, positioning, and matching accuracy. Inasmuch as the rectum exhibits daily variation in volume and consequently also in location [59,113], different doses per fraction can be absorbed over a long treatment period. Accordingly, the rectal wall mucosa, which is the origin of the bleeding, is exposed to varying doses of radiation. With a modern RT technique, such as IMRT or VMAT, the sparing of the rectal wall, and mucosa, may not be as successful as expected, because that the mucosa is located in such close proximity to the PTV, and the dose constraints for rectum are based on the entire rectal volume. Gomez et al. [114] investigated the difference between contouring the whole rectal volume and the rectal wall in IMRT treatment of primary PC, and they found that the relative volume of the rectal wall that was irradiated was larger than the corresponding whole rectal volume. Consequently, a thorough positioning and matching procedure is recommended to as far as possible avoid rectal toxicity, and this should preferably be accomplished by use of a CBCT that allows alignment to the bladder and rectum [31], the organs that are nearest, part of, the target. Both treatment groups in our study (paper II) were positioned according to bony anatomy by orthogonal kV imaging, which we perceive as an aspect that can be improved. Further research needs to be conducted to bring clarity regarding the significance of positioning in PRT and its correlation with patient reported toxicity. In addition, there is a strong connection between the volume and the location of the rectum and the bladder. A voluminous rectum pushes the bladder ventrally and superiorly and thus primarily affects the upper area of the target, and it can be considered to have some influence on the PTV. The bladder volume and location are of importance in the treatment, both to achieve delivery of the correct dose to the cancer cells and to spare the surrounding tissue. This is one reason for performing bladder preparations meaning bladder filling protocols, an approach that is generally accepted and employed in RT for PC [53]. Also, there are many different filling protocols that stipulate volumes varying from an

empty to a full bladder [54,115]. In our study, Paper IV, we compared two different bladder filling protocols regarding their effect on bladder filling and compliance, and we found that neither of these strategies could fulfill the intention of a constant bladder volume during the treatment sessions. The measurements of volume and bladder extension distance were accomplished through a weekly CBCT from which volumes and measured distances were extracted. Variations in volume were seen in both groups, both within each patient, between patients, and between groups. With increasing volume, the bladder extended cranially, but the caudal position of the bladder seemed fixed, that is, it did not change with variation in bladder volume. Inasmuch as the target always includes the inferior part of the bladder, the fixed inferior part allows one static matching point when the superior part of the bladder undergoes changes in volume and positioning. The positioning and matching in PRT constitute a challenging issue that includes a PTV consisting of the bladder and its environment and the variable rectum in the vicinity. The concept of positioning and matching through CBCT that has been proposed by some authors seems adequate for future use [116].

The objective of trying to maintain a constant bladder volume, preferably full or half full, is assumed to reduce the development of side effects. This includes side effects in the small intestine, which is pushed away from the treatment region, and also the superior part of the bladder, which is not included in the PTV region [117]. Moore et al. [118] conducted a retrospective dosimetry study and observed that 150 ml in bladder volume in primary radiation for PC was a threshold that should be observed to avoid violating the constraint dose to the bladder specified in the dose plan, even though the bladder volume at pCT was larger. Another reflection is that, in women with cervical cancer, it is often recommended that treatment be performed with an empty bladder, and there are reports indicating better reproducibility when maintaining an empty bladder [119]. It is evident that a great deal remains to be investigated regarding the effect of different bladder volumes on the development of side effects in the urinary tract after

PRT for PC. The dose-response relationship is not clear and is often based on primary radiation, and reports on hot spot theories have proposed it is more likely that the dose to the trigone and bladder neck is involved in appearance of side effects [80,81]. Still, these regions will unavoidably always have to be part of the CTV and receive the full treatment dose. Our second aim in paper IV was to evaluate how changes in bladder filling could affect the CTV and its coverage. Since 95% dose coverage is a dose criterium for the PTV and includes the caudal part of the bladder, we examined the correlation between the $V_{95\%bladder}$ and the total bladder volume, to evaluate if the variation in bladder volume could interfere with the localization of the target. We compared the increase in $V_{95\%bladder}$ as the result of the increase in total bladder volume and found no appreciable dependence between those two aspects suggesting a minimal change in CTV coverage. Though, this proposal is only applicable if the EORTC delineation guideline is adopted since it has a smaller bladder volume included in CTV compared to other delineation guidelines.

From a patient perspective, there was somewhat limited compliance with the bladder filling protocol, which presumably reflects the patients' real-life situation. The treatment period was long, and many patients met each other in the waiting room at the facility or on the bus during the ride to the clinic. Therefore, we assumed that the patients influenced each other with respect to how to manage fluid intake and voiding before treatment, and such bias is difficult to control. Fluid intake and voiding according to a special schedule can also influence the patients by creating a feeling that inadequate compliance with the protocol instructions might affect the possibility of being cured. The same apprehension can be a problem at treatment set-up, when the patient is anxious and has problems relaxing on the examination table.

In summary

In the four studies included in the present research, we have obtained information on the extent to which late side effects appear after PRT, both as reported by patients and as revealed by retrospective database evaluations. The finding of a higher incidence of surgical interventions in the urinary tract that increased steadily over time in the PRT group is both serious and convincing. Notwithstanding, it seems doubtful that strategies will emerge that can help us avoid the need for such interventions, because the radiation energy in PRT must be delivered to the inferior part of the bladder and sphincter area, the locations where the injuries originally appear. However, these results should compel us to be very cautious when recommending PRT to patients with a history of postoperative bladder neck strictures. On the other hand, we believe that there are strategies that can potentially diminish the development of side effects in the rectum, e.g., rectal bleeding. For example, the choice of treatment technique can be part of an improvement, and a more appropriately planned positioning and matching procedure would provide even better results.

Postoperative radiation therapy in PC is still a treatment alternative for carefully selected patients based on our regional and national findings. However, each patient should be counseled regarding the scenario of risks that exist in relation to the possibility of cure.

6 CONCLUSIONS

Paper I
There were small differences between the groups when evaluating the PROM responses in a long follow-up time perspective, in median 6.7 years after SRT and 10 years after RP. Still, there was a subset of men in the SRT group that developed more severe side effects, as rectal bleeding, and from this finding arises a challenge to develop a better implementation of the treatment technique.

Paper II
In this study we could identify a dose-response relationship between rectal dose distribution and the risk of self-reported rectal bleeding in a long-term perspective for men treated with 3DCRT. From these calculations we could estimate an average risk of rectal bleeding for a contemporary cohort of patients treated with VMAT as being lower than the risk in the 3DCRT group.

Paper III
Evaluation of severe, treatment demanding, side effects after PRT in prostate cancer, in a 15-year follow-up perspective, revealed small differences between the groups according to surgical interventions in the rectal tract, overall mortality and development of secondary malignancies in the rectum. However, we found a six folded increased risk of interventions in the urinary tract, steadily increasing, and a doubled risk of developing bladder cancer when comparing the groups. Still, in absolute figures the cumulative incidence is low.

Paper IV
We found no differences between the two bladder protocols studied in ability to maintain a constant bladder volume during the treatment period. Furthermore, we could not find that changes in bladder volume interfered with the localization of the CTV.

7 FUTURE PERSPECTIVES

To continue the work on optimization of PRT in prostate cancer new areas of research has appeared, usually at the time of investigating the results of the ongoing studies.
Hence, further research in this, the PRT field, has been planned and started. To be able to better understand the extension and possible delineation of the postoperative fossa a pilot study has been initiated. We hypothesize that the marking of the surgical area during surgery with gold markers, would make it possible to reproduce the current area if/when postoperative radiation therapy is imminent. Seven patients have been included in this trial so far and the procedure is to perform a MRT prior to the surgical procedure, RALP. During surgery 5 gold markers (Gold Anchor®) are positioned at: top of vesicles, mid position of bladder neck and laterally, mid-prostate, towards pelvic wall, in the same laparoscopic way as the surgery is performed. Three months after surgery a new MRT is performed and an evaluation of the prior prostatic fossa is made from the MRT images. The postoperative prostatic fossa or bed, will be evaluated and compared to, both the prior prostate size and site, and to the existing delineation guidelines for PRT. This could lead to better understanding and validation of existing guidelines and possibly propose changes in future delineation techniques. Until now we have evaluated the method according to best placement of fiducial markers, and to what MRT protocol will best fit to analyze the images, addressing this question.

Another ongoing, but temporarily postponed, study is focused on evaluating the variation in rectal volume during the 35 treatment days in PRT. We found large variations in rectal volume in the earlier described, bladder filling study. In short, there were both inter- and intra-individual differences in extension of the rectum in an anteroposterior direction between different days during the treatment period, in some cases as much as 4 cm for the same patient where both the bladder and the rectum were delineated on the weekly CBCT

images. The hypothesis is that these daily changes in volume and extension of rectum may lead to underdosage of the target and overdosage of organs at risk. In this study, a CBCT is performed on each treatment day, and the original dose plan is then transferred to the CBCT image in which the CTV, PTV, and OaR are re-delineated. A new dose distribution analysis can be conducted, and a summary plan for doses actually delivered to participating volumes can be calculated. Consequently, we will be aware of variations in the rectal wall and thereby be able to consider whether, and probably how, positioning and matching should be modified.

To evaluate the side effects we will use the PROM evaluation form that is distributed to all patients before treatment start and then after 3, 12 and 36 months. The results of this PROM survey can then be compared to the earlier PROM-evaluation from the 3DCRT series (paper I).

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