Towards restored physical and psychological health among irradiated prostate-cancer survivors

Avoiding long-lasting symptoms from the bowel and the anal-sphincter region after radiotherapy for prostate cancer

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“Le vrai sage ne s’occupe pas de ce qui est bon ou mauvais dans ce monde. Raisonne toujours dans ce sens: c’est le secret de la vie.” – Ludwig van Beethoven

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ABSTRACT

There are an increasing number of irradiated prostate-cancer survivors in the world today. For many of these men survival comes at a cost: unwanted debilitating side effects due to exposure of healthy normal tissue to ionizing radiation. Identifying clinical and dosimetric factors associated with these long-lasting side effects could provide a way of attaining the ultimate goal – curing prostate cancer with radiotherapy while restoring physical and psychological health for the prostate-cancer survivor.

Following a preparatory qualitative phase, we constructed a study-specific questionnaire. In addition, we conducted a pilot study to evaluate the variation in position and volume of the organs at risk in the small pelvis. We received filled-in questionnaires from 874/985 (89%) prostate-cancer survivors and from 243/332 (73%) population-based controls. We found that prostate-cancer survivors who smoked had an increased risk of long-lasting defecation urgency, diarrhea, the sensation of bowel not completely emptied after defecation and sudden emptying of all stools into clothing without forewarning compared to never smokers. We also found that men with loose stools and abdominal distension at least once a week had a higher prevalence of several long-lasting symptoms, such as defecation urgency, fecal leakage and sudden emptying of all stools into clothing compared to those with regular stools. Prostate-cancer survivors with abdominal distension at least once a week had an increased prevalence of unexpected passing of gas compared to those with regular stools. Finally, our data showed that mean absorbed dose of ionizing radiation to the anal-sphincter region of more than

40 Gy causes an increased occurrence of fecal leakage among irradiated prostate-cancer survivors.

Keywords: Prostate cancer, radiotherapy, late gastrointestinal toxicity

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SAMMANFATTNING PÅ SVENSKA

Prostatacancer är den vanligaste cancerformen bland män i västvärlden. Ungefär femton procent av alla män med prostatacancer genomgår strålbehandling i syfte att bota sjukdomen. Dessvärre löper dessa män en risk att utveckla långvariga biverkningar till följd av att frisk vävnad omkring tumören exponerats för joniserande strålning. Att identifiera kliniska och dosimetriska faktorer av betydelse för uppkomsten av långvariga biverkningar kan vara en väg fram mot det slutgiltiga målet – att männen botas från prostatacancer med återställd fysisk och psykisk hälsa för de överlevande männen.

Vi har skapat en studiespecifik enkät för att mäta förekomst och intensitet av långvariga urinvägs- och tarmsymtom samt sexuell funktion efter strålbehandling mot prostata. Enkäten är baserad på en strukturerad genomgång av tidigare enkäter från enheten samt fyra kompletterande djupintervjuer. I huvudstudien inkluderade vi alla levande män som fått strålbehandling för prostatacancer på Jubileumskliniken, Sahlgrenska Universitetssjukhuset mellan år 1993 och 2006. Vi skickade också ut enkäter till slumpvis utvalda populationsbaserade kontroller som matchats för ålder och kommun. Vi genomförde även en mindre förberedande studie där vi undersökte hur tio riskorgan varierar i läge och volym på datortomografiska serier över lilla bäckenet.

Av de 985 prostatacanceröverlevare som inkluderades i studien svarade 874 (89 %) på enkäten. Av de 332 kontrollerna var det 243 (72 %) som svarade. Vi fann att den S-formade delen av tjocktarmen varierar mest i position medan urinblåsan varierar mest i volym. Vi fann också en ökande lägesvariation i ändtarmens främre vägg kranialt (mot huvudet) i strukturen. Vidare observerade vi att rökande prostatacanceröverlevare har en ökad risk för känslan av ofullständigt tömd tarm, ofta förekommande lös avföring, plötslig ofrivillig total tarmtömning i kläderna och trängningar till avföring jämfört med aldrig rökare. Vi noterade även att prostatacanceröverlevare med ändrad konsistens och sammansättning av tarminnehållet såsom lös avföring (ökad vattenmängd) eller uppblåst tarm (ökad gasmängd) hade en ökad risk för långvariga självskattade symtom orsakade av dysfunktion i tarmen eller analsfinktern, exempelvis avföringsläckage, avföringsträngningar och ofrivillig gasavgång. Slutligen kunde vi visa att en absorberad dos till ändtarmens slutmuskel (analsfinktern) på 40 Gy eller mer ökar risken för långvarigt avföringsläckage efter strålbehandling mot prostatacancer. Kunskapen som utfaller från den här avhandlingen kan om den används bidra

till ökade möjligheter för återställd fysisk och psykisk hälsa efter strålbehandling mot prostata.

LIST OF PAPERS

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

I. Waldenström AC*, **Alsadius D***, Petterson N, Johansson KA, Steineck G, Müller M.

Variation in Position and Volume of Organs at Risk in The Small Pelvis.
Acta Oncol. 2009;49:491

II. **Alsadius D**, Hedelin M, Johansson KA, Petterson N, Wilderäng U, Lundstedt D, Steineck G.

Tobacco Smoking and Long-Lasting Symptoms from The Bowel and The Anal-Sphincter Region.
Radiother Oncol. 2011;101:495

III. **Alsadius D**, Hedelin M, Lundstedt D, Wlideräng U, Steineck G.

Disordered Bowel Habits are Associated with Long-Lasting Functional Symptoms among Irradiated Prostate-Cancer Survivors.

Submitted

IV. **Alsadius D**, Hedelin M, Petterson N, Lundstedt D, Wilderäng U, Steineck G.

Mean Absorbed Dose to The Anal-Sphincter Region and Fecal Leakage Among Irradiated Prostate-Cancer Survivors.

Submitted

** Waldenström and Alsadius contributed equally*

CONTENT

ABBREVIATIONS IV
1 INTRODUCTION 1
2 BACKGROUND 2
2.1 Prostate cancer 2
2.1.1 History 2
2.1.2 Epidemiology 2
2.2 Radiotherapy 3
2.2.1 General history 3
2.2.2 External beam radiotherapy 4
2.2.3 Brachytherapy 5
2.2.4 Normal tissue reactions 5
2.2.5 Organ movement during radiotherapy 6
3 THE BOWEL AND THE ANAL-SPHINCTER REGION 7
3.1 Anatomy [70,71] 7
3.1.1 The small intestine 7
3.1.2 The large intestine 7
3.1.3 The rectum 8
3.1.4 The anal canal 8
3.2 Gastrointestinal physiology [72,73] 9
4 LATE GASTROINTESTINAL TOXICITY 11
4.1 Radiotherapy-induced late toxicity 11
5 AIM 13
6 PATIENTS AND METHODS 14
6.1 Previous questionnaires and in-depth interviews 14
6.2 The questionnaire 14
6.2.1 Contents 14
6.3 Main study 16
6.3.1 Study population 16

6.3.2 Data collection 16
6.4 Reactivating dose-plans and delineation of organs at risk 17
6.4.1 Reactivation procedure 17
6.4.2 Delineation of organs at risk 17
7 RESULTS 20
7.1 Pilot study 20
7.2 Main Study 21
8 DISCUSSION 24
8.1 Validity 24
8.2 Confounding 25
8.3 Misrepresentation 26
8.4 Misclassification 26
8.5 Random error 27
8.6 General Discussion 28
8.6.1 Tobacco smoking and long-lasting gastrointestinal symptoms; consequences of vascular injury? 28
8.6.2 Altered composition and consistency of bowel contents and long-lasting functional symptoms. 30
8.6.3 Mean absorbed dose to the anal-sphincter region and long-lasting fecal leakage 31
9 CONCLUSION 33
10 FUTURE PERSPECTIVES 34
ACKNOWLEDGEMENTS 35
REFERENCES 37
APPENDIX 47

ABBREVIATIONS

BED	Biological Equivalent Dose
CI	Confidence Interval
CT	Computerized Tomography
CTV	Clinical Target Volume
EQDy	Equal Dose in y Gray
Gy	Gray (Joule/ kg)
HDR	High Dose Rate
I	Iodine
Ir	Iridium
ICRU	International Commission on Radiation Units
KeV	Kiloelectron volt
LDR	Low Dose Rate
MLC	Multileaf Collimator
Pa	Palladium
PTV	Planning Target Volume
RTOG	Radiation Therapy Oncology Group
SPCG	Scandinavian Prostate Cancer Group

1 INTRODUCTION

As a resident in oncology, or in any medical speciality for that matter, you sooner or later come across the question: “Why are we doing this?" Such a question gives rise to many different answers ranging from providing scientific evidence to “We’ve always done it this way and it seems to work”. The simple truth is that the vast landscape of medical knowledge is filled with holes and question marks.

It was these holes and question marks that led me to seek an education in science. I believe that the scientific method, as any other human system for procuring knowledge, holds some uncertainty but it has proven to be most useful in describing our sensory reality and to predict consequences of changes to that reality. Or to quote the renowned epidemiologist Dr. Kenneth Rothman: *“All of the fruits of scientific work, in epidemiology or other disciplines, are at best only tentative formulations of a description of nature, even when the work itself is carried out without mistakes. The tentativeness of our knowledge does not prevent practical applications, but it should keep us skeptical and critical, not only of everyone else’s work, but of our own as well. Sometimes etiologic hypotheses enjoy an extremely high, universally or almost universally shared, degree of certainty. The hypothesis that cigarette smoking causes lung cancer is one of the best-known examples. These hypotheses rise above “tentative” acceptance and are the closest we can come to “proof”. But even these hypotheses are not “proved” with the degree of absolute certainty that accompanies the proof of a mathematical theorem.”* The scientific method actually encompasses a wide array of methods that aim to provide as accurate and in a sense true descriptions of natural occurring phenomena as possible. In medicine, these descriptions can be used to diagnose and decide on the proper treatment for an illness or – as in the research presented in this thesis – to predict and prevent the consequences of such treatment.

The taming of ionizing radiation for medical application is vexing. What really occurs and how the energy is transferred to the body remains a mystery. Actually, the whole nature of energy is mysterious. This thesis presents some findings that hopefully may cast a small ray of light on the issues surrounding long-lasting gastrointestinal side effects after radiotherapy for prostate cancer. For me personally, this thesis presents a document from my first journey into the fascinating realm of science.

David Alsadius, Göteborg, Sweden 2012-02-10

2 BACKGROUND

2.1 Prostate cancer

2.1.1 History

In 1817, George Langstaff, a 19th century British surgeon provided the first thorough description of prostate cancer in the medical literature, a work based on the gross appearance at autopsies [1]. Adams reported the first case of prostate cancer established by histological examination in the 1853 January issue of the Lancet and in 1867 Theodore Billroth attempted the first perineal prostatectomy for prostate carcinoma [2]. But it was Johns Hopkins urologist Hugh Hampton Young who made radical prostatectomy an accepted treatment in 1904 [3].

In 1941, Charles Brenton Huggins showed that eliminating circulating androgens by the use of orchidectomy or the administration of estrogens inhibited metastatic prostate cancer and he was awarded the 1966 Nobel Prize in Physiology or Medicine for his discoveries concerning hormonal treatment of prostate cancer [4]. The androgen-regulated glycoprotein called Prostate-Specific Antigen, PSA, which has revolutionized diagnosis and follow-up of prostate cancer was first isolated and defined in the 1970s.

2.1.2 Epidemiology

In 2008 prostate cancer was the most common cancer and the third most common cause of cancer related death among men in the developed world [5]. Ferlay et al. estimated the 2006 incidence of prostate cancer in Europe to be 345 900 new cases per year and in the U.S., Jemal et al. estimated the 2010 incidence to be 217 370 new cases per year [6-7]. In Sweden prostate cancer is the most common cancer among men with an incidence of 10 371 new cases in 2009, representing 35.7 percent of male cancers that year [8]. In 2009, a Swedish man less than 75 years old had a 14.1 % cumulative probability of developing prostate cancer. A man's lifetime risk of prostate cancer has risen from 8 percent in the early 1980s to almost 18 percent today [9]. Suggested reasons for this increase include the introduction of PSA-testing (which is likely to explain most of the increase), an ageing male population, improved diagnostic techniques as well as a true increase in incidence.

In the early 1980s a newly diagnosed prostate cancer presented itself as an incurable disease in almost one out of every two men [10]. Digital rectal examination was the mainstay method for diagnosing a prostate cancer at that time. Soon after the introduction of PSA-testing as a diagnostic tool most of the diagnosed prostate cancers was curable [11]. Men diagnosed with prostate cancer between 1999 and 2003 had a 5-year overall survival of 84 percent [12]. However, the prognosis in men with distant metastases is poor with a median survival of 2.5 years [13].

The etiology of prostate cancer is still subject to scrutiny. Prostate cancer incidence has been shown to vary with age [14], ethnicity [15,16], geographic location [5] and heredity [17]. Prostate cancer incidence is 60 percent higher and mortality rate two-fold increased among black men compared to Caucasian men in the U.S. [15]. Moreover, African Americans are the highest risk-group in the U.S. The underlying cause for this difference might be attributed to social, economic, educational, hereditary and dietary differences [18-22]. In the developed world, age adjusted mortality rate for prostate cancer is among the highest in Sweden (21.4 deaths per 100 000 men in 2008) and among the lowest in Japan (5.0 deaths per 100 000 men in 2008) [5]. Studies on Japanese migrants to the U.S. show that the incidence is higher among migrant Japanese than in Japanese who have not emigrated and approaches that of the U.S.-population at large (9.7 deaths per 100 000 men in 2008) [23,24]. These changes in incidence are probably due to several factors such as changes in environment or diet as well as different diagnostic procedures. A patient with prostate cancer is 3.1 times more likely to report a history of prostate cancer in his father and 4.3 times more likely to report the same in his brother compared to a population-based control [25].

2.2 Radiotherapy

2.2.1 General history

When William Conrad Roentgen discovered X-rays in 1895 this marked the beginning of a new era in medicine. However, it was not until the 1930s that external beam radiation therapy of prostate cancer would attract attention. In 1934 Bertrand Pierre Widmann reported significant palliation in relieving pain and obstructive symptoms using orthovoltage treatments, a technique based on Roentgen's discovery [26]. In Sweden, Hultberg also found that orthovoltage and external beam radiation from a high-intensity radium source provided "palliative help" [27]. However, the introduction of radiotherapy as a curative treatment modality for prostate cancer had to wait until the 1950s and the pioneering works of Malcolm Bagshaw of Stanford University

[28,29]. The history of brachytherapy begins with the discovery of Radium by Marie Curie in 1898. Building on this knowledge Pasteau and Degrais presented in 1914 a method for the treatment of prostate cancer with radium inserted into the prostate through a urethral catheter [30].

2.2.2 External beam radiotherapy

Modern technique has revolutionized the radiotherapy field with developments such as computerized tomography (CT), computerized planning and treatment control, 3-D conformal and intensity modulated radiotherapy and mega-voltage linear accelerators with multi-leaf collimators (MLC). These new methods provide excellent means of attaining the general aim of radical radiotherapy – to deliver as high and homogenous dose as possible to the target without causing unwanted side effects [31]. In order to achieve this, modern radiotherapy requires that the planning target volume (PTV) is properly defined [32]. According to the International Commission on Radiation Units and Measurements (ICRU) the PTV is defined as the clinical target volume (CTV) plus a margin to allow for uncertainties in delineation, variation in target position and volume and in patient set-up. The margin-sizes range from 5 to 20 mm with smaller margins in set-ups using higher target doses and intensity modulated radiotherapy [33-40]. To enable margin reduction, different techniques have been employed in order to minimize prostate mobility such as bladder filling and inflatable rectal balloons [41-44]. In addition, residual gold-markers and on-line portal images are used to verify target localization during treatment.

Pooled Radiation Therapy Oncology Group (RTOG) data have shown that a target dose of more than 66 Gy decreases prostate cancer specific mortality with 29 percent compared to lower doses [45]. The M.D. Anderson randomized dose escalation trial showed that increasing the target dose to 78 Gy resulted in a 66 percent freedom from failure compared to 43 percent freedom from failure for a target dose of 70 Gy in patients with intermediate or high-risk prostate cancer [46]. However, with a median follow-up of 60 months this study showed no difference in overall survival. A before-after study conducted at the Memorial Sloan Kettering Cancer Center showed that dose escalation from 64.8 Gy to 81 Gy resulted in statistically significantly improved survival for men with intermediate or high-risk prostate cancer compared to lower doses [40]. The SPCG-7 study showed that addition of local radiotherapy to endocrine treatment for advanced localized capsule penetrating prostate cancer, stage cT3, increased survival by ten percent ten years after irradiation [47]. More recently several publications have also provided evidence of the benefits from the use of hypofractionation [48-53].

2.2.3 Brachytherapy

There are two major methods for prostate brachytherapy: low dose-rate (LDR) permanent seed implantation using ^{125}I (27 KeV) or ^{103}Pa (25 KeV) and high dose-rate (HDR) temporary brachytherapy using ^{192}Ir sources (412 KeV). The half-life is 60 days for ^{125}I, 17 days for ^{103}Pa and 74 days for ^{192}Ir. The target volume is usually the prostate with a 2-3 mm margin [54]. The prescribed dose is normally 145 Gy for ^{125}I and 125 Gy for ^{103}Pa at the periphery of the target volume [54,55]. The prescribed dose for HDR brachytherapy is usually 10-15 Gy per fraction in two weekly fractions combined with 40-50 Gy external beam radiotherapy [56]. The dose at the target center is always higher than at the periphery, exceeding 100 per cent of prescribed dose. One of the advantages of brachytherapy is the steep dose gradient around the radioactive source, which can help to attain a highly conformal dose distribution to any given target volume provided that the radioactivity of the source is sufficiently high.

2.2.4 Normal tissue reactions

Radiotherapy induced toxicity is usually divided into acute and late toxicity. Acute toxicity arises during or soon after radiotherapy whereas late toxicity can occur from months to several years after radiotherapy [57]. Acute toxicity typically involves rapidly induced changes occurring within hours, such as vascular endothelial cell swelling resulting in increased permeability and edema as well as lymphocyte adhesion and infiltration [58]. Apoptosis is an important feature of acute radiation damage. Thus, the acute response is reflected by the rates of radiation-induced cell death and stem cell regeneration. Late toxicity, however, is primary the result of depletion of tissue-specific stem cells and progenitor cells leading to fibrosis, hypoxia and necrosis.

The linear-quadratic (LQ) model describes cell survival (S) as a function of radiation dose per fraction (d):

$$S = e^{-(\alpha d + \beta d^2)}$$

Where α and β are two constants and the ratio α/β has been shown to provide good representation of tissue-specific radiosensitivity [59]. The α/β ratio is normally expressed for a specific tissue and a specific side effect, e.g., necrosis of the medulla oblongata. A high α/β indicates low sensitivity to dose per fraction and a high proliferation whereas a low α/β indicates the opposite, high fractionation sensitivity and low proliferation [60]. Typically

acute normal tissue responses have an α/β ratio of approximately 6-13 Gy and late response has an α/β ratio of approximately 1-5 Gy [61]. As the model implies, different dose per fraction results in different cell survival and the formulae below are used to estimate and compare the biological effect of different dose per fraction.

$$\mathrm{BED}_{\alpha/\beta} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right)$$

$$\mathrm{EQD}_{\mathrm{y}} = \mathrm{nd}\left(\frac{\alpha/\beta + \mathrm{d}}{\alpha/\beta + \mathrm{y}}\right)$$

BED_x = Biological Effective Dose for $\alpha/\beta=x$; EQD_y = EQual Dose in y Gy fractions (usually y=2); d = dose per fraction; n = number of fractions.

Determining appropriate target dose is a matter of weighing tumor control probability (TCP) against normal tissue complication probability (NTCP) [62]. Several models have been proposed for the estimation of NTCP-curves.

2.2.5 Organ movement during radiotherapy

It has been shown that pelvic organs such as the sigmoid and the rectum change in size and shape and also move during radiotherapy [63-65]. Naturally occurring peristalsis, bowel and rectal filling with air and fecal matter as well as tumor shrinkage and inflammatory edematous swelling cause these alterations in position and volume [66,67]. The rectal volume has been shown to vary between 35 cm^2 and 182 cm^2 during radiotherapy for prostate cancer [68]. Moreover, Fiorino et al. found a systematic anterior shift of the anterior and posterior rectal wall in the cranial half of the rectum [69].

3 THE BOWEL AND THE ANAL-SPHINCTER REGION

3.1 Anatomy [70,71]

3.1.1 The small intestine

The bowel begins with the small intestine, which extends from the pylorus to the *ileocecal junction*, where it joins the large intestine. The duodenum is the first, shortest and widest part of the small intestine. It begins at the pylorus and pursues a C-shaped course around the head of the pancreas. The second part is the jejunum, which begins at the *duodenojejunal junction*. The jejunum continues into the third part of the small intestine, the ileum. Together, the jejunum and ileum are six to seven meters long; the jejunum constitutes about two fifths and the ileum the remainder. The jejunum is primary located in the umbilical region whereas most of the ileum lies in the suprapubic and right inguinal regions. The terminal part of the ileum is usually in the pelvis and from there it ascends to end in the medial aspect of the cecum, where it folds to form the *ileocecal valve*.

3.1.2 The large intestine

The *cecum* is the first part of the large intestine and is continuous with the ascending colon. Usually it lies in the *right iliac fossa* where it is almost entirely enveloped by peritoneum. The *ascending colon* passes superiorly from the cecum on the right side of the abdominal cavity to the liver, where it turns to the left as the *right colic flexure*. It lies retropertoneally along the right side of the posterior abdominal wall, but it is covered by peritoneum anteriorly and on the sides. The *transverse colon* is the largest and most mobile part of the large intestine. It crosses the abdomen from the *right colic flexure* to the *left colic flexure*, where it bends inferiorly to become the *descending colon*. The *left colic flexure* lies inferior to part of the left kidney and is attached to the diaphragm by the *phrenicocolic ligament*. The *descending colon* passes retroperitoneally from the left colic flexure into the left iliac fossa where it continues into the *sigmoid*, which is an S-shaped loop that links to the *rectum*. The *rectosigmoid junction* is about 15 cm from the anus. The sigmoid is usually very mobile due to a long mesentery.

3.1.3 The rectum

The *rectum* is the fixed terminal part of the large intestine. It begins at the *rectosigmoidal junction*, anterior to the level of the S3 vertebra. It follows the curve of the sacrum and coccyx and ends anterioinferior to the coccyx where it turns posterioinferior, becoming the *anal canal*. The dilated terminal part of the rectum is called the *rectal ampulla,* which supports and holds the fecal mass before defecation. The rectum is S-shaped with three sharp flexures that form three concavities with infoldings of the mucosal and submucosal layers called *transverse rectal folds*.

3.1.4 The anal canal

The anal canal begins where the rectal ampulla narrows at the level of the U-shaped sling formed by the *puborectalis muscle*. It ends at the *anus* on the surface of the perineum. It is surrounded by the *external and internal anal sphincters* and is usually collapsed except during passage of feces. *The external anal sphincter* is a voluntary sphincter that forms a broad band on each side of the inferior two-thirds of the anal canal and is mainly supplied by S4 via the *inferior rectal nerve*. *The internal anal sphincter* is an involuntary sphincter that surrounds the superior two-thirds of the anal canal. It forms a thickening of the intestinal circular muscle layer and is innervated by the *pelvic splanchnic nerve*.

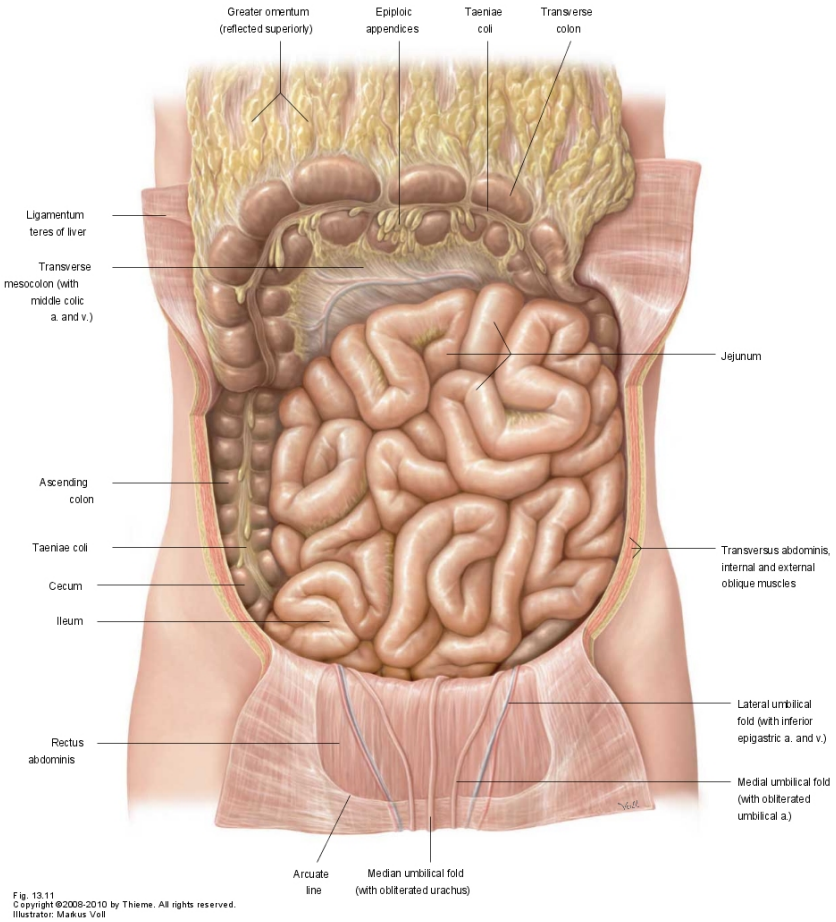

Figure 1. Overview of gastrointestinal anatomy

3.2 Gastrointestinal physiology [72,73]

Although the structure varies from region to region, there are some general features of organization throughout the whole gastrointestinal tract. The *mucosa* consists of an epithelium, *lamina propria*, and the *muscularis mucosae* – the thin innermost layer of intestinal smooth muscle. The *submucosa* consists largely of loose connective tissue and in some regions submucosal glands are present. The larger blood vessels of the intestinal wall travel in the submucosa. A dense network of nerve cells in the submucosa is called the *submucosal plexus (Meisner's* plexus). The *muscularis interna* consists of two layers of smooth muscle – an inner circular layer and an outer longitudinal layer. The *myenteric nerve plexus (Auerbach's plexus)* is located

between the circular and longitudinal muscle layers. The submucosal and myenteric nerve plexuses together with other neurons and plexuses of the gastrointestinal tract constitute the *enteric nervous system*, which plays a key role in the integration of motor and secretory activities of the gastrointestinal system. This system is also responsible for the *gastroileal*, *ileogastric and gastrocolic reflexes*. Elevated secretory and motor functions of the stomach increase the motility of the terminal part of the ilium, the gastroileal reflex. A distension of the ileum, however, decreases gastric motility, the ileogastric reflex. Finally, the motility of the colon and the frequency of mass movement increase after a meal enters the stomach, the gastrocolic reflex.

Digestion and absorption of carbohydrates typically occur in the upper gastrointestinal tract. The duodenum and upper jejunum have the highest capacity to absorb sugars, whereas the capacities of the lower jejunum and proximal ileum are progressively less. Protein digestion and absorption occur in the small intestine with the aid of pancreatic enzymes. The largest part of the net absorption of water, approximately nine liters per day, takes place in the small intestine, especially in the jejunum. With the aid of bile the absorption of dietary lipids is typically complete by midjejunum. Bile acids are absorbed largely in the terminal ileum where it enters the enterohepatic circulation. About 10 to 20 percent of the bile acid pool is excreted in the feces each day.

4 LATE GASTROINTESTINAL TOXICITY

4.1 Radiotherapy-induced late toxicity

Late toxicities typically occur several months or even years after radiotherapy but can occur as late as 20 years after radiotherapy and are often irreversible and long lasting [60,69]. The functional expression depends on which tissue or organ has been affected by the ionizing radiation [74]. The way in which radiotherapy is delivered affects the severity of the specific side effect [74]. However, many side effects also show considerable individual variability even after similar treatment, which likely is due to deterministic, patient-related factors, rather than stochastic factors [57,74,75]. The cause of such variability is not yet fully understood but it has been attributed to both genetic factors and environmental factors such as high blood pressure, diabetes mellitus, hormonal treatment, previous abdominal surgery, pretreatment symptoms and smoking [76-82]. Cellular atrophy, hypoxia, tissue fibrosis and necrosis have been described as underlying pathophysiological mechanisms behind late side effects [83-86]. In normal tissue, ionizing radiation activates the normal wound-healing process via the TGF-β pathway leading to fibroblast activation [74]. However, in contrast to normal wound healing, the radiation induced fibrogenic process is perpetuated over a long period of time.

Increasing target doses have been shown to result in higher incidence of late gastrointestinal toxicity [78,87,88]. Peeters et al. studied 669 patients with localized adenocarcinoma in the prostate that received external beam radiotherapy in a randomized phase III trial. The study showed that raising the dose from 68 Gy to 78 Gy resulted in a higher incidence of late gastrointestinal toxicity but the difference was only statistically significant for the occurrence of late rectal bleeding requiring treatment [78]. They also found that previous abdominal surgery and pretreatment gastrointestinal symptoms were associated with an increased risk of late grade ≥2 gastrointestinal toxicity. From the randomized M.D. Anderson Controlled Clinical (MDACC) trial Storey et al. reported that 5-year rates of grade ≥ 2 gastrointestinal complications were 14 percent among patients treated with 70 Gy external beam radiotherapy to the prostate and 21 percent among men treated with 78 Gy. The difference was not statistically significant [88]. However, at 5-years follow-up 37 percent of the men who received 70 Gy to more than 25 percent of the rectum reported ≥ 2 gastrointestinal

complications compared to 13 percent of those who received 70 Gy to 25 percent of the rectum or less (p=0.05).

The irradiated volume has been discussed as a determinant for the risk of late gastrointestinal toxicity. In 616 patients treated between 1986 and 1994 with doses ranging from 68.3 Gy to 72 Gy with either conventional or conformal technique at Fox Chase Cancer Center, Schultheiss et al. reported central axis dose but not prescribed dose to be the only dose variable statistically significantly related to the occurrence of grade $\geq$ 3 late gastrointestinal toxicity [89]. Among 72 patients treated with three-dimensional conformal radiotherapy none of the 13 men who received 35 Gy or more to maximum 60 percent of the anal-sphincter region developed fecal leakage [90]. The same result applied for the 19 men who received 40 Gy or more to maximum 40 percent of the anal-sphincter region. However 20 percent of the patients who received 35 Gy to more than 60 percent of the anal-sphincter region reported fecal leakage at least twice a week. Similarly, 17 percent of the patients who received 40 Gy or more to more than 40 percent of the anal-sphincter region reported this symptom. Several publications have also described statistically significant associations between irradiated rectal volume and the occurrence of late rectal bleeding [91-94]. Three-dimensional conformal radiotherapy has been shown to reduce the occurrence of late gastrointestinal toxicity compared to conventional radiotherapy [95-97]. However, recent studies indicate that late gastrointestinal toxicity is even lower following intensity-modulated radiotherapy [98-100]. Data also suggest that the pattern of spatial dose distribution to the inner rectal wall is associated with the development of late gastrointestinal toxicity [101]. Evaluation of endorectal balloons as a means for altering the spatial dose-distribution on the inner rectal wall indicates that this could be one way to reduce the occurrence of such toxicity [102,103,104]. Recently published data indicate that fecal incontinence shows a specific dose-effect relationship to individual pelvic floor muscles [105]. Moreover, effect-modifying factors such as tobacco smoking, diabetes, hypertension and GnRH-therapy can increase the risk of late gastrointestinal toxicity after prostate irradiation [82,100,106-107].

5 AIM

The vision of the research program as whole, to which this thesis is but one contribution, is to forward knowledge to attain the ultimate goal of curing prostate cancer with ionizing radiation while restoring physical and psychological health for the prostate-cancer survivor – to cure without harm.

The aim of this thesis is to present advances in knowledge of long-lasting symptoms from the bowel and anal-sphincter region after radiotherapy for prostate cancer. In this thesis I strive to present conceptually clear, ”atomized”, definitions of these long-lasting symptoms in the context of how they were described by the prostate-cancer survivors themselves. More specifically the research on which this thesis is based aimed at investigating the specific presentation, frequency of occurrence, interassociations, and risk factors for the occurrence and development of these long-lasting socially debilitating symptoms.

This thesis also provide a framework (paper I) for assessing insecurity in the delineation of organs at risk, a framework we have used in publications herein and will continue to use in future publications from this particular data set.

6 PATIENTS AND METHODS

6.1 Previous questionnaires and in-depth interviews

In the initial phase of the study our goal was to identify all long-lasting symptoms experienced by irradiated prostate-cancer survivors. We started out by making a structural assessment of previous questionnaires from other projects at our division concerning long-lasting symptoms after pelvic irradiation or prostatectomy. We categorized the questions in these questionnaires according to the long-lasting symptoms they measured. For example all questions on the involuntary passing of fecal matter were categorized as fecal leakage. Eventually we were able to conceptualize clear-cut, "atomized" definitions of the long-lasting symptoms in each category, which we used to construct the questions in a new study-specific questionnaire. To certify that we did not miss any common symptoms we conducted four in-depth interviews with irradiated prostate-cancer survivors. We approached these men by sending them an introductory letter and a few days later we contacted them by telephone to ask if they would be willing to participate. The interviews were semi-structured and conducted at a location chosen by the responder. Each interview started in an open manner and then successively narrowed down. All interviews were audio recorded and transcribed for data analysis. The focus lay on identifying all radiotherapy-induced long-lasting symptoms experienced by the survivors. As a result of the interviews we added the symptom genital pain after orgasm to the questionnaire.

6.2 The questionnaire

6.2.1 Contents

The questionnaire included 165 questions on long-lasting symptoms and quality of life after radiotherapy for prostate cancer as well as question on demographic and possible confounding factors. Of these questions, 34 concerned the frequency and intensity of long-lasting gastrointestinal symptoms (Table 3). The prostate-cancer survivors were asked to assess the occurrence of long-lasting symptoms during the previous six months using a person-prevalence or a person-incidence scale. The questionnaire also

contained questions on 17 different categories of intercurrent diseases, which were assessed by the question “Do you have, or have had any of the following diseases the last year?” Moreover, the men were asked to state if they had ever been admitted to a hospital because of angina pectoris, myocardial infarction or cerebrovascular disease. The responses to these questions were either “Yes” or “No”.

We tested the questionnaire for face validity on 15 men until no further changes were suggested. To test logistics, participation rate and frequency of missing answers we conducted an unpublished pilot study on 30 prostate-cancer survivors. The response rate in this study was 96 per cent, which was considered sufficient to move on to the main study.

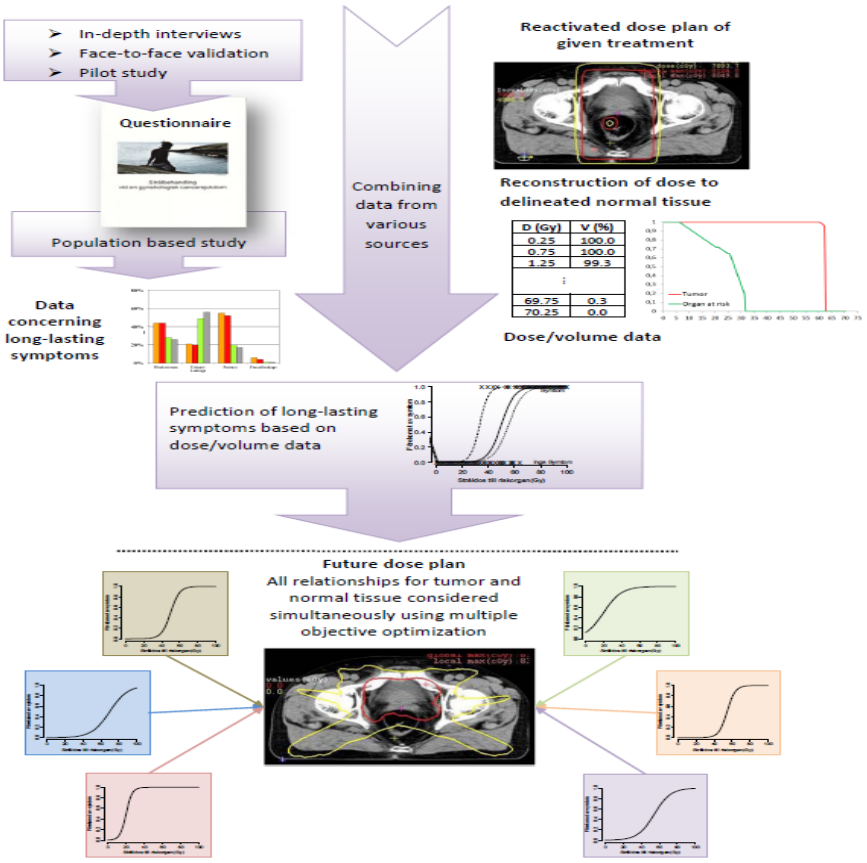

Figure 2. The research process

6.3 Main study

6.3.1 Study population

For the main study we identified 1 007 men, 80 years old or younger, who were consecutively treated with radiotherapy for localized prostate cancer between 1993 and 2006, at the Sahlgrenska University Hospital, Gothenburg, Sweden. We included all men who had not been diagnosed with distant metastasis, had a sufficient knowledge of the Swedish language to read and understand the written questions and were resident in Sweden at the time of follow-up. Furthermore, using the Swedish Total Population Register, we identified 350 population-based controls matched for age and area of residence. The Regional Ethical Review Board in Gothenburg approved of the project.

6.3.2 Data collection

We started the data collection by sending an introductory letter to the eligible prostate-cancer survivors, explaining the study and inviting them to participate. A week later we telephoned them asking for their willingness to participate in the study. To those who agreed we mailed a questionnaire together with a pre-stamped return envelope. Two weeks later we sent out a thank-you postal card that also served as a reminder for those who had not returned the questionnaire. This reminder was followed-up by a telephone call one week later, if necessary. A similar method was used for the population-based controls. This method has been used in several previous studies the Division of Clinical Cancer Epidemiology [108-111]. The questionnaires were sent out between February and June 2008 for the prostate-cancer survivors and between September and November 2008 for the population-based controls.

The data from questionnaires was entered into computerized forms using the Epi-Data software, which was pre-programmed to identify possible false entries (inappropriate values) in order to minimize errors. Furthermore, thirty randomly chosen questionnaires were re-entered to test the reliability of data entering. All statistical analyses were done using STATA and SAS 9.2 for Windows software packages (see manuscript I to III for details of statistical analyses in each study).

6.4 Reactivating dose-plans and delineation of organs at risk

6.4.1 Reactivation procedure

Computerized tomography (CT) based dose-plans from the prostate-cancer survivors' original radiotherapy were stored as computer-based media. Dose-plans were stored in Eclipse™ treatment planning system or CAD-PLAN software (Varian, Palo Alto, CA). All dose plans that we were able to reactivate were entered into the Eclipse™ treatment planning system and matched to bony pelvic structures.

6.4.2 Delineation of organs at risk

We defined nine organs at risk in the small pelvis (Table 1.). The anatomical definitions of these organs at risk were elaborated by two oncologists reaching a consensus and also evaluated by a senior radiologist. A pilot study was undertaken to examine the variation in position and volume of the organs at risk delineated with our definitions (Paper I). In order to minimize systematic errors due to interpersonal variation, the delineation on the reactivated dose-plans was done by only one person and verified by the same oncologist.

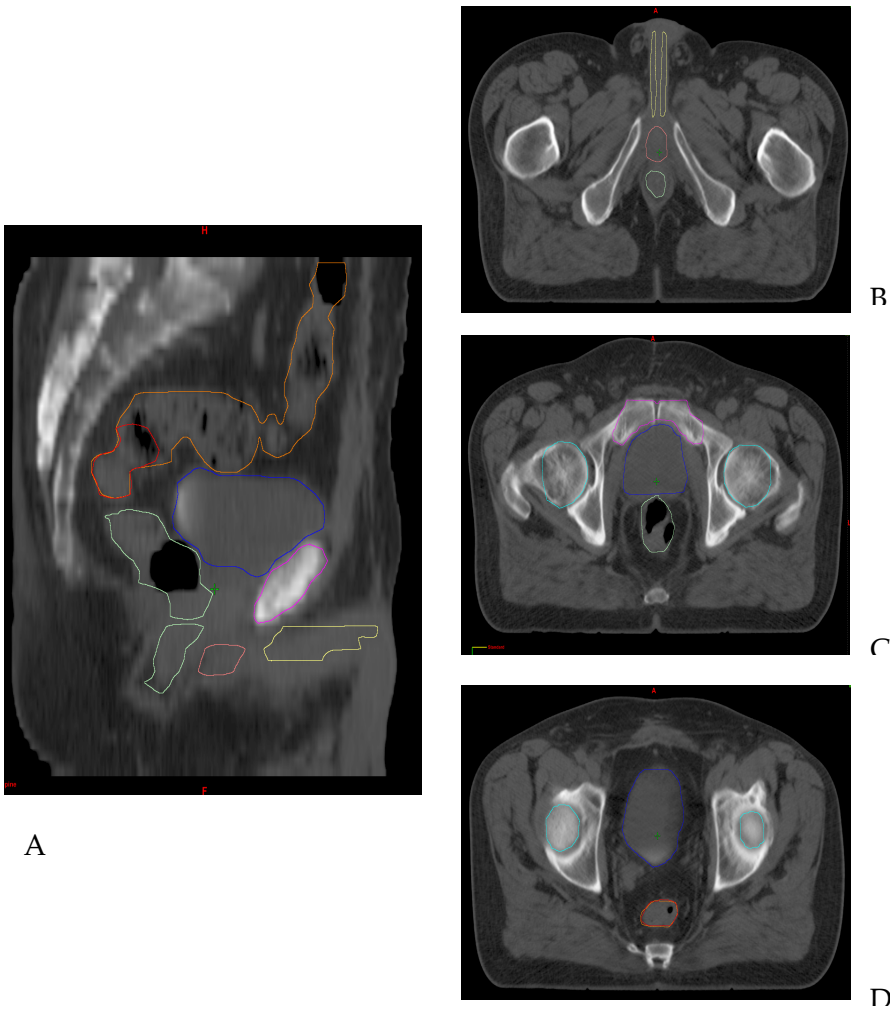

Figure 3. Delineation of organs at risk in the small pelvis

Organ at risk	Delineated structure
Anal-sphincter region	Outer contour of the joint external and internal sphincter muscle. *(Fig 3A and 3B, green)*
Rectum	Outer contour; cranial to the anal-sphincter region, where there is no visible air or content in the bowel and no visible sphincter muscle. *(Fig 3A and 3C, green)*
Sigmoid	Outer contour; starts at the rectosigmoidal junction, where the bowel deviates anteriorly towards the descending colon. *(Fig 3A, orange and Fig 3D, red)*
Distal 4 cm of the sigmoid colon	Outer contour, from the rectosigmoidal junction and 4 cm orally. *(Fig 3A and Fig 3D red)*
Cavernous bodies	Inner caverns. (Fig 3A and Fig 3B, yellow)
Penile bulb	Outer contour. (Fig 3A and Fig 3B, pink)
Urinary bladder	Outer contour. (Fig 3A, Fig 3C and Fig 3D, blue)
Pubic symphysis	Outer contour, to the border of the ramus superior ossis pubis. *(Fig 3A and Fig 3C, purple)*
Femoral head	Outer contour. (Fig 3C and Fig 3D, cyan)

Table 1. Delineation of organs at risk in the small pelvis

7 RESULTS

7.1 Pilot study

Paper I – Variation in position and volume of organs at risk

In the first paper we wanted to establish our delineation of the organs at risk in the small pelvis. We also wanted to examine how large a variation in the position and volume of the organs at risk we could expect. We found that the sigmoid varied considerably in both position and volume. We also found increasing movement in the cranial part of the anterior rectal wall. The bladder showed the largest variation in volume, with the major extension cranially. The cavernous bodies, the penile bulb, the anal sphincter and the rectum as a whole, showed little variation in position and volume.

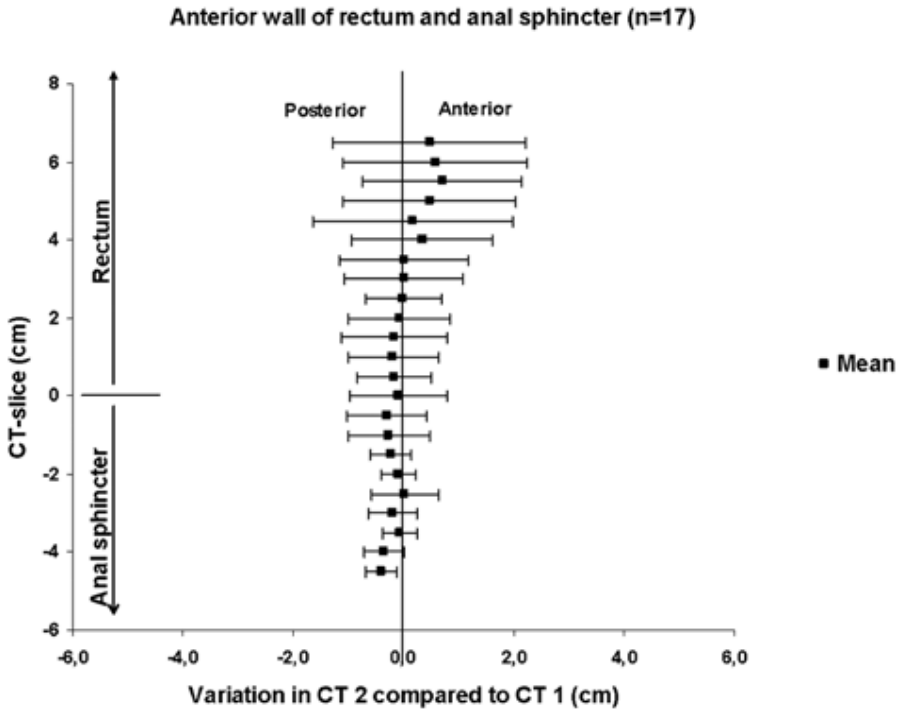

Figure 4. Variation in position of the anterior wall of the rectum and anal-sphincter (cm) between two CT-series in 17 patients, 10 male and 7 female.

7.2 Main Study

Paper II – Tobacco smoking and long-lasting symptoms

The purpose of this study was to find out if tobacco smoking affected the risk of long-lasting symptoms from the bowel and the anal-sphincter among irradiated prostate-cancer survivors. This seemed like a plausible hypothesis, since previous studies have shown that both radiotherapy and tobacco smoking can cause vascular endothelial damage. We found that current smokers had an increased risk of defecation urgency (prevalence ratio 1.6; 95% CI 1.2–2.2), the sensation of the bowel not being completely emptied after defecation (prevalence ratio 2.1; 95% CI 1.3–3.3) and sudden emptying of all stools into clothing (prevalence ratio 4.7; 95% CI 2.3-9.7).

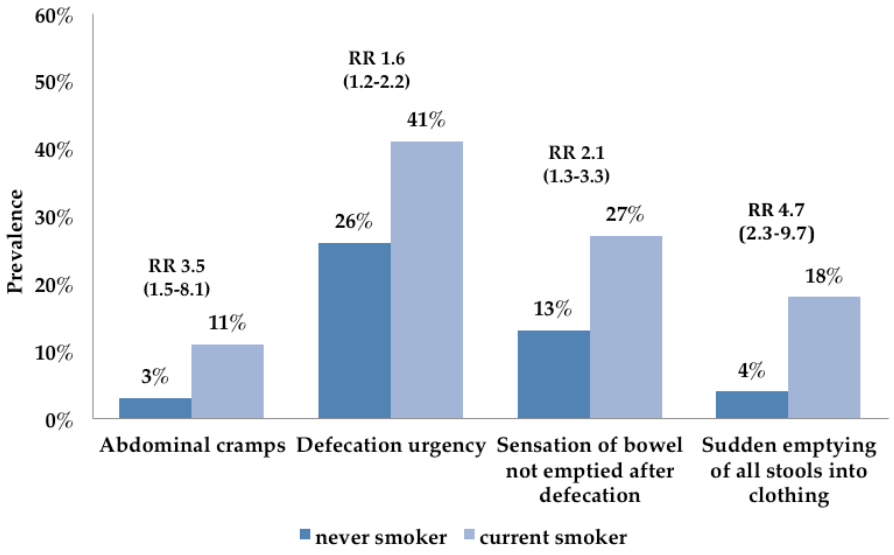

Figure 5. Prevalence of long-lasting symptoms from the bowel and the anal-sphincter region among irradiated prostate-cancer survivors; current smokers compared to never smokers

Paper III – Disordered bowel habits and long-lasting functional symptoms

In this paper we reported the association between altered composition and consistency of bowel content and self-assessed long-lasting functional symptoms due to bowel and anal-sphincter dysfunction. Among men with loose stools we found the highest prevalence ratio of defecation urgency (prevalence ratio 4.1; 95% CI 3.1–5.5), fecal leakage (prevalence ratio 4.9; 95% CI 2.8–8.6) and sudden emptying of all stools into clothing (prevalence ratio 8.1; 95% CI 3.7-17.7) compared to men with regular bowel habits. Among men with abdominal bloating at least once a week 51 percent reported uncontrolled passing of gas compared to nine percent among those with regular stools (prevalence ratio 5.6; 95% CI 3.7–8.6). Men with blood in stools and men with hard stools reported a statistically significantly increased occurrence of sudden emptying of all stools into clothing (prevalence ratio 4.5; 95% CI 1.1-18.4) and the sensation of the bowel not being completely emptied after defecation (prevalence ratio 2.8; 95% CI 1.5–5.3) respectively, compared to men with regular bowel habits.

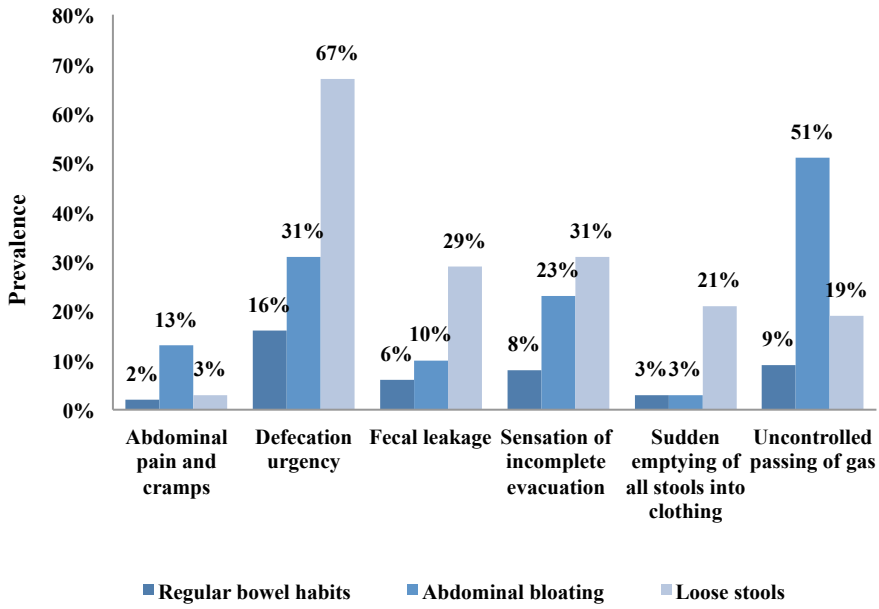

Figure 6. Prevalence of self-assessed long-lasting symptoms due to bowel and anal-sphincter dysfunction among irradiated prostate-cancer survivors with or without disordered bowel habits.

Paper IV – Dose to the anal-sphincter region and fecal leakage

The purpose of this paper is to report the association between mean absorbed dose of ionizing radiation to the anal-sphincter region and the occurrence of fecal leakage. Among men who received 40 Gy or more to the anal-sphincter region, 16.7 percent reported fecal leakage, compared to 4.4 percent of who received less than 40 Gy (prevalence ratio 3.8; 95% CI 1.6–8.6).

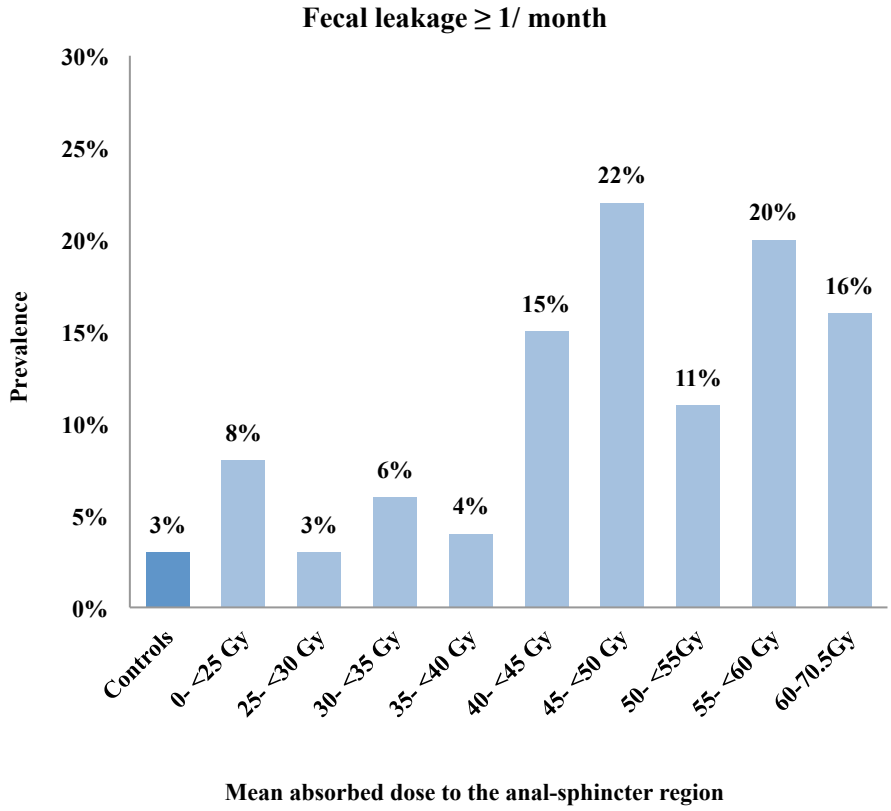

Figure 7. Prevalence of fecal leakage at least once per month in relation to absorbed dose to the anal-sphincter region among prostate-cancer survivors

8 DISCUSSION

8.1 Validity

"The perfect study" is a concept towards which everyone who wants to design a study should strive. However, in real life all studies are flawed by systematic or random errors. The former may introduce bias to a study while the latter is closely related to precision and statistical issues. At our division, we have used epidemiological methods for study design and data interpretation adapted to the cancer survivorship field according to the hierarchical step-model for causation of bias [112]. This model describes how the final, adjusted effect-measure deviates from the "perfect", counterfactual effect-measure (Figure 5). In the model, each new phase of a study introduces a novel and specific source of error. In this chapter we will go through each step of the model and deal with the potential threats to the validity of our study, i.e., confounding, misrepresentation and misclassification.

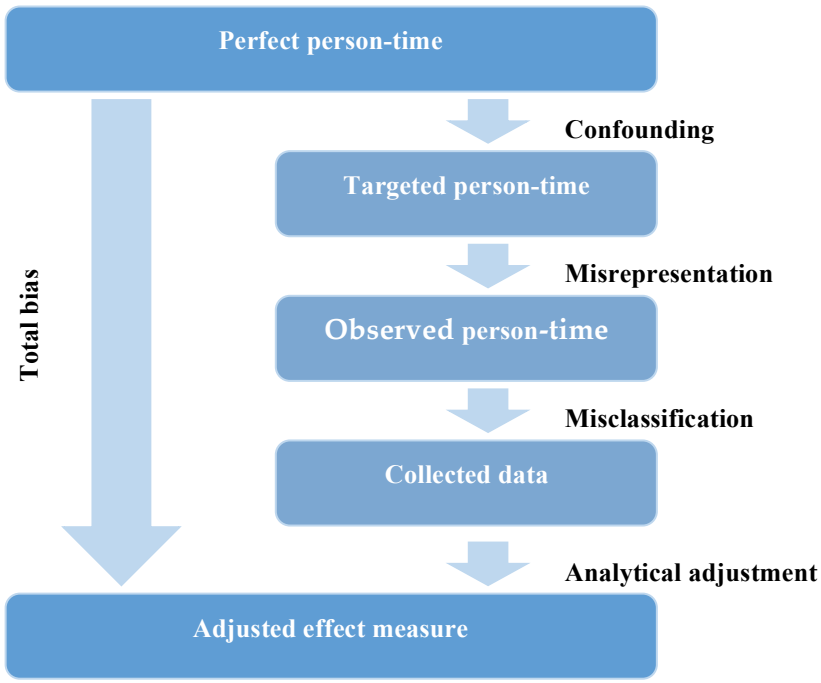

Figure 8. A hierarchical step-model for causation of bias

8.2 Confounding

In 1973 the American philosopher David Kellogg Lewis published his work "Counterfactuals", which contained an analysis of counterfactuals in terms of the theory of possible worlds. A simple illustration of Lewis' theory is to imagine that we could create an exact duplicate of our world by a stroke with a magic wand. We could then introduce an exposure, e.g., pelvic radiotherapy for prostate cancer, in our world but not in the duplicate. The imaginary duplicate would reflect the counter-to-fact situation where all else is equal to our world, *ceteris paribus,* except for the radiotherapy. As a consequence all differences between the two worlds could be attributed to the radiotherapy and a causal relation could be deduced.

In the hierarchical step-model the counterfactual situation is described as the "perfect person-time". For obvious reasons this situation is unattainable, therefore we strive diligently to find an appropriate "targeted person-time" that would support valid conclusions. Shifting from the "perfect person-time" to the "targeted person-time", the first step in the hierarchical step-model, introduces errors known as confounding. In observational studies such errors are unavoidable but may be often be foreseen. Having the means to control confounding is of central importance for an epidemiological study [113]. In our study we reduced the risk confounding by excluding prostate-cancer survivors who had diagnosed distant metastases and by selecting population-based controls matched for age and area of residence, who had not been diagnosed with prostate cancer. We also included several questions on possible confounders such as age, education, occupational status, marital status, intercurrent diseases, and tobacco smoking to be able to control for these factors in the analysis if necessary. In paper II on tobacco smoking and long-lasting symptoms from the bowel and the anal-sphincter region, the overlapping dose-volume histograms for the anal-sphincter region, the rectum and the sigmoid comparing current smokers to never smokers rule out dose-distribution as a confounding factor. Controlling for age, body-mass index, time to follow-up, diabetes, GnRH-therapy and hypertension did not change the prevalence ratios substantially. Certainly regarding papers II-IV, possible confounders that we have not taken into account are conceivable, such as diet, physical activity or alcohol use. In paper III confounding is not a strong issue, since this paper only deals with associations and not with causal relations. For example, if high age were associated with both loose stools and defecation urgency this would not affect the fact that there is an association between the occurrences of these two symptoms.

8.3 Misrepresentation

When shifting from the "targeted person-time" to the "observed person-time", the second step in the hierarchical step-model, systematic errors may be introduced due to non-participation or loss to follow-up. In our study we had a large study-population and a relatively high participation rate (89% for prostate-cancer survivors and 73% for population-based controls), which might reduce the risk of selection-induced systematic errors. However, we cannot exclude that non-participants differ from the participants in crucial aspects. In paper II, if for example current smokers and never smokers were equally likely to dismiss participation due to emotional problems with answering questions about long-lasting gastrointestinal symptoms, this would not affect our results substantially. However, if non-participation due to such reasons were more common among current smokers, this might have shifted the effect measure towards 1.0, i.e., no effect. Misrepresentation would also occur if current smokers with a high prevalence of long-lasting gastrointestinal symptoms were selectively included in the attrition group. We can only speculate about the circumstances among those lost to follow-up and the only way to minimize their impact on validity is to achieve as high a participation rate as possible.

8.4 Misclassification

Incorrect information due to measurement errors can inflict systematic errors when shifting from the "observed person-time" to the "data", the third step in the hierarchical step-model. Measurement errors could concern both the exposure and outcome under study and can be differential or non-differential. Differential misclassification is dependent on and varies with either the exposure or the outcome, whereas non-differential misclassification is independent of these two measures. Therefore, non-differential misclassification is expected to shift the effect measure towards 1.0, i.e., no effect, while differential misclassification will affect the effect measure in different and sometimes unpredictable ways. We placed a lot of effort in trying to diminish the risk of misclassification – repeated interviews with men who have experienced the same treatment as the source population, taking their perspective into account when constructing the questionnaire and testing the questionnaire for face validity, participation rate and response rate to single questions before conducting the main study.

Nevertheless, we cannot avoid the risk of misclassification completely. In our study misclassification can occur due to over- or underestimation when trying to recall symptom occurrence the last six months. However, it is probably

more likely to estimate correctly a symptom occurring more frequently than one that occurs rarely. Therefore we place the cut-of level for most of the questions at experiencing a symptom at least once a week. Moreover, wrongful entering of data into the computer could result in misclassification. For the dose-volume calculations errors in delineation and matching is a source of misclassification.

In paper II misclassification is likely to be non-differential, i.e., it is unlikely that tobacco smokers are more prone to overestimate the occurrence of long-lasting symptoms from the bowel and the anal-sphincter than never-smokers. The results in paper III, however, could be affected by differential misclassification. It could be that men with disordered bowel habits are more likely to overestimate of long-lasting functional symptoms from the bowel and the anal-sphincter region. This would lead a systematic overestimation of the effect measures. However, the prostate-cancer survivors were not asked to report any association between symptoms and there was no specific order in the questionnaire sorting out disordered bowel habits from long-lasting functional symptoms. In paper IV again, non-differential misclassification is likely to be the issue as it is unlikely that men who had received a mean absorbed dose to the anal-sphincter region of 40 Gy or more with would systematically overestimate the occurrence of long-lasting fecal leakage.

8.5 Random error

Random errors are conceived as those errors that remain when systematic errors are eliminated. Such errors are unpredictable and have null expected value, i.e., they are inconsistently scattered around the true value. Statistical significance is used to test whether or not a result is likely to have occurred by random chance. We use prevalence ratios with 95 percent confidence intervals for statistical evaluation of the effect and the precision of the point estimate. In papers II and IV we also use p-values to investigate whether or not noise explains the deviation from unity for the effect measure.

8.6 General Discussion

8.6.1 Tobacco smoking and long-lasting gastrointestinal symptoms; consequences of vascular injury?

In paper II we argue that tobacco smoking increases the risk of long-lasting defecation urgency, diarrhea, sensation of the bowel not being completely emptied after defecation and sudden emptying of all stools into clothing without forewarning. We derived the hypothesis for this paper from the fact that both smoking and ionizing radiation can cause vascular endothelial injuries resulting in intimal thickening and chronic fibrosis (Figure 9) [114-116]. In 1986, Carr et al analyzed microvascular changes in irradiated human bowel. They found a reduction in vascularization affecting all intestinal layers at the site of fully developed radiation strictures [84]. Furthermore, they found occlusive fibrin thrombi together with severe and sometimes total intimal fibrosis in small intramural arterial vessels. In addition they found avascular zones, intramural infarctions and reduced submucosal vascularity in the vicinity of radiation-induced perforations. Building on the findings of radiation-induced atherosclerosis in irradiated dogs [117,118], Pazat et al, showed an increased risk of myocardial infarction among women irradiated for a left sided breast cancer [119]. The authors argued that the underlying pathophysiology consisted of radiation injuries to the coronary arteries. Recently, Russel and co-workers investigated biopsies from irradiated medium-sized arteries and un-irradiated control arteries in 147 patients undergoing reconstructive surgery after head and neck or breast irradiation [83]. They found an increased intimal thickness and intimal-media ratio in irradiated tissue. The association between tobacco smoking and atherosclerosis development is well established [120]. Moreover, data from irradiation of other cancer sites shows that smoking can aggravate late radiotherapy-induced toxicity [76,82,121]. Altogether, our results in paper II and the data from others support the findings that tobacco smoking increases the risk of the specific long-lasting symptoms mentioned above, among irradiated prostate-cancer survivors. Why the risk of these specific symptoms is increased among tobacco smokers remains to be elucidated. One could speculate that hypoxia-induced fibrosis leading to a less compliant, malabsorbing and non-distensible bowel and rectum is particularly important in the pathophysiology of these symptoms.

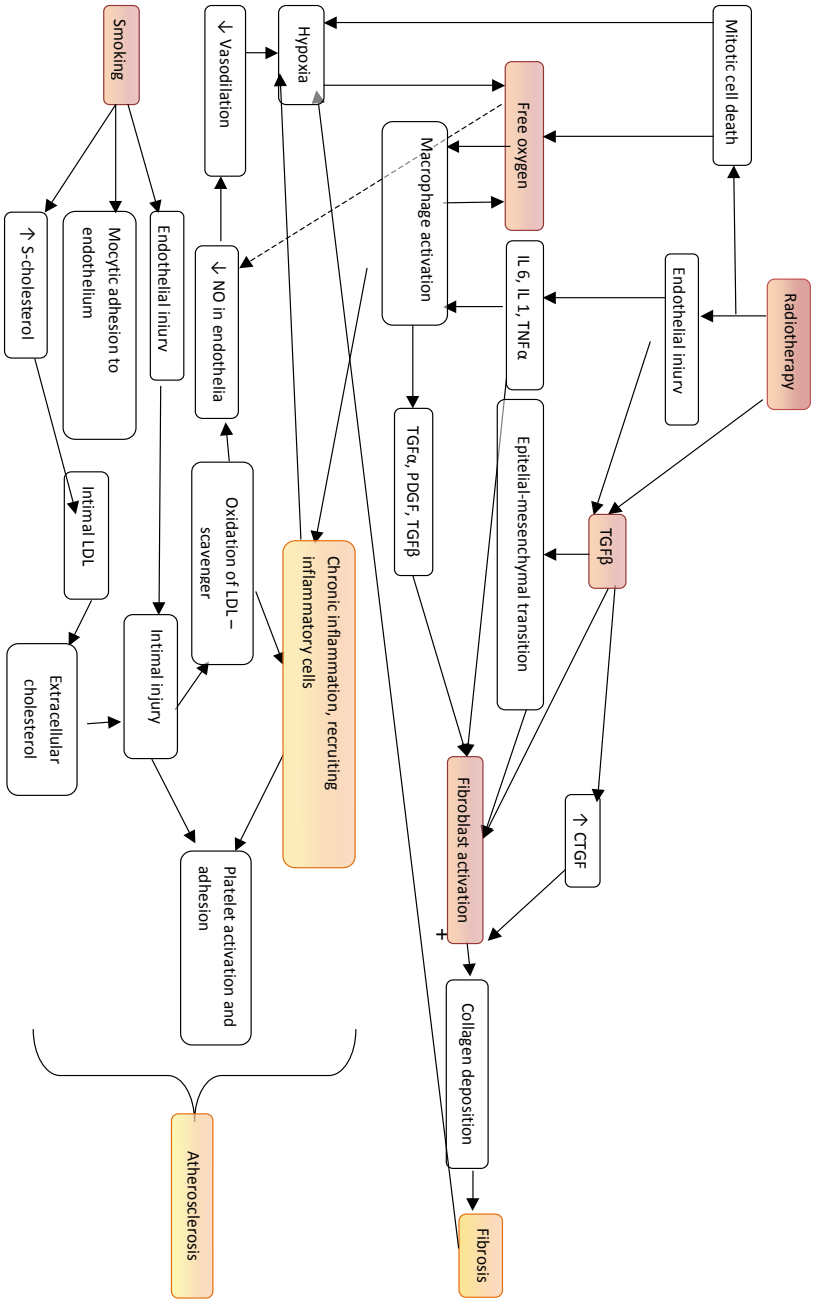

Figure 9. Hypothesized pathophysiological mechanisms for synergistic vasculotoxic effect of ionizing radiotherapy and tobacco smoking.

8.6.2 Altered composition and consistency of bowel contents and long-lasting functional symptoms.

Disordered bowel habits imply altered composition and consistency of bowel contents [122], which for irradiated prostate-cancer survivors could entail abdominal bloating due to excess gas, blood in stools, hard stools, loose stools due to excess water or mucus in stools. In paper III we investigated the hypothesis that altered composition and consistency of bowel content are associated with the increased occurrence of long-lasting self-assessed symptoms due to bowel or anal-sphincter dysfunction. Examples of the latter are fecal leakage and uncontrolled passing of gas (defective anal-sphincter function) or defecation urgency and sensation of incomplete evacuation (hypothetically due to a defective sensory function in the rectum). Studies using bowel diaries suggest that the occurrence of bowel symptoms in a non-irradiated population is influenced by stool form [122]. Several studies on disordered bowel habits among women in Olmsted County, MN, USA, showed that alternating stools and loose or watery stools were associated with fecal incontinence [123,124] and that diarrhea was associated with rectal urgency [125]. In addition, we have shown an increased occurrence of defecation urgency with fecal leakage and sudden emptying of all stools into clothing among irradiated women loose stools after pelvic irradiation [126]. We found that loose stools and abdominal bloating were associated with increased risk of several long-lasting functional symptoms. More than 80 percent of the prostate-cancer survivors with these disordered bowel-habits reported one or more long-lasting functional symptoms. Bacterial overgrowth, bile salt and carbohydrate malabsorption as well as increased intestinal transit are pathophysiological mechanism that has been proposed to contribute to the occurrence of loose stools after pelvic radiotherapy [127]. Although, several studies have reported the occurrence of long-lasting symptoms, this paper is to our knowledge the first attempt to investigate the influence of disordered bowel habits on the occurrence of long-lasting functional symptoms after radiotherapy for prostate cancer. We believe that our results and available data support our findings that certain alterations of the composition and consistency of bowel content are indeed associated with an increased occurrence of self-assessed long-lasting symptoms due to bowel or anal-sphincter dysfunction after prostate irradiation. Our findings do not establish a causal relationship between these two phenomena. It could be that the occurrence of excess water and excess gas in the bowel content implies a more serious radiation injury to the bowel and therefore are associated with a high frequency of self-assessed symptoms of bowel and anal-sphincter dysfunction. However, we suggest that it is plausible to believe that

"normalization" of the composition and consistency of bowel contents could improve the possibility for a dysfunctional bowel or anal-sphincter to function sufficiently in order to avoid, or at least decrease the occurrence of long-lasting symptoms such as fecal leakage after radiotherapy for prostate cancer. Knowledge about these associations could provide a means to establish improved medical and life-style interventions for altered composition and consistency of bowel content to control long-lasting symptoms of bowel and anal-sphincter dysfunction.

8.6.3 Mean absorbed dose to the anal-sphincter region and long-lasting fecal leakage.

The study of dose of ionizing radiation to the small pelvis and late toxicity is complicated by the fact that the organs at risk are not anatomically fixed but distensible and moving. In preparation for future studies we assessed the variation in both position and volume of organs at risk in the small pelvis on 10 men and 7 women irradiated for prostate and gynecological cancers (Paper I). We found the largest variation in documented position for the sigmoid and the bladder. Although, the anal-sphincter region and the rectum as a whole were relatively consistent in position and volume, the anterior rectal and anal wall showed increased mobility in the aboral parts. Similar results regarding the bladder and the anorectal-wall have been reported previously by several different researchers [65-66,68,128]. The findings in paper I imply that the true absorbed dose to the anal-sphincter region after radiotherapy is fairly well represented by dose-volume calculations on the planning CT-scan, given the accuracy of the dose-planning system. Building on these findings we set out to investigate the relation between absorbed dose to the anal-sphincter region and the occurrence of long-lasting fecal leakage. In paper IV we show that prostate-cancer survivors who received a mean absorbed dose of 40 Gy or more to the anal-sphincter region had an increased risk of fecal leakage at least once a month compared to those who received less than 40 Gy and to population-based controls. Our results suggest that in order to avoid fecal incontinence, a mean absorbed dose of 40 Gy could be a proper restriction dose when planning external beam radiotherapy for prostate cancer. These results are supported by the findings of Peeters et al. in the randomized multicenter study CKVO-96-10 [78]. The authors reported an association between mean absorbed dose to the anal wall and fecal incontinence. In the two-year follow-up of the AIROPROS-01-02 study, Fiorino et al. showed that rectal V_{20} to V_{70} and mean dose to the rectum were associated with fecal

incontinence although these result were not statistically significant in the three-year follow-up [106,129]. Recent results from the AIROPROS-01-02 study imply two main patterns for the occurrence of fecal incontinence after radiotherapy for prostate cancer. They argue that the first pattern peak incontinence is the result of acute effects while the second, chronic incontinence mainly results from irradiation of large fractions of the rectum to doses of 40 Gy or more [130]. Al-Abany et al, showed an increased risk of fecal leakage for a mean absorbed dose of 46 Gy or more to the anal-sphincter [131]. However, inconsistent results do exist; Vordemark et al. showed that minimum dose to the anal canal was the only dosimetric parameter statistically significantly related to fecal incontinence after radiotherapy for prostate cancer [132]. Moreover, Guilliford et al. and Fonteyne et al. found that rectal V_{60} and rectal V_{70} respectively were the only parameters statistically significantly associated with fecal incontinence after prostate irradiation [100,133]. One explanation for this inconsistency in results is the apparent differences in the anatomical-radiological definition of the rectum [134]. However, several studies suggest, consistent with our results, that irradiation of the lower part of the rectum or irradiation of the anal sphincter is correlated with the occurrence of fecal leakage [106, 135-136]

Radiotherapy improves survival for men with locally advanced prostate cancer [47]. However, for many prostate-cancer patients avoiding gastrointestinal toxicity might be at least as important as improving survival. When faced with a choice between two treatment options: radiotherapy to 70 Gy or 74 Gy, the latter being associated with a better chance of cure and more toxicity, 75 % choose the lower dose [137]. Improving scientific knowledge concerning dose-volume effects, effect-modifying factors and patterns of co-occurrence for long-lasting gastrointestinal symptoms in irradiated prostate-cancer survivors could be a way to improve the possibility of curing prostate-cancer with radiotherapy while avoiding late gastrointestinal toxicity. What hopefully would result from such knowledge is the implementation of proper restriction doses, efforts to avoid detrimental effect-modifiers and proper post-radiation interventions which together could provide a means of restoring physical and psychological health for irradiated prostate-cancer survivors.

9 CONCLUSION

We hope that the knowledge from this study can provide meaningful contributions to the growing literature on long-lasting side effects among irradiated prostate-cancer survivors. The studies presented in this thesis show that:

The variation in position and volume of the sigmoid, the anterior rectal wall and the bladder are important aspects to be considered when evaluating radiotherapy dose-plans, especially when there is a steep dose gradient across these organs. The large variation in position, which we found for the sigmoid, indicates that we can expect substantial uncertainties when calculating dose-volume effects to this organ as a whole.

Irradiated prostate-cancer survivors who smoke could have an increased risk of long-lasting symptoms. For some survivors, in addition to limiting ionizing radiation to organs-at-risk in the small pelvis, quitting smoking could be an important measure to prevent certain long-lasting symptoms from the bowel and the anal-sphincter region.

Disordered bowel habits are associated with several functional symptoms from the bowel and the anal-sphincter region. Interventions that succeed in permanently changing these disordered bowel habits could potentially reduce the occurrence of abdominal cramps and pain, defecation urgency, the sensation of the bowel not being completely emptied after defecation, the sensation of passing gas but in effect passing feces, sudden emptying of all stools into clothing and uncontrolled passing of gas among cancer-survivors after pelvic irradiation.

A mean absorbed dose of 40 Gy or more to the anal-sphincter region causes an increased risk of fecal leakage after radiotherapy for prostate cancer.

10 FUTURE PERSPECTIVES

“Knowledge advances by steps and not by leaps” a famous quote by the English politician and historian Thomas B Macaulay. The knowledge presented herein could be seen as a small step towards restored physical and psychological health among irradiated prostate-cancer survivors. However, these results raise new questions – how does the timing of smoking cessation affect the occurrence of long-lasting symptoms? What is the best treatment for altered composition and consistency of bowel content? Which is the most correct functional anatomical definition of the anal-sphincter region?

The answers could be provided by future clinical and complex intervention studies. Evaluation of intestinal biopsies from current and never smokers would increase our knowledge of the pathophysiological mechanisms behind the effects of tobacco smoking. Intervention studies can be designed to evaluate the timing of smoking cessation as well as the point in the course of the disease that offers the best possible conditions for a ”teaching moment” to achieve permanent freedom from tobacco. Different smoking cessation programs, which clearly should be offered to all men receiving radiotherapy for prostate cancer, could also be evaluated by proper intervention studies. Similarly, randomized clinical trials can be used to investigate how different treatments of disordered bowel habits affect the occurrence of long-lasting functional symptoms. In addition, the rich material that we have obtained can be used to answer many other questions regarding the occurrence of long-lasting gastrointestinal, sexual and urinary symptoms and their association with absorbed dose of ionizing radiation to the organs at risk among irradiated prostate-cancer survivors.

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APPENDIX

	Population-based controls N=243	Prostate-cancer survivors N=874
Age in years, *mean (SD)*	70.4 (6.0)	71.0 (5.7)
Follow-up in years, mean (SD)	n.a.	5.9 (3.1)
Treatment, *No. (%)*		
EBRT*	n.a.	304 (35)
EBRT-BT†	n.a.	371 (42)
Post-operative EBRT	n.a.	199 (23)
Mean absorbed dose to organ at risk in Gy, *mean (SD)*		
Anal-sphincter region	n.a.	38.2 (10.9)
Rectum	n.a.	40.1 (10.9)
Sigmoid	n.a.	5.1 (6.3)
Maximum absorbed dose to organ at risk in Gy, *mean (SD)*		
Anal-sphincter region	n.a.	61.5 (10.8)
Rectum	n.a.	63.0 (10.4)
Sigmoid	n.a.	33.1 (22.1)
Tobacco smoking, *No. (%)*		
Current smoker	99 (41)	82 (9)
Former smoker	0 (0)	396 (45)
Never smoker	24 (10)	353 (40)
Missing	120 (49)	43 (5)
Education, *No. (%)*		
College/ postgraduate	62 (26)	313 (36)
High school	75 (31)	200 (23)
Primary school	104 (42)	350 (40)
Missing	2 (1)	11 (1)
Body mass index in kg/ m^2, *mean (SD)*	25.9 (3.7)	26.6 (3.3)
Diabetes mellitus, *No. (%)*		
Yes	39 (16)	86 (10)
No	195 (80)	756 (86)
Missing	9 (4)	32 (4)
Salvage GnRH-treatment, *No (%)*		
Yes	n.a.	65 (7)
No	n.a.	792 (91)
Missing	n.a.	17 (2)

* External beam radiotherapy

† Brachytherapy

Table 2. Characteristics of the study-population

	Population-based controls	Prostate-cancer survivors
	N=234	N=874
	No. with symptom/ Total No. (%)	
Abdominal bloating, at least once a week	29/ 237 (12)	150/ 863 (17)
Abdominal cramps, at least once a week	8/ 237 (3)	37/ 867 (4)
Abdominal pain, at least once a week	16/ 237 (7)	74/ 867 (9)
Blood in stools, at least once a week	4/237 (2)	66/ 859 (8)
Constipation, at least once a week	21/ 237 (9)	119/ 860 (14)
Defecation urgency, at least once a week	30/ 238 (13)	254/ 865 (29)
Diarrhea, at least once a week		
Fecal leakage, at least once a month	8/ 239 (3)	100/ 860 (12)
Mucus in stools, at least once a week	1/ 238 (0.5)	78/ 864 (9)
Sensation of incomplete evacuation, at least half of the occasions	20/239 (8)	143/865 (17)
Sensation of passing gas but in effect passed feces, at least once a week	7/ 238 (3)	78/ 864 (9)
Sudden emptying of all stools into clothing, at least once the last six months	6/ 238 (3)	55/ 837 (7)
Uncontrolled passing of gas, at least once a week	32/ 238 (13)	174/863 (20)

Table 3. Prevalence of long-lasting symptoms from the bowel and the anal-sphincter region among population-based controls and prostate-cancer survivors.