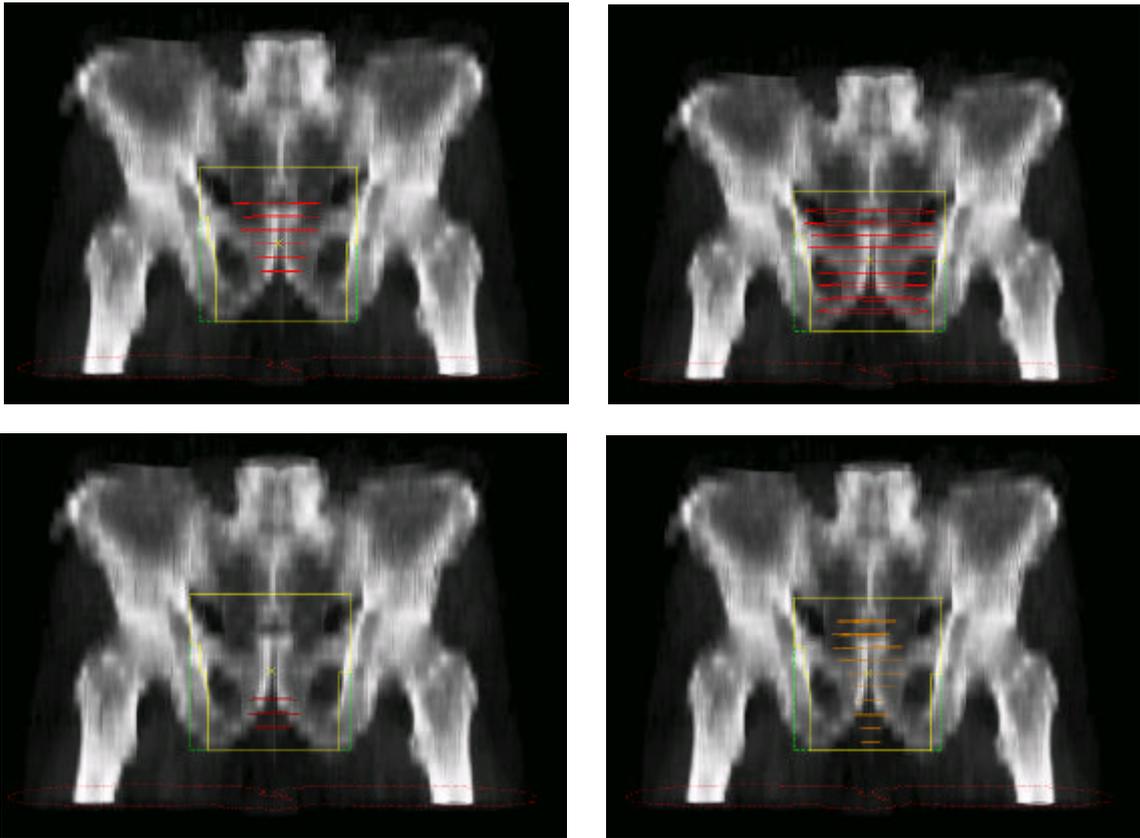


Towards Elimination of Anal-sphincter and Rectal Dysfunction after Radiation Therapy for Prostate Cancer

Massoud al-Abany



Stockholm 2004

From the Clinical Cancer Epidemiology and Medical Radiation Physics,
Department of Oncology-Pathology, Karolinska Institutet,
Radiumhemmet, Karolinska University Hospital, S-171 76 Stockholm, Sweden.

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Cover: AP-PA fields with prostate target volume (GTV) in top left, the planning target volume (PTV) in top right, the anal-sphincter region in bottom left, the rectum in bottom right.

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To

My mother

My wife

My children

Abstract

Background: External radiation therapy is one of the best management options available for localized prostate cancer. The higher the radiation therapy dose administered, the more likely local control will be obtained, but the radiation dose that can be given is limited by the need to restrict the frequency and severity of unwanted effects. Late side effects can permanently decrease well-being and the quality of life. The technology of 3-dimensional treatment planning has opened up a possibility of quantitatively analyze the relationship between radiation long-term effects, dose and the volume of irradiated tissue. Little attention has been paid to assess fecal leakage in relation to the dose given to the anal-sphincter region. **Patients and Methods:** A self-administered questionnaire for assessing symptoms indicating anal sphincter, large-bowel, urinary-tract and sexual dysfunction was sent to all patients with clinically localized prostate adenocarcinoma treated by external beam radiation in 1993-96 in Stockholm. Information on the external beam radiation therapy was retrieved from hospital records. The dose-planning treatment data were restored to the treatment planning system and dose-volume histograms of the anal-sphincter region and rectum were produced. Long-term effects on anal sphincter and large-bowel function were investigated. **Results:** Of all the 158 available patients, 145 (92%) answered and returned the questionnaire. Defecation-urgency was reported by 28% (8/29) of the patients irradiated using 4 fields with a multi-leaf collimator and 20 percent (8/40) of the patients treated using 3 fields (one AP, two lateral) without multi-leaf collimator. Seven out of 29 patients (24%) treated with 4field reported diarrhea or loose stools. None of the patients treated with 3 fields (one AP, two oblique) with a multi-leaf collimator reported this symptom. A statistically significant correlation was obtained between DVHs of the anal-sphincter region and risk of fecal leakage at intermediate dose (45-55 Gy). None of patients who received a dose of 35 Gy or more or 40 Gy or more to, at the most, 60 or 40 percent, respectively, of the anal-sphincter region volume reported fecal leakage. There was a statistically significant correlation between DVHs of the rectum and the risk of defecation-urgency and diarrhea in the dose interval 25-42 Gy. Preserved erectile function at 9-18 months was found in 17 of the 31 men (55%) and at the 4 to 5-year follow-up in five of 22 (23%). **Conclusions:** Among patients irradiated with a multi-leaf collimator, defecation-urgency, diarrhea and loose stools were more common after four fields than after three, but fecal leakage necessitating the use of pads and distress from the gastrointestinal tract were less common. Three fields (one AP and two lateral) without a multi-leaf collimator entailed a higher risk of defecation-urgency than three fields (one AP and two oblique) with a multi-leaf collimator. Among bowel symptoms, the strongest association with gastrointestinal distress was found for fecal leakage. Careful monitoring of unwanted radiation to the anal-sphincter region as well as rectum may reduce the risk of fecal leakage, blood and phlegm in stools, defecation-urgency, and diarrhea; it is probably possible to define a threshold for a by and large harmless dose (in terms of induced dysfunction) to the anal sphincter region (35 Gy or more to, at the most, 60% or 40 Gy or more to, at the most, 40% of the anal sphincter region?).

Key words : fecal leakage, rectal bleeding, defecation urgency, diarrhea, dose, volume, and potency.

List of Papers

This thesis is based on the following papers, which are referred to by their Roman numerals:

- I al-Abany M, Helgason AR, Ågren Cronqvist AK, Svensson C, Steineck G. Long-term symptoms after external beam radiation therapy for prostate cancer with three or four fields. *Acta Oncologica* 2002;41:532-542.
- II al-Abany M, Helgason AR, Ågren Cronqvist AK, Lind B, Mavroidis P, Wersäll P, Lind H, Qvanta E, Steineck G. Dose to the anal-sphincter region and risk of fecal leakage. *Acta Oncol.* 2004;43:117-118.
- III al-Abany M, Helgason AR, Ågren Cronqvist AK, Lind B, Mavroidis P, Wersäll P, Lind H, Qvanta E, Steineck G. Towards a definition of a threshold for harmless doses to the anal-sphincter region and the rectum (Submitted).
- IV al-Abany M, Steineck G, Agren Cronqvist AK, Helgason AR. Improving the preservation of erectile function after external beam radiation therapy for prostate cancer. *Radiother Oncol.* 2000;57:201-6.
- V al-Abany M, Helgason AR, Adolfson J, Steineck G. Reliability in Assessing Urgency and Other Symptoms Indicating Anal sphincter, Large-bowel or Urinary Dysfunction (Submitted).
- VI Steineck G, Bergmark K, Henningsohn L, al-Abany M, Dickman P, Helgason AR. Symptom documentation in cancer survivors as a basis for therapy modifications. *Acta Oncol.* 2002;41:244-252.

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1. The aims of the thesis

- To define organs at risk of practical importance when irradiating the prostate cancer.
- To investigate how dose and radiation techniques influence frequency, intensity, and duration of symptoms from organs at risk.
- To define by and large harmless (in terms of dysfunction) doses to organs at risk when irradiating the prostate gland.
- To investigate the reliability of symptom assessment indicating anal sphincter, large-bowel or urinary dysfunction.

2. Background

External beam radiation therapy is one of the best management options available for localized prostate cancer. The development of an advanced technology of 3-dimensional treatment planning based on computed tomography (CT) or magnetic resonance imaging (MRI) has not only improved local control of the tumor and reduced the amount of normal tissue irradiated but it has also greatly enhanced the possibility of quantitatively analyzing the relationship between radiation long-term effects, dose and the volume of tissue irradiated. Today's documented frequencies of long-term effects after radiotherapy to the small pelvis refer to yesterday's technology. However, we can use historical data to refine today's treatment, follow up patients with radiation sequelae better and define a threshold making future radiation harmless.

2.1 Incidence

Prostate cancer is the most frequently diagnosed male malignancy in the EU and the USA [83]. In the USA the estimated incidence of prostate cancer and the mortality rate in 2003 are 220,900 (170.1 per 100,000) [205] and 28,900, respectively. In Sweden, with a total population of 8.9 million people, 7866 new cases of prostate cancer were diagnosed in 2002 (178 per 100,000), making it the most common cancer among Swedish men. The incidence of prostate cancer increased by 40 percent compared with the incidence in 1992 [111]. The pronounced increase in incidence is probably primarily due to the widespread use of prostate-specific antigen (PSA) testing [83,111]. The strongest risk factor for prostate cancer is age. The incidence of prostate cancer is extremely low for men under 50 years of age; it rises exponentially with advancing age and reaches a maximum after the age of 80. African-American men have a higher risk than white men. Nutritional factors have been hypothesized to be associated with the incidence of prostate cancer [171]. There is a marked difference in the incidence of prostate cancer in various countries. Asian men have much lower incidences of prostate cancer than their Western counterparts. Asian men consume a low-fat, high-fiber diet which is rich in phytoestrogens (isoflavonoids, flavonoids, and lignans); these may account for some of these differences [43,57]. Genetic factors also appear to play a role, particularly for families in which the disease occurs in men under age 60 [24]. The risk for prostate cancer rises with the number of close relatives who have the disease [24].

Many studies have failed to show improvement in mortality or morbidity from PSA-screening for prostate cancer [38,118,140]. The potential harm screening includes anxiety of waiting for results, actions taken after false positive results (unnecessary biopsies, radical

surgery entailing a risk of erectile dysfunction, or urinary incontinence), and detecting and treating early cancer that may never have become clinically significant. The evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA or digital rectal examination (DRE) [135]; although screening can find cancer early, it is uncertain whether the potential benefits justify the potential harms. If early detection through screening improves health outcomes, those who most likely would benefit are: men aged 50-70 at average risk and men older than 45 who are at increased risk (men whose 1st degree relative has had prostate cancer).

2.2 Classification

The TNM classification is the internationally accepted system for staging all forms of newly detected cases of cancer and the TNM-stage is for many tumors the most significant prognostic factor [192]. There are two types of tumor classifications for prostate cancer. The *clinical stage* is based on tests before surgery, such as PSA results and assessment of DRE. The *pathologic stage* is based on the surgery and examination of the removed tissue. The TNM system is used to numerically describe the anatomical extent of cancer and is based on three components: **T**, extent of the primary tumor; **N**, absence or presence of the disease in the regional lymph nodes; **M**, absence or presence of distant metastasis. The numerical staging aids oncologists in planning treatment and evaluating treatment results. The TNM-staging system considers the disease only at diagnosis and has been suggested to use the clinical state from diagnosis to death as a dynamic model of disease progression [168]. The histopathology can be assessed with a *Gleason score*; the system describes a score between 2 and 10, with 2 indicating the least aggressive and 10 the most aggressive tumor [60].

T-Primary tumor		M-Distant Metastasis	
Tx	Primary tumor cannot be assessed	Mx	Distant metastasis cannot be assessed
T0	No evidence of primary tumor	M0	No distant metastasis
T1	Clinically inapparent tumor not palpable or visible by imaging	M1	Distant metastasis
T1a	Tumor incidental histological finding in 5% or less of tissue resected	M1a	Non-regional lymph node(s)
T1b	Tumor incidental histological finding in more than 5% of tissue resected	M1b	Bone(s)
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)	M1c	Other site(s)
T2	Tumor confined within the prostate	N-Regional lymph nodes	
T2a	Tumor involves one lobe	Nx	Regional lymph nodes cannot be assessed
T2b	Tumor involves both lobes	N0	No regional lymph node metastasis
T3	Tumor extends through the prostatic capsule	N1	Regional lymph node metastasis
T3a	Extracapsular extension (unilateral or bilateral)	G-Histopathological grading	
T3b	Bilateral extracapsular extension	Gx	Grade cannot be assessed
T3c	Tumor involves seminal vesicle(s)	G1	Well-differentiated (slight anaplasia) (Gleason 2-4)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	G2	Moderately differentiated (moderate anaplasia) (Gleason 5-6)
		G3-4	Poorly differentiated/undifferentiated (marked anaplasia) (Gleason 7-10)

3. Management Options

Currently used approaches to treat localized prostate cancer are “watchful waiting”, external beam radiation therapy, brachytherapy, and radical prostatectomy. Others, such as High intensity Focused Ultrasound and the Cryotherapy are also used. The choice of strategy is a decisive issue for both physician and patient, each strategy has its pros and cons in terms of expected survival time and the risk of several different long-term distressful symptoms. Surgical patients have higher rates of urinary incontinence and probably also erectile dysfunction than irradiated patients [1,36,144,152,183]. In contrast, anal sphincter and large-bowel dysfunction develops as a consequence of radiation therapy but not radical prostatectomy [9,36,69,144,152,183,208,211]. Hormone therapy may allow a reduction in the radiotherapy target volume of 20–50 percent [52,222]. On comparing patients with T2–T4 primary tumors treated with combined androgen blockade for 2 months before and during radiotherapy to a group treated with radiation alone, the improvements were in both local disease control at 5 years (75% vs. 64%) and freedom from metastasis (71% vs. 61%) [149]. A pooled analyses of single patient series showed that radical prostatectomy, as compared to watchful waiting, halves the risk of dying of prostate cancer among men with moderately or highly differentiated localized prostate cancer [2,81]. In a randomized trial, the findings were almost identical: the absolute difference of prostate cancer-specific mortality risk was 6.6 percent in favor of radical prostatectomy after 8 years of follow-up [81]. The efficacy of irradiating prostate cancer is unclear; no randomized trial has been conducted comparing radiation therapy with prostatectomy or watchful waiting. Unrandomized data evaluating survival indicate that the radiation therapy efficacy is less compared with the other managements [2,119]. In a population-based study, the 10-year prostate cancer-specific survival in patients with clinically localized prostate cancer for patients analyzed as intention-to-treat, was 83, 75, and 82 percent, respectively, after radical prostatectomy, radiotherapy and watchful waiting [119]. It has also been found that differential staging can significantly influence the observed outcomes [119]. The worse outcome after radiotherapy, as compared with radical prostatectomy or watchful waiting, may be explained in some part by bias owing to observation of different parts of a nonconstant hazard curve over time [182]; if the worse outcome is real, a suggested mechanism is that the residual tumor may become more aggressive after radiotherapy due to radiation-induced chromosomal changes. Indirect evidence that such may occur comes from the excess risk of secondary malignant neoplasms after radiation [190]. In an evaluation of second malignant neoplasms in 32,251 women with ovarian cancer, the cumulative risk of a second cancer at 20 years was 18.2 percent, compared with a population-expected risk of 11.5 percent [190].

3.1 Radical Prostatectomy (RP)

Radical prostatectomy is the surgical procedure for localized prostate cancer; in it one removes the entire prostate gland between the urethra and bladder, with resection of both seminal vesicles [6]. Radical prostatectomy has been used to treat prostate cancer since 1903 when it was applied by Young [6]. Radical prostatectomy is indicated in the clinically localized stages (T1-T2), and patients advised to undergo the procedure need to have a life expectancy of at least 10 years at many centers, i.e. the absence of, or moderate, comorbidity. Current surgical techniques, include an open retropubic, an open transperineal approach, and laparoscopic radical prostatectomy [6]. Survival is very good after surgery, cancer-specific survival is about 90 percent at ten years and 82 percent at 15 years [59,153,223]. Long-term side effects may include slight stress urinary “incontinence” (4-50%), severe stress urinary “incontinence” (0-15%), and erectile dysfunction (29-100%) [6]. In a randomized study, the incidence of urinary leakage at least once a week, moderate or severe leakage, bladder emptying problems (weak urinary stream), and erectile dysfunction was 49, 18, 28 and 80 percent, respectively. With nerve-sparing radical prostatectomy, a procedure introduced by Walsh and Donker in 1982 [201], erectile function can be preserved [170]. Risk factors for having a high risk of late side effects such as incontinence and impotency after prostatectomy include old age, the surgical technique, the presence of an anastomotic stricture, the preservation of the neurovascular bundles, the quality of preoperative erection, the pathological stage, the surgeon’s experience, and the number of patients treated at the hospital [13]. Finally, the documented prevalence of late side effects depends on the method used to assess these effects.

3.2 Deferred Treatment (DT) or Watchful and waiting (WW)

“Watchful waiting” is an appropriate course of initial action in patients who will die with their prostate cancer rather than of it [6]. An expected survival, based on age and intercurrent disease (comorbidity), of less than ten years increases the possibility that the man will die before his prostate cancer bothers him. DT avoids treatment-related risks, but it may subject the man to symptoms from an enlarged prostate and its growing tumor, constant anxiety about progression of his cancer, and the possibility of a protracted, painful death [183].

3.3 Radiation Therapy

Radiotherapy can sterilize prostate tumors in patients with the disease confined to the prostate. The higher the radiation therapy dose administered, the more likely local control will be achieved, but the radiation dose that can be given is limited by the need to restrict the frequency and severity of acute and chronic unwanted effects. Late side-effects can permanently decrease well-being and the self-assessed quality of life. Pooled data from 1,465 men treated in Radiation Therapy Oncology Group (RTOG) studies have shown that, for high-grade tumors, a radiation dose of 66 Gy or more decreased the risk of death from prostate cancer to 29 percent compared with men treated with lower doses [193].

3.3.1 Target Volume and Treatment Procedure

The normal prostate gland is quite small and has nearly the same size and shape as a walnut. The normal gland volume is 20-30 cm³. It consists of muscular and glandular tissue [95]. It is located in front of the rectum and between the bladder and urogenital diaphragm. The prostate wraps around the upper part of the urethra at the neck of the urinary bladder. The prostate is divided into five histologically distinct lobes (anterior, posterior, median, and two lateral) and three zones, a central, a peripheral and a transitional zone [62,95]. The peripheral zone, consisting of 70% of the glandular prostate is the site of most carcinomas of the prostate [62].

A computerized treatment planning system based on CT scanning (x-ray computerized tomography) allows a slice-by-slice delineation of the region that is to be irradiated. This allows the radiotherapist to outline the gross tumor volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV), and radiation treatment fields are designed to cover the PTV entirely and deliver a uniform dose distribution to it. Several image fusion algorithms are available for correlating magnetic resonance images (MRI) or ultrasound (US) studies with the CT images, resulting in a more accurate segmentation of the GTV. In two studies, the volumes produced by MRI were smaller than those produced on CT scans by a factor of 1.3 or 1.4 [156,159]. The CT-depicted prostate was 8 mm larger at the base of the seminal vesicles and 6 mm larger at the apex of the prostate than the axial MRI [156]. In the future, the matching of single-photon emission computed tomography (SPECT), positron-emission tomography (PET), and magnetic resonance spectroscopy (MRS) of functional imaging data sets with the CT study may help to identify the individual CTV for each patient [114].

According to the International Commission on Radiation Units and Measurements (ICRU), the PTV is defined as the CTV plus a margin to allow for geometrical uncertainty in its shape and variations in its location relative to the beams due to organ mobility, organ deformation and patient set-up variations [85,86]. Margins around the GTV must be applied to account for microscopic tumor spread and lymph node involvement [85,86]. In the treatment of localized prostate cancer, the CTV is usually equivalent to the GTV and includes the prostate with or without the seminal vesicles. Several studies have investigated the set-up variation and prostate motion uncertainty [4,37,67,164,187]. Some recommend that the margins to be used in radical radiotherapy should be 8.0-12.4 mm, 5.6-7.2 mm and 7.0-13.0 mm in the anterior-posterior (AP), medio-lateral (ML), and cranial-caudal (CC) directions, respectively [4,37,164,187]. These recommendations are based on margins with a magnitude of 2-standard deviations (SD) of the total CTV variability in each direction. When the dose was increased to 79-81 Gy the clinicians used the margin from 5.0 to 10.0 mm around the CTV [65,126,133,219].

Organs at risk (OR) (normal tissues whose radiation sensitivity and location in the vicinity of the CTV may significantly influence treatment planning and/or the prescribed dose) when irradiating the prostate, include the urinary bladder, the urethra, the anal-sphincter region, the rectum, sigmoid colon and small bowel, and the penis bulb as well as the nerves and vessels involved in erectile function.

3.3.2 History of External Beam Radiation Therapy for Prostate Cancer

The external beam radiation therapy of prostate cancer attracted attention in the 1930s when Widmann reported significant palliation in relieving pain and obstructive symptoms using orthovoltage treatments [207], a technique developed after the discovery of X-rays by Roentgen in 1895. In Sweden, Hultberg reported “palliative help” in a retrospective review using orthovoltage and external beam radiation delivered from a high-intensity radium source (radium teletherapy gamma rays) [84]. Definitive external beam radiation therapy of prostate cancer was started in the 1950s using a linear accelerator, ^{60}Co (Cobalt-60) units, and high-energy megavoltage radiation (2 MeV x-ray source) [10,22,41,58].

3.3.3 Conventional External Beam Radiotherapy

The aim of radical radiotherapy is to deliver as high and homogeneous a dose as possible to the tumor target without causing unwanted and unnecessary side effects to the patient [203]. The development of conventional radiotherapy was mainly based on empirical experience and “trial and error,” by which several factors such as the field size, beam angles, the weights of the beam, and dose per fraction varied [181]. In conventional radiotherapy for localized prostate cancer, a variety of techniques, including two opposing anterior-posterior, a box techniques and rotational fields have been used to deliver the radiation to the target volume. Field sizes depend on tumor stage, including whether or not tumor growth has been found in the lymph nodes [11,46]. Conventional treatment techniques currently in use include those based on CT-assisted planning and consist of initial irradiation to the whole pelvis using a 4-field technique, planned to include the prostate, seminal vesicles, and the regional lymph nodes with a dose of 45-50 Gy [46]. Irradiation to the whole pelvis is followed by a boost to increase the dose to the prostate only to 70 Gy or higher [46]. The beams are shaped by a block collimator (conventional collimator) to define the target area resulting in a square or rectangular field. The cross sections of the fields are shaded with customized cerrobend blocks to shield as effectively as possible the posterior wall of the rectum, the anal-canal and anal sphincter, small bowel, and the uninvolved urethra and bladder [11]. High photon energies (>10 MV) have the advantage of reducing the dose load to superficial tissues. Treatment doses are delivered in daily fractions of 1.8-2.0 Gy (five fractions per week). These techniques partly achieve the aim of limiting the radiation doses to healthy tissue in the “line of beam” while still providing a high dose to the tumor [106]. However, normal tissues close to the prostate still receive potentially damaging doses [106].

3.3.4 External Beam Three-Dimensional Conformal Radiotherapy (3-D CRT)

In conventional radiotherapy, the therapeutic dose is often limited by normal tissue tolerance [66]. Three-dimensional conformal radiotherapy has been developed to reduce the dose load to normal tissue by exactly tailoring the dose distribution to match the planning target volume (PTV). To be successful, 3-D conformal radiotherapy requires that PTV is properly defined [155]. The introduction of three-dimensional patient imaging, three-dimensional treatment planning systems, computer-controlled treatment machines equipped with multi-leaf collimators (**Figure 1**), and a continuing increase in computer power and software sophistication has allowed the clinical implementation of conformal treatment planning [54].

CT scanners are important since they can be used to obtain a detailed three-dimensional description of a patient's internal anatomy [54]. The three-dimensional information is used to create elaborate three-dimensional models of the tumor volume and any organs at risk to be protected during irradiation. Conformal radiation therapy employs carefully shaped beams to maximize the destruction of cancer cells while limiting damage to the surrounding tissue. The beam-shaping can be achieved using the backup jaws, cerrobend blocks, or a multi-leaf collimator (MLC) [203,204].

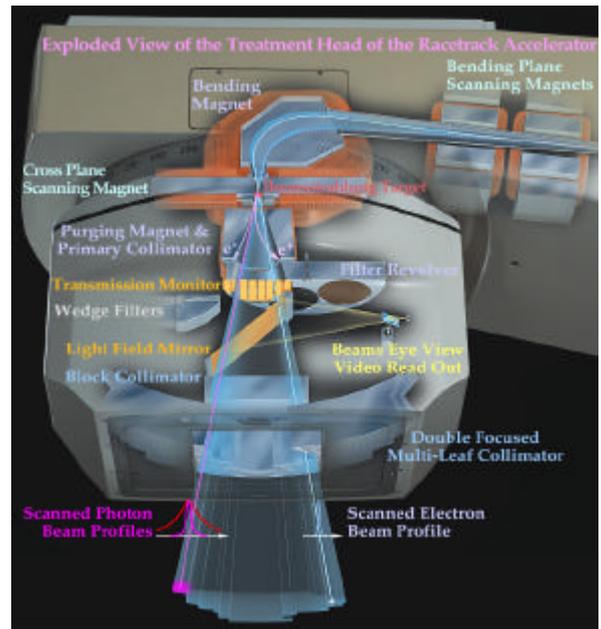


Figure 1. Exploded view of treatment head of the racetrack accelerator.

Multi-leaf collimators were developed to shape the radiation field from the beam's-eye view (BEV). The beam's-eye-view is a computer-generated image that presents a patient's anatomy as it would appear to a viewer located at the radiation source and looking toward the isocenter of the PTV to outline the planning target volume. A multi-leaf collimator consists of a set of parallel focused opposed metal leaves; each leaf can be controlled separately in the forward or reverse direction (**Figure 2**) [204]. Several authors have described various

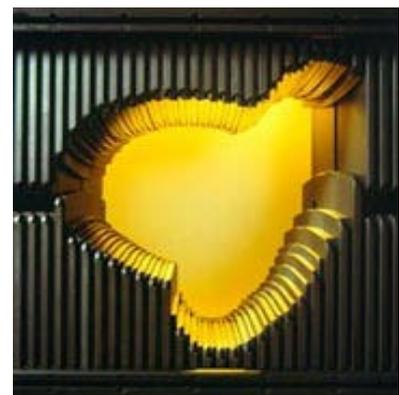


Figure 2. Multi-leaf collimator

technical approaches to 3-dimensional treatment planning and conformal radiotherapy [56,103-108,145,154,155,157,203,204,220]. The exact location of the prostate and seminal vesicles depends on the filling of the surrounding hollow organs such as the urinary bladder or rectum. When the dose to target is increased the importance of keeping organs at risk out of the high-dose region increases. It is possible to achieve prostate immobilization by fixed bladder filling using a catheter, rectal balloons [125,142,186,200] and on-line portal verification (CT taken on a treatment couch, portal imaging). Set-up margins can be reduced by a more accurate set-up, immobilization of the patient (via laser alignment and skin marks, rubber feet banded, alpha cradle immobilization) and improved mechanical stability of the machine [82,86,122]. It is reasonable that reducing the volume of normal tissues receiving high doses is of significant importance in the effort to reduce acute and long-term effects. Randomized clinical trials have demonstrated a clinically significant reduction of late effects

in patients with prostate cancer treated with 3-D conformal radiotherapy as compared with conventional radiotherapy [40]. Randomized trials of escalating radiation dose using 3-D conformal radiotherapy comparing patients with localized disease receiving 70 Gy vs. 78 Gy have resulted in a highly significant improvement in tumor control for patients at intermediate-to-high risk, but in an increase in late rectal and bladder toxicity [150,151]. Other unrandomized clinical studies have suggested that dose escalation in 3-D conformal radiotherapy improves tumor control [65,221]. Improved local control may be obtained by increasing the radiation dose, but at the expense of increased radiation-induced side effects.

3.3.5 Intensity Modulation Radiation Therapy (IMRT)

Intensity-modulated radiotherapy is a new form of three-dimensional conformal radiotherapy. With IMRT the intensity of radiation varies in a controlled way across the beams [101,203]. Theoretically, the impact of radiotherapy would be far greater if it were possible to deliver the radiation so that only the target, regardless of its shape, received a lethal dose. This theoretical benefit provides the principal motivation for

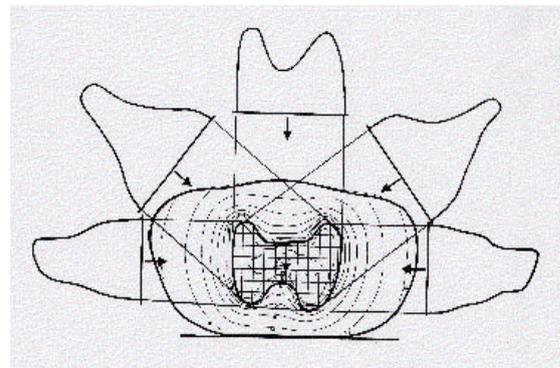


Figure 3. Intensity modulated beam profiles.

intensity-modulated radiotherapy, i.e. that the delivery of a high radiation dose should be confined to a spatial distribution that conforms as tightly as possible to the spatial distribution of cancer cells, thereby reducing the radiation dose to the radiosensitive normal tissues close to the tumor even if they lie within a concavity surrounded by the planning target volume [21,203]. For a first approximation, the intensity is roughly proportional to the target thickness along the beam as assessed from the beam's-eye view. Where the target has the largest diameter, the beam intensity has the largest value and where the target has the shortest diameter, the intensity has the smallest value (**Figure 3**). Intensity-modulated radiotherapy offers an opportunity to escalate tumor doses while restricting the dose to adjacent organs at risk below a tolerance threshold. The intensity distribution can be delivered to the patient by a variety of methods, using compensators, tomotherapy or a multi-leaf collimator (“step and shoot” or dynamic sliding window technique) [120,121,127,203]. Two recent advances that make the clinical implementation of intensity-modulated radiotherapy a reality are the development of inverse treatment planning algorithms [20,21,29,110,113,139,169,180] and the dynamic multi-leaf collimator. In the processes of inverse treatment planning, doses to the target volumes and organ at risk are specified by applying dose-volume constraints. Various

optimization algorithms have been developed to calculate the optimal intensity modulated photon beam profiles that generate the described dose distributions. To clinically deliver an intensity-modulated beam, a dynamic multi-leaf collimator is used to sweep opposing pairs of tungsten-leaves across the field. Modulation is achieved by varying the size of the gap between the leaves as well as the length of time the gap remains open at each location in the beam. Intensity-modulated radiotherapy could be used for the whole duration of radiotherapy or as a boost. The incidence of long-term effects after 3-D conformal radiotherapy has been shown to be dose-dependent [94,151,217]. However, intensity-modulated radiation therapy with doses up to 81 Gy significantly decreased the incidence of late long-term rectal bleeding compared with 3-D conformal radiotherapy but did not affect the incidence of long-term urinary symptoms [217,218].

3.3.6 Brachytherapy

The history of interstitial brachytherapy began in 1917 with the use of inserted radium needles [80]. In 1914, Pasteau and Degrais presented a method for the treatment of prostate cancer with radium inserted into the prostate through a urethral catheter [141]. Radium was discovered by Marie Curie in 1898 two years after radioactivity was discovered by Becquerel in 1896. Some recommend brachytherapy for patients with T1 or T2 tumors and a Gleason score of 6 or lower, PSA below 10 ng/ml, and a tumor volume below 50 cm³ [5,47]. The target volume, the volume to be implanted, includes the whole prostate within the capsule plus a 2-3-mm margin [47]. Transverse images of the prostate are taken every 5 mm from base to apex. The images are transferred into a treatment planning system based on CT scanning or transrectal ultrasound (TRUS) for dose calculations and to determine the number and position of seeds required to deliver the prescribed minimal peripheral dose to the margins [47]. There are two major methods of prostate brachytherapy, permanent seed implantation (low dose rate, LDR) using iodine-125 (27 KeV) or palladium-103 (25 KeV) and high-dose rate (HDR) temporary brachytherapy using iridium-192 (412 KeV). The half-life of iodine-125, palladium-103, and iridium-192 is 60, 17, and 74 days, respectively. The dose prescribed is 145 Gy for iodine-125 and 125 Gy for palladium-103 at the periphery of the target volume [5,47]. The dose at center is always higher and should be kept at below or equal to 150 percent of the prescribed dose. The prescribed dose for temporal brachytherapy is usually 10-15 Gy/2 fractions added to 40-50 Gy using external beam radiation therapy [93]. The risk of urinary incontinence is higher for patients having undergone transurethral resection of the prostate (TURP) than for patients not having done so [5,53]. One of the advantages of brachytherapy is the steep dose-gradient around the radioactive sources. In

principle, it can generate a highly conformal dose distribution to any given target volume, provided that the radioactivity is sufficiently high. Some believe [197] that complications associated with high dose-rate brachytherapy are similar to those of a combined low-dose-rate permanent implant with external beam radiation therapy.

3.3.7 Radiotherapy for Prostate Cancer in Stockholm

In the beginning of the 1990s, dose-planning was guided by CT scanning using a TMS 3-dimensional (3-D) treatment planning system (TMS, MDS Nordion) at Radiumhemmet (*Karolinska University Hospital*) and a Theraplan 3-D treatment planning system at Stockholm Söder Hospital (*Karolinska University Hospital*). A multi-leaf collimator was introduced at Radiumhemmet in 1994 and later at Stockholm Söder Hospital. A symmetric block collimator (conventional collimator) to define the target area, resulting in a square or rectangular fields, was used otherwise. The dose was delivered using a four-field box technique (two opposing anteroposterior [AP-PA] fields and two opposing lateral fields at 90° and 270°) that has been used since 1995 instead of the three-field technique (one anteroposterior [AP] field and two oblique posterior fields at 115° and 245°) at Radiumhemmet. On the other hand, the dose has been delivered using a three-field technique (one AP field and two opposing lateral fields at 90° and 270°) at Stockholm Söder Hospital.

The prescribed dose was escalated from 63-64 Gy to 68-70.2 Gy in 1994 at both Radiumhemmet and Stockholm Söder Hospital. The treatment dose has been given as 16-21 MV photons in daily fractions of 1.8 Gy, 5 fractions per week at Radiumhemmet and with 18 MV photons of 2 Gy, 5 fractions per week at Stockholm Söder Hospital. The number of sessions, which is dependent on the prescribed dose and dose per fraction, ranged from 32 to 39.

CT scans were made to outline CTV delineation and to contour the critical structures. Patients were scanned in the treatment position (supine), with a slice thickness of 0.5-1.0 cm at 0.5-1.0-cm intervals through the region of the prostate and seminal vesicles, and with a slice thickness of 1.0 cm at 1.0-cm intervals above and below this region.

The GTV was the entire prostate gland and, in most patients, the seminal vesicles as visualized on the planning CT scan. The CTV was not distinguished from the GTV. The PTV was equal to the GTV plus a 1.5-2.0-cm margin around it, with the exception of at the apex, where the margin was 2.0-2.5 cm to allow for positioning errors and mobility and uncertainty

about the localization of the apex. To ensure the accuracy of the set-up, portal films were taken. Patients were treated in the supine position and advised to empty the urinary bladder before treatment at Radiumhemmet or to have a full bladder at Stockholm Söder Hospital (the rationale being to reduce the dose to the bladder and small intestine). At Stockholm Söder Hospital, the treatment technique involved the placing of Foley catheters and contrast in the bladder and rectum during the CT scanning procedure.

Since the end of 1996, patients have been treated in both Hospitals with a combination of external beam radiation with a dose of 50 Gy using a multi-leaf collimator and 20 Gy by brachytherapy in two fractions (10 Gy per fraction) using a high dose-rate technique. The PTV has been equal to the GTV plus a 1.5-2.0 cm margin around it, with the exception of at the apex, where the margin was 2.0 cm. The posterior margin in external beam radiation therapy was reduced to 0.8-1.5 cm to minimize the dose to the rectum. The PTV in brachytherapy is the prostate plus a 3.0-mm margin around it.

4. Anal Sphincter and Large-Bowel Function

Physiology of defecation: Mass peristaltic movements push fecal materials from the sigmoid colon into the rectum. The resulting distension of the rectal wall stimulates stretch receptors, which initiates a defecation reflex that empties the rectum. The defecation reflex occurs as follows: in response to distension of the rectal wall, the receptors send sensory nerve impulses to the sacral spinal cord. Motor impulses from the cord travel along parasympathetic nerves back to the descending colon, sigmoid colon, rectum, and anus. Contraction of the longitudinal rectal muscles shortens the rectum, thereby increasing the pressure inside it. This pressure, along with voluntary contractions of the diaphragm and abdominal muscles, and parasympathetic stimulation, opens the internal sphincter, and the feces are expelled through the anus. The external sphincter is voluntarily controlled. If it is voluntarily relaxed, defecations can be postponed. Voluntary contractions of the diaphragm and abdominal muscles aid defecation by increasing the pressure inside the abdomen, which pushes the wall of the sigmoid colon and rectum inward [188].

In external beam radiation therapy of prostate cancer, a large portion of the cecum, ileum, sigmoid colon, rectum, and anal sphincter is involved in the treatment. The acute effects are due to the death of large numbers of cells and occur in tissues with a rapid cell turnover rate, whereas late reactions occur in tissues with slow cellular regeneration. In such tissues, the radiation produces little change in the function of mature, differentiated cells and therefore

produces no evidence of tissue malfunction until these mature cells are gradually lost by normal wear and tear or by additional trauma. When the tissue attempts to replace lost cells by cell division, the radiation damage inflicted months or years earlier is manifested as the cells are unable to produce viable cell-daughters [143]. After radiation therapy, the intestine with long-term radiation damage has been described as showing fibrosis, ischemia (vascular insufficiency), stenosis, ulceration, fistulas, telangiectasis, strictures, and fibroblasts [7,30,90,191]. The clinical signs and symptoms of the long-term effect of radiation therapy of prostate cancer include urgency, diarrhea, tenesmus, excessive flatulence, soiling, anal sphincter dysfunction (fecal leakage), constipation, mucus in stools, blood in stools or bleeding with ulceration [30,31,90,146,148,208,212]. Patients with chronic small-bowel damage can show an increase in the intraluminal bile salt contents owing to a combination of malabsorption and bacterial overgrowth [136]. It has been suggested that diarrhea without tenesmus, blood, or mucus discharge may be a manifestation of injury at the more proximal segments of the bowel [146,148]. A history of diabetes mellitus, hypertension, and adjuvant hormonal therapy may be associated with an increased risk of long-term intestinal damage after radiotherapy [33,79,173]. Physiological studies using anal manometry in patients with long-term fecal leakage after pelvis radiation therapy showed a reduced maximum resting pressure, an abnormality rectoanal reflex and a decrease in the functional sphincter [17,91,96,195,196,198,210,211,213]. Chronic radiation injury of the lumbosacral nerve plexus has been reported after external beam radiation therapy with subsequent fecal leakage [87]. The mechanism of anal sphincter dysfunction after pelvic irradiation is unclear. It has been suggested that anal sphincter dysfunction was likely to be myogenic or neurogenic in origin [210,211] or due to fibrosis [18].

Long-term or chronic complications may develop 1 to 2 years following treatment and they are of substantial concern to patients [191]. Most late rectal reactions are seen within 2 years of the completion of radiotherapy [151]. A randomized trial has shown that conformal techniques reduce the risk of long-term proctitis and rectal bleeding compared with conventional techniques; no reduction in urinary symptoms was achieved, however [40]. Normal tissue long-term effects probably depend on the radiation dose, irradiated volume, treatment techniques, beam arrangement and size, dose per fraction, the time between fractions, the number of fields per fraction and the follow-up time [19,27,40,48,89,100,102,109,112,148,151,163,176,194,216,217]. Also, the method used to assess these late effects influences the assessed prevalence of long-term symptoms [19,42,109,117,151,202].

In the self-assessed quality of life study, the bowel symptoms were found to be the most distressful symptoms after radiotherapy [8,69]. Fecal leakage has been documented as the most distressful ones among cervical cancer survivors [16]. *In previous reports*, the prevalence of lasting fecal leakage was 7-27 percent after external beam radiation therapy for prostate cancer [1,34,208,211]. Also, fecal leakage has been noted in 17 percent of the subjects who have undergone radiation therapy for bladder cancer in Stockholm [78]. A study compared the impact of bowel and urinary function on the quality of life for patients treated with 3-D conformal therapy to the prostate alone vs. the whole pelvis with a prostate boost of 64-78 Gy. The prevalence of bowel control, using pads, diarrhea, urgency and rectal bleeding was 15, 0, 24, 22 and 37 percent, respectively, for patients treated with 3-D conformal therapy to the prostate only [69]. The prevalence of these symptoms in patients in whom the whole pelvis was treated with a prostate boost was 26, 10, 39, 40, and 44 percent, respectively [69].

The prevalence of rectal bleeding and diarrhea was 14-34 and 9-25 percent, respectively, after 3-D conformal therapy with 60-66 Gy [40,109]. In contrast, the prevalence of defecation-urgency, rectal bleeding and diarrhea was 26-33, 12-50, and 12-17 percent, respectively, using conventional radiotherapy with 64-70 Gy [34,39,40,42,109,208]. In a normal population, the prevalence of fecal leakage, defecation-urgency, diarrhea, and blood or phlegm in the stools has been found to be 2-4, 2-11, 11 and 2 percent, respectively [1,77,208].

Diarrhea, cramping, bowel movements, mucous, and bleeding will probably be included in the reports on gastrointestinal (GI) complications or morbidity using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score (RTOG/EORTC) [32]. Fecal leakage is not assessed in the RTOG/EORTC score. In contrast, the fecal leakage is included in the SOMA (Subjective Objective Management analytic)/LENT (Late Effects Normal Tissue) score [19,68,143] and it will probably be included in reports on the GI complication or morbidity. The prevalence of “rectal complications” ranged from 1 to 43 percent according to the treatment technique, dose, and score used [65,68,132,172,173]. In recently published data from an escalating dose trial of 77 Gy in 3-D conformal therapy, the prevalence of late bowel effects (= grade 2) was 12 percent when seminal vesicles were irradiated at 54 Gy and 6 percent when only the prostate was included in treatment [134].

It has been shown in a randomized trial using 3-D conformal therapy that “late rectal complication (grade = 2)” significantly increased in patients treated with 78 Gy as compared with a 70-Gy group (26% vs 12%) [151]. The prevalence of rectal complications was 46 percent when more than 25 percent of the rectal volume had been exposed to 70 Gy or more, as opposed to 16 percent when 25 percent or less was exposed [94,151,185]. Previous studies of rectal bleeding have demonstrated that rectal bleeding depends on the volume receiving doses higher than 70 Gy [14,19,70,89,151,173]. It has been reported that increasing the doses of 50 Gy or more to 60 percent or more or of 65 Gy or more to 50 percent or more of the rectum is associated with increased risk of rectal bleeding [48,49,134].

Previously, fecal leakage was not assessed, possibly owing to a lack of awareness of this socially embarrassing side effect [109]. Before this thesis project, we had no knowledge on the risk of fecal leakage symptoms in relation to the dose given to the anal-sphincter region.

5. Urinary Function

The urinary bladder stores urine under low pressure, but when the tension of the bladder wall increases, at a certain point, a micturition reflex is initiated. Micturition is preceded by relaxation of the external urinary sphincter, which is located at the tip of the prostate. The bladder neck is opened passively as contraction of the detrusor muscle proceeds [189]. A large portion of the bladder and urethra is included in the PTV and receives the dose intended for the tumor during external beam radiation therapy for prostate cancer. The exact mechanisms of radiation-induced long-lasting bladder dysfunction are not fully understood. It has been suggested that damaged vascular endothelial cells (leading to bladder fibrosis with subsequent reduced bladder capacity) and urothelial damage (leading to voiding symptoms) constitute the pathophysiology behind chronic radiation cystitis [124]. The majority of late bladder reactions are seen within 2 to 3 years of the completion of radiotherapy [124]. The clinical signs and symptoms of urinary tract dysfunction after radiotherapy may include bladder emptying (voiding) symptoms (frequency or urgency), dysuria (painful burning urination), bladder neck obstruction, a weak stream, bleeding (hematuria), fistula, incontinence, and urethral stricture.

In previous studies, the risk of late urinary effects in patients treated with the conventional technique (grade = 3) has been 3-12 percent [3,63,98,102,163,165]. Urethral stricture occurred in 0-5 percent of patients treated with the conventional technique without a prior

transurethral resection of the prostate (TURP) and increased to 6-16 percent in patients with TURP performed prior to radiotherapy [3,63,98,175]. This symptom has occurred in 4 percent of the patients who had TURP prior to 3-D conformal therapy with a dose of 68-81 Gy, but a higher risk of stress incontinence was observed [166]. The risk of urinary complications (grade = 3) using hypofractionated techniques with a dose per fraction of 5.17 Gy or hyperfractionation with 3 fractions per day (2 Gy per fraction) with 4 hours in between (inadequate normal tissue repair) were 19 and 25 percent, respectively [112,194]. In other studies, the prevalence of urinary complications assessed by the RTOG-scale in patients treated with conventional or conformal radiotherapy with a dose > 65 Gy was 3.4-6.0 percent [172,173]. The complication rate in the genitourinary (GU) tract has been estimated to be 5-10 percent at doses of 50-65 Gy to about one-third of the bladder or of 65-75 Gy to 20 percent of the bladder [124]. The prevalence (grade = 2) of late effects on the bladder was similar (17 vs 13%) when the seminal vesicles was irradiated at 54 Gy or were not included in the treatment field [134]. In dose escalation trials with 3-D conformal therapy, the prevalence (grade = 2) of late effects on the urinary tract was 8-14 percent [65,151].

In self-assessment studies, the prevalence of urinary incontinence, wearing protection against incontinence, occasional hematuria, more frequent nocturia, weak stream, after 3-D conformal therapy with a dose of 65-78 Gy was 30-36, 2-11, 12, 24, and 25 percent, respectively [34,115,137]. In another study, incontinence was the only problem in the area of urinary symptoms that was slightly increased 3 years after treatment, in comparison to pretreatment values using the stereotactic BeamCath[®] external beam radiotherapy technique [55].

In review data, the risk of hematuria, cystitis and incontinence has been found to be 8, 49-52 and 10-12 percent, respectively [39]. A history of diabetes mellitus, hypertension, adjuvant hormonal therapy, TURP prior to radiotherapy, and prostatectomy may be associated with an increased risk of long-term urinary tract dysfunction after radiotherapy [124,173].

6. Sexual Function

Penile erection is a neurovascular event modulated by neurotransmitters and the hormonal status. The penis is innervated by autonomic and somatic nerves [64]. In the pelvis, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa (the main erectile tissue in the penis) to regulate blood flow during erection and detumescence. The parasympathetic visceral efferent fibers arise from S 2-4 to

supply the pelvic plexus located on the lateral wall of the rectum [64]. External beam radiation therapy has been reported to affect erection stiffness to a lesser extent than radical prostatectomy two years after therapy [74,109,152]. The mechanism of radiation-induced impotence is not well documented; it has often been attributed to vascular injury and it has been suggested that the predominant etiology of radiation-induced impotence is arteriogenic [61,215]. Furthermore, neurological damage cannot be excluded. It has been found that a dose of 50 Gy or more to 50 percent of the bulb of the penis was associated with increased erectile dysfunction, but there was no relationship between the radiation dose to the neurovascular bundles and erectile dysfunction after brachytherapy [129-131]. This has also been suggested after external beam radiation therapy [50]. It is possible to deliver the high doses of radiation necessary to treat prostate cancer while reducing the doses to erectile tissues with intensity-modulated radiotherapy [23,174].

In previous studies, the incidence of erectile dysfunction after 3-D conformal therapy has been reported to be 17-48 percent at two to three years after treatment [34,76,109,123,137,158,209,214] compared with 11-73 percent using conventional technique [88]. In a meta-analysis, the predicted probability of erectile dysfunction after external beam radiation therapy, external beam radiation therapy combined with brachytherapy, brachytherapy (= 2 years), nerve-sparing radical prostatectomy and standard radical prostatectomy was 45, 40, 24, 66 and 75 percent, respectively [160]. In a randomized trial comparing conventional treatment with a dose of 70 Gy and 3-D conformal therapy with a dose of 78 Gy, the percentage of patients with full or partial erection before treatment decreased by 10 percent for conventional treatment and by 16 percent in a conformal group at 2-year follow-up [115]. The difference in patients maintaining their potency (full or partial erection) between the groups increased to 16 percent at the 3-year follow-up [115]. It has been reported that a dose escalation higher than 76 Gy was associated with an increased the risk of erectile dysfunction [214]. Erectile function appears to diminish with advancing time after treatment, with 33 to 61 percent of patients maintaining their erectile function at 5 years or longer after irradiation [177].

It has been suggested that the addition of hormone therapy to radiation therapy for prostate cancer does not increase the risk of sexual dysfunction [25,147]. Men are more at risk of having erection problems after radiation therapy if the quality of erections before treatment was borderline [12,170]. Also, patients having undergone prostatectomy are at a higher risk of becoming impotent after external beam radiation therapy compared with patients who did

not have a prostatectomy [26]. In addition, many factors such as age, a history of diabetes mellitus, hypertension, myocardial infraction and drugs, may be associated with the waning of sexual function after radiotherapy [74]. Other factors, such as the varying definitions of intact erectile function given in the literature and the method used to assess potency may over or underestimate the prevalence of erectile dysfunction after therapy [75,202].

7. Patient and Methods

7.1 Study Bases

In I-IV, the study population included all patients with clinically localized prostate adenocarcinoma treated by external beam radiation therapy in Stockholm in 1993-96 as follows (**Figure 4**):

- In I, all patients treated at Radiumhemmet in 1995 or 1996 and at Stockholm Söder Hospital in 1993-96.
- In II, all patients treated at Radiumhemmet in 1995 or 1996.
- In III, as in study II, all patients treated at Radiumhemmet in 1995 or 1996.
- In IV, 51 patients agreeing to participate in a cohort to investigate sexual dysfunction before and after radiotherapy following treatment at Radiumhemmet in 1993 or 1994
- In V, 89 randomly selected patients diagnosed with prostate cancer and answering a self-assessment questionnaire twice, with a 3-week interval in between.

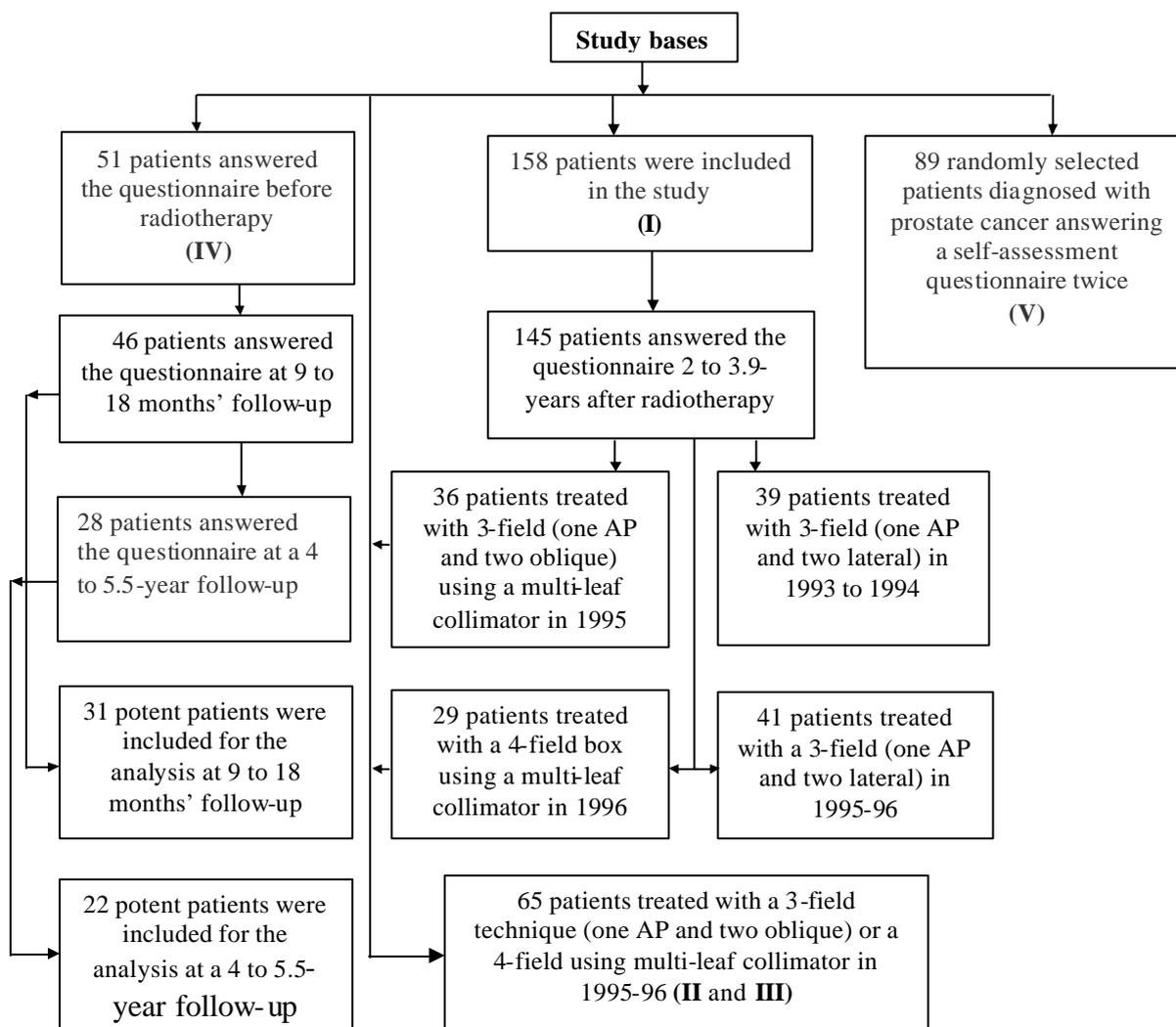


Figure 4: Study bases

7.2 Data Collection

An informative letter was sent to each patient included in studies I, II, III, and V before the questionnaire was sent. In the letter, we explained the aim of the study and the importance of the treatment evaluation to improve health care. One week later, the patients received the questionnaire and a letter explaining the relevance of the study. All respondents received a letter of gratitude, which also served as a reminder, 2 weeks after the questionnaire had been sent. A telephone call followed to those who did not return the questionnaire.

In study IV, a nurse in the Urology Department at Radiumhemmet asked all patients receiving external radiation therapy for localized prostate cancer in 1993 and 1994 if they wanted to participate in the study. Patients agreeing received a questionnaire at the clinic and mailed it back to us. All patients received the same questionnaire by mail 1-1.5 years after the treatment. All participating patients in the study who were still alive received the questionnaire for the third time in February, 1998. A telephone call followed to those who did not return the questionnaire.

None of the studies were anonymous owing to the need to follow up the patients and to relate the symptoms to the treatment techniques, dose, treated volume, or dose given to the anal-sphincter region and rectum. Therefore, the patients were coded to allow for additional information relating to the investigated variables. We coded the questionnaire to guarantee the anonymity of the information. The studies were approved by the Regional Committee at the Karolinska Institutet (92-135, 93-281 and 98-247).

7.3 Questionnaire

The questionnaire, which had been developed on the basis of successive in-depth interviews with patients and clinicians, was similar to our previously used questionnaires [15,71,72,75,78]. It contained 80 questions assessing anal sphincter, large-bowel, urinary-tract and sexual functions. Each symptom was assessed separately, followed by an assessment of the extent to which the symptom distressed the patient. The bowel questions addressed diarrhea or loose stool, constipation, defecation-urgency, blood and phlegm in stools and fecal leakage. Urinary questions addressed the frequency of urination during the day and night, incomplete bladder evacuation, urinary control, straining to initiate micturition, weak stream, urinary urgency, and urinary leakage. The frequency and intensity of the symptom was assessed using six response alternatives (**appendix 1, V**). The questionnaire also included questions about urinary and fecal leakage quantity and if any

protective devices had been used. The level of symptom distress was assessed using a 'verbal' 4-category scale (none/little/moderate/much) [78]. Parts of the "Radiumhemmet Scale of Sexual Functioning" [75] were used to assess sexual symptoms. It contains questions on three functional aspects of sexuality including desire, erection, and orgasm, using from five to eight ordinal categories as response alternatives. "Potency" was defined as an erection "sufficiently stiff for intercourse most of the time" or better during sexually stimulated erections or night/morning erections or spontaneous erections [75].

In studies I, II, and III, the baseline function was collected from the patients retrospectively. The men were asked to assess their anal sphincter, large-bowel, urinary-tract and sexual function before radiotherapy. Patients reporting the same frequency or intensity of symptoms at follow-up and pre-treatment (or the symptom progression was less than or equal to two frequency steps) were classified as "relatively symptom-free". Patients reporting a symptom frequency of twice a week or more often were classified as patients having the symptom. Patients reporting a symptom frequency of once a week or less often were classified as "relatively symptom-free".

Additional questions assessed possible confounders, including patient age, hormonal manipulation, history of radical prostatectomy, orchidectomy, cardiovascular symptoms, smoking, diabetes mellitus, and psychological depression and other diseases that may affect anal sphincter, large-bowel, urinary or sexual function.

7.4 Hospital Records

Information on the external beam radiation therapy including dose, treatment protocol, collimation technique, treatment period, and disease stage and, grade was retrieved from the hospital records. The dose planning data for all patients treated at Radiumhemmet in 1995 or 1996 were restored from the archives to the TMS system. We were not able to include patients treated at Stockholm Söder Hospital owing to technique limitations. The rectum was defined anatomically as extending from the sigmoid flexure to the anal verge. The whole rectum (rectum including its filling) and anal-sphincter region were delineated on each CT image for each patient (**Figure 5; Figures 1a and 1b, III**) [51]. In addition, the structure of the rectal wall was outlined by the interior and exterior borders (**Figure 1b, III**). The caudal-cranial lengths of the rectum and the sphincter were defined as 8.0 to 11.0 cm and 3.0 cm, respectively. Dose-volume histograms (DVHs) were defined at 0.5 Gy intervals. We also delineated the lower bowel tract on one or two slices, which included at least 50 percent

isocenter dose. All delineated volumes were done by the present author with the assistance of Panayiotis Mavroidis using the Anatomy in Diagnostic Imaging as a reference guide [51]. To confirm the delineation, Oncologist Helena Lind, Urologist Peter Wersäll and Radiologist Eva Qvanta checked the delineated organs.

7.5 Dose-Volume Histograms

To assess the difference between DVHs for patients with and without each of the bowel symptoms and to find the dose and volume threshold at which patient groups reported more or fewer symptoms, we did the following calculation: the differential and cumulative dose-volume histograms of the rectum and the anal-sphincter region were assessed for each patient. The cumulative volume was normalized to the total volume of the rectum or anal sphincter. The mean percentage DVHs for each patient group was then calculated. The area under a percentage volume DVH is 100 times the mean dose. The area under the mean percentage DVH for patients with and without the specific symptom was calculated [89].

7.6 Statistical Analyses

In the analysis, the correlation between the mean dose, the area under DVHs, and the anatomical volume of the rectum and anal-sphincter region, and the long-term effects of bowel dysfunction was assessed by nonparametric rank tests (Mann-Whitney and Wilcoxon rank sum test). Also, the statistical significance of the difference between DVHs at each dose and these long-term effects was assessed by these tests for each symptom. In addition, the percentage volume of the anal-sphincter region irradiated of equal to or more than 35, 40, 45 and 50 Gy, and the risk of fecal leakage were assessed. The risk of having symptoms was evaluated as the percentage of patients above the various cut-offs reporting the particular symptom divided by the percentage of patients below the limit reporting the same symptom. A corresponding 95% confidence interval (CI) was calculated by the Mantel-Haenszel method [162]. Statistical analyses were done using the software package “SPSS (Version 10.1.3)” and the FREQ procedure of the SAS System (Version 8.2 TS2M0) [167]. All reported p values are two-sided. In paper V, the patients’ first and second answers were compared for each question using kappa (κ) statistics to measure test-retest reliability [44]. We categorized kappa values as suggested by Landis and Koch (1977): $\kappa = 0.4$, poor-to-fair agreement; 0.41-0.6, moderate agreement; 0.61-0.8, substantial agreement; and 0.81-1.00, almost perfect agreement [97].

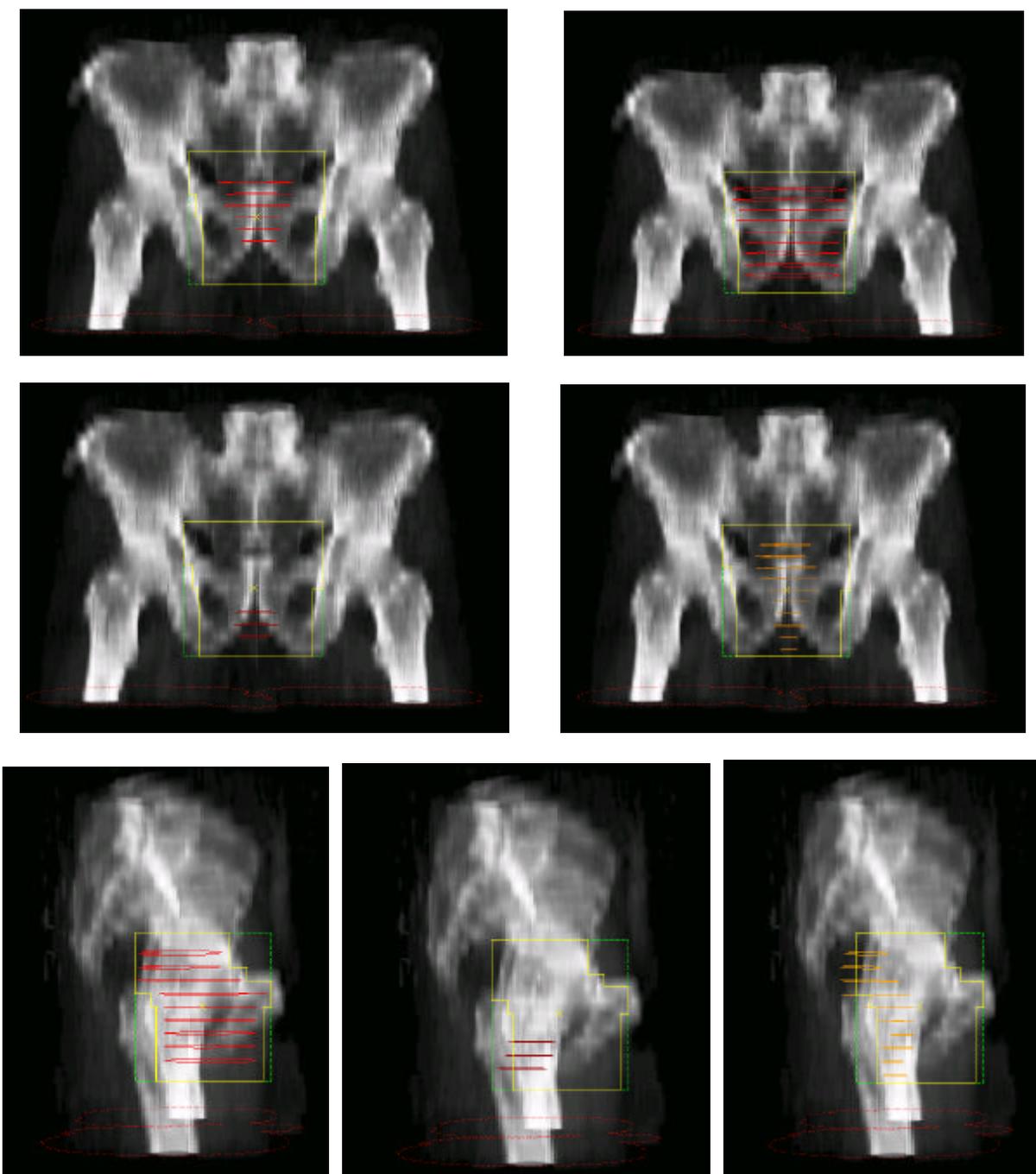


Figure 5. Conformal radiation therapy of prostate cancer. AP-PA fields with prostate target volume (GTV) in top left row, and the planning target volume (PTV) in top right row, the anal-sphincter region in the middle left row, and the rectum in middle right row. Lateral fields with PTV in bottom left row, the anal-sphincter region in bottom middle row, and the rectum in bottom right row.

8. Results

8.1 Study I

Of all the 158 available patients, 145 (92%) answered and returned the questionnaire (Table 2). Reasons for nonresponse were that no contact was established (3 patients), refusal (8 patients) and the patient's poor health (2 patients). Defecation-urgency was reported by 28 percent (8/29) of the patients treated with the 4-field technique using a multi-leaf collimator and 20 percent (8/40) of the patients treated with a 3-field (one anteroposterior (AP) and two lateral) technique without a multi-leaf collimator. Only 6 percent (2/36) of the patients treated with a 3-field (one AP and two oblique) using a multi-leaf collimator reported such urgency. The relative risk (RR) on comparing patients treated using 4 fields technique with patients treated using 3 fields technique with a multi-leaf collimator was statistically significant (RR = 4.5) (95% CI, 1.1 – 21.0). Seven out of 29 (24%) patients treated with 4 fields reported diarrhea or loose stool. None of the patients treated with 3 fields (one AP and two oblique) with a multi-leaf collimator reported this symptom (**Figure 6**). Twenty-three percent (18/79) of the patients treated with three fields (one AP and two lateral) using a block collimator reported defecation-urgency compared to 6 percent of patients treated with three fields (one AP and two oblique) using a multi-leaf collimator, corresponding to a relative risk of 4.1 (95% CI, 1.0 –16.0) (P = 0.03) (**Figure 6**). The most distressful bowel symptom was fecal leakage; 47 percent of the patients with this symptom reported that they were distressed or much distressed by “bowel symptoms” (**Figure 7**). For patients treated with the four-field box technique, the mean volume of the lower bowel tract receiving a dose of 35 Gy or more was 65 cm³ compared to 51 cm³ for patients treated with three fields. There was no statistically significant difference concerning urinary or erectile dysfunction between patients treated with a 3 or 4-field technique with the exception of an increased prevalence of a weak urinary stream in patients treated with four fields compared to with three.

Table 2. Patient characteristics.

Response rate (%)	Age at follow-up Years (SD)	Follow-up time Years (SD)	No. of fields	Beam collimator	Prescribed dose (Gy)
36/42 (86)	72 (6.6)	3.2 (0.4)	3 (one AP and two oblique)	multi-leaf	70.2
29/30 (97)	71 (5.3)	2.4 (0.3)	4 (box technique)	multi-leaf	70.2
41/45 (91)	71 (5.5)	3.0 (0.5)	3 (one AP and two lateral)	block collimator	70
39/41 (95)	73 (6.1)	4.9 (0.5)	3 (one AP and two lateral)	block collimator	68

8.2 Studies II and III

Of the 72 eligible patients who were treated with a 3 or 4-field technique using a multi-leaf collimator, 65 (90%) answered the questionnaire (Table 2). The mean of the anal-sphincter region and rectal wall rectal volumes is 22 cm^3 (SD, 4) and 42 cm^3 (SD, 9), respectively. Nine patients reported fecal leakage, 10 blood and phlegm in stools, 10 defecation-urgency, and 7 diarrhea or loose stools. The mean doses to the anal-sphincter region were 45 Gy (SD, 13; range, 16-69) for patients without fecal leakage and 52 Gy (SD, 10; range, 36-69) for patients with this symptom ($P = 0.15$). One of the 18 (6%) patients received a mean dose of 10-39 Gy to the anal-sphincter region had fecal leakage compared to the finding that 8 of the 47 (17%) patients receiving a mean dose of 40-69 Gy had this symptom. A statistically significant correlation was found between DVHs of the anal-sphincter region and the risk of fecal leakage at an intermediate dose (45-55 Gy) (**Figure 8**). None of the 19 or 13 patients who received, respectively, a dose of 35 Gy or more or 40 Gy or more to, at the most, 60 or 40 percent of the anal-sphincter region volume reported fecal leakage (**Figure 9**). Of the 36 patients who received a dose of 50 Gy or more to no more than 60% of the anal-sphincter region volume, two (6%) reported fecal leakage compared to seven (24%) of the 29 patients reporting this symptom who received this dose to more than 60 percent of the anal-sphincter region (**Figure 9**). The relative risk on comparing patients reporting fecal leakage above and below this cut-off was 4.3 (95% CI 0.98-18.35). In the interval 25 to 42 Gy, a statistically significant difference was found between radiation to the rectal wall and the risk of defecation-urgency and diarrhea ($P < 0.05$) but no relation was found between DVHs and the risk of blood and phlegm in stools. Of the 10 patients who reported defecation-urgency, four (40%) reported fecal leakage compared with only five (9%) of the patients not reporting this symptom, giving a relative risk of 4.4 (95% CI, 1.4 –13.6). Only one of the 7 patients who reported diarrhea or loose stools reported blood and phlegm in stools. Of the seven patients who reported diarrhea or loose stools, three (43%) reported fecal leakage compared with six (10%) of the 58 patients who did not have diarrhea, giving a relative risk of 4.1 (95% CI, 1.3 –13.0).

8.3 Study IV

Thirty-four of the 50 (68%) men were “potent” before the irradiation. There was little difference regarding the pre-treatment prevalence of potency in the patient group over 60 years of age when compared with the prevalence in a randomly selected, age-matched population of men using the same potency assessment criteria [73]. At the first follow-up, two of these patients had died and one had been given a different type of treatment, leaving

31 patients for assessment. Fourteen of them were treated with a conventional collimator and 17 were given three-dimensional conformal therapy with the aid of a multi-leaf collimator. The mean age of the patients who were potent before treatment was 68 years (SD, 6; range, 55-76 years) for the patients treated with the conventional technique and 67 years (SD, 5; range 58-75 years) for those treated with the multi-leaf collimator technique. Twelve of the 17 patients (71%) maintained their potency at 9-18 months' follow-up compared to 5 of the 14 (36%). Preserved erectile function at 9-18 months was found in 17 of the 31 men (55%) and at the 4-5-year follow-up in five of 22 (23%). There was no correlation between the treated volume and erection stiffness after the treatment.

8.4 Study V

The mean age of the 89 patients was 70 years (SD, 2.4; range, 65-73). The response rate for individual patients to specific questions regarding anal sphincter, large-bowel, and urinary function ranged from 94 percent (79/89) to 98 percent (84/89). The kappa value was equal to or higher than 0.60 for all symptoms, indicating anal sphincter and large-bowel dysfunction, except for defecation-urgency (kappa = 0.40-0.55). The observed agreement on symptoms indicating anal sphincter and large-bowel dysfunction was high (=76%) except for defecation-urgency. Weighted kappa (for tables larger than 2x2) ranged from 0.56 to 1.0. The kappa value was 0.76-0.86 for the distress owing to gastrointestinal tract symptoms compared with 0.42-0.63 for distress owing to fecal leakage. The coefficient Kappa value for urinary symptom items ranged between 0.43 and 1.0, except for urinary urgency (Kappa = 0.30-0.39). In most cases, the disagreement between the two assessments was no more than one step to a higher or lower frequency.

8.5 Blood and Phlegm in Stools and Dose to the Anal-Sphincter Region

Figure 10 depicts the population distribution of the patients' mean dose to the anal-sphincter region for two collapsed groups according to blood and phlegm symptom frequency. The population means were 45 Gy (SD, 13) for patients without symptom and 53 Gy (SD, 7) for patients with blood and phlegm. None of the 18 patients (0%) who received a mean dose of 10-39 Gy to the anal-sphincter region had blood and phlegm compared to the finding that 10 of the 47 patients (21%) receiving a mean dose of 40-69 Gy had this symptom (**Figure 11**). The difference in the mean dose to the anal-sphincter region between patients with blood and phlegm in stools and those without this symptom indicated that a higher mean dose to anal-sphincter region was associated with blood and phlegm in stools (P = 0.06).

The mean dose-volume histograms for the patients with blood and phlegm in stools and patients without the symptom are shown in **Figure 12a**. The difference between the groups was statistically significant at the dose interval 38 to 45 Gy ($P < 0.03$, Wilcoxon rank sum test) (**Figure 12b**).

None of the 19 or 13 patients who received, respectively, a dose of 35 Gy or more or 40 Gy or more to no more than 60 or 40 percent of the anal-sphincter region volume reported blood and phlegm in stools compared to 10 of the 46 patients or 10 of the 52 patients who received, respectively, a dose of 35 Gy or more or 40 Gy or more to more than 60 or 40 percent of the anal-sphincter region volume reported this symptom ($P < 0.05$) (**Figure 13**).

There was no relationship between the mean dose to the rectal wall and anal-sphincter region (**Figure 14**). The dose volume histograms of the rectal wall and the whole rectum were similar and the mean doses correlated (**Figure 15**)

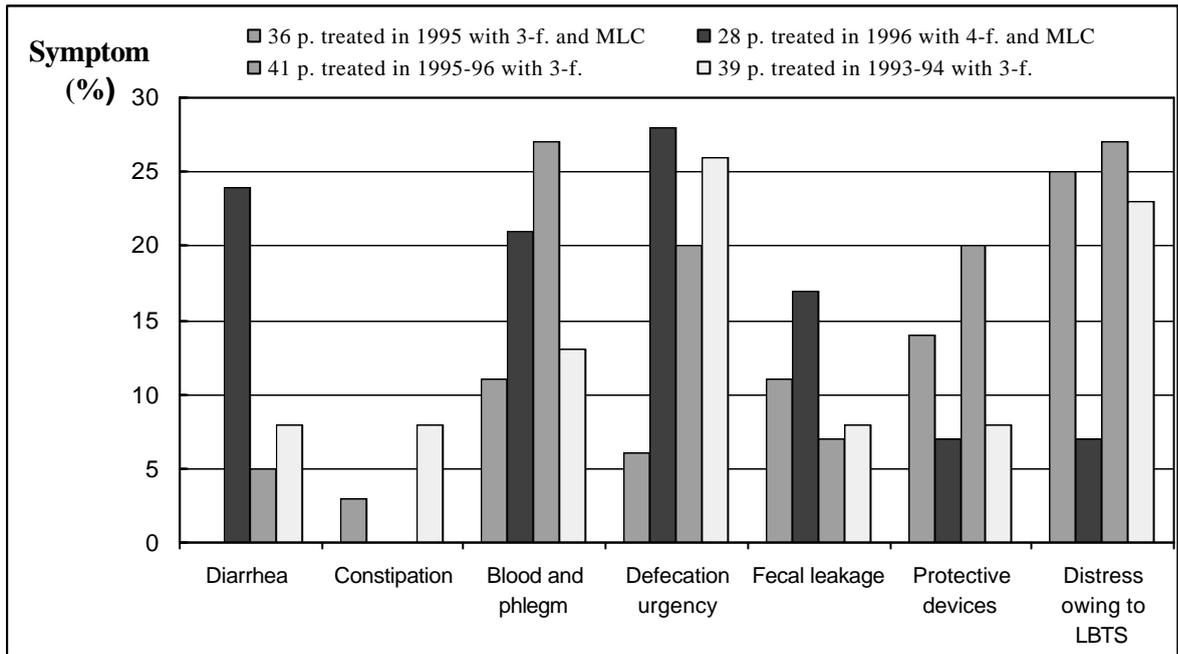


Figure 6: Symptoms indicating anal sphincter and large bowel dysfunction, occurrence and symptom distress (percentage of total patient group) (LBTS=Lower bowel tract symptoms).

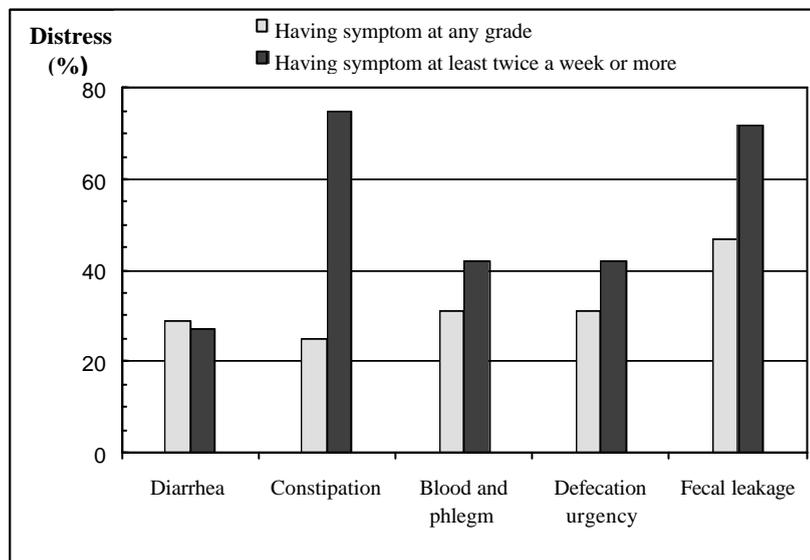


Figure 7: Percentage reporting moderate or considerable distress due to 'symptoms of anal sphincter and large bowel dysfunction' among patients reporting or not reporting five different specific symptoms.

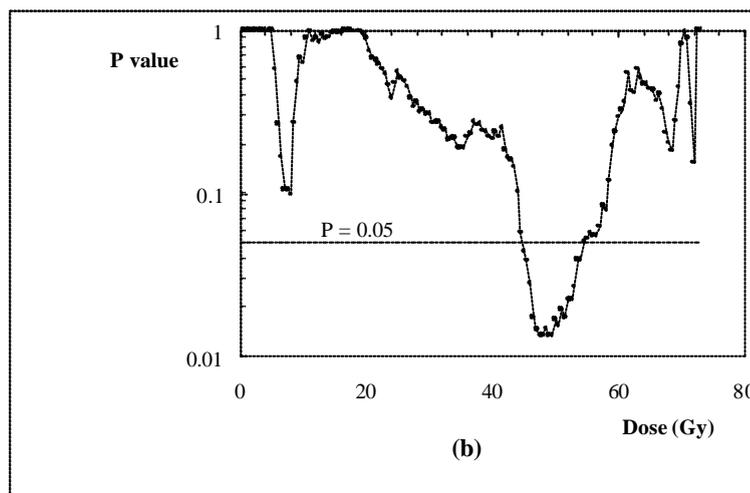
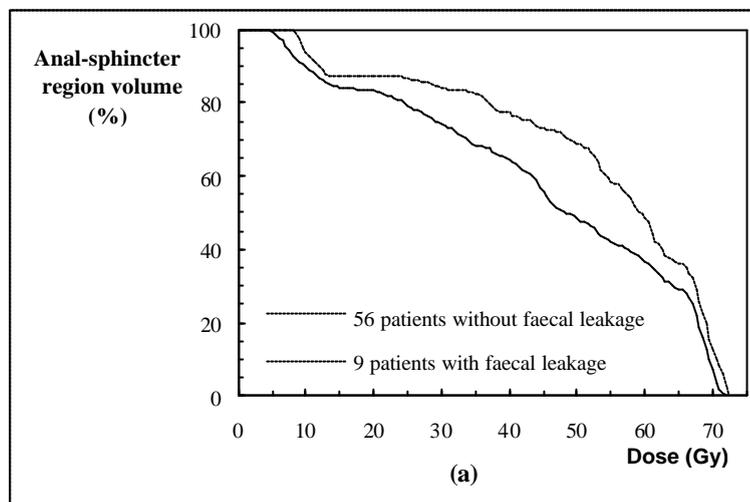


Figure 8: The mean percentage DVHs of the anal sphincter region for patients with fecal leakage (dashed curve) and patients without the symptom (solid curves) (a). Patients treated with 3 or 4-field external beam radiotherapy using a multi-leaf collimator and 70.2 Gy. P value at each dose, comparing areas under the curve (Wilcoxon rank sum test) (b).

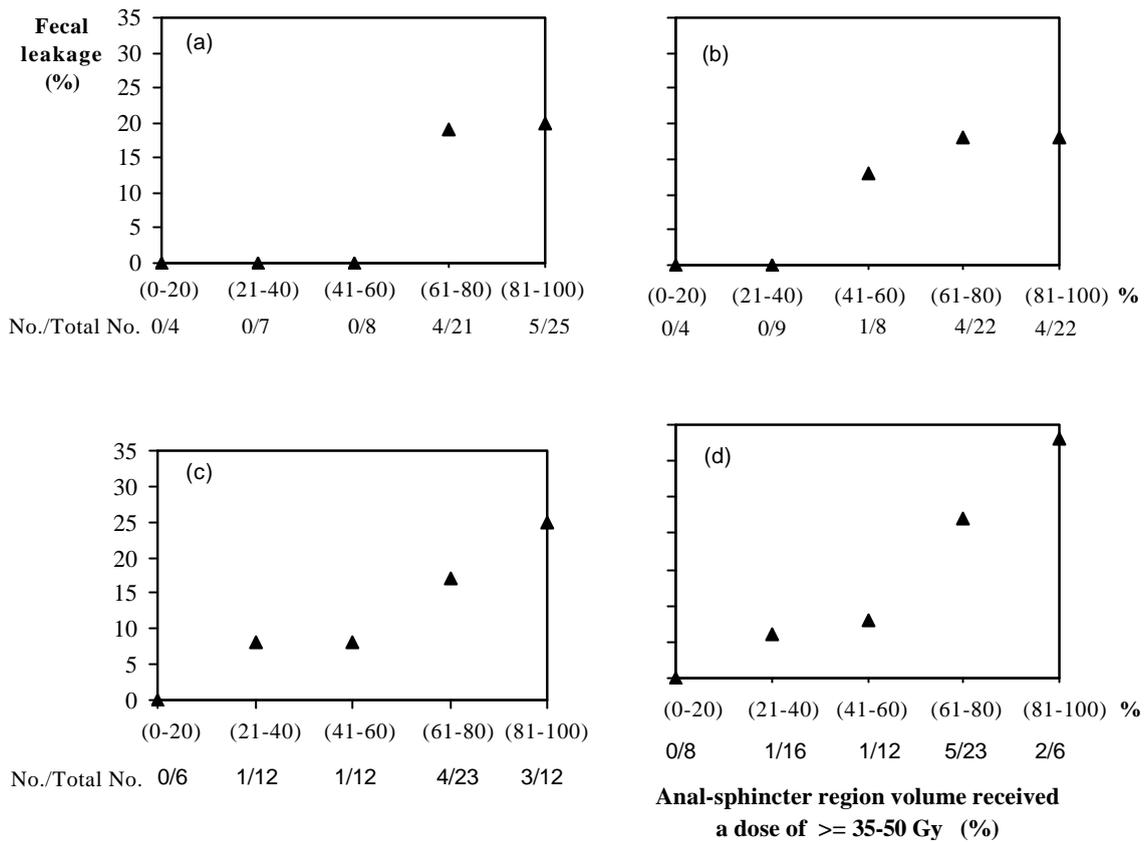


Figure 9: Percentage of volume of the anal-sphincter region that received a dose of 35 Gy or more (a), 40 Gy or more (b), 45 Gy or more (c) and 50 Gy or more (d) in relation to the percentage of fecal leakage in 65 prostate cancer patients treated with 70.2 Gy

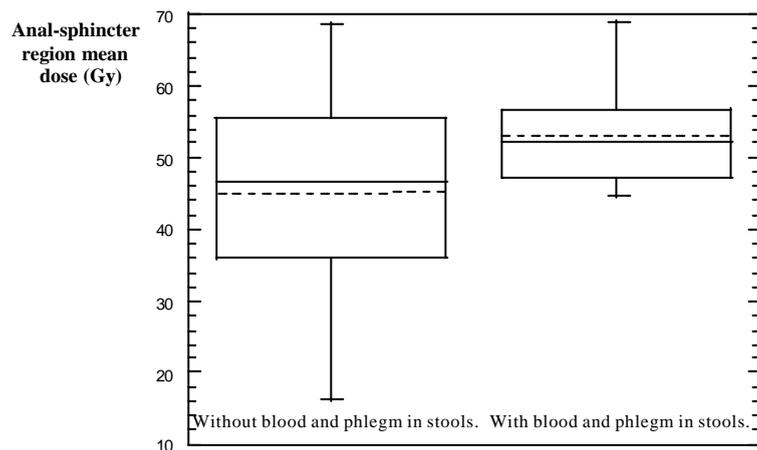


Figure 10: Distribution of mean dose to the anal-sphincter region for patients with and without blood and phlegm in stools. Bars and boxes show the 10th, 25th, 75th, and 90th percentiles of the distribution. The solid and dashed lines through the boxes show the median and mean dose, respectively. In comparing mean values P = 0.06.

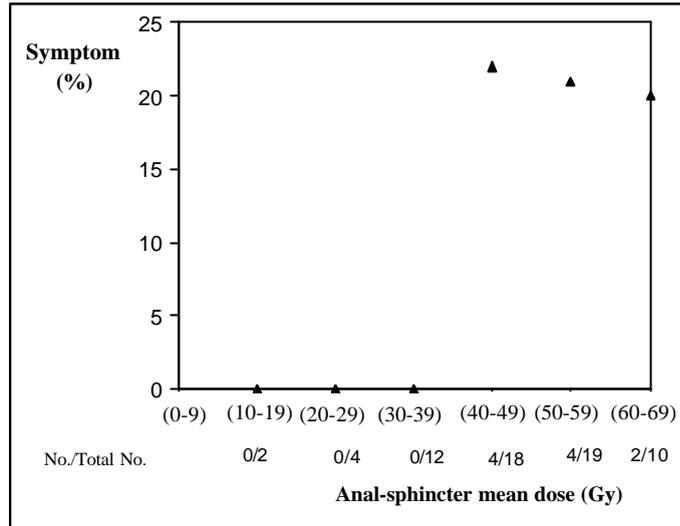


Figure 11: Mean dose to the anal-sphincter region in relation to the percentage of blood and phlegm in stools symptom in 65 prostate cancer patients treated with 70.2 Gy.

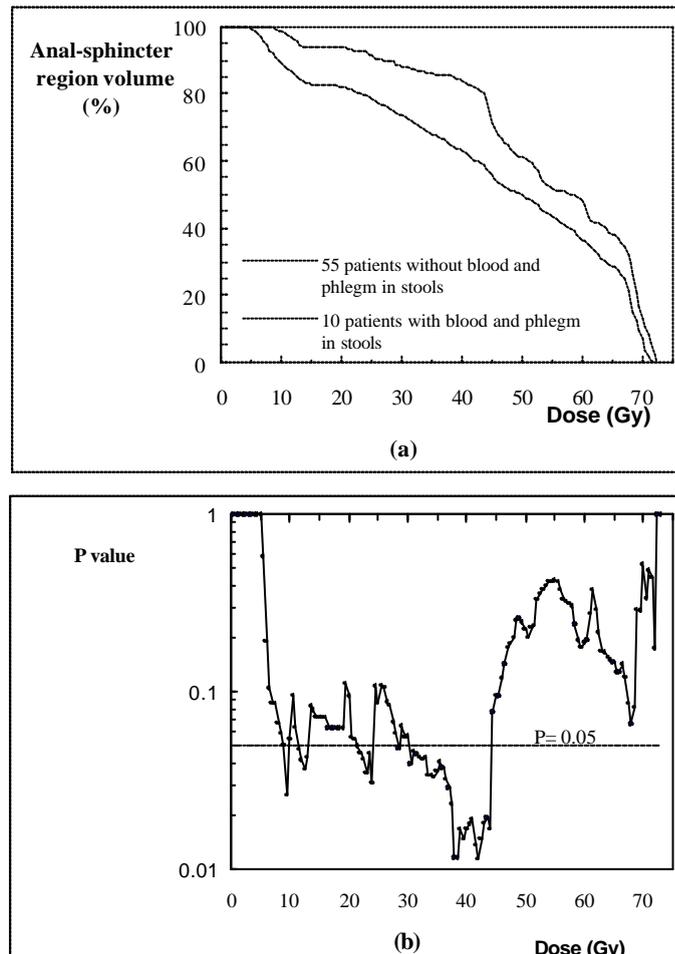


Figure 12: The mean percentage DVHs of the anal sphincter region in patients with blood and phlegm in stools (dashed curve) and patients without the symptom (solid curve) (a). Patients treated with 3 or 4field external beam radiotherapy using a multi-leaf collimator and 70.2 Gy. P value at each dose in comparing areas under the curve (Wilcoxon rank sum test) (b).

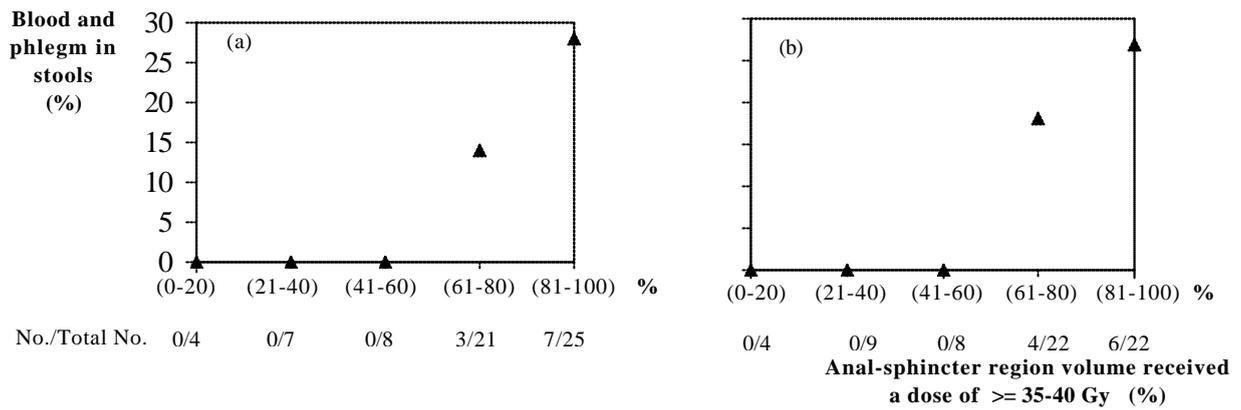


Figure 13: Percentage of volume of the anal sphincter region which received a dose of 35 Gy or more (a), 40 Gy or more (b), in relation to the percentage of blood and phlegm in stools for 65 prostate cancer patients treated with 70.2 Gy.

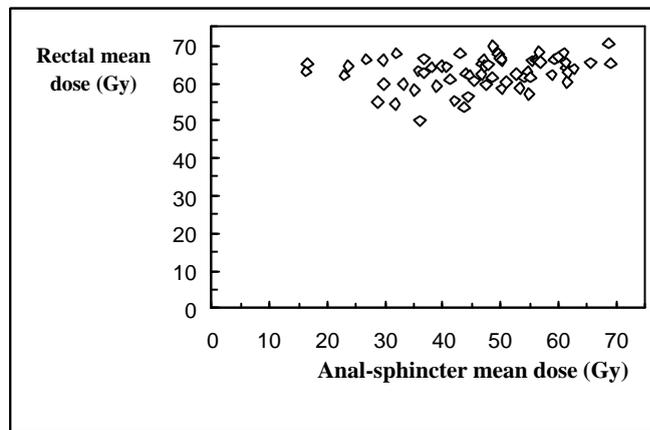


Figure 14: Mean dose to the anal-sphincter region in relation to the mean dose to the rectal wall in 65 prostate cancer patients treated with 3 or 4-field external beam radiation therapy with 70.2 Gy.

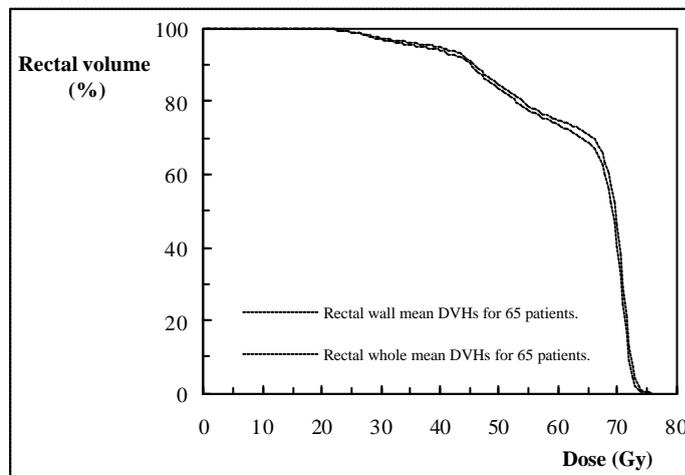


Figure 15: Rectal wall and whole (including filling) DVHs in 65 patients treated with 3 or 4-field technique using a multi-leaf collimator and 70.2 Gy.

9. Discussion

9.1 Validity

A perfect study would be large, randomized, placebo-controlled, without measuring errors and with no censored data. This perfect study exists only in theory. In practice, there are always problems. Real-life empirical studies in medicine tend to deviate from the ideal to various degrees owing to systematic errors [184]. The accuracy of the results depends on the degree of absence of errors in the assessment of the effect. The systematic errors can be grouped under confounding, misrepresentation, misclassification and analytical deviation (**Figure 16**).

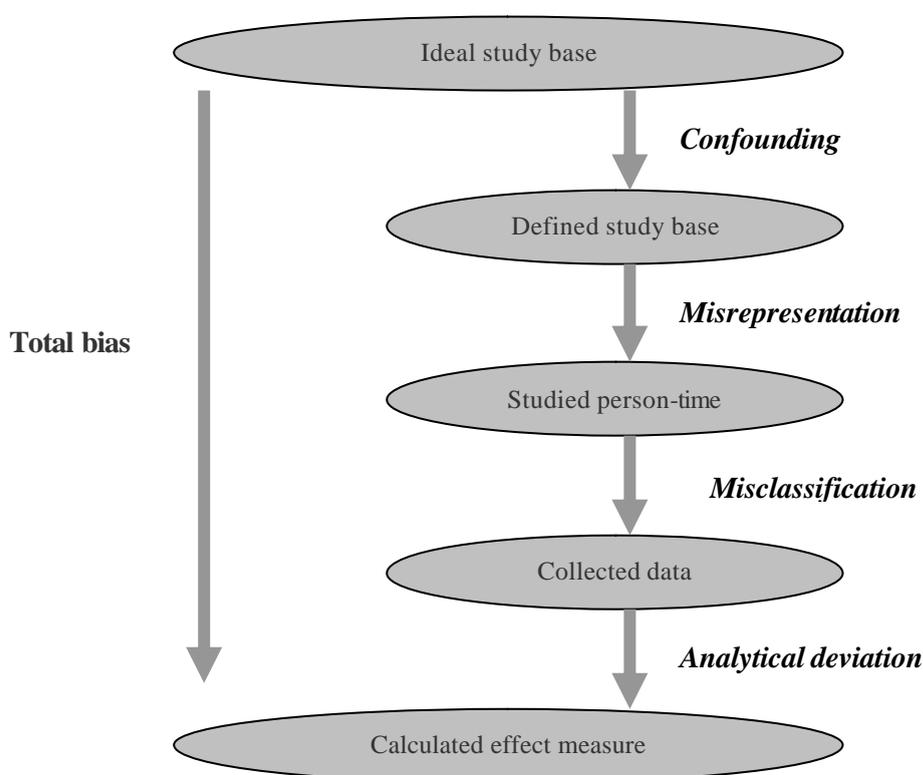


Figure 16: Different stages in a clinical study with corresponding biasing factors.

9.1.1.1 Confounding

A factor related to both the dependent and independent variables may introduce a systematic error. In our study, we tried to accumulate as much information as possible on potential confounding factors such as the patient's age, follow-up time, tumor stage, history of TURP, prostatectomy, orchidectomy, androgen depletion, hypertension, diabetes mellitus, claudicatio intermittens, angina pectoris, disease in joints or muscles, history of heart attack, use of any medical devices to improve erection stiffness, smoking, depression, and other diseases and medications.

In study I, for example, when comparing the effect of the treatment technique (patients treated with 3-field technique using a multi-leaf collimator vs. patients treated with other techniques) on anal sphincter, large-bowel, urinary-tract, and sexual dysfunction, most factors such as age and intercurrent diseases were similarly distributed between the patient groups. A powerful technique to exclude the influence of a confounder is to restrict the study base to men not having the confounder. However, restricting or stratifying the data to assess confounding that was not similarly distributed between patient groups did not change the results. For example, radical prostatectomy was more common in the group treated with 3-field technique using a multi-leaf collimator as compared with other groups. This may have underestimated the relative risk of urinary or sexual dysfunction when comparing the other treatment techniques with the 3-field technique using a multi-leaf collimator group. However, excluding patients who had undergone prostatectomy changed the relative risk by no more than 0.5 with an exception of straining to initiate micturition and urinary urgency.

In study III, we found the risk of fecal leakage to be about four times higher in patients with defecation-urgency or diarrhea or loose stools than in patients without these symptoms. When defecation-urgency or diarrhea is caused by radiotherapy it may be a mechanism in the relation between radiotherapy and fecal leakage. Thus, therapy-induced defecation-urgency or diarrhea (or both) may entail a mechanism for fecal leakage separate from damage to the anal sphincter. In the current study, excluding patients with defecation-urgency or diarrhea from the analysis did not change our findings concerning fecal leakage. Herold and coworkers reported that diabetics have an increased risk for the development of late grade 2 gastrointestinal complication after external-beam radiotherapy for prostate cancer [79]. In our study, we did not find any statistically significant relationship between symptoms indicating anal sphincter or large-bowel dysfunction (blood and phlegm in stools, fecal leakage, defecation-urgency, or diarrhea) and diabetes mellitus, claudicatio intermittens or hypertension. In a randomized comparison between prostatectomy and watchful waiting to evaluate symptoms and the self-assessed quality of life in men with localized prostate cancer, Steineck and coworkers found no indication that radical prostatectomy induces defecation disturbances or symptoms of bowel dysfunction [183]. Thus, prostatectomy probably did not contribute to the risk of fecal leakage or defecation-urgency in the present study.

In study IV, most of the potential confounding factors were similarly distributed in both patient groups. However, the mean follow-up was one year shorter at the 4 to 5.5-year follow-up. This factor may overestimate the relative risk of erectile dysfunction to some extent when comparing conventional with conformal technique.

9.1.1.2 Misrepresentation

Loss of follow-up can bias the results when the nonrespondents differ in terms of the relation between the independent and dependent variables from the respondents, so as to lead to a misrepresentation of the true relative risk in the study base. Efforts were made to enhance a high response rate by preparation in in-depth interviews, face validation, a satisfactory layout of the questionnaire, establishment of contact with the men (by letter) before sending the questionnaire, and a quick reminder by telephone if the questionnaire was not returned. Our response rates were equal to or higher than 90 percent. In study I, 35 percent of the total number of patients treated in 1993 and 1994 at the Stockholm Söder Hospital had died before the follow-up. However, no clear differences, in base-line characteristics between this group and the group treated with a similar technique, were found. In study IV, 39 percent of the patients participating in the first follow-up were lost (17 had died and one did not participate) to the 4 to 5.5-year follow-ups. However, the percentage of potent patients lost to the second follow-up was similar in both patients groups irradiated with the conventional or conformal technique.

9.1.1.3 Misclassification

Two main types of misclassification may deviate the association between dependent and independent variables: nondifferential and differential misclassification. Nondifferential exposure misclassification occurs when individuals on average have the same measuring errors of outcome in respective groups defined by exposure status. We could not blind our subjects completely since the studies were not anonymous. However, no investigation-related bias is likely to occur when subjects fill out a questionnaire in their home; this procedure can be regarded as having the same effects as “blinding” in a clinical trial. In studies III, measuring errors due to organ movement [67,99,128,161], set-up errors and errors in delineation of the anal-sphincter region and rectum may dilute the association between the dose to the anal-sphincter region and long-term fecal leakage or blood and phlegm in stools. Also, these errors may dilute the association between the rectal dose and defecation-urgency or diarrhea. If the measuring errors in the groups being compared are equal, they tend not to affect the relative risk (sensitivity <1) or bias (specificity <1) in the direction of a relative risk

of 1.0 [44,162,184]. If the misclassification is different between the groups, this may affect the relative risk in either direction. Organs (anal-sphincter region, rectum and lower bowel tract) have been delineated uniformly as agreed on by two investigators and controlled by three physicians, a urologist, an oncologist, and a radiologist. These actions were taken without knowledge of the patient's symptom status or questionnaire answers, resembling "blinding". This procedure should minimize any possible bias owing to differential misclassification. The anal-sphincter region is more fixed than the rectum; we did not include the effects of uncertainty on organ motion and set-up errors in these studies. It was practically impossible since the DVHs were generated from planning scans.

Great efforts to make the questions conceptually and intuitively clear have been made during in-depth interviews, face validity and test-retest reliability. Moreover, in studies I-III, the base line symptoms were retrieved retrospectively, and the men were asked to rate their anal sphincter, large-bowel, urinary-tract, and sexual function before radiotherapy. To clear up uncertainties owing to memory failure regarding symptom frequency, patients in these studies reporting the same frequency/intensity of symptoms (or the symptom progression was less than or equal to two frequency steps) at follow-up and pretreatment were classified as "relatively symptom-free".

A decrease of reliability, introducing measuring errors, may dilute the observed association. When the questionnaire assessment of "physiological potency" was compared with a RigiScan® assessment, the sensitivity was 80 percent, and the specificity was 100 percent, [75]. In study V, the test-retest results for our questionnaire showed substantial agreement on symptoms indicating anal sphincter, large-bowel and urinary dysfunction, and distress due to gastrointestinal or lower urinary tract symptoms; an exception was defecation and urinary urgency. However, stratifying patients in terms of therapy or no therapy did not change the results with the exception of the agreement concerning defecation-urgency, which was higher reliability in treated patients than in untreated ones.

9.1.1.4 Analysis

In the analyses, we calculated the relative risks, mean dose and mean dose volume histograms. Other statistics than the mean dose and analyses than dose-volume histograms may be more appropriate than the set we used. In studies I-III, the data were collected at the same time for all patients and we did not know the exact time of the onset of the long-term symptoms, which probably resulted in measuring errors. For example, we were unable to use

the Cox proportional-hazards analysis or the Kaplan-Meier method since we had no information about the time of the symptoms' occurrence during the follow-up period. However, a Cox proportional-hazards analysis for study III showed the same result on assuming that all patients had been at risk for the same period of time (constant follow-up time) [178].

9.1.2 Random Error

If our study bases had been larger, we obviously would have been more certain that uncounted or random errors could not explain the deviation from unity. In studies I-IV, the size of the study population is determined by the number of patients treated at Radiumhemmet and Stockholm Söder Hospital, and this may be insufficient to maintain good precision. In studies II and III, technical problems prevented us from including patients from Stockholm Söder Hospital in the DVHs analyses. We stress that the statistical power of our data is limited chiefly by the relatively small number of patients with symptoms or the number of patients available for the assessment.

9.1.3 Symptom Documentation (study VI)

Detailed information on the occurrences of different long-term distressful symptoms related to details of the specific therapy is needed in order to suggest therapy modifications with the aim of improving the situation of cancer survivors. Our method of research is described in detail in study VI. We focus on the subjective long-term sequelae and define symptoms as a perceived abnormality. For conceptual clarity, we abandon summarizing items/scores/questionnaires and consider instead one symptom at a time. Also, when single symptoms are clearly elucidated; specific pathophysiological mechanism may be possible to find. Measures of disease occurrence in the population are translated epidemiologically into measures of symptom occurrence in the individual facilitating clarity. The measures developed can be applied in clinical practice as well.

A symptom has different dimensions, i.e. nature, occurrence, intensity and duration. *Nature* distinguishes one symptom from another. *Occurrence* describes how often the symptom appears and is measured in terms of incidence or prevalence. Incidence is the number of events per unit of time (e.g number of defecations per week) and prevalence is the proportion of occasions with a condition/symptom divided by the total number of occasions (e.g defecation occasions with intense urgency divided by the total number of defecation occasions). *Intensity* describes the severity of a specific symptom and can be measured on a

verbal category scale (e.g. none/little/moderate/much), a visual digital (e.g. a 7-point numbered scale anchored by the worst possible and the best possible situations) scale, or a visual analogue scale (e.g. the VAS scale for pain where no numbers but only a line is seen). *Duration* describes the time dimension of a symptom, for example, how long it persists on each occasion.

In the next phase, each symptom's specific degree of distress is evaluated in order to measure its relevance. This can be evaluated either by asking questions about the effects of symptom on, for example, travel frequency or by asking to what degree the symptom would distress (none/little/moderate/much) the subject if he/she had to live with the symptom for the rest of his/her life. The distress a specific symptom causes depends not only on the dimensions mentioned above (nature/occurrence/intensity/duration) but also on the individual's ability to cope with them. Many factors influence this last factor, including personality characteristics, religion, and the social factor.

9.2 General Discussion

Diminishing the dose given to the anal-sphincter region may be important to reduce the risk of long-term fecal leakage and diminishing the dose to the rectum may reduce the risk for defecation-urgency (II-III). Dose-volume histograms concerning the anal-sphincter region differed statistically significantly between those having, or not having, fecal leakage in the range 45-55 Gy (III). Increasing the dose to a large portion of the anal-sphincter region was associated with an increased risk for long-term fecal leakage (III). Increasing the dose of 35 Gy or more to more than 60 percent or 40 Gy or more to more than 40 percent of the anal-sphincter region was associated with fecal leakage and blood and phlegm in stools. Dose-volume histograms for the rectum in the interval 25-42 Gy were statistically significantly related to the risk of defecation urgency and diarrhea (III). No statistically significant association was found between blood and phlegm in stools and the dose to the rectum or anatomical rectal volume (III). Increasing the mean dose to more than 39 Gy to the anal-sphincter region was associated with fecal leakage and blood and phlegm in stools. Among those treated with a multi-leaf collimator, four fields entailed a higher risk of defecation-urgency and diarrhea compared to three fields (one PA and two oblique) (I). However, the risk was lower (although not statistically significant) for pad-requiring fecal leakage and distress involving the gastrointestinal tract (I). Fecal leakage ranked highest when gastrointestinal distress was related to the occurrence of specific bowel symptoms (I). Three fields (one PA and two lateral) with a conventional collimator entailed a higher risk of

defecation-urgency than the three-field technique with a multi-leaf collimator (I). The percentage of men with preserved erectile function after external beam radiation therapy for localized prostate cancer can be increased by using a conformal therapy and there was no relationship between the treated volume and erectile dysfunction (IV).

9.2.1 Anal Sphincter and Large-Bowel Dysfunction

Today's documented frequencies of fecal leakage after radiotherapy to the small pelvis refer to yesterday's technology. However, we can use historical data to refine today's treatment, better follow up patients with radiation sequelae, and define a threshold making future radiation harmless. Any comparison of the present results with those of previous studies is compromised by variations in the prescribed dose, the planning target volume, the treatment techniques, and the methods of assessing anal sphincter and large-bowel symptoms. External beam radiation therapy for prostate cancer may result in fecal leakage. In previous studies, Widmark and coworkers reported fecal leakage in 27 percent of the men irradiated in 1986-89 [208]. Yeoh and coworkers found fecal incontinence in 26 percent (9/34) of patients having received 55 or 64 Gy for prostatic carcinoma in 1996-97 [211]. In the present study, we found fecal leakage in 14 percent (9/65). However, our data indicate that this distressful late effect can be avoided.

Recently, Vordermark and coworkers reported a statistically significant difference in minimum dose to the anal canal with higher doses for severe fecal leakage [199]. They also found a significant difference in the inferior extension of the fields between patients with and without the symptom [199]. In the present data, we did not find any relationship between a minimum dose to the anal-sphincter region and fecal leakage, but we found a correlation between mean dose and fecal leakage. Also, the DVHs at 45-55 Gy were statistically significantly correlated with fecal leakage.

Yeoh and coworkers reported that the fecal incontinence score was inversely related to basal anal pressures and anal pressures in response to squeezing in patients with persistent anorectal symptoms at one year after radiotherapy for prostatic carcinoma. Anorectal symptoms are associated with rectal sensitivity [211]. An early study reported that fecal incontinence was associated with a minor reductions in anal-sphincter region pressures four to six weeks after radiotherapy [213]. Damage to the blood vessels that supply blood to the anal-sphincter muscles, fibrosis, and loss of function may have contributed to the leakage.

Adolfsson and coworkers previously found a prevalence of 4 percent of fecal leakage and 10 percent of defecation-urgency symptoms (any degree) in the general Stockholm population [1]. In a separate study from Stockholm, population controls reported a 2 percent prevalence of fecal leakage (at least once a month), 11 percent of diarrhea (at least once a month) and 2 percent of defecation-urgency (every other time or more) [77]. The prevalence of fecal leakage, defecation-urgency, diarrhea, and blood or phlegm in stools in all four groups in the present study was higher than the previously found background prevalence in the Stockholm population. Thus, radiotherapy for prostate cancer in Stockholm during 1993-96 increased the risk of symptoms of fecal leakage, defecation-urgency, diarrhea, and blood and phlegm in stools.

Diarrhea was reported by 25 percent (14/57) of patients treated with a four-field box (multi-leaf collimator, 64-66 Gy) [109]. However, diarrhea was reported by 9 percent (10/114) of patients treated with three fields (using customized cerrobend blocks to shape the radiation beam) and a treatment dose of 60-64 Gy [40]. More than one third of patients treated with a four-field box (using a conventional collimator and a treatment dose of 70 Gy) have reported urgent bowel movements [137]. In addition, 20 percent (37/189) of patients who received the same treatment with a dose of 66 Gy reported rectal urgency [206].

The development of radiation sequelae is dependent on the dose and volume of normal tissues irradiated [138,191]. Tubiana et al. suggest that a dose of at least 40 Gy is required before the risk of complications in the “abdominal cavity” increases [191]. Pilepich and coworkers reported that the lateral and perineal techniques of the prostatic boost were associated with an increased incidence of diarrhea as compared with multiple fields and rotational techniques [148]. The mean lower bowel tract volume that received a dose of 35 Gy or more for patients treated with four fields was 27 percent higher than that for patients treated with the three-field techniques. The higher prevalence of defecation-urgency and loose stools in patients treated with a four-field technique may be due to the higher dose received by the lower bowel tract in patients treated with four fields compared with those treated with the three-field technique. Increasing the dose of 35 Gy or more to a large portion of the rectum was associated with an increase in the risk of long-term defecation-urgency and diarrhea. We found that the mean dose volume histograms correlated statistically significantly with defecation-urgency and diarrhea at dose range 25-42 Gy. It has been suggested that diarrhea without tenesmus, blood, or mucus discharge may be a manifestation of injury at the more proximal segments of the bowel [146,148]. Built on a biological

rationale one might argue that diarrhea depends primarily on the dose to the more proximal segment of the bowel and defecation-urgency depends on the dose to the sigmoid colon region. We have no data to judge whether the dose to different parts of the rectum is of varying importance for defecation-urgency.

A 14 percent prevalence of rectal bleeding in irradiated prostate cancer patients was reported by Lilleby and coworkers [109] and a 34 percent prevalence was reported by Dearnaley and coworkers [40]. In comparison, Henningsohn and coworkers reported a prevalence of 2 percent blood or phlegm in stools (at least once a month) in the general Stockholm population [77]. Undoubtedly, radiotherapy, as given in our study and to the men in the published cohorts, results in an excess risk of blood and phlegm in stools.

Emami and coworkers found that there was no volume-effect for severe late effects in the rectum [45]. Smit and coworkers stated that the two-year actuarial prevalence of moderate or severe proctitis was 22 per cent for anterior rectal doses of less than 70 Gy and 60 percent with a dose of more than 75 Gy [179]. The authors found a statistically significant association between the dose to the anterior rectum and proctitis, but they did not find any association with the dose to the posterior rectum. However, Cho and coworkers found that a dose exceeding 50 Gy to the posterior rectum was associated with an increased prevalence of proctitis after radiation therapy [28]. In the present study, no correlation was found between the dose to the rectum and blood and phlegm in stools 2-4 years after radiotherapy. However, the association between these symptoms and the dose to the anterior or posterior rectum was not studied and our study has limited precision due to small numbers.

In a recently published study comparing the dose to the rectum or anal-sphincter region and rectal bleeding in patients treated with 66 Gy using conventional and conformal techniques, Koper and coworkers found a statistically significant difference of 2.9 Gy between the average percentage DVHs of the rectum with or without inclusion of the anal-sphincter region for bleeders and nonbleeders [92]. They also found a difference between the average percentage DVHs of the anal-sphincter region for bleeders and nonbleeding patients but it was not a statistically significant [92]. Interestingly, their delineation of the anal-sphincter region was similar to ours (3 cm caudally). We found a difference of 8.2 Gy between the average percentage DVHs of the anal-sphincter region for patients with or without blood and phlegm in stools.

In a multi-institutional study, Fiorino and coworkers suggested that exposing the rectum to a dose of 50 Gy or more to less than 60 percent of the rectal volume may keep the risk of late rectal bleeding reasonably low [48]. Jackson and coworkers reported that there was a statistically significant association between rectal bleeding and the percent volumes exposed to intermediate doses (40-50 Gy) and doses over 70 Gy. In addition, they stated that the likelihood of bleeding increased significantly for patients with smaller rectal wall volumes [89]. Moreover, in a randomized trial comparing conformal radiation therapy with 70 Gy vs. 78 Gy, Pollack and coworkers found that increasing a dose of 70 Gy or more to more than 25% of the rectum was associated with a 4-fold increased risk of rectal complications of grade 2 or more [94,151]. In the present data, we found no association between the mean dose to the rectum and blood and phlegm in stools at intermediate or higher doses. Also, there was no relationship between the anatomical rectal wall volume and blood and phlegm in stools. In the current study, all men received a dose of 67 Gy or more to 45 percent or more of the rectal volume. Furthermore, all men received a dose of 70 Gy or more to 25 percent or more of the rectal volume, indicating that all men in our study ran a certain risk of rectal bleeding. At these doses, the risk of bleeding is high. This fact, and our small-sample study, may partly explain why we found no correlation between blood and phlegm in stools and rectal dose volume histograms. We found a statistically significant correlation between dose volume histograms of the anal-sphincter region and blood and phlegm in stools at doses less than 37-54 Gy. Here, also, it may be possible to correlate the dose to the lower part of the rectum and with blood phlegm in stools in a future study.

In contrast to Michalski and coworkers, we found no statistically significant association between a depicted anatomical rectal volume exceeding 100 cm³ and blood and phlegm in stools [133]. We obtained a relative risk of fecal leakage and defecation-urgency that was about four times higher in patients with 100 cm³ or more of anatomical rectal volume (including the filling) than in patients with a rectal volume of more than 100 cm³. However, the relationship was not statistically significant. In addition, excluding patients with a whole rectum volume of = 100 cm³ did not change the results.

In a study including 130 patients, Boersma and coworkers found no correlation between late rectal bleeding (≠ grade II) observed in 16 patients and any of the dose volume histogram parameters examined. However, severe rectal bleeding (requiring = one laser treatment or blood transfusion) was statistically significantly associated with a received dose of 65 Gy or more to 40 percent, 70 Gy or more to 30 percent, or 75 Gy or more to 5 percent of the rectal

wall volume [19]. Dale and coworkers investigated the lower bowel-tract symptoms of 52 patients and found no statistically significant correlation between dose volume histogram parameters and rectal bleeding [35]. The high dose volume fractions of DVHs were best correlated with the occurrence of late effects in the rectum [35]. However, in their study, fecal leakage was not assessed. We found no relationship between rectal DVHs and blood and phlegm or fecal leakage.

9.2.2 Sexual Dysfunction

The present data support the view that the relationship between age and insufficient erectile function is worsened by radiation. The percentage of men with preserved erectile function in the respective age groups, was lower at the 4 to 5.5-year follow-up than at the 1 to 1.5-year follow up. This effect was most pronounced among men 71-80 years of age. Such a "delayed effect" on erectile function by radiation has been described previously by Mantz and coworkers [123]. If this interaction between age and radiation is substantiated by further clinical data, the phenomenon should be considered when mechanisms pertaining to the effect of radiation on potency are proposed.

The dose to the bulb of the penis may determine the risk of erectile dysfunction [50,130,131]. A dose of 50 Gy or more to 50 percent of the bulb of the penis was associated with an increased risk of erectile dysfunction [130,131]. But, there was no relationship between radiation dose to the neurovascular bundles and erectile dysfunction [129]. If our findings are substantiated, we need to find a mechanism to explain why primarily the collimation technique and not the treated volume determines the proportion of men becoming impotent after external beam radiation therapy. It is reasonable to assume that the nervi erigentes are included in the target volume in both techniques. The multi-leaf collimator probably decreases tissue exposure outside the target area (the bulb of the penis) and thus prevents unwanted damage of, for example, blood vessels. However, we do not know if vascular changes, rather than endocrine or neurological ones, are the most important reason for altered erectile function after external beam radiation therapy [61,129,215].

In study **I**, the preservation of potency in a patient population treated with the three-field technique using a multi-leaf collimator was lower than in a patient population treated with a similar treatment protocol in study **IV** at a 1-1.5-year follow-up but was similar to the results of the 4 to 5.5-year follow-up. The risk of erectile dysfunction probably increases with time to follow-up [116,177].

9.2.3 Urinary Dysfunction

In the present study, the data showed that there were no statistically significant differences between the patient groups treated with the 3-field and 4-field techniques regarding urinary symptoms, with the exception of the increased prevalence of a weak urinary stream in patients treated with four fields. In fact, the bladder base, the urinary sphincter and the involved urethra lie within the radiation target volume when using 3 or 4-field technique; this may explain why there were no statistically significant differences between the patient groups.

10. Conclusions

? Careful monitoring of unwanted radiation to the anal-sphincter region, rectum may reduce the risk of fecal leakage, blood and phlegm in stools, defecation-urgency, and diarrhea; it is probably possible to define a threshold for a by and large harmless dose (in terms of induced dysfunction) to the anal-sphincter region (35 Gy or more to, at the most, 60% or 40 Gy or more to, at the most, 40% of the anal-sphincter region?). Diminishing the dose to small bowel may reduce the risk of diarrhea and the dose to sigmoid-colon region may reduce the risk of defecation-urgency.

? Among patients treated with a multi-leaf collimator, defecation-urgency, diarrhea and loose stools were more common in those treated with four fields than in patients treated with three (AP, two oblique), but fecal leakage necessitating the use of pads and distress involving the gastrointestinal tract were less common. Three fields (one AP and two lateral) without a multi-leaf collimator entailed a higher risk of defecation-urgency than three fields (one AP and two oblique) with a multi-leaf collimator. Among bowel symptoms, the strongest association with gastrointestinal distress was found for fecal leakage. The choice of three or four fields may imply a contrasting risk scenario for defecation-urgency or diarrhea in comparison to fecal leakage.

? Conformal therapy may increase the percentage of men preserving erectile function, after radiotherapy for localized prostate cancer; it is possible that the difference compared to conventional therapy may not depend on the treated volume.

? The test-retest reliability for anal sphincter, large-bowel, and urinary symptoms indicates that the surveys yield meaningful information. When comparing the impact of different symptoms of anal sphincter, large-bowel, or urinary tract dysfunction, it may be important to consider that defecation urgency and urinary urgency have the highest measuring error (low reliability).

11. Study Implementations

- The findings in this study could serve as a basis/impetus for large investigation to explore DVHs and anal sphincter and large-bowel function in the era of *Intensity Modulation Radiation Therapy*.
- Limiting the dose of 35 Gy or more to 60 percent or of 40 Gy or more to 40 percent to the anal-sphincter region during pelvic treatment may prevent fecal leakage, which is the most distressing symptom in the pelvic region. At this threshold, it may possible to prevent or decrease blood and phlegm in stools.
- Delivering the dose with a 3-field (one PA and two oblique) conformal technique may be a better choice if the dose to the anal sphincter is kept to 35 Gy or more to, at the most, 60 percent or of 40 Gy or more to, at the most, 40 percent of the anal-sphincter region. In contrast, with a 4-field technique the dose to the anal-sphincter region should be limited as with three fields and the dose to the sigmoid colon to less than 35 Gy.
- It may be fruitful to delineate the organs at risk such as the anal sphincter, rectum, sigmoid colon and the bulb of the penis during the treatment planning to limit the dose to these organs.
- Using all advanced imaging techniques may minimize the target volume, target mobilization, and the dose to organs at risk surrounding the prostate. This may prevent or decrease the damage to the anal sphincter and large-bowel, and sexual dysfunction.

12. Future Studies

? Chronic fecal leakage after radiotherapy is the most distressing symptom among those involving organs in the small pelvis. The anal sphincter receives unwanted radiation during treatment of the bowel, the ovary, the prostate, the urinary bladder, the uterine cervix, the uterine corpus and the vagina. Reports on fecal leakage after radiotherapy are scarce and of late appearance. Based on the present and previous data one could estimate (roughly) the prevalence of fecal leakage in the survivors of cancer in the small pelvis as a consequence of radiotherapy. To confirm the present data, we need a large study comprising subjects with an earlier cancer in the small pelvis treated with radiotherapy, and we need to reconstruct dose planning using a method similar to that in the present study. A questionnaire with detailed information on fecal leakage, and other symptoms that may result from a dysfunctional anal sphincter and modifiers of fecal leakage such as the solidity of the stools (loose stool leak more easily than hard once) should be constructed. If the observation in the present data holds in a second larger study base fecal leakage in future patients could be prevented by giving a dose of 35 Gy or more or 40 Gy or more to, at the most, 60 or 40 percent to the anal-sphincter region.

? Since 1997 the treatment procedure at Karolinska University Hospital in Stockholm has been a combination of conformal external beam radiation therapy using a 4-field box or 3-field (one AP and two lateral) technique and high-dose-rate (HDR) temporary brachytherapy. There is a need to confirm the present data on the dose threshold to the anal-sphincter region and rectum to prevent or minimize long-term effects such as fecal leakage, rectal bleeding, defecation-urgency, and diarrhea and to evaluate the effect of HDR on these long-term effects.

? Increasing dose to the rectum is associated with higher risk of bleeding and phlegm discharge in stools. Also, increasing dose to the anal sphincter region is associated with higher risk of fecal leakage. In this thesis, we suggested that increasing the dose to small bowel may be associated with higher risk of diarrhea and increasing the dose to the sigmoid-colon region may be associated with higher risk of defecation-urgency. However, the association between the dose to lower bowel tract and symptoms such as flatulence, abdominal pain, pain during defecation, and problems initiating defecation are still unknown. In the present thesis, we suggested that inclusion of the lower part of the rectum in the anal-sphincter region may explain the correlation between the dose to the anal-sphincter region and the symptom of blood and phlegm in stools. It is possible to investigate these suggestions

by dividing the delineated rectal volume to two parts, a lower and higher part (sigmoid-colon region). A correlation between the dose to the lower part and blood and phlegm in stools and the dose to the higher part (sigmoid-colon region) and the defecation-urgency symptom may clarify our hypothesis. A delineation of a certain volume of small bowel in the pelvis may provide an opportunity to investigate the relation between dose to small bowel and diarrhea. It is also possible to investigate the relation between dose to the anal-sphincter region, rectum and sigmoid-colon region and abdominal pain, pain during defecation, and problems initiating defecation.

? The dose to the bulb of the penis may determine the risk of erectile dysfunction and conformal technique lowered this risk. It is possible to investigate the dose to sexual tissues by delineating these tissues in all potent patients who participated in the first follow-up in study IV and comparing the DVHs and, the mean, maximum and minimum dose to the delineated volumes.

13. Swedish Summary

Bakgrund: Extern strålterapi är en viktig behandling vid lokaliserad prostatacancer. Ju högre stråldos som ges desto fler botas, men möjligheten att ge höga doser begränsas av frekvensen och allvarligheten av oönskade långtidseffekter, resulterande i nedsatt välbefinnande och livskvalitet. Tredimensionell teknologi har givit stora möjligheter att analysera sambandet mellan kroniska bieffekter av strålning i förhållande till dos och volym av strålad vävnad. Hittills har sambandet mellan given dos till anala sfinkter-regionen och avföringsläckage fått relativt liten uppmärksamhet.

Patienter och metoder: Alla patienter med klinisk lokaliserad prostatacancer som fått extern strålterapi mellan åren 1993 och 1996 i Stockholm fick en enkät hemskickad med frågor indikerande dysfunktion av anala sfinktern, tunntarm, tjocktarm, ändtarm, urinvägarna och sexuellt. Information om extern strålterapi hämtades från sjukhusjournaler. Dos-volymhistogram (DVH) beräknades för anala sfinkter-regionen och rektum. Sambandet mellan dos till anala sfinkter-regionen och rektum och kroniska biverkningar undersöktes. **Resultat:** Av 158 patienter, svarade 145 (92%) och returnerade enkäten. Av de patienter som behandlats med 4fält och multi-leaf collimator (MLC) rapporterade (8/29) 28% avföringsträngningar respektive (8/40) 20% av de patienter som behandlats med 3fält teknik utan MLC. Sju av 29 (24%) behandlade med 4fält teknik angav diarréer eller lös avföring. Ingen som behandlats med 3fält teknik (en AP, två sned) och MLC rapporterade detta symptom. Korrelationen mellan DVH för anala sfinkter-regionen och risken för fekalt läckage vid 45-55 Gy var statistiskt signifikant ($p < 0.05$). Ingen patient som erhållit 35 Gy eller mer till som mest 60 procent respektive 40 Gy eller mer till som mest 40 procent av anala sfinkter-regionen rapporterade avföringsläckage. Vi fann en statistisk signifikant korrelation mellan DVH för rektum och risk för avföringsträngningar och diarré i dosintervallet 25 till 42 Gy ($p < 0.05$). Sjutton av 31 (55%) män hade bevarad erektil funktion vid 9 till 18 månader och fem av 22 (23%) efter 45 år. **Slutsatser:** Patienter som behandlats med MLC hade högre frekvens av avföringsträngningar, diarréer och lös avföring då fyra fälts används jämfört med tre fält (en AP och två sned). Däremot var avföringsläckage som stress av symptom från bäckenregionen mindre vanligt vid fyra fält. Tre fält (en AP och två lateral) utan MLC gav högre risk för avföringsträngningar än tre fält (en AP och två sned) med MLC. Fekalt läckage var det symptom från bäckenregionen som var mest stressande för männen. Minskning av oönskad strålning till anala sfinkter-regionen liksom rektum i samband med dosplanering kan minska risken för avföringsläckage, blod och slem i avföringen, avföringsträngningar samt diarré. En kritisk gräns för fekalt läckage tycks vara 35 Gy eller mer till som mest 60 procent eller 40 Gy eller mer till som mest 40 procent av anala sfinkter-regionen.

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