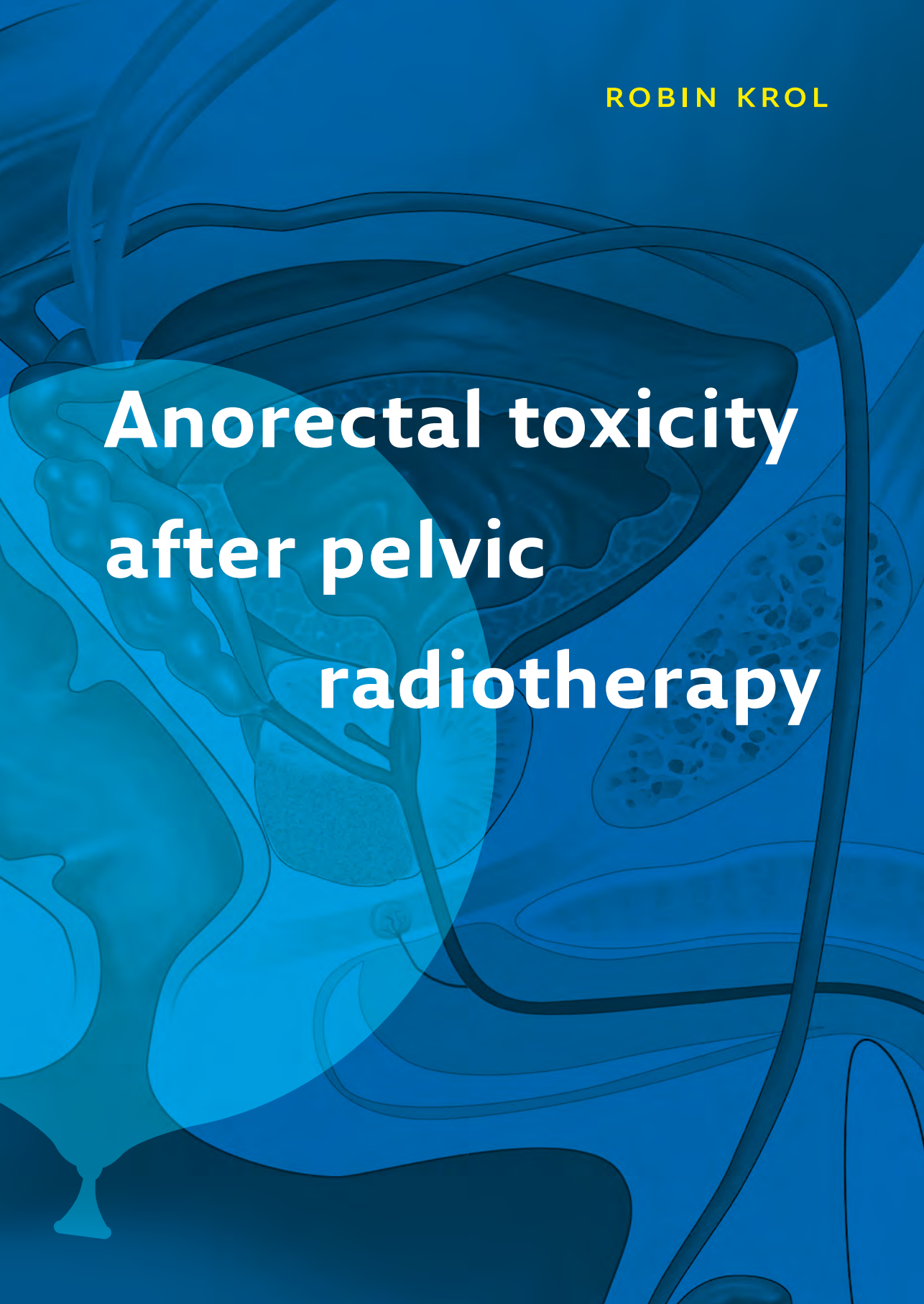
ROBIN KROL



Anorectal toxicity after pelvic radiotherapy

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Anorectal toxicity after pelvic radiotherapy

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
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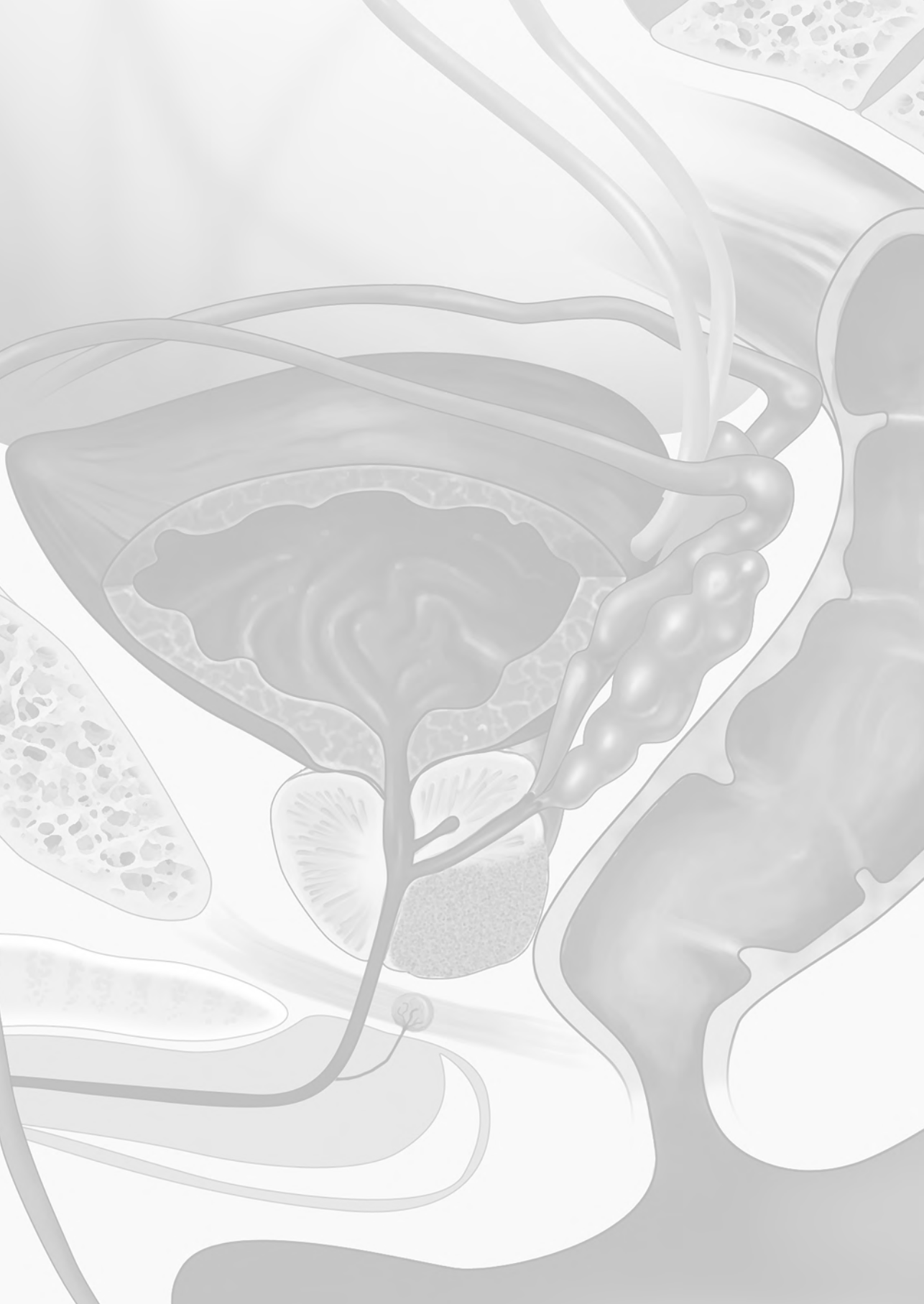
TABLE OF CONTENTS

CHAPTER 1

Introduction and Outline



Prostate cancer (PCa) is the most common type of cancer amongst men in the Western World. The number of diagnoses in the Netherlands has more than doubled in recent years, from 4.299 in 1990 to 10.935 in 2013. PCa comprises 20.7% of all cancer diagnoses (52.800 men).[1] With an incidence of 138 in every 100.000 men, the risk of being diagnosed with PCa before the age of 80 is about 10%.[2] Autopsy results show that only a minority of men will be diagnosed with PCa during life. In men aged greater than 60 years, the prevalence of PCa in autopsies is about 40%. Above the age of 79 the prevalence is reaching 60%.[3,4]

The main contributors to this rise in incidence are probably an increased PCa awareness and the introduction of PSA (prostate specific antigen) testing. Over the last two decades, PCa related mortality has declined, most likely due to more early detection.[5]

From the age of fifty, the incidence of PCa slightly rises amongst age groups. Due to aging and an increase of the Dutch population, it is expected that the incidence of PCa will rise up to 17.000 annually in 2020.[6] Assuming that PCa related mortality remains stable or declines even further, the prevalence of Dutch men with PCa will increase in the near future. The expected prevalence of PCa in 2020 in the Netherlands will be above 100.000 men.[2]

Treatment of prostate cancer

The treatment options for PCa depend on the tumor stage, tumor-associated risk factors, age and comorbidity. For localized PCa (cT1-2), the options are active surveillance/ watchful waiting, or active treatment with curative intent like radical prostatectomy, external beam radiotherapy (EBRT) or brachytherapy. For locally advanced PCa (cT3-4) treatment options consist usually of EBRT, preferably combined with hormonal therapy. In selected cases, radical prostatectomy can be considered. For metastatic disease, palliative systemic treatment regimens are required, but those are outside the scope of this thesis.

The above-mentioned curative treatment strategies have similar cure rates.[7-12] The 5-years survival rate for prostate cancer, localized and metastatic PCa combined, in the Netherland is 88%. For localized PCa, TNM stage I-III, the 5-years survival rate is $\geq$ 95%. However, it has to be noted that no randomized controlled clinical trials have been conducted to compare the treatment options in terms of oncological outcomes.

Each of the above mentioned treatment modalities have their own (dis)advantages. The therapeutic choice depends on several factors like the patient's age, performance status, comorbidity, tumor-associated risk factors and own preference. EBRT is a non-invasive treatment, with no risk of surgical complications. This could be favorable in patients with a poor general health or of high age.

Anorectal toxicity and quality of life

With survival rates of ≥95% for localized PCa, the survival after treatment almost equals the survival rate of men in the same group of age without PCa. Due to these high survival rates, the focus of attention in the treatment of PCa has shifted towards maintenance of quality of life (QoL) after PCa treatment which is mainly affected by long-term adverse events.2

Radical prostatectomy is associated with urinary and sexual dysfunction, whereas with radiotherapy (either external beam radiotherapy or brachytherapy) gastrointestinal side effects are more prevalent.[2,13,14]

Gastrointestinal symptoms which occur directly or shortly after the start of EBRT are classified as acute radiation toxicity. Symptoms arising ≥3 months after EBRT are termed late radiation toxicity and specifically for gastrointestinal sequelae "late anorectal toxicity" (LAT). LAT comprises different symptoms like rectal blood loss, increased frequency of defecation, urge and fecal incontinence.[15,16]

These symptoms are often called radiation proctitis, although (late) anorectal toxicity is a more accurate name because inflammation is not the only pathophysiologic mechanism involved. Fibrosis of the rectal wall, mucosal atrophy and vascular changes also contribute.

This thesis will focus on LAT after prostate EBRT.

External beam radiotherapy

Prevention of LAT after prostate EBRT is an important goal of modern radiation techniques. The volume of the anorectal complex inside the irradiated volume and the radiation dose in this area are directly correlated to LAT.[17,18] The close anatomic relation of the prostate with the rectum and anal canal makes it inevitable that those structures receive some radiation dose.

New radiation techniques like intensity-modulated radiotherapy (IMRT), volumetric rapid arc therapy (VMAT) and image-guided radiotherapy (IGRT) are implemented in contemporary radiation programs. All these techniques have led to a significant reduction of radiation dose to rectum and anal canal without compromising the dose and dose-homogeneity to the tumor. IGRT made it possible to check prostate position prior to each treatment session and, if necessary, correct a patient's position. This made it possible to narrow safety margins to the treatment volume and to reduce the dose to the anorectal structures.[15,19-21] Currently, hypofractionated radiotherapy is increasingly being used. With this technique the radiation dose is given in less fractions. The thought behind this hypofractionation is the proposition that prostate cancer has a high fractionation sensitivity, even higher than some late responding healthy tissues.[22,23] There-

fore, a higher fraction dose can create a greater dissociation of radiotherapy effects between tumor and healthy tissues. The first comparative studies with hypofractionated radiotherapy for PCa are published. Oncological outcome measures for hypofractionated EBRT seem to be non-inferior compared to conventional EBRT, with overall equal or just a slight increase in toxicity.[24-26]

Increasing the distance between the prostate and rectum, by use of a daily inserted endorectal balloon during EBRT (**Figure 1**), decreases radiation doses on lateral and dorsal parts of the rectal and anal wall.[27-29] The balloon is inserted during every session of irradiation to push large parts of the rectum out of the high-dose radiation field. Furthermore, an endorectal balloon (ERB) immobilizes the prostate during treatment, thereby reducing intrafraction motion and uncertainty margins.[30-33]

Although many planning studies suggested a beneficial effect of the ERB and several reports described toxicity rates after EBRT with daily inserted ERBs, only one comparative clinical study has been published so far. *Van Lin et al*. showed that patients treated with ERB experienced significantly less rectal toxicity objectified by repeated rectoscopy.[29]

Despite the improvements in radiation techniques over the last decades LAT still occurs quite often. More than 65% of men who received 3D conformal radiotherapy or IMRT for PCa suffer from Grade 1 anorectal toxicity, about 35% Grade ≥2 and up to 6% has Grade ≥3, scored by the EORTC toxicity-scale. Symptoms related to LAT can influence QoL, especially Grade 3 and 4 toxicity may have major influence on QoL.[34,35]

Figure 1 *An endorectal balloon*

Anorectal structure and function after EBRT

Radiation causes cell death in the target tissue, but also damages the surrounding healthy tissues. This tissue damage results in function loss, which can lead to symptoms and an impaired QoL. Therefore, the occurrence and severity of LAT is related to the radiation dose and volume of the rectal and anal wall exposed (**Figure 2**).[16,36,37] Pathophysiological changes that lead to the development of LAT are poorly understood. Reduced rectal sensory function, anorectal motor function, vascular changes and fibrosis are all putative causes for LAT. Several studies indicate that with higher radiation dose on the anorectal wall the prevalence of radiotherapy related symptoms increases. Especially the surface of rectal wall receiving an intermediate- or high dose determines the risk of developing symptoms and the severity.[36,38,39]

Yeoh et al. showed a deterioration of anorectal motor and sensory function over time after prostate irradiation.40,41 Weakness of internal anal sphincter function and rectal sensory volumes seem to contribute to the development of symptoms like incontinence and an increased stool frequency.[16,41,42] Furthermore, reduced rectal capacity is seen after prostate EBRT.[16,40,42]

Besides deterioration of anal and rectal motor function, EBRT causes mucosal changes in the rectal wall including telangiectasias, congested mucosa and ulceration (**Figure 3**).[43]

Figure 2 *The steps after prostate irradiation leading to impaired quality of life.*

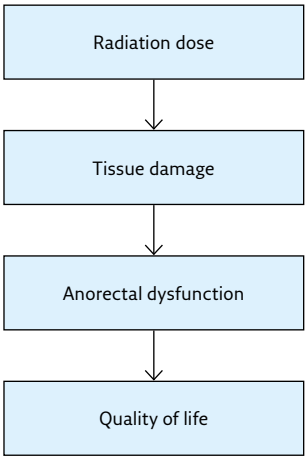
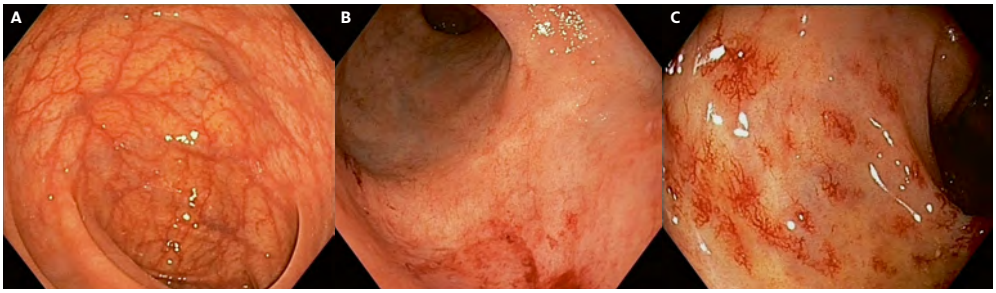


Figure 3 *Endoscopic findings after EBRT for prostate cancer.*



A Normal endoscopic view of the rectum. B Congested rectal mucosa. C Telangiectasias after prostate radiotherapy.

Understanding the contribution of specific anatomical and functional disturbances to symptoms and QoL after prostate EBRT is important as this may enable prevention of LAT by selectively sparing the relevant anatomic structures in EBRT planning. Insight into the changes in anal and rectal function and structure after EBRT will help to understand the underlying pathophysiology. It will advance our knowledge about the role of each factor and may guide future prevention and management of LAT.

Gaps in our knowledge

Most studies on LAT use physician-based scoring systems as primary endpoint, some studies describe patients reported outcome measures like the Expanded Prostate Index Composite Bowel Bother score.[44] Only a few articles describe the results of anorectal function tests or endoscopy to objectify LAT. In addition, most of these studies used conformal EBRT. objective data on contemporary radiation techniques like IMRT, VMAT or IGRT are scarce.[16,29] One study reported mucosal changes after EBRT with and without ERB and another study described anorectal function after EBRT with ERB.

Outline of the thesis

The general aim of this thesis is to gain insight into the pathophysiology of late anorectal toxicity (LAT) in men irradiated for localized prostate cancer with current state-of-the-art radiation techniques and a daily inserted endorectal balloon (ERB). In these patients symptoms, specific anal and rectal function and rectal mucosa are studied.

We will address the following questions:

1 What is the influence of prostate EBRT on anorectal function as measured by anal manometry and rectal barostat? (**Chapters 2**, **4**, **5**, **7** and **8**)
2 What is the influence of EBRT on rectal mucosa, observed during endoscopy after prostate irradiation? (**Chapters 2**, **6** and **8**)
3 Does a daily inserted ERB during EBRT reduce the frequency and severity of LAT? (**Chapters 5** and **6**)
4 Which LAT related symptom has the largest influence on QoL? (**Chapter 3**)
5 Is there a correlation between QoL and anorectal function? (**Chapters 3** and **5**)

In **Chapter 2**, an overview of objective outcome measures for LAT after prostate EBRT are given based on the literature up to 2012. The effects of EBRT on anal internal and external sphincter function, measured by anal manometry, is described. Furthermore, rectal compliance and capacity and rectal sensory function after prostate irradiation are discussed. In the same chapter, an overview of changes in rectal mucosa after EBRT is given. Finally, recommendations for future studies are made.

LAT comprises different symptoms. These symptoms seem to have different underlying pathophysiologic causes and subsequent impact on QoL. Because of the good oncologic outcomes and favorable survival, QoL after PCa treatment is gaining importance and it will be useful to know which complaints affect QoL the most. Future research should focus on the prevention and treatment of these complaints. In **Chapter 3** we describe the relation between the individual symptoms of LAT and quality of life. A cohort of 85 consecutive patients, with and without LAT underwent anal and rectal function tests and completed validated questionnaires.

It is known that there is a relation between radiation dose and volume and LAT. Identifying dose-volume parameters that are related to LAT can help to develop prevention strategies. **Chapter 4** reports on one of the largest prospective cohorts of men irradiated for PCa and the relation between the dosimetric parameters and anorectal function up to 3 years after EBRT. Furthermore, the influence of nutrients during EBRT is described.

All studies that noted rectal wall stiffness after prostate irradiation used rubber balloons to investigate rectal compliance. **Chapter 5** is the first article using the electronic barostat and an infinitely compliant bag to examine rectal compliance before and after prostate EBRT. Furthermore, patients underwent anal manometry and filled out a questionnaire on LAT prior to and one year after EBRT. Relations between function tests and symptoms of LAT are investigated.

Rectal blood loss is the symptom of LAT that has received ample attention in the current literature. However, follow-up of most studies is no longer three years. **Chapter 6** is the 5-years continuation of a comparative study between patient irradiated with and without ERB. Patients underwent repeated rectoscopies six months, one year, two years, three years and five years after prostate EBRT. The focus of this article is on mucosal telangiectasias, objectified and reported with the Vienna Rectoscopy Score.[43] Congestion, ulceration, strictures and necrosis are also described.

The influence of the ERB on anal and rectal function and thereby LAT is investigated in **Chapter 7**. This chapter describes a homogeneous group of men, irradiated with current state-of-the-art radiation techniques. Patients were investigated by anal manometry and rectal barostat on four fixed time points, prior to EBRT, and 6 months, one year and two years after EBRT.

Chapter 8 is a supplementary chapter. It is an overview written in Dutch. This chapter is partially based on the review described in **Chapter 2** and supplemented with recommendations for the treatment of LAT, giving the reader handles on which therapeutic options there are for men with LAT.

A general discussion and future perspectives, based on the abovementioned chapters, is given in **Chapter 9**.

Finally an English and Dutch summary are given in the last chapter, **Chapter 10**.

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CHAPTER 2

Systematic review: anal and rectal changes after radiotherapy for prostate cancer

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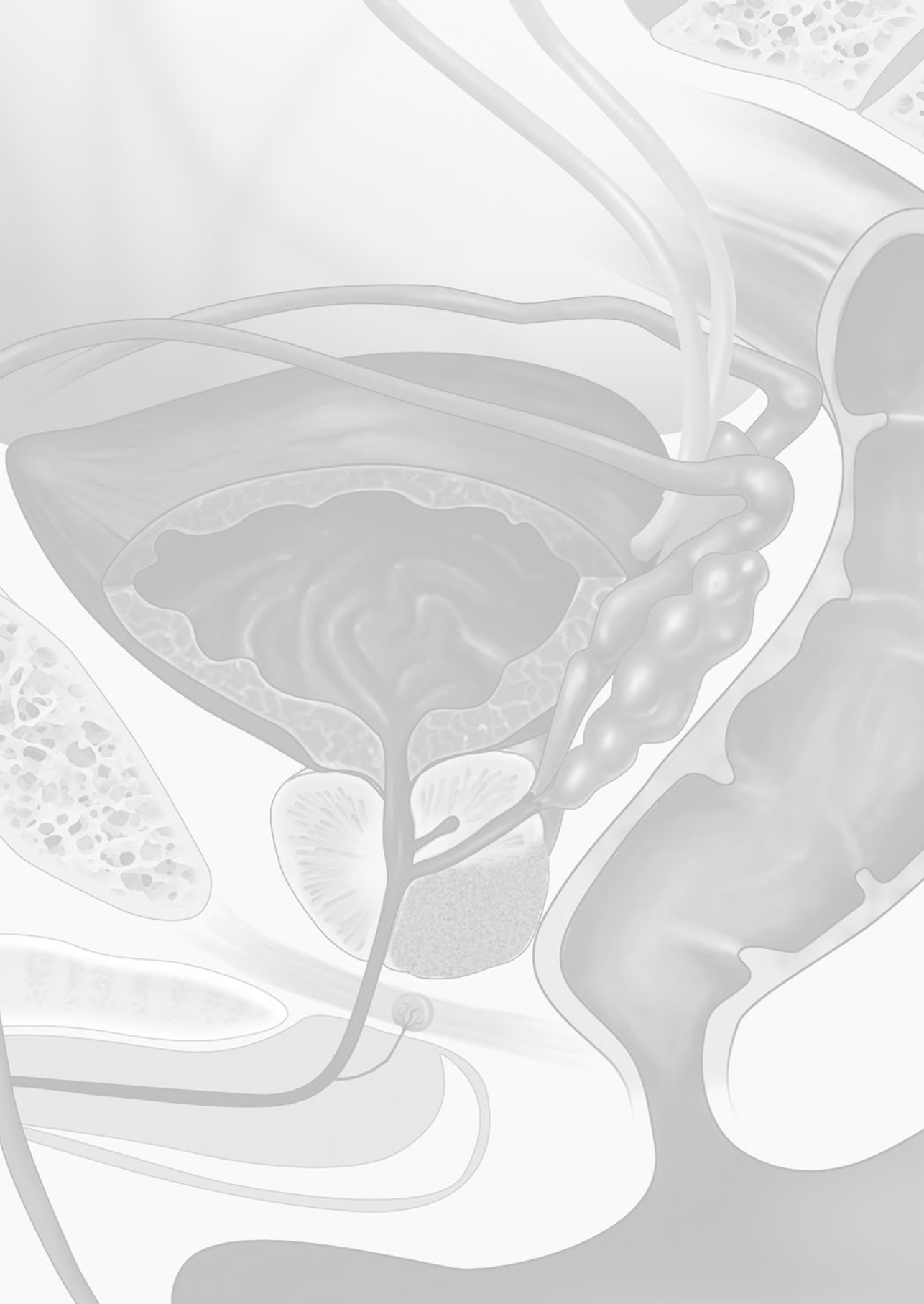

Abstract

PURPOSE Pelvic radiotherapy may lead to changes of anorectal function resulting in incontinence-related complaints. The aim of this study was to systematically review objective findings of late anorectal physiology and mucosal appearance after irradiation for prostate cancer.

METHODS MEDLINE, EMBASE and the Cochrane library were searched. Original articles in which anal function, rectal function or rectal mucosa were examined ≥3 months after EBRT for prostate cancer were included.

RESULTS Twenty-one studies were included with low to moderate quality. Anal resting pressures significantly decreased in 6 of the 9 studies including 277 patients. Changes of squeeze pressure and rectoanal inhibitory reflex were less uniform. Rectal distensibility was significantly impaired after EBRT in 7 of 9 studies (277 patients). In 4 of 9 studies on anal and in 5 of 9 on rectal function, disturbances were associated with urgency, frequent bowel movements or faecal incontinence. Mucosal changes as assessed by the Vienna Rectoscopy Score revealed telangiectasias in 73%, congestion in 33% and ulceration in 4% of patients in 8 studies including 346 patients, but no strictures or necrosis. Three studies reported mucosal improvement during follow up. Telangiectasias, particularly multiple, were associated with rectal bleeding. Not all bowel complaints (30%) were related to radiotherapy.

CONCLUSIONS Low to moderate quality evidence indicates that EBRT reduces anal resting pressure, decreases rectal distensibility and frequently induces telangiectasias of rectal mucosa. Objective changes may be associated with faecal incontinence, urgency, frequent bowel movements and rectal bleeding, but these symptoms are not always related to radiation damage.

KEY WORDS anal physiology; rectal physiology; rectal mucosa; radiation toxicity; systematic review.

Introduction

External beam radiation therapy (EBRT) is frequently used as curative treatment for prostate cancer. Although radiation techniques have improved over the last years, EBRT still causes intestinal adverse events regularly. The close anatomic relation of the prostate with the rectum and anal canal makes it almost inevitable that structural damage will occur in a small group of patients.[1-3] However, despite improvement in radiation techniques over the last decade, symptoms of anorectal dysfunction still occur often as evidenced by a 65% or more prevalence of Grade 1 or more anorectal toxicity and a 35% or more prevalence of Grade 2 or more anorectal toxicity at 7 years after 3D conformal or intensity modulated radiotherapy.[4,5] Common symptoms of late (defined as 3 months or more after EBRT) anorectal toxicity (LAT) are increased frequency and urgency of defecation, fecal incontinence and rectal bleeding.[1,6]

Attention for quality of life (QoL) has increased over the last few years, since the 5-years survival rate of prostate cancer is above 95%.[7] After prostate irradiation, QoL is largely determined by symptoms of LAT.[1,8] Improving QoL can be achieved by preventing or reducing toxicity. Several studies evaluated the prevalence and severity of LAT after prostate irradiation[1,3] or its relation with QoL.[9-11] Furthermore, reviews and overviews described the relation between radiation dose or radiation technique and the incidence of LAT.[12-14]

Therapeutic options for LAT are limited and often not as effective as desired.[15-18] It is necessary to understand the etiologic mechanisms underlying these symptoms if we want to optimize EBRT treatment and prevent toxicity. Identifying structures which are damaged after EBRT for prostate cancer and even in the absence of demonstrable morphologic changes, relating functional changes to symptoms is important. However, there is limited knowledge in these areas.[14,19,20]

A systematic review about the pathophysiology of LAT is lacking in present literature. The aim of this study was to systematically review the impact of external beam radiotherapy for prostate cancer on anorectal physiology and on mucosal changes of the rectal wall in patient irradiated for prostate cancer. There were 3 specific questions: 1) does EBRT affect anal pressures?; 2) does EBRT alter rectal distensibility and sensibility?; 3) does EBRT cause alterations of rectal mucosa, macroscopic and/or microscopic? If present, we also report any association of symptoms of LAT with objective findings.

Methods

A systematic electronic search of MEDLINE, EMBASE and the Cochrane Library was performed and included online published articles up to April 2012. The search consisted of a combination of the following entry-terms: prostatic neoplasm, radiotherapy, pathology and rectal capacity (or one of their related terms, **Table 1**).

Table 1 *Search terms*

Key-term	Related terms
Prostate neoplasm	Prostatic neoplasms; prostate cancer; prostate carcinoma; prostate
Radiotherapy	Radiation; radiation oncology; external beam radiotherapy; EBRT; intensity-modulated radiotherapy; IMRT; conformal radiotherapy; 3D-CRT
Pathology	Pathophysiology; histology; endoscopy; sigmoidoscopy; proctoscopy; colonoscopy; barostat; manometry; anal manometry; rectal manometry; anal ultrasound
Rectal capacity	Rectal sensitivity; sensory threshold; rectal compliance; compliance; rectal wall; anal wall; anal pressure; pressure; mucosa; mucosal healing; mucosal damage; telangiectasia

Search was performed by combing the key-terms or their related terms

To be eligible for inclusion, studies had to be original articles regarding the anorectal function or pathophysiology of anorectal complaints after prostate radiotherapy in men. Furthermore, the articles had to be published as full-text paper in a peer-reviewed journal. Articles were excluded if they were: written in a language other than English, German or Dutch; a review, case-report or a letter to the editor; follow-up <3 months after EBRT; Studies regarding pelvic radiotherapy, but with only a minority of prostate cancer.

All selected articles were scored by using a valid checklist, first described by Downs et al.[21] Only items applicable for the study design were scored. Therefore, we did not score items regarding lost to follow-up for cross-sectional studies and items of randomization and similarity between groups for articles with an one-group design. (RK and WH independently scored all articles and disagreements were resolved by consensus).

Finally, an adapted Data Extraction Form was used to systematically extract relevant data from the articles (RK and WH).[22]

After the description of the search results and quality of included articles, the results section consecutively reviews anal changes, rectal changes, mucosal changes and the histological changes.

Results

Systematic literature searches

The search in the various databases identified 388 articles (222, 157 and 9 in MEDLINE, EMBASE and the Cochrane Library respectively), of which 54 were selected based on their title and abstract. After removing duplicates, manual search of references and

reading the full-text, there were 21 articles that fulfilled all in- and exclusion criteria (RK and WH). A detailed overview is given in **Figure 1**.

Figure 1 *Flow-chart literature search*

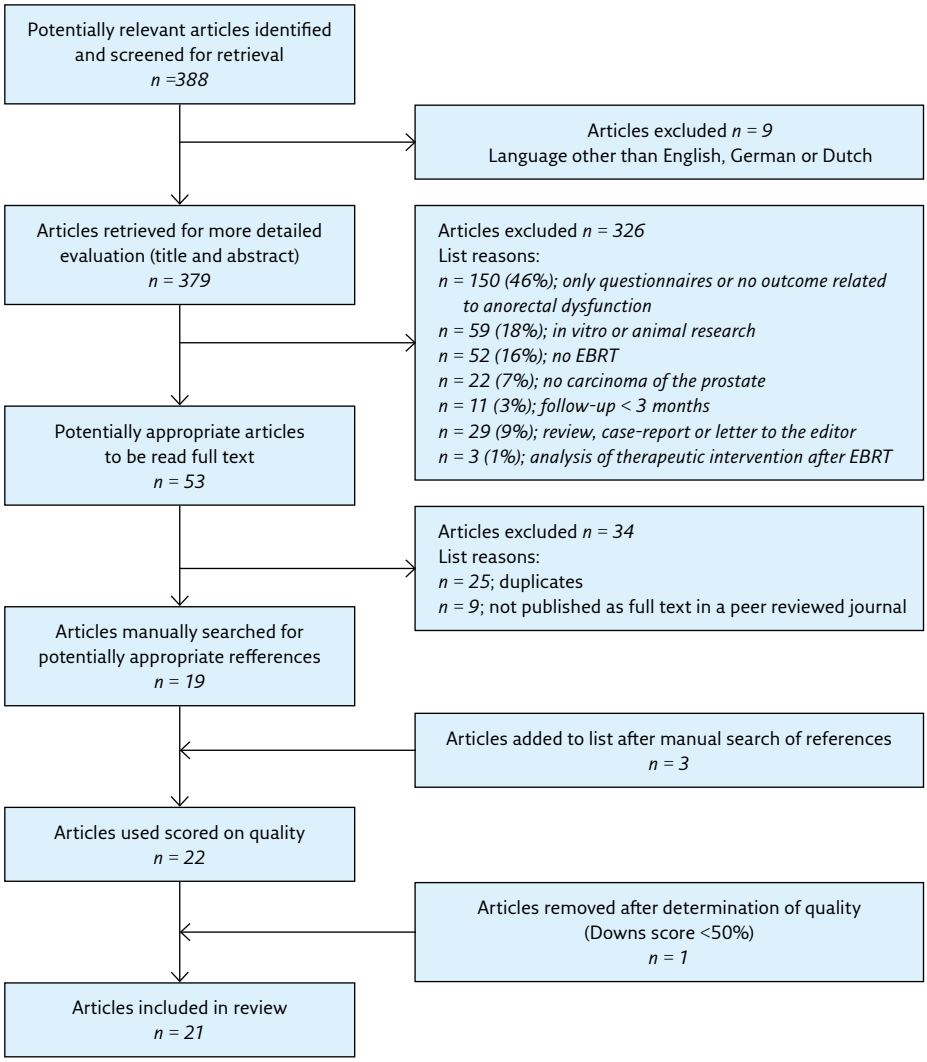

Table 2: overview included articles

Author	Year	n	Radiation Technique	Dose (Gy)	Type of study	Control	Time after EBRT	Check-list Downs
Andreyev	2005	265	3D	60-74	Cross-sectional	-	2.5 years	56%
Berndtsson	2002	10 vs. 10	3D	70	Cross-sectional	Age/gender matched	22 months	69%
Friedland*	2006	20	n.r.	74	Cross-sectional	Own control	7.2 years	72%
Goldner	2011	20	3D	70-74	Pretest-Posttest	Prior to EBRT	65 months	56%
Goldner	2007	166	3D	70-74	Pretest-Posttest	Prior to EBRT	2 years	72%
Ippolito	2012	101	3D / IMRT	74	Cross-sectional	-	1 year	59%
Krol	2012	32	n.r.	64-78	Pretest-Posttest	Prior to EBRT	1 year	81%
Kushwaha	2002	25	3D	60-64	Pretest-Posttest	Prior to EBRT	6 months	56%
Moore	2000	63	3D	60-70	Cross-sectional	-	1 year	59%
Muanza	2005	18	3D	66-76	Pretest-Posttest	Prior to EBRT	3 months	69%
O'Brien	2004	20	3D	65	Pretest-Posttest	Prior to EBRT	3 years	63%
Sedgwick	1994	9	2D / 3D	50-53	Pretest-Posttest	Prior to EBRT	4 months	66%
Smeenk	2012	60 vs. 30	3D / IMRT	67.5-70	Cross-sectional	Age-gender matched	35 months	78%
Van Lin	2007	24 vs. 24	3D	67.5	Cohort control	With vs. without ERB	2 years	69%
Varma	1985	10 vs. 10	Small-field	50	Cross-sectional	Age/gender matched	3.5 years	59%
Varma	1986	10 vs. 10	Small-field	50	Cross-sectional	Age/gender matched	3.5 years	56%
Wachter	2000	44	3D	66	Cross-sectional	-	29 months	75%
Yeoh	2000	35	2D	55-64	Pretest-Posttest	Prior to EBRT	1 year	69%
Yeoh	2004	38	2D	55-64	Pretest-Posttest	Prior to EBRT	2 years	66%
Yeoh	2009	29	2D / 3D	55-64	Pretest-Posttest	Prior to EBRT	2 year	72%
Yeoh	2010	38	2D / 3D	55-64	Pretest-Posttest	Prior to EBRT	1 year	75%

Abbreviations: n = number of patients; EBRT = External Beam Radiotherapy; 3D = 3 dimensional conformal radiotherapy; IMRT = Intensity-modulated Radiotherapy; nr = not reported; ERB = Endorectal balloon

Quality of the studies

This review comprises 21 articles. Nine of the included studies had a pretest-posttest design. One study was a comparative cohort study, one studies had a posttest-posttest design and the remaining studies had cross-sectional designs, most of them with an age and gender matched control group (**Table 2**).

All studies scored at least 55% of the available points on the quality scale, the modified Downs score. Not reporting lost to follow-ups and a lack of blinding were the main reasons for losing points.

A large heterogeneity between the studies was noticed. Some selected patients based on symptoms after EBRT, whilst others had a prospective design starting prior to radiotherapy. Furthermore, there were multiple primary outcomes and measurement techniques used in the included studies. The estimated overall quality of the evidence according to the GRADE system for most outcomes was low.[23]

Table 3 *Anal pressures after EBRT and sphincter morphology*

	Study characteristics			
References	**Year**	**N**	**Control group**	**Mean Follow up**
Varma, et al	1986	10/10	Control group	3.5 year
Yeoh, et al *	2000	35	Baseline	1.5 year
Berndtsson, et al	2002	10/10	Control group	2 years
Kushwaha, et al	2003	25	Baseline	0.5 year
Yeoh, et al * *(1yr/2yr)*	2004	38	Baseline	2 years
Yeoh, et al *	2009	29	Baseline	2 years
Yeoh, et al *	2010	38	Baseline	1 year
Smeenk, et al	2012	60/30	Control group	2.5 years
Krol, et al	2012	32	Baseline	1 year

Abbreviations: IAP = Intra-abdominal pressure; RAIR = Rectoanal inhibitory reflex; IAS = internal anal sphincter; EAS = external anal sphincter; NS = non significant.

Influence EBRT on anal canal

1 Anal function: **Table 3** lists studies on anal function. Various manometric techniques were used to assess anal canal pressures including the sleeve sensor[24-27] and the station pull-through method.[20,28,29]

Most studies compared results after EBRT with measurements prior to irradiation in the same group. Six of the 9 studies showed a significant decrease in anal resting pressure after EBRT. One study showed anal resting pressure increased at 1 year compared with baseline.[25] Five of the nine studies reported a deterioration of the squeeze pressure[20,24,26,27,30], the other 4 studies showed no significant difference. An important difference between the studies conducted by the group of Yeoh and the other groups was that squeeze pressures were reported without correcting for anal resting pressures by the Yeoh group, but this group was the only one to use a sleeve sensor which records the maximum resting and squeeze pressures independent of the axial and radial position of the anorectal manometric assembly.

Anal function				**Anal morphology**	
Resting pressure	**Squeeze pressure**	**Response to increased IAP**	**RAIR**	**Diameter IAS**	**Diameter EAS**
Decreased	NS	-	Decreased amplitude	-	-
Increased	Increased	NS	-	NS	NS
Decreased	Decreased	-	-	-	-
Decreased	Decreased	NS	-	-	-
Decreased/ Decreased	Decreased/ Decreased	Decreased/ Decreased	-	NS/ NS	NS/ Increased
Decreased	Decreased	Decreased	NS	NS	Decreased
NS	Decreased	Decreased	-	NS	NS
Decreased	NS	-	-	-	-
NS	NS	-	-	-	-

* Yeoh et al report the squeeze pressure as maximum pressure in the anal canal during active squeezing, without correcting for the anal resting pressure. Other studies report squeeze pressure as maximum pressure during active squeezing with correction for the resting pressure.

Recto-anal inhibitory reflex was not different after EBRT when compared to the measurements prior to EBRT.[24,30] In contrast, an earlier study showed an increased duration but not depth of anal relaxation in response to rectal distention[26] and amplitude of the reflex was decreased in a selected group of patients, compared to a healthy control group[31] (**Table 3**).

After radiotherapy anal pressures in response to increased intra-abdominal pressure were lower in half of the studies (**Table 3**). When the decrease was noted, it started directly after EBRT, as it was measured after 1 month.

Anal electrosensitivity, measured with an urethral ring electrode, stayed unaffected after EBRT.[20]

2 Morphology: 4 studies reported external and internal anal sphincter diameters as measured by ultrasonography. Internal anal sphincters did not change and opposite changes in maximum thickness of the external anal sphincter after EBR were found in 2 studies (**Table 3**).

3 Symptoms: Urgency of defecation was related to lowered anal pressures in two studies.[28,29] One study reported reduced anal resting pressures[29], whilst another found reduced squeeze and maximum pressures.[28] *Yeoh et al* also observed inverse relationships between scores for urgency or fecal incontinence with anal canal pressures, including resting and squeeze pressures.[24,25]

Table 4 *Rectal capacity, compliance and sensory thresholds after EBRT*

References	Year	Number of patients	Mean Follow up	Control group	Rectal capacity	Rectal compliance
Varma, et al	1985	10	3.5 year	Control group (n=10)	Decreased	Decreased
Yeoh, et al	2000	35	1.5 year	Baseline	-	-
Berndtsson, et al	2002	10	2 years	Control group (n=10)	-	-
Kushwaha, et al	2003	25	0.5 year	Baseline (n=31)	NS	-
Yeoh, et al *(1yr/2yr)*	2004	38	2 years	Baseline	-	Decreased/ Decreased
Yeoh, et al	2009	67	2 years	Baseline	-	Decreased
Smeenk, et al	2012	60	2.5 years	Control group(n=30)	Decreased	-
Krol, et al	2012	32	1 year	Baseline	Decreased	NS

Abbreviations: FS = First sensation; FU = First urge; MTV = Maximum tolerated distension; NS = non significant

4 Potential influencing factors: irradiation with a daily inserted endorectal balloon resulted in a significantly higher squeeze pressures compared to irradiation without endorectal balloons.[29] Furthermore, the effects of different radiation techniques, 2D-conformal vs. 3D-conformal EBRT, and hypofractionated vs. a conventional radiation schedule on the anal function were compared. There were no clinically relevant differences between these techniques.[24-26] The external anal sphincter was thicker in patients treated with 2D-conformal radiotherapy, compared to patients treated with 3D-conformal radiotherapy, based on a non-randomised comparative study.[24]

Influence EBRT on the rectum

1 Rectal function: Nine studies investigated rectal function (**Table 4**). All studies showed a decrease in at least one of the outcomes of rectal function. Only two studies used the electronic barostat[28,29] which is generally accepted as most reliable method to asses rectal distensibility and sensory function.[32]
Rectal compliance (defined as ΔV/ΔP) was decreased in five out of the six studies . Only one study did not find a significant reduction, though a reduction in the area under the pressure volume curve was observed which is consistent with the downward trend observed for rectal compliance in this study (**Table 4**).[28]
Rectal capacity was measured in most studies as the maximum tolerated volume. One study used the volume at a pressure of 40 cm H2O to objectify a maximum

Volume threshold			**Pressure threshold**		
FS	**FU**	**MTD**	**FS**	**FU**	**MTD**
Decreased	Decreased	Decreased	NS	NS	NS
Decreased	-	-	-	-	-
-	Decreased	-	-	NS	-
NS	NS	NS	-	-	-
Decreased/ Decreased	Decreased/ decreased	-/ -	-	-	-
NS	NS	-	-	-	-
NS	Decreased	Decreased	NS	NS	NS
NS	NS	Decreased	NS	NS	NS

volume.[30] Four out of 5 studies reported a reduction of rectal capacity. The other study did not find a significant difference.[20] The volumes corresponding to sensory thresholds tended to decrease after EBRT. None of the studies detected a significant change in the pressures corresponding to first sensation, first feeling of urge and maximum tolerated distention.

Rectal electrosensitivity was increased 6 months after EBRT.[20]

2 Morphology: No imaging techniques were used to determine whether EBRT influences the morphology of the rectum, i.e. thickness of rectal wall.

3 Symptoms: An increased frequency of bowel movements was associated with a reduction of rectal capacity or compliance.[27,29] Rectal urgency and incontinence were associated with reduced sensory thresholds.[29] Two years after EBRT fecal incontinence was inversely related to rectal compliance.[26] Total score of anorectal symptoms was also related to rectal compliance.[33]

4 Potential influencing factors: The use of an endorectal balloon had no significant effect on the rectal capacity after EBRT.[29] Comparisons between 2D and 3D-conformal EBRT, and hypofractionated and a conventional dose schedule showed no differences in rectal function.[24,26]

Influence EBRT on rectal mucosa

1 Mucosal changes: 13 studies performed endoscopy at least 3 months after EBRT for prostate cancer.[30,34-40,41-45] Most studies used the Vienna Rectoscopy Score (VRS) to describe rectal mucosa.[37-42,44,45] The VRS divides the inner rectal mucosa into 12 mucosal areas. Furthermore, the VRS scores every area on the presence and grading of telangiectasias (Grade 0-3), mucosal congestion (Grade 0-3), ulceration (Grade 0-4), stricture (Grade 0-4) and necrosis (Grade 0-1). Other studies did not use a structured outcome measure to describe their findings.

Telangiectasias and congested mucosa were the most frequent endoscopic findings, with a prevalence of 73% and 33% respectively (**Table 5**). Only 13 of 346 patients (4%) of the patients scored with the VRS had ulcerations (all <1 cm). Neither strictures, nor necrosis were found in these patients.

Endoscopic mucosal changes were rarely seen three months after EBRT.[44] Prospective studies with a follow-up of two years or more showed a peak incidence of mucosal changes between the first and second year after EBRT. An improvement of rectal mucosa after 5 years, compared to 1 or 2 years post radiotherapy was observed in 66% of the patients.[45] Mucosal recovery at 3 years was seen after EBRT in 5 out of the 16 patients who had developed telangiectasias, 4 of them had multiple telangiectasias.[38] Another study showed a decrease in damaged mucosal areas with a low grade telangiectasias score 2 years after EBRT.[40]

Six of the 13 patients who had Grade 1 ulceration had another protocolled endoscopy after the ulceration was discovered. In 5 patients (83%) the ulcerations spontaneously recovered.[40,41]

Friedland et al showed that there was no significant difference in mucosal ischemia in patients with multiple telangiectasias compared to more proximal healthy rectal mucosa in the same patients.[36]

Table 5 *Distribution of Vienna Rectoscopy Scores in patients after prostate radiotherapy*

	Study	Year	*n*	Follow-up (years)	Grade 0	Grade 1	Grade 2	Grade 3	Grade ≥1
Telangiectasias	Wachter	2000	44	2	25	8	7	4	19
	Ben-Josef	2002	29	1	10	16	3	0	19
	O'Brien[a]	2004	20	2	4	3	12	1	16
	van Lin[b]	2007	48	2	1	4	29	14	47
	Goldner[a]	2007	84	2	36	22	19	7	48
	Goldner[a]	2011	20	5	6	n.r.	n.r.	n.r.	14
	Ippolito	2012	101	1	12	38	26	25	89
	Total		**346**		**94**				**252**
Congestion	Wachter	2000	44	2	19	14	7	4	25
	van Lin[a]	2007	48	2	44	0	0	4	4
	Goldner[a]	2007	84	2	50	24	8	2	34
	Goldner[a]	2011	20	5	15	n.r.	n.r.	n.r.	5
	Ippolito	2012	101	1	71	19	11	0	30
	Total		**297**		**199**				**98**
Ulceration	Wachter	2000	44	2	42	2	0	0	2
	Ben-Josef	2002	29	1	29	0	0	0	0
	O'Brien[a]	2004	20	2	20	0	0	0	0
	van Lin[a]	2007	48	2	43	5	0	0	5
	Goldner[a]	2007	84	2	83	1	0	0	1
	Goldner[a]	2011	20	5	20	0	0	0	0
	Ippolito	2012	101	1	96	5	0	0	5
	Total		**346**		**333**				**13**

Abbreviations: n.r. not reported

a The results with the longest follow-up after radiotherapy are displayed in case of longitudinal studies with multiple measurements after radiotherapy.

b Study shows maximum grade of telangiectasias in patients instead of the maximum score at 1 time level.

Most endoscopic changes were found on the anterior rectum wall, followed by the lateral walls.[39,40,42] The posterior rectal wall, which has the largest distance from the prostate, had the least amount of endoscopic changes.

2 Symptoms: Multiple telangiectasias were strongly related to rectal bleeding, in contrast to patients who had only single telangiectasias.[39-41] Pathologic findings at endoscopy were not always associated with rectal bleeding.[43] Endoscopy was more sensitive to reveal changes compared to the frequently used EORTC/RTOG score. On the other hand, up to 34% of patients experienced rectal bleeding for reasons other than radiation-induced pathology such as hemorrhoids, diverticular disease and small adenomas.[35,39]
Furthermore, there was no relation found between congestion or micro-ulcerations and rectal bleeding.[40]

3 Potential influencing factors: The use of an endorectal balloon significantly reduced the number of telangiectasias on the lateral and posterior rectal wall compared to patients irradiated without balloon.[40]

Histological changes

Only two studies described histological findings more than 3 months after EBRT.[31,33] Unfortunately, they did not use a predefined method to describe their findings.

Two years after radiotherapy there was no sign of active inflammation, but the muscularis mucosae and propria were hypertrophic. Furthermore, the plexus of Auerbach showed hypertrophy of the nerve fibers and ganglion cells were diminished in number and had eccentrally placed nuclei.[31,33] Both studies had a cross-sectional design and selected patients with anorectal symptoms. Therefore it was impossible to determine whether these findings could be related to the radiotherapy.

Discussion

This review indicates that EBRT for prostate cancer diminishes anal canal pressure, particularly resting pressure. Furthermore, it presents evidence for a decreased rectal compliance and rectal capacity. Finally, it shows that prostate irradiation frequently leads to pathological changes of the rectal mucosa including telangiectasias and congestion. However, the amount and quality of data on objective outcome measures is limited.

The influences of EBRT on anal and rectal function

Most studies showed impaired anal pressures after EBRT. These decreased anal pressures reflect radiation damage to the sphincters and may contribute to rectal urgency and fecal incontinence. This is in line with studies which examined anal function after irradiation for anal and cervical cancer.[46-48] Deterioration of anal function was larger in

anal cancer patients when compared with the patients irradiated for prostate cancer. A plausible explanation for this difference is the higher radiation dose received by the anal canal which is the primary target of irradiation in the anal cancer patients.

In general rectal compliance after EBRT was reduced. Irradiation led to a less compliant rectal wall.[49] This explains the high frequency of complaints like rectal urgency and an increased frequency of bowel movements after pelvic irradiation.[28] Two of the most recent studies showed a smaller decrease of rectal compliance and capacity, compared to older studies.[28,29] This could be attributed to 1) the use of advanced radiation techniques, 2) the use of an endorectal balloon during EBRT, which by displacing a large part of the rectal wall away from the prostate target of irradiation has been reported to reduce radiation damage to the mucosa of the rectum.[40] In addition to the endorectal balloon, recent studies show promising dose reductions on rectal wall with the use of injected hydrogel between the prostate and rectum, a so called spacer.[50,51] Furthermore, more accurate radiation techniques involving image guidance would be expected to contribute to further reduction in structural radiation damage and thereby improve rectal function.

This review suggests that different incontinence related complaints are related to specific anorectal dysfunctions.[29] Fecal urgency and incontinence were related to decreased anal sphincter function and to impaired rectal distensibility[28,29], whereas frequency of defecation was associated with impaired rectal capacity.[29] Impairment of anal or rectal function was related to radiation doses on these structures. Therefore, not only the rectum, but also the anal canal should be delineated separately in radiotherapy planning. Modern techniques like intensity modulated radiotherapy (IMRT) can be used to spare the important structures from the damaging effects of EBRT[52], particularly as the use of a daily inserted balloon during IMRT has been shown to further reduce radiation dose the anal wall.[18]

Other potential influencing factors, like co-morbidities and medication use were not explored in the included articles. It might be interesting to know if anorectal function is worse in patients with a systemic vascular disease or pelvic surgery, for example a prostatectomy, when compared to patients without one of these factors.

Currently, complaints of anal or rectal dysfunction are often treated with anti-diarrheal agents, physiotherapy, dietary advice or sacral nerve stimulation. However, evidence for these therapies is very limited or not available.[12,18]

The influence of EBRT on rectal mucosa

Telangiectasias and congestion are the most frequently seen alterations of rectal mucosa, with a total prevalence of 73% and 33% respectively. Signs of severe mucosal ischemia such as large ulcerations or necrosis were not found in this review suggesting that severe complications of prostate irradiation such as rectal fistulae are rare if at all a long term event. The absence of evidence of chronic ischaemia in the telangiectatic

areas in the rectal mucosa by Friedland et al in no way precludes a role for ischemic damage to deeper rectal wall tissues nor the tissues or surrounding structures such as the pelvic muscles which have an impact on the pathophysiology of LAT and the fecal continence mechanism.[36]

This review shows that vascular changes sometimes decrease or disappear, without interventions, during follow up after EBRT. In addition, not every vascular change causes rectal blood loss.[35]

There is limited evidence regarding the optimal management of rectal bleeding. The following clinical approach for patients with radiation induced rectal bleeding has been advocated.[11] First determine the cause of bleeding by at least flexible sigmoidoscopy to exclude other pathology.[53] 2) Optimize bowel function and stool consistency, 3) If bleeding affects quality of life stop or reduce anticoagulants and start sucralfate or short chain fatty acid enemas.[18] Finally, consider definitive treatment to ablate telangiectasia. Current options include hyperbaric oxygen, argon plasma coagulation and formalin therapy.[11,18] In a recent randomized controlled trial colonic irrigation with tap water and oral antibiotics was superior to topical formalin application.[50]

Study level

Present review has several limitations. The first limitation is that it does not include randomized controlled trials. Currently, there are no published randomized controlled trials comparing the effects of therapeutic intervention to reduce LAT including the use of endorectal balloons during EBRT. Another limitation is the lack of studies after IMRT. Furthermore, most studies were performed in large centers of excellence and may not be representative for departments of radiation oncology in all hospitals. There was also a large heterogeneity between the different studies in patient populations and measurement techniques. This heterogeneity made a meta-analysis impossible. However, modified Downs scores were of moderate to high levels. In addition, a lot of studies showed consistency of results, which improves the quality of evidence. Other limitations include selection bias and bias resulting from patients lost to follow up.

Taken together, the present review provides an overview of the best available evidence on objective damage after prostate EBRT. It generates better understanding of current gaps in knowledge. However, the quality of the evidence according to the GRADE system was low to moderate.[23]

Gaps and new studies

Up to April 2012, there is no prospective study examining anal and rectal function for a follow-up of more than 3 years. Large prospective studies with a follow-up of more than 3 years, need to be performed to gain more insights into the pathophysiology of LAT using state-of-the art EBRT planning and treatment delivery techniques such as IMRT with image guidance. Furthermore, randomized studies with and without the in-

sertion of a daily endorectal balloon or studies of endorectal balloon vs. spacer should be performed. Such studies can be used to test the hypothesis that new planning and treatment delivery techniques not only lessen rectal and anal damage but also prevent anorectal dysfunction.

A long-term randomized trial with groups irradiated with and without an endorectal balloon will provide information whether a balloon reduces late anorectal toxicity. The results of such a randomized trial of patients with and without an endorectal balloon will lead to the wider adoption, if not the standard of care for EBRT for prostate cancer world-wide if LAT is shown to be reduced by the daily insertion of an endorectal balloon.

Placebo-controlled randomized trials regarding the different treatment possibilities for patients with incontinence related complaints have to be performed to be able to develop an evidence based guideline.

Currently, there is no consensus about the treatment of rectal blood loss after EBRT. A prospective trial can determine whether invasive treatment with argon plasma coagulation is better than conservative treatment .

Furthermore, there is limited prospective longitudinal data of the changes in the histology of rectal mucosa and rectal wall after prostate irradiation. Future studies should attempt to correlate radiation dose to damage to the different parts (anterior and posterior wall) of the rectum and to damage to the different (neural, muscular of vascular) tissues constituting each part of the rectal wall.

Conclusion

Studies of objective outcomes measures of late anorectal toxicity after external beam radiotherapy for prostate cancer are limited and have a low to moderate quality. Functional changes such as decreases in anal pressures and rectal distensibility are generally well documented, but currently data are limited to 3 years of follow up. Telangiectasias of the rectal mucosa are very frequent and a major cause of bleeding, but may resolve spontaneously after 3 years. This supports a conservative policy regarding argon plasma coagulation. Easy accessibility to endoscopy is emphasized, since bleeding may be caused by other pathology in a considerable number of patients. There is a need for prospective, longitudinal studies with follow-up of more than 3 years to examine the effect of EBRT for prostate cancer on anorectal structural and functional changes as well as a need for randomized trials to strengthen the evidence for therapeutic interventions, particularly the effect of the daily insertion of an endorectal balloon in reducing LAT.

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CHAPTER 3

Impact of late anorectal dysfunction on quality of life after pelvic radiotherapy

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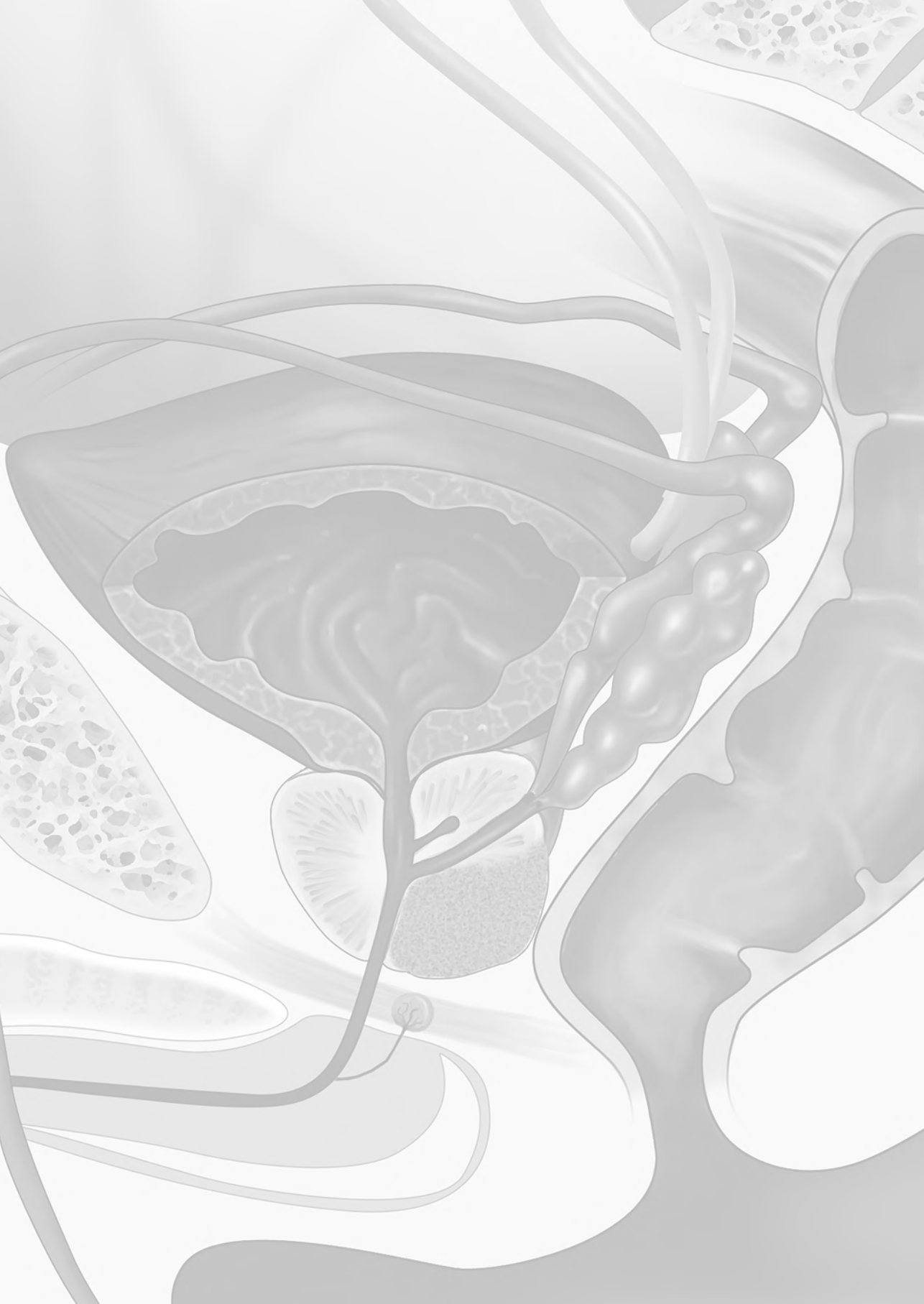

Abstract

PURPOSE Anorectal dysfunction is common after pelvic radiotherapy. This study aims to explore the relation of subjective and objective anorectal function with quality of life (QoL) and their relative impact in patients irradiated for prostate cancer.

METHODS Patients underwent anal manometry, rectal barostat measurement and completed validated questionnaires, at least one year after prostate radiotherapy (range 1-7 years). QoL was measured by the Fecal Incontinence Quality of Life scale (FIQL) and the Expanded Prostate Cancer Index Composite Bowel domain (EPICB)-bother subscale. Severity of symptoms was rated by the EPICB function subscale.

RESULTS Anorectal function was evaluated in 85 men. Sixty-three percent suffered from one or more anorectal symptoms. Correlations of individual symptoms ranged from r=0.23 to r=0.53 with FIQL domains and from r=0.36 to r=0.73 with EPICB-bother scores. They were strongest for fecal incontinence and urgency. Correlations of anal sphincter pressures, rectal capacity and sensory thresholds ranged from r=0.00 to r=0.42 with FIQL domains and from r=0.15 to r=0.31 with EPICB-bother scores. Anal resting pressure correlated most strongly. Standardized regression coefficients for QoL outcomes were largest for incontinence, urgency and anal resting pressure. Regression models with subjective parameters explained a larger amount (range 26-92%) of variation in QoL outcome than objective parameters (range 10-22%).

CONCLUSIONS Fecal incontinence and rectal urgency are the symptoms with the largest influence on QoL. Impaired anal resting pressure is the objective function parameter with the largest influence. Therefore, sparing the structures responsible for an adequate fecal continence is important in radiotherapy planning.

KEYWORDS Quality of life, anorectal toxicity, anorectal function, prostate carcinoma, external beam radiotherapy.

Introduction

Persistent and troublesome anorectal symptoms occur frequently after external beam radiotherapy (EBRT) for pelvic cancer.[1-3] These symptoms of anorectal toxicity include complaints such as frequency and urgency of defecation, rectal bleeding and fecal incontinence.[1,4,5] More than half of the patients, who received prostate radiotherapy, mention an alteration of their bowel habit after treatment and at least 9% experience considerable distress one year after EBRT.[1,6,7] Bowel dysfunction remains to cause significant concerns among early-stage prostate cancer treatment survivors 4 years after irradiation.[8,9] Weakness of the internal anal sphincter and reduction of rectal sensory volumes occur, but the impact of specific functional disturbances on daily activities, social and emotional well being is unclear.[10-12]

Understanding the contribution of specific functional disturbances to health related quality of life after pelvic radiotherapy is important. It advances our knowledge about the role of each factor and may guide future prevention and management of side effects. For instance, important anorectal dysfunctions can be identified with this knowledge and subsequently used to locate anatomic structures involved. Sparing these structures in radiotherapy planning can prevent side effects.[13,14]

Subjective disturbances of anorectal function that may affect QoL include urgency and frequency of defecation, incontinence, loose or liquid stool, bloody stool, painful bowel movements and cramps in the pelvis or rectum.[1,8,15,16] Objective parameters of anorectal function which may be involved are anal sphincter pressures, rectal capacity and rectal sensibility.[11,17] Disturbances in subjective parameters can possibly be traced back on these objective function parameters. The hypothesis of this study is that these factors are associated with QoL and that fecal urgency and incontinence have the largest impact among these factors.

The primary goal of this study is to explore the relation of subjective parameters of anorectal function with QoL in a cohort of patients irradiated for prostate cancer and to determine their relative impact. Furthermore, we determined whether subjective or objective anorectal function parameters are better to explain variances in QoL.

Materials and Methods

Patients and methods

In this cross-sectional study, we retrospectively analyzed the collected data. From January 2006 until January 2011, 85 consecutive patients who underwent anorectal function testing after prostate EBRT completed a questionnaire. Fifty-one patients (60%) were referred by the department of Radiation Oncology because they reported symptoms of

anorectal radiation toxicity. It is advisable to include as wide a range of values as possible in correlation and regression analysis. Therefore, to obtain a broader spectrum of scores, 34 participants (40%) in a prospective longitudinal study of the Department of Radiation Oncology of the Radboud University Medical Centre were studied after prostate EBRT, as this cohort also comprised patients without anorectal complaints.

The questionnaire contained questions about anorectal complaints and quality of life. All patients were referred for anorectal function evaluation to the department of Gastroenterology and Hepatology of the Radboud University Medical Centre between January 2006 and February 2011. Informed consent was obtained from all patients and there was approval of The Medical Research Ethics Committee of the Radboud University Medical Centre for the prospective study of the Department of Radiation Oncology.

Questionnaires

QoL was assessed by the Fecal Incontinence Quality of Life Scale (FIQL) and the Expanded Prostate Cancer Index Composite Bowel domain (EPICB). These are condition specific measures. They are more sensitive to detect changes in QoL due to anorectal dysfunction than general QoL scores.[9,16,18]

The FIQL scale consists of 29 items covering four domains of QoL. Ten items are related to lifestyle, 9 items to coping/behavior, 7 items to depression/self perception and 3 items to embarrassment. The scores for one question of the depression scale ranged from 1 (lowest quality of life) to 6 (best quality of life) and for another question from 1 to 5. All other items ranged from 1 to 4. The final score for each domain was the average score for all items in that scale. Therefore, the maximum score of the domains lifestyle, coping/behavior and embarrassment was 4.0. The maximum score for depression was 4.4. A higher score represents a better QoL.

The EPICB comprises a function score (EPICB-F), which measures the presence and severity of bowel symptoms, and a bother score (EPICB-B) to determine the amount of bother caused by specific symptoms. The EPICB-F is a 7 item subscale. It rates frequency of bowel movements, rectal urgency, uncontrolled leakage of stool, loose or liquid stool, bloody stool, painful bowel movements and abdominal cramps in the abdomen, pelvis or rectum on a likert scale. The EPICB-B rates the bother caused by these symptoms. The items of the EPICB-F and EPICB-B can be transformed to a scale ranging from 0 to 100, with a lower score representing a higher symptom severity.

Anorectal function tests

All 85 patients underwent anal manometry to determine anal pressures and barostat testing to determine rectal capacity and sensory threshold. Manometry and barostat procedures have been described in detail previously.[14,17] For manometry testing a water-perfused anorectal motility catheter, with four radially oriented recording points and a 4,8 mm outer diameter (Arndorfer Medical Specialties, Greendale, WI, USA) was con-

nected to the Solar GI system (MMS, Enschede, The Netherlands). A standard station pull-trough technique was used to assess anal resting pressure, squeeze pressure and maximal anal pressure at consecutive levels of 1 cm in four separate quadrants.[19,20] Resting pressures were allowed to stabilize for a period of at least 20 seconds after pulling back the catheter. Rectal pressure was the reference pressure. Resting pressure was defined as the highest resting pressure, maximal pressure as the highest pressure during squeezing and maximal squeeze pressure as the highest increase over resting pressure during squeezing in each of the four quadrants. All patients were studied in the left lateral position. Resting-, squeeze-, and maximal pressure (Anal-P resting, Anal-P squeeze and Anal-P maximum respectively) were calculated as the highest values recorded throughout the anal canal by each recording point and expressed as a mean of these four values. The internal anal sphincter maintains approximately 70-80% of Anal-P resting and the external anal sphincter accounts for the remaining component of the resting tone.[21] Anal-P squeeze comprises the functions of the external anal sphincter and the puborectalis muscle.[22]

For barostat testing a probe with an infinitely compliant polyethylene bag connected to an electronic barostat was used (Distender II, G&J Electronics Inc., ON, Canada) and positioned approximately 5 cm from the anal verge. After an initial conditioning staircase distension (4 mm Hg steps, 30 s per step) procedure to reduce variability, a rectal staircase distension was performed.[19,23] Starting at an intrabag pressure of 0 mm Hg, the intrabag pressure was increased with 2 mm Hg at 1-minute intervals and kept at a constant level. Intrabag volumes corrected for intrabag pressures, were averaged beginning 25 s at each distension step and recorded. The pressures (P) and volumes (V) at three sensory thresholds were noted [i.e., the moment the patient became aware of something present in the rectum (first sense), the first feeling of urge (first urge) and the moment the patient experienced an uncontrollable urge to defecate or a feeling of discomfort (maximum tolerated distension, MTD)].[24] Rectal capacity was defined as the intrabag volume at MTD.[17]

Analysis

Data are presented as mean ± 1 SEM unless stated otherwise. For statistical calculations the SPSS 18.0 software for Windows was used (SPSS Inc, Chicago, Illinois, USA). The Spearman rank correlation coefficient (rho) was used to determine the relation between anorectal symptom, function and QoL scores. Correlations ≤ .32 were considered weak, .33 - .45 moderate, and > .45 strong.[25] Multiple linear regression analysis was performed to assess the influence of individual symptoms and function parameters on QoL outcomes. All symptoms and function parameters were included as independent predictors in the full models and then a stepwise backward elimination method was used to

remove predictors which were not statistically significant ($P > 0.05$). To determine the relative importance of the significant predictors, standardized regression coefficients were calculated. For comparison of variables between subgroups of patients we used the independent *t*-test. A two tailed probability value of less than 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

GENERAL AND THERAPEUTIC CHARACTERISTICS All men (mean age 72 yrs; range 53-84 yrs) finished prostate EBRT at least one year before anorectal function testing and received a cumulative radiation dose between 63-78 Gy in daily fractions of 2-3.4 Gy. In fifty patients (59%) a daily inserted air-filled endorectal balloon was used to reduce the radiation dose to the rectal wall and anal sphincter complex.[26] The mean time between irradiation and completing the questionnaire was 2 years (range 1-7 years). General patient and tumor characteristics are illustrated in **Table 1**.

ANORECTAL SYMPTOMS AND QOL Sixty-two patients (73%) reported one or more symptoms of anorectal dysfunction after prostate EBRT. Loose or liquid stools was reported by 48%, rectal urgency by 31%, frequent defecation and bloody stool both by 22%, fecal incontinence by 18%, painful defecation by 14% and abdominal cramps by 12%. FIQL scores (mean±SD) for lifestyle (3.7±0.5 vs. 4.0±0.0; $P<0.005$), for coping (3.3 ±0.8 vs. 3.8±0.3; $P=0.001$) and for depression (3.9±0.4 vs. 4.2±0.2; $P<0.001$) were all significantly lower in patients with anorectal complaints compared to patients without complaints.

FIQL scores (mean ± SD) were 3.9±0.3 for lifestyle, 3.7±0.5 for coping, 4.1±0.3 for depression and 3.9±0.4 for embarrassment in the prospective group and 3.7±0.5, 3.3±0.8, 3.9±0.4 and 3.6±0.7 respectively in the group who was referred because of complaints. The mean EPICB-B was 92±11 for the group of prospective patients and 84±16 for the group referred for complaints. No formal comparison between these two subgroups was performed for reasons stated in the discussion.

ANORECTAL FUNCTION Anal pressures (mean ±SD) after radiotherapy were 48 ±16 mm Hg, 153±57 mm Hg and 190±62 mm Hg for respectively Anal P-resting, Anal-P squeeze and Anal-P maximum. Pressure and volume (mean±SD) for the sensory threshold first sense were 14±5 mm Hg and 98±77 mL, for first urge they were 19±6 mm Hg and 141±82 mL and for the maximum tolerated distention 32±9 mm Hg and 213±94 mL.

Table 1 *Characteristics of patients and tumor characteristics (n = 85).*

Patient Characteristics	**Mean**	**SD**	**n**	**(%)**
Age (years)	72	6		
Time (months)	29	21		
Heigth (cm)	176	7		
Weight (kg)	82	13		
BMI (kg/m2)	27	4		
Comorbidity				
DM			5	(6%)
COPD/Asthma			9	(11%)
Hypertension			14	(16%)
Heart failure			16	(19%)
BPH			7	(8%)
Other			28	(33%)
Medication				
α1-inhibitor			10	(12%)
Anticoagulants			5	(6%)
Laxatives			3	(4%)
Antidiarrheals			1	(1%)
Other			38	(45%)
Operation pelvic region/genitals			(6%)	
Tumor characteristics			**n**	**(%)**
PSA (range)	15 (3 – 58)			
Gleason-score (median; range)	6 (5 – 9)			
T-stadium				
T1			11	(13%)
T2			31	(36%)
T3			43	(51%)

Abbreviations: SD = standard deviation; Time = time between radiotherapy and completing the questionnaire; BMI = body mass index; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen.

Relation of anorectal dysfunction with QoL

ANORECTAL SYMPTOMS WITH QOL **Table 2** shows the relation of specific symptoms of bowel dysfunction with QoL outcomes. There was a strong association of rectal urgency and fecal incontinence with most domains of the FIQL and with the EPICB-B score.

ANORECTAL FUNCTION WITH QOL Anal P-resting was moderately related to three domains of the FIQL and weakly related to the FIQL domain embarrassment and the EPICB-B score. Rectal capacity was related to four of the QoL scores. Most of the other function parameters were related to at least one of the FIQL or EPICB-B scores. **Table 3** represents all correlation coefficients.

Impact on QoL

ANORECTAL SYMPTOMS Apart from painful bowel movements, all other symptoms of anorectal toxicity were independent predictors for the EPICB-B score. Standardized regression coefficients (β) ranged between 0.18 for bloody stool and 0.37 for rectal urgency; all *P*-values <0.001; **Table 4**). The largest coefficients were found for rectal urgency and fecal incontinence.

Table 2 *Correlations of EPICB-F score with FIQL domains and EPICB-B score.*

	FIQL				
Symptom (EPICB-F)	**Lifestyle rho**	**Coping rho**	**Depression rho**	**Embarrassment rho**	**EPICB-B rho**
Rectal urgency	.65**	.61**	.49**	.41**	.73**
Fecal incontinence	.63**	.56**	.41**	.54**	.53**
Loose stool	.31**	.29*	.27*	.26*	.55**
Bloody stool	.35**	.34**	.21	.37**	.46**
Painful defecation	.23*	.24*	.35**	.09	.36**
Frequent defecation	.32**	.31**	.39**	.25*	.52**
Abdominal cramps	.27*	.32**	.33**	.16	.41**

Abbreviations: EPICB-F = Expanded Prostate Index Composite Bowel Function score; FIQL = Fecal Incontinence Quality of Life Scale; EPICB-B = Expanded Prostate Index Composite Bowel Bother score; rho = Spearman's rank order correlation coefficient. * indicates P < 0.05; ** indicates P < 0.005.

Table 3 *Correlations of anorectal function parameters with FIQL domains and EPICB-B score.*

	FIQL				
Anorectal function parameter	**Lifestyle rho**	**Coping rho**	**Depression rho**	**Embarrassment rho**	**EPICB-B rho**
Anal P-resting	.32**	.42**	.36**	.35**	.31**
Anal P-squeeze	.24*	.32**	.12	.04	.15
Anal P-maximum	.28*	.38**	.19	.10	.21
P first sense	.11	.12	.20	.14	.20
P first urge	.11	.11	.16	.00	.16
P MTD	.20	.24*	.20	.12	.24*
V first sense	.17	.22*	.23*	.13	.23*
V first urge	.22*	.29*	.19	.09	.20
V MTD	.29*	.39**	.25*	.14	.28*

Abbreviations: FIQL = Fecal Incontinence Quality of Life Scale; EPICB-B = Expanded Prostate Index Composite Bowel Bother score; rho = Spearman's rank order correlation coefficient; P = pressure; V = volume; MTD = maximum tolerated distension. * indicates P < 0.05; ** indicates P < 0.005.

Stepwise backward regression analysis also revealed that fecal incontinence and rectal urgency were independent predictors and had the largest impact on most FIQL domains. β's were 0.39 and 0.38 for rectal urgency with the lifestyle and coping domain respectively (both P <0.01) and β's for fecal incontinence ranged between 0.29 and 0.52 (P <0.01 for all FIQL domains). Frequency of defecation was also an independent predictor for lifestyle and coping, but had lower β's (**Table 4**). Regression analyses showed that patients age at the start of irradiation was a confounder for the FIQL depression and self perception. Adjusted standardized regression coefficients in the FIQL depression/self perception domain were 0.40 (P <0.01) for fecal incontinence, 0.39 (P <0.01) for abdominal cramps and the adjusted coefficient for frequency of defecation was β=0.26 (P <0.01).

The amount of variation in FIQL score explained by symptoms of anorectal dysfunction ranged between 26% and 44% and was 92% for the EPICB-B score as reflected by the adjusted R^2 (**Table 4**).

Anorectal function

Anal P-resting served as an independent predictor for all FIQL domains and the EPICB-B score. Standardized regression coefficients ranged between 0.31 and 0.38 for the FIQL domains and was 0.24 for the EPICB-B score. In addition, V MTD was an independent

Table 4 *Multiple regression analyses of symptoms, FIQL and EPICB-B scores.*

	FIQL								EPICB-B	
	Lifestyle		Coping		Depression		Embarrassment			
Symptom	B (SE)	β	B (SE)	β	B (SE)	β	B (SE)	β	B (SE)	β
Rectal urgency	0.005 (0.001)	0.39*	0.009 (0.002)	0.38*	NS	NS	0.171 (0.019)	0.37*		
Fecal incontinence	0.005 (0.002)	0.29*	0.012 (0.003)	0.36*	0.006 (0.002)	0.36*	0.014 (0.002)	0.52*	0.196 (0.024)	0.30*
Loose stool	NS	NS	NS	NS	0.122 (0.021)	0.21*				
Bloody stool	NS	NS	NS	NS	0.151 (0.030)	0.18*				
Painful defecation	NS	NS	NS	NS	NS					
Frequent defecation	0.004 (0.002)	0.18	0.006 (0.003)	0.18	NS	NS	0.140 (0.025)	0.21*		
Abdominal cramps	NS	NS	0.008 (0.002)	0.42*	NS	0.183 (0.031)	0.23*			
Adjusted R2	0.38	0.44	0.31	0.26	0.92					

Abbreviations: FIQL = Fecal Incontinence Quality of Life Scale; EPICB-B = Expanded Prostate Index Composite Bowel Bother score; adjusted R2 = adjusted square of multiple correlation coefficient; B = regression coefficient ; SE = standard error ; β = standardized regression coefficient; P = pressure; V = volume; MTD = maximum tolerated distension. Stepwise backward selection $P < 0.05$. * Indicates $P < 0.005$.

predictor for the EPICB-B score (β=0.24), P first sense for the lifestyle domain (β=0.01) and V first urge for the coping domain (β=0.23). Adjusted R^2 revealed that objective parameters of anorectal function explained 10-22% of variation in the FIQL score and 14 % of variability in EPICB-B score (**Table 5**).

Discussion

In this study the influence of specific anorectal symptoms and functions on QoL was evaluated in patients with radiation toxicity after EBRT for localized prostate cancer. Fecal incontinence and rectal urgency are the symptoms which had the largest impact on QoL. Anal resting pressure was the objective function parameter with the highest influence. Rectal capacity and other symptoms such as frequent defecation and lower abdominal cramps also contribute, but less profoundly.

Table 5 *Multiple regression analyses of anorectal function parameters, FIQL and EPICB-B scores.*

	FIQL								EPICB-B	
	Lifestyle		Coping		Depression		Embarrassment			
Function parameter	**B (SE)**	**β**	**B (SE)**	**β**	**B (SE)**	**β**	**B (SE)**	**β**	**B (SE)**	**β**
Anal P-resting	0.008 (0.003)	0.31**	0.016 (0.004)	0.37**	0.007 (0.002)	0.33**	0.013 (0.004)	0.38**	0.214 (0.096)	0.24*
Anal P-squeeze	NS		NS		NS		NS		NS	
Anal P-maximum	NS		NS		NS		NS		NS	
P first sense	0.018 (0.008)	0.01*	NS		NS		NS		NS	
P first urge	NS		NS		NS		NS		NS	
P MTD	NS		NS		NS		NS		NS	
V first sense	NS		NS		NS		NS		NS	
V first urge	NS		0.002 (0.001)	0.23*	NS		NS		NS	
V MTD	NS		NS		NS		NS		0.036 (0.017)	0.24*
Adjusted R2	0.15		0.22		0.10		0.14		0.14	

Abbreviations: FIQL = Fecal Incontinence Quality of Life Scale; EPICB-B = Expanded Prostate Index Composite Bowel Bother score; adjusted R2 = adjusted square of multiple correlation coefficient; B = regression coefficient ; SE = standard error ; β = standardized regression coefficient; P = pressure; V = volume; MTD = maximum tolerated distension. * indicates $P < 0.05$; ** indicates $P < 0.005$.

The data of the present study support the earlier results that fecal incontinence and urgency have the largest impact on QoL.[27,28] Severity of rectal urgency, fecal incontinence, loose or liquid stool, frequent defecation and bloody stool were strongly associated with an increased bother from anorectal complaints as measured by the EPICB-B score. In addition QoL as measured by FIQL was strongly related to fecal incontinence and urgency. Standardized regression coefficients were largest for urgency and fecal incontinence implicating that they had the largest impact on QoL. These findings extend previous observations in prostate cancer patients.[28-30] *Bacon et al* showed that the level of bother caused by symptoms of bowel dysfunction was greater than that of urinary and sexual dysfunction.[30] An unvalidated questionnaire revealed the strongest association for fecal leakage with gastrointestinal distress.[27] Fecal incontinence and rectal urgency

were also independently associated with lower global QoL levels.[28] In contrast to these studies, a disease specific outcome measure for QoL and a validated questionnaire was used in the present study.

Anal resting pressure was associated with all QoL outcomes and had the strongest association. Anal resting and squeeze pressure decreased at 1 and 2 years after radiotherapy.[5,10] The present study supplies evidence that this decreased anal sphincter pressure has a profound impact on daily life. Anal resting pressure was an independent predictor for all QoL outcomes with standardized regression coefficients of a similar magnitude as rectal urgency and fecal incontinence. This supports the previously found association of our group between anal resting pressure and the symptoms fecal leakage and rectal urgency.[14]

Other functional parameters such as rectal volume at first urge and rectal capacity were also involved. This indicates that previously observed reduction of rectal capacity after radiotherapy also contributes to reduction of QoL.[17] This is in line with the results of *Felt-Bersma et al*, who showed that extreme rectal volumes have a direct clinical impact.[31]

The amount of variation in QoL explained by subjective parameters of anorectal dysfunction was larger than that explained by objective parameters. This finding emphasizes the relevance of subjective patient reported assessments in evaluation of anorectal toxicity. It is in line with the recommendation to use validated patient reported measures in functional gastrointestinal disorders.[32] An explanation for this finding is that the objective function parameters measured in present study not fully cover all the subjective symptoms, like rectal blood loss and loose or liquid stool. The fact that objective parameters are less useful to explain the amount of variation in QoL is not a valid reason to pass these tests. They maintain their important role in exploring underlying pathophysiology, thereby providing information about treatment options.

All participants from the prospective cohort study of the Department Radiation Oncology were irradiated with a daily inserted endorectal balloon and analyzed one year after irradiation. One year after irradiation is a relatively short period of follow-up for detection of dysfunction, as it has been reported that anorectal sequelae increase with time after EBRT.[10] In contrast, almost every patient who was referred because of existing anorectal complaints was irradiated without an inserted balloon, as these patients were irradiated before the introduction of endorectal balloons in our practice. These patients were mostly analyzed 3-5 years after irradiation and received dosages ranging from 63 Gy to 78 Gy. Due to these differences and the abovementioned advances in radiation techniques over time, direct comparison between the group with endorectal balloon and the group without endorectal balloon was not appropriate.

A possible limitation of the study is that the FIQL score is less sensitive to detect the impact of non-incontinence related symptoms like rectal bleeding and pain. However, fecal incontinence and urgency were also independent predictors with the largest im-

pact on another QoL outcome measure, the EPICB-B score. Furthermore, the FIQL is a well validated QoL scale developed to address issues related specifically to accidental bowel leakage.[18] It is considered among the best measures available for comprehensive assessment of quality of life impact associated with anal incontinence.[33]

The EPICB-F questionnaire asks for uncontrolled leakage of stool or feces to assess incontinence. Therefore, it may miss patients with unintentional leakage of small amounts of stool or with fecal staining of undergarments.[34] This soiling or passive incontinence was associated with lower resting pressures, whereas urge incontinence was associated with reduced squeeze pressures and diminished rectal capacity.[34]

The heterogeneous group of patients participating in this study may be another limitation. The year of irradiation varied from 2000–2010, a period in which several advances in radiation techniques were made, like the introduction of three dimensional conformal radiotherapy and intensity modulated radiotherapy, as well as the application of endorectal balloons. Furthermore, the patients consisted of two groups. Sixty percent of patients were referred because of anorectal symptoms, 40% participated in a cohort study on anorectal function. The mixture of these two groups led to a high prevalence of anorectal symptoms which is not representative for the prevalence in the entire population of men after prostate irradiation. We think that this variance had no influence on the outcome, because the aim was to examine the influence of individual symptoms and functional parameters on QoL and not to evaluate the technique with the least amount of late anorectal toxicity. Moreover, it has the additional advantage that correlations are found more easily when there is greater variability in symptom severity.

This study shows that most QoL can be gained by unraveling the etiology of fecal leakage and rectal urgency after EBRT. Multiple factors are involved in the maintenance of an adequate continence mechanism. Anal sphincter dysfunction, anatomic disturbances of the pelvic floor, neuropathy and stool consistency are just a few examples of factors which may cause incontinence.[35,36] Exploring these factors after pelvic radiotherapy is a logical continuation of this study. Future research should focus on preventing deterioration of anal sphincter function and rectal distensibility. The data support the recommendation to reduce the dose not only on the rectal wall but also on the anal wall.[13,14] With the use of current radiation techniques it is possible to decrease the dose on these specific structures[37], thereby preventing symptoms and maintaining QoL.

In conclusion: Among the symptoms of late anorectal toxicity, fecal leakage and rectal urgency have the largest impact on QoL. Anal resting pressure is the objective parameter which best explains variance in QoL after irradiation. Overall, subjective parameters contribute more strongly to QoL than objective parameters of anorectal dysfunction in patients with radiation toxicity after prostate radiotherapy. The influence of subjective and objective continence related parameters underscores the importance of preserving adequate continence mechanism in radiotherapy planning.

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CHAPTER 4

Predictors of radiation-induced gastrointestinal morbidity: a prospective, longitudinal study following radiotherapy for carcinoma of the prostate

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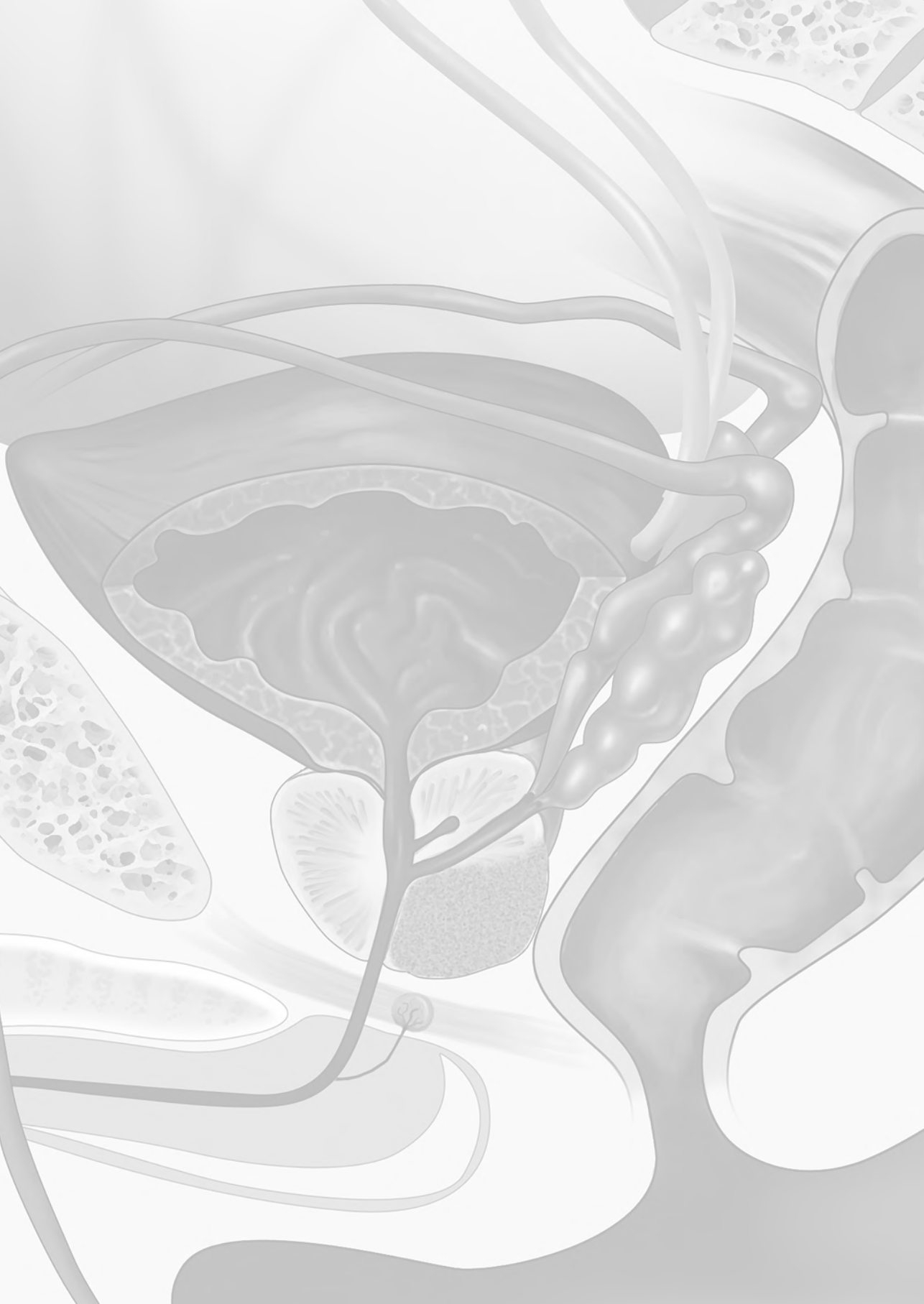


Abstract

BACKGROUND Chronic gastrointestinal (GI) morbidity occurs in ≥50% of patients after external beam radiotherapy (EBRT) for carcinoma of prostate (PCa). This prospective, longitudinal study examines which baseline measurements of: 1) homocysteine and micronutrients in plasma; 2) chromosome damage/misrepair biomarkers; and 3) anal and rectal dose volume metrics predict GI morbidity after EBRT.

PATIENTS AND METHODS In total, 106 patients with PCa had evaluations of GI symptoms (modified LENT-SOMA questionnaires) before EBRT and at one month, one, two and three years after its completion. Other variables measured before EBRT were: 1) plasma concentrations of homocysteine and micronutrients including caroteinoids and selenium; 2) chromosome damage/DNA misrepair (micronuclei/nucleoplasmic bridge) indices; and 3) mean anal and rectal wall doses and volumes of anal and rectal walls receiving ≥40 Gy and ≥60 Gy. Univariate and multivariate analyzes examined the relationships among: 1) plasma levels of homocysteine and micronutrients; 2) indices of chromosome damage/DNA misrepair; and 3) mean anal and rectal wall doses and volumes of anal and rectal walls receiving ≥40 Gy and ≥60 Gy and total GI symptom scores from one month to three years after EBRT.

RESULTS Increased frequency and urgency of defecation, rectal mucous discharge and bleeding after EBRT resulted in sustained rises in total GI symptom scores above baseline at three years. On univariate analysis, total GI symptom scores were significantly associated with: 1) plasma selenium and a tocopherol; 2) micronuclei indices of DNA damage; 3) mean anal and rectal wall doses; and 4) volumes of anal and rectal wall receiving ≥40 Gy and ≥60 Gy ($p = 0.08 - <0.001$). On multivariate analysis, only volume of anal wall receiving ≥40 Gy was significant for increased GI symptoms after EBRT ($p <0.001$).

CONCLUSION The volume of anal wall receiving ≥40 Gy predicts chronic GI morbidity after EBRT for PCa.

KEYWORDS Biomarkers Morbidity, Radiotherapy, Prostate Carcinoma

Introduction

External beam radiotherapy (EBRT) is the preferred treatment especially for older men with carcinoma of the prostate (PCa).[1] Despite advanced EBRT techniques including intensity modulated radiotherapy (IMRT), acute radiation proctitis, characterized by increased frequency and urgency of defecation, fecal incontinence and rectal bleeding still occurs in 73% of patients during IMRT for PCa.[2] The prevalence of chronic radiation proctitis (CRP), defined as persistence of anorectal symptoms3 months after EBRT, ranges between 5% and 65%.[2] Studies reporting lower rates of CRP have used Radiation Therapy Oncology Group (RTOG) Gastrointestinal (GI) toxicity scoring system which does not include the evaluation of the more commonly occurring anorectal symptoms of fecal urgency and incontinence. As these symptoms also have a greater adverse impact on quality of life than rectal bleeding, use of the RTOG GI toxicity system under-estimates radiation morbidity.[3,4] Higher CRP prevalence rates of 50–65% following EBRT for PCa using advanced techniques including IMRT occur when patient orientated questionnaires are included, such as the Late Effect Normal Tissue-Subjective Objective Management Analytic (LENT-SOMA) and Expanded Prostate Cancer Index Composite Bowel domain (EPICB) bother scales.[3-5] The volume of rectum receiving ≥60 Gy is the only dose volume histogram (DVH) parameter consistently associated with the risk of RTOG Grade ≥2 CRP.6 Different definitions of the anatomy of the rectum, particularly with respect to its length and the finding that anal DVH parameters correlate better with anorectal symptoms other than rectal bleeding have led to the proposal that anal DVH parameters should be evaluated separately from the rectum.[5-7]

Despite wide variations in radiation sensitivity, the same radiation dose is prescribed for similar risk PCa.[8] The Cytokinesis Block Micronucleus Cytome (CBMNCYT) assay, which evaluates spontaneous DNA damage and DNA damage induced following ex vivo irradiation in peripheral blood lymphocytes, is used to measure radiation sensitivity and to study the effects of nutritional factors on DNA damage and repair.[9-12] The micronucleus (MN) index of DNA damage in the CBMNCYT assay following ex vivo irradiation have been reported to predict for RTOG grades 2 and 3 GI and genitourinary (GU) morbidity approximately three years after EBRT for PCa in a previous study.[8] Dietary micronutrients, such as b-carotene and vitamin E and above average intakes of fruits and vegetables, have been reported to reduce spontaneous DNA damage and may also reduce DNA damage induced by ionizing radiation through their actions as antioxidants or cofactors of DNA repair enzymes.[10-12]

However, the previous study of radiation sensitivity based on the CBMNCYT assay[8] did not account for the potential confounding effects of dietary micronutrients and radiation dose volume metrics on chronic GI and GU morbidity.

The aims of this prospective, longitudinal study were to determine which of baseline measurements of: 1) homocysteine and dietary micronutrients including carotenoids, vitamin E and selenium in plasma; 2) indices of chromosome damage/misrepair in the

CBMNCYT assay; and 3) anal and rectal radiation dose volume parameters predict GI morbidity after EBRT for PCa.

The significance of this prospective, longitudinal study includes the possibilities of: 1) improved treatment planning approaches for EBRT of PCa; and 2) dietary interventional studies to lessen radiation-induced chronic GI morbidity

Material and methods

The study population was derived among patients referred to the Radiation Oncology Department, Royal Adelaide Hospital for radical EBRT for localized PCa (UICC TNM Stage T1-T3, No Mo) between 21 July 2004 and 10 May 2007, who met the eligibility criteria of: 1) suitability for EBRT ± hormonal manipulation; and 2) patient consent based on the written protocol approved by the institutional and laboratory Research Ethics Committees.

Risk categorization based on National Comprehensive Cancer Center (NCCN) criteria[13] defined as target(s) of irradiation the prostate only for low-risk PCa, and the prostate and seminal vesicles for intermediate- or high-risk disease using three-dimensional (3D) computed tomography (CT) scans of the pelvis. Patients were provided with written instructions to empty their bowels on the morning of their CT planning pelvic scans and then to start drinking 500 ml of water slowly 1.5 hours before the time of their appointment.

For the intermediate- and high-risk disease patients, two planning target volumes (PTV), PTV 1 and PTV 2 were derived by applying anisotrophic (1.5 cm anteriorly, superiorly and inferiorly, 1.2 cm posteriorly and laterally) margins around the seminal vesicles plus prostate and the prostate only, respectively, using the automatic expansion device of the 3D planning (ADAC Pinnacle) system. For the low-risk disease patients, the same anisotrophic margins were applied around the prostate to derive one PTV only.

3D conformal radiotherapy (CRT) based on multi-leaf collimation of the radiation beams for the irradiated target volumes was used to treat all patients. The aim was to deliver a total radiation dose to the ICRU reference point of the prostate of 74.4 Gy for intermediate- and high-risk disease (1.8 Gy x 28 for PTV1 plus 2 Gy x 2 for PTV2) and 70 Gy (2 Gy x 35) to the prostate only PTV for low-risk disease.

The majority (see Results section for percentage) of patients with high-risk disease, also received hormonal therapy (androgen deprivation therapy in the form of either one of the two luteinizing hormone releasing hormone agonists, goserlin acetate or leuprorelin acetate depot injections) as well as internal and external iliac nodal irradiation.

The dose range to prostate achieved for the whole patient population was 66–74.4 Gy in 33–40 increments over 6.6–7.6 weeks as five patients failed to meet the pre-specified dose constraint of V 70 Gy outer rectal wall (contoured separately from the anal canal as discussed under DVHs of rectal and anal walls below).

Experimental protocol

Before EBRT, 1) plasma concentrations of homocysteine and dietary micronutrients, 2) indices of chromosome damage/DNA misrepair measured by the CBMNCYT assay, and 3) rectal and anal wall dose volume metrics were determined for each patient.

Individual and total GI symptom scores, using a modified version of the LENT-SOMA scales of GI morbidity reported to correlate with a validated health-related quality of life instrument following EBRT for PCa[14], were also evaluated before EBRT, and at one month, one, two and three years after its completion.

Homocysteine and dietary micronutrient measurements

Plasma concentrations of: 1) homocysteine, B12 and folate; 2) zinc and selenium; and 3) carotenoids were determined by: 1) the ARCHITECT folate assay[15]; 2) inductively coupled plasma optical emission spectroscopy (ICPOES)[16]; and 3) High Performance Liquid Chromatography (HPLC)[17], respectively.

Cytokinesis block micronucleus cytome assay

The CBMNCYT assay was used to measure the MN and nucleoplasmic bridge (NPB) frequency in peripheral blood lymphocytes. The MN and NPB biomarkers in the CBMNCYT assay have been used successfully to study radiation sensitivity phenotyping and the effects of micronutrient deficiency on genome integrity. MN and NPB originate from acentric chromosome fragments and dicentric chromosomes, respectively, and thus provide a reliable measure of chromosome DNA damage and DNA misrepair, respectively, in peripheral blood lymphocytes.[9]

The CBMNCYT assay was performed using 500 ml of a specimen of fresh whole blood suspended in 4.5 ml of Roswell Memorial Park Institute (RPMI)-1640 culture medium (Thermo Trace, Australia) supplemented with 10% fetal calf serum (FCS) (Thermo Trace, Australia) and phytohemagglutinin at 37°C. Cells were cytokinesis blocked using cytochalasin-B after 44 hours of culture and harvested 28 hours later using a previously published protocol.[9]

Spontaneous DNA damage in the CBMNCYT assay was first measured by determining MN and NPB frequency. Radiationinduced DNA damage in the CBMNCYT assay was measured after exposure of the whole blood suspension to 3 Gy γ-rays from a 137Cs source (Cis Bio IBL 437 C Blood Product Irradiator, dose rate 5.34 Gy/min) and then determining MN and NPB frequency.

Dose volume histograms of rectal and anal walls

Derivation of DVH parameters for the rectal and anal walls involved contouring both structures as solid organs in their entire extent. As the rectum normally contains gas

and is not solid like the anal canal, it was defined as the ring structure between the outer and inner rectal walls. The outer wall of the rectum from the recto-sigmoid junction above to the anorectal junction below was first contoured. The inner wall of the rectum was then derived by contracting the outer wall of the rectum by 5mm as previously described.[7] The 3D (ADAC Pinnacle) planning system was finally used to assign a ring structure between the outer and inner wall of the rectum as a region of interest.

Gastrointestinal radiation morbidity measurements

Individual GI symptom scores were based on a five (0–4) point modified LENT-SOMA GI toxicity scale.[3] The total GI symptom scores (0–24) were derived by summation of the individual symptom scores.[3]

As it was not possible to determine which individual GI symptom had the most clinical significance in patients after EBRT, the effect of total GI symptoms on activities of daily living (ADL) of the patients after EBRT was also derived. The latter was based on a four (0–3) point categorical scale, higher scores reflecting worsening impact on ADL as in a previous study.[3]

Data analysis

The means and medians of plasma homocysteine and micronutrient concentrations were calculated using individual values measured for each patient. The individual values were the calculated means of duplicate measurements of homocysteine and micronutrients for each patient.

MN and NPB frequency was determined on a minimum 1000 binucleated lymphocytes using previously described scoring criteria.[9] Scoring MN frequency in a minimum of 1000 binucleated lymphocytes provides the required statistical power to detect individual differences in radiation sensitivity with high probability and has been widely accepted as the standard CBMNCYT protocol for radiation biology studies.[9,18]

The medians of the mean anal (D mean anal) and rectal (D mean rectal) ring doses and volumes of anal wall and rectal ring receiving ≥40 Gy (V 40 Gy anal) and ≥60 Gy (V 60 Gy rectal), respectively, were calculated.

The medians of the individual and total GI symptom scores, using the modified LENT-SOMA toxicity scales before EBRT and at one month, one, two and three years after completion of EBRT, were determined. The median of the effect of total GI symptoms on ADL of scores after EBRT was also calculated.

Statistical analysis

Individual and total LENT-SOMA GI symptoms scores before EBRT and at the pre-determined intervals after its completion were examined by Friedman repeated analysis of

variance (ANOVA). X^2-tests were used to compare the percentage of patients with and without increases in individual and total GI symptom scores and the percentage of patients with D mean anal <40 Gy versus D mean anal >40 Gy, V 40 Gy anal >65% versus V 40 Gy anal >65% and percentage of patients with V 60 Gy rectal ≤40% versus V 60 Gy rectal >40%.[5] Linear regression examined the relationship between total GI symptom scores and the effect of GI symptoms on ADL scores after EBRT.

A two-sided p-value of ≤0.05 was considered significant in all analyses.

To adjust for correlations between the error terms of the repeated measures and to allow for modeling of both continuous and dichotomized (only one predictor variable, before EBRT total GI symptom score <versus> median value of 1, was dichotomized) variables, generalized estimating equations (GEE) were used to analyze the best joint predictors of the outcome variable of increased total GI symptom scores from one month to three years after EBRT (see below for justification of this as a valid measure of chronic GI morbidity). Due to the large number of predictor variables, the three groups of variables were separately analyzed, the final model combining significant group predictor variables. The groups were: 1) plasma homocysteine and dietary micronutrient levels; 2) spontaneous and radiation-induced MN and NPB indices of the CBMNCYT assay; and 3) D mean anal, D mean rectal, V 40 Gy anal and V 60 Gy rectal (correlations of group predictor variables were tested in the GEE model and no evidence of ill conditioning was found. In particular, most correlations between the radiation dose metrics were of the order of ≤0.2, e.g. r=0.13 between V 40 Gy anal and mean anal dose suggesting minimal overlap between the dose metrics). In each group, univariate analysis was first used to determine which of the variables were significantly associated (p ≤0.10) with increased total GI symptom scores. Multivariate analysis was undertaken by including all the significant predictor variables from the univariate analysis, followed by backwards elimination until all remaining predictor variables within the group were statistically significant (p ≤0.05), forward elimination of the variables producing the same results. The final overall model of best fit was then found by combining the statistically significant predictor variables from the three groups of variables, again using backwards elimination, until all the remaining variables were statistically significant (p ≤0.05). Notably, all GEE models were adjusted for the baseline (before EBRT) total GI symptom scores for the dependent variable and for time as RT as a nominal variable when univariate analysis was performed in the development of the models. The time variable gives an indication of the pattern of response of total GI symptom scores from one month to three years after EBRT. There appeared to be an increase in GI symptoms at one year and two years compared with one month and total GI symptoms decreased at three years compared with one month, thus justifying the outcome variable of increased total GI symptom scores from one month to three years after EBRT as a valid measure of chronic GI morbidity. It is important to note that the outcome variable of total GI symptom scores after EBRT is an interval (range 0–24) and not a dichotomous variable (only one

predictor variable was dichotomized in the development of the multivariate model as specified above).

Stata 13 software package was used for all statistical analyses.

Results

A total of 106 patients, [median age 72 (range 49–84) years, body mass index 27.3 (range 17.7–41.7)] who met the eligibility criteria formed the study population.

Of the 106 patients, 29, 46 and 31 were categorized to have low-, intermediate- and high-risk PCa, respectively, based on National Comprehensive Cancer Center (NCCN) criteria. Twenty-one of the 31 patients with high-risk disease received hormonal therapy (see Methods and Materials for details) as well as EBRT.

The means (± standard error) and medians (range) of the plasma concentrations of homocysteine and dietary micronutrients before EBRT are summarized below and detailed in **Table 1**.

For 1) homocysteine and 2) selenium, the values in mmol/l were 12 ± 1 and 10 (5–84) and 116 (±2) and 115 (72–158), respectively.

For 3) Vitamin B12, the values in ρmol/l were 277 ± 16 and 235 (44–1450).

For 4) folate the values in nmol/l were 18 (±1) and 16 (3–45).

For 5) zinc, 6) lutein, 7) retinol, 8) α-tocopherol, 9) lycopene, 10) α-carotene, 11) β-carotene the values in mg/ml were 5) 0.8 (±0.01) and 0.7 (0.5–1.2), 6) 0.18 (±0.01) and

Table 1 *Baseline (before EBRT) homocysteine and micronutrient concentrations in plasma.*

	Before RT (n=103-105)	
	Mean ± SE	**Median (range)**
Homocysteine (μmol/L)	12 ± 1	10 (5-94)
Vitamin B12 (pmol/L)	277 ± 16	235 (44-1450)
Folate (nmol/L)	18 ± 1	16 (3-45)
Zinc (μg/ml)	0.8 ± 0.01	0.7 (0.5-1.2)
Selenium (μmol/L)	116 ± 2	115 (72-158)
Lutein (μg/ml)	0.18 ± 0.01	0.16 (0.03-0.55)
Retinol (μg/ml)	0.66 ± 0.02	0.63 (0.41-1.08)
α-Tocopherol (μg/ml)	13.3 ± 0.4	12.6 (7.1-37.5)
Lycopene (μg/ml)	0.18 ± 0.01	0.17 (0.01-0.66)
α-Carotene (μg/ml)	0.05 ± 0.004	0.03 (0.00-0.27)
β-Carotene (μg/ml)	0.19 ± 0.01	0.14 (0.02-0.70)

0.16 (0.03–0.55) 7) 0.66 (±0.02) and 0.63 (0.41–1.08), 8) 13.3 (±0.4) and 12.6 (7.1–37.5), 9) 0.18 (±0.01) and 0.17 (0.01–0.66), 10) 0.05 (±0.00) and 0.03 (0.00–0.27), 11) 0.19 (±0.01) and 0.14 (0.02–0.70), respectively.

The means (±standard error) and medians (range) of the spontaneous and ex vivo irradiation MN and NPB frequencies in the CBMNCYT assay data before EBRT are summarized below and detailed in **Table 2**.

Table 2 *Baseline (before EBRT) spontaneous and ex-vivo irradiation MN and NPB frequency in CBMNCYT assay.*

	Median (range) (n= 103)	**Mean ± SE (n= 103)**
0Gy (MN/1000 BNCs)	10 (2-44)	12 ± 0.6
3Gy (MN/1000 BNCs)	633 (249-1057)	632 ± 13
3Gy Induced (MN/1000 BNCs)	619 (233-1037)	620 ± 12
0Gy (NPB/1000 BNCs)	4 (0-12)	4 ± 0.3
3Gy (NPB/1000 BNCs)	147 (6-252)	150 ± 4
3Gy Induced (NPB/1000 BNCs)	143 (0.2-252)	146 ± 4

MN = micronucleus, BNCs = binucleated cells, NPB = nucleoplasmic bridge, CBMNCYT = Cytokinesis Block Micronucleus Cytome.

For 1) spontaneous MN frequencies, and 2) ex vivo irradiation MN frequencies (minus spontaneous frequencies), the values in MN/1000 binucleated cells are 1) 12 (±0.6) and 10 (2–44) and 2) 620 (±12) and 619 (233–1037), respectively.

For 3) spontaneous NPB frequencies, and 4) ex vivo irradiation NPB frequencies (minus spontaneous frequencies), the values in NPB/1000 binucleated cells are 3) 4 (±0.3) and 4 (0–12) and 4) 146 (±4) and 143 (0.2–252), respectively.

The medians (range) of the baseline (before EBRT) planning volume, D mean, V ≥40 Gy, V ≥60 Gy of the outer rectal wall, rectal ring and anal wall are summarized below and detailed in **Table 3**.

For the planning volume, the values in cm2 are 62 (19–252) for outer rectal wall, 30 (14–60) for rectal ring and 38 (12–64) for anal wall. For D mean, the values in Gy are 51 (31–65) for outer rectal wall, 51 (34–64) for rectal ring and 43 (15–62) for anal wall. For V ≥40 Gy, the values in percent are 64 (26–100) for outer rectal wall, 60 (9–100) for rectal ring and 46 (3–94) for anal wall.

For V ≥60 Gy, the values in percent are 40 (14–81) for outer rectal wall, 41 (17–74) for rectal ring and 26 (1–63) for anal wall.

Table 3 *Median (range) of baseline (before EBRT) planning dose volume histogram parameters of outer rectal wall, rectal ring and anal wall (see text for definitions of these).*

	Outer Rectal Wall (n= 106)	Rectal Ring (n= 106)	Anal Wall (n= 106)
Volume (cm3)	61.6 (18.9-251.8)	30.1 (14.1-59.6)	38 (12.1-64.3)
Dmean (Gy)	51.4 (31-64.6)	51.4 (34.1-63.8)	43.1 (14.6-62)
Dmax (Gy)	70.4 (51.3-74.4)	70.4 (51.3-96.8)	69.8 (51.2-72.8)
V>40Gy (%)	64 (25.8-100)	60 (9.2-100)	45.7 (3.5-94.1)
V>60Gy (%)	39.7 (13.7-80.6)	41.4 (17.4-74.2)	25.8 (0-63.9)

Total GI symptom scores persisting above baseline values at all the pre-determined times after EBRT resulted from increased stool frequency, urgency of defecation, rectal mucous discharge and rectal bleeding scores (**Table 4**).

Table 4 *Modified LENT-SOMA Gastrointestinal (GI) symptom scores before EBRT and at1 month, 1 year, 2 years and 3 years after completion.*

Individual and total GI symptoms (Range of scores)	Baseline (n= 104-106)	1 Month (n= 105-106)	1 Year (n= 102-103)	2 Years (n= 89-92)	3 Years (n= 84-88)	Overall p value
Stool Frequency (0-4)	0 (0-2)	1 (0-2)	1 (0-4)**	1 (0-2)	1 (0-2)	p<0.0001
Diarrhea (0-4)	0 (0-2)	0 (0-2)	0 (0-3)	0 (0-2)	0 (0-2)	0.25
Rectal Pain (0-4)	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-3)	0 (0-3)	0.16
Rectal Mucous Discharge (0-4)	0 (0-2)	0 (0-3)	0 (0-4)*	0 (0-4)	0 (0-3)	p<0.0001
Urgency of Defecation (0-4)	0 (0-3)	1 (0-4)	1 (0-4)	1 (0-4)	1 (0-4)	p<0.01
Rectal Bleeding (0-4)	0 (0-1)	0 (0-3)	0 (0-3)	0 (0-3)	0 (0-4)**	p<0.0001
Total GI Symptoms (0-24)	1 (0-7)	3 (0-10)**	3 (0-12)***	2 (0-15)**	2 (0-11)***	p<0.0001
Effect of GI Symptoms on Activities of Daily Living (0-3)	†NA	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	NA

**p<0.01, ***p<0.001, ****p<0.0001 cf Baseline
Data shown represent median (range)
†NA= Not assessed

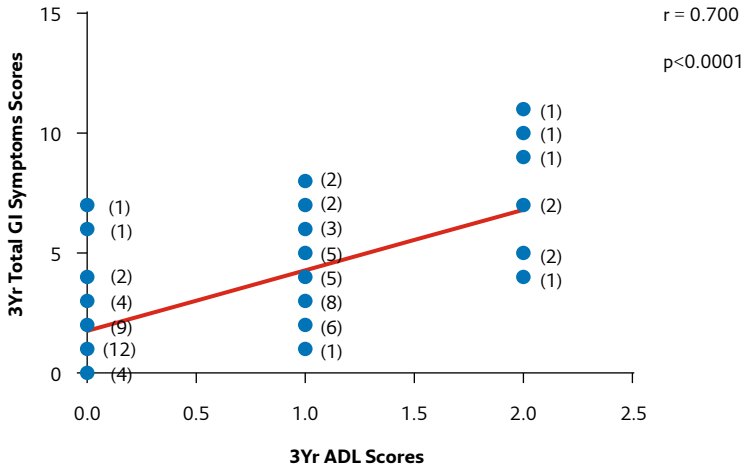
At three years, scores of: 1) stool frequency; 2) diarrhea; 3) rectal pain; 4) mucous discharge (anal incontinence); 5) urgency of defecation; 6) rectal bleeding; and 7) total GI symptoms were persistently increased above baseline in: 1) 23%; 2) 20%; 3) 22%; 4) 26%; 5) 40%; 6) 41%; and 7) 72% of the patients, respectively. Whilst X^2 comparisons of percentage of patients with and without increases of individual symptom scores, such as mucous discharge (anal incontinence) and rectal bleeding at three years and the measured dose volume parameters at baseline (before EBRT, dichotomized as detailed in statistical analysis), X^2-tests percentage of patients with and without increases in total GI symptom scores at three years were significant for D mean anal <40 Gy versus D mean anal >40 Gy and for V 40 Gy anal ≤65% versus V 40 Gy anal >65% ($p < 0.05$ for both, data not shown).

Total GI symptom scores and the effect of GI symptoms on ADL were directly related at each time point after EBRT (r=0.32–0.70, p <0.001–0.0001, **Figure 1** for three-year data).

Univariate analysis

Direct associations of significance (defined as $p \leq 0.10$ for univariate analysis as detailed in statistical analysis section) existed between the predictor variables of D mean anal, D mean rectal, V 40 Gy anal, V 60 Gy rectal, spontaneous and ex vivo irradiation MN

Figure 1 *Relationship between total GI symptom scores and scores of activities of daily living (ADL) in patients 3 years after radiation therapy. Data based on observations in 84 patients, the numbers in parentheses representing ties in the data points.*



frequency, spontaneous and ex vivo irradiation NPB frequency, plasma levels of homocysteine, Vitamin B12, folate, zinc, selenium, lutein, retinol, α-tocopherol, lycopene, α-carotene, β-carotene, and the outcome variable of increased GI symptoms from one month to three years after EBRT (p=0.96–<0.001, **Table 5**).

Table 5 *Univariate and multivariate predictor variables of increased Total GI Symptom Score from 1 month to 3 years after EBRT.*

Variable	Coefficient (B)	95% CI (B)	p values.	p value.*
Anal Wall Dmean (Gy)	0.001	-0.031, 0.033	0.96	
Rectal Ring Dmean (Gy)	0.010	0.002, 0.019	0.02	
AnalWall V≥40 (Gy)	0.032	0.014, 0.049	<0.001	<0.001
Rectal Ring V≥60 (Gy)	0.031	0.004, 0.058	0.03	
0Gy (MN/1000 BNCs)	0.062	0.006, 0.119	0.03	
3Gy Induced (MN/1000 BNCs)	0.002	-0.001, 0.005	0.17	
0Gy (NPB/1000 BNCs)	0.043	-0.085, 0.170	0.51	
3Gy Induced (NPB/1000 BNCs)	0.002	-0.006, 0.010	0.66	
Homocysteine (μmol/L)	0.021	-0.013, 0.056	0.23	
Vitamin B12 (pmol/L)	0.001	-0.002, 0.003	0.55	
Folate (nmol/L)	<0.001	-0.037, 0.037	0.99	
Zinc (μg/ml)	2.096	-0.450, 4.641	0.11	
Selenium (μmol/L)	0.020	-0.002, 0.042	0.08	
Lutein (μg/ml)	-2.363	-6.469, 1.743	0.26	
Retinol (μg/ml)	1.857	-0.424, 4.137	0.11	
α-Tocopherol (μg/ml)	0.073	-0.010, 0.156	0.09	
Lycopene (μg/ml)	-1.086	-4.193, 2.021	0.49	
α-Carotene (μg/ml)	6.375	-5.215,17.966	0.28	
β-Carotene (μg/ml)	0.909	-1.611, 3.429	0.48	

Models based on Generalized Estimating Equations (GEE) and including adjustment for time (nominal variable) and baseline Total GI Symptom Score. All micronutrients measured at baseline.
*Final multivariate model.
MN = micronucleus, BNCs = binucleated cells, NPB = nucleoplasmic bridge.

Multivariate analysis

On multivariate analysis, only V 40 Gy anal predicted for increased GI symptom scores following EBRT ($p < 0.001$, **Table 5**) after, adjusting for before EBRT total GI symptom score and time since EBRT as a nominal variable.

Discussion

This prospective longitudinal study is the first to examine a range of nutritional and DNA damage biomarkers together with several anal and rectal DVH parameters to determine which predictor variable(s) is of independent prognostic significance for chronic GI morbidity after EBRT for PCa.

Previous studies have examined anal and/or rectal DVH parameters and patient-risk factors including radiosensitive phenotype which may be predictive of GI morbidity after EBRT for PCa in isolation.[5-8] With the possible exception of the consistent association of V ≥60 Gy rectum and RTOG Grade ≥2 chronic radiation proctitis, there is no conclusive anal radiation dose metric to provide a definite basis for radiation treatment planning.

Although reports that dietary micronutrients and above average intakes of fruits and vegetables may reduce DNA damage induced by ionizing radiation through their actions as antioxidants or co-factors of DNA repair enzymes[10-12], there have hitherto been no studies of their impact on chronic radiation-induced GI morbidity. The likely explanation for the absence of such studies is the theoretical concern among radiation oncologists that antioxidants may diminish the therapeutic efficacy of RT although a recent study reported that supplements of β-carotene did not to result in worse outcomes after EBRT for PCa compared with placebo.[19]

In the present study, plasma selenium and α-tocopherol levels were associated with chronically increased GI symptoms after EBRT on univariate but not multivariate analysis. The wide range of concentrations of homocysteine, vitamin B12, folate, selenium and carotenoids, such as lycopene, found in the plasma of patients in our study indicate large variation in intake and possible B vitamin deficiency.

The CBMNCYT biomarker data also show a wide range in spontaneous and radiation-induced MN and NPB frequency indicating substantial variation in genome integrity and radiation sensitivity.

Our finding of the association of spontaneous (0 Gy) MN with worsening GI symptoms on univariate analysis differs from the report that radiation-induced (3 Gy ex vivo) but not spontaneous MN predicted increased chronic GI and GU morbidity after EBRT in a previous study of radiation sensitivity based on the CBMNCYT assay.[8] A likely explanation for the discordance in findings is that the confounding effects of nutritional factors on the expression of the radiosensitive phenotype were not examined in the previous

study.[8] For example, it is likely that the association of GI symptoms with spontaneous MN frequency in our study may reflect carotenoid and α-tocopherol intake as well as zinc, selenium, folate and vitamin B12 status as lower levels of DNA damage in lymphocytes have been reported with increased intake of retinol, β-carotene, α-tocopherol, folate and higher plasma carotenoid, homocysteine and lower zinc, selenium, folate and vitamin B12 concentrations.[20-22]

We acknowledge that the in vitro radiation challenge model used in the CBMNCYT assay in not replicating the in vivo conditions, particularly with respect to tissue type and dose fractionation clinically constitutes one of the limitations of the study. Three Gy γ-rays was used to test variation in ex vivo radiation sensitivity in this study because MN frequency after ex vivo radiation doses of between 2 Gy and 4 Gy γ-rays, in particular, were reported to be significantly different between patients with normal and abnormal radiosensitivity (measured as RTOG grades 0 or 1 versus RTOG grades 2 or 3 chronic GI and GU morbidity) in a previous study.[8] Although the dose rate of γ-rays used in this study is greater than the 0.9 Gy/min in the previous study[8], it is outside of the well-recognized steep dose effect range of (0.01 and 1 Gy/min) for cell survival data. Furthermore, the 5.43 Gy/min in this study more closely approximates the dose rate of the linear accelerators used in

EBRT clinically. The use of peripheral blood lymphocytes is thus a practical surrogate model assuming that normal tissue sensitivity is dictated by intrinsic genetic defects in DNA strand break repair that would be evident across tissues. The peripheral blood lymphocyte model could theoretically be improved to test effects of radiation under the same in vivo conditions which apply in EBRT of patients. However, with respect to dose fractionation, it would only be practical to use just two dose fractions which should be enough to test adaptive Capacity of cells to an initial radiation dose and also possibly to reveal another aspect of the phenotype of resistance or sensitivity to radiation lethality.

Unlike the previous study of radiation sensitivity based on the CBMNCYT assay[8], our study also examined the influence of DVH parameters on radiation-induced GI morbidity. Although the range of volumes of outer rectal and anal wall of 19–252 cm^3 and 12–64 cm^3 in our study are at variance with the 37–193 cm^3 and 7–22 cm^3, respectively, in another study[23], the apparent discrepancies can be attributed to different definitions of the anal canal. In our study, the 3–4 cm length of the anal canal is defined from the anorectal junction to the anal verge instead of the standard 2 cm length from the anal verge definition previously reported.23 D mean for outer rectal (31–65 Gy) and anal wall (15–62 Gy) in our study closely corresponds with the calculated 32–64 Gy and 10–62 Gy parameters in yet another study of the influence of radiation dose metrics on GI morbidity.24

The association between all anal and rectal DVH parameters examined and increased total GI symptom scores on univariate analysis in this study is consistent with the data from previous studies.[5-7,25] However, the finding that only V 40 Gy anal independently predicted for increased GI symptoms from one month to three years after EBRT in our

study differs from a previous report that D mean anal440 Gy increased the risk of fecal incontinence.[5] There are a number of possible

explanations for the discordant findings between our study and that of the previous study.[5] These include differences in the design, definition and analysis of the outcome variables between the previous study and our study.[5] Whilst Alsadius et al. examined the relationship between the prevalence of fecal incontinence at a varying point of 2–15 years after completion of primary or post-operative EBRT for PCa and mean anal dose determined retrospectively from the treatment plans of the patients, the findings in our prospective longitudinal study were based on univariate and multivariate analyses of variables which predict for increased total GI symptom scores in patients from one month and three years after EBRT for PCa.[5] Of these differences, a plausible explanation for the discordant findings in radiation dose metrics between the previous study5 and our study lies in the outcome measures of chronic GI morbidity in the two studies. Increased total GI symptoms in our study includes anorectal symptoms other than fecal incontinence and the finding that a 1% increase in volume of the anal wall receiving ≥40 Gy results in 0.32 rise in total GI symptom score from one month to three years after EBRT in our multivariate model suggests the predominance of a volume effect. In contrast, the large increase in the prevalence of fecal incontinence between patients receiving D mean dose ≥40 Gy versus <40 Gy suggests a greater dose effect in the previous study by *Alsadius et al*.[5]

A third smaller study of radiation dose metrics only and GI morbidity based on 65 patients who had completed EBRT for localized PCa 2–4 years earlier found correlations between the 25–42 Gy dose interval for rectum and defecation urgency/diarrhea and 45–55 Gy interval for anal sphincter region and fecal leakage but was inconclusive in defining threshold volumes and doses for increased GI morbidity after EBRT for PCa.[25] Whilst the greater sample size of 106 in this study is still modest, the multivariate analysis is based on 424 observations, albeit not independent ones. However, our modeling strategy was carefully designed to avoid over-fitting and all models were adjusted for baseline total GI symptom score and time since EBRT as a nominal variable.

The relationships between dose metrics and chronic GI morbidity in this study like others are based on the assumption that the dose structures defined on the basis of a single planning scan applies throughout the 7–7.4 week's course of radiation treatment. The finding that V 40 Gy anal independently predicted for increased GI symptoms from one month to three years after EBRT in our study is therefore not conclusive.

However, the data in our study supports: 1) previous recommendations that the DVHs of the anal wall should be derived separately from the rectal wall; and 2) minimizing the volume and dose received by the rectum and anal canal, in particular V ≥40 Gy anal wall and D mean anal<40 Gy in order to reduce all GI symptoms which contribute to chronic GI morbidity after EBRT for PCa.

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CHAPTER 5

Increased rectal wall stiffness after prostate radiotherapy: relation with fecal urgency

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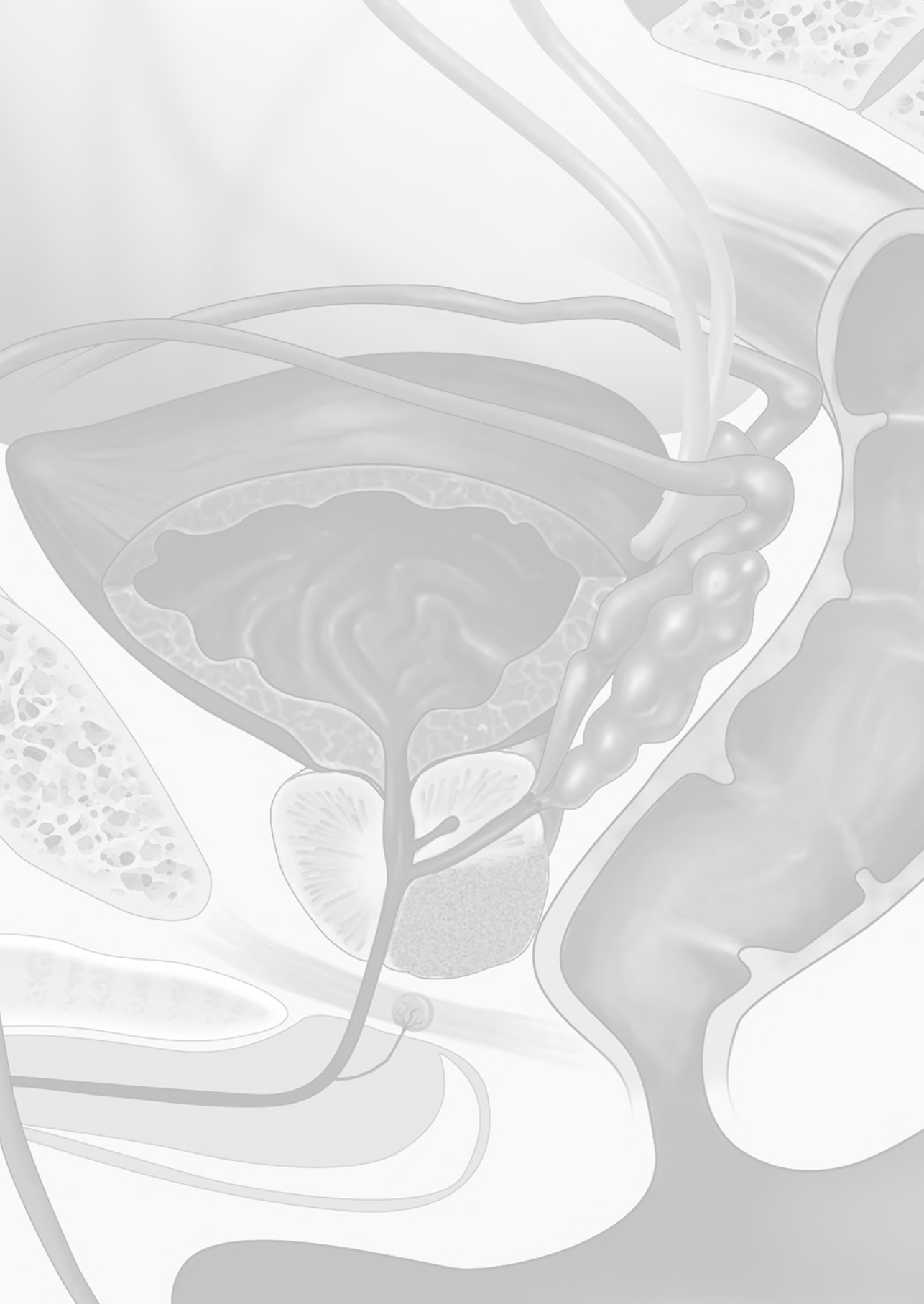


Abstract

BACKGROUND Late anorectal toxicity is a frequent adverse event of external beam radiotherapy (EBRT) for prostate cancer. The pathophysiology of anorectal toxicity is unknown but we speculate that rectal distensibility is impaired due to fibrosis. Our goal is to determine whether EBRT induces changes of rectal distensibility as measured by an electronic barostat and to explore whether anorectal complaints are related to specific changes of anorectal function.

METHODS Thirty-two men, irradiated for localized prostate carcinoma, underwent barostat measurements, anorectal manometry, and completed a questionnaire prior to and one year after radiotherapy. The primary outcome measure was rectal distensibility in response to stepwise isobaric distensions. In addition, we assessed sensory thresholds, anal pressures and anorectal complaints.

KEY RESULTS EBRT reduced maximal rectal capacity (227±14 mL vs. 277±15 mL; $p<0.001$), area under the pressure-volume curve (3212±352 mL·mm Hg vs. 3969±413 mL·mm Hg; $p<0.005$) and rectal compliance (15.7±1.2 mL·mm Hg^{-1} vs. 17.6±0.9 mL·mm Hg^{-1}; $p=0.12$). Sensory pressure thresholds did not significantly change. Sixteen of the 32 patients (50%) had one or more anorectal complaints. Patients with urgency (n=10) had a more reduced anal squeeze and maximum pressure (decrease 29±11 mm Hg vs. 1±7 mm Hg; $p<0.05$ and 31±12 mm Hg vs. 2±8 mm Hg; $p<0.05$ respectively) compared to patients without complaints, indicating a deteriorated external anal sphincter function.

CONCLUSIONS & INFERENCES Irradiation for prostate cancer leads to reduced rectal distensibility. In patients with urgency symptoms, anal sphincter function was also impaired.

KEYWORDS rectal distension, external beam radiotherapy, electronic barostat, localized prostate cancer, quality of life.

The most common late side-effects of external beam radiotherapy (EBRT) for prostate cancer are of intestinal origin and include symptoms like urgency and frequent defecation.[1-4] Recent studies have shown that up to 50% of patients suffer from late anorectal radiation toxicity.[2,5,6]

Anorectal radiation toxicity comprises different symptoms, such as an increased frequency of defecation, fecal urgency, fecal incontinence, bloody stools and mucus loss. These complaints can interfere with daily activities. The quality of life (QoL) after EBRT for prostate cancer is largely determined by these adverse effects.[7,8] Indeed, complaints of urgency and fecal incontinence have the largest impact on QoL.[4,5,8] Therefore, it is important to prevent these symptoms.

The occurrence and severity of anorectal toxicity is related to radiation dose on the anal and rectal wall.[9,10] However, the pathophysiological changes that lead up to the development of these complaints are poorly understood. Understanding these changes may guide EBRT and may help to identify predictors for late anorectal complaints.

The rectal wall is exposed to high radiation doses during EBRT[11,12] and late anorectal toxicity is accompanied by mucosal changes as observed by endoscopy.[13] Whether EBRT also induces late changes of rectal function, for instance by scarring or fibrosis, is largely unclear.[14] Pressure-volume relations of the rectum after irradiation are not well studied and data limited.[6] EBRT reduces rectal volumes associated with sensory perception and desire to defecate[2,6] and it has been suggested that rectal compliance decreases over time[2] after radiotherapy. However, the function tests used in these studies were suboptimal. The current state of the art technique for measuring rectal distensibility is the barostat, but there is a paucity of studies in the field.[15] The barostat allows measurement of rectal volumes under isobaric conditions. The hypothesis of this study is that EBRT induces stiffness of the rectal wall and thereby contributes to the development of late anorectal toxicity in prostate cancer.

Therefore, the primary aim of this study was to evaluate whether there are changes in rectal distensibility after radiotherapy as measured by an electronic barostat. Secondary aims were to explore the relation between anorectal complaints and specific changes of anorectal function.

Materials and Methods

Study design

This was a prospective longitudinal study, with a one group pretest-posttest design. All patients were tested prior to and one year after EBRT. Rectal distensibility (rectal compliance, capacity and area under the pressure-volume curve) in response to stepwise

isobaric distensions was the primary outcome measure. In addition, we measured the proportionate volume levels, sensory thresholds and anal pressures. Furthermore, all patients were asked to complete a questionnaire about anorectal complaints prior to anorectal function testing.

Patients and treatment

Over a two year period, 32 consecutive Dutch men who visited the Radboud University Nijmegen Medical Centre for irradiation of a localized prostate carcinoma ($T_{1-3}N_0M_0$; mean age 68, range 52-79 years) agreed to participate in this study. All patients who underwent anorectal function tests prior to and approximately one year after EBRT for prostate cancer were included. Patients received a cumulative radiation dose between 64.4-78 Gy in daily fractions of 2.0-3.4 Gy. More than half of the patients received 70 Gy in daily fractions of 2.5 Gy, four times a week. Nineteen men (59%) used adjuvant androgen suppression therapy before start of EBRT. During EBRT, a daily inserted air-filled endorectal balloon was used to reduce radiation dose to the anal and rectal wall in all patients.[16,17] The mean time between the anorectal investigations was 12.7 months (range 7-17 months). Patient characteristics are shown in **Table 1**. The study protocol was approved by the local ethics committee. Informed consent was obtained from all patients according to standard clinical procedures.

Electronic barostat testing

Patients were studied in the left lateral position and were asked to empty their bowel before start of the function tests. An electronic barostat (Distender II, G&J Electronics Inc., Ontario, Canada) was used to measure rectal capacity, pressure-volume relations, rectal compliance and sensory thresholds. An infinitely compliant 800 mL polyethylene bag tied 10 cm from the distal end of a probe connected to the barostat, was positioned approximately 5 cm from the anal verge and inflated with air via the central lumen. Barostat procedures were performed in accordance with previously described and validated techniques.[18,19] After an initial conditioning staircase distension (4 mm Hg steps, 30 seconds per step) to reduce variability, a rectal staircase distension is performed starting at an intrabag pressure of 0 mm Hg. At one minute intervals the intrabag pressure is increased by 2 mm Hg and kept constant. Intrabag volumes corrected for intrabag pressures, are averaged beginning 25 seconds at each distension step. Both the pressures and volumes at each distension step were recorded.[18-20]

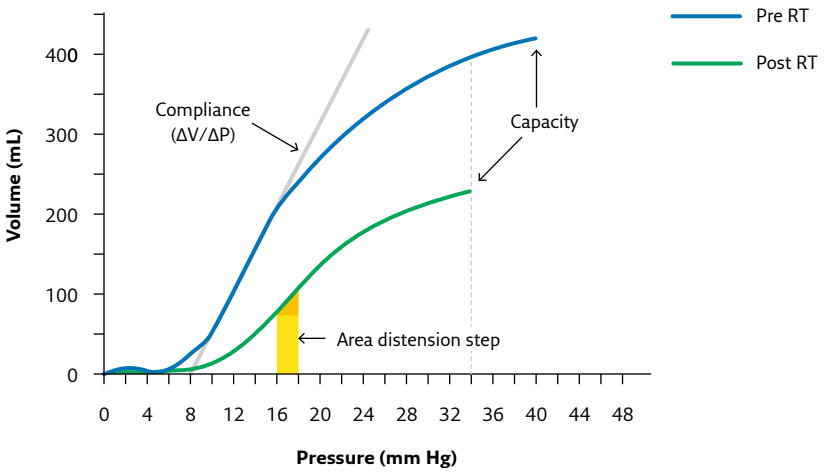
Rectal capacity was defined as intrabag volume at maximum tolerated distension. Rectal compliance was defined as the maximum slope of the pressure-volume curve (ΔVolume/ΔPressure). The third parameter of rectal distensibility was the area under the pressure-volume curve (AUC). This parameter allows evaluation of the entire pressure-volume curve, instead of one point and was determined by summing the areas of every

Table 1 *Characteristics of patients and tumor characteristics prior to radiotherapy (n=32).*

Characteristics	**Mean**	**SD**	**n**	**(%)**
Age (years)	68	6		
Time between tests (months)	13	3		
Length (cm)	175	7		
Weight (kg)	80	13		
BMI (kg·m-2)	26	4		
Comorbidity			17	(53%)
DM			1	(3%)
COPD/Asthma			4	(13%)
Hypertension			9	(28%)
Heart failure			2	(6%)
BPH			3	(9%)
Other			1	(3%)
Medication			20	(63%)
α1-inhibitor			7	(22%)
Anticoagulants			1	(3%)
Laxatives			0	(0%)
Antidiarrheals			0	(0%)
Other			1*	(3%)
Operation pelvic region/ genitals			6	(19%)
Tumor characteristics			**n**	**(%)**
PSA (range)	17.4 (0.9 - 63.0)			
Gleason-score (median; range)	7.0	(5-9)		
T-stadium				
T1			4	(13%)
T2			8	(25%)
T3			20	(63%)

Abbreviations: SD = standard deviation; BMI = body mass index; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen. * Patient used Levothyroxine.

Figure 1 *Pressure-volume relations in one patient. Rectal capacity is defined as intrabag volume at maximum tolerated distension, rectal compliance as the maximum slope of the pressure-volume curve and area under the pressure-volume curve as the summation of area under the curve between subsequent distension steps. The AUC is calculated till the lowest maximum distension step in both tests, represented by the dotted line.*



distension step. The area of each distension step was calculated by the formula Area distension step = $Vdistension_{(i)}$· 2 mm Hg + 0.5· 2 mm Hg·($Vdistension_{(i+1)}$ – $Vdistension_{(i)}$), where i is distension step number and V is volume at i-th distension step.

If the maximum distension steps prior to and after EBRT were not equal for a patient, the AUC was calculated up to the lowest maximum distension step in both curves.

Figure 1 is the pressure-volume curve of one of the patients and visualizes the parameters of rectal distensibility.

The last parameters of distensibility were the proportionate volume levels (P10%, P50% and P90%), respectively representing the pressures at 10%, 50% and 90% of rectal capacity. These parameters were obtained from the pressure-volume curve expressing volume as percentage of rectal capacity.[20]

Sensory thresholds (i.e. the moments the patient became aware of something present in the rectum (first sense), the first feeling of urge (first urge) and the moment they experienced discomfort or an uncontrollable urge to defecate (maximum tolerated distension)) were also determined during barostat measurements.[21]

Anal manometry

An anorectal motility catheter with 4.8 mm outer diameter, with 4 radially oriented recording points 90 degrees apart (Arndorfer Medical specialties, Greendale, WI, USA) connected to the Solar GI system (MMS, Enschede, The Netherlands), was inserted via the anal canal. A standard station pull-trough technique19,22 was used with a water perfused catheter to assess resting and squeeze pressures in the anal canal at consecutive 1 cm levels of the anal canal in four separate quadrants. Rectal pressure was the reference pressure. Resting anal pressure (P resting) was defined as the highest resting pressure and maximal anal squeeze pressure (P squeeze) as the highest increase over resting pressure during maximal squeezing in each of the four quadrants. Resting and squeeze pressures were calculated as the highest values recorded throughout the anal canal by each recording point and expressed as a mean of these four values.[19] All patients were studied in the left lateral position.

Questionnaire

The function score of the bowel domain of the Expanded Prostate Cancer Index Composite (EPICB-F)[23] and two additional questions were used to characterize defecatory symptoms particularly the complaint of urgency.[24,25] The EPICB-F was developed and validated in men with prostate cancer to measure severity of bowel symptoms.[23] Frequency of bowel movements, rectal urgency, uncontrolled leakage of stool, loose or liquid stool, bloody stool, painful bowel movements and crampy pain in the abdomen, pelvis or rectum were rated on a Likert scale.

Two additional questions were used to determine presence or absence of urgency ("Do you have to rush to the toilet because you experience an urgent need to empty your bowels?" and "Can you defer bowel movements for 15 minutes as soon as you feel the need?"). These items were obtained from previously validated questionnaires for fecal incontinence.[24,26] Presence of a specific symptom was defined as an increased symptom score after radiotherapy. Recent studies showed that complaints of fecal incontinence, urgency and increased frequency have the largest impact on QoL.[4] Therefore, we compared patients with these complaints to patients without complaints.

Analysis

Data are presented as mean ± 1 SEM unless stated otherwise. For statistical calculations the SPSS 16.0 software for Windows was used (SPSS Inc, Chicago, Illinois, USA). Based on prior studies, it was assumed that the variables had a normal distribution.[2,19] The paired t-test was used for comparison of functional parameters prior to and after EBRT. For comparison of the parameters between patients with and without complaints we used the unpaired t-test. A two tailed probability value of less than 0.05 was considered to indicate statistical significance. The Bonferroni method was used to correct for multiple testing when appropriate.

Results

Patient characteristics

The mean body mass index (BMI) remained equal during the study. BMI ± SD prior to EBRT was 26.3 ± 4.0 kg·m^{-2},compared to 26.7 ± 4.0 kg·m^{-2} after EBRT.

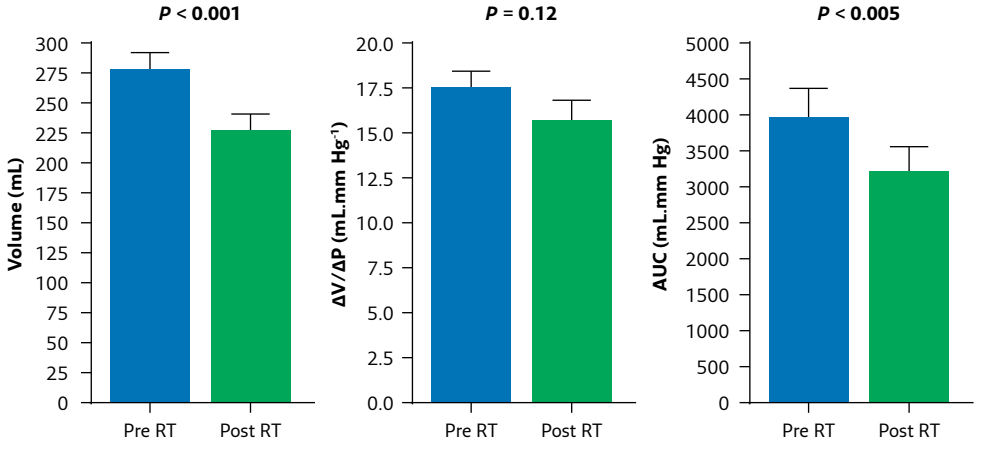
Rectal distensibility

After EBRT rectal capacity decreased by 51 ± 11 mL ($p < 0.001$) and AUC by 758 ± 221 mL·mm Hg ($p < 0.005$). Rectal compliance was also decreased after EBRT, but not significantly (2 ± 1 mL·mm Hg-1; p=0.12). The P10% was significantly increased after EBRT by 1.1 ± 0.5 mm Hg (p=0.03). Results are illustrated in **Figure 2** and **Table 2**. There were not enough patients in each of the 4 different groups of radiation fractionation schedules to perform sub-group analysis.

Sensory thresholds and anal pressures

Pressures of sensory thresholds were not significantly different for first sense, first urge and maximum tolerated distension post RT compared to pre RT (p=0.06, p=0.15 and p=0.86 respectively). However, the volume of the maximum tolerated distension significantly decreased after radiation (227 ± 14 mL vs. 277 ± 15 mL; $p < 0.001$).

Figure 2 *Rectal capacity, rectal compliance and area under the pressure-volume curve (AUC) in 32 patients prior to (Pre RT) and after radiotherapy (Post RT) for prostate cancer. Rectal capacity, compliance and AUC all decreased after EBRT (p < 0.001, p = 0.1 and p = 0.002 respectively).*



No significant changes of anal pressures were seen after EBRT. All results of anorectal parameters pre RT and post RT are summarized in **Table 2**.

Anorectal function by complaint

Two men had anorectal symptoms prior to radiotherapy. Sixteen out of 32 men had an increased symptom score after radiotherapy. Of these 16 men with complaints, 10 men reported urgency, 10 loose or liquid stools, 4 an increased frequency of defecation, 2 painful defecation, 2 bloody stools and 1 fecal incontinence.

Patients with urgency had a significantly larger decrease in anal squeeze pressure (mean decrease 29 ± 11 mm Hg in patients with urgency vs. 1 ± 8 mm Hg; $p < 0.05$) and

Table 2 *Results of barostat measurements and anorectal manometry in patients prior to and after EBRT for localized prostate cancer. Bold entries indicate p < 0.05 after Bonferroni correction.*

Functional assessment	Pre RT Mean	(±s.e.m.)	Post RT Mean	(±s.e.m.)	p
Rectal distensibility					
Rectal capacity (mL)	277	(±15)	227	(±14)	**0.000**
AUC (mL·mm Hg)	3969	(±413)	3212	(±352)	**0.002**
Compliance (mL·mm Hg-1)	17.6	(±0.9)	15.7	(±1.2)	0.12
Pr10% (mm Hg)	8.4	(±0.5)	9.5	(±0.5)	0.03
Pr50% (mm Hg)	14.7	(±0.6)	15.5	(±0.7)	0.21
Pr90% (mm Hg)	27.2	(±1.3)	26.1	(±1.2)	0.38
Sensory threshold					
P first sense (mm Hg)	12	(±0.7)	14	(±1.0)	0.06
P first urge (mmHg)	19	(±0.9)	20	(±1.1)	0.15
P MTD (mm Hg)	33	(±1.6)	33	(±1.6)	0.86
V first sense (mL)	104	(±12.8)	103	(±10.0)	0.95
V first urge (mL)	181	(±13.5)	155	(±11.7)	0.07
V MTD (mL)	277	(±15.1)	227	(±14.4)	**0.000**
Anal P- resting (mm Hg)	56.9	(±3.0)	58.1	(±2.6)	0.54
Anal P- squeeze (mm Hg)	170.3	(±11.3)	160.5	(±12.2)	0.10
Anal P- maximum (mm Hg)	216.2	(±11.9)	207.9	(±13.0)	0.21

Abbreviations: AUC = area under the pressure-volume curve; P = pressure; V = volume; MTD = maximum tolerated distension; s.e.m. = standard error of mean.

Table 3 *Results of anal manometry in patients with urgency vs. patients without any complaints.*

Functional assessment	Urgency (n=10) Mean	(±s.e.m.)	No complaints (n=16) Mean	(±s.e.m.)	p
Anal P- resting (mm Hg)					
Pre RT	59.9	(±5.5)	56.6	(±3.8)	
Post RT	56.7	(±4.6)	58.3	(±2.8)	
Change (Pre RT - Post RT)	3.2	(±3.2)	-1.6	(±2.5)	0.25
Anal P- squeeze (mm Hg)					
Pre RT	167.6	(±23.8)	179.9	(±15.1)	
Post RT	138.4	(±19.3)	179.0	(±18.9)	
Change (Pre RT - Post RT)	29.2	(±11.0)	0.9	(±7.5)	0.038
Anal P- maximum (mm Hg)					
Pre RT	213.7	(±24.3)	227.8	(±15.4)	
Post RT	182.4	(±18.5)	226.3	(±19.7)	
Change (Pre RT – Post RT)	31.3	(±12.2)	1.5	(±8.2)	0.046

Abbreviations: P = pressure; s.e.m. = standard error of mean.

in maximal anal pressure (mean decrease 31 ± 12 mm Hg in patients with urgency vs. 2 ± 8 mm Hg; $p < 0.05$) compared to patients without complaints. Results of anal manometry before and after radiotherapy in the subgroups of patients with and without urgency are shown in **Table 3**. There were no significant differences observed in barostat outcomes between the subgroups.

Patients with an increased frequency of defecation (n=4) did not have significant differences compared to patients without complaints. Fecal incontinence was not further analyzed, because it was reported by only one patient.

Discussion

This study shows that patients after EBRT for prostate cancer had an increased stiffness of the rectal wall. Rectal capacity and pressure-volume relations were reduced, reflecting decreased distensibility. This outcome helps to clarify the major factor underlying pathophysiology of anorectal radiation toxicity.

Currently, the pathophysiology of anorectal complaints is poorly understood. Radiation initiates an inflammatory response and can cause fibrosis of the rectal wall.[14] Therefore, one of the explanations of a reduced rectal distensibility could be that radiation causes fibrosis, and thereby stiffness of the rectal wall. *Van Lin et al* showed that a reduced rectal wall surface exposed to intermediate- or high doses of radiation results in less mucosal changes and rectal toxicity.[13] This could be interpreted as that less exposure of the rectal wall to intermediate- or high doses of radiation leads to less fibrosis of the rectal wall. Whether fibrosis or other changes of the rectal wall are involved remains to be established by future studies including endoscopy with (sub)mucosal biopsies.

The reduction in rectal capacity and AUC, combined with the increase of the P10% after radiotherapy confirms our hypothesis that rectal distensibility reduces after EBRT. It was interesting to note that besides an impaired rectal distensibility, patients with urgency also had a reduced anal sphincter function in the present study. This suggests that both mechanisms, a reduced rectal distension and anal function, are involved in the development of this symptom. This supports the recommendation to separately delineate these structures in radiotherapy planning[27] to reduce the dose not only on the rectal wall, but also on the anal wall. This rectal and anal wall dose sparing is possible by applying contemporary imaged-guided radiotherapy planning and treatment delivery techniques.[12]

To study rectal distensibility, we used an infinitely compliant polyethylene bag connected to an electronic barostat, which is unique for this group of irradiated patients. The polyethylene bag is preferred over a rubber balloon, because the bag has no intrinsic compliance in volumes smaller than the maximum volume.[15] This is a limitation of studies with a rubber balloon in irradiated patients.[28] Furthermore, the electronic barostat allowed to control the rate of distention and to correct volumes for intrabag pressures. Previous studies after radiotherapy for prostate cancer did not use the barostat technique. *Yeoh et al* calculated rectal compliance by the maximum slope over a fixed volume interval of the pressure-volume curve from 40 to 100 mL in response to volume based distensions of a manually inflated balloon.[2,28] We calculated the maximum slope of the pressure-volume curve without restrictions to pressures or volumes in response to pressure based stepwise distensions.

Rectal compliance, prior to EBRT, found in this study (17.6 $\pm$ 0.9 mL mm Hg^{-1}) was in agreement with values found in healthy volunteers with an electronic barostat.[19] Rectal compliance is the pressure-volume ratio at the steepest point of the pressure-volume curve. The compliance represents one parameter of the pressure-volume curve. However, rectal compliance alone is an incomplete index to characterize rectal distensibility (**Figure 1**).[15] Therefore we also measured the AUC, P10%, P50% and P90% and rectal capacity. Reduction of rectal capacity after radiotherapy was consistent with the results of other studies.[6,27]

The frequency of individual complaints in the present study tended to be lower than that observed in other studies which also reported all grades of complaints.[4,28] The use of a daily inserted endorectal balloon to reduce radiation dose to the rectal wall[13,17] or differences in EBRT techniques between studies might explain this discrepancy. The high number of patients reporting urgency and the low frequency of bloody stools in our study is in agreement with related studies.[27]

Anal resting pressures, largely determined by the internal anal sphincter, did not change after EBRT, neither in the whole group nor in the subgroup of patients with fecal urgency. There was a reduction in anal squeeze and maximum pressures in patients with urgency, reflecting decreased voluntary muscle contraction of the external anal sphincter. In contrast, *Smeenk et al* showed that anal resting pressures were reduced in patients with urgency compared to patients without urgency.[27] The reason for this discrepancy is not known. One reason may be that they did not compare intra-individual pressure changes, but only compared post radiotherapy data between patients with and without complaints. Therefore, differences in anorectal parameters before radiotherapy may have biased post radiotherapy data.

This study had a pretest posttest design, which revealed intra-individual changes over time. This rules out inter-individual variations of anorectal functioning by confounding factors, such as body mass index, co-morbidities and use of medication. Furthermore, there were no changes in instrumentation, measurement techniques or test conditions since the start of this study in 2007. Barostat measurements and anal manometries were done by one investigator (WH). This excludes bias due to changed test conditions and inter-observer bias.

A limitation of this study is the lack of a control group. This precludes correction for the natural course of anorectal function and for the fact that patients are better prepared for the second test cycle. Blinding and randomization was not possible. Another limitation is the use of an ascending method of limits to test rectal sensory thresholds. The stepwise distension procedure is a commonly used and validated method to measure rectal compliance.[18,19] Although previous studies also showed good reproducibility for testing sensory thresholds[29], this procedure may be vulnerable to psychological bias.[30,31] This could be a reason for absence of a significant difference in sensory perception pre versus post EBRT. For measurement of rectal perception a random staircase procedure has been advocated as the method of choice.[30,31]

A standard station pull-trough technique[19,22] was used with a water perfused catheter for anal manometry. In contrast to the multiport technique with a rectal balloon, this technique did not allow assessment of rectoanal reflexes such as the rectoanal inhibitory reflex, the rectoanal contractile reflex or the sensory-motor reflex.[32] Therefore, the current study does not rule out damage to these reflexes as a factor contributing to anorectal complaints after radiotherapy.

Additional studies comparing anorectal functions of patients with complaints to patients without complaints are necessary to clarify the pathophysiology. Because the development of toxicity after EBRT is a dynamic process, which improves or deteriorates, additional studies with repeated barostat measurements over time (i.e. 6 months, 1 year and 2 years after EBRT) are needed.[2,13] For complete understanding of the pathophysiology of radiation toxicity, not only more studies of anorectal functions are required, but it will also be necessary to further investigate the changes in anorectal mucosa after EBRT. We recently started a prospective study to correlate radiation doses on the anal and rectal wall with anorectal functions, rectal mucosal changes and anorectal complaints. Only when pathophysiology is understood, it may be possible to prevent and decrease treatment related toxicity and thereby increase QoL.

In summary, by application of the current state of the art test, the electronic barostat, this study shows that EBRT for localized prostate cancer results in an impaired rectal distensibility. Fifty percent of irradiated patients develop complaints of late anorectal radiation toxicity, with urgency as most reported complaint (31%). Urgency was related to dysfunction of both the anal and rectal wall. This supports the recommendation to separately delineate these structures in radiotherapy planning.

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CHAPTER 6

Endoscopic proof of mucosal improvement 5 years after prostate irradiation with endorectal balloon

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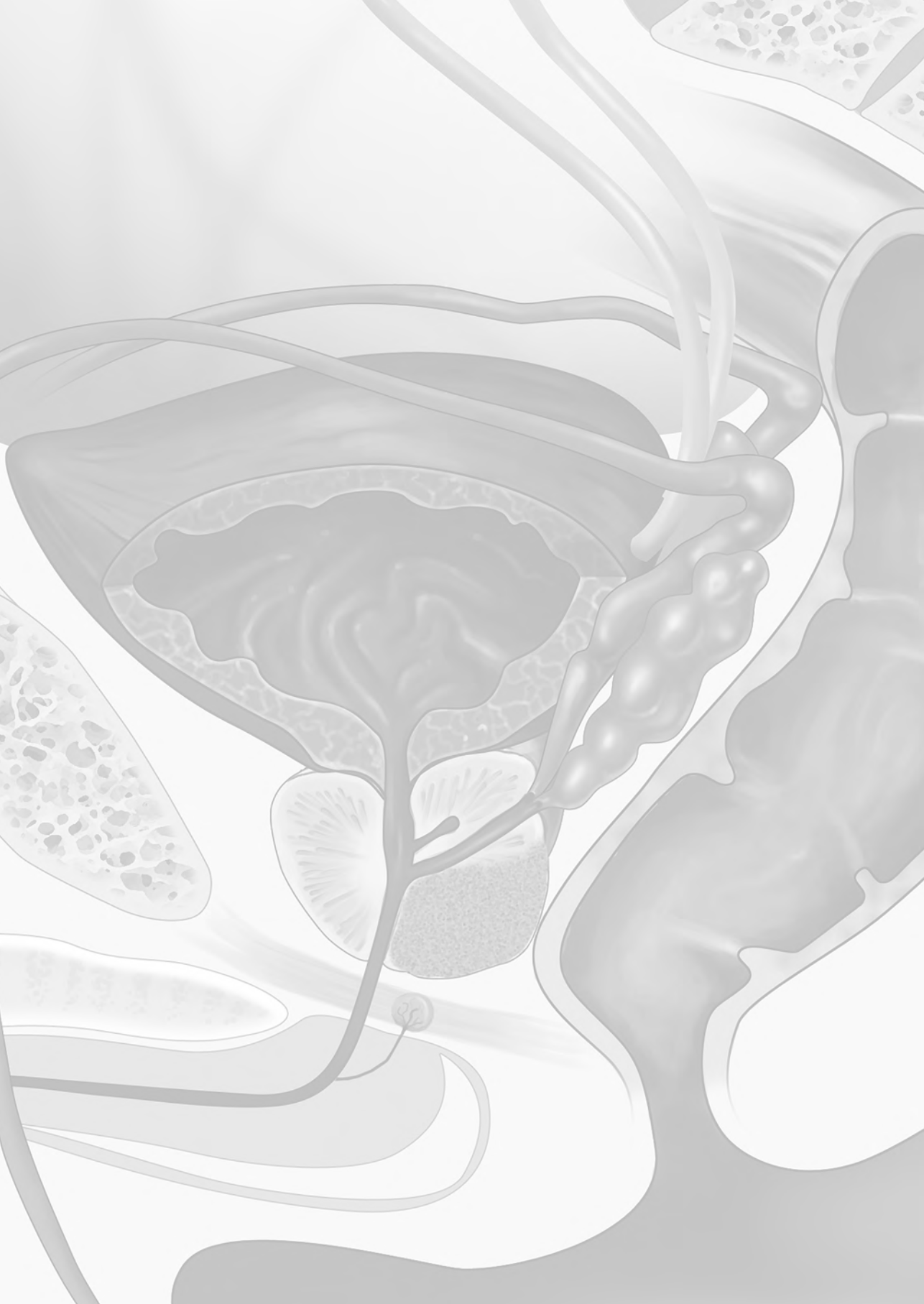


Abstract

PURPOSE Gastrointestinal complaints are frequently seen adverse events of external beam radiotherapy for prostate cancer. Daily inserted endorectal balloons (ERB) during radiotherapy are used to reduce rectal toxicity. The aim of this prospective study was to compare objective rectal toxicity between patients treated with and without ERB by means of repeated rectoscopy for a period of 5 years.

METHODS AND MATERIALS Forty-eight patients (mean age 71 years) were randomly assigned to the ERB group or no-ERB group (24 patients in both groups). After radiotherapy, endoscopies were performed on settled time points over a 5-year follow-up. Rectal toxicity was scored by the Vienna Rectoscopy Score. Endoscopists were blinded for treatment group and prior endoscopy scores.

RESULTS Five years after radiotherapy there were 16 patients left in both groups. In total, 160 rectoscopies, creating over 2500 mucosal regions of interest (ROI) were analysed. Telangiectasias were most often found. The highest prevalence of rectal toxicity was found at one year (45% and 33% of ROIs in the no-ERB group and ERB group, respectively), and this decreased to 27% and 11% after 5 years, respectively. Patients in the ERB group had more mucosal areas irradiated to low doses (<40Gy) compared to patients in the no-ERB group.

After irradiation with ERB there was less rectal toxicity observed compared to irradiation without ERB in areas that received the same dose. Furthermore, patients treated with ERB reported less symptoms compared to patients treated without ERB.

CONCLUSION After radiotherapy, rectal mucosal damage improves during a 5-year period after treatment. There were less ROIs with low grade and high grade toxicity in the ERB group compared to the no-ERB group. Patients in the ERB group experienced less toxicity compared to patients in the no-ERB group. These observations suggest a beneficial effect of ERBs in prostate radiotherapy.

Introduction

The incidence of prostate cancer has increased over the last decades and prostate cancer is now the most common cancer in men in the Western World.[1,2] One of the most frequently used treatment modalities is external beam radiotherapy (EBRT). Due to their proximity to the prostate, it is inevitable that parts of the rectum and anal canal are exposed to high radiation doses, potentially leading to anorectal toxicity. Up to 50% of the irradiated patients experience changes in their bowel habits after prostate EBRT.[3,4]

Anorectal toxicity comprise different symptoms like an increased frequency of defecation, mucus discharge, fecal incontinence and rectal blood loss.[5] This toxicity can have a considerable impact on quality of life (QoL)[6], more than sexual or genito-urinary symptoms.[7,8] Rectal blood loss has a reported prevalence of approximately 30%[9-12] and is one of the most common reasons for referral to a gastroenterologist after radiotherapy.[13,14]

The prevalence of these symptoms is related to the radiation dose received by the rectal and anal wall.[11,15-17] Reducing the spatial dose distribution on the rectal wall should therefore prevent blood loss. This can be achieved by using a daily inserted endorectal balloon (ERB).[18-20] Previously, we have shown that the use of an ERB reduces mucosal changes after prostate EBRT and reduces radiation toxicity.[5,10] However, both studies have a maximum follow-up of 2-3 years, while it is known that late radiation sequelae can appear after more than 2 years.[21] In this paper, we present long-term follow-up data of our prospective trial comparing mucosal damage in patients treated with and without ERB.

To our knowledge, this study is one of the first prospective studies examining rectal mucosal changes with a follow-up period of 5 years, but it is also the first study to compare these changes between irradiated patients with and without ERB.

Subjects and methods

Patients

All study patients were participants of a former study of our group.[10] Every participant of this prior study was asked to continue follow-up to a period of five years instead of the initial two years, implying two extra rectoscopies at 3 and 5 years after EBRT. After informed consent was given, all participants, who were willing to continue into this prolonged study and completed the follow-up of 5-years, were included. None of the participants had pre-existing anorectal complaints before the start of prostate irradiation as these were exclusion criteria of the initial study.[10]

Sixteen of the 32 included patients (50%) were irradiated with a daily inserted ERB. The other half was treated without an ERB (ERB-group and no-ERB-group, respectively). A

detailed description of preparation and treatment is given elsewhere.[10] In short, every patient was randomly assigned to one of the two treatment groups over a 12-month period during the year 2002.[10] All patients received neo-adjuvant hormonal therapy for 6 months prior to irradiation. Four gold markers for radiotherapy positioning verification and correction were inserted under ultrasound guidance. A planning CT-scan was obtained at 3-mm slice thickness. In the ERB-group, the planning CT was performed with an inserted ERB. This ERB had a length of 90-mm, a diameter of 45-mm and was inflated with 80 cc of air. Rectum delineation was performed by previously described methods.[22,23] In all patients, the clinical target volume was defined as the prostate plus seminal vesicles, and expanded with a 9-mm 3D margin to the planning target volume. A beam's-eye-view based 3D-conformal treatment plan was designed, with individual shielding of normal tissues and full tissue heterogeneity correction. With an orthogonal, equally weighted 18-MV photon 4-field isocentric technique, a dose of 67.5 Gy was delivered in daily fractions of 2.25 Gy (4 fractions a week for 7.5 weeks).

In the ERB-group, an ERB was inserted daily and inflated with air prior to every treatment fraction by the attending radiation oncologist.

Patient reported outcome measure

Anal and rectal complaints were scored by using the standardized morbidity scales of the Radiation Therapy Oncology Group and the Fox Chase Modified Late Effects Normal Tissue Task Force.[24] Complaints were scored during every visit at the outpatient clinic, the first 2 years after EBRT every 3 months, afterwards once every 6 months.

Endoscopy and Vienna Rectoscopy Score

Patients received a rectoscopy 3 months, 6 months, 1 year, 2 years, 3 years and 5 years after completion of prostate radiotherapy. This study will focus mainly on the results of 1- to 5-year evaluation. The endoscopies were performed by 9 well-trained and experienced endoscopists. A sodium-phosphate enema of 133 mL was given 20 minutes before the start of the endoscopy. The Vienna Rectoscopy Score (VRS) was used as mucosal mapping and scoring system, as first described by Wachter et al.[25] The VRS divides the inner Rwall mucosa into 4 distance levels in caudo-cranial direction, as measured from the anus (0-4 cm, 4-8 cm, 8-12 cm, and 12-16 cm). Every level was subdivided in 4 mucosal areas (anterior wall, left-lateral wall, posterior wall and right-lateral wall), creating a total of 16 mucosal regions of interest (ROI) per patient to examine. All mucosal ROIs were individually scored on 5 pronounced endoscopic items; the presence and grading of telangiectasia (grade 0-3), congested mucosa (grade 0-3), ulceration (grade 0-4), stricture (grade 0-4) and necrosis (grade 0-1).[25]

Grading for telangiectasia per mucosal area was as follows: grade 0 is no telangiectasias (T0), grade 1 is a single telangiectasia (T1), grade 2 is multiple non-confluent tel-

angiectasias (T2), and grade 3 is multiple confluent telangiectasias (T3).[10,25] Low-grade telangiectasia was defined as the presence of T1. High-grade telangiectasia was defined as the presence of T2 or T3, which is predictive for rectal blood loss.[25,26]

The endoscopists were blinded for the use of ERB or not. The grading scores were noted on a scoring list and transferred to the department of radiation oncology for further analyses. The endoscopists had no information about previous grading data of the patient they were examining.

Rectal wall dose surface maps and equivalent uniform dose

Spatial dose distribution over the inner Rwall was visualized by creating Rwall dose-surface maps, generated from the definitive treatment plans. Rwall dose-surface maps were divided into 16 areas corresponding to the VRS-areas. As described previously[10] the generalized equivalent uniform dose (EUD) was computed to correlate endoscopic findings to the radiation dose of the same mucosal ROI. The generalized EUD represents the uniform dose leading to the same probability of injury as the corresponding inhomogeneous dose distribution of each mucosal area. According to Wu et al the tissue-specific parameter describing the dose-volume effect (a) was set to 6.0.[10,27] More detailed descriptions on construction of the Rwall dose-surface maps have been previously presented.[10]

Statistical analysis

The rectal dose and toxicity data were analysed within a Matlab environment to assess whether there was any association between the two. The analysis was performed by constructing a 2D histogram of the data, with dose and toxicity as the histogram axes. The dose was quantised into bins of 5 Gy width, while the toxicity data did not require binning since it was already quantised into 5 levels (0, 1, 2, 3, or 4). In forming the 2D histogram, only the effect of dose on toxicity was under analysis. That is, the analysis did not attempt to test for any correlations between the location of the dose to the rectum and toxicity, or between dose and the time from irradiation to the occurrence of toxicity.

Differences in VRS outcomes between the ERB and no-ERB group were analysed by using the Chi-square test.

Results

The dataset comprised two groups of each 16 patients, with a mean age of 71 years in the ERB group and 72 years in the no-ERB group prior to prostate EBRT. In total, 79 and 81 endoscopies were performed in the ERB-group and no-ERB group, translating into a compliance of 82% and 84%, respectively. Regarding the performed endoscopies ≥1 year after EBRT, compliance was even higher (92% and 94% respectively). The ERB group missed 5 endoscopies ≥1 year after EBRT: 2 men missed their endoscopy one year

post-EBRT, one patient missed endoscopy 2 years post-EBRT and 2 patients missed their rectoscopy three years after treatment. For the no-ERB group numbers at one, two and three years after EBRT were respectively 1, 1 and 2 rectoscopies. Al patients finished their endoscopy 5 years after EBRT. For each endoscopy, the toxicity was assessed in 16 ROIs, yielding a total of 1264 and 1296 ROIs for analysis in the two groups.

Patient reported outcome

Five years after prostate EBRT, 5 patients in the no-ERB group (31%) experienced rectal blood loss, compared to only one patient (6%) in the ERB group. At two years, these numbers were 33% and 13%, respectively.[10] Furthermore, in the no-ERB group 10 patients had grade 1 rectal complaints (urgency, frequency or slight rectal discharge) and 2 patients experienced grade 2 rectal complaints (frequency requiring medication). In the ERB group, 2 patients experienced grade 1 complaints and one patient scored grade 2 rectal complaints (leakage requiring bondages).

Dose-surface parameters

Rwall dose-surface maps were calculated for each individual patient, mean dose-volume histograms for the ERB and no-ERB group are shown in **Figure 1a** and **1b**. These figures show the ability of an ERB to push the posterior and lateral parts of the Rwall away from the prostate, resulting in a lower dose for these parts. Furthermore there appears to be a small offset in the caudal-cranial direction between the two groups. In the ERB group the high-dose regions shifts a bit towards the cranial direction, compared to the no-ERB group.

Figure 1a *Mean dose surface map for the no-ERB group.*

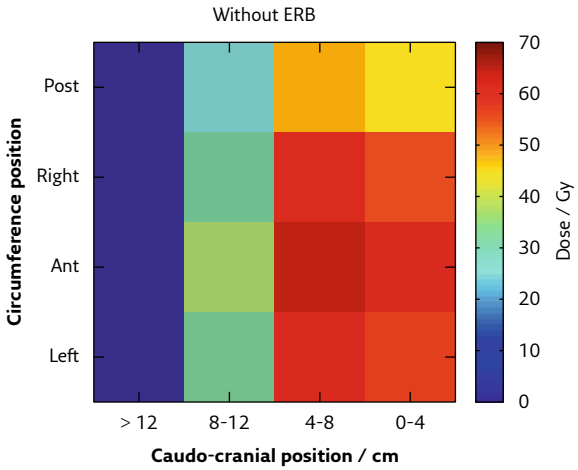
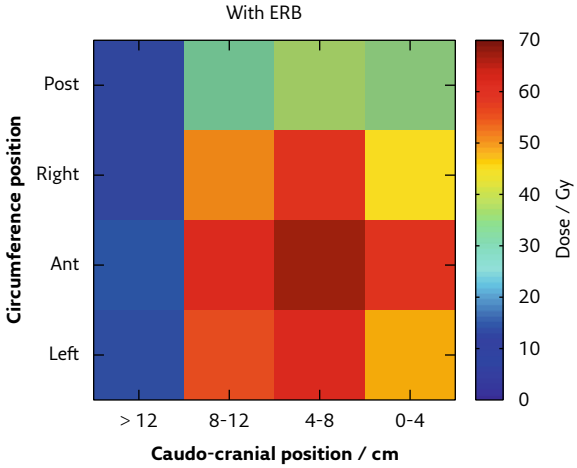


Figure 1b *Mean dose surface map for the ERB group.*



Dose surface maps for the no-ERB group (**figure 1a**) and the ERB-group (**figure 1b**).

The volume of the anorectal complex inside the irradiated volume and the radiation dose in this area are directly correlated to LAT. In both groups, the EUD did not exceed 68 Gy. Percentages of ROIs receiving 40-60 and 60-68 Gy were significantly lower in the ERB group ($p < 0.05$ for both dose ranges).[10] Consequently, significantly more rectal ROIs were exposed to lower doses, ranging from 0-20 Gy and 20-40 Gy ($p < 0.05$ and $p < 0.02$ respectively).[10] The ERB mainly reduced the dose to the posterior and lateral ROIs. The mean dose on the anterior Rwall from 0-8 cm did not differ significantly between the two groups.[10]

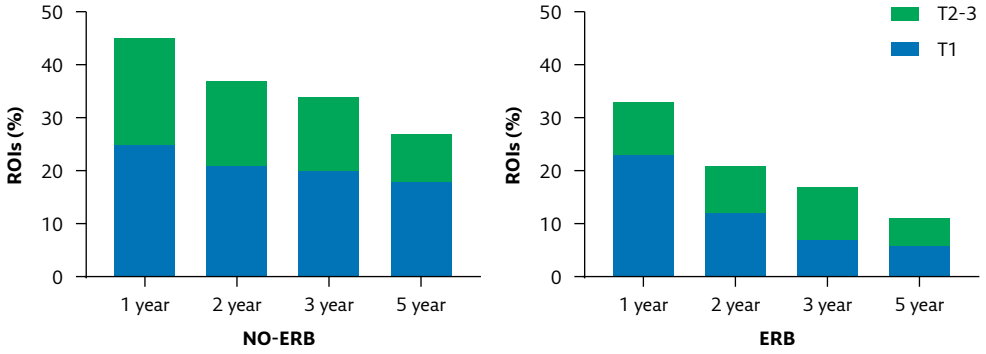
Endoscopic findings

Of all items scored with the VRS, telangiectasias were most frequently seen. Strictures and necrosis were not seen in both groups. In one ROI (one patient in the ERB group) a micro-ulceration was detected, which resolved spontaneously within one year.

Congestion was seen in 84 ROIs in the no-ERB group and in 75 ROIs in the ERB group (6% of ROIs in both groups). In the no-ERB group there were 40 ROIs (3%) with grade 2 or 3 toxicity, compared to 8 ROIs (1%) in the ERB group ($p < .001$). After 5 years, there were only 12 ROIs in 2 patients from the ERB group with grade 1 congestion left.

Over the years the absolute number of ROIs showing grade 1 or more telangiectasias decreased in both groups. In the no-ERB group the number of affected ROIs decreased from 108 at one year (45%) to 54 (27%) at 5 years after radiotherapy, and in the ERB group from 75 (33%) to 29 (11%) (**Figure 2**).

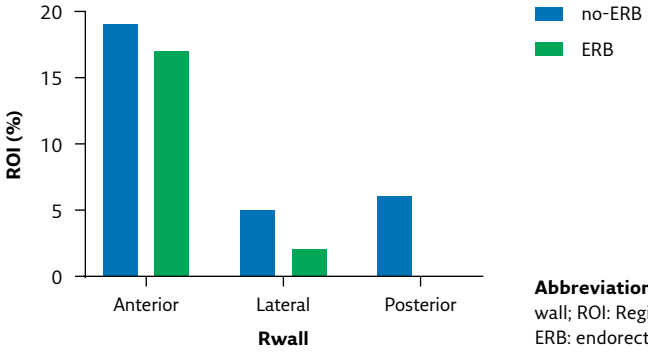
Figure 2 *Telangiectasias one to five years after EBRT. The difference between the no-ERB group and ERB group are visualised.*



Abbreviations: EBRT: External beam radiotherapy; ERB: endorectal balloon; ROI: Region of interest.

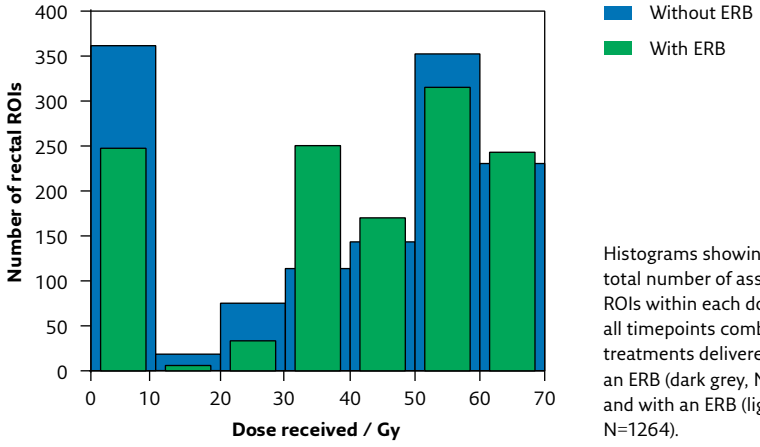
The percentages of posterior Rwall high-grade telangiectasias in the no-ERB group remained stable during follow-up, with an observed percentage of 6% after 5 years. The ERB-group showed a decrease from 3.6% to 0% 5 years after therapy. The lateral Rwall ROIs showed 5% of high-grade telangiectasias in the no-ERB group, compared to 2% in the ERB Group (p=0.08), **Figure 3**.

Figure 3 *High-grade telangiectasias 5 years post radiotherapy. Illustrating the distribution of telangiectasias over the Rwall.*



Abbreviations: Rwall: rectal wall; ROI: Region of interest; ERB: endorectal balloon.

Figure 4 *Number of ROIs in each dose bin*



Histograms showing the total number of assessed ROIs within each dose bin at all timepoints combined, for treatments delivered without an ERB (dark grey, N=1296) and with an ERB (light grey, N=1264).

Dose-toxicity relations

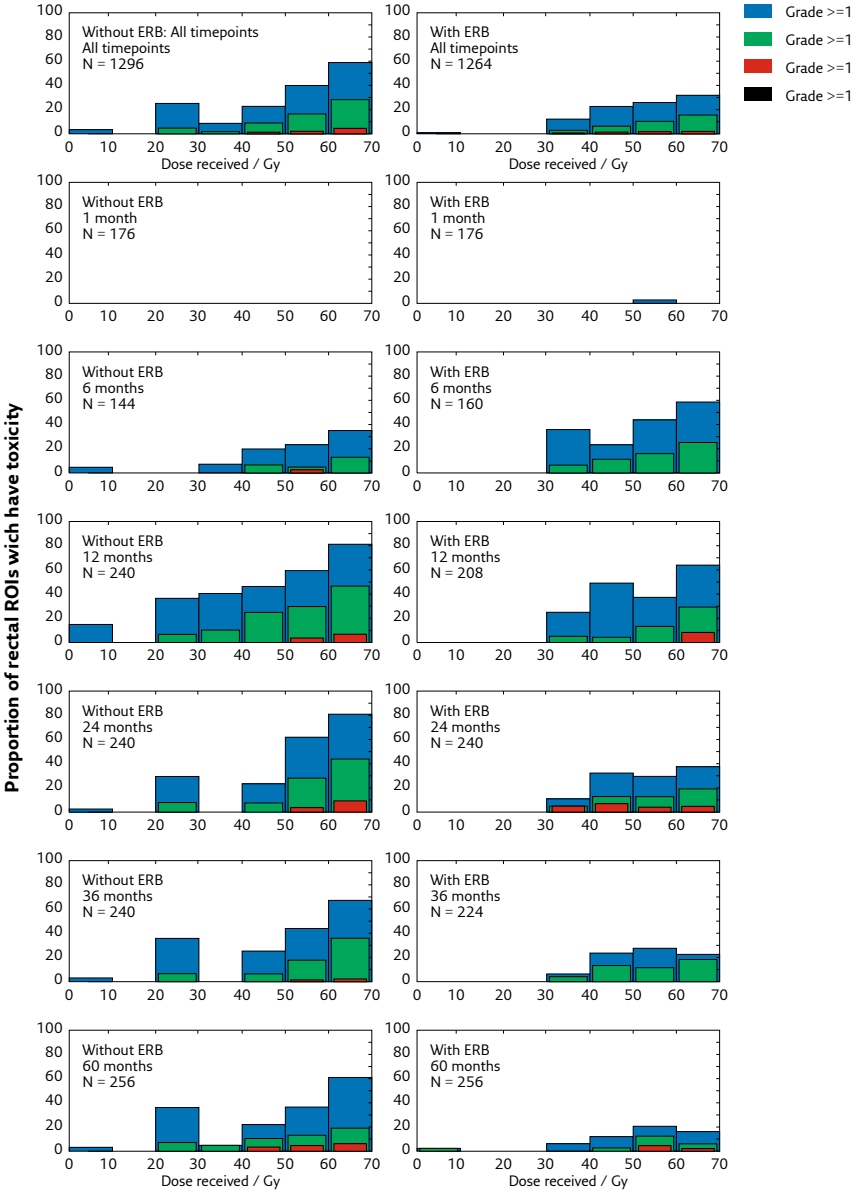
Figure 4 displays the total number of rectal ROIs per dose bins, up to the maximum of 70 Gy. The figure shows that patients in the ERB-group have less ROIs who received a high amount of radiation dose (≥50 Gy) compared to patients in the no-ERB group.

The number of mucosal changes/toxicity per dose-bin in each arm of the study and at each timepoint are showed in **Figure 5**. The histograms display that the use of an ERB reduces the number of altered ROIs. When an ERB is present during treatment, there exists a threshold dose below which almost no toxicity was observed, while increasing frequency and severity of rectal changes occurred above this threshold. This threshold occurs at approximately 30 Gy (**Figure 5**). When no ERB is present during treatment, it is difficult to identify a threshold dose for toxicity. This may be due to the relative instability of the rectum in the absence of an ERB, with inter- and intra-fraction motion of the rectum resulting in a poor correspondence between the planned and delivered rectal dose.

Discussion

In this study, the influence of a daily inserted ERB on rectal mucosa toxicity was examined for a follow-up period of 5 years after EBRT for prostate cancer. Telangiectasias were the most frequently seen rectal changes. The number of ROIs with telangiectasias and the grade of toxicity decreased during follow-up and there were less ROIs with telangiectasias during all time-points in the ERB group compared to the no-ERB group. Application of an

Figure 5 *Dose-effect plots for each individual timepoint for the no-ERB and ERB group.*



Histograms showing the proportion of rectal ROIs which showed toxicity, as a function of dose. The left column shows data for treatments delivered without an ERB and the right column with an ERB. The top row shows data for all timepoints combined, and the subsequent rows show data for each individual timepoint (1, 6, 12, 24, 36 and 60 months). For each plot, the total number N of rectal ROIs assessed is noted. (Note that there are 16 ROIs per patient, and therefore the number of patients = N/16.)

ERB not only reduced the rectal wall dose, but also objectively reduced rectal wall damage. Furthermore, this study provides evidence that ROIs in the same dose bins in the ERB group express less toxicity compared to patients irradiated without a rectal balloon.

Endoscopic findings

Results of present study, especially the decrease in telangiectasias over time, are in line with other prospective studies.[10,26,28] The current study shows that mucosal healing continues for a follow-up of 5 years.Only one other study measured endoscopic outcome with a follow-up of 5 years, Goldner et al showed a significant mucosal improvement in 66% of patients 5 years after EBRT compared to 1 or 2 years (25).[28] These two studies support the notion that rectal mucosal toxicity after EBRT is a dynamic process, with repair, not only in the acute phase but also over extended time.

The sparing effect of the ERB on posterior and lateral Rwall can be explained by the mechanism of the ERB, which is developed to push the posterior and lateral Rwall away from the high dose regions, thereby leading to a reduced dose on the posterior and lateral Rwall.[10,18-20]

In the ERB group a cut-off dose of 30 Gy was found for observable mucosal changes. There were a total of 286 rectal ROIs in the six dose bins below 30 Gy only one of which had a toxicity grade > 0, albeit the number of ROI in the dose bins between 5 Gy and 30 Gy was small (44 ROIs). Nevertheless, the results strongly suggest that there exists a cut-off dose for observable rectal toxicity at approximately 30 Gy. This is in agreement with the known relation between dose and toxicity, which is analysed in related articles.[11,15,17,29] Vargas et al showed that an increasing Rwall volume receiving ≥70Gy is associated with increasing percentages of Grade ≥2 toxicity (9%, 18%, and 25% for the Rwall relative V70 <15%, 25%-40%, and >40% respectively). Rwall volumes irradiated to ≤40 Gy are non-predictive for the development of chronic anorectal toxicity.[17,29]

This cut-off value was not found in the no-ERB group. The increased level of noise in that data may be because an ERB is not present to stabilise the rectum, with the consequence that inter- and intra-fraction motion of the rectum is greater, leading to a poorer correspondence between the planned and delivered rectal dose.[30,31]

The present study not only shows evidence that the ERB group develops less long-term toxicity overall, but also that there is less toxicity observed in individual dose bins in the ERB group compared to the same dose bins in the no-ERB group. In other words, even if ROIs in the ERB group receive the same dose, there is still less risk for developing toxicity compared to the ROIs of the same dose in the no-ERB group. There are several potential explanations for this notable finding. The first explanation could be due to the inflation of the ERB that stretches out the Rwall, thereby leading to a higher degree of hypoxia in the rectal tissues, with consequent radioresistance and protection of these tissues. The

second explanation may be the insertion of an air cavity, creating a dose build-up effect and thereby reducing the dose at the Rwall surface.

This study is the first prospective study comparing objective outcome measures of patients treated with and without ERB for a period of 5 years after ERB. Therefore, the present study provides important information on the natural history of mucosal changes after EBRT and new information on long-term effects of the use of an ERB.

To reduce the risk of bias, all patients received the same treatment (6 months of neoadjuvant hormonal therapy, gold-markers for positioning verification and a dose of 67.5 Gy in daily fractions of 2.25 Gy. The only difference was the use of an ERB in half of the patients determined by randomization. Furthermore, the endoscopists were blinded for the treatment a patient had received, prior VRS scores, and the time after radiotherapy.

A limitation of the present study are the patients who did not want to extend the follow-up from 2 to 5 years after EBRT. The load of 2 supplementary endoscopies could be the reason for this and could potentially lead to selection bias of the study population. Patients with more health related problems and in less good general condition, whether or not related to their treatment, may be more likely to stop follow-up. Another potential reason can be travel distance, which, however, is unlikely to create bias in outcome measures. A second limitation is the fact that due to the long-term follow-up, results from the present study were obtained from 3D-CRT, while the current state-of-art technique for prostate irradiation is IMRT or VMAT. Future studies on the effect of an ERB in contemporary RT techniques may be needed to confirm the beneficial effect of an ERB in these techniques.

A second technique is investigated to reduce LAT. Hereby, collagen is injected between the prostate and rectum to form a "spacer" to increase the distance between the two organs.[32] A long term follow-up study comparing mucosal changes after EBRT in patients treated with ERB versus a spacer would be interesting, as both methods are used to reduce gastrointestinal toxicity.

In conclusion, this study shows evidence that rectal toxicity, as observed by repeated rectoscopy, spontaneously improves up to 5 years after EBRT in most of the irradiated patients. There were less ROIs with low grade and high-grade toxicity in the group irradiated with a daily inserted ERB compared to the no-ERB group. As a consequence, patients in the ERB group experienced less toxicity compared to patients in the no-ERB group.

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CHAPTER 7

Anal and rectal function after intensity-modulated prostate radiotherapy with endorectal balloon

SUBMITTED

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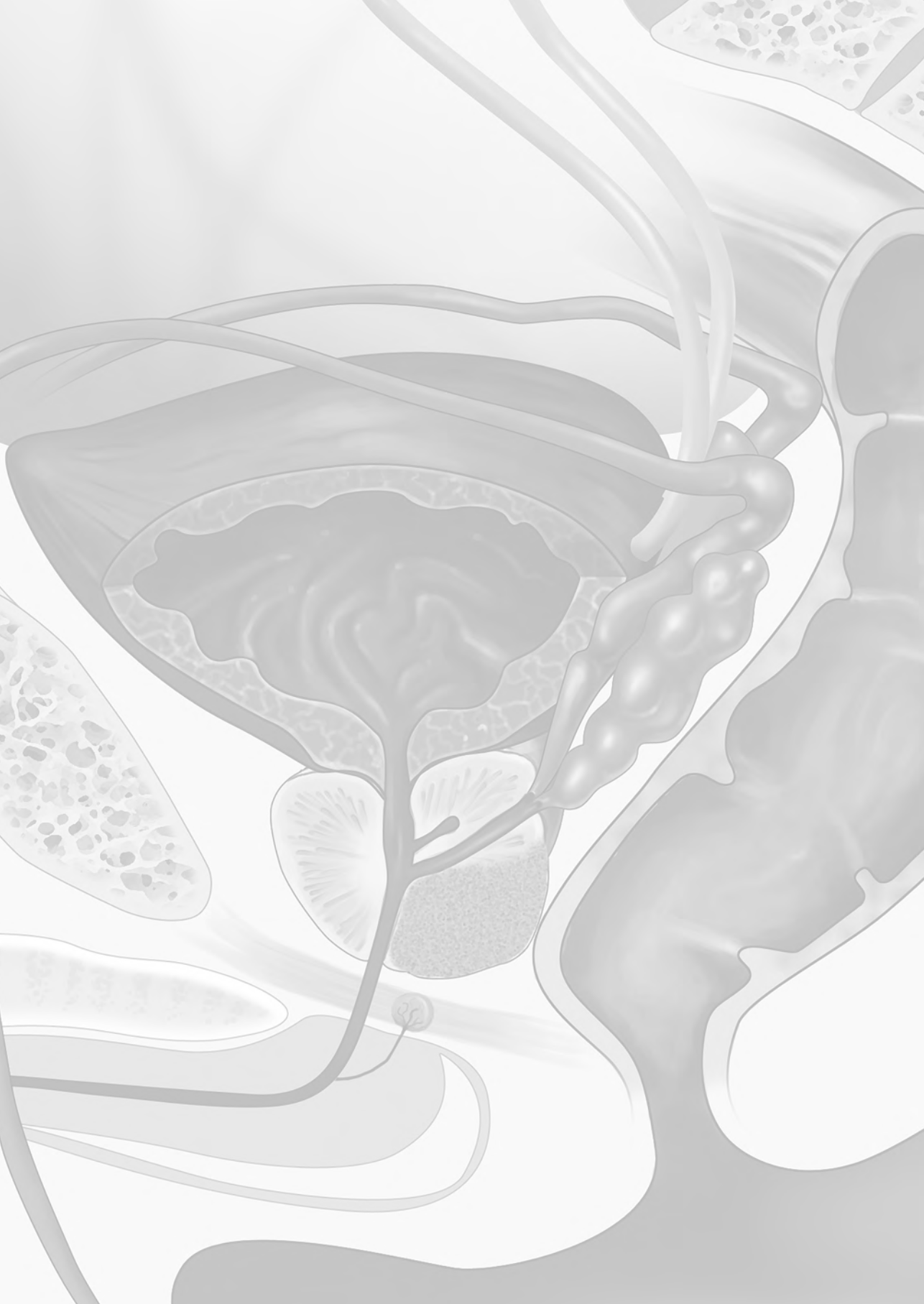


Abstract

BACKGROUND Late anorectal toxicity has a negative impact on quality of life after external beam radiotherapy (EBRT) for prostate cancer. Modern EBRT techniques, such as the use of intensity modulated radiotherapy (IMRT) and the application of a daily inserted endorectal balloon (ERB) aim to reduce anorectal toxicity. Our goal is to describe the changes of anorectal function over time in men irradiated with IMRT and ERB.

METHODS Sixty men, irradiated with IMRT and a daily inserted ERB for localized prostate carcinoma, underwent barostat measurements and anorectal manometry prior to EBRT and 6 months, one year and 2 years after radiotherapy. The primary outcome measure was rectal distensibility in response to stepwise isobaric distensions. In addition, we assessed sensory thresholds, anal pressures and anorectal complaints.

RESULTS EBRT reduced maximal rectal capacity 2 years after EBRT (250±10 mL vs. 211±10 mL; p <0.001), area under the pressure-volume curve (2878±270 mL·mm Hg vs. 2521±305 mL·mm Hg; p=0.043) and rectal compliance (24.6±1.3 mL·mm Hg^{-1} vs. 21.7±1.1 mL·mm Hg^{-1}; p=0.11). Sensory pressure thresholds for first sense (12±0.6 mm Hg vs. 14±0.8 mm Hg; p=0.002) and first urge (19±0.8 mm Hg vs. 23±1.1 mm Hg; p <0.001) increased. Anal maximum pressure diminished after IMRT (192±8 mm Hg vs. 176±9 mm Hg; p=0.006).

CONCLUSIONS With use of IMRT and ERB, rectal capacity and sensory function are increasingly affected over time after radiotherapy. However, there is an indication that these reductions are less with IMRT compared to conventional radiation techniques. The use of a daily inserted ERB seems an efficient aid to spare anal and rectal function.

KEYWORDS rectal distension, external beam radiotherapy, intensity modulated radiotherapy, electronic barostat, localized prostate cancer, manometry.

Introduction

Late gastrointestinal side effects have an important impact on quality of life after external beam radiotherapy (EBRT) for localized prostate cancer.[1] Up to 50% of patients after EBRT report late gastrointestinal symptoms and some studies report that in 90% of patients changes in their bowel habits are reported.[2] Most often these symptoms are mild and, fortunately, more severe symptoms, interfering with quality of life (QoL), are less frequently seen. Symptoms of late gastrointestinal toxicity comprise rectal blood loss, increased stool frequency, loose stools, fecal urgency and fecal incontinence.[3,4] Reduction of these side effects will help to improve QoL after treatment.[5,6] Especially complaints like fecal incontinence and fecal urgency have a large influence on QoL.[7]

At this moment, the underlying pathophysiology of late anorectal toxicity is poorly understood. Prior studies showed that there is a relation between radiation dose to the anal wall and rectal wall on the one hand, and the frequency and severity of late toxicity on the other.[8-10] Associations between anorectal dose and anal and rectal functions, especially rectal capacity, rectal sensibility and anal pressures have recently been found.[11-13]

Improvements in radiation techniques, such as intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) and image-guided EBRT, made it possible to better avoid healthy structures and tissues.[14,15] Unfortunately, due to the close anatomic relation between the rectum, anal canal and the prostate, it is still inevitable to completely spare the rectum and anal canal. A daily inserted endorectal balloon (ERB) during EBRT pushes the lateral and posterior rectal walls out of the high dose radiation volume, with the aim to reduce anorectal toxicity.[16,17] Prospectively collected data on anorectal function after EBRT with state-of-the-art radiation techniques and a daily inserted ERB are scarce.

Currently available publications on late anorectal function after prostate radiotherapy report on relatively small patient cohorts of around 30 patients.[11,18,19] A few studies included significantly more patients, but these 1) were of retrospective or cross-sectional design, or 2) included more heterogeneous patient cohorts including prostate, cervical and rectal cancer, or 3) used outdated radiation techniques.[15,20,21]

So far, only one study used electronic barostat measurements to assess rectal capacity and compliance11, while barostat is currently seen as the most reliable test to explore rectal pressure-volume relations.[22,23]

Therefore, the primary aim of this study is to describe changes over time in anorectal function up to two years after EBRT using objective function tests, in a large group of men irradiated with image-guided intensity modulated radiotherapy and a daily inserted ERB for localized prostate carcinoma.

Materials and Methods

Study design

This study is a prospective and longitudinal cohort study with a pretest-posttest design. All patients underwent anorectal function testing prior to EBRT (baseline), 6 months, 1 year and 2 years after EBRT.

Primary outcome measures consist of rectal distensibility (rectal capacity, rectal compliance and area under the pressure-volume curve), rectal sensibility and anal pressures.

The local ethics committee approved the study protocol and all patients had to give informed consent before start of the study.

Patients and treatment

All patients who were to receive EBRT in the Radboud University Medical Center for localized prostate cancer (T1c-3bN0-1M0) between November 2009 and May 2012 were invited. A total of 60 men were included.

Patients who had prior radiotherapy, major abdominal surgery or inflammatory bowel disease in their medical history were excluded.

All patients received IMRT with a cumulative radiation dose of 64.6–78 Gy in 2.0-3.4 Gy fractions and a daily inserted ERB. A more detailed overview of patient-, tumor- and treatment characteristics is given in **table 1**.

Anal and rectal function tests

To measure rectal distensibility and sensibility an electronic barostat (Distender II, G&J Electronics Inc., ON, Canada) was used. Anal pressures were measured by manometry with a Solar GI system (MMS, Enschede, The Netherlands). A detailed description of techniques can be found elsewhere.[11,24,25]

In short, a single-use infinitely compliant barostat catheter is used. A rectal staircase distension is performed starting at an intrabag pressure of 0 mmHg. At one-minute intervals the intrabag pressure is increased by 2 mm Hg and kept constant. Intrabag volumes are averaged beginning 25 s at each distension step. Both the pressures and volumes at each distension step were recorded. Maximum distension was noted for the moment a patients encounters a strong feeling of discomfort or an uncontrollable urge to defecate. For safety, the maximum distension step was limited at 48 mm Hg.

Three different parameters were used to reflect rectal distensibility: 1. rectal capacity, 2. rectal compliance and 3. the area under the pressure-volume curve (AUC). Rectal capacity is the volume, measured at the maximum tolerated distension (or 48 mm Hg). Rectal compliance is the maximum slope (ΔVolume/ΔPressure) of the pressure-volume curve. The AUC is the area under the pressure volume curve. This curve is divided in

Table 1 *Characteristics of patients and tumor characteristics prior to radiotherapy (n = 60).*

Characteristics	Mean	SD	n	(%)
Patient characteristics				
Age (years)	69	5.8		
Length (cm)	176	6.0		
Weight (kg)	84	11.4		
BMI (kg m-2)	27.0	3.2		
Tumor characteristics				
PSA (range)	15.8	(2.1 – 93)		
Gleason (median; range)	7	(6 – 9)		
T-stadium				
T1			4	(7)
T2			18	(30)
T3			38	(63)
Treatment characteristics				
Adjuvant hormonal therapy			31	(52)
Radiation dose (cumulative dose/ fraction dose)				
64.6/ 3.4 Gy			21	(35)
70/ 2.5 Gy			27	(45)
78/ 2.0 Gy			12	(20)

Abbreviations: BMI, Body Mass Index; PSA, prostate specific antigen; T-stadium, tumor stadium; Gy, Gray.

separate distension steps. The AUC represents the sum of all individual distension steps. The area of each distension step was calculated by the formula:

Area distension step = $Vdistension_{(i)}$· 2 mm Hg + 0.5· 2 mm Hg·($Vdistension_{(i+1)}$ – $Vdistension_{(i)}$), where i is distension step number and V is volume at i-th distension step.

If maximum distension steps at the different time points were different for one patient, the AUC was calculated up to the lowest maximum distension step for this patient.[11]

Rectal sensibility was measured by use of 3 sensory thresholds: 1. First sense (the first moment a patient became aware of any sensation in the rectum), 2. First urge (the first moment a patient experienced urge) and 3. Maximum tolerated distension (the moment a patients encounters a strong feeling of discomfort or an uncontrollable urge to defecate). During barostat measurements distension steps corresponding to the sensory thresholds were noted.

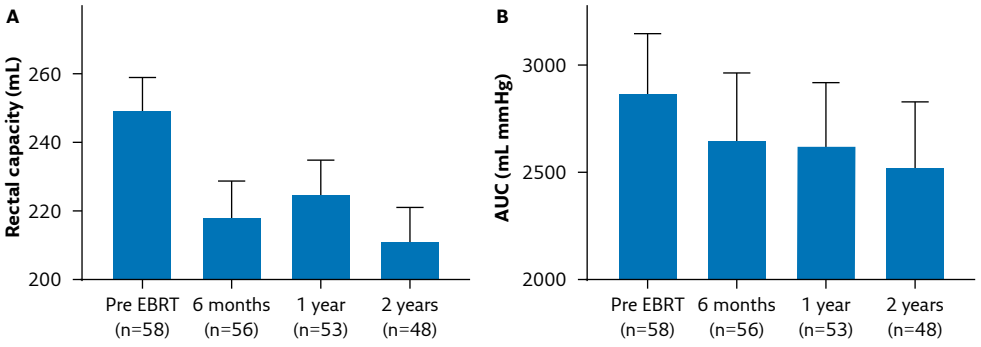
Anal pressures were measured by anal manometry. A standard station pull-trough technique with a water perfused 4-channel 14 french single use catheter was used to determine anal resting pressures, anal squeeze pressure and maximum anal pressure (respectively P-resting, P-squeeze and P-max).

Statistics

Patient characteristics and data are presented as mean ± 1 SEM, unless stated otherwise. The paired t-test was used to compare functional parameters prior to and after EBRT. Functional parameters were assumed to have a normal distribution, based on prior results. A *P* value of <0.05 was considered to indicate statistical significance. If appropriate, the Bonferroni correction for multiple testing was used.

The repeated-measures ANOVA was used to determine whether there was a significant change over time per outcome measure. The Greenhouse-Geisser correction was used to correct for possible violated sphericity.

Figure 1 *Reduction in rectal distension after EBRT for prostate cancer.*



A) Rectal capacity after EBRT for prostate carcinoma, b) AUC after EBRT. The error-bars represent the s.e.m.
Abbreviations: EBRT: External beam radiotherapy; AUC: Area under the pressure-volume curve.

Results

Patients

Sixty patients were included, with a mean age of 69 years (range 54-78 years). Forty-eight men completed all examinations. One patient stopped participation due to painful bone metastases. Two patients received systematic therapy for metastatic disease other than prostate carcinoma and discontinued participation (metastatic melanoma and stage IV lung cancer). Nine patients withdrew because of other or unknown reasons.

Rectal distensibility

Rectal capacity decreased after EBRT. Prior to EBRT the average rectal capacity was 250 ± 10 mL, compared to 211 ± 10 mL after treatment ($P < 0.001$). This reduction in capac-

Table 2 *Results of barostat measurements and anorectal manometry in patients prior to and 6 months, one year and two years after prostate EBRT for localized prostate cancer. Paired T-test comparing Pre RT results with Post RT.*

	Pre RT		6 months Post RT (n =56)		
Functional assessment	**Mean**	**(±SEM)**	**Mean**	**(±SEM)**	**P**
Rectal distensibility					
Rectal capacity (mL)	250	(±10)	219	(±11)	**0.001**
AUC (mL mmHg)	2878	(±270)	2648	(±279)	0.12
Compliance (mL $mmHg^{-1}$)	24.6	(±1.3)	21.3	(±1.3)	**0.017**
Sensory treshold					
P first sense (mmHg)	12	(±0.6)	13	(±0.6)	0.16
P first urge (mmHg)	19	(±0.8)	20	(±0.8)	0.16
P MTD (mmHg)	32	(±1.4)	32	(±1.4)	0.81
V first sense (mL)	82	(±8.0)	91	(±8.1)	0.29
V first urge (mL)	167	(±9.1)	153	(±9.1)	0.15
V MTD (mL)	250	(±9.6)	219	(±10.7)	**0.001**
Anal pressure					
Anal P-resting (mmHg)	55.2	(±2.2)	52.6	(±2.3)	0.92
Anal P-maximum (mmHg)	191.8	(±8.4)	186.6	(±8.7)	0.31
Anal P-squeeze (mmHg)	146.6	(±7.5)	144.4	(±7.6)	0.59

Abbreviations: RT, External beam radiotherapy; SEM, standard error of mean; AUC, area under the curve; P, pressure; MTD, maximum tolerated distention; V, volume.

ity was observed 6 months after EBRT and remained stable up to two years after EBRT (**Table 2**). Mean reductions in rectal capacity were respectively 29.6 ± 8.6 mL, 27.7 ± 7.7 mL and 40.0 ± 9.9 mL for 6 months, 1 year and 2 years after EBRT (**Figure 1**).

Also, rectal compliance was significantly lowered 6 months after EBRT compared to the baseline measurement (24.6 ± 1.3 mL $mmHg^{-1}$ prior to EBRT vs. 21.3 ± 1.3 mL $mmHg^{-1}$ at 6 months, *P*=0.017). One and 2 years after irradiation the compliance was still lower, but the difference with baseline was not statistically significant anymore.

After one year, the AUC was decreased compared to the pre-EBRT AUC (2878 ± 270 mL mmHg prior to EBRT vs. 2623 ± 293 mL mmHg one year after EBRT, *P*=0.014). The AUC 2 years after EBRT was even slightly lower, 2521 ± 305 mL mmHg (*P*=0.043), but this was not significant after Bonferroni correction.

	1 year Post RT (n =53)			**2 years Post RT (n =48)**	
Mean	**(±SEM)**	**P**	**Mean**	**(±SEM)**	**P**
225	(±10)	**0.001**	211	(±10)	**0.000**
2623	(±293)	**0.014**	2521	(±305)	0.043
22.8	(±1.3)	0.21	21.7	(±1.1)	0.11
14	(±0.7)	0.15	14	(±0.8)	**0.002**
22	(±1.0)	**0.002**	23	(±1.1)	**0.000**
32	(±1.1)	0.89	32	(±1.1)	0.84
93	(±8.8)	0.44	91	(±10.2)	0.34
168	(±9.8)	0.99	164	(±10.4)	0.93
225	(±9.7)	**0.001**	221	(±10.1)	**0.000**
51.9	(±2.1)	0.16	50.5	(±2.0)	0.68
180.2	(±8.5)	0.086	176.4	(±9.3)	**0.006**
144.3	(±7.5)	0.77	143.7	(±8.0)	0.52

Table 3 *Repeated-measures ANOVA with use of the Greenhouse-Geisser correction (n=48).*

Functional assessment	df	F	P
Rectal distensibility			
Rectal capacity (mL)	2.6	7.0	**0.000**
AUC (mL mmHg)	2.6	1.7	0.17
Compliance (mL $mmHg^{-1}$)	2.6	1.4	0.26
Sensory Treshold			
P first sense (mmHg)	2.7	2.9	**0.044**
P first urge (mmHg)	2.9	5.8	**0.001**
P MTD (mmHg)	2.1	0.1	0.89
V first sense (mL)	2.9	0.9	0.42
V first urge (mL)	2.6	0.3	0.77
V MTD (mL)	2.6	7.0	**0.000**
Anal pressure			
Anal P-resting (mmHg)	2.7	1.1	0.34
Anal P-maximum (mmHg)	2.6	2.2	0.10
Anal P-squeeze (mmHg)	2.5	0.1	0.97

Abbreviations: df, degrees of freedom; F, F-ratio; AUC, area under the curve; P, pressure; MTD, maximum tolerated distention; V, volume.

The repeated-measures ANOVA were only significant for rectal capacity as shown in **Table 3**.

Rectal sensory thresholds

Pressures of sensory thresholds did not differ prior to EBRT and 6 months after EBRT. However, pressures thresholds significantly increased at two years after EBRT for first sense and at one and two years for first urge (**Table 2**). Repeated-measures ANOVA showed changes for pressures of first sense and first urge (P=0.044 and P<0.005, respectively).

Pressures of maximum tolerated distention did not change. Also, volumes of first sense and first urge did not differ after irradiation compared to baseline measurements (**Table 2** & **3**).

Volumes of maximum tolerated distension were significantly different at all time points after EBRT compared to the baseline measurements. Outcomes are equal to rectal capacity, as rectal capacity is defined as the volume at maximum distension.

Anal pressures

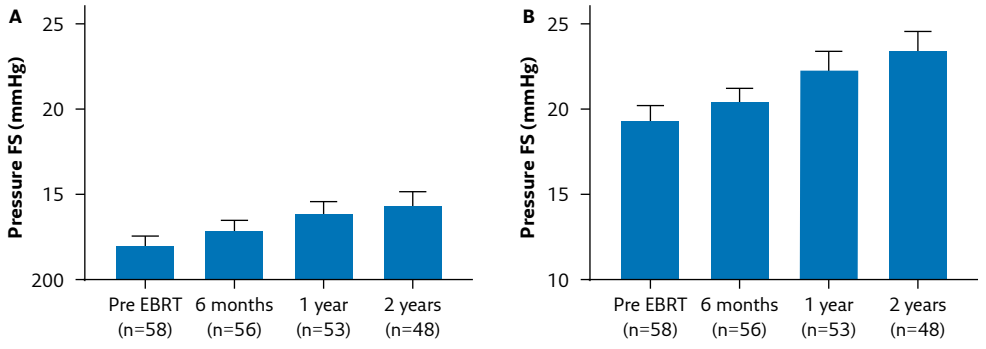
Overall, anal pressure parameters decreased with time after EBRT but this decrease was significant only for P-max at 2 years (**Table 2**, **Figure 2**).

Discussion

This study shows that prostate irradiation with current state-of the-art techniques leads to small but significant reductions of rectal capacity and anal maximum pressure and increase of first sense and first urge thresholds, suggesting that higher pressures are needed to trigger sensory nerve fibers.

The reduced rectal capacity, measured by barostat, is in line with prior studies of our group.[11,12] To our knowledge, our group is the only using electronic barostat for rectal capacity assessment. Mean difference in rectal capacity was 27.7 ± 7.7 mL one year after EBRT in the current study, compared to a mean reduction of 50mL in our prior study. The smaller reduction in rectal capacity could be explained by the improved radiation techniques as our prior study used 3D-conformal EBRT and IMRT compared to only IMRT in present study.[11] Yeoh et al. show a decrease from 75 ± 7 mL at baseline to 43 ± 4 mL two years after EBRT.[2,15] A Swedish group compared capacity after EBRT with an age-matched control group and showed a significant lower capacity after radiotherapy (150 ± 19 mL vs. 253 ± 54 mL respectively).[26] Although these groups use different ways to assess rectal capacity, their results support our findings that capacity decreases after radiotherapy. Rectal capacity is related to the frequency of defecation and is important

Figure 2 *Rectal sensibility after EBRT for prostate cancer.*



A) Mean pressure of first sense after EBRT for prostate carcinoma, b) Mean pressure of first urge after EBRT. The error-bars represent the s.e.m. Abbreviations: EBRT: External beam radiotherapy; FS: first sense; FU: first urge.

to maintain fecal continence.[13,27] Therefore, the better preservation of rectal capacity after IMRT is promising for the prevention of LAT, especially incontinence related symptoms and increase of stool frequencies.

Other parameters reflecting rectal distensibility, respectively rectal compliance and AUC, also tended to diminish but did not reach statistical significance in this large cohort. This suggests a minor effect, but makes a large and clinically more relevant effect highly unlikely. In contrast to the current study, previous studies found a significant decrease in rectal compliance after EBRT compared to before treatment.[2,15,19,26] There are two plausible explanations for this discrepancy. The first one is a difference in measurement protocols. The present study uses an infinitely compliant plastic bag instead of a rubber balloon. A plastic bag is preferred over a rubber balloon because it has no intrinsic compliance.[23] Furthermore, *Yeoh et al*. manually inflated the rubber balloon and measured rectal compliance over a fixed volume interval. The second, and likely more important reason is the use of modern radiotherapy techniques in the present study, combined with the application of a daily inserted ERB during EBRT. This study and a previous study from our group are the only two studies that did not find significant differences in rectal compliance after EBRT. They are unique in that they are also the only two studies applying an ERB to diminish radiation toxicity. The inflated ERB pushes the lateral and posterior rectal wall away from the intermediate and high dose radiation areas, thereby reducing the radiation dose to the anal and rectal wall.[13,16,17]

Rectal wall sensory function diminishes over time and the differences in pressures for first sense and first urge increase with time following prostate EBRT. These findings are consistent with the results of other prospective studies.[2,15,28] Results were measured by use of an electronic barostat, which is a more reliable method than a compliant rubber balloon.[22] The elevated sensory threshold for first sense and first urge feed the notion that there is a deterioration of rectal neuron function after EBRT besides affected rectal muscle function.

Anal resting pressure was not significantly affected by EBRT, consistent with prior results of our group.[11,12] *Yeoh et al*. did show a significant deterioration of anal resting pressure after EBRT.[3,42,12,15,28] The use of the daily inserted ERB could be a plausible explanation for these discordant findings, as it is shown to decrease radiation dose to the anal wall as well.[16] Slightly different techniques in anal manometry could also be an explanation. The use of the standard pull-through methods for anal manometry provided trustworthy data on anal pressures[24,30], but this technique is not suitable for the measurement of anorectal inhibitory reflex, sensory-motor reflex or anorectal contractile reflex to provide additive information. The multiport technique with rubber balloon is more appropriate to measure anorectal reflexes.[31]

Two years after EBRT anal maximum pressure was lowered. The only other study that measured anal maximum pressure did not show a significant difference.11 The shorter follow-up of one year in this earlier study could be the reason for this discrepancy, as in the present study only after two years a significant difference was reached. This supports the notion that the pathophysiology of radiation damage of the anorectal complex is a dynamic process that continues for at least two years.[32-34]

Up to date, this study describes the largest cohort of patients irradiated for localized prostate cancer prospectively followed with multiple post-treatment rectal and anal function measurements. All patients received IMRT, which is the current state-of-the-art technique for prostate EBRT, and a daily inserted ERB. To our knowledge, this is also the first study to explore anal and rectal function after IMRT. All other studies used patient cohorts with older radiation techniques or describe cohorts of which only a part of men is irradiated with IMRT without subgroup analyses.[12]

Furthermore, the present study uses the electronic barostat, which is currently seen as the most reliable test to measure rectal pressure-volume relations.[22] Thus, this study presents long-term data on anal and rectal function after IMRT, assessed by currently considered best practice methods.

The pretest-posttest design helped to rule out inter-individual variance and divulged the intra-individual changes after EBRT with time. Furthermore, there were no changes in instrumentation, test conditions or measurement techniques made during the period of current study. This excludes bias due to changed test conditions.

The lack of a control group is one of the most important limitations of this study. A control group could enable objectifying and correcting for the effect of aging on anal and rectal function.[29]

A randomized controlled clinical trial can give more insight on the effect of a daily inserted ERB during EBRT. It will be the most reliable way to judge the effect of the ERB during prostate irradiation.

In summary, this study shows that, with the use of current state-of-the-art radiation techniques and function tests, rectal capacity and sensory function are increasingly affected over time after prostate radiotherapy. However, there is an indication that these effects are less with IMRT than with conventional radiation techniques. The use of a daily inserted ERB seems an efficient aid to spare anal and rectal function.

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CHAPTER 8

Anorectale klachten na prostaatbestraling (Chapter in Dutch)

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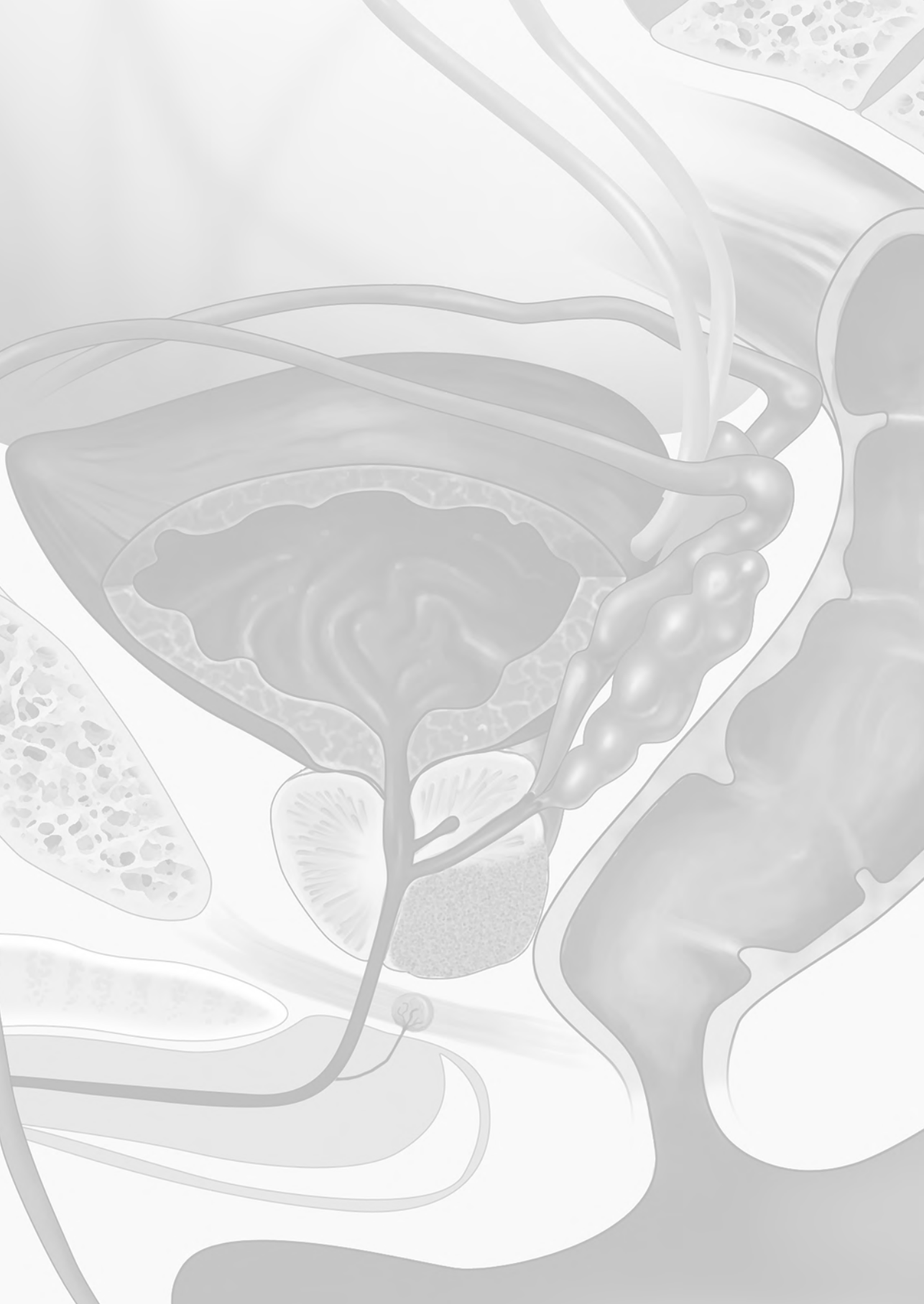


Casus

Een 69-jarige man komt ter controle op het spreekuur van de radiotherapeut. Twee jaar geleden heeft hij in opzet curatieve, hoog gedoseerde uitwendige bestraling gekregen in verband met een prostaatcarcinoom (T2aNoMo, Gleason score 3+4). Daarnaast is hij bekend met atriumfibrilleren waarvoor hij acenocoumarol gebruikt. Sinds 2-3 maanden is er sprake van helderrood rectaal bloedverlies, bij bijna iedere ontlasting. Daarnaast is de ontlasting dunner en is de ontlastingsfrequentie toegenomen. De radiotherapeut denkt aan radiatietoxiciteit van het rectum (RTOC/EORTC Late radiatie morbiditeitsscore graad 2).

Introductie

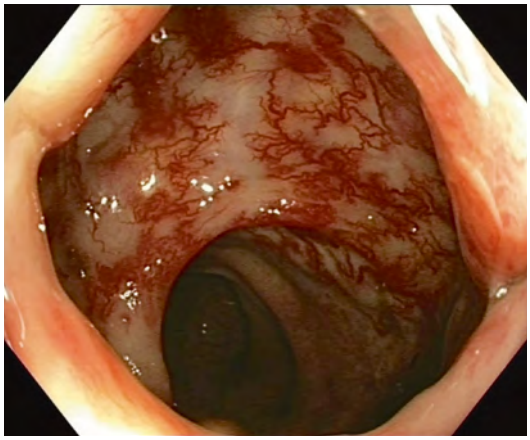
Met een incidentie van meer dan 10,000 nieuwe diagnosen in 2013 is prostaatkanker de meest voorkomende vorm van kanker bij de Nederlandse man (www.cijfersoverkanker.nl). De overleving van gelokaliseerde prostaatkanker is de laatste jaren sterk verbeterd en de 5-jaars overleving ligt al enige jaren boven de 95%. De opties voor de behandeling van gelokaliseerde prostaatkanker bestaan uit een actief volgen-beleid, radicale prostatectomie, inwendige of uitwendige radiotherapie. Met name radiotherapie kan aanleiding geven tot het ontstaan van gastro-intestinale klachten. Na uitwendige prostaatbestraling wordt bij 75% van de patiënten verandering van de ontlasting gezien. De klachten kunnen ontstaan tijdens of in aansluiting aan de behandeling maar ook maanden tot jaren na de bestraling.[1]

Veel voorkomende late klachten na prostaatbestraling (>3 maanden) zijn rectaal bloedverlies, een toegenomen ontlastingsfrequentie, urgentieklachten en incontinentie.[2,3] Veelal worden deze klachten geschaard onder de noemer 'radiatie proctitis'. Een betere term is anorectale toxiciteit, omdat ontstekingskenmerken meestal ontbreken. Anorectale toxiciteit ontstaat door beschadiging van gezond weefsel tijdens bestraling. De laatste jaren hebben nieuwere bestralingstechnieken zoals intensiteit gemoduleerde bestraling (IMRT) en beeldgestuurde bestraling (IGRT) ervoor gezorgd dat er doelgerichte sparing van omliggende organen mogelijk is en het bestralingsveld verkleind kan worden, waardoor de bestralingsdosis op gezonde weefsels lager is geworden. Hierdoor zijn de frequentie en ernst van anorectale toxiciteit na bestraling afgenomen.[4-6]

Desondanks is herkenning van late anorectale toxiciteit belangrijk. Het totaal aantal bestraalde patiënten neemt toe omdat de overleving na een behandeld gelokaliseerd prostaatcarcinoom is verbeterd. Bovendien kunnen anorectale klachten na prostaatradiotherapie de kwaliteit van leven negatief beïnvloeden.[7,8]

Dit artikel geeft een overzicht van late anorectale toxiciteit na prostaatbestraling. Het gaat in op pathofysiologie, klinisch beeld, diagnostiek, therapie en preventie. De

Figuur 1 *Beeld bij sigmoïdoscopie van een patiënt met multipele teleangiëctasieën, 2 jaar na uitwendige bestraling.*



literatuur bij dit artikel is gebaseerd op een recente systematic review over anorectale toxiciteit, aangevuld met enkele recente artikelen over behandelstrategieën en nieuwe bestralingstechnieken.[9]

Klinisch beeld en diagnostiek

Rectaal bloedverlies

Met een incidentie van 30-50% is rectaal bloedverlies een frequent gerapporteerd laat symptoom na bestraling. Bij 6% van de patiënten leidt rectaal bloedverlies zelfs tot een verminderde kwaliteit van leven.[10]

De oorzaak van het bloedverlies kan worden geobjectiveerd door endoscopisch onderzoek (figuur 1). Hierbij kan de Vienna Rectoscopy Score (VRS) worden toegepast. Dit is een scoringssysteem dat de rectumwand in 16 velden verdeelt, waarbij per veld de ernst van afwijkingen (teleangiëctasieën, congestieve mucosa, ulceratie, stricturen en necrose) gescoord wordt. Hierdoor zijn de afwijkingen in ernst en locatie systematisch vast te leggen en in de tijd te vervolgen.[11]

De meest voorkomende afwijking die bij endoscopie wordt vastgesteld zijn teleangiectasieën in de rectumwand. Op basis van de VRS wordt dit gescoord van graad 0 (geen teleangiëctasieën) tot graad 3 (multipele confluerende teleangiëctasieën). Graad 2 en 3 zijn geassocieerd met rectaal bloedverlies. Bovendien heeft 78% van de mannen met

een EORTC/RTOG toxiciteitsgraad (European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group) van ≥2 ook een VRS graad ≥2, hetgeen door radiotherapeuten een veel gebruikt scoringssysteem is.[11,12]

In de eerste 2 jaar na bestraling neemt het aantal en de grootte van de teleangiëctasieën toe om daarna weer af te nemen. Bij een deel van de patiënten verdwijnen deze zelfs volledig.[12,13] Bij beperkt rectaal bloedverlies als gevolg van deze teleangiëctasieën kan dus in de meeste gevallen een expectatief beleid worden gevoerd. Wanneer rectaal bloedverlies leidt tot symptomatische anemie of langdurig aanhoudt, kan het nodig zijn een coloscopie te verrichten om een alternatief bloedingsfocus te achterhalen. Bij 20-30% van de patiënten met rectaal bloedverlies na bestraling is er een alternatieve verklaring voor het bloedverlies zoals adenomen, hemorroïden en divertikelbloedingen.[14] Goede studies over de beste behandelstrategie bij deze patiëntengroep zijn er echter helaas niet.

Klachten die samenhangen met de ontlasting

Naast rectaal bloedverlies, kan prostaatbestraling ook leiden tot frequente ontlasting en fecale urgentie of incontinentie. Hier is in veel spreekkamers minder aandacht voor, terwijl dit vaak een grote impact op de patiënt heeft. Incontinentie-gerelateerde klachten gaan vaak samen met een verminderde functie van rectum of anus.[9] Barostatmetingen van het rectum en manometrie van het anale kanaal hebben bijgedragen aan het verkrijgen van inzicht in de mechanismen die hierbij een rol spelen.

De toename van de ontlastingsfrequentie gaat gepaard met een verminderde rectale capaciteit en compliantie, terwijl urgentie- en incontinentieklachten meer met de functie van het anale kanaal en de sensibiliteit van de rectumwand lijken samen te hangen.[9]

De compliantie en ook de capaciteit van het rectum neemt bij meer dan 80% van de patiënten af. Na bestraling van de prostaat voelen patiënten sneller aandrang, die ontstaat bij een lager volume in het rectum. Dit gaat gepaard met een toegenomen gevoeligheid van het rectum. Bovendien is de rustdruk in het anale kanaal verminderd evenals de anale knijpkracht.[9]

Therapeutische benadering

Rectaal bloedverlies

Wij hanteren het volgende beleid bij patiënten met rectaal bloedverlies na prostaatbestraling:

Indien er sprake is van sporadisch rectaal bloedverlies zonder vermindering van kwaliteit van leven kan er worden gekozen voor een expectatief beleid. Om de ernst van de klachten en de impact hiervan op de kwaliteit van leven te kunnen beoordelen wordt naast de anamnese ook de EPIC-26 vragenlijst gebruikt. Bloedverlies, leidend tot anemie waarvoor ijzersuppletie of bloedtransfusie nodig is, dient altijd verder in kaart te worden gebracht.

Als behandeling vereist is, kan er worden gestart met dagelijks sucralfaatklysma's van 2 gram, een- tot tweemaal daags. Sucralfaat hecht aan darmmucosa en stimuleert lokaal de prostaglandine productie, waarmee het een beschermend effect op de mucosa heeft. Hiermee wordt bij meer dan 70% van de patiënten een afname van klachten gezien en bij een derde van de patiënten verdwijnt het bloedverlies volledig.[15] De behandeling kan gestaakt worden zodra het bloedverlies is gestopt, of indien er na 8 weken geen verbetering is opgetreden.[16,17]

Wanneer met sucralfaat onvoldoende effect wordt bereikt, of wanneer het bloeden snel moet stoppen, is endoscopische behandeling een effectieve methode. Argon plasma coagulatie (APC) zorgt bij 80-90% van de patiënten voor een duidelijke afname van het bloedverlies en in 40-70% stopt het in zijn geheel. APC is direct effectief, maar bij uitgebreide teleangiëctasieën zijn er vaak meerdere sessies nodig om alle teleangiëctasieën te behandelen. Tot 2% van de patiënten ervaart na behandeling complicaties op de lange termijn zoals ulcera en pijnklachten.[16,18] Topicaal formaline heeft ongeveer vergelijkbare succespercentages als APC, maar vanwege vaker voorkomende en meer ernstige complicaties (met name chemische brandwonden) heeft dit niet de voorkeur.[16]

Wanneer na medicamenteuze behandeling ook endoscopische benadering faalt, valt hyperbare zuurstoftherapie te overwegen. In een kleinschalig retrospectief cohortonderzoek werd een afname van bloedverlies gezien bij 95%.[19] Gedegen wetenschappelijk bewijs voor de effectiviteit van hyperbare zuurstoftherapie bij anorectale toxiciteit ontbreekt echter. Bovendien is de behandeling kostbaar en erg intensief.[20]

Functieverlies anus/rectum

Bij patiënten met incontinentie gerelateerde klachten kunnen op proef dieetmaatregelen worden overwogen. Vezelrijke voeding danwel suppletie van vezels vermindert de klachten van fecale incontinentie bij patiënten met soiling of incontinentie voor dunne ontlasting.[21] Bij urgentieklachten kan juist een vezelarm dieet verbetering van klachten geven (eigen waarneming), mogelijk doordat het rectum minder snel gevuld wordt en hierdoor minder snel een gevoel van aandrang ontstaat. Er is geen wetenschappelijk bewijs voor een behandelstrategie voor incontinentie gerelateerde klachten.[9]

Nieuwe inzichten in anorectale toxiciteit

Gezien de uitstekende levensverwachting van patiënten met een gelokaliseerd prostaatcarcinoom zal het verbeteren van de kwaliteit van leven na behandeling leidend moeten zijn bij toekomstig wetenschappelijk onderzoek.

Dit kan worden bereikt door de klachten te voorkómen of betere behandelingen voor complicaties te ontwikkelen.

Ontwikkelingen binnen de radiotherapie

De laatste jaren is er toenemende aandacht voor het voorkómen van anorectale toxiciteit. Het verminderen van de bestralingsdosis op het rectum en anale kanaal is hiervoor van groot belang. Het volume van het anorectum dat in het bestralingsveld ligt en de bestralingsdosis op dat gebied zijn direct gecorreleerd aan het risico op toxiciteit. De ontwikkeling en het gebruik van nieuwe bestralingstechnieken, zoals intensiteit gemoduleerde radiotherapie (IMRT) en beeldgestuurde bestraling (IGRT) hebben er voor gezorgd dat de bestralingsdosis op het rectum en anale kanaal fors is gedaald. Met behulp van IGRT is het mogelijk om dagelijks voorafgaand aan therapie de positie van de prostaat in beeld te brengen en zo nodig de patiëntpositie te corrigeren. Dit heeft het gebruik van kleinere onzekerheidsmarges rondom de prostaat en daarmee een verlaging van de dosis op het anorectum mogelijk gemaakt. IMRT technieken hebben geleid tot een meer conformele dosisafgifte, waarbij gerichte behandeling van het doelvolume mogelijk is, terwijl omliggende kritieke structuren specifiek kunnen worden gespaard. Met deze strategie komt anorectale toxiciteit minder vaak voor.[5,22,23]

Op dit moment wordt in toenemende mate de totale bestralingsdosis in een kleiner aantal fracties gegeven (hypofractionering). De verwachting is dat hypofractionering geen significant effect zal hebben op de incidentie van late toxiciteit. Ook de opkomst van focale therapieën (radiotherapie, cryotherapie, hoog intensiteit gefocuste radiogolven/HIFU) waarbij niet de gehele prostaat, maar slechts het afwijkende focus wordt behandeld, zou kunnen leiden tot minder klachten. Er is echter geen bewijs voor de effectiviteit (ziektecontrole) noch voor de veiligheid (late anorectale schade) voorhanden zodat focale therapie vooralsnog gezien wordt als experimenteel.

Eén van de nieuwe ontwikkelingen die in ons ziekenhuis wordt toegepast het gebruik van een endorectale ballon tijdens bestraling. Deze ballon wordt voorafgaand aan iedere bestralingsbehandeling rectaal ingebracht en opgeblazen, waardoor met name de laterale wanden en de achterwand van het anorectum uit het bestralingsveld worden gedrukt. Ondanks het feit dat de rectumvoorwand dichter tegen de prostaat aan wordt gedrukt, neemt de totale dosis op het anorectum af.[12] De endorectale ballon verlaagt de kans op het ontstaan van teleangiëctasieën en beschermt de anale knijpkracht als ook de rectale capaciteit, waardoor het risico op anorectale klachten lijkt af te nemen.[3,12] Een gerandomiseerde studie wordt momenteel uitgevoerd om deze studies meer kracht bij te zetten.

Naast een endorectale ballon wordt in studieverband ook gebruik gemaakt van ‘spacers’ om de anorectale toxiciteit te verminderen. Hierbij wordt de ruimte tussen de prostaat en het rectum vergroot door injectie van bijvoorbeeld een hydrogel in het anterieure perirectale vetweefsel. Ook dit heeft als doel om de afstand tussen de prostaat en het rectum te vergroten. De geïnjecteerde hydrogel is biologisch afbreekbaar en is na 6 maanden na implantatie afgebroken. Zowel de endorectale ballon als de spacer worden door patiënten goed verdragen.

Conclusie

Als gevolg van de toegenomen incidentie van prostaatcarcinoom, in combinatie met een zeer goede overleving na behandeling van gelokaliseerde prostaatkanker, worden artsen steeds vaker geconfronteerd met patiënten met anorectale klachten na prostaatbestraling. Rectaal bloedverlies ontstaat vaak na prostaatbestraling en is meestal van voorbijgaande aard.

Klachten als urgentie en in mindere mate fecale incontinentie zijn een late complicatie van prostaatbestraling. Met de huidige bestralingstechnieken wordt echter wel een afname in frequentie en ernst van deze klachten gezien en wordt met name fecale incontinentie sinds het gebruik van de nieuwe bestralingstechnieken nog maar zelden gezien.

Ondanks het feit dat incontinentie gerelateerde klachten minder voorkomen, hebben deze een grotere impact op de kwaliteit van leven dan rectaal bloedverlies. Tot op heden is er echter geen effectieve behandeling voor deze klachten voorhanden, waardoor de nadruk moet liggen op preventie.

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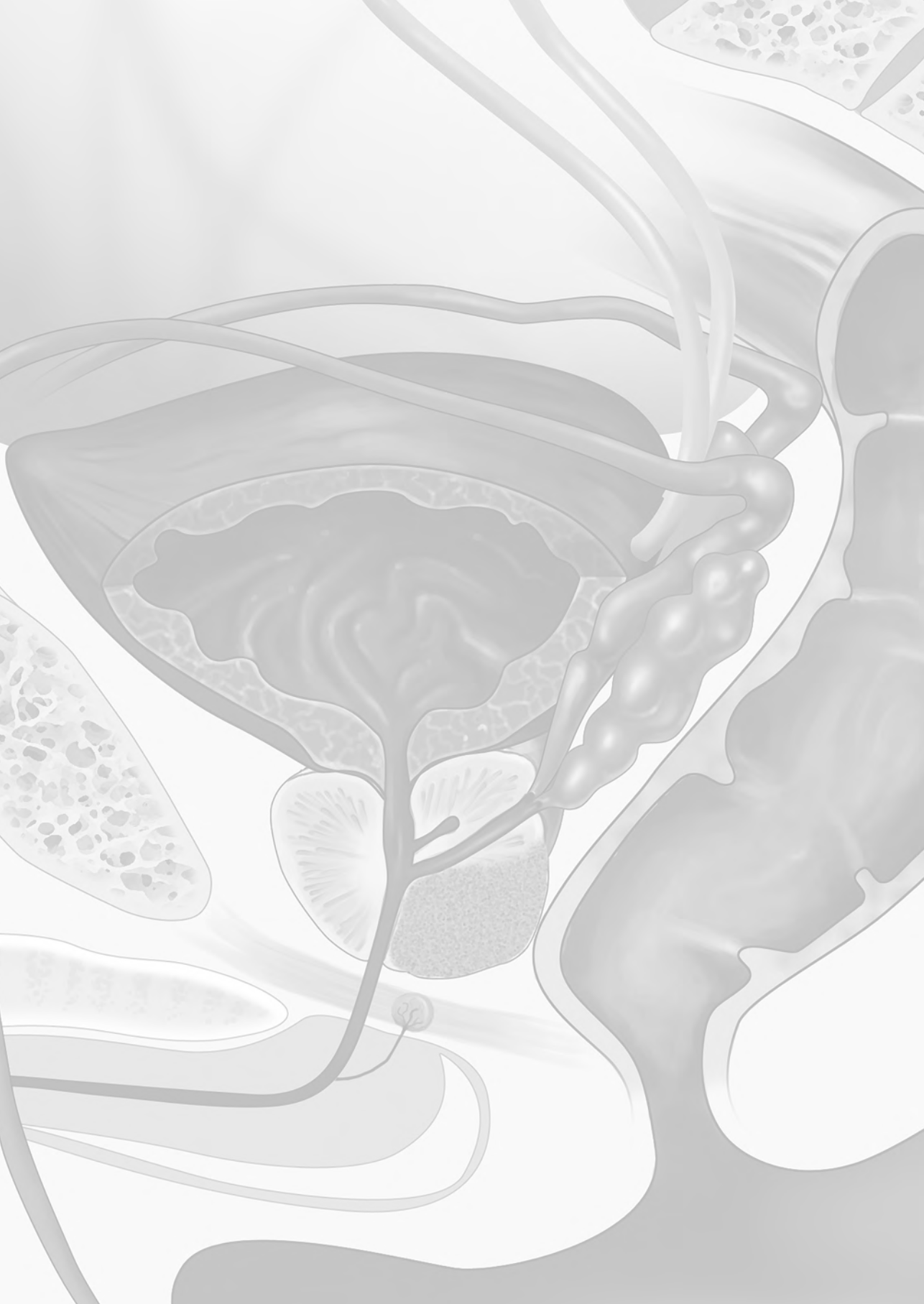
CHAPTER 9

General discussion and future perspectives



General discussion

Prostate carcinoma (PCa) is the most common diagnosed type of cancer in men in the Western World. In the Netherlands, more than 20% of all men diagnosed with cancer have PCa.[1] Over the last decades the overall survival of localized PCa has improved. Early detection of PCa, due to the widespread availability of PSA measurement (prostate specific antigen), and improvement of treatment modalities have contributed to this improved survival.[2,3] With survival rates of ≥95% for localized PCa, the survival after treatment almost equals the survival rate of men in the same group of age without PCa. Therefore, apart from improving survival, maintenance of quality of life (QoL) after PCa treatment has become an important issue. QoL is mainly affected by the prevalence and severity of long-term adverse events.[4]

External beam radiotherapy (EBRT) is a frequently used curative treatment for localized PCa.

The radiation used by EBRT is absorbed by the target tissue. This absorption leads to the formation of radicals and free electrons (ionization). These free radicals and electrons cause damage to the DNA in cells. When the damage to the DNA is large enough it conducts cell death.[11] Not only malignant cells are sensitive for this damage, but also normal healthy tissue is damaged by EBRT, leading to both acute (i.e. within 90 days after irradiation) and late effects. Cells with a high speed of tissue proliferation, like gastro-intestinal mucosa and skin show an acute reaction within several weeks after start of EBRT. These acute reaction in the first few weeks is mainly caused by an acute inflammatory reaction.[11,12] Late toxicity is engendered by fibrosis and ischemia.[12] Furthermore it is, at least in part, related to the severity of the acute toxicity, the so called consequential effect.[12-14] The long-term adverse events of EBRT for PCa are mainly of gastrointestinal origin (so-called late anorectal toxicity (LAT)).[4,5] LAT comprises different symptoms like rectal blood loss, loose stools, an increased frequency of defecation and fecal incontinence.[6,7] The incidence and severity of LAT depends on radiation dose to rectum and anal sphincter complex. In recent years, several dose-effect relationships for LAT have been identified.[8-10] Depending on the severity of complaints they can effect QoL. **Figure 2** of the general introduction proposes a simplified model of the above mentioned (Page 15).

Improvements in radiation techniques have resulted in a decrease of LAT, without losing the effect on oncologic outcome. Nevertheless, EBRT still causes LAT regularly.[15-17]

Most studies describe LAT after EBRT by use of one of the available physician-based toxicity scales.[18] Only few studies measured anal and rectal function in an attempt to get more insight into the underlying pathophysiology of individual symptoms of LAT. Understanding the contribution of specific functional and anatomic disturbances is important. It will advance our knowledge about the role of each factor and may guide

future prevention (e.g. by selectively sparing involved anatomic regions in RT planning) and management of LAT.

The general aim of this thesis was to gain insight into development and impact of LAT in men irradiated for localized prostate cancer with current state-of-the-art radiation techniques and a daily inserted endorectal balloon (ERB). In these patients quality of life, symptoms, specific anal and rectal functions and rectal mucosa were studied.

In order to reach this goal we addressed the following questions:

1 What is the influence of prostate EBRT on anorectal function as measured by anal manometry and rectal barostat? (Chapters 2, 4, 5, 7 and 8)
2 What is the influence of EBRT on rectal mucosa, observed during endoscopy after prostate irradiation? (Chapters 2, 6 and 8)
3 Does a daily inserted ERB during EBRT reduce the frequency and severity of LAT? (Chapters 5 and 6)
4 Which symptom of LAT has the largest influence on QoL? (Chapter 3)
5 Is there a correlation between QoL and anorectal function? (Chapters 3)

In the next paragraphs the findings related to each of these questions will be discussed.

One of the strengths of this thesis is the relatively large patient cohorts studied, especially in the studies described in Chapter 4 and 7. This increases the power of these studies. Furthermore, the techniques for measuring anal and rectal pressures are current state-of-the-art. The use of the electronic barostat to measure rectal pressure-volume curves and rectal sensation is unique in this setting. It is considered to be the most reliable way to measure these functions, but currently our research group is the only group to use this valuable instrument in irradiated patients.

Further, the collaboration between the departments of Radiation Oncology and Gastroenterology is unique. The majority of studies regarding LAT are done by radiation oncologists with or without help of urologists. Only a minority of groups included gastroenterologist in their research, whilst gastrointestinal complaints are the most important side effect of prostate EBRT. Considering the complexity of LAT, in our opinion a multidisciplinary approach is required.

Question 1: What is the influence of prostate EBRT on anorectal function as measured by anal manometry and rectal barostat?

The principal findings of this thesis are that 1) rectal capacity decreases after EBRT even using intensity modulated radiotherapy and an endorectal balloon and that 2) anal

sphincter function also deteriorates, particularly reflected by a reduction of maximum squeeze pressure.

An overview of all studies in which anorectal function after prostate EBRT was measured up to April 2012 is described in Chapter 2. Ten studies objectified anal and/or rectal function after prostate irradiation. Limitations of these studies were the use of older radiotherapy techniques, relatively small patient cohorts and the use of less valid techniques than the current state-of-the-art electronic barostat to measure pressure-volume relations. The group of Yeoh published most studies regarding this topic. The patients they studied were mostly treated with 3-dimensional conformal radiotherapy.[16,19] Besides the results of our research group, only one new study has published new results on anorectal function since April 2012.[20] This study shows anorectal function up to 5 years after prostate EBRT. Results are in line with the results described in this thesis (Chapter 2, 4, 5 and 7). Anal pressures remained lower and rectal compliance decreases progressively in a follow-up period of 5 years. The reduction in rectal capacity seems to recover over time. Regrettably, the authors do not mention this remarkable result in their discussion. Adaptation over sensory perception or aging could be plausible explanations.

In Chapter 5 and 7 we demonstrate that the rectal wall stiffens after prostate radiotherapy. All patients were irradiated with IMRT and a daily inserted ERB during radiotherapy. Pressure-volume relations of the rectum were measured by electronic barostat. The reduced compliance of the Rwall on long term is most likely caused by fibrosis, whilst acute changes in rectal compliance are due to edema.12

Especially rectal capacity is influenced by prostate EBRT. These results are in line with other research groups who investigated rectal distension.[19,21,22] Other parameters related to rectal distensibility, like rectal compliance are also diminished. In addition, reports from Yeoh et al. describe a decreased compliance too, but they used a different method to calculate compliance. In their studies, rectal compliance was calculated from the maximal slope between 40 and 100 mL of the pressure-volume curve and the balloon was manually inflated.[16,19,20,23] Rectal compliance was progressively deteriorated up to 5 years after treatment.[20] Also, they used another method to determine rectal capacity. They measured rectal capacity up to a maximum of 150mL, whilst our group measured the volume at a pressure of 48mm Hg when rectal capacity was not reached earlier (with mean rectal capacity ≥150mL in both studies). Other groups used a rubber balloon to calculate rectal compliance, but the compliance of the rubber itself influences the outcome. Currently, the electronic barostat connected to an infinitely compliant plastic bag is considered the most reliable method to assess rectal pressure-volume relations and rectal sensibility.[24-26]

We showed that rectal sensibility changes after prostate irradiation. After EBRT a higher pressure is needed for a patient to experience a first sense and to experience a feeling of urgency (Chapter 5 and 7). Other research groups used manually inflated

balloons for rectal sensations, but results were comparable.[16,23] Reduced rectal sensory threshold were also measured by use of urethral ring electrodes.[27] These findings provide evidence for involvement of the nerve system in LAT. The altered sensory function of anus and rectum can possibly be explained by hypertrophy of Auerbach's plexus as showed in biopsies after prostate EBRT.[28] A new study with biopsies after EBRT should be performed to confirm this theory as radiation techniques has been forcefully improved since 1986.[28]

Anal function is deteriorated after EBRT. Several studies report a reduction of anal resting pressure and/or anal squeeze pressure (Chapter 2). In particular results regarding anal squeeze pressure are in line with our findings. Anal pressure, and thereby anal function, are important to maintain fecal incontinence. Reduced anal pressures are related to bothersome symptoms like urgency and fecal incontinence. Both symptoms are associated with a loss of QoL (Chapter 3).[20,29,30] Fibrosis of the anal complex, caused by a high radiation dose, is found in 80% of patients irradiated for rectum carcinoma.[31] Although the radiation dose on anal canal is often lower, compared to the dose received by the Rwall, the close anatomic relation between the prostate and anal canal makes fibrosis a plausible contributing factor for the reduced anal function.

In Chapter 5 we showed a tendency towards lowered maximum anal pressure during squeezing. A significant reduction in anal maximum squeeze pressure was found two years after EBRT (Chapter 7). Anal maximum pressure decreased from 192 ± 8 prior to EBRT to 176 ± 9 mm Hg after 2 years. Anal resting pressure was not significantly affected in these two studies. Possible explanations are the use of a daily inserted ERB in these cohorts, which is known to spare the radiation dose on the anal canal.[32] Another possible explanation could be the introduction of anal wall delineation in the radiotherapy planning protocol to specifically spare the anal wall, which is not routinely done in other studies.

Modern techniques of EBRT, like intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) and image-guided radiotherapy (IGRT) can reduce the radiation dose on rectal wall and anal canal. As there is a clear relation between radiation dose and LAT, these modern techniques probably prevent deterioration of anal and rectal function and leads to less LAT.[8,9]

The radiation dose received by anal canal and rectum is directly related to the function of these structures (Chapter 4). Especially the volume of the anal canal receiving ≥ 40 Gy is related to complaints after EBRT. Furthermore, univariate analysis shows that the mean dose received by the rectal ring (Rectal ring Dmean) and the volume of the rectal ring receiving ≥ 60 Gy (Rectal ring V ≥ 60 Gy) are correlated to LAT. These findings are in line with prior studies. Smeenk et al. found that the dose received by anal and rectal wall are both related to rectal urgency.[33] The multifactorial pathophysiology of LAT and the involvement of rectum and anal canal has already been suggested by others.[16,34]

Anal function, in particular anal resting pressure, is related to fecal incontinence, while an increased frequency of defecation and rectal blood loss are more related to the dose received by the rectal wall.[33-36] Separately delineating the rectum and anal canal in radiotherapy planning contributes to the maintenance of anorectal function, as these structures can then be selectively spared in RT treatment planning.

Question 2: What is the influence of EBRT on rectal mucosa, observed during endoscopy after prostate irradiation?

Prostate irradiation causes telangiectasias, especially on the anterior rectal wall. In addition, congested mucosa is frequently observed. Especially multiple telangiectasias are related to clinical symptoms like rectal blood loss. Incidental telangiectasias are usually not related to symptoms.[37,38] Primarily when bleeding is severe and causes anemia it will influence QoL. Ulceration and necrosis can also result in blood loss, but these mucosal changes are rarely seen. Histological analysis of LAT shows a vasculitis leading to thrombosis of small arteries and arterioles causing several degrees of ischemia of the rectal wall.[39-41] This ischemia may lead to mucosal friability when telangiectasias form. The combination of ischemia and telangiectasias are predisposing for bleeding and the formation of ulceration, strictures and necrosis.[42]

The peak incidence of mucosal changes was seen between the first and second year after prostate EBRT. Spontaneous recovery of rectal mucosa occurs in a substantial percentage of patients.

In Chapter 2 we review 13 studies that describe radiation effects on rectal mucosa observed by endoscopy. Overall, telangiectasias were observed in 73% of patients, whilst congested mucosa was seen in 33% of irradiated men.

Ulceration was sporadically observed (4%) and stricture or necrosis was not seen at all.

Chapter 6 further elaborates on these observations. Telangiectasias are the most frequently recorded mucosal changes. After a follow-up of 5 years natural regression of blood loss and decrease of telangiectasias was seen in a considerable group of irradiated men (Chapter 6). This natural improvement of rectal mucosa is compatible with prior published results and is associated with less rectal blood loss.[38,43] This spontaneous improvement is remarkable and, to our knowledge, has not been described for skin or oral mucosa. An explanation for this observation has not yet been hypothesized. Friedland et al. showed that there was no ongoing hypoxemia after prostate EBRT.[44] Perhaps, the recovered oxygenation of the rectal mucosa causes a reduction of vasodilatation of the telangiectasias.

Due to this natural improvement a conservative treatment strategy is recommended when patients experience minor rectal blood loss. Sometimes watchful waiting can be considered. (Chapter 8 describes the approach for the treatment of radiotherapy-associated blood loss in more detail).

The absence of strictures and necrosis are probably due to the improvements of radiation techniques. The radiation dose received by the rectal wall has decreased since the introduction of 3D-conformal radiotherapy, IMRT and IGRT, causing less damage to the rectal mucosa.

Question 3: Does a daily inserted ERB during EBRT reduce the frequency and severity of LAT?

A daily inserted ERB reduces the severity of mucosal changes. Also, there are strong indications that the ERB helps to spare anal and rectal function and reduces LAT. Although a randomized controlled trial to confirm these findings is lacking, prior studies from our research team showed evidence that the ERB helps to reduce the amount of radiation received by the anal canal and rectal wall.[32,33,38] As LAT is related to radiation dose[8-10], it seems only plausible that the ERB helps to prevent LAT. Smeenk et al. proved that patients irradiated with ERB had less incontinence related LAT compared to men irradiated without ERB.[33] Due to these results, our department of radiation oncology is convinced that the ERB contributes in maintaining a better QoL and the daily inserted ERB is nowadays enclosed in the standard treatment protocol for prostate EBRT.

In Chapter 6 a direct comparison is made between patients irradiated with and without a daily inserted ERB. Five years after EBRT men irradiated with ERB had significantly less telangiectasias compared to men irradiated without ERB.

At the beginning of the collaboration between the departments of Radiation Oncology and Gastroenterology, the attention was mainly focused on rectal blood loss. Over time, our attention expanded to all symptoms of LAT. Chapter 5 describes frequencies of symptoms of LAT in a group of men irradiated with an ERB. Fecal urgency was the most frequently reported complaint and was reported in 10 out of 32 men (31%), followed by an increased frequency of defecation (13%) and rectal blood loss (6%). This frequency of symptoms tends to be lower compared to studies reporting symptom frequencies in men irradiated without ERB. For example, Yeoh et al. reported 55%, 58% and 39% for fecal urgency, increased frequency of defecation and rectal blood loss, respectively. It should be noted, however, that no definite conclusions can be drawn from these results, as no direct comparison was performed. Furthermore, these results are patient-reported outcomes and, in general, these scoring systems lead to higher scores compared to physician based systems.[18]

Earlier studies from our group showed that patients treated with ERB reported significantly less complaints compared to patients treated without ERB.[33,38] Furthermore, the ERB-group had a better preservation of their anal squeeze pressure. This was associated with the ERB-group receiving significantly lower doses to the anal canal and rectal wall.[33] Although a comparison between patients treated with and without ERB was not the primary aim of this study (i.e. the study was not powered to support these

conclusions), the results strongly suggest a beneficial effect of an ERB. These results demonstrate that the use of an ERB reduces the dose received by the anal and rectal wall, resulting in better QoL after prostate EBRT.[45-48]

Besides the ERB, other devices are used to enlarge the distance between prostate and rectum. One of the most investigated approaches is a spacer, a biodegradable hydrogel[49] or biodegradable balloon50 that is injected in the anterior perirectal fat to push the rectum away from the prostate. First studies report a reduction in dose on rectal wall after IMRT for PCa.[51,52] Although ERBs and spacers are both used to increase the distance between the prostate and the anorectum, there are some differences. Spacers reduce doses to the anterior wall, whereas the benefit of ERBs mainly seems to involve the posterior and lateral wall. The ERB has proven to reduce radiation dose on the anal wall, while the anal wall sparing effect of spacers is not yet addressed. The sparing effect of the anterior rectal wall of spacer makes it potentially beneficial for treatments with a steep dose fall-off, e.g. brachytherapy or stereotactic radiotherapy. ERBs may be even counteractive for brachytherapy, as an ERB pushes the anterior rectal wall towards the prostate.[53] A comparative study between an ERB or the use of a spacer for prostate IMRT would be useful, preferably a randomized controlled trial.

Question 4: Which symptoms of LAT have the largest influence on QoL?

Fecal incontinence and rectal urgency are symptoms with the largest influence on QoL.

In current literature regarding the symptoms of LAT, most emphasis is put on rectal blood loss after EBRT. Studies dedicated to incontinence related symptoms, such as increased stool frequency after EBRT or involuntary loss of stools are sparse. Several reasons for this discrepancy can be mentioned: a) rectal blood loss is a symptom that is easily recognized and can be objectified, b) it is one of the most frequently seen symptoms and c) there are several effective treatments described. However, the results described in Chapter 3 show that fecal incontinence and urge related symptoms have a larger impact on QoL after prostate EBRT. Fecal incontinence and urge were strongly correlated to all four subdomains of the FIQL quality of life questionnaire and to the EPICB-B score (Expanded Prostate Index Composite Bowel Bother score). Loose stools was also correlated to all subdomains of QoL. Specific and validated patient-reported outcome measures were used to assess symptoms and QoL, instead of the physician-based questionnaires used in most other studies. Our results are in line with other studies with patient-reported approach.[54,55] In a Swedish cohort of irradiated men fecal leakage was the gastrointestinal symptom which caused the most distress.[54] Forty-seven percent of the patients with fecal incontinence experienced severe distress. In females irradiated for cervical cancer, loose stools caused most distress.[56] Fecal incontinence caused a moderate level of distress. One reason for this discrepancy in results between men and women might be the difference in age at the moment of therapy. In general,

women with cervix carcinoma are 20-25 years younger at the moment of treatment compared to men irradiated for prostate carcinoma. Anal pressures diminish by aging.[57] Therefore, it seems conceivable that fecal incontinence will occur more easily in older men, as a smaller deterioration in anal pressure can lead to fecal incontinence.

Most scoring systems for LAT are physician-based. They are difficult to compare due to different definitions and inter-observer variations. In addition, not every system is appropriate to score all the various symptoms associated with LAT. As an example, the frequently used RTOG/EORTC scoring system (Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer) lacks fecal incontinence which is the most distressing symptom.[58] And, obviously, the most accurate reporter of QoL is the patient himself.

Question 5: Is there a correlation between QoL and anorectal function?

A simplified pathway, showing by which steps radiation can lead to impaired QoL, is presented in Chapter 1 (page 15, **Figure 2**). The first two steps, from radiation dose to anorectal dysfunction, are funded by the results of Chapter 4-7. These Chapters show that EBRT leads to impaired anal and rectal function and changes in rectal mucosa. Besides reduced anal and rectal function after EBRT, Chapter 4 shows that the volume of the anal wall receiving ≥40 Gy is a predictor for LAT. Furthermore, Chapter 5 supports the relation between urgency related symptoms and a decrease of anal function.

The last step, from anorectal dysfunction to an impaired QoL, is investigated in Chapter 3. Chapter 3 shows that anorectal dysfunction correlates well with QoL. An impaired anal resting pressure is the function parameter with the largest influence. This is in line with the finding that fecal incontinence and fecal urgency have the largest influence on QoL and underscores the importance of anal sphincter function in preventing fecal incontinence.[26]

Chapter 3, 4 and 5 all show that the radiation dose sparing of the anal canal is at least as important to preserve QoL as rectum sparing. This is in concordance with other results published by our research group[33,59] and others.[9,10,60]

To preserve QoL the anal canal should be delineated separately in EBRT planning.

Future perspectives

Currently, a randomized controlled trial is being conducted in Adelaide with patients irradiated for localized PCa, where they randomize between EBRT with or without endorectal balloon. This study will hopefully support our hypothesis that a daily inserted ERB helps to preserve LAT. Patient-reported questionnaires and anorectal function, measured by manometry, will be the outcome measures of this study

Furthermore, the influence of current state-of-the-art EBRT on anal and rectal function over a period of ≥5 years should be investigated. Yeoh et al. published the only study so far measuring anal and rectal function up to 5 years after radiotherapy.[20] Modern radiation techniques like IMRT and VMAT, as well as ERBs were not used in this study. Especially their results for desire to defecate (rectal capacity) are interesting and should be repeated in men irradiated with IMRT and measured by use of an electronic Barostat.

In Chapter 4 we determined the influence of micronutrients on gastrointestinal toxicity. Plasma selenium and α-tocopherol levels were associated with chronically increased GI symptoms after EBRT on univariate but not multivariate analysis. The influence of (micro)nutrients on LAT is a new area of interest, with almost no publications and expertise. Perhaps further research can reveal protective micronutrients.

Reduction or prevention of fecal incontinence and rectal urgency are corner stones to improve QoL after prostate EBRT. A lot of attention is given to the prevention of LAT, as current literature lacks large prospective and comparative studies regarding the treatment of LAT. Especially for incontinence related symptoms the results are disappointing.[61,62] Longitudinal studies with dietary advices or pelvic floor training by a specialized physical therapist as intervention can be investigated, as these interventions have proven their use in patients with fecal incontinence due to other causes. For rectal blood loss a large placebo-controlled RCT using sucralfate enema's lacks current literature as well as a large RCT with argon plasma coagulation as treatment for more severe rectal blood loss. Besides sucralfate enema's and argon plasma coagulation, hyperbaric oxygen therapy can be considered as treatment for LAT. However, recently there are increasing doubts regarding the benefits of this intensive treatment.[63,64]

All future research should be performed with a goal to improve QoL. Therefore, future research must take patient reported outcome measures into account apart from physician based assessments.

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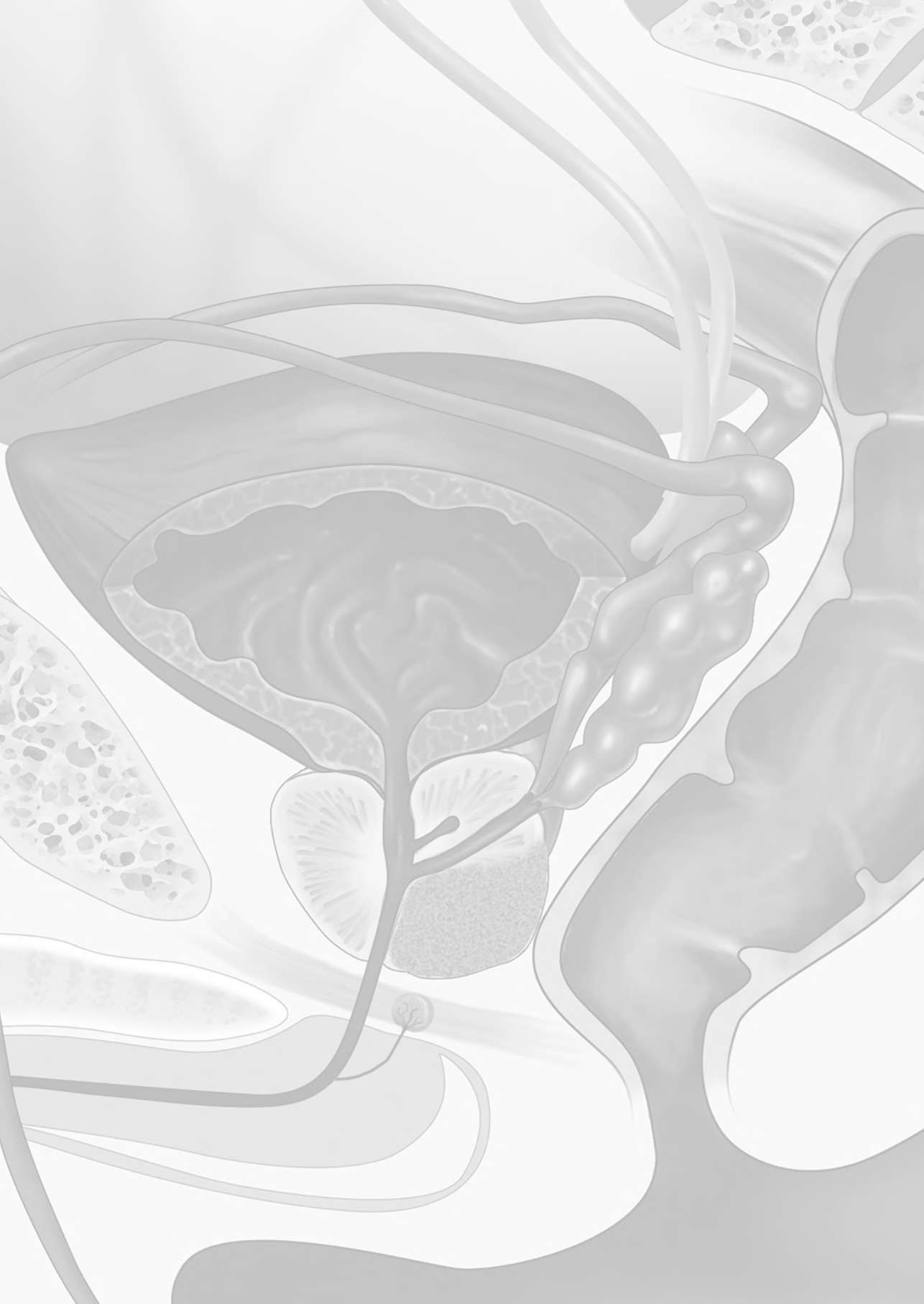
CHAPTER 10

English and Dutch summary



English summary

Prostate cancer is the most common cancer amongst men in the Western World. Treatment possibilities depends on tumor stage, tumor-associated risk factors, comorbidities and a patients age. For localized prostate cancer (PCa), external beam radiotherapy (EBRT) is one of the preferred options. Last decades the oncological outcome and overall survival has improved. For localized PCa, TNM stage I-III, the 5-years survival is ≥95%.

Due to these good survival rates, the attention shifts toward maintaining quality of life (QoL) after treatment. QoL after treatment is largely determined by long-term side effects. For prostate EBRT these long-term side effects are called "late anorectal toxicity" (LAT) and comprises several symptoms like rectal blood loss, increased stool frequency, loose or liquid stools, painful bowel movements, urgency of defecation and fecal incontinence.

The general aim of this thesis was to gain insight into the pathophysiology of LAT in men irradiated for localized prostate cancer with current state-of-the-art radiation techniques and a daily inserted endorectal balloon (ERB). In these patients, symptoms, specific anal and rectal functions and changes in rectal mucosa were studied.

In **Chapter 2**, the results of a systematic review of the literature is presented, regarding anal and rectal function, and changes in rectal mucosa after EBRT for PCa. Twenty-one studies were included. Anal resting pressures significantly decreased in 6 of the 9 studies including 277 patients. Rectal distensibility was impaired after EBRT in 7 of 9 studies.

Mucosal changes as assessed by the Vienna Rectoscopy Score revealed telangiectasias in 73%, congested mucosa in 33% and ulceration in 4% of patients in 8 studies (including 346 patients). Three studies reported spontaneous mucosal improvement during follow up.

Changes in anal and rectal function are associated with fecal incontinence, rectal urgency and frequent bowel movements. Telangiectasias are related to rectal blood loss.

Chapter 3 explores the relation between QoL and objective and subjective anorectal function in 85 men after prostate EBRT. QoL was measured by the Fecal Incontinence Quality of Life scale (FIQL) and the Expanded Prostate Cancer Index Composite Bowel domain (EPICB)-bother subscale. Subjective anorectal function (symptoms) was measured by the EPICB-function subscale.

Anorectal function was evaluated in 85 men. Sixty-three percent suffered from one or more anorectal symptoms. Correlations of individual symptoms were strongest for fecal incontinence and urgency. Anal resting pressure was the objective anorectal function parameter which correlated most strongly with QoL.

In **Chapter 4**, we attempted to find baseline factors which are predictive for the development of LAT. Besides anal dose-volume parameters, micronutrients and misrepair biomarkers were also investigated in 106 men irradiated for PCa.

On univariate analysis, total GI symptom scores were significantly associated with: 1) plasma selenium and α-tocopherol; 2) micronuclei indices of DNA damage; 3) mean anal and rectal wall doses; and 4) volumes of anal and rectal wall receiving ≥40 Gy and ≥60 Gy. On multivariate analysis, only volume of anal wall receiving ≥40 Gy was significant for increased GI symptoms after

EBRT. This supports the importance to delineate the anal canal separately in EBRT planning for PCa.

We determined whether EBRT induces changes of rectal distensibility as measured by an electronic barostat in **Chapter 5**. Furthermore, we explored whether anorectal complaints are related to specific changes of anorectal function.

Thirty-two men, irradiated for localized prostate carcinoma, underwent barostat measurements, anorectal manometry, and completed a questionnaire prior to and one year after radiotherapy. EBRT reduced maximal rectal capacity, area under the pressure-volume curve and rectal compliance. Sensory pressure thresholds did not significantly change. Sixteen of the 32 patients (50%) had one or more anorectal complaints. Patients with urgency had a more reduced anal squeeze and maximum pressure compared to patients without complaints, indicating a deteriorated external anal sphincter function contributes to the development of urgency.

Daily inserted endorectal balloons (ERB) during radiotherapy are used to reduce rectal toxicity. In **Chapter 6**, objective rectal toxicity is compared between patients treated with and without ERB by means of repeated rectoscopy for a period of 5 years.

Telangiectasias were the most often found mucosal lesions. The highest prevalence of rectal toxicity was found at one year, and this decreased over time. Patients in the ERB group had more mucosal areas irradiated to low doses (<40Gy) compared to patients in the no ERB group.

After irradiation with ERB there was less rectal toxicity observed compared to irradiation without ERB in areas that received the same dose. Furthermore, patients treated with ERB reported less symptoms compared to patients treated without ERB. These observations suggest a beneficial effect of ERBs in prostate radiotherapy.

In **Chapter 7**, the changes of anorectal function over time in men irradiated with IMRT and ERB are presented. Sixty men underwent barostat measurements and anorectal manometry prior to EBRT and 6 months, one year and 2 years after radiotherapy.

In concordance to Chapter 5, rectal distensibility decreased after EBRT. However, this study showed that capacity is progressively diminished over time. Furthermore after

two years, sensory function is also affected after radiotherapy. However, there is an indication that these effects are less with IMRT compared to conventional radiation techniques. The use of a daily inserted ERB seems an efficient aid to spare anal and rectal function.

In **Chapter 8**, we showed an overview of LAT based on the systematic review presented in **Chapter 1**. Furthermore, a step-up approach for the treatment of LAT, especially rectal blood loss due to radiation, is given.

A general discussion and suggestions for future research can be found in **Chapter 9**.

In conclusion, this thesis provides new or additive insights in the prevention, pathophysiology and consequences of LAT:

- Fecal incontinence and urgency are the symptoms of LAT with the largest influence on quality of life.
- The anal canal and rectum should be delineated as two individual organs to prevent symptoms of LAT.
- The use of a daily inserted ERB can help to reduce toxicity after EBRT.
- Prostate EBRT increasingly reduce rectal distension and anal pressures over time. Furthermore it increases sensory thresholds.
- Mucosal lesions after prostate irradiation can heal spontaneously, suggesting that aggressive treatment strategies are not always necessary.

Nederlandse samenvatting

Prostaatkanker is de meest gediagnostiseerde vorm van kanker bij mannen uit de Westerse wereld. De keuze voor behandeling hangt mede af van het tumorstadium, tumorgeassocieerde risicofactoren en de leeftijd en comorbiditeit van de patiënt. Voor gelokaliseerde prostaatkanker is uitwendige bestraling (EBRT) een van de meest gekozen behandelingen. De afgelopen decennia is de overleving van patiënten met prostaatkanker gestegen tot een 5-jaars overleving van ≥95% voor stadium I-III prostaatkanker.

Vanwege de goede overleving bij gelokaliseerde prostaatkanker, verschuift de aandacht geleidelijk naar het handhaven van een goede kwaliteit van leven (QoL) na behandeling. De QoL na behandeling wordt grotendeels bepaald door het optreden van bijwerkingen. Voor EBRT van de prostaat worden deze bijwerkingen late anorectale toxiciteit genoemd (LAT). LAT omvat verschillende symptomen zoals rectaal bloedverlies, toegenomen ontlastingsfrequentie, diarree of dunnere ontlasting, pijn tijdens ontlasting, rectale urgentie en fecale incontinentie.

Het hoofddoel van dit proefschrift in om meer inzicht te verkrijgen in de pathofysiologie van LAT bij mannen die bestraald zijn vanwege prostaatkanker met state-of-the-art technieken en een dagelijks ingebrachte endorectale ballon (ERB). Bij deze mannen werden symptomen, specifieke anale en rectale functies en veranderingen in rectummucosa bestudeerd.

In **Hoofdstuk 2** worden de resultaten van een systematische review over anale functie, rectale functie en veranderingen in rectale mucosa na prostaatbestraling gepresenteerd. Eenentwintig publicaties zijn geïncludeerd in deze systematische review. De anale rustdruk nam significant af in 6 van 9 studies die dit gemeten hebben. Rectumdistensie neemt af in 7 van de 9 studies.

Mucosale veranderingen, geobjectiveerd door middel van de "Vienna Rectoscopy Score" worden frequent gezien. Na prostaatbestraling heeft 73% van de patiënten teleangiëctasieën, 33% congestieve mucosa en 4% een ulceratie. Drie publicaties beschrijven een spontane verbetering van mucosale afwijkingen gedurende follow-up.

Zowel anale als rectale functie is geassocieerd met fecale incontinentie, rectale urgentie en een toegenomen ontlastingsfrequentie. Teleangiëctasieën zijn gerelateerd aan rectaal bloedverlies.

Hoofdstuk 3 verkent de relatie tussen QoL en objectieve en subjectieve anorectale functie na prostaatbestraling bij 85 mannen. QoL werd gemeten met de Fecal Incontinence Quality of Life schaal (FIQL) en de Expanded Prostate Cancer Index Composite Bowel domain (EPICB)-bother subschaal. Subjectieve anorectale functies (symptomen) werden gemeten met de EPICB-function subschaal.

Drieënzestig procent van de participanten ervoer één of meer anorectale symptomen. Correlaties tussen QoL en symptomen waren het sterkste voor fecale incontinentie en rectale urgentie. Anale rustdruk was de objectieve functieparameter met de sterkste correlatie met QoL.

In **Hoofdstuk 4** hebben we gezocht naar baseline factoren die voorspellend zijn voor het ontstaan van LAT. Naast dosis-volume parameters is er ook gekeken naar micronutriënten en misrepair biomarkers bij 106 bestraalde mannen.

Na univariate analyse was de totale gastro-intestinale symptoomscore onder andere gerelateerd aan: 1) plasma selenium en α-tocopherol, 2) de gemiddelde dosis op het anale kanaal en op het rectum en 3) het volume van het rectum en het anale kanaal dat ≥40 Gy en ≥60 Gy heeft ontvangen. Bij multivariate analyse is alleen het volume van het anale kanaal dat ≥40 Gy heeft gekregen significant gerelateerd aan de ontwikkeling van LAT. Deze bevinding benadrukt het belang om bij planning van radiotherapie het anale kanaal en het rectum als 2 aparte organen te beschouwen.

In **Hoofdstuk 5** hebben we gekeken of EBRT zorgt voor veranderingen in rectale distensibiliteit, gemeten met een elektronische barostat. Daarnaast hebben we de relatie van anorectale klachten met specifieke veranderingen in anorectale functie onderzocht.

Tweeëndertig mannen, bestraald vanwege prostaatkanker, ondergingen barostatmetingen en anale manometrie voorafgaand aan en 1 jaar na prostaatbestraling. Daarnaast vulden zij vragenlijsten in. EBRT verminderde de rectale capaciteit, de oppervlakte onder de druk-volume curve en de rectale compliantie. Sensorische drempelwaarden veranderden niet. Zestien patiënten ervoeren minstens 1 symptoom van LAT. Patiënten met klachten van rectale urgentie hadden een sterker verminderde anale knijpkracht en maximale anale druk in vergelijking met patiënten zonder deze klachten. Dit suggereert dat een verminderde functie van de anale externe sfincter bijdraagt aan de ontwikkeling van rectale urgentie.

Dagelijks ingebrachte endorectale ballonnen (ERB) gedurende prostaatbestraling worden gebruikt om gastro-intestinale toxiciteit te verminderen. In **Hoofdstuk 6** is rectale schade geobjectiveerd door middel van endoscopie. Mannen bestraald met en zonder ERB werden met elkaar vergeleken in een studieverband gedurende de eerste 5 jaar na prostaatbestraling.

Teleangiëctasieën waren de meest frequent waargenomen rectale verandering na therapie. De hoogste prevalentie van mucosale afwijkingen na bestraling werd 1 jaar na prostaatbestraling gevonden, daarna nam het aantal afwijkingen af gedurende de follow-up. Mannen die werden bestraald met ERB hadden meer gebieden in het rectum die werden blootgesteld aan een lage bestralingsdosis (<40 Gy) in vergelijking met mannen uit de groep zonder ERB.

Na EBRT met ERB werd er minder rectale toxiciteit waargenomen in vergelijking met bestraling zonder ERB in gebieden die een vergelijkbare bestralingsdosis hebben gekregen. Bovendien rapporteerden mannen na bestraling met ERB minder symptomen in vergelijking tot mannen uit de bestralingsgroep zonder ERB. Deze bevindingen suggereren een voordelig effect van ERB bij prostaatbestraling.

Hoofdstuk 7 beschrijft de veranderingen in de anorectale functie in de tijd bij mannen die IMRT met ERB hebben gekregen als behandeling voor gelokaliseerd prostaatcarcinoom. Zestig mannen ondergingen zowel barostat metingen als anale manometrie voorafgaand aan de bestraling en op verschillende momenten nadien (na 6 maanden, 1 jaar en 2 jaar).

Conform de resultaten uit **Hoofdstuk 5** leidt prostaatbestraling tot een vermindering van rectale distensibiliteit. Deze studie toont echter ook dat er een progressieve achteruitgang is van rectale capaciteit. Daarnaast blijkt dat twee jaar na bestraling er ook sprake is van een verslechterde sensorische functie van het rectum. Toch zijn er aanwijzingen dat deze achteruitgang minder groot is in vergelijking met conventionele bestralingstechnieken. Het gebruik van de ERB lijkt een efficiënt hulpmiddel te zijn om de anale en rectale functie te sparen bij prostaatbestraling.

In **Hoofdstuk 8** wordt een overzicht gepresenteerd over LAT, gebaseerd op de systematische review beschreven in **Hoofdstuk 1**. Daarnaast wordt er een step-up benadering voor de behandeling van LAT gegeven. Dit stappenplan richt zich vooral op rectaal bloedverlies als gevolg van bestraling.

Een algemene discussie en suggesties voor toekomstig onderzoek worden beschreven in **Hoofdstuk 9**.

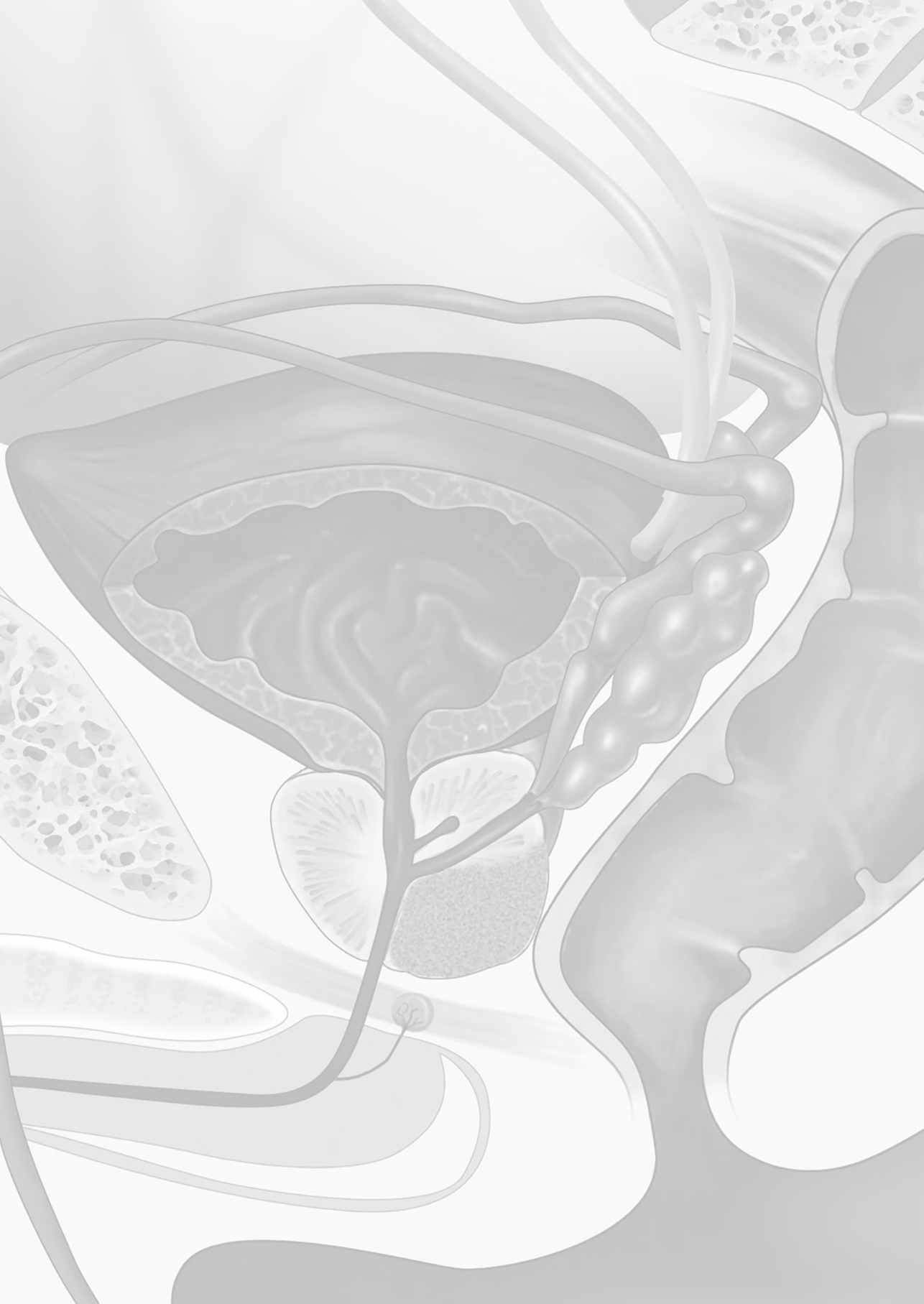
Concluderend, dit proefschrift biedt nieuwe inzichten en ondersteunt eerder geformuleerde inzichten over de preventie, pathofysiologie en gevolgen van LAT:

Fecale incontinentie en rectale urgentie zijn de symptomen van LAT met de grootste impact op kwaliteit van leven.

- Het anale kanaal en het rectum moeten als twee aparte organen worden beschouwd bij het intekenen van de radiotherapie, ter preventie van LAT.
- Het gebruik van een ERB tijdens bestraling leidt tot minder toxiciteit.
- Prostaatbestraling zorgt voor een afname van rectale distensie en anale drukken, deze afnames zijn progressief in de tijd.
- Mucosale laesies na prostaatbestraling kunnen spontaan verminderen. Derhalve is een agressieve behandelstrategie niet altijd noodzakelijk.

APPENDIX

Dankwoord
Curriculum Vitae
List of publications



DANKWOORD

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De "Limburgers", JEROEN en MARTIJN HULSHOF in het bijzonder, door de reisafstand zien wij elkaar niet wekelijks of maandelijks, maar het is altijd gezellig, of we elkaar nu in het zonnige Zuiden of in "Holland" zien. Jullie zorgen altijd voor welkome afleiding, veel humor en af en toe een klein en koud drankje…

Ooms, tantes, neven en nichten, de afgelopen jaren is er veel gebeurd. Zowel bij feestelijkheden als in moeilijke tijden zijn wij er voor elkaar. Een veilig, maar vooral ook warm gevoel!

Lieve pa en ma, dank voor al jullie steun! Niet alleen voor de totstandkoming van dit proefschrift, maar vooral omdat ik altijd bij jullie terecht kan. Jullie hebben mij gevormd tot wie ik ben en waar ik nu sta. Dit proefschrift is dan ook zeker gedeeltelijk jullie verdienste! Nu het proefschrift af is, hoop ik ook weer vaker en vooral langer bij jullie in Elst te kunnen zijn.

Tot slot. Lieve EVELIEN, naast mijn vriendin ben je ook mijn maatje. De afgelopen periode is erg druk geweest met het afronden van mijn proefschrift en de verhuizing. Maar met jou zijn alle dingen die we doen leuk, naast onze vakanties geniet ik ook van een avondje op de bank hangen met jou. Dank voor de vele mooie momenten, je steun, geduld, gezelligheid en je liefde!

CURRICULUM VITAE

ROBIN KROL werd geboren op 2 juni 1984 te Rhenen en groeide op in Elst.

In 2003 behaalde hij zijn VWO-diploma aan het Gelders College te Arnhem. Dat jaar startte hij vervolgens aan de studie Farmacie in Utrecht. Na het behalen van zijn propedeuse werd hij in 2004 alsnog ingeloot voor de studie geneeskunde aan de Radboud Universiteit.

Tijdens zijn coschap interne geneeskunde in het Rijnstate is, mede door de enthousiaste begeleiding van Peter Wahab en Marcel Spanier, zijn liefde voor de Maag-, Darm- en Leverziekten ontstaan. Het seniorcoschap en de onderzoeksstage op de afdeling MDL van het RadboudUMC versterkten deze interesse alleen maar.

In 2011 behaalde Robin zijn artsendiploma. Direct aansluitend startte hij met een promotietraject over anorectale toxiciteit na prostaatbestraling. Een promotietraject waarin de afdelingen Maag-, Darm- en Leverziekten en Radiotherapie samenwerken. Onder begeleiding van PROF. DR. JOOST DRENTH, DR. WIM HOPMAN, PROF. DR. HANS KAANDERS en DR. ROBERT JAN SMEENK heeft dit geleid tot de vorming van dit proefschrift.

Robin is in januari 2013 begonnen aan zijn opleiding tot Maag-, Darm- en Leverarts. Via de afdelingen Interne Geneeskunde en Maag-, Darm- en Leverziekten van het Rijnstate ziekenhuis en de afdeling Maag-, Darm- en Leverziekten van het RadboudUMC hoopt Robin eind 2018/begin 2019 zijn opleiding af te ronden.

Robin woont momenteel samen met Evelien Keltjens in Nijmegen.

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