External beam prostate radiotherapy: anorectal toxicity and the influence of endorectal balloons

Robert Jan Smeenk

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Thesis Radboud University Nijmegen

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External beam prostate radiotherapy: anorectal toxicity and the influence of endorectal balloons

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Contents

1

General Introduction and Outline

General Introduction

Prostate carcinoma is the most frequently diagnosed malignancy in men over 45 years old, with an incidence of over 9500 in the Netherlands [1], and a worldwide incidence of almost 900,000 [2]. External beam radiotherapy (RT) is a curative treatment option for patients with localized prostate cancer, both as definitive treatment [3], and in patients relapsing after radical prostatectomy [4]. Due to setup uncertainties, such as interfraction variation and intrafraction motion of the prostate [5], margins are applied around the clinical target volume (CTV), thus creating the planning target volume (PTV). Application of these margins, however, inevitably leads to irradiation of surrounding normal tissues, potentially leading to radiation induced toxicity. After prostate RT, anorectal toxicity has the largest impact on quality of life [6]. It should be noted, however, that late anorectal toxicity comprises different symptoms [7], and patients seem to be bothered most by complaints like urgency, soiling and fecal loss, rather than by symptoms like blood loss or mucus loss [8].

Given the dose-response relationship for prostate carcinoma in RT [9;10], there is a tendency towards dose escalation. However, while increasing the tumor dose improves control rates, care must be taken not to pay a high price in treatment morbidity [11], inasmuch as several dose-effect relationships for anorectal toxicity have been identified [12-14]. It has been shown that, when offered the choice, patients prefer a lower radiation dose over a higher dose, in order to reduce the risk of side effects [15], indicating that, from the patients' point of view, toxicity reduction is more important than improving tumor control rates.

In the previous years, the development of three-dimensional conformal RT (3D-CRT) [16] and intensity-modulated RT (IMRT) [17] has allowed more conformal dose distributions to the target volume, while selectively sparing surrounding tissues. In reports on prostate IMRT, anorectal toxicity rates vary from 26% to 73% for acute toxicity, and from 5% to 65% for late toxicity [18-21]. These numbers indicate on the one hand that anorectal toxicity is a serious problem, even after highly conformal IMRT, and on the other hand that toxicity rates vary largely between studies, dependent on the used scoring instrument [22]. Besides conformal RT techniques, image-guided RT, like fiducial marker based portal imaging and cone beam CT imaging [23], is used for prostate position verification and correction, enabling smaller CTV-to-PTV margins. In addition to improved treatment delivery and image guidance, daily inserted endorectal balloons (ERBs) have been applied in prostate RT because of its rectal wall sparing effect [24-26], and its assumed prostate immobilizing effect [27;28], thereby reducing CTV-to-PTV margins.

The aim of the abovementioned techniques is to enable dose escalation to the tumor, while reducing the risk of radiation induced toxicity. To effectively prevent anorectal complaints, however, knowledge of its pathophysiology is needed, in order to be able to selectively spare the structures involved in the development of these symptoms. Identification of objective changes in patients with anorectal complaints after RT might help to unravel its underlying pathogenesis. In patients with rectal bleeding, for example, mucosal changes have been observed on endoscopy [25]. In addition, several dose-volume and dose-surface parameters for the rectal wall have been identified as predictor for rectal bleeding [13]. Regarding the bothering fecal incontinence-related complaints, however, less is known about its origin and development. Yeoh *et al*. observed progressive anorectal dysfunction after prostate RT, using anorectal manometry testing, with an inverse relationship between fecal incontinence scores and rectal compliance and anal squeeze pressure [29], suggesting that both rectal and anal factors are involved in its development. Others have confirmed this hypothesis [30], although the exact pathophysiology, especially the relation between anatomic substrates and radiation doses, is still unknown.

To enable dose evaluation to normal tissues, such as the anorectum, structures of interest are delineated on patients' planning CT scans and the dose parameters to these organs (*e.g.* mean dose), as calculated by a treatment planning system, are retrieved. It has been suggested that when evaluating dosimetric parameters as predictors for anorectal toxicity, not only the anorectum as a whole should be considered, but also doses to the anal wall separately [14], suggesting that the anal wall and rectal wall are different anatomic substrates. Furthermore, normal fecal continence is a complex process, and rather than just the anal wall, four specific pelvic floor muscles are thought to be involved in maintaining fecal continence: the internal anal sphincter, external anal sphincter, puborectalis muscle, and levator ani muscles [31;32]. The role of these muscles in radiation-induced fecal incontinence has yet to be elucidated.

As mentioned above, ERBs are used in prostate RT, as it has been shown that rectal wall doses are reduced when an ERB is applied, which may lead to reduced late rectal toxicity [24-26]. Clinical data on this effect, however, are scarce. Furthermore, its effect on anal wall doses and fecal incontinence-related complaints is not known. Another unsolved issue of ERB application is whether or not it has a prostate immobilizing effect, which has been observed in some studies [27;28] and which may lead to smaller CTV-to-PTV margins and potentially lower anorectal toxicity rates. There is, however, no consensus on this issue, as other investigators have not observed this effect [33;34].

Outline of the thesis

The aim of this thesis is to identify anatomic structures that may be involved in the development of fecal incontinence-related complaints after RT and to investigate potential dose-effect relationships for these structures. Furthermore, it is investigated whether an ERB has a beneficial effect on the doses to these structures and subsequently on the development of anorectal toxicity.

In **Chapter 2**, an overview of the use of ERBs in prostate RT is given, based on the international literature. The effects of different types of ERBs on prostate motion, target localization, dosimetric consequences and anorectal toxicity are discussed. Furthermore, patients' tolerance, clinical practice and potential pitfalls are described. Finally, recommendations about ERB application and future research are made.

Although the effect of ERBs on rectal wall doses has been described previously [24-26], its effect on anal wall doses is not known. Given the dose-effect relationships for fecal incontinence regarding the anal wall [14], **Chapter 3** describes a planning study, in which the effect of an ERB on anal wall dose parameters is investigated in 3-field and 4-field 3D-CRT, and IMRT. Furthermore, a method for delineation of the anal wall is suggested, both with and without an ERB.

In contrast to the application of ERBs in definitive RT, its use in post-prostatectomy RT has only been mentioned sporadically, and no comparative studies on its dosimetric effect have been performed. Therefore, in **Chapter 4**, a comparative study is described, investigating the effect of an ERB on both anal wall and rectal wall doses in post-prostatectomy IMRT, using international guidelines for CTV delineation.

Chapter 5 presents the results of a study using anorectal function testing in patients with and without fecal incontinence-related complaints after prostate RT. The differences in anorectal functions are compared between these groups, and more specifically between patients with and without incontinence, urgency and frequency. Furthermore, dosimetric parameters to the anal wall and rectal wall are compared between these groups, and the associations between both functional and dosimetric parameters and the different complaints are analyzed. Based on these associations, hypotheses regarding anatomic substrates for these complaints are described. Also, the effect of an ERB on the investigated parameters is explored.

Subsequently, in **Chapter 6** an attempt is made to separately delineate four individual pelvic floor muscles considered to be involved in normal fecal continence, on planning CT scans of patients irradiated for prostate cancer. Dosimetric parameters to

these structures are obtained from the treatment planning system and are compared between patients with and without urgency, incontinence and frequency, and differences in muscle involvement are described. In addition, dose-effect curves are presented for these muscles and for the anal wall and rectal wall, and dose constraints are formulated that can be used in RT planning. Finally, differences in the prevalence of complaints and in dosimetric parameters between patients treated with ERB and without ERB are described.

As there is no consensus on the effect of ERBs on interfraction variation and intrafraction prostate motion, in **Chapter 7** the results of a comparative study are presented, which was conducted at the M.D. Anderson Cancer Center Orlando, FL, USA. Fifteen patients were treated without ERB and fifteen patients were irradiated with a daily inserted ERB. In all patients, intrafraction prostate motion was continuously monitored with an electromagnetic tracking system. The effect of the ERB on both interfraction variation and on intrafraction motion is presented in this chapter.

A general discussion, based on the abovementioned chapters is given in **Chapter 8**; **Chapter 9** provides a summary of the thesis.

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2

Is There a Role for Endorectal Balloons in Prostate Radiotherapy? A Systematic Review

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Abstract

Background and purpose: Endorectal balloons (ERBs) are being used in prostate radiotherapy for prostate immobilization and rectal wall (Rwall) sparing. Some of their aspects, however, have been questioned, like patient's tolerance and their value in modern high-precision radiotherapy. This paper gives an overview of published data concerning ERB application in prostate radiotherapy.

Materials and methods: Systematic literature review based on PubMed/MEDLINE database searches.

Results: Overall, ERBs are tolerated well, although patients with pre-existing anorectal disease have an increased risk of developing ERB-related toxicity. Planning studies show reduced Rwall and anal wall (Awall) doses with ERB application. Clinical data, however, are scarce, as only one study shows reduced late rectal damage. There is no consensus about the immobilizing properties of ERBs and it is recommended to use additional set-up and correction protocols, especially because there are potential pitfalls.

Conclusion: ERBs seem well-tolerated and in planning studies reduce anorectal wall doses. This may lead to reduced anorectal toxicity, although clinical studies are warranted to confirm this hypothesis and to further investigate the immobilizing properties of ERBs, preferably in combination with advanced techniques for position verification.

Introduction

There is a dose-response relationship of prostate cancer in external beam radiotherapy (RT) [1,2]. However, dose-escalation is limited by toxicity of surrounding normal tissues, and improved tumor control might be at the cost of higher toxicity rates [3]. In particular anorectal toxicity has a great impact on patients' quality of life [4].

Three-dimensional conformal radiotherapy (3D-CRT) [5] and intensity-modulated radiotherapy (IMRT) [2] have allowed more conformal dose distributions to the prostate, while selectively sparing surrounding normal tissues. Anorectal toxicity rates in IMRT range from 26% to 73% (acute) and from 5% to 65% (chronic) [6-9].

Despite highly conformal RT, uncertainties due to patient set-up errors and prostate motion [10] require a margin around the clinical target volume (CTV), thus creating the planning target volume (PTV). Minimizing these uncertainties allows smaller margins, thereby reducing the dose to the anorectal complex. However, as 74% of prostate cancer foci are located in the peripheral zone and in the close proximity of the rectum [11], care must be taken not to underdose the tumor.

In addition to improved treatment delivery and developments in image-guided RT [12,13], daily inserted endorectal balloons (ERBs) are being used to immobilize the prostate, thereby reducing CTV-to-PTV margins [14-20]. A second reason for ERB application is its rectal wall (Rwall) sparing effect by pushing parts of the rectum away from the high-dose regions [15,19-28].

In this paper, experience with the application of ERBs in prostate 3D-CRT, IMRT, and proton therapy, published in the international literature, is reviewed.

Materials and methods

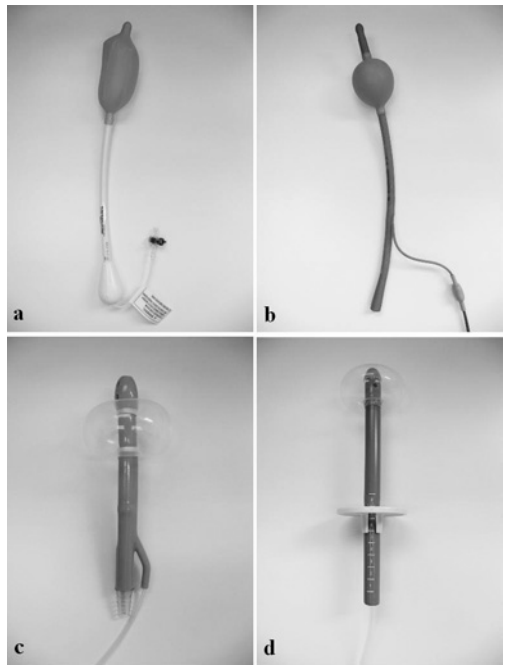
We performed a systematic literature review based on database searches in PubMed/MEDLINE and included articles up to June 2009. Terms used for the search were 'balloon', 'endorectal balloon', 'rectal balloon', 'rectal catheter' and synonyms combined with one or more of the following: 'prostate', 'prostate cancer', 'radiotherapy', 'radiation', 'IMRT', 'rectal toxicity' and synonyms. Furthermore, these terms were combined with the respective key words for each paragraph. Publications mentioned in the reference list of articles found in the automatic search and considered suitable were manually searched for. Only papers published in English were included.

Results

Types of endorectal balloons

In 1979, for the first time, ERB application in prostate RT was reported [29]. To our knowledge, four different ERBs have been described since then, three originating from diagnostic radiology, and one especially developed for RT purposes (Fig. 1).

Fig. 1 The endorectal balloons, mentioned in the literature: ERB1 (**a**), ERB2 (**b**), ERB3 (**c**), and ERB4 (**d**). See text for specifications.



The first ERB (referred to as ERB1) consists of a 9-cm-long latex balloon fixed on a 33-cm flexible shaft of polyvinylchloride (Medrad, Pittsburgh, PA). It was originally designed as an endorectal coil in magnetic resonance imaging (MRI) and the balloon has a concave shape for optimal conformation to the prostatic-rectal interface. In prostate RT 60, 80, and 100 cc of inflated air have been reported [24,30,31], resulting in balloon diameters of 4.0-4.5 cm. The second ERB (ERB2) is a 5-cm-long silkolatex balloon, fixed on a 30-cm-long two-way rectal tube, made of soft rubber with a

silkolatex coating, used for barium enema procedures (Nordmann, Rüsch AG, Kernen, Germany). Balloon diameters with 40 cc and 60 cc of air are 3.7 and 4.3 cm, respectively [26]. The third balloon (ERB3) consists of a 15-cm-long rigid shaft with a non-latex retention cuff (4.5-cm-long) fixed on it (EZ-EM, Westbury, NY). Air volumes of 60 and 100 cc [22,32] create balloon diameters of 5.5-6.0 cm.

In a direct comparison of these three balloons [24] patients preferred ERB2; inflation of ERB3 was painful in 25%, because of the largest ERB diameter. Technologists preferred the ERB1, as it was easiest to handle and to insert. Insertion of ERB3 was more difficult, because of the rigid, short shaft. Recently, a RT-specific ERB was reported on (ERB4), consisting of a 20-cm-long flexible shaft of polyvinylchloride with a 3-cm-long silicon balloon (QLrad B.V., Dalfsen, The Netherlands) [33]. It is not open-ended and equipped with a stopper and depth markers; inflated with 80 cc of air its diameter is 6.0 cm.

In addition to different ERB types, both prone [18] and supine [24] treatment positions have been reported.

Prostate motion and target localization

The role of ERBs as prostate immobilizers, to reduce interfraction and intrafraction variations in prostate position and thus CTV-to-PTV margins, has been investigated. D'Amico *et al.* evaluated intrafraction prostate motion by obtaining CT-images at 1-min time intervals, both with and without an air-filled (60 cc) ERB1 in place [14]. They concluded that gland immobilization is possible with ERBs, as the balloon reduced the maximum prostate displacement in any direction from 4 mm to ≤1 mm. A reduction in interfraction motion was observed with an air-filled (40 cc) ERB2 in repeated CT-examinations: maximum displacement in the AP direction of >5 mm occurred in 2/10 patients, compared to 8/10 patients without ERB [15]. With a 100 cc air-filled ERB3, only small interfraction displacements were observed. The largest mean (1 SD) displacement was in the SI direction: 0.92 mm (1.78) [17,20]. Additionally, no organ displacement was seen during normal breathing with an ERB inserted. Given this limited prostate motion, smaller CTV-to-PTV margins were advised when using an ERB.

However, not all reports were able to confirm these immobilizing features. No differences in systematic and random prostate deviations were found between patients with and without an 80 cc air-filled ERB1 using fiducial marker-based daily portal imaging [12]. The largest interfraction variation was in the AP direction (4.7 mm, 1 SD), which was attributed to the presence of stool and gas between the ERB and Rwall. In addition, off-line corrections reduced the systematic prostate displacements equally in both groups. Based on these findings, it was concluded that ERB application does not effectively reduce interfraction prostate motion and the use of positioning

correction protocols was advocated. A similar recommendation was made for dose-escalation with a 60 cc air-filled ERB2 [34].

Drawing definite conclusions on the immobilizing properties of ERBs is difficult, because of (a) different imaging techniques for positioning verification, (b) differences in imaging frequency, (c) non-uniformity in scoring of variations (*e.g.* maximum displacements, SDs), (d) variation in patient position, and (e) different ERBs and inflated volumes. Therefore, in accordance with the abovementioned suggestions, we recommend that, when using ERBs, position verification and correction protocols continue to be used to prevent large day-to-day variations.

As the ERB is situated directly adjacent to the anterior Rwall and can be well visualized by portal imaging [14,15], it can assist in localizing the prostate and thus reduce CTV-to-PTV margins. A posterior field margin of 1 mm behind the anterior ERB surface has been suggested when online portal imaging is used, as the anterior Rwall could be defined with an accuracy of 1-2 mm, which was equal to the maximum AP prostate displacement. [14]. Others confirmed this improved set-up due to ERBs, although they advised more conservative posterior PTV margins: 10 mm in 3D-CRT and 4 mm in IMRT [21,35].

Dosimetric consequences

As numerous reports have described dose-volume and dose-surface relationships of anorectal toxicity [36], several groups have investigated the dosimetric effect of ERBs in an attempt to reduce toxicity.

3D-CRT and IMRT

A 40 cc air-filled ERB2 significantly reduced Rwall doses in 4-field 3D-CRT [15,21], especially high-dose exposure to the posterior Rwall. This phenomenon was attributed to an increased distance between the prostate and the posterior Rwall. However, with seminal vesicles (SVs) included in the target volume, only inflation with 60 cc led to significant reductions of intermediate and high Rwall doses [26], without significantly altering the bladder dose [27]. Based on these findings, inflation with 60 cc of air was recommended. A 60 cc air-filled ERB3 reduced Rwall volumes exposed to >60 Gy in six-field 3D-CRT, irrespective of SV inclusion in the CTV [22]. Rwall sparing with ERB1 (60 cc) in four-field 3D-CRT proved to be best when the ERB was applied during all 40 treatment sessions, compared to 0 and 15 fractions [23]. However, it should be noted that in this study fairly wide PTV margins of 15 mm were used for treatment without ERB, compared to 5 mm with ERB.

Van Lin *et al.* directly compared ERB1 (80 cc), ERB2 (40 cc), ERB3 (100 cc) and no ERB in four-field 3D-CRT plans [24]. Significant reductions in normal tissue complication probability (NTCP), Rwall mean dose and Rwall volumes exposed to ≥50 Gy and ≥70 Gy (V_{50} and V_{70}, respectively) were seen with all ERBs, both with and without SV inclusion in the CTV. Large volume ERBs (ERB1 and ERB3) were the most advantageous. Additional analysis of spatial dose distribution over the inner Rwall mucosa using dose-surface maps (DSMs) showed an ERB-induced reduction of relative surface exposed to intermediate and high doses.

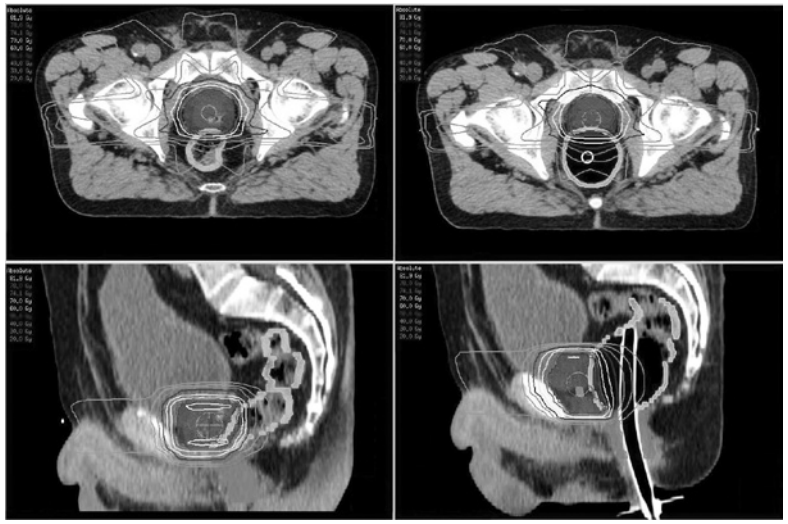
Although scarce, some reports have described the dosimetric effect of ERBs in IMRT. In the previously mentioned study by Patel *et al.* ERB3 reduced absolute Rwall V_{60}, V_{65}, and V_{70} in IMRT as well [22]. Interestingly, Rwall doses in 3D-CRT with ERB were the same as in IMRT without ERB. IMRT combined with ERB increased Rwall sparing even more. Despite some differences in V_{50} and V_{70} , Van Lin *et al.* observed no significant reductions in NTCP or Rwall mean dose by any of the ERBs in IMRT [24]. However, relative Rwall surfaces exposed to intermediate and high doses were significantly reduced. In another study, IMRT with ERB3 (100 cc) was superior in normal tissue sparing, especially the rectum and femoral heads, as compared to six-field 3D-CRT with ERB3 [28].

In conclusion, in photon therapy ERBs have a Rwall sparing effect for the intermediate- and high-dose regions. As both dose-levels are predictive factors for late rectal bleeding [36,37], ERBs may consequently reduce late toxicity. Even in highly conformal IMRT, ERBs appear to add extra sparing. With SV inclusion in the CTV, larger volume ERBs seem most beneficial. Similar to Rwall sparing, a recent study demonstrated that an 80 cc air-filled ERB4 also significantly reduces anal wall (Awall) doses in both 3D-CRT and IMRT, with a reduction in Awall mean dose of 12 Gy in 3D-CRT and 7.5 Gy in IMRT [33]. Comparable to the Rwall, this effect was attributed to Awall displacement. Fig. 2 shows an IMRT planning with and without a modified air-filled ERB4 (100 cc).

Introduction of an air cavity, influencing the dose distribution, may also contribute to Rwall dose reduction. Due to electronic disequilibrium in air cavities, perturbation of the dose near the air-tissue interface occurs, which leads to lower doses in the tissues adjacent to the air cavity. Monte Carlo calculations of parallel-opposed photon beams have shown dose reductions up to 21% at the air-rectum interface [38]. Reductions at 1 and 2 mm depth were 15% [39] and 11%, respectively [38].

In similar simulations using multiple-beam IMRT, a 15% dose reduction at the air-tissue interface was observed [19,32]. At distance from the cavity the dose built up rapidly, with 8% and 5% lower doses at 1 mm and 2 mm, respectively. The posterior part of

Fig. 2 Transverse (top) and sagittal (bottom) dose distribution of IMRT plans without (left) and with ERB (right) in place (prescribed dose 78 Gy). Contours: rectal wall (green), anal wall (purple) and PTV (blue). Color figure at p 161.



the prostate, located 6 mm from the air-tissue interface, received the same dose, compared to the phantom without air cavity. These results suggest that ERBs have an anterior Rwall sparing effect without underdosing the prostate. Although not showing Rwall sparing, another study confirmed that an air-filled ERB did not underdose the prostate, compared to a water-filled ERB [35].

Proton therapy

In proton therapy water-filled ERBs are used, in order to optimize the proton dose distribution. Vargas *et al.* compared plans with a 100 cc saline-filled ERB1 and 100 cc saline placed directly in the rectum, prescribing a total dose of 78-82 Gray equivalents [31]. For the whole rectal volume the ERB significantly reduced V_{10} -V_{65}, whereas for the Rwall improved V_{10} -V_{50} were observed. For the Rwall volume at the PTV level, V_{10} -V_{30} were significantly reduced. With SV inclusion in the CTV, the ERB led to no significant improvement. The authors concluded that Rwall doses were low for both ERB and water alone and that the latter is an alternative for most patients. However, in selected cases application of an ERB led to significant, though small improvements in rectal dose.

Anorectal toxicity

Although many planning studies have shown a beneficial effect of ERBs and several reports have mentioned toxicity rates after treatment with ERBs, only one comparative clinical study has been published so far. Van Lin *et al.* compared 24 patients with and 24 patients without ERB1, treated with four-field 3D-CRT to a total dose of 67.5 Gy, by repeated rectosigmoidoscopies [25]. Patients treated with ERB showed significantly less late rectal toxicity, with no grade 2 or grade 3 toxicity. Grade 3 rectal bleeding was experienced by 1 patient in the no-ERB group. Grades 1-3 late rectal bleeding was experienced by 33% and 13% in the group without and with ERB, respectively. However, given the small group sizes, this difference did not reach statistical significance. During follow-up, high-grade Rwall telangiectases, indicating severe late mucosal damage, were significantly less frequently observed in the group with ERB. DSM analysis showed that in the ERB group a significantly higher proportion of the mucosa was exposed to doses <40 Gy, while less mucosa received higher doses, compared to the group without ERB. Interestingly, in mucosal areas exposed to >40 Gy at the anterior Rwall less high-grade telangiectases were observed in the ERB group, which was attributed to either a physical property of the ERB (*i.e.* dose build-up), or a radiobiological phenomenon (*i.e.* stretching of the Rwall, leading to hypoxia and therefore radioresistance).

Endoscopy was also performed by Goldner *et al.* in 166 of 486 patients, treated with 3D-CRT and ERB in a prospective multicenter dose-escalation study, showing an overall 2-year rate of telangiectases of 57%, 40% congested mucosa and 2 patients having grade 1 ulceration [40]. At 40 months, the actuarial EORTC/RTOG late rectal grade ≥2 toxicity rate was 36%. Recently, 5-year results of the trial have been published, showing an actuarial late rectal grade ≥2 toxicity rate of 29% for all patients with no difference between the two dose-levels [41].

Woel *et al.* described acute toxicity in patients treated with four-field 3D-CRT (total dose 75.6 Gy), using ERB1 during the first 15 fractions [42]. At the end of the treatment course a significant increase in hemorrhoidal irritation and anal skin reaction was observed. At 3 months after treatment, all investigated symptoms had returned to baseline values with standard interventions. One year later, the primary endpoint of this study was presented, being late rectal bleeding grade 3, which was estimated to be 10% after 2 years. All patients with rectal bleeding used anti-coagulants, whereas none of the non-bleeders did [43].

The Baylor College of Medicine/Methodist Hospital group has been using ERBs in prostate IMRT since 1998. Acute side effects in 100 patients, treated to a prescribed dose of 76 Gy were low with 11% and 6% grades 1 and 2 gastrointestinal (GI) toxicity,

respectively, and grades 1 and 2 GU toxicity occurring in 38% and 35%, respectively [18]. After a median follow-up of 31.3 months rectal toxicity grades 1, 2, and 3 were seen in 10.3%, 6.9%, and 1.7%, respectively [32].

Toxicity rates in 1255 patients treated with conformal proton therapy (with or without photon therapy) and a 120 cc water-filled ERB were low: acute grade ≥3 GI toxicity was seen in <1%, whereas late grades 3 and 4 GI toxicity occurred in 1% and 0.2%, respectively, presenting within 2.5 years after treatment. Late GU toxicity, mainly urethral strictures, was reported in 14 patients [44].

Reports on ERBs in post-prostatectomy radiotherapy are scarce. However, minimization of CTV motion, target volume consistency and reproducibility have been arguments to use ERBs in post-operative RT as well. Irradiated to a median dose of 64 Gy, the acute toxicity profile was acceptable: 82.5% grades 0-1 and 17.5% grade 2 GU toxicity [45].
In conclusion, although potentially leading to increased acute anal irritation, ERB application may reduce late Rwall damage, and subsequently lower late toxicity rates. However, clinical data are scarce, making it hard to draw definite conclusions on this topic. More comparative, clinical studies are needed on the use of ERBs, especially combined with modern treatment techniques, such as IMRT.

Patient's tolerance
In a direct comparison 5/20 patients experienced a painful inflation of ERB3 [24]. This was reported to disappear after approximately 1 min, although no formal scoring was performed. Many investigators report a good ERB tolerability [12,15,20,22,42], although three studies specifically addressed this issue.

A prospective multicenter trial showed that a 40 cc air-filled ERB2 did not cause major complaints in 79% of patients receiving 3D-CRT. Twenty-one percent experienced signs of blood and/or pain and in 4% treatment with ERB had to be stopped [46]. Balloon discomfort was significantly correlated to acute RT-related rectal side effects. Patients with pre-existing hemorrhoids did not have an increased risk of complaints, whereas in another study this was considered a contra-indication for the use of ERBs, as ERB1 application led to grade 3 anal irritation in a patient with hemorrhoids [12]. Tolerance in a study employing IMRT was even better, with none of 396 investigated patients stopping the treatment with a 100 cc air-filled ERB3 [47]. Only 0.8% required volume reduction to 50 cc and 4.3% required local anesthetic gel facilitating the insertion. Patients with pre-existing anorectal disease had a higher risk of developing acute anorectal toxicity. Equally good results were found in a group of 3561 patients, treated with conformal proton therapy with 120 cc water-filled ERBs [48]. An overall tolerance rate of 97.6% was seen with only 2.4% of the patients receiving 1 or more fractions without ERB.

These studies indicate that application of ERBs is safe and well-tolerated, although care must be taken in patients with pre-existing anorectal disease.

Caveats
Some reports specifically address potential disadvantages or caveats in ERB application. The reproducibility of daily ERB insertion has been questioned. Court *et al.* observed a mean intrafraction shift of the anterior ERB wall of 1.8 mm (maximum 7.2 mm), mainly in the posterior direction [30], which was attributed to patient relaxation after insertion. It was suggested that this could be reduced by a waiting period between insertion and irradiation. In addition, an interfraction change in the angle of the balloon of 2.5-5.7° was observed. Wang *et al.* reported random errors in balloon positioning of up to 4.5 mm and maximum variations in balloon diameter of 2.8 mm, which were not correlated [49]. The variation in isocenter position was considered acceptable with ERB. Both groups advised frequent use of image-guidance to reduce set-up errors. In contrast, others called balloon placement "highly reproducible", with the largest variability in the SI direction (mean SD 3.1 mm) [22]. As mentioned previously, not all studies are conclusive about ERBs reducing prostate motion. Added to these data, it can be concluded that position verification strategies are necessary when using ERBs.

Another caveat is the finding that application of a 50 ml fluid-filled Medrad endorectal coil, identical to the one used in prostate RT, significantly changed prostate shape and volume in prostate MRI, with reductions in prostate diameter and volume up to 15.7% and 18%, respectively [50]. Apart from its influence on RT planning, in combination with balloon displacement and deformation this may lead to an extra set-up uncertainty. Three-dimensional image-guidance (*e.g.* cone-beam CT), may be useful to investigate this phenomenon.

Although phantom studies did not show a disadvantageous effect of ERBs on the dose distribution in the target volume, two reports have mentioned possible underdosage due to set-up variations. Ahmad *et al.* compared IMRT plans with ERB3 in place with two plans with a set-up error of ±5 mm [51]. Despite minimal impact on the mean doses to the prostate and SV, coverage of the latter significantly changed, increasing the volume exposed to <70 Gy from 0.53% to 6.26%, while for the prostate this increase was minimal. They concluded that set-up deviations of 5 mm had minimal impact on doses to the tumor and normal tissues, and that clinical research must determine the clinical impact of SV dose inhomogeneity. The same group investigated plans with ERBs in both the most superior and inferior positions, and without ERB, simulating ERB repositioning inaccuracies and failure to inflate, respectively [52]. Again, SV doses significantly decreased by ERB repositioning,

without affecting the normal tissue doses. ERB failure led to a significant dose reduction to both the prostate and SV and decreased the mean dose to the upper rectum, which was attributed to posterior displacement of these organs. Portal imaging was suggested to visualize these failures. Given the underdosage after failure of placement or inflation, it can be concluded that when ERB application cannot be continued, *e.g.* because of complaints, new treatment planning is necessary.

Air-filled ERBs introduce a significant density heterogeneity into the treatment volume. Song *et al.* evaluated how a conventional treatment planning system handles this heterogeneity by comparing its dose calculations with those of a Monte Carlo simulation, using a four-field box technique [53]. They observed consistent and predictable differences between the calculation methods, with a reduction in the high-dose regions and a widening of the low-dose regions in the Monte Carlo calculations. In addition, a potential underdosage of 3.4% mean dose near the peripheral zone of the prostate was found for the posterior beam. One might argue, however, that even without an ERB variable amounts of gas can be present in the rectum over a treatment course. By applying an ERB this amount can be held constant and accounted for in treatment planning.

Workload and clinical practice

Published data on the workload of ERB application show an additional 2-3 min set-up time needed per treatment session [12,22]. In our institution (Radboud University Nijmegen Medical Centre), a physician inserts the first ERB at the CT-scanner to ensure a proper position and checks patient's acceptance. To maintain this position, the ERB is gently pulled towards the anal canal and the stopper is adjusted to minimize ERB movement. The technologists insert the ERB before every treatment fraction. For hygienic reasons, disposable ERBs are used.

Conclusions and future perspectives

Several planning studies have shown dosimetric advantages with ERB application, although comparative clinical studies, preferably using IMRT, are essential before drawing definite conclusions. Other potential benefits of ERBs may be improved target localization and reduced prostate motion. However, as there is no consensus about these topics, further investigation is warranted. Until then, additional set-up and correction protocols, and image-guidance are recommended, especially because there are potential pitfalls. Overall, ERBs are well-tolerated, although they should be omitted in patients with pre-existing anorectal disease.

Modern techniques for position verification could be useful in further clinical research on ERB application. For example, cone-beam CT can visualize interfraction variation of both ERB position and shape, and its influence on the CTV and surrounding pelvic anatomy, as well as changes in SV position. Electromagnetic tracking can be used to get real-time information on intrafraction prostate variability when using ERBs [54]. It could be very interesting to use these techniques for direct comparison of situations with and without ERB. Additional factors to investigate could be strategies to reduce gas and stool (*e.g.* medication, gas release before ERB insertion) and to cope with relaxation after ERB insertion, for example, to wait some minutes before starting the treatment [16,30].

Finally, ERBs themselves could be further modified. Customized balloons could lead to optimal conformation to individual anatomic variations. In the future, ERBs could be applied in the treatment of other pelvic tumors, *e.g.* gynecological malignancies [55]. These are topics for future research.

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3

Anal Wall Sparing Effect of an Endorectal Balloon in 3D Conformal and Intensity-Modulated Prostate Radiotherapy

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Abstract

Background and purpose: To investigate the anal wall (Awall) sparing effect of an endorectal balloon (ERB) in 3D conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) for prostate cancer.

Materials and methods: In 24 patients with localized prostate carcinoma, two planning CT-scans were performed: with and without ERB. A prostate planning target volume (PTV) was defined, and the Awall was delineated, using two different methods. Three-field and 4-field 3D-CRT plans, and IMRT plans were generated with a prescription dose of 78 Gy. In 144 treatment plans, the minimum dose (D_{min}), maximum dose (D_{max}), and mean dose (D_{mean}) to the Awall were calculated, as well as the Awall volumes exposed to doses ranging from ≥20 Gy to ≥70 Gy (V_{20} -V_{70}, respectively).

Results: In the 3D-CRT plans, an ERB significantly reduced D_{mean}, D_{max}, and V_{30} -V_{70}. For IMRT all investigated dose parameters were significantly reduced by the ERB. The absolute reduction of D_{mean} was 12 Gy in 3D-CRT and was 7.5 Gy in IMRT for both methods of Awall delineation.

Conclusions: Application of an ERB showed a significant Awall sparing effect in both 3D-CRT and IMRT. This may lead to reduced late anal toxicity in prostate radiotherapy.

Introduction

Dose escalation leads to improved treatment outcomes in prostate radiotherapy, especially for intermediate- and high-risk patients [1-3]. However, the major dose-limiting factor is anorectal toxicity, resulting in both acute and late adverse effects. Bowel symptoms have a greater impact on quality of life than urinary and sexual symptoms [4]. In addition, patients appeared to be most bothered by complaints such as soiling, fecal loss and urgency rather than by symptoms of proctitis, such as mucus discharge and bleeding [5]. In a large prospective trial the fecal incontinence rate was 17% at 4 years after a dose of 78 Gy [6].

Several reports have described the relationship between dose-volume parameters to the anal canal and fecal incontinence [6-10]. A statistically significant correlation was shown between radiation doses to the anal-sphincter region and the risk of fecal leakage in the dose range of 45-55 Gy [9]. Recently Peeters *et al.* have found a dose-volume effect for anal incontinence by separately delineating the contour of the anal wall (Awall) from the rectal wall (Rwall) [6]. These results suggest that reducing the dose to the Awall may result in reduction of the incidence of radiation-induced anal toxicity.

Nowadays, 3D conformal radiotherapy (3D-CRT) and especially intensity-modulated radiotherapy (IMRT) offer the possibility to selectively spare surrounding normal tissues. Daily inserted endorectal balloons (ERBs) have been used to reduce rectal toxicity [11-14] and have been shown to have a significant Rwall sparing effect in both 3D-CRT and IMRT [14].

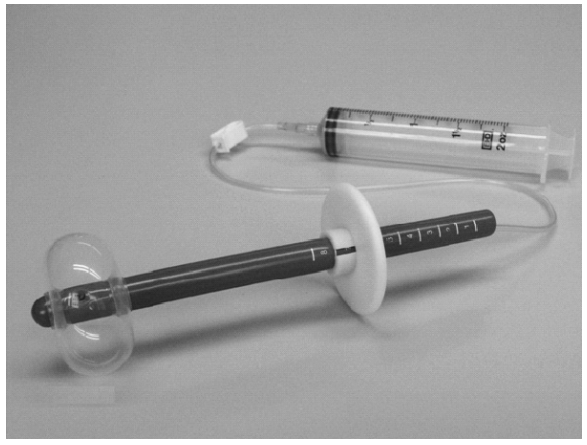
The purpose of this planning study was to investigate the Awall sparing effect of an ERB for both 3-field 3D-CRT and 4-field 3D-CRT and IMRT, by comparing treatment plans with and without ERB, in localized prostate cancer patients.

Materials and methods

Twenty-four patients with localized adenocarcinoma of the prostate were included in this study after informed consent was given. Besides apparent preexisting anal irritation or hemorrhoids, no exclusion criteria were applied. Before CT-scanning, patients used a laxative suppository (bisacodyl 5 mg) and were advised to use a light breakfast. Additionally they were instructed to drink 500 mL of water for bladder filling.

The ERB (Fig. 1) consists of a 20-cm-long flexible shaft of polyvinylchloride with a silicon balloon (Hospimed International B.V., Dalfsen, The Netherlands). Deflated, the ERB has a diameter of 13 mm. After inflation with 80 cc of air, the diameter is 60 mm and the length is 30 mm. Within 20 min, two planning CT-scans (one without and one with an 80-cc inflated ERB) per patient were obtained in a supine position at 3-mm slice thickness (AcQsim spiral CT, Philips Medical Systems, Bothell, WA). All balloons were inserted by the same person (R.J.S.) and were gently pulled towards the anal sphincter to ensure a proper position in relation to the prostate. To maintain this position, the ERB was fixed, using a clamp, preventing it from sliding more cranially (Fig. 1).

Fig. 1 The inflated endorectal balloon (Hospimed International B.V.).

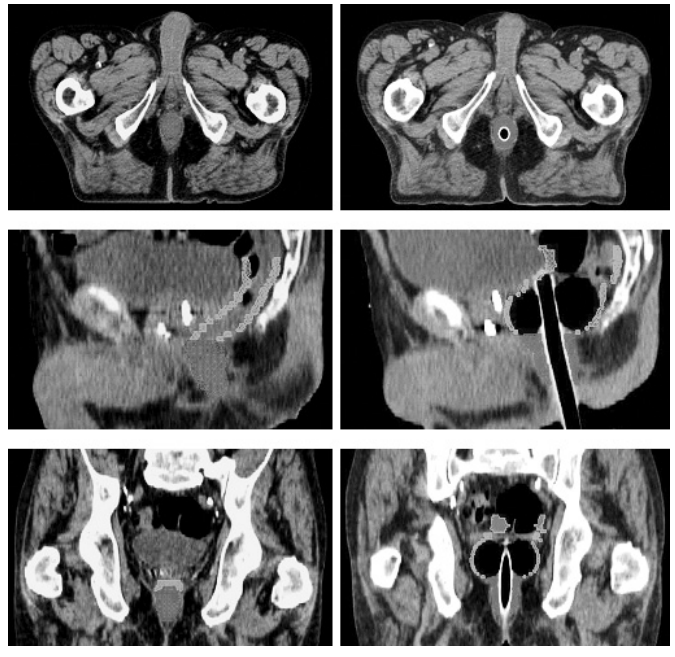


All CT images were imported into the Pinnacle^3 treatment planning system (Philips Medical Systems, Fitchburg, WI). The clinical target volume (CTV) was defined as the prostate and was outlined on each CT slice. Furthermore, the following structures were delineated: femoral heads, bladder and anorectal wall, the latter being subdivided into Rwall and Awall.

In the literature, different methods for Awall delineation have been described. In this study, two delineation methods were used. The first method was derived from Vordermark *et al.* [7], using the rectal lumen as the cranial boundary for the anal canal. First, a distinction between Rwall and Awall was made on the CT images with ERB. The Awall was outlined extending from the anal verge to the slice below the lowest

slice with a visible ERB lumen and was defined as the difference between the outer contour and inner contour of the anal canal, the latter being delineated around the ERB shaft. On the CT images without ERB the outer contour was delineated starting at the anal verge, using the same length as was obtained from the images with ERB. As the anal canal is actively closed by the internal and external anal sphincters and no anal lumen was seen on the CT slices without ERB, no inner anal canal contour was delineated separately. Therefore, the Awall on these images was defined as the total volume within the outer anal canal contour. The delineation of the Awall derived by this method is referred to as $Awall_{methA}$ (Fig. 2). The second method used to contour the Awall, was performed by considering the anal canal as the distal 3 cm of the anorectum [6, 9, 16]. Based on this definition, for each patient a second Awall contour was defined, consisting of the caudal 3 cm of the anorectum starting at the anal verge, referred to as $Awall_{methB}$.

Fig. 2 Transversal (top), sagittal (middle) and frontal (bottom) view of delineated Rwall (green) and Awall (purple) for CT-scans without ERB (left column) and with ERB in place (right column). Color figure at p 162.



To obtain the planning target volume (PTV) a 3D CTV-to-PTV margin of 7 mm was used [14]. A total dose of 78 Gy in 2 Gy-fractions was prescribed to the ICRU reference point in 3D-CRT and to the PTV in IMRT. Three-field 3D-CRT, 4-field 3D-CRT [15] and IMRT treatment plans were generated in all patients and for both CT-scans with and without ERB, resulting in a total of 144 plans.

In the 3-field technique three coplanar photon beams of 18 MV were used (anterior, left-lateral and right-lateral). The 4-field technique was planned with four coplanar 18 MV photon beams (anterior, posterior, left-lateral and right-lateral). In both 3D-CRT plans a higher weight was given to the lateral beams than to the anterior and posterior beams with a restriction of 50 Gy to the femoral heads [15]. A multileaf collimator was used to individually spare the bladder and rectum.

Inverse planned step-and-shoot IMRT plans were generated, consisting of five coplanar, non-opposing 10 MV photon beams (0°, 50°, 95°, 265°, and 310°) with a maximum of 60 segments. Table 1 shows the objectives for the inverse planning. A maximum dose of 30 Gy was tolerated outside the delineated structures.

Table 1 IMRT treatment planning objectives and weight factors.

ROI	Type	Target dose (Gy)	Volume (%)	Weight
Bladder	Max DVH	50	15	2
Bladder	Max DVH	68	2	3
Left femur	Max Dose	40		1
Right femur	Max Dose	40		1
Rwall	Max DVH	32	8	10
Rwall	Max DVH	40	5	10
Rwall	Max DVH	55	4	1
Rwall	Max Dose	70		10
Awall	Max DVH	20	20	1
Awall	Max DVH	30	13	1
Awall	Max DVH	40	8	1
Awall	Max DVH	50	4	1
Awall	Max Dose	60		10
PTV	Max Dose	79.5		80
PTV	Uniform Dose	78		80
PTV	Min Dose	77		

Abbreviations: ROI: region of interest; Rwall: rectal wall; Awall: anal wall; PTV: planning target volume; Max/Min Dose: maximum/minimum allowable dose; DVH: dose volume histogram.

In all treatment plans doses to the PTV, urinary bladder, femoral heads and rectum were calculated, as well as several dose parameters to the Awall: minimum, maximum and mean dose (D_{min}, D_{max}, and D_{mean}, respectively) and Awall volumes (%) exposed to ≥20 Gy (V_{20}), ≥30 Gy (V_{30}), ≥40 Gy (V_{40}), ≥50Gy (V_{50}), ≥60 Gy (V_{60}), and ≥70 Gy (V_{70}).

The mean Awall V_{20} -V_{70} of the total population were plotted for each planning technique to create a mean dose-volume histogram (DVH).

The SPSS 14.0 software for Windows (© SPSS Inc., 1989-2005) was used for statistical calculations. The Wilcoxon signed rank test was used for paired comparison of the measured parameters in the same subjects with and without ERB. Differences with a two-tailed *p*-value < 0.05 were considered significant.

Results

The mean prostate volumes (±1 SD) with and without ERB were 41.70 (±19.42) cc and 42.68 (±21.22) cc, respectively, and did not differ significantly ($p = 0.475$). The length of the $Awall_{methA}$ ranged from 2.1 to 3.6 cm with a median length of 3.0 (±0.44) cm. The mean $Awall_{methA}$ volumes were 14.60 (±3.21) cc with ERB and 13.96 (±3.12) cc without ERB ($p = 0.407$); the $Awall_{methB}$ volumes were 15.07 (±3.09) cc and 14.03 (±2.91) cc, respectively, and were also not significantly different ($p = 0.265$).

In five randomly chosen patients the Awall was delineated thrice by two independent observers (R.J.S. and E.v.L.). No large variations were found: the interobserver and intraobserver co-efficients of variation (± 1 SD) were 2.8 ± 0.9% and 1.9 ± 1.2% in the plans without ERB and were 4.1 ± 1.1% and 4.0 ± 2.0% in the plans with ERB, respectively.

The dose to the PTV was equal in all plans without ERB and with ERB, with mean doses (±1 SD) of 77.1 (±0.4) and 76.8 (±0.3) Gy in the 3-field technique, 76.9 (±0.3) and 76.2 (±0.4) Gy in the 4-field technique, and 78.4 (±0.2) and 78.2 (±0.2) Gy in IMRT, respectively. The ERB did not significantly alter the doses to other organs at risk: Rwall D_{mean} (±1 SD) without and with ERB were 31.8 (±6.2) and 31.6 (±6.6) Gy in 3-field 3D-CRT, 33.7 (±6.3) and 32.9 (±7.1) Gy in 4-field 3D-CRT, and 26.6 (±4.7) and 26.9 (±5.0) Gy in IMRT, respectively. Bladder D_{mean} were 25.4 (±14.1) and 21.9 (±13.0) Gy, 25.1 (±13.7) and 22.7 (±13.9) Gy, and 20.8 (±11.3) and 18.1 (±11.4) Gy, respectively. D_{max} to the femoral heads were equal in plans with and without ERB, and ranged from 47.3 (±2.8) Gy in IMRT to 51.9 (±0.6) Gy in 3-field 3D-CRT.

Table 2 Mean doses (± 1 SD) to the anal wall in 3-field and 4-field 3D-CRT.

3D-CRT	3-field						4-field					
	$Awall_{methA}$			$Awall_{methB}$			$Awall_{methA}$			$Awall_{methB}$		
	No ERB	ERB	*p*-value	No ERB	ERB	*p*-value	No ERB	ERB	*p*-value	No ERB	ERB	*p*-value
D_{mean} (Gy)	41.4 (± 10.9)	29.4 (± 12.6)	<0.001	41.1 (± 11.3)	29.2 (± 11.7)	<0.001	40.9 (± 11.0)	29.0 (± 13.0)	<0.001	40.5 (± 11.5)	28.8 (± 12.1)	<0.001
D_{min} (Gy)	6.4 (± 7.8)	5.1 (± 6.9)	0.13	6.4 (± 7.8)	5.1 (± 6.9)	0.13	5.3 (± 7.5)	4.2 (± 6.6)	0.23	5.7 (± 7.5)	4.2 (± 6.6)	0.076
D_{max} (Gy)	76.7 (± 2.5)	68.6 (± 14.5)	0.001	76.7 (± 2.6)	72.1 (± 8.6)	0.001	76.2 (± 2.9)	66.1 (± 14.3)	<0.001	76.2 (± 2.7)	69.5 (± 9.2)	<0.001

Abbreviations: $Awall_{methA}$: anal wall delineation, based on rectal lumen; $Awall_{methB}$: anal wall delineated as last 3 cm of the anorectum; D_{mean}: mean dose; D_{min}: minimum dose; D_{max}: maximum dose; ERB: endorectal balloon.

As displayed in Table 2, in 3-field 3D-CRT both Awall D_{mean} and D_{max} were significantly reduced by the ERB, lowering D_{mean} to the $Awall_{methA}$ by 12.0 Gy ($p < 0.001$) and D_{max} by 8.0 Gy ($p = 0.001$). These differences were also statistically significant for $Awall_{methB}$: D_{mean} and D_{max} were reduced by 11.9 Gy ($p < 0.001$) and 4.6 Gy ($p = 0.001$), respectively. D_{min} was not significantly different between the plans with and without ERB. With ERB mean parameters V_{30} -V_{70} to the $Awall_{methA}$ were significantly reduced with absolute reductions of 15-25% ($p < 0.001$; Fig. 4). For $Awall_{methB}$ a significant reduction in all volumes receiving 20-70 Gy was seen with ERB in place (data not shown).

The ERB significantly reduced D_{mean} and D_{max} to the $Awall_{methA}$ in the 4-field technique by 11.9 Gy ($p < 0.001$) and 10.1 Gy ($p < 0.001$), respectively (Table 2). D_{mean} and D_{max} to $Awall_{methB}$ were also significantly reduced by 11.7 Gy ($p < 0.001$) and 6.7 Gy ($p < 0.001$), respectively. The ERB did not alter Awall D_{min} significantly. Insertion of an ERB resulted in a significant reduction of V_{20} -V_{70} for both delineation methods of the Awall, with absolute reductions of 10-27% (p-value ranging from 0.03 to <0.001; Fig. 4).
In IMRT, all Awall dose parameters were significantly decreased in the plans with ERB (Table 3). $Awall_{methA}$ D_{mean} was reduced by 7.5 Gy ($p < 0.001$). D_{min} without ERB was 3.1 Gy, compared to 2.4 Gy with ERB ($p = 0.001$), whereas the balloon lowered D_{max} by 10.4 Gy ($p = 0.002$). All these differences remained statistically significant for the $Awall_{methB}$ delineation method. The ERB resulted in significant mean absolute reductions of V_{20} -V_{70} in both $Awall_{methA}$ and $Awall_{methB}$ (Table 3).

Table 3 Mean doses and dose-volume parameters (± 1 SD) to the anal wall in IMRT technique.

IMRT	$Awall_{methA}$			$Awall_{methB}$		
	No ERB	ERB	*p*-value	No ERB	ERB	*p*-value
D_{mean} (Gy)	27.5 (± 8.5)	20.0 (± 10.1)	< 0.001	27.2 (± 8.6)	19.7 (± 9.0)	< 0.001
D_{min} (Gy)	3.1 (± 1.5)	2.4 (± 1.4)	0.001	3.4 (± 1.6)	2.4 (± 1.4)	< 0.001
D_{max} (Gy)	79.4 (± 7.2)	69.0 (± 20.0)	0.002	78.9 (± 12.1)	71.2 (± 15.5)	0.001
V_{20} (%)	48 (± 16)	36 (± 21)	0.001	48 (± 16)	34 (± 19)	< 0.001
V_{30} (%)	36 (± 14)	22 (± 16)	< 0.001	35 (± 14)	21 (± 14)	< 0.001
V_{40} (%)	28 (± 12)	15 (± 13)	< 0.001	27 (± 13)	14 (± 11)	< 0.001
V_{50} (%)	22 (± 11)	11 (± 11)	< 0.001	21 (± 11)	10 (± 9)	< 0.001
V_{60} (%)	16 (± 9)	8 (± 8)	< 0.001	16 (± 9)	8 (± 7)	< 0.001
V_{70} (%)	10 (± 7)	5 (± 6)	< 0.001	10 (± 6)	4 (± 5)	0.001

Abbreviations: V_{20}-V_{70}: volumes (%) of the anal wall receiving 20-70 Gy; other as in Table 2.

In Fig. 3 the differences in dose distribution on the Awall between the six different treatment techniques, represented by iso-dose lines, for one patient, are displayed.

Fig. 4 shows a graph of the mean $Awall_{methA}$ V_{20} -V_{70} of all patients in the six different plans. In the plans without ERB, IMRT reduced all investigated parameters compared to 3D-CRT. Interestingly, when an ERB was applied in combination with 3D-CRT, no differences were seen in the high-dose regions compared to the IMRT plans without ERB. However, V_{20} and V_{30} were significantly higher in the 3D-CRT with ERB plans ($p < 0.003$), except for V_{30} in the 3-field technique with ERB ($p = 0.09$). When Awall D_{mean} were compared, no significant differences were seen between 3D-CRT *with* ERB (29.4 Gy and 29.0 Gy in the 3-field and 4-field techniques, respectively) and IMRT *without* ERB (27.5 Gy) (Tables 2 and 3).

Fig. 3 Differences in dose distribution on the anal wall (purple contour) between 6 different plans within 1 patient (3-field technique without ERB (**a**), 3-field technique with ERB (**b**), 4-field technique without ERB (**c**), 4-field technique with ERB (**d**), IMRT without ERB (**e**), and IMRT with ERB (**f**), respectively. Blue area: planning target volume; green contour: rectal wall). Color figure at p 163.

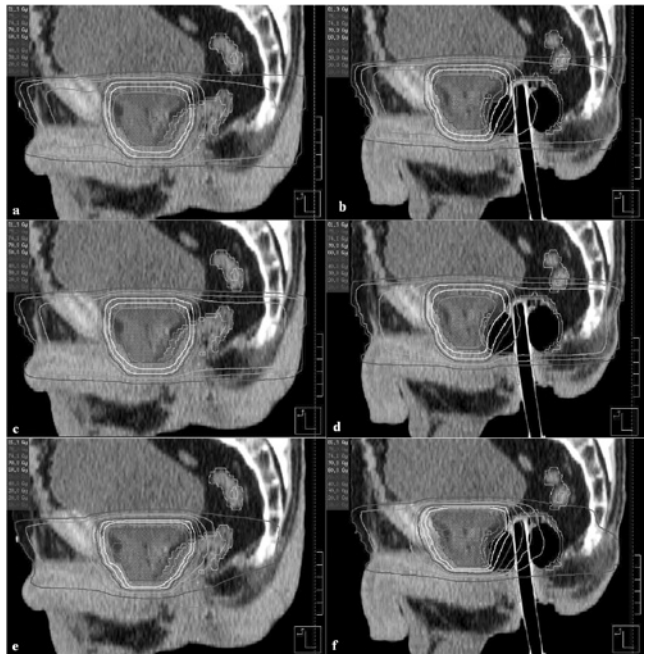
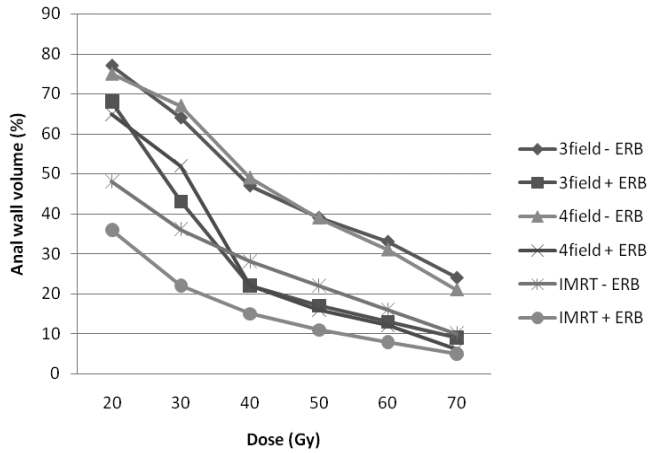


Fig. 4 Mean V20-V70 of the 6 different techniques.



Abbreviations: 3field: 3-field technique; 4field: 4-field technique; - ERB: without ERB; + ERB: with ERB.

IMRT with ERB resulted in the lowest dose parameters to the Awall with absolute D_{mean} reductions of 20 Gy compared to 3D-CRT without ERB, 9 Gy compared to 3D-CRT with ERB, and 7.5 Gy compared to IMRT without ERB, respectively.

The ERB was tolerated well by all patients. During inflation, all patients experienced a raise in local pressure on the rectum, which was described as a tendency to defecate and had disappeared within 15 s after inflation.

Discussion

This planning study has shown that application of an ERB in prostate radiotherapy significantly reduces doses to the Awall in both 3D-CRT and IMRT with an average reduction in D_{mean} of 7.5-12.0 Gy. This dose reduction can be explained by two properties of the ERB, as demonstrated in Fig. 3. First, the inflatable part of the balloon causes an anterior shift of the prostate, thereby increasing the distance between the PTV and the anal wall. Second, the shaft of the ERB pushes the posterior and lateral parts of the anal wall away from the high-dose regions.

According to the literature, there is no uniform way for Awall delineation. In the present study two different methods were used. The first method is based on a study by Vordermark *et al.* [7], although in their study no ERBs were applied. They found a median sphincter length of 4 cm, whereas in the present study this was 3 cm (range 2.1-3.6 cm). An explanation for this variation might be the fact that Vordermark *et al.* used a CT slice thickness of 1 cm at the anal canal, whereas in our study 3-mm slices were obtained. Furthermore, by application of an ERB the cranial Awall boundary might be easier to assess. As a result, the Awall length might be estimated more accurately. A median Awall length of 3 cm is in concordance with several previous studies, where the anal wall was defined as the lowest 3 cm of the anorectum [6, 9, 16]. However, these authors used this definition in all patients, irrespective of individual variations, whereas anal endosonography measurements have shown individual differences in length of the anal canal in a group of healthy volunteers [17].

The mean $Awall_{methA}$ volumes on the CT-scans with and without ERB were 13.7 and 14.6 cc, respectively. For $Awall_{methB}$ these volumes were 14.0 and 15.1 cc, respectively. Compared to those reported by Peeters *et al.* [6] these volumes are slightly larger, as they found a mean anal volume of 10 cm^3 by constructing an inner wall contour of the anorectum, using the model of Meijer *et al.* [18], which automatically constructs an inner wall from a delineated outer wall. However, as mentioned in their discussion they assumed that on every slice the wall volume is the same in the whole anorectum, which is debatable. al-Abany *et al.* on the other hand described a mean (±SD) anal-sphincter region volume of 22 (±4) cm^3, calculated as the total volume within the outer contour of the anal-sphincter region [9]. In the present study, the Awall was also considered to be a solid organ. When the scans with and without ERB were compared, no significant differences between the Awall volumes were found. This suggests a justification to delineate the anal wall as a solid organ. For both Awall delineation methods, application of an ERB led to significant dose reductions to the Awall.

Fecal incontinence is a serious problem after prostate radiotherapy, bothering a significant subpopulation of irradiated prostate cancer patients [5]. Its impact might be underestimated, especially when not actively asked for. Peeters *et al.* [6] analyzed 641 patients, who were divided into four groups, based on Awall D_{mean} (range) quartiles: 52 Gy (46-67), 41 Gy (38-46), 33 Gy (28-38) and 19 Gy (2-28). They observed a significant association between RTOG/EORTC gastrointestinal (GI) toxicity grade ≥2 and anal parameters in the low- and intermediate-dose regions as well as D_{mean}. Also, a significant correlation between the endpoint "incontinence requiring pads" and all investigated dosimetric parameters was found, except for D_{max}. When comparing the lowest and highest Awall D_{mean} groups, this resulted in an increased incidence of incontinence from 5% to 17%, while the 4-year cumulative incidence of GI toxicity

grade ≥2 almost doubled (16% vs. 31%). Compared to these data, results from the present study suggest that application of an ERB may decrease the incidence of both GI toxicity grade ≥2 and incontinence requiring pads. The highest Awall D_{mean} was found in the 3D-CRT plans without ERB (41 Gy), whereas in the IMRT plans with ERB this was reduced to 20 Gy. According to the data provided by Peeters *et al.* [6], this would imply a reduction in 4-year cumulative incidence of GI toxicity grade ≥2 from 29% to 16% and a reduction in incontinence requiring pads from 9% to 5%. As the present results are obtained from a planning study, the beneficial effect of an ERB needs to be confirmed in the clinical situation to evaluate and quantify the reduction in anal toxicity rates. The reduction of rectal toxicity by insertion of an endorectal balloon has been described previously [19].

Although the abovementioned studies show a dose-volume effect for fecal incontinence, the exact pathophysiology of radiation-induced anal toxicity is not clear. Petersen *et al.* [20] hypothesized that there are two categories of factors influencing incontinence: core factors and associated factors. The first category contains aspects of the anorectal organ itself, including changes in anal resting tone, squeezing pressure, and rectal volume or compliance, while the second category includes other disturbances of the lower digestive tract, such as diarrhea and proctitis. With respect to the first category, Yeoh *et al.* prospectively evaluated the effect of prostate radiotherapy on anorectal motor and sensory function, using anorectal manometry [21]. They concluded that at 2 years after radiotherapy there was a reduction of basal anal pressures and anal pressures in response to squeezing and increased intra-abdominal pressure. Also, there was a decrease in rectal compliance and rectal volumes associated with sensory perception and the desire to defecate. The fact that fecal incontinence is caused by a combination of anal and rectal factors is in concordance with a study done by Kushwaha *et al.* [22]. As a result, the Rwall and the Awall should be considered as separate critical normal tissues and both should be delineated and evaluated in treatment planning.

As insertion of an endorectal balloon increases the distance between the main part of the anorectal wall and the PTV, both the Awall and Rwall are spared. Recently, excellent long-term biochemical control rates have been reported in localized prostate cancer patients treated with hypofractionated IMRT utilizing a rectal balloon, indicating no disadvantageous effect of the ERB on tumour control [Teh BS, *et al.*, personal communication, 2008].

The fact that the DVH parameters for the high-dose regions and Awall D_{mean} in the 3D-CRT plans with ERB in place were comparable to those in the IMRT plans without ERB indicates that an ERB in 3D-CRT might lead to a comparable Awall dose exposure

as can be achieved with IMRT *without* ERB. Given the previously described low toxicity rates in prostate IMRT [23,24], this suggests that application of an endorectal balloon in 3D-CRT might lead to a comparable low incidence of anal toxicity. In our department, IMRT combined with ERB is now daily practice in prostate radiotherapy.

In conclusion, according to this planning study, application of an endorectal balloon is a patient friendly way to significantly reduce doses to the Awall in both prostate 3D-CRT and IMRT with the most beneficial effect for IMRT combined with an ERB. This dose reduction may lead to a decrease in fecal incontinence. However, clinical research is warranted to confirm the expected beneficial effect on anal toxicity. The anal canal should be considered as a separate and important critical normal organ, to be spared in prostate radiotherapy.

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4

Endorectal Balloon Reduces Anorectal Doses in Post-Prostatectomy Intensity-Modulated Radiotherapy

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Abstract

Background and purpose: To investigate the effect of an endorectal balloon (ERB) on anal wall (Awall) and rectal wall (Rwall) doses in high-dose post-prostatectomy intensity-modulated radiotherapy (IMRT).

Materials and Methods: For 20 patients, referred for salvage IMRT after prostatectomy for prostate cancer, two planning CT-scans were performed: one with and one without an air-filled ERB. A planning target volume (PTV) was defined, using international guidelines. Furthermore, the Awall and Rwall were delineated. On both scans, IMRT plans were generated with a prescribed dose of 70 Gy. The mean dose (D_{mean}), maximum dose, minimum dose and volumes exposed to doses ranging from ≥20 Gy to ≥70 Gy (V_{20}-V_{70}) to the Awall and Rwall were calculated. Finally, inner Rwall surface areas exposed to doses ranging from ≥20 Gy to ≥70 (A_{20}-A_{70}) were calculated. Dose-parameters were compared between plans with and without ERB.

Results: All Awall parameters, except V_{70}, were significantly reduced by the ERB with an overall D_{mean} reduction of 6 Gy. Absolute reductions in dose-volume parameters varied from 5% to 11%. Significantly reduced Rwall V_{30}, V_{40}, and A_{40} were observed with ERB, irrespective of the target volume size.

Conclusions: ERB application significantly reduces Awall and to a lesser degree Rwall doses in high-dose post-prostatectomy IMRT.

Introduction

Salvage radiotherapy (RT) is a curative treatment option for prostate cancer patients relapsing after radical prostatectomy. Recently, as in definitive prostate RT, a dose-response relationship has been established for this salvage treatment [1;2]. Increasing the dose from 60 Gy to 70 Gy led to an improved 5-year biochemical relapse-free survival from 25% to 58% [2]. However, an increase in dose inevitably leads to higher doses to surrounding normal tissues, especially to the rectum and anal canal.

In a cohort of more than 950 patients acceptable late anorectal toxicity rates have been reported after post-prostatectomy RT with a median dose of 64 Gy [3]. However, given the abovementioned advantage of dose-escalation up to a dose of 70 Gy, toxicity rates mentioned in previous reports may increase, as several authors have mentioned dose-effect relationships for anal and rectal toxicity [4-6].

One way of sparing surrounding normal tissues is the use of highly conformal intensity-modulated radiotherapy (IMRT). In addition, in definitive prostate RT endorectal balloons (ERBs) are applied to decrease doses to the rectal wall (Rwall) and anal wall (Awall) [7-10]. To our knowledge, the effect of an ERB on anorectal doses or toxicity in post-prostatectomy RT has not been investigated, although a single report has mentioned favourable genitourinary toxicity rates after postoperative IMRT with ERB [11].

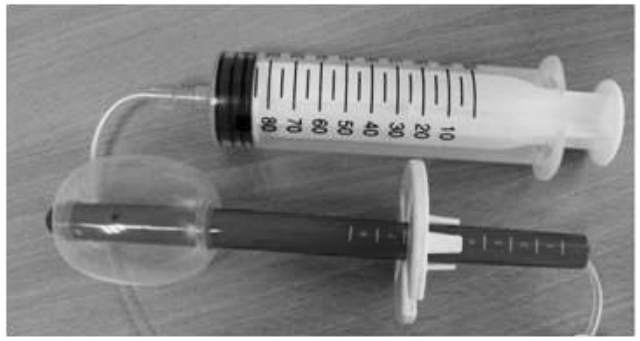
We performed a planning study to investigate whether application of an ERB has a beneficial effect on anorectal doses in post-prostatectomy IMRT, i.e. if its use can counteract the potential increase in toxicity, caused by a dose-escalation up to 70 Gy. Therefore, treatment plans with and without ERB were compared, applying international guidelines for delineation of the clinical target volume (CTV).

Materials and methods

Twenty consecutive patients, referred for salvage RT after prostatectomy, were included in this study, after informed consent was given. Two planning CT-scans per patient with 3 mm slice thickness were obtained in a supine position (Brilliance Big Bore CT, Philips Medical Systems, Bothell, WA, USA): one with ERB and one without ERB. No exclusion criteria were applied, except preexisting anorectal disease [12]. Before scanning, patients used a laxative suppository (bisacodyl 5 mg) and were advised to eat a light breakfast. Furthermore, they were instructed to drink 500 ml of water for bladder filling.

The ERB consists of a 20-cm-long flexible shaft of polyvinylchloride with a silicon balloon fixed on it (QLRAD B.V., Dalfsen, The Netherlands). The shaft diameter is 13 mm. Inflated with 100 cc of air, the diameter of the balloon is 6.0 cm and its length is 6.5 cm. After insertion and inflation, the ERB was gently pulled towards the anal canal. To maintain this position and to prevent a longitudinal shift, the ERB was fixed with an individually adjustable stopper (Fig. 1).

Fig. 1 The endorectal balloon. See text for specifications.



All CT-images were imported into the Pinnacle^3 treatment planning system, version 8.0h (Philips Medical Systems, Andover, MA, USA). The post-prostatectomy CTV was delineated according to international consensus guidelines [13;14]. First, the vesicourethral anastomosis was identified on both CT-scans. After that, the retropubic space was delineated from the superior edge of the symphysis pubis to 9-12 mm below the vesicourethral anastomosis, using the levator ani and obturator internus muscles (lateral) and anterior rectal wall (posterior) as anatomic boundaries. Above the superior edge of the symphysis pubis, the CTV was extended 3-4 cm cranially, including seminal vesicle remnants and up to the transected remnants of the vas deferens. Altogether, the cranial border did not extend more than 4 cm above the superior edge of the symphysis pubis. Anteriorly, 1-2 cm of the posterior bladder was included, posterior the CTV was bound by the mesorectal fascia. The sacrorectogenitopubic fascia or obturator internus muscle acted as lateral boundary at this level. The same boundaries were used on both scans. Fig. 2 shows an example of a CTV in a patient without and with ERB. According to our local protocol, a 9 mm isotropic margin from CTV to planning target volume (PTV) was applied.

Delineation of the Awall and Rwall has been described previously [7;15]. The Awall was considered a continuation of the Rwall and included the muscular structures forming the anal canal. On the scans with ERB, on each slice an outer anal wall contour was delineated from the anal verge up to the lowest slice with an ERB lumen. The inner anal wall contour was delineated around the ERB shaft. The difference between the outer and inner anal wall contour was defined as the Awall volume. On the scans without ERB, the same Awall length was applied as was obtained from the scans with ERB, starting at the anal verge. Furthermore, the same method was used, although the Awall volume was defined as the volume within the outer anal wall contour, as no inner anal wall contour could be identified, due to active closure of the anal canal. Recently, these delineation methods were shown to be reproducible and to lead to similar Awall volumes [7]. Next, outer rectal wall contours were delineated, followed by construction of inner rectal wall contours, using 5 mm wall thickness on slices without ERB and 3 mm on slices with ERB [15]. The inner rectal wall contours were subtracted from the outer rectal wall contours, thus creating the Rwall volume. The Rwall was delineated from the top of the Awall up to the rectosigmoid flexure. Finally, the urinary bladder and femoral heads were delineated, and the bladder volume was calculated.

On both the scans with and without ERB, step-and-shoot IMRT plans were generated with the inverse planning module Direct Machine Parameter Optimization, consisting of 5 coplanar, non-opposing 10 MV photon beams (0°, 50°, 95°, 265° and 310°) with a maximum of 60 segments. The prescribed dose to the PTV was 70 Gy in 2 Gy fractions [2], requiring >99% of the PTV to receive 95% of the prescribed dose.

In all treatment plans, doses to the PTV, urinary bladder and femoral heads were calculated, as well as the mean dose (D_{mean}), maximum dose (D_{max}) and minimum dose (D_{min}) to the Rwall and Awall. Also Rwall and Awall volumes (%) exposed to ≥20 Gy (V_{20}), ≥30 Gy (V_{30}), ≥40 Gy (V_{40}), ≥50 Gy (V_{50}), ≥60 Gy (V_{60}), and ≥70 Gy (V_{70}) were deducted from the treatment plans. Rectal wall dose-surface maps were generated for calculation and visualization of the spatial dose distribution to the rectal mucosa [16]. These maps were constructed by virtually "unfolding" the rectum and displaying the spatial dose distributions to the inner rectal wall (Fig. 3). To be able to compare these dose distributions between plans with and without ERB, the surface areas (%) exposed to ≥20 Gy (A_{20}), ≥30 Gy (A_{30}), ≥40 Gy (A_{40}), ≥50Gy (A_{50}), ≥60 Gy (A_{60}), and ≥70 Gy (A_{70}), were calculated in bins of 1 cm^2. All dose parameters were compared between the plans with and without ERB.

Fig. 2 Sagittal (**a**), transverse (**b**-**d**) and coronal (**e**-**g**) views of delineated CTV on CT-scans without endorectal balloon (left column) and with endorectal balloon (right column). Red contour: CTV; blue contour: PTV; green contour: rectal wall; purple contour: anal wall. Color figure at p 164.

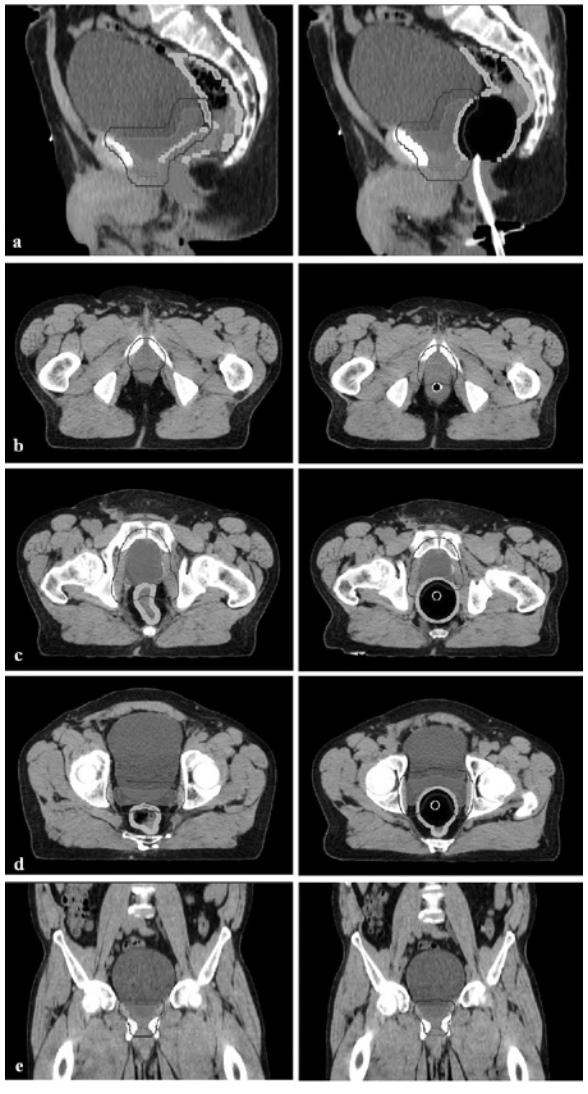


Fig. 2 Continued. Color figure at p 165.

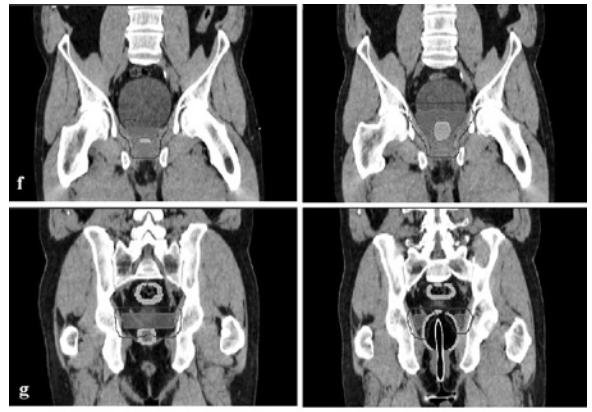
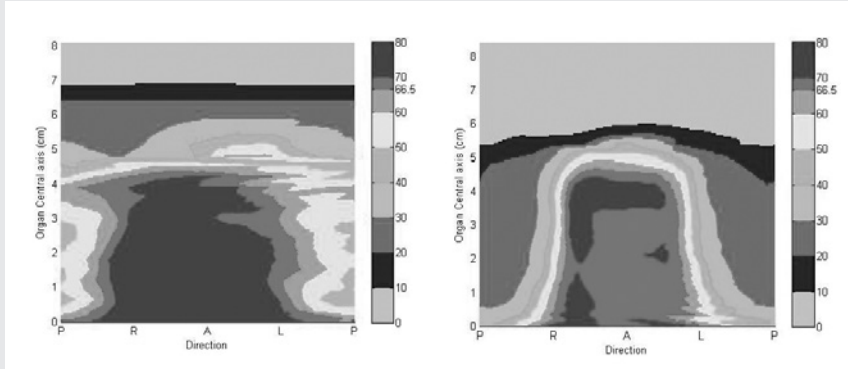


Fig. 3 Example of a relative rectal wall dose-surface map in a patient without endorectal balloon (left) and with endorectal balloon (right). Color figure at p 165.



For statistical calculations, the SPSS 16.0.2 software for Windows was used (SPSS Inc. 1989-2007). The Wilcoxon signed rank test was used for comparison of the measured parameters between the plans with and without ERB. Spearman's rho was calculated to investigate possible correlations between CTV volume and normal tissue doses, and to investigate whether the difference in dose, induced by an ERB, was correlated with the CTV volume. Differences with a p-value < 0.05 were considered statistically significant.

Results

The mean CTV volumes (± SD) without and with ERB were slightly different: 117 (± 27, range 83-203) cc and 110 (± 20, range 77-157) cc, respectively ($p = 0.02$).

Awall volumes with and without ERB were not significantly different (mean 13.8 cc and 14.2 cc, $p = 0.10$). However, significant differences in Rwall and bladder volumes were observed: mean Rwall volume without ERB was 36.5 (± 9.0) cc vs. 41.8 (± 6.2) cc with ERB ($p = 0.003$); bladder volumes were 343.5 (± 179.7) cc and 384.3 (± 179.8) cc, respectively ($p < 0.001$). PTV coverage was good in all plans, with >99% of the PTV receiving 95% of the prescribed dose. The median PTV dose was 70.6 Gy and 70.3 Gy for the plans with and without ERB, respectively. $D_{2\%}$ was 72.7 Gy and 73.0 Gy, respectively, and $D_{98\%}$ was 68.0 Gy and 67.8 Gy, respectively.

Table 1 shows the differences in dosimetric parameters on the Rwall and Awall between the treatment plans without and with ERB. A significant reduction of all Awall parameters, except V_{70}, was observed with an ERB inserted, with an overall D_{mean} reduction of 6 Gy. Absolute reductions in dose-volume parameters varied from 5% (V_{70}) to 11% (V_{30} and V_{40}). Rwall V_{30} and V_{40} were significantly reduced by 8% and 5%, respectively. Dose-surface map analysis showed a significant reduction in Rwall A_{40}, with an absolute reduction of 6%. In addition, the mean dose to the urinary bladder was significantly lower in the plans with ERB (45.9 Gy vs. 38.8 Gy, $p < 0.001$). D_{max} to the femoral heads did not differ between both plans (55.7 vs. 56.6 Gy, $p = 0.30$). Fig. 4 shows an example of the dose distributions with and without ERB.

The CTV volume without ERB significantly correlated with Rwall V_{30} (Spearman's rho 0.513, $p = 0.02$), but not with Awall doses. This indicates that increasing CTV volumes lead to higher Rwall V_{30}. With ERB inserted, only Rwall D_{min} correlated with the CTV volume (Spearman's rho 0.541, $p = 0.01$). In addition, the dosimetric advantage of ERB (i.e. the difference in Rwall doses between plans without and with ERB) correlated with neither of the CTV volumes, suggesting that the gain from ERB insertion is not dependent on the CTV volume.

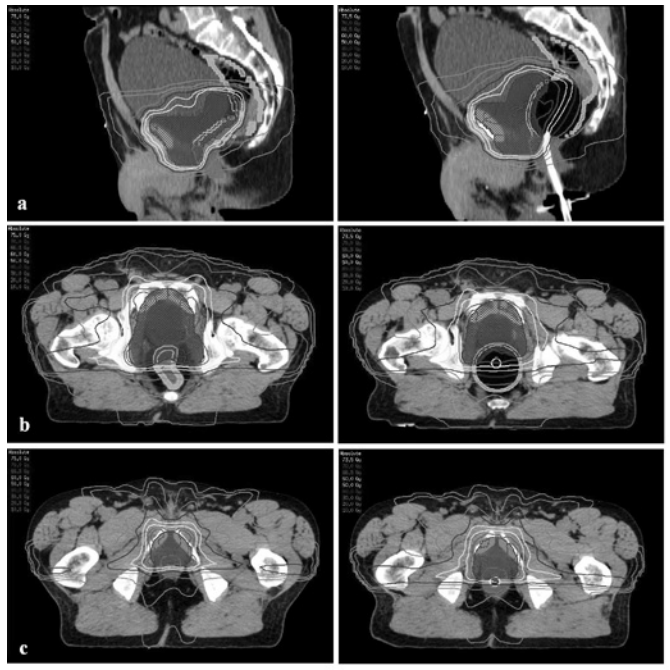
All patients tolerated the ERB well and reported no complaints, other than the slight urge to defecate during inflation due to an increase in local pressure to the Rwall. This sensation disappeared after 10-20 s.

Table 1 Mean (± SD) dosimetric parameters on rectal wall (Rwall) and anal wall (Awall) in situations without and with endorectal balloon (ERB). Bold entries indicate significant differences.

		No ERB	ERB	*p*-value
Rwall	**D_{mean} (Gy)**	42.3 (± 4.2)	40.1 (± 5.5)	0.15
	D_{min} (Gy)	6.5 (± 5.7)	5.5 (±4.1)	0.48
	D_{max} (Gy)	**74.4 (± 0.9)**	**73.7 (± 0.9)**	**0.01**
	V_{20} (%)	84 (± 10)	80 (± 12)	0.26
	V_{30} (%)	**61 (± 8)**	**53 (± 9)**	**0.004**
	V_{40} (%)	**48 (± 7)**	**43 (± 7)**	**0.03**
	V_{50} (%)	41 (± 6)	39 (± 6)	0.27
	V_{60} (%)	35 (± 5)	35 (± 6)	0.72
	V_{70} (%)	19 (± 4)	16 (± 6)	0.08
	A_{20} (%)	82 (± 11)	84 (± 11)	0.36
	A_{30} (%)	71 (± 11)	66 (± 12)	0.22
	A_{40} (%)	**58 (± 10)**	**52 (± 8)**	**0.03**
	A_{50} (%)	49 (± 9)	46 (± 7)	0.64
	A_{60} (%)	40 (± 7)	40 (± 7)	0.56
	A_{70} (%)	21 (± 6)	17 (± 7)	0.07
Awall	**D_{mean} (Gy)**	**42.0 (± 9.0)**	**36.1 (± 8.9)**	**0.005**
	D_{min} (Gy)	**7.8 (± 3.4)**	**6.0 (± 3.4)**	**0.03**
	D_{max} (Gy)	**75.1 (± 1.5)**	**73.3 (± 3.3)**	**0.002**
	V_{20} (%)	**74 (± 13)**	**66 (± 16)**	**0.006**
	V_{30} (%)	**60 (± 16)**	**49 (± 15)**	**0.001**
	V_{40} (%)	**51 (± 17)**	**40 (± 14)**	**0.003**
	V_{50} (%)	**43 (± 16)**	**34 (± 14)**	**0.01**
	V_{60} (%)	**35 (± 15)**	**27 (± 13)**	**0.03**
	V_{70} (%)	19 (± 12)	14 (± 9)	0.08

Abbreviations: D_{mean} = mean dose; D_{min} = minimum dose; D_{max} = maximum dose; V_x = relative volume exposed to x Gy; A_x = relative surface area exposed to x Gy.

Fig. 4 Sagittal (**a**) and transverse (**b**-**c**) views of dose distributions in one patient without endorectal balloon (left) and with endorectal balloon (right). Contours as in Fig. 2. Color figure at p 166.



Discussion

This planning study shows that application of an ERB leads to reduced anorectal doses in high-dose post-prostatectomy IMRT, which can be explained by an increased distance between the PTV and posterior and lateral Rwall and Awall. This observation is in concordance with studies on ERB application in definitive prostate RT [7;15-17] and suggests that an ERB can be helpful in dose-escalated post-prostatectomy RT, as it may reduce anorectal toxicity. Furthermore, we observed that this ERB-induced reduction in anorectal dose was not influenced by the size of the CTV volume.

Several planning studies with ERB have shown reduced Rwall doses in both 3D conformal RT and IMRT, mainly in the intermediate- and high-dose range [16;17]. In the present study, significant reductions of V_{30}, V_{40}, and A_{40} were observed in the plans

with ERB. Regarding Awall dose parameters, all parameters, except V_{70}, were significantly reduced by the ERB, with a D_{mean} reduction of 6 Gy. A recent study has shown the same effect of ERBs in primary prostate RT planned to a total dose of 78 Gy, with an Awall D_{mean} reduction of 7.5 Gy in IMRT [7]. Also, the absolute reductions in V_{20}-V_{70} were in the same range as they are in the present study (5-14%).

In several reports, dose-effect relationships for anorectal toxicity after definitive RT have been mentioned, implying that increasing doses lead to higher toxicity rates [4-6]. Regarding Awall doses, several dose-volume parameters, as well as D_{mean} have been found to be associated with fecal incontinence; for an increase of Awall D_{mean} by 1 Gy, a hazard ratio for incontinence of 1.039 has been observed [4]. This means that in the present study, patients treated without ERB, which showed an increased Awall D_{mean} of 6 Gy, would have an increased incidence of incontinence by a factor (1.039^6 =) of 1.26 compared to patients treated with ERB. In the same study, patients having an Awall D_{mean} of 41 Gy, which is almost equivalent to the No-ERB group from the present study, had a 4-year risk of developing fecal incontinence requiring pads of almost 10%. The incidence of incontinence not requiring pads may have been even higher. Given the bothering nature of these complaints [18], every effort should be made to reduce the risk of these complaints. This may be accomplished by using ERBs. With regard to Rwall parameters, not only volumes exposed to high doses [4], but also volumes and surfaces exposed to intermediate doses (30-40 Gy) are predictive for the development of late rectal bleeding [5;6]. This suggests that, although the absolute reductions in the present study were small, with application of an ERB in post-prostatectomy RT, late rectal bleeding may be reduced. These dose-effect relationships, however, have been derived from patients undergoing definitive RT. In the post-prostatectomy setting, Cozzarini *et al.* have found correlations between late rectal bleeding and rectal V_{50}-V_{60}. However, volumes exposed to lower doses were not investigated [19]. Furthermore, as in many previous studies, they delineated the rectum from the anal verge up to the rectosigmoid flexure, thus including the anal canal, while it is clear from this and other studies [4] that dose- and volume-effect relationships are different for rectum and anal canal.

Teh *et al.* have used ERBs in post-prostatectomy RT for consistency of the target volume by reducing prostate bed movement [11]. To our knowledge, however, no comparative study on this subject between the situation with ERB and without ERB has been performed so far. Without ERB, gold marker based portal imaging showed interfraction prostate bed motion to be minimal, [20], while Fiorino *et al.* showed a mean anterior shift of 2.5 mm for the anterior Rwall, changing the posterior border of the CTV, using weekly repeated CT-imaging [21]. This shift of the posterior CTV border, however, was observed only in the cranial half of the rectum. No shift was observed

in the caudal half of the rectum, which included the anal canal, as defined in the present study. In addition, Showalter *et al*. found a mean posterior shift of the anterior Rwall of 1.6-2.7 mm using cone beam CT, which they attributed to a reduced rectal volume over time during RT [22]. All these studies were performed without ERB. With application of an ERB, the rectal volume might be held more constant during all treatment sessions, thereby possibly reducing prostate bed, and thus CTV, variation. However, this has yet to be confirmed in a clinical study, e.g. by using daily cone beam CT. In addition to shifts of the rectum, large variations in bladder volumes have been observed in post-prostatectomy RT [21]. These variations, however, were only in the cranial and anterior direction, suggesting no influence of bladder filling on the CTV or present observations regarding Awall and Rwall doses. In the present study, bladder volumes were increased on the scans with ERB, which can be attributed to the sequence of scanning: in all patients the scans with ERB were obtained approximately 15 minutes after the scans without ERB, leading to increased bladder filling. This might also explain the significantly reduced bladder dose on the plans with ERB.

Due to the abovementioned variations and other setup uncertainties, CTV-PTV margins are applied. In our institution, an isotropic 9 mm margin is used. Electronic portal imaging of fiducial markers, implanted in the prostate bed has shown a relatively large number of fractions in which the total setup error exceeded 5 mm [20]. In addition, cone beam CT imaging of the pelvic anatomy led to the recommendation to use non-uniform margins, with nonetheless a posterior margin of 8.6 to 10.2 mm [22]. These data indicate that care must be taken not to use too small margins, as this might lead to underdosage of the CTV. Although ERBs potentially have a stabilizing effect, clinical data are warranted before margins can be reduced. In the meantime, adaptive RT, based on the image-guidance modalities mentioned above, might be helpful in reducing uncertainties, and thus CTV-PTV margins.

Different groups have suggested guidelines for CTV delineation [13;14;23-25], based on patterns of local failure. As most of the failures are located around the vesicourethral anastomosis, it is advocated to extend the caudal border of the CTV low enough to include this structure. Inevitably, this will lead to higher doses to the Awall. To counteract this effect, ERB application can reduce these doses, as shown in the present study. Although different guidelines for CTV delineation exist, the variation in delineation of the caudal part (i.e. near the Awall) is small between these guidelines. Therefore, the observed advantages regarding Awall doses are probably within the same range when another guideline is used.

Compared to the Awall, less pronounced differences in Rwall doses were observed, possibly because of deformation of the prostatic fossa. By inflating the ERB, the

anterior Rwall protrudes, which causes the cranial CTV to move backwards and shape around the ERB (Fig. 2b), so the PTV inevitably includes a larger portion of Rwall. This effect is potentially larger than it is in primary prostate RT, as in the latter situation the prostate prevents the rectum to protrude any further. However, in definitive RT, seminal vesicles can also be pushed around the Rwall, when an ERB is applied, and still a beneficial effect has been observed in this situation [16;17]. The present study showed that a small increase in Rwall volumes was observed on the scans with ERB. Further analysis revealed that on the scans without ERB the mean length of rectum was 8.7 cm, compared to 9.1 cm on the scans with ERB, which may explain this difference. Furthermore, as IMRT plans were generated based on our class solution for prostate IMRT, we acknowledge that in individual patients Rwall doses may be somewhat lower.

It should be noted that the abovementioned guidelines for CTV delineation were provided for salvage RT without ERB, whereas in this study they were used in both situations without and with ERB. However, the anatomic landmarks suggested as CTV boundaries in the used consensus guidelines could be identified on the scans with ERB as well. In addition, the CTV volumes in the plans without and with ERB were only slightly different (mean 117 and 110 cc).

Finally, as the present observations were derived from a planning study, a clinical trial is needed to investigate whether the application of ERBs will lead to a decrease in anorectal toxicity.

In conclusion, in this planning study application of an ERB in high-dose post-prostatectomy IMRT up to 70 Gy leads to reduced anorectal doses, especially regarding the Awall, with a mean reduction in D_{mean} of 6 Gy. Intermediate-dose parameters to the Rwall were also reduced. These observations suggest that ERB application can be helpful in post-prostatectomy dose-escalation, as it may reduce anorectal toxicity.

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5

Differences in Radiation Dosimetry and Anorectal Function Testing Imply That Anorectal Symptoms May Arise from Different Anatomic Substrates

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Abstract

Purpose: To explore the influence of functional changes and dosimetric parameters on specific incontinence-related anorectal complaints after prostate external beam radiotherapy and to estimate dose-effect relationships for the anal wall and rectal wall.

Methods and materials: Sixty patients, irradiated for localized prostate cancer, underwent anorectal manometry and barostat measurements to evaluate anal pressures, rectal capacity and rectal sensory functions. In addition, thirty untreated men were analyzed as a control group. In thirty-six irradiated patients, the anal wall and rectal wall were retrospectively delineated on planning CT-scans and dosimetric parameters were retrieved from the treatment plans. Functional and dosimetric parameters were compared between patients with and without complaints, focussing on urgency, incontinence and frequency.

Results: After external beam radiotherapy, reduced anal pressures and tolerated rectal volumes were observed, irrespective of complaints. Patients with urgency and/or incontinence showed significantly lower anal resting pressures (mean 38 and 39 vs. 49 and 50 mm Hg) and lower tolerated rectal pressures (mean 28 and 28 vs. 33 and 34 mm Hg), compared to patients without these complaints. In patients with frequency almost all rectal parameters were reduced. Several dosimetric parameters to the anal wall and rectal wall were predictive for urgency (*e.g.* Anal D_{mean} >38 Gy), whereas some anal wall parameters correlated to incontinence and no dose-effect relationship for frequency was found.

Conclusions: Anorectal function deteriorates after external beam radiotherapy. Different incontinence-related complaints show specific anorectal dysfunctions, suggesting different anatomical and pathophysiologic substrates: urgency and incontinence seem to originate from both anal wall and rectal wall, whereas frequency seems associated with rectal wall dysfunction. Also dose-effect relationships differed between these complaints. This implies that anal wall and rectal wall should be considered separate organs in radiotherapy-planning.

Introduction

Late anorectal toxicity is a concern after dose-escalated external beam radiotherapy for prostate cancer. A recent update of a Dutch dose-escalation trial showed a 35% cumulative incidence of late anorectal toxicity grade ≥2 after 78 Gy [1]; the incidence of late grade ≥1 anorectal toxicity after intensity-modulated radiotherapy (IMRT) is up to 65% [2]. Anorectal toxicity comprises different symptoms [3], of which fecal incontinence and urgency seem to bother patients most [4]. Identification of specific anatomical and functional changes in patients with anorectal symptoms after radiotherapy might help to unravel its underlying pathophysiologic mechanisms, which are still unclear. Furthermore, if there is a relationship with radiation dose, this could help to define specific constraints in radiotherapy-planning.

Several reports have described objective changes in patients with rectal toxicity after external beam prostate radiotherapy, like mucosal changes on endoscopy in patients suffering from late rectal bleeding [5;6]. Dosimetric predictors for late rectal bleeding have been identified, in particular rectal volumes receiving intermediate or high doses [7;8]. Yeoh *et al.* have reported progressive anorectal dysfunction, evaluated with anorectal manometry, demonstrating a deterioration of anorectal motility and sensory function over time [9]. However, a dose-effect relationship for the anal canal and rectum was not investigated.

The goal of the present study is to explore the associations between dosimetric parameters, functional changes and specific anorectal complaints after external beam prostate radiotherapy by evaluating anorectal functions in patients with and without late anorectal toxicity. The results are compared to an untreated control group. Dose-effect relationships are investigated for the anal wall and the rectal wall separately.

Methods and materials

Sixty patients with localized prostate cancer, treated at our department between January 2000 and December 2007 were included in this study during regular follow-up. All patients were treated with external beam radiotherapy, either 3-field or 4-field 3D-conformal radiotherapy, or 5-field IMRT, at least 90 days before inclusion in this study. The prescribed dose was 67.5 Gy or 70.0 Gy in fractions of 2.25 Gy or 2.50 Gy, respectively. In 30 of the 60 patients a daily inserted endorectal balloon filled with 80 cc of air was applied for rectal wall sparing (QLRAD B.V., Dalfsen, The Netherlands). In addition, 30 patients with a localized prostate carcinoma were analyzed prior to radiotherapy and served as a control group. All men had given informed consent.

Late toxicity and functional assessment

During follow-up, all patients were seen every three months during the first two years after treatment and every year afterwards. Late anorectal toxicity was scored, based on items of the late 'Radiotherapy-Induced Lower Intestinal Toxicity' scoring system [3]. This system includes eight symptoms: anal blood loss, mucus loss, abdominal cramps, diarrhea, frequency, urgency, incontinence, and anal pain, scored 0 to 4 (0 = complaint is absent; 1 = complaint is present, although no therapy is required; 2 = first line treatment is required (*e.g.* peroral therapy); 3 = second line treatment is required (*e.g.* IV therapy); 4 = serious treatment is required (*i.e.* surgery or transfusions; not all complaints have a grade 4 score)). It has been shown that incontinence-related complaints (urgency, incontinence and frequency) bother patients most [4] and therefore we have focused on these three symptoms, as did previous investigators [10]. Because the majority of complaints were classified as grade 1 toxicity, the items were scored binary (*i.e. absent* or *present*). Complaints were considered present when they were reported at the most recent follow-up. Patients with and without complaints after radiotherapy are referred to as *Complaints*-group and *No-complaints*-group, respectively. Next, based on the presence or absence of urgency, incontinence and frequency these patients were divided into *Urgency*- and *No-urgency*-, *Incontinence*- and *No-incontinence*- and *Frequency*- and *No-frequency*-groups, respectively.

All ninety patients underwent anorectal manometry and barostat testing to evaluate anal pressures, rectal capacity and rectal sensory functions. During anorectal function testing patients were in left lateral position. In manometry, a customized anorectal motility catheter (Arndorfer Medical Specialties, Greendale, WI) with four radially oriented recording points 90 degrees apart and a 15-cm-long polyethylene bag attached to the distal end was inserted via the anal canal. A standard station pull-through technique was used [11] with a water-perfused catheter to assess resting and squeeze pressures at consecutive 1-cm levels of the anal canal in four separate quadrants. The resting anal canal pressure (P-resting) was defined as the highest resting pressure and the anal squeeze pressure (P-squeeze) as the highest increase over resting pressure during maximal active squeezing. Both values were calculated as the average pressure in the four recording points.

Rectal sensory thresholds were assessed during inflation of the bag, positioned at 5 cm of the anal verge, using an electronic barostat (Distender II®, G&J Electronics Inc., Ontario, Canada). Barostat procedures were performed in accordance with previously described and validated techniques [11;12]. After an initial staircase distension (4 mm Hg steps, 30 s per step) to reduce variability, a rectal staircase distension was performed starting at an intrabag pressure of 0 mm Hg. At 1 min intervals, the intrabag pressure was increased 2 mm Hg and kept constant. Both the pressures (P) and

volumes (V) at which patients reported the moment when they first became aware of something present in the rectum (P-sense and V-sense, respectively), the first desire to defecate (P-urge and V-urge, respectively) and the moment they experienced an uncontrollable urge to defecate or discomfort (P-discomfort and V-discomfort, respectively) were recorded.

Dose evaluation

Of thirty-six irradiated patients planning CT-scans were available for retrospective 2D delineation of the anal wall and rectal wall, using the Pinnacle^3 treatment planning system (Philips Medical Systems, Fitchburg, WI). Of these patients, 17 were treated with an endorectal balloon and 19 were treated without a balloon. In the remaining 24 patients, CT-planning had been performed as well. Due to the use of an older treatment planning system, however, retrospectively contouring the abovementioned structures was not possible. Therefore, these were excluded from analyses regarding dosimetry.

As described previously [13], the anal wall was considered a continuation of the rectal wall and was outlined from the anal verge to the slice below the lowest slice with a rectal or endorectal balloon lumen. The outer anal wall contour encompassed the muscular structures forming the anal canal. In case of a balloon, an inner anal wall contour was delineated around the balloon shaft, and the anal wall volume was defined as the difference between the outer and inner anal wall contour. In patients without balloon the anal wall was defined as the volume within the outer anal wall contour, inasmuch as the anal canal is actively closed. Recently, it has been shown that these delineation methods are well reproducible and lead to identical anal wall volumes [13].

After the outer rectal wall contours were delineated on each CT-slice, an inner rectal wall was constructed using a 5 mm wall thickness on slices without endorectal balloon, and 3 mm on slices with balloon [14]. The volume of the inner rectal wall contour was subtracted from that of the outer rectal wall contour and this was defined as the rectal wall volume. The rectal wall was delineated from the top of the anal wall up to the rectosigmoid flexure.

From all treatment plans the anal wall and rectal wall minimum, maximum and mean dose (D_{min}, D_{max}, and D_{mean}, respectively) and volumes (%) exposed to ≥20 Gy (V_{20}), ≥30 Gy (V_{30}), ≥40 Gy (V_{40}), ≥50Gy (V_{50}), ≥60 Gy (V_{60}), and ≥70 Gy (V_{70}), were derived. In addition, to visualize the spatial dose distribution to the rectal mucosa, the dose to the inner rectal wall contours was displayed by means of virtual rectum "unfolding", thus generating dose-surface maps [15]. In order to be able to compare these dose

distributions between patients, the surface areas (%) exposed to ≥10 Gy (A_{10}), ≥20 Gy (A_{20}), ≥30 Gy (A_{30}), ≥40 Gy (A_{40}), ≥50Gy (A_{50}), ≥60 Gy (A_{60}), ≥65 Gy (A_{65}), and ≥70 Gy (A_{70}), were calculated in bins of 1 cm^2.

To correct for differences in biological effect of the different fractionation schedules, all mean, maximum and minimum doses were recalculated to an equivalent dose in 2-Gy fractions (EQD_2) using the following formula, based on the linear-quadratic (LQ) model [16]:

$$EQD_2 = D\,(d + [\alpha/\beta]) / (2 + [\alpha/\beta])$$

where D is the total physical dose (Gy) given in fractions of d Gy and α/β is a measure of fractionation sensitivity, which was set to 3 Gy for late anorectal toxicity [17].

Statistical analysis

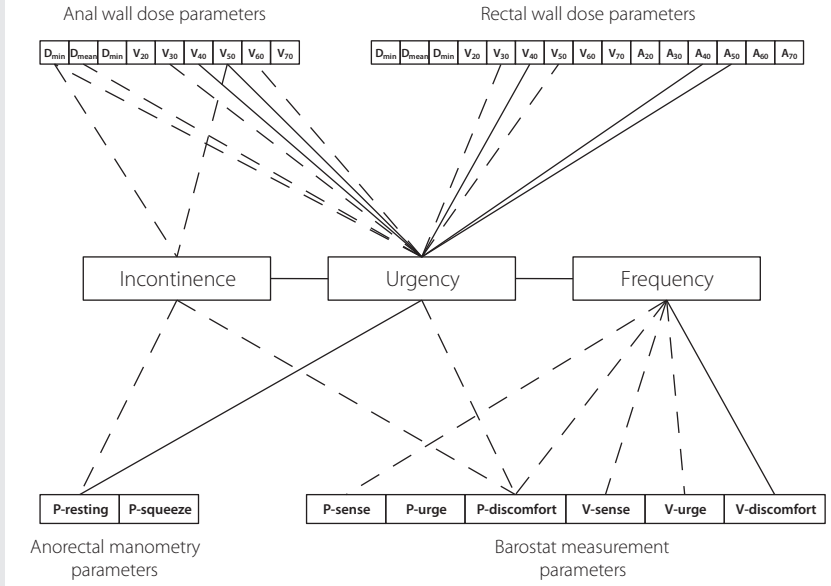
The SPSS 14.0 software for Windows (© SPSS Inc., 1989-2005) was used for statistical calculations. The Kolmogorov-Smirnov test showed a normal distribution of the measured values for all parameters. One-way analysis of variance was performed to compare means between the *Complaints*- and *No-complaints*-group, and the control group. The independent *t*-test was used for comparison of both functional and dose parameters between the *Complaints*- and *No-complaints*-group. For comparison of categorical data (*i.e.* complaints and risk factors) between groups the chi-square test was used. Contingency tables were constructed and Pearson's chi-square was calculated to determine the correlation between complaints. Regression analysis was performed to investigate possible associations between duration of follow-up and manometry outcomes (linear regression) and the presence of symptoms (logistic regression). *P*-values ≤ 0.05 were considered indicative for significant differences, although differences with *p*-values < 0.01 should be considered clearly significant, given the number of statistical tests (*e.g.* see Fig. 1)

Results

There were no statistically significant differences in baseline and treatment characteristics between patients with complaints (n=38) and patients without complaints (n=22), nor when comparing with controls (n=30) (Table 1).

Thirty-eight (63%) of the irradiated patients reported one or more complaints, with the following distribution: frequency: 26 (43%), urgency: 22 (37%), incontinence: 19 (32%), anal blood loss: 12 (20%), mucus loss: 11 (18%), diarrhea: 7 (12%), abdominal cramps: 1 (2%), and anal pain: none. Of the complaints related to incontinence (*i.e.*

Fig. 1 Associations between complaints and the investigated parameters (solid lines represent *p*-values < 0.01; dashed lines represent *p*-values 0.01-0.05). This figure summarizes the associations listed in Tables 2 and 3 with $p < 0.05$. In addition, Anal D_{mean}, V_{20} and V_{30} were associated with V-sense and V-urge (*p*-values ranging from 0.02 to 0.05).



frequency, urgency and incontinence) eight patients reported all three complaints, fifteen reported to have a combination of two complaints, and ten patients had only one of these symptoms. Both urgency and incontinence, and urgency and frequency were significantly correlated ($p = 0.001$), whereas incontinence and frequency were not. Of the 36 patients, whose treatment plans were evaluated, 23 (64%) reported complaints, with frequency, incontinence and urgency reported in 14 (39%), 11 (31%) and 11 (31%) cases, respectively. In the control group no complaints were reported.

When the results of the anorectal function tests between the *Complaints*- and *No-complaints*-group were compared, the *Complaints*-group tolerated a significantly lower V-discomfort than the latter (181 vs. 231 mL, $p = 0.03$). The other parameters did not significantly differ between these groups, although a borderline significant reduced P-resting was observed in the *Complaints*-group (43 vs. 51 mm Hg, $p = 0.06$). When patients were categorized according to specific symptoms, however, more

Table 1 Patient characteristics.

		Complaints	No-complaints	Control
n		38	22	30
Age (± 1 SD)		74 (5.2)	72 (6.0)	68 (8.0)
T-stage:	*T1*	8	1	4
	T2	11	13	8
	T3	18	8	18
	T4	1	0	0
Grade:	*2*	25	11	11
	3	13	11	19
PSA (ng/ml) **pre-treatment** (range)		18.2 (0.48-159)	20.2 (1.59-61.7)	17.3 (0.68-63.0)
Follow-up (months)		35 (4-84)	30 (4-96)	n.a.
Technique:	*4-field 3D-CRT*	29	11	n.a.
	3-field 3D-CRT	6	9	n.a.
	IMRT	3	2	n.a.
Total dose/fraction dose (Gy):				
	67.5/2.25	32	12	n.a.
	70.0/2.5	6	10	n.a.
Treatment with ERB		14	16	n.a.
Potential risk factors:				
	Previous abdominal surgery	13	9	13
	Diabetes	3	1	1
	Anticoagulant drugs	11	8	6

Abbreviations: PSA = prostate-specific antigen; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; ERB = endorectal balloon.

measurements demonstrated significant differences between the groups (Table 2). The *Urgency*-group, irrespective of the presence of other complaints, showed a significantly lower P-resting and lower P-discomfort than the *No-urgency*-group. The same differences applied to the *Incontinence*- and *No-incontinence*-group. Compared to the *No-frequency*-group, the *Frequency*-group had reductions in almost all sensory thresholds.

In Table 3, anorectal dosimetric parameters are displayed, only including data with statistically significant differences between patients with and without complaints. No overall differences were observed between the *Complaints*- and *No-complaints*-group. When specific complaints were compared, however, several differences were observed. The *No-urgency*-group received significantly lower doses to the anal wall

Table 2 Differences in anorectal manometry and barostat measurements (mean ± 1 SD) in patients with and without complaints after EBRT, and the control group. Bold entries indicate $p \leq 0.05$.

	Urgency			Incontinence			Frequency			Control group
Functional assessment	**Present**	**Absent**	***p***	**Present**	**Absent**	***p***	**Present**	**Absent**	***p***	
Anal P-resting (mm Hg)	**38 (17)**	**51 (15)**	***<0.001***	**39 (16)**	**49 (16)**	***0.03***	43 (17)	49 (17)	*0.18*	59 (17)
Anal P-squeeze (mm Hg)	139 (46)	162 (64)	*0.15*	139 (51)	160 (60)	*0.09*	165 (57)	145 (58)	*0.18*	175 (61)
P-sense (mm Hg)	13 (5)	14 (6)	*0.60*	12 (6)	15 (5)	*0.14*	**12 (5)**	**15 (5)**	***0.05***	13 (4)
P-urge (mm Hg)	18 (5)	19 (7)	*0.85*	17 (7)	19 (6)	*0.14*	18 (6)	19 (6)	*0.26*	19 (6)
P-discomfort (mm Hg)	**28 (9)**	**34 (9)**	***0.02***	**28 (10)**	**33 (8)**	***0.03***	**29 (10)**	**34 (8)**	***0.03***	32 (8)
V-sense (mL)	71 (56)	100 (84)	*0.15*	77 (66)	95 (80)	*0.39*	**66 (61)**	**107 (81)**	***0.04***	108 (68)
V-urge (mL)	108 (63)	140 (89)	*0.13*	108 (73)	138 (84)	*0.17*	**103 (68)**	**147 (86)**	***0.04***	164 (81)
V-discomfort (mL)	172 (80)	214 (91)	*0.07*	173 (88)	211 (88)	*0.13*	**162 (71)**	**272 (92)**	***0.004***	266 (88)

Abbreviations: P = pressure; V = volume.

Table 3 Significant differences in dosimetric parameters (mean ± 1 SD) between patients with and without complaints after external beam radiotherapy, measured in 36 patients.

		Symptom		
	Dosimetric parameter	**Present**	**Absent**	***p*-value**
Urgency	Anal D_{min} (Gy)	10.1 (9.1)	4.9 (5.3)	*0.04*
	Anal D_{mean} (Gy)	42.1 (12.1)	31.6 (10.6)	*0.02*
	Anal V_{30} (%)	72 (27)	49 (25)	*0.02*
	Anal V_{40} (%)	48 (21)	26 (19)	*0.004*
	Anal V_{50} (%)	36 (17)	18 (15)	*0.003*
	Anal V_{60} (%)	25 (14)	13 (15)	*0.04*
	Rectal D_{mean} (Gy)	45.3 (8.6)	39.6 (6.3)	*0.03*
	Rectal V_{30} (%)	76 (15)	62 (20)	*0.04*
	Rectal V_{40} (%)	54 (15)	39 (10)	*0.001*
	Rectal V_{50} (%)	42 (13)	33 (7)	*0.03*
	Rectal A_{40} (%)	62 (15)	48 (12)	*0.007*
	Rectal A_{50} (%)	52 (14)	39 (9)	*0.002*
Incontinence	Anal D_{min} (Gy)	10.0 (9.1)	5.0 (5.4)	*0.04*
	Anal V_{50} (%)	33 (20)	20 (15)	*0.04*
Frequency	-	-	-	-

Abbreviations: D_{min} = minimum dose; D_{mean} = mean dose; V_x= relative volume exposed to at least x Gy; A_x= relative surface area exposed to at least x Gy.

and rectal wall than the *Urgency*-group and a number of volume- and surface-area parameters were lower in the *No-urgency*-group. In addition to the data in Table 3, a borderline significant reduction in Anal V_{70} and Rectal A_{65} was observed. In the *Incontinence*-group, besides a higher Anal D_{min} and Anal V_{50}, Anal D_{mean} (40.1 vs. 32.5 Gy, p = 0.08), Anal V_{40} (42% vs. 28%, p = 0.08) and Anal V_{60} (24% vs. 14%, p = 0.08), and Rectal D_{min} (2.1 vs. 5.1 Gy, p = 0.052) were higher as compared to the *No-incontinence-group*. No significant dosimetric differences were observed between the *Frequency*- and *No-frequency*-group. The only significant correlations between function testing and dosimetry were Anal D_{mean}, V_{20} and V_{30} negatively correlating with V-sense and V-urge

(correlation coefficients ranging from -0.376 (p = 0.02) to -0.334 (p = 0.05)). Fig. 1 displays the associations between complaints and the investigated parameters.

Based on the significant differences in dosimetric parameters between the *Urgency*- and No-*urgency*-group an attempt was made to define low-risk and high-risk groups for the development of late anorectal toxicity. In the present study, when applying a cut-off value of Anal D_{mean} = 38 Gy, patients with D_{mean} <38 Gy had a 15% risk of developing urgency, compared to 62% in patients with D_{mean} >38 Gy. Approximately equal differences were observed for Rectal D_{mean} = 44 Gy and several volume and surface parameters. For incontinence, cut-off values Anal D_{min} = 5 Gy and Anal V_{50} = 39% were observed.

The control group scored significantly better on P-resting, V-urge, and V-discomfort compared to the irradiated patients, irrespective of the presence of complaints (Table 4). Measurements in patients with none of the investigated complaints were not significantly different from the control group. However, many differences were seen between the *Complaints*-groups and the control group (Table 2).

Table 4 Mean (± 1 SD) anorectal manometry and barostat measurements in irradiated patients and the control group.

			Irradiated	**Control**	***p*-value**
P-resting (mm Hg)			**46 (17)**	**59 (17)**	***0.001***
P-squeeze (mm Hg)			153 (58)	175 (61)	*0.11*
Rectal distension	**P (mm Hg)**	Sense	14 (5)	13 (4)	*0.44*
		Urge	19 (6)	19 (7)	*0.94*
		Discomfort	32 (9)	32 (8)	*0.89*
	V (mL)	Sense	90 (76)	108 (68)	*0.27*
		Urge	**128 (81)**	**164 (81)**	***0.05***
		Discomfort	**199 (89)**	**266 (88)**	***0.001***

Abbreviations: as in Table 2.

Interestingly, when manometry data between the three groups were compared (*Complaints*-group, *No-complaints*-group and control group), for most items a gradual deterioration was observed, with the best and worst outcomes for the control group and *Complaints*-group, respectively.

Regression analysis revealed that duration of follow-up had only a significant association with P-squeeze (B = -1.08 (95% confidence interval -1.71 to -0.46), beta coefficient = -0.414, $p = 0.001$). For all other investigated parameters (*i.e.* manometry outcomes and presence of complaints) no such effect was observed.

Finally, patients treated with endorectal balloon showed significantly less complaints than patients treated without balloon, as well as lower doses to the anal wall and rectal wall. Furthermore, P-squeeze was significantly higher in patients treated with ERB (Table 5).

Table 5 Significant differences between patients treated without and with endorectal balloon.

		No endorectal balloon	Endorectal balloon	*p*- value
Complaints	Urgency (%)	57	17	*0.001*
	Incontinence (%)	43	20	*0.05*
	Frequency (%)	60	27	*0.009*
Function testing	P-squeeze (mm Hg)	138 (47)	169 (65)	*0.04*
Dosimetric parameters	Anal D_{mean} (Gy)	39.2 (11.6)	29.9 (11.1)	*0.02*
	Anal V_{30} (%)	68 (23)	43 (26)	*0.005*
	Anal V_{40} (%)	44 (20)	20 (17)	*0.001*
	Anal V_{50} (%)	32 (17)	14 (14)	*0.001*
	Rectal D_{max} (Gy)	71.4 (2.0)	74.9 (3.6)	*0.001*
	Rectal V_{30} (%)	73 (16)	58 (21)	*0.02*
	Rectal V_{40} (%)	49 (15)	38 (9)	*0.008*
	Rectal V_{50} (%)	39 (11)	32 (7)	*0.03*
	Rectal A_{10} (%)	81 (13)	89 (8)	*0.04*
	Rectal A_{20} (%)	75 (14)	83 (8)	*0.05*

Abbreviations: as in Tables 2 and 3.

Discussion

This study shows that external beam prostate radiotherapy can lead to specific anorectal dysfunction. The type of dysfunction varies between patients with urgency, incontinence and frequency, suggesting different anatomical and pathophysiologic substrates. Also anorectal dosimetric parameters differ between patients with and without the respective complaints. Urgency showed a clear association with P-resting and with dosimetric parameters Anal V_{30} and V_{40}, as well as Rectal V_{40}, A_{40} and A_{50}. Frequency was strongly associated with V-discomfort. Based on these findings, frequency seems to originate from changes in rectal function, suggesting it may be caused by an impaired rectal capacity and sensory function. Urgency, and to a lesser degree incontinence, seems to have a more complicated pathophysiology, *i.e.* a combination of reduced rectal capacity and anal pressures, as it is associated with both anal and rectal wall parameters.

When patients who were examined before and after radiotherapy were compared, significantly reduced anal pressures and tolerated rectal volumes were observed in the latter group. These results are consistent with previous studies, where anorectal functions in prostate cancer patients were measured before radiotherapy and were prospectively followed with repeated function testing [9;10;18]. During a 2-year follow-up, Yeoh *et al.* found progressive deteriorations of anal pressures, rectal compliance and rectal volumes associated with sensory perception and the desire to defecate. Furthermore, an inverse relationship between fecal incontinence scores and rectal compliance and anal squeeze pressure was observed [9;10]. In the present study, patients with incontinence tolerated significantly lower pressures to the rectal wall than patients without incontinence, and had significantly reduced basal anal pressures. Comparable differences applied to patients with and without urgency. Interestingly, when patients were classified according to the presence of frequency, several differences in sensory functions and rectal capacity were seen in favour of the *No-frequency*-group, whereas anal pressures were not significantly different. Based on these results, we hypothesize that frequency is mainly caused by changes in rectal wall sensory functions and compliance, leading to an impaired rectal capacity, while the pathophysiology of incontinence and urgency involves impairment in both anal and rectal functions. The multifactorial pathogenesis of fecal incontinence has been acknowledged previously [18;19]. Petersen *et al.* stated that both the anal sphincter muscles and rectal compliance and volume are so-called *core factors* in the etiology of incontinence, while *associated factors*, like mucosal sensory function, also contribute to its development [19]. The role of individual muscles of the continence apparatus on specific complaints and possible dose-effect relationships are topics for future research (*e.g.* by separately delineating these structures in treatment planning).

Gradual deteriorations in function scores between patients with and without complaints, and the control group were observed. As expected, the first group scored worse than the last group. Although not all differences reached statistical significance, it is interesting to note that the scores of the patients without complaints were in between these groups. A possible explanation for this phenomenon might be that radiation-induced damage remains subclinical until a certain threshold is reached. Furthermore, as the development of late radiation damage is a dynamic process [5;10], patients without complaints could theoretically still be in the "developing phase", and reveal complaints (and more deteriorated functional measurements) later on. However, as in this study the follow-up time between the *Complaints*- and *No-complaints*-group was not significantly different, this is probably not the (only) explanation for these observations. Future research with repeated measurements can be useful in further investigating possible subclinical damage and its relationship to radiation dose.

To our knowledge, this is the first attempt to correlate specific incontinence-related anorectal complaints to both functional measurements and dosimetric data for the anal canal and the rectum. Previous studies showed no influence of the radiation technique (*i.e.* 2D or 3D) or the radiation dose schedule (*i.e.* 55 Gy in 20 fractions or 64 Gy in 32 fractions) on anorectal dysfunction [9;10]. Although in the study comparing 2D- and 3D-radiotherapy a description of relative D_{min}, D_{mean} and D_{max} to the anorectum was given, this was only mentioned for patients after 3D-radiotherapy and no distinction was made between patients with and without complaints [9]. Also, in these studies no dose parameter assessments were performed for anal wall and rectal wall separately.

Retrospective analysis of the treatment plans in the present study shows that dosimetric differences in patients with and without urgency, incontinence and frequency varied. The *Urgency*-group had received significant higher doses on both the anal wall and the rectal wall, compared to the *No-urgency*-group (Table 3). Fokdal *et al*. found that Anal D_{min}, D_{mean}, D_{max} and V_{30}-V_{60} were significantly correlated to fecal urgency [20], while Al-Abany *et al*. observed a significant correlation between urgency and rectal wall doses in the range of 25-42 Gy [21]. Almost all of these parameters proved to be significantly different between the *Urgency*- and *No-urgency*-group in our study.

When the *Incontinence*- and *No-incontinence*-group were compared, some dosimetric parameters were significantly reduced in the latter group, mainly concerning the anal wall. In a previous study in 641 patients, however, all dosimetric anal parameters, except D_{max} were found to be predictive for incontinence requiring pads [22]. The

smaller sample size in our study might explain this discrepancy. Surprisingly, despite several differences in rectal functions, no differences in dose parameters were seen between the *Frequency*- and *No-frequency*-group.

Based on anorectal dose-surface map analysis, Heemsbergen *et al*. also suggested that complaints originate from specific regions [23]. In concordance with the present results, they found a dose-effect relationship for soiling and fecal incontinence in the anal region and lower rectum, and no dose parameters predicting frequency. However, no dose-effect relationships for urgency were found either, whereas in our study many differences were seen between the *Urgency*- and *No-urgency*-group. Differences in toxicity-scoring might contribute to this discrepancy.

In the present study, D_{min}, D_{max}, and D_{mean} were recalculated to EQD_2 to correct for differences in fractionation schedule. Dose-volume and dose-surface parameters, however, were obtained from physical dose-volume histograms (DVHs) and dose-surface histograms, respectively. A comparison of physical DVHs and LQ-scaled DVHs of two patients showed only small differences (<5%) between the two fractionation schedules in the dose regions 40-70 Gy. Based on this comparison, we expect the volumes exposed to low EQD_2-doses to be somewhat lower, and the volumes exposed to ≥70 Gy somewhat higher, but the differences between the groups with and without complaints will be of the same magnitude.

To extensively describe the effect of endorectal balloons on the abovementioned data is beyond the scope of this paper. Although our study showed less complaints and lower anorectal doses in the group irradiated with balloon, this is a topic for further research.

The observations from this study can have consequences for clinical practice. First, the results suggest that the rectal wall and anal wall are different organs to be delineated and spared separately in radiotherapy-planning. Although in this study only prostate cancer patients were included, this recommendation could be extended to pelvic radiotherapy in general. In women irradiated for cervical or uterine carcinoma, 67% reported fecal urgency and anorectal function testing showed reduced anal pressures and rectal compliance [24]. Furthermore, rectal cancer patients treated with short-course preoperative external beam radiotherapy reported significantly more incontinence, soiling and increased bowel movements than patients treated with surgery alone [25]. Using anorectal manometry, the first group showed significantly reduced anal pressures. Secondly, based on the defined low- and high-risk groups for the development of urgency, the following constraints for dose planning can be deduced for pelvic RT: Anal D_{mean} <38 Gy, V_{30} <65%, V_{40} <41% and

V_{50} <30%, and Rectal D_{mean} <44 Gy, V_{30} <70%, V_{40} <45% and V_{50} <37%. Anal D_{min} <5 Gy can be added as constraint, based on differences between the *Incontinence*- and *No-incontinence*-group.

However, care must be taken in drawing definite conclusions, as this study is hypothesis generating and has some limitations. First is the design, as it is an observational study with a cross-sectional design in which we explore the relation between anorectal function, dosimetric parameters and symptoms. Delineation has been performed retrospectively. This design introduces potential biases. Secondly, anorectal function testing was performed only once in each patient, thereby ignoring the dynamic process of toxicity development. Furthermore there was no fixed time-point for all patients at which function testing and symptom scoring was performed. A third caveat is the co-existence of multiple complaints per patient, which can be a confounding factor in the exact determination of the role of anorectal dysfunction and dose on individual complaints or specific clusters of complaints. Because the overall number of analyzed patients was relatively small, it was impossible to perform further sub-analysis of these groups. Finally, dosimetry could be performed in only 36/60 patients, which is a relatively small number and could be subject to selection bias. Still, despite these limitations, the present analysis shows interesting findings, suggesting specific factors being involved in the development of different complaints, which is a basis for future research.

In conclusion, this study shows reduced anorectal functions after external beam prostate radiotherapy, with deterioration of anal pressures and rectal volumes associated with sensory perception, the desire to defecate and discomfort. Furthermore, when patients with and without complaints after radiotherapy were compared, each symptom seems to be associated with specific changes on anorectal manometry. While frequency seems mainly caused by deterioration of rectal function, urgency and incontinence are associated with both anal and rectal dysfunction. Finally, significant dosimetric differences have been observed between patients with and without complaints, with a different impact of doses to the anal canal and rectum for the various complaints. It seems that the anal wall and rectal wall are separate organs to be delineated and spared in pelvic radiotherapy.

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6

Dose-Effect Relationships for Individual Pelvic Floor Muscles and Anorectal Complaints after Prostate Radiotherapy

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Abstract

Purpose: To delineate individual pelvic floor muscles, considered to be involved in anorectal toxicity, and to investigate dose-effect relationships for fecal incontinence-related complaints after prostate radiotherapy (RT).

Methods and Materials: In 48 patients, treated for localized prostate cancer, the internal anal sphincter (IAS), external anal sphincter (EAS), puborectalis muscle (PRM) and levator ani muscles (LAM) were retrospectively delineated on planning CT-scans, in addition to the anal wall (Awall) and rectal wall (Rwall). Dose parameters were obtained and were compared between patients with and without fecal urgency, incontinence and frequency. Dose-effect curves were constructed. Finally, the effect of an endorectal balloon, which was applied in 28 patients, was investigated.

Results: The total volume of the pelvic floor muscles together was about thrice that of the Awall. The PRM was exposed to the highest RT dose, whereas the EAS received the lowest dose. Several anal and rectal dose-parameters, as well as doses to all separate pelvic floor muscles, were associated with urgency, while incontinence was mainly associated with doses to the EAS and PRM. Based on the dose-effect curves, the following constraints regarding mean doses can be deduced to reduce the risk of urgency: ≤30 Gy (IAS), ≤10 Gy (EAS), ≤50 Gy (PRM) and ≤40 Gy (LAM). No dose-effect relationships for frequency were observed. Patients treated with endorectal balloon reported significantly less urgency and incontinence, while their treatment plans showed significantly lower doses to the Awall, Rwall and all pelvic floor muscles.

Conclusions: Incontinence-related complaints show specific dose-effect relations to individual pelvic floor muscles. Dose constraints for each muscle can be identified for RT planning. When only the Awall is delineated, substantial components of the continence apparatus are excluded.

Introduction

Although dose escalation has proven to lead to improved treatment outcomes in external beam radiotherapy (EBRT) for localized prostate cancer [1], higher doses to normal tissues lead to increased toxicity rates [2], of which late anorectal toxicity (*e.g.* fecal incontinence, urgency and frequency) is of major concern.

Several reports have described relationships between dose-volume parameters to both the rectum and anal canal and late anorectal toxicity [3;4]. In addition, attempts have been made to identify specific anatomic indicators of late rectal toxicity, *e.g.* by correlating late rectal bleeding to rectal dose-surface maps [5;6]. Incontinence-related complaints, which appear to bother patients most [7], are thought to be caused by a combination of both rectal and anal factors [8]. There are indications that different incontinence-related complaints may arise from specific anorectal subsites [5;9]. Knowledge of specific regions involved in the development of late toxicity may play a key role in the prevention of these side effects, as with modern intensity-modulated radiotherapy (IMRT) techniques even small surrounding normal tissues can be selectively spared [10].

Rather than just the rectum and anal canal (mostly defined as the distal 3 cm of the anorectum), specific pelvic floor muscles are considered to be involved in normal fecal continence: the internal anal sphincter, external anal sphincter, puborectalis muscle and levator ani muscles [11;12]. The goals of the present study were to separately delineate these pelvic floor muscles and to investigate dose-effect relationships for fecal incontinence-related complaints after prostate radiotherapy. Furthermore, it was assessed whether the anal wall (Awall), used in prostate EBRT delineations to represent the anal sphincter complex, is a good representative of the total continence apparatus.

Methods and materials

Patients and treatment

Between July and December 2009, during regular follow-up, 48 consecutive patients who were at least 90 days after treatment with EBRT for localized prostate cancer (T1-4N0M0), were included in this study. For all patients, complete follow-up data and CT-based treatment plans were available (Pinnacle^3, Philips Medical Systems, Fitchburg, WI). Treatment consisted of 3-field or 4-field 3D conformal radiotherapy (3D-CRT) and 5-beam IMRT techniques. The prescribed total dose was 67.5 or 70.0 Gy in 2.25 or 2.50 Gy fractions, respectively. The clinical target volume (CTV) comprised

the prostate, with or without seminal vesicles, depending on the tumor stage. In 28 patients a daily inserted air-filled (80 or 100 cm^3) endorectal balloon (ERB) had been applied (QLRAD B.V., Dalfsen, The Netherlands). Not all patients were treated with IMRT and/or ERB due to a sequential cohort effect, *i.e.* some patients were treated before introduction of IMRT and/or ERB in our clinical practice. In all patients, late anorectal toxicity was scored every 6 months using the radiotherapy-induced lower intestinal toxicity (RILIT) instrument [3]. As most patients reported grade 1 toxicity, we focused on the presence or absence of fecal incontinence-related complaints (*i.e.* incontinence, urgency and frequency [13]). Complaints were considered present when they were reported at the most recent follow-up.

Organ delineation

On the axial CT-slices (thickness 3 mm) of all patients, the Awall and rectal wall (Rwall) were retrospectively delineated. The Awall was considered a continuation of the Rwall [4]. The outer Awall contour was outlined, extending from the anal verge to the slice below the lowest slice with a rectal or ERB lumen. In case of an ERB, an inner Awall contour was delineated around the ERB shaft, and the Awall volume was defined as the difference between the outer and inner Awall contours. In patients without ERB, the Awall volume was defined as the volume within the outer Awall contour, as no inner Awall was visible, due to active closure of the anal canal [14]. After the outer Rwall contours were indicated on each CT-slice, an inner Rwall was constructed by applying a 5 mm wall thickness on slices without ERB, and 3 mm thickness on slices with ERB [15]. The Rwall volume was defined as the difference between the outer and inner Rwall contours and was delineated from the top of the Awall up to the rectosigmoid flexure.

After delineation of these structures, four pelvic floor muscles, considered to be involved in normal fecal continence [11;12], were separately delineated: the internal anal sphincter (IAS), external anal sphincter (EAS), puborectalis muscle (PRM) and levator ani muscles (LAM), using the following description:

1. The IAS is the distal continuation of the smooth muscle layer of the rectum.
2. The EAS partially encircles the IAS. It is separated from the IAS by the intersphincteric space, which can be distinguished on the axial CT-slices.
3. The PRM is a U-shaped muscle, which forms a sling around the anorectal junction and is connected to the pubic bone.
4. Cranially, the LAM form a plate-like continuation of the PRM [16].

All structures were delineated by the same operator (R.J.S.). In three randomly chosen patients the muscles were delineated thrice by two operators (R.J.S. and E.v.L.), who were blinded for the presence or absence of complaints, to determine the intra-operator and inter-operator co-efficients of variation of their volume (defined as the ratio of the standard deviation to the mean). Fig. 1 shows an example of the separately delineated muscles.

Dose evaluation

In all treatment plans, the minimum, maximum and mean dose (D_{min}, D_{max}, and D_{mean}, respectively) to the Awall, Rwall and to the IAS, EAS, PRM, and LAM were calculated. To correct for differences in biological effect of the two fractionation schedules, these doses were recalculated to a biologically equivalent dose in 2-Gy fractions (EQD_2) using the following formula, based on the linear-quadratic model [17]:

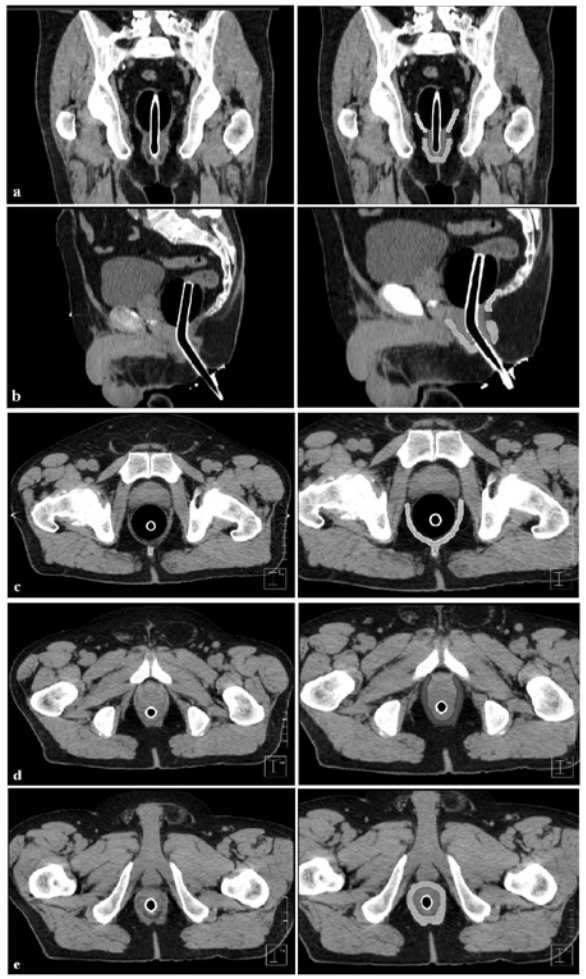
$$EQD_2 = D\,(d + [\alpha/\beta])/(2 + [\alpha/\beta])$$

where D is the total dose given in fractions of d Gy and α/β is a measure of fractionation sensitivity, which was set to 3 Gy for late anorectal toxicity [18]. All D_{min}, D_{max}, and D_{mean} are therefore reported in EQD_2 doses. In addition, volumes (%) exposed to ≥20 Gy (V_{20}), ≥30 Gy (V_{30}), ≥40 Gy (V_{40}), ≥50Gy (V_{50}), ≥60 Gy (V_{60}), and ≥70 Gy (V_{70}), to both the Awall and Rwall were calculated. The spatial dose distribution to the inner rectal wall mucosa was visualized by generating dose-surface maps by means of virtual rectum 'unfolding' [19]. In order to be able to compare these dose distributions between patients, the areas (%) exposed to ≥20 Gy (A_{20}), ≥30 Gy (A_{30}), ≥40 Gy (A_{40}), ≥50Gy (A_{50}), ≥60 Gy (A_{60}), and ≥70 Gy (A_{70}) were calculated in bins of 1 cm^2. All dose parameters were compared between patients with and without complaints and between patients treated with and without ERB.

Statistical analysis

The SPSS 16.0.2 software for Windows (© SPSS Inc., 1989-2007) was used for statistical calculations. As Kolmogorov-Smirnoff tests revealed normal distributions of the investigated parameters, parametric tests were performed to compare the dose parameters. Independent *t*-tests were used for comparison of the measured parameters between patients with and without reported toxicity, and between patients treated with and without ERB. One-way analysis of variance was performed to compare means between the 3 treatment groups. Pearson's chi-square was calculated to investigate the correlation between the use of ERBs and the presence of complaints. The Mann-Whitney U-test was used for comparison of median follow-up duration. Differences with a two-tailed p value ≤ 0.05 were considered significant.

Fig. 1 Example of the delineated pelvic floor muscles in coronal (**a**), sagittal (**b**) and transverse (**c**-**e**) view in a patient with endorectal balloon inserted. Red contour: internal anal sphincter; green contour: external anal sphincter; blue contour: puborectalis muscle; yellow contour: levator ani muscles. Color figure at p 167.



Dose-effect curves were constructed by plotting the incidence of the respective complaints and the dose to a specific subsite, in bins of 5 Gy. A logistic distribution model was used for curve fitting, using the formula

$$P(D) = \frac{1}{1+\left(\frac{D50}{D}\right)^{4.\gamma 50}}$$

where P(D) is the risk (%) of developing a certain complaint at a certain dose D, D_{50} is the dose leading to a 50% risk, and γ_{50} is the normalized dose-response gradient at the 50% response level (GraphPad Prism, version 4.00, GraphPad Software, Inc. 1992-2003). Goodness of fit (R^2) was calculated for each curve.

Results

Patient characteristics

The mean age at evaluation was 71.8 years and did not differ between patients with and without complaints. Other predisposing factors for the development of anorectal toxicity (use of anticoagulant drugs, previous abdominal surgery, pre-existing anorectal complaints, and diabetes (20;21)) were also equally distributed between these groups (Table 1). Eighteen patients were treated with 3-field 3D-CRT, 25 with 4-field 3D-CRT and 5 with IMRT. The median follow-up time was longer in patients with complaints, but this difference did not reach statistical significance: 30 (range 6-55) months vs. 23 (range 8-48) months ($p = 0.06$).

Table 1 Predisposing factors for anorectal complaints in patients without and with complaints.

Predisposing factor	No complaints	Complaints	*p*-value
Mean age (SD)	71 (5.9)	72 (4.2)	*0.44*
Diabetes	0	4	*0.07*
Preexisting anorectal complaints	0	1	*0.33*
Previous abdominal surgery	6	3	*0.12*
Anticoagulant drugs	8	9	*0.72*

Organ delineation and dosimetry

The mean volume (±SD) of the Awall was 16.0 (±4.1) cm^3, whereas the mean volumes (±SD) of the separate muscles were 13.1 (±3.6), 12.2 (±3.4), 8.30 (±2.2), and 13.2 (±3.6) cm^3 for IAS, EAS, PRM, and LAM, respectively. This led to a mean volume (±SD) of 46.7

(±9.2) cm^3 for all muscles together. These volumes were not significantly different between patients treated with ERB and without ERB. Co-efficients of variation were 4.2% (IAS), 3.9% (EAS), 4.7% (PRM) and 6.4% (LAM) for intra-operator delineation variation. The respective co-efficients of variation for inter-operator variation were 2.6%, 1.4%, 1.4% and 0.8%. The mean Rwall volume (±SD) was 37.7 (±4.1) cm^3 and was significantly larger in patients treated with ERB: 41.5 vs. 33.6 cm^3 (p = 0.002). No significant differences in Awall, Rwall and separate muscle volumes were observed between patients with and without complaints.

The mean doses (±SD) to the IAS, EAS, PRM, and LAM were 33.7 (±13.2), 18.7 (±10.8), 46.0 (±10.1), and 40.5 (±7.3) Gy, respectively, and differed significantly ($p < 0.001$), indicating that, overall, the EAS received the lowest dose and the PRM is exposed to the highest dose. The mean dose to all muscles together was 34.0 (±9.5) Gy, whereas D_{mean} Awall was 33.6 (±12.6) Gy. Rwall D_{mean} was 40.5 (±7.3) Gy.

Toxicity and dose parameters

Twenty-two patients reported one or more incontinence-related symptoms with the following distribution: frequency (15), urgency (12) and incontinence (10). The occurrence of urgency was strongly correlated with both incontinence (p = 0.004) and frequency (p = 0.002), whereas incontinence and frequency showed no significant correlation (p = 0.16). No significant differences in toxicity rates were seen between 3-field 3D-CRT, 4-field 3D-CRT, and IMRT.

In Table 2, doses to the pelvic floor muscles in patients with and without any complaint, urgency, incontinence, and frequency are displayed. In Table 3, the dose parameters for the Awall and Rwall that showed significant differences between these groups are given. Patients with any complaint had an Awall D_{mean} that was on average 7.6 Gy higher compared to patients without complaints (Table 3a). Also the mean doses to all individual muscles were higher in the former group. In addition to the data in Table 3a, an absolute reduction in Rwall A_{60} of 6% was observed in favor of the group without complaints (p = 0.06).

When patients were categorized according to the presence or absence of urgency, irrespective of other complaints, it appeared that all mean doses were significantly higher in the group with urgency, with an 11 Gy difference in Awall D_{mean}, 7 Gy in Rwall D_{mean} (Table 3b) and 8-13 Gy in D_{mean} of the individual muscles (Table 2). The largest differences in mean doses were seen for the IAS, EAS and PRM. Also most of the dose-volume and dose-surface parameters on both Awall and Rwall were higher in the patients reporting urgency.

Table 2 Mean (SD) doses to pelvic floor muscles in patients with and without any complaint, urgency, incontinence, and frequency, respectively.

		Complaints			**Urgency**			**Incontinence**			**Frequency**		
		Present	Absent	*p-value*	Present	Absent	*p*-value	Present	Absent	*p*-value	Present	Absent	*p*-value
IAS	D_{min}	8.2 (7.9)	6.1 (6.0)	*0.30*	10.0 (8.8)	6.1 (6.0)	*0.17*	10.6 (9.5)	6.1 (5.9)	*0.18*	7.4 (7.0)	6.9 (7.0)	*0.82*
	D_{mean}	**38.1 (12.7)**	**29.9 (12.7)**	***0.03***	**43.4 (11.4)**	**30.5 (12.2)**	***0.002***	39.5 (13.7)	32.2 (12.8)	*0.12*	36.0 (13.3)	32.6 (13.2)	*0.42*
	D_{max}	66.4 (11.1)	63.8 (13.4)	*0.48*	69.2 (9.0)	63.6 (13.1)	*0.18*	67.7 (9.7)	64.3 (12.9)	*0.45*	64.4 (12.8)	65.3 (12.3)	*0.82*
EAS	D_{min}	5.3 (5.5)	3.7 (4.2)	*0.28*	6.6 (5.8)	3.7 (4.3)	*0.07*	7.3 (7.0)	3.7 (3.9)	*0.14*	4.8 (5.3)	4.2 (4.7)	*0.73*
	D_{mean}	**23.1 (11.1)**	**14.9 (9.2)**	***0.008***	**28.9 (10.0)**	**15.2 (8.9)**	***< 0.001***	**27.0 (11.5)**	**16.5 (9.6)**	***0.005***	22.1 (12.3)	17.1 (9.9)	*0.18*
	D_{max}	**61.5 (14.8)**	**48.4 (21.6)**	***0.02***	**66.8 (10.7)**	**50.3 (20.5)**	***0.001***	**65.5 (11.6)**	**51.5 (20.5)**	***0.009***	58.8 (17.0)	52.4 (20.9)	*0.27*
PRM	D_{min}	**29.0 (8.9)**	**23.9 (9.1)**	***0.05***	**33.6 (7.0)**	**23.8 (8.7)**	***0.001***	**31.9 (8.3)**	**24.8 (9.0)**	***0.03***	27.4 (9.7)	25.7 (9.2)	*0.58*
	D_{mean}	**50.4 (9.5)**	**42.3 (9.3)**	***0.005***	**55.5 (8.5)**	**42.9 (8.6)**	***< 0.001***	51.3 (9.0)	44.6 (10.1)	*0.06*	48.7 (10.6)	44.8 (9.8)	*0.25*
	D_{max}	72.2 (2.5)	70.9 (5.3)	*0.26*	72.4 (2.4)	71.2 (4.7)	*0.40*	72.0 (2.3)	71.4 (4.7)	*0.68*	72.2 (2.5)	71.2 (4.9)	*0.34*
LAM	D_{min}	28.0 (9.1)	25.7 (6.7)	*0.31*	**31.5 (7.3)**	**25.2 (7.5)**	***0.02***	29.4 (9.3)	26.0 (7.5)	*0.24*	27.1 (9.1)	26.6 (7.5)	*0.86*
	D_{mean}	**43.2 (8.5)**	**38.3 (5.2)**	***0.03***	**46.6 (8.7)**	**38.5 (5.5)**	***< 0.001***	43.4 (9.7)	39.8 (6.4)	*0.17*	41.5 (7.7)	40.1 (7.1)	*0.57*
	D_{max}	70.7 (6.6)	70.8 (6.2)	*0.95*	69.7 (8.5)	71.1 (5.4)	*0.50*	68.9 (9.1)	71.3 (5.3)	*0.29*	70.0 (7.7)	71.1 (5.6)	*0.61*

Abbreviations: IAS = internal anal sphincter; EAS = external anal sphincter; PRM = puborectalis muscle; LAM = levator ani muscles; D_{min} = minimum dose; D_{mean} = mean dose; D_{max} = maximum dose. Bold entries indicate significant differences.

Table 3 Mean (SD) dose parameters to the anal wall and rectal wall showing significant differences between patients with and without complaints; **a**) any complaints and **b**) urgency. No significant differences were observed between patients with and without incontinence or frequency.

a)		NO COMPLAINTS	COMPLAINTS	*p*-value
Awall	**D_{mean} (Gy)**	30.1 (11.4)	37.7 (11.4)	*0.04*
	V_{30} (%)	44 (27)	61 (28)	*0.04*
	V_{40} (%)	24 (19)	39 (24)	*0.02*
	V_{50} (%)	17 (14)	30 (19)	*0.01*
	V_{60} (%)	11 (14)	21 (15)	*0.03*
Rwall	**V_{40} (%)**	38 (10)	46 (16)	*0.04*
	A_{40} (%)	44 (13)	53 (17)	*0.04*
	A_{50} (%)	36 (10)	45 (15)	*0.02*

b)		NO URGENCY	URGENCY	*p*-value
Awall	**D_{mean} (Gy)**	31.7 (13.6)	42.8 (11.9)	*0.002*
	V_{20} (%)	65 (23)	82 (23)	*0.03*
	V_{30} (%)	45 (26)	73 (26)	*0.002*
	V_{40} (%)	25 (19)	50 (21)	*<0.001*
	V_{50} (%)	18 (15)	38 (17)	*<0.001*
	V_{60} (%)	12 (14)	26 (15)	*0.004*
Rwall	**D_{mean} (Gy)**	38.9 (6.2)	45.5 (8.2)	*0.005*
	V_{30} (%)	58 (21)	77 (14)	*0.001*
	V_{40} (%)	37 (10)	54 (14)	*<0.001*
	V_{50} (%)	31 (7)	43 (12)	*0.008*
	V_{60} (%)	25 (6)	33 (11)	*0.02*
	A_{30} (%)	62 (18)	77 (13)	*0.02*
	A_{40} (%)	43 (13)	63 (17)	*<0.001*
	A_{50} (%)	36 (10)	54 (14)	*<0.001*
	A_{60} (%)	28 (7)	38 (12)	*0.001*

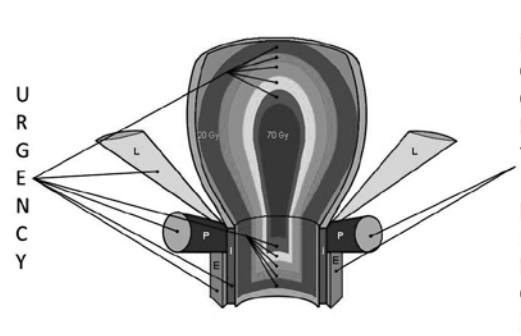
Abbreviations: Awall = anal wall; Rwall = rectal wall; D_{min} = minimum dose; D_{mean} = mean dose; D_{max} = maximum dose; V_x = relative volume exposed to ≥ x Gy; A_x = relative surface area exposed to ≥ x Gy.

When patients with and without incontinence were compared, less pronounced differences were observed (Table 2). Although non-significant differences were seen in Awall parameters, only D_{mean} and D_{max} of the EAS and D_{min} of PRM were significantly higher in patients with incontinence. PRM D_{mean} showed a borderline-significant difference ($p = 0.06$).

Patients with and without frequency showed no significant differences in dose parameters (Table 2). Rwall A_{40} and A_{50} were 10% and 8% lower in the latter group ($p = 0.06$).

Fig. 2 shows a schematic image of the Awall, Rwall and pelvic floor muscles, as well as the observed associations with the incontinence-related complaints. It shows that urgency is associated with rectal, anal and all pelvic floor muscle dose parameters, while incontinence is only associated with doses to the EAS and PRM. As mentioned above, no associations were found for frequency.

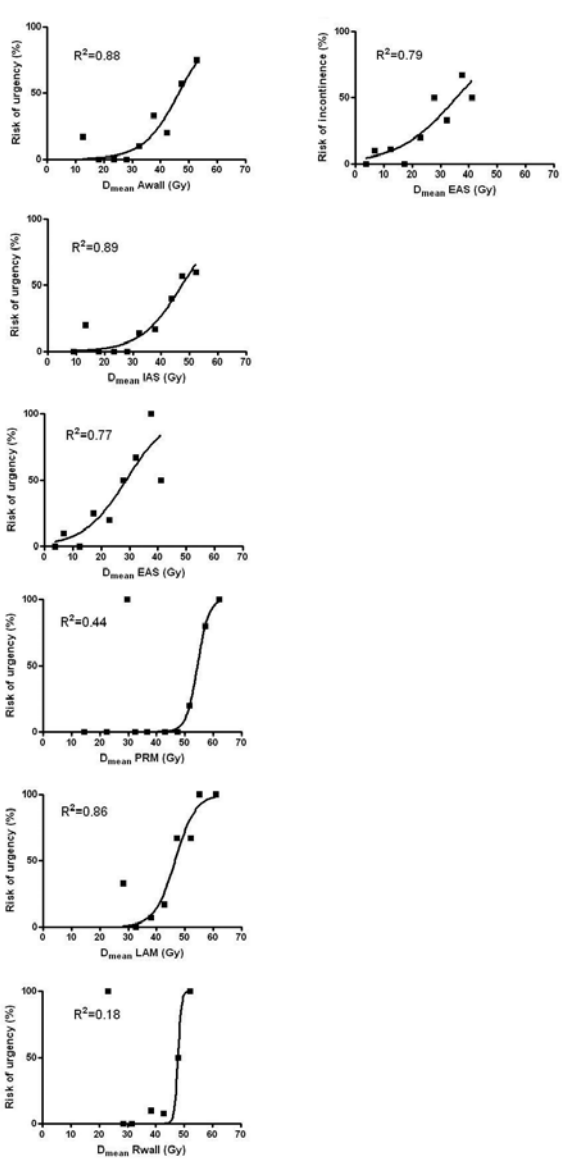
Fig. 2 Schematic image of the rectum, anal canal and individual pelvic floor muscles (I: internal anal sphincter; E: external anal sphincter; P: puborectalis muscle; L: levator ani muscles). Lines represent associations between complaints and subsites. Color figure at p 168.



Dose-effect relationships

The graphs in Fig. 3 show dose-effect relationships for urgency and incontinence with mean doses to the different structures. Estimation of mean doses at which 50% of patients report the respective complaint (D_{50}) ranged from 30 Gy (EAS) to 55 Gy (PRM). As shown, best fits were obtained for urgency and doses to the Awall, IAS, EAS and LAM (R^2 ranging from 0.77 to 0.89), and for incontinence and dose to the EAS ($R^2 = 0.79$). Based on these dose-effect relationships, the following constraints for D_{mean} to the pelvic floor muscles can be deduced to keep the risk of complications ≤5%: ≤30 Gy (IAS), ≤10 Gy (EAS), ≤50 Gy (PRM) and ≤40 Gy (LAM).

Fig. 3 Dose-effect curves for urgency (left column) and incontinence (right column) with doses to different structures.



Abbreviations: D_{mean}: mean dose; Awall: anal wall; IAS: internal anal sphincter; EAS: external anal sphincter; PRM: puborectalis muscle; LAM: levator ani muscles.

Effect of ERBs

Significantly fewer complaints were observed in patients treated with ERB compared to those treated without ERB: 29% vs. 70% ($p = 0.005$). Regarding specific symptoms, urgency and incontinence occurred less frequently in the group treated with ERB: 7% vs. 50% ($p = 0.001$) and 7% vs. 40% ($p = 0.006$), respectively. Frequency was reported by 40% of the patients treated without ERB and in 25% of patients irradiated with ERB ($p = 0.27$). It should be noted, however, that due to a sequential cohort effect, median follow-up in patients treated with ERB was significantly shorter than in patients treated without ERB (17 vs. 36 months, $p < 0.001$).

Table 4 Mean (SD) dose parameters to the anal wall, rectal wall and pelvic floor muscles showing significant differences between patients treated with and without endorectal balloon.

		No ERB	ERB	*p*-value
Awall	**D_{mean} (Gy)**	39.9 (11.6)	30.6 (14.4)	*0.02*
	V_{20} (%)	77 (20)	63 (24)	*0.03*
	V_{30} (%)	69 (23)	40 (26)	*<0.001*
	V_{40} (%)	45 (20)	21 (17)	*<0.001*
	V_{50} (%)	33 (17)	15 (14)	*<0.001*
	V_{60} (%)	22 (14)	11 (14)	*0.008*
Rwall	**D_{max} (Gy)**	71.4 (2.0)	75.2 (3.2)	*<0.001*
	V_{30} (%)	74 (15)	54 (21)	*0.001*
	V_{40} (%)	50 (14)	36 (9	*0.001*
	V_{50} (%)	39 (11)	30 (7)	*0.001*
	V_{60} (%)	31 (9)	24 (6)	*0.007*
	A_{40} (%)	57 (15)	42 (13)	*0.001*
	A_{50} (%)	47 (15)	35 (10)	*0.005*
	A_{60} (%)	34 (11)	28 (8)	*0.04*
IAS	**D_{mean} (Gy)**	40.4 (11.6)	28.9 (12.3)	*0.002*
	D_{max} (Gy)	68.9 (5.5)	62.2 (15.0)	*0.04*
EAS	**D_{mean} (Gy)**	24.5 (11.0)	14.5 (8.8)	*0.001*
	D_{max} (Gy)	62.8 (13.2)	48.4 (21.6)	*0.006*
PRM	**D_{min} (Gy)**	30.7 (9.8)	23.1 (7.6)	*0.004*
	D_{mean} (Gy)	53.0 (7.1)	41.0 (9.0)	*<0.001*
LAM	**D_{min} (Gy)**	32.0 (7.3)	23.0 (6.0)	*<0.001*
	D_{mean} (Gy)	46.8 (5.6)	36.1 (4.6)	*<0.001*

Abbreviations: Awall = anal wall; Rwall = rectal wall; D_{min} = minimum dose; D_{mean} = mean dose; D_{max} = maximum dose; V_x = relative volume exposed to ≥ x Gy; A_x = relative surface area exposed to ≥ x Gy; IAS = internal anal sphincter; EAS = external anal sphincter; PRM = puborectalis muscle; LAM = levator ani muscles.

When the treatment plans of patients treated with and without ERB were compared, doses to the Awall, Rwall, and all pelvic floor muscles were significantly lower when an ERB was applied (Table 4). Only Rwall D_{max} was significantly increased in the ERB group (75.2 vs. 71.4 Gy, $p < 0.001$).

Discussion

This study shows that pelvic floor muscles can be delineated separately on planning CT scans, and are not equally exposed to radiation doses in prostate EBRT. When the Awall is delineated, approximately two-thirds of this total continence apparatus is excluded. Although all muscles seem to be involved in the development of late anorectal toxicity, different incontinence-related complaints seem to be associated with different structures. Furthermore, specific dose-effect relationships were shown for different incontinence-related complaints.

To our knowledge, this is the first attempt to separately delineate and evaluate pelvic floor muscles that may play a role in anorectal toxicity after prostate EBRT. In previous reports, the anal canal, considered to be a continuation of the rectal wall, has been used as a surrogate for the continence apparatus and evaluated as such [4;5]. By separately delineating the individual muscles considered to be involved in fecal continence, we observed an almost threefold increase in volume as compared to the Awall. Regarding dosimetry and anatomy, the Awall seems to be more or less equal to the IAS. This means that by delineating the Awall substantial components of the continence apparatus are excluded.

We observed that the puborectalis muscle receives the highest radiation dose in prostate EBRT, followed by the levator ani muscles, internal anal sphincter and external anal sphincter. The anatomical relation of these muscles to the target volume (*i.e.* a large portion of the PRM is adjacent to the prostate) might explain these findings. It has been suggested that the PRM is most directly responsible for fecal continence [11]. Its function is maintaining the anorectal angle, thereby preventing the passage of solid stool. Fernández-Fraga *et al.* mentioned failure of the LAM as major contributor to fecal incontinence. However, they regarded the PRM to be a component of the LAM [12]. The fact that the PRM receives the highest radiation dose in prostate EBRT might thus be hazardous for fecal continence. In the future, this might be a consideration in defining, especially lateral, margins around the CTV, in order to spare the PRM as much as possible. The fact that prostate motion is least in the lateral direction [22], may support the consideration to use small lateral margins. In the present study, a borderline significant difference in PRM D_{mean} and a significant difference in PRM D_{min} were observed between patients with and without

incontinence. Also, a significant difference in doses to the EAS was observed in favor of the latter group. Although the IAS is thought to be responsible for anal continence in rest, as it contributes 70-85% of the resting pressure of the anal sphincter complex [23], the dose to the IAS was not significantly higher in patients with incontinence, compared to patients without incontinence. These observations might indicate that in the development of radiation-induced incontinence, in particular the EAS and PRM play a role. As Awall D_{mean} was not significantly different between patients with and without incontinence, the Awall might not be a good surrogate for the continence apparatus when the influence of radiation dose on incontinence is investigated.

When patients with and without urgency were compared, D_{mean} to both the Awall, Rwall and all individual pelvic muscles were significantly lower in the latter group, as well as several dose-volume and dose-surface parameters. This suggests that urgency is caused by a combination of not only anal, but also rectal factors, and that all pelvic muscles play a role in its development. Besides a borderline significant difference in Rwall A_{40} and A_{50} between patients with and without frequency, no dose-effect relationships for frequency were found. This might explain why no significant difference in the occurrence of frequency between patients treated with and without ERB was observed, despite a beneficial effect on anorectal doses. Possibly, additional factors contribute to the development of frequency.

Applying constraints for pelvic floor muscles might reduce incontinence-related complaints. Based on the results from the present study, although hypothesis-generating, we suggest ≤30 Gy, ≤10 Gy, ≤50 Gy and ≤40 for D_{mean} to IAS, EAS, PRM and LAM, respectively, with an associated risk of urgency or incontinence ≤5%. It has been shown previously that sparing of rather small structures (*e.g.* vessels involved in penile erection) is feasible with prostate IMRT [10].

Yeoh *et al.* observed an increased bowel frequency, urgency and fecal incontinence at 2-year follow-up after prostate EBRT [13]. Furthermore, repeated anorectal manometry testing showed progressive reductions of anal pressures, rectal compliance and rectal volumes associated with sensory perception and the desire to defecate. Weakening of both the IAS and EAS was observed, while ultrasonography showed an increased EAS thickness, without changes in IAS thickness. According to the authors, this weakness was most likely a result of pudendal nerve damage, as striated muscle (EAS) is thought to be radioresistant. This does, however, not explain the increased EAS thickness. It was suggested that this increased thickness is due to hypertrophy of motor units spared from radiation damage. Although no difference was observed between two radiation schedules, dose-effect relationships regarding specific anorectal subsites were not investigated.

The suggestion that specific anorectal complaints originate from different anatomic regions was published previously [9]. Heemsbergen *et al.* came to similar conclusions, based on anorectal dose-map analysis [5]. In their study, a dose-effect relationship for incontinence was observed in the anal and lower rectal region. No such explanatory effects were observed for urgency and frequency. In the present study, it was observed that several dose-parameters were associated with urgency and only some to be associated with incontinence. A possible explanation for this discrepancy might be a difference in toxicity scoring. As anorectal toxicity comprises different symptoms, precise categorization is essential to be able to compare results between studies. Patients reporting a sudden urge to have a bowel movement may be scored as urgency. In some cases, however, especially when one is far from a toilet, this urge might cause loss of stools and could therefore be scored as incontinence too.

The reduced Awall and Rwall doses due to ERBs is in concordance with previous studies [14;15;19;24;25]. Only Rwall D_{max} was significantly higher in patients treated with ERB, probably because the anterior rectal wall is pushed towards the CTV. Previously, however, it has been shown that, despite this, a reduction in Rwall damage and toxicity was observed with ERB application [24]. The present study shows that, when pelvic floor muscles are delineated separately, the sparing effect of an ERB applies to all muscles. Given the abovementioned dose-effect relationships, this might explain that in patients treated with ERB less incontinence and urgency were reported than in patients treated without ERB. However, it should be noted that this is not a prospective trial, but an observational study with cross-sectional design, potentially leading to bias. Furthermore, the number of patients reporting complaints was relatively low (*e.g.* 10 reported incontinence). Other limitations include differences in length of follow-up between different groups (*e.g.* with and without ERB and also between patients with and without complaints), and bias due to the sequential cohort effect of ERB application. Given the dynamic process of toxicity development over time [13], shorter follow-up might underestimate the eventual toxicity incidence. Finally, given the relative small number of patients, multivariate testing to investigate the dose parameters independently was not possible. Hence, conclusions derived from this study should be considered hypothesis-generating, and might be a basis for future research.

As this is the first attempt to delineate the pelvic floor muscles separately, no comparison with previous studies can be made regarding these delineations. Although CT-imaging is not a regularly used diagnostic tool in the evaluation of fecal incontinence [16], it proved to be possible to recognize the separate muscles on the planning CT-scans. However, fusion of the CT-images with magnetic resonance images might improve the accuracy of the delineation. Furthermore, one might

question the day-to-day reproducibility of the rather small delineated individual muscles, *i.e.* whether the dosimetric parameters obtained from the planning CT-scan are representative for the whole treatment due to movement and other setup uncertainties. However, in our opinion, the same accounts for Awall and Rwall doses from previous studies. Daily cone-beam CT-imaging with adaptive planning might be useful to investigate this issue, as well as the influence of ERBs on anatomic consistency.

In conclusion, pelvic floor muscles, considered to be involved in normal fecal continence are not exposed equally to radiation doses in prostate EBRT: the EAS is exposed to the lowest dose, while the PRM receives the highest dose. By delineating the Awall, most of the continence apparatus is excluded from evaluation. Incontinence, urgency and frequency show associations with different subsites, suggesting different pathogenesis. Incontinence seems associated with doses to the PRM and EAS, while in the development of urgency both anal and rectal factors are involved. Based on dose-effect curves for urgency and incontinence, constraints for treatment planning could be established. No dose-effect relationships for frequency were observed. Finally, patients treated with ERB showed several reduced dose parameters to both the Awall and Rwall, as well as to all individual pelvic floor muscles, and reported significantly less urgency and incontinence. This suggests that ERBs might reduce anorectal toxicity. Prospective trials, however, are needed to confirm this hypothesis.

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7

An Endorectal Balloon Reduces Intrafraction Prostate Motion During Radiotherapy

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Abstract

Purpose: To investigate the effect of endorectal balloons (ERBs) on intrafraction and interfraction prostate motion during radiotherapy.

Methods and Materials: 30 patients were treated with intensity-modulated radiotherapy, to a total dose of 80 Gy in 40 fractions. In 15 patients a daily-inserted air-filled ERB was applied. Prostate motion was tracked, in real-time, using an electromagnetic tracking system. Interfraction displacements, measured before each treatment, were quantified by calculating the systematic and random deviations of the center of mass of the implanted transponders. Intrafraction motion was analyzed in timeframes of 150 s, and displacements >1 mm, >3 mm, >5 mm and >7 mm were determined in the anterior-posterior (AP), left-right (LR), and superior-inferior (SI) direction, and for the 3D-vector. Manual table corrections, made during treatment sessions, were retrospectively undone.

Results: 576 and 567 tracks have been analyzed in the No-ERB-group and ERB-group, respectively. Interfraction variation was not significantly different between both groups. After 600 s, 95% and 98% of the treatments were completed in the respective groups. Significantly fewer table corrections were performed during treatment fractions with ERB: 88 vs. 207 ($p = 0.02$). Intrafraction motion was significantly reduced with ERB. During the first 150 s, only negligible deviations were observed, but after 150 s, intrafraction deviations increased with time. This resulted in cumulative percentages of 3D-vector deviations >1 mm, >3 mm, >5 mm and >7 mm that were 57.7%, 7.0%, 0.7% and 0.3% in the ERB-group vs. 70.2%, 18.1%, 4.6% and 1.4% in the No-ERB-group after 600 s. The largest reductions in the ERB-group were observed in the AP direction. These data suggest that a 5 mm CTV-to-PTV margin is sufficient to correct for intrafraction prostate movements when using an ERB.

Conclusions: ERB significantly reduces intrafraction prostate motion, but not interfraction variation, and may in particular be beneficial for treatment sessions longer than 150 s.

Introduction

During the course of radiotherapy (RT) the prostate position varies [1], both during the actual treatment and in-between fractions, commonly characterized by intrafraction and interfraction variation, respectively [2]. Planning target volume (PTV) margins are applied to ensure proper dose coverage of the clinical target volume (CTV). Applying these margins inevitably leads to irradiation of normal tissues, potentially causing radiation-induced toxicity. However, when using tight margins, the prostate motion may compromise dosimetric coverage of the CTV. In particular for hypofractionated or stereotactic body RT, consisting of only a few fractions, target motion at a single fraction may have a large impact [3].

Endorectal balloons (ERBs) have been applied in prostate RT to reduce anorectal toxicity, mainly because of their rectal wall sparing effect by pushing parts of the rectal wall out of the high-dose regions [4-7], but also for its assumed prostate immobilizing effect [7-9], thereby enabling smaller CTV-to-PTV margins. There is, however, no consensus on the effect of ERBs on interfraction prostate motion, and additional position verification and correction protocols have been advised [10;11]. Two studies reported reduced intrafraction motion in patients with ERB, compared to patients without ERB, one using repeated CT-imaging [8], another using cine-MRI [12]. Recently, real-time tracking data on the effect of an ERB on prostate motion during treatment have been described [13]. However, no direct comparison was made to patients treated without ERB.

The main purpose of the present study is to investigate whether an air-filled ERB has a prostate immobilizing effect in RT, by comparing intrafraction prostate gland motion between prostate cancer patients treated with ERB and without ERB. The second goal is to assess the influence of an ERB on interfraction prostate variation. A four-dimensional electromagnetic tracking system was used for continuous, real-time tracking of intrafraction prostate motion [14].

Methods and materials

Patients and treatment

Thirty patients were treated for localized prostate cancer at the M.D. Anderson Cancer Center Orlando, FL, USA, using a 5- to 7-field IMRT technique, delivered with a Novalis system (BrainLAB AG, Heimstetten, Germany). A total dose of 80 Gy in 2-Gy fractions to the prostate was given to all patients, 5 times a week. An isotropic CTV-to-PTV margin of 6 mm was applied, except in the posterior direction, where a margin of 4 mm was used.

Calypso four-dimensional localization system

In all patients, three electromagnetic transponders, each with a unique resonant frequency (Beacon transponders, Calypso Medical Technologies, Seattle, WA, USA) were transrectally implanted into the prostate under ultrasound guidance, at least 4 days before the planning CT-scan was performed. In addition to the transponders, the Calypso system consists of an array, containing source and receiver coils, an infrared camera for localization of the array within the treatment room, and data acquisition and analysis computers. The source coils, placed in a known position above the patient, excite the transponders. After excitation, the transponders emit an electromagnetic signal, which is detected by the receiver coils, at a frequency of 10 Hz. The position of the transponders, relative to the isocenter, is detected by the system and can be used for both patient positioning and to continuously monitor the transponders' position during treatment. An extensive description of the system and its properties has been published previously [14;15].

Endorectal balloon

Prostate motion data from 30 patients were analyzed under an IRB-approved study. In 15 consecutive patients an ERB was used daily, the other patients were treated without ERB, referred to as the ERB-group and the No-ERB-group, respectively. The ERB consists of a 20-cm-long flexible shaft of polyvinylchloride with a silicon balloon (QLRAD B.V., Dalfsen, The Netherlands). A deflated ERB has a diameter of 13 mm and after inflation with 100 cc of air, the diameter and length of the balloon are 60 mm and 65 mm, respectively. Radiotherapists inserted the deflated balloon before CT-simulation and before each treatment fraction, facilitated by lubricant, with the patients lying on their left side. To maintain a good ERB position in relation to the prostate, it was fixed with an individually adjustable stopper after inflation, preventing ERB movement in the superior-inferior direction.

Protocol

All patients were scanned and treated in a supine position according to local protocol, which included the application of a knee cushion for patient comfort, a rubber band around their feet for immobilization, and no instructions regarding bladder and rectum filling. Before each treatment fraction, the transponders were localized, and after the patients were aligned properly using the coordinates of the transponders at simulation as a reference, continuous tracking of the transponders' position commenced.

Whenever a displacement in a certain direction exceeded 3 mm for a prolonged time (*i.e.* did not resolve by the end of a single beam delivery), a manual table correction was made by the radiotherapists in-between two treatment beams. The delivery of a single beam was never interrupted, regardless of any observed prostate displacement.

These corrections were documented to enable retrospective calculation of the uncorrected prostate position during treatment (*i.e.* without table shifts).

Data analysis

MATLAB, version R2007b (The Mathworks, Natick, MA, USA) was used for data analysis. Interfraction variation of the transponder displacement after initial patient positioning, relative to the position at simulation, was determined for the AP, LR and SI direction. It was quantified by calculating the mean of means (MoM) of all patients, the systematic dispersion $\sum$ and the random variation σ [16] of the centre of mass of the three transponders for both treatment groups in all directions. Similar calculations were carried out for the 3D-vectors and the rotations around the AP, LR and SI axes. For the analysis of intrafraction displacements, each track (*i.e.* continuously tracked data during one treatment fraction) was divided into time frames of 150 s, for which the deviations >1 mm, >3 mm, >5 mm, >7 mm, and >10 mm were assessed for each direction, as well as the 3D-vector. The cumulative percentages of tracked data over the elapsed time frames, exceeding these thresholds, were determined. To discriminate between the impact of the ERB on slow and rapid intrafraction motion, each track was divided into 3 separate signals, representing (1) "trends", persisting more than 1 min, (2) somewhat faster "transients" that were present several seconds, and (3) "spikes" that lasted less than 1 s and were attributed to instrumental noise. For that purpose, a running average filter was used over 1000 and 20 data points to detect and subsequently subtract the slow trends and the faster transients respectively, while the remainder of the original track was attributed to the signal noise. Finally, the number of manual table corrections was recorded in all patients.

Statistical analysis

A left-sided independent-samples t-test, using a significance level of $p \leq 0.05$ was used for (a) the comparison of the interfraction random variation σ between both patient groups, and (b) the comparison of the mean intrafraction percentages of tracked data exceeding specific thresholds. The differences between the variances around the mean percentage, as well as the systematic interfraction dispersion Σ of both groups, were tested using the F-test, also with a significance level of $p \leq 0.05$.

Results

Prostate motion data of 1143 treatment sessions were available for analysis: 576 in the No-ERB-group and 567 in the ERB-group, corresponding to an average of 38.4 and 37.8 tracks per patient in the respective groups. The remaining 57 tracks were not useful for analysis due to a short duration of tracking or data acquisition interruptions.

Ninety-eight percent and 95% of the treatment sessions were completed within 600 s for the ERB-group and No-ERB-group, respectively. Therefore, data analysis was limited to 600 s.

In the ERB-group, 88 manual table corrections were made, compared to 207 in the No-ERB-group ($p = 0.02$). The maximum number of corrections per patient was 22 and 42, respectively. In each group, one patient needed no corrections.

Interfraction variation

Interfraction variations in the ERB-group and No-ERB-group are displayed in Table 1. The largest MoM in the ERB-group was -2.6 mm in the AP direction, and in the No-ERB-group this was -2.2 mm in the LR direction. No significant differences between both groups in Σ ($p = 0.06$-0.92) and σ ($p = 0.10$-0.32) were observed. Maximum Σ was observed in the AP direction in both groups (5.6 and 6.7 mm), while maximum σ occurred in LR direction (5.4 and 6.3 mm). Maximum rotational displacement was observed around the LR-axis, both with and without ERB, and was also not significantly different between the groups.

Table 1 Interfraction variation in the ERB-group (top) and No-ERB-group (bottom).

ERB	LR (mm)	SI (mm)	AP (mm)	Rot LR (˚)	Rot SI (˚)	Rot AP (˚)
MoM	-0.8	1.5	-2.6	3.0	-0.8	0.9
Σ	3.9	3.2	6.7	16.0	5.8	4.6
σ	6.3	3.0	3.9	4.3	2.6	1.7
No-ERB	**LR (mm)**	**SI (mm)**	**AP (mm)**	**Rot LR (˚)**	**Rot SI (˚)**	**Rot AP (˚)**
MoM	-2.2	0.6	-0.4	3.8	-0.1	-1.2
Σ	3.8	5.3	5.6	10.2	7.0	2.9
σ	5.4	2.7	3.8	3.9	1.5	1.3

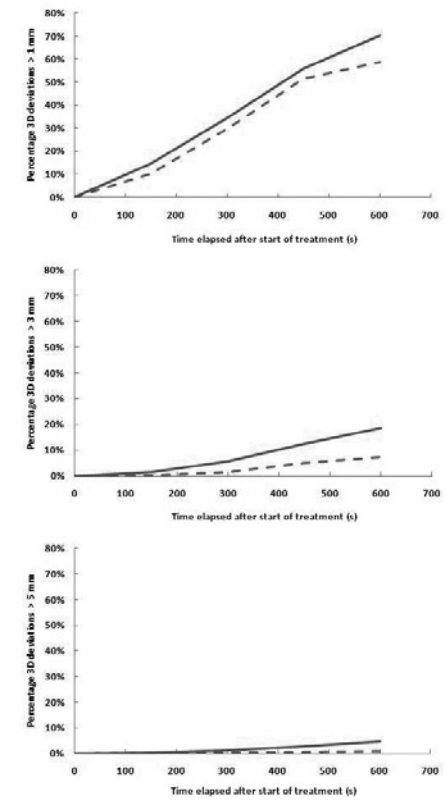
Abbreviations: ERB = endorectal balloon; MoM = mean of means; **Σ** = systematic displacement; **σ** = random displacement; Rot = rotation; LR = left-right; SI = superior-inferior; AP = anterior-posterior.

Intrafraction variation

An overview of the cumulative percentage of tracked data with displacements >1 mm, >3 mm, >5 mm, and >7 mm for both the ERB-group and No-ERB-group is given in Table 2. By far, most displacements were smaller than 5 mm. Displacements >10 mm were negligible in frequency and were therefore not included in the analysis.

Fig. 1 shows the graphs representing the cumulative percentage of 3D-vector displacements >1 mm, >3 mm and >5 mm for the ERB-group and No-ERB-group. During the first 150 s, only small displacements were observed in both groups, with 3D-vector displacements >1 mm in 14.7% and 10.0% in the No-ERB-group and ERB-group, respectively ($p = 0.001$). There was, however, a linear increase with time, which increased after 150 s, especially for displacements >3 mm. For example, after 150 s, for displacements >3 mm a constant rate equal to 2.3%.min^{-1} and 0.8%.min^{-1} was observed for the No-ERB-group and ERB-group, respectively. After 600 s, most of the fractions had finished, resulting in flattening of the curves and leading to a cumulative percentage of 18.1% and 7.0% displacements >3 mm in the No-ERB-group and ERB-group, respectively.

Fig. 1 Cumulative percentage of 3D-vector deviations >1 mm, >3 mm and >5 mm. Solid line: patients without ERB; dashed line: patients with ERB.



As shown in Fig. 1, the cumulative percentages of 3D displacements were always smaller in the ERB-group than in the No-ERB-group and were significantly different for 3D displacements <7 mm (Table 2). Eventually, after 600 s, absolute differences in favor of the ERB-group of 12.5% ($p = 0.008$), 11.1% ($p = 0.008$), 3.9% ($p = 0.02$), and 1.1% ($p = 0.06$) were observed for 3D-vector displacements >1 mm, >3 mm, >5 mm, and >7 mm, respectively. The variances of the cumulative percentage of 3D displacements >3 mm, >5 mm, and >7 mm were significantly smaller for the group of patients treated with ERB.

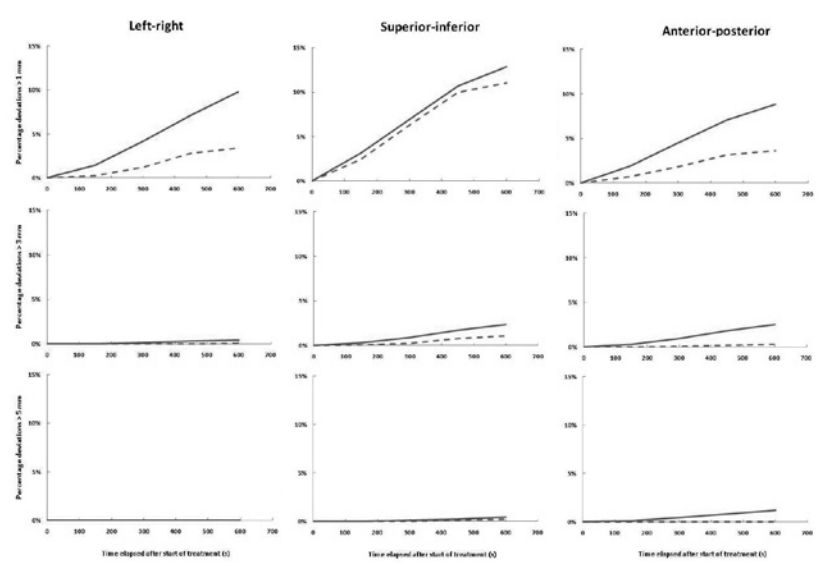
Table 2 Cumulative percentages of deviations exceeding 1, 3, 5, and 7 mm in patients without and with ERB. Bold entries indicate significant differences (t-test), * significantly different variances (F-test).

		> 1 mm		> 3 mm		> 5 mm		> 7 mm	
		No ERB	ERB	No ERB	ERB	No ERB	ERB	No ERB	ERB
LR	**150 s**	**1.4%***	**0.3%***	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	300 s	4.0%*	1.2%*	0.1%*	0.0%*	0.0%	0.0%	0.0%	0.0%
	450 s	6.8%*	2.7%*	0.3%*	0.0%*	0.0%	0.0%	0.0%	0.0%
	600 s	9.3%*	3.3%*	0.4%*	0.0%*	0.0%	0.0%	0.0%	0.0%
AP	**150 s**	**2.0%***	**0.7%***	**0.4%***	**0.0%***	0.1%*	0.0%*	0.0%*	0.0%*
	300 s	**4.8%***	**1.9%***	1.0%*	0.1%*	0.4%*	0.0%*	0.1%*	0.0%*
	450 s	7.6%*	3.3%*	1.9%*	0.2%*	0.9%*	0.0%*	0.2%*	0.0%*
	600 s	**9.4%***	**3.8%***	2.6%*	0.3%*	1.2%*	0.0%*	0.4%*	0.0%*
SI	**150 s**	3.2%	2.5%	**0.3%***	**0.0%***	0.0%*	0.0%*	0.0%	0.0%
	300 s	7.2%	6.7%	1.0%*	0.3%*	0.1%*	0.0%*	0.0%*	0.0%*
	450 s	11.1%	10.9%	1.8%	0.8%	0.3%	0.1%	0.0%*	0.0%*
	600 s	13.3%	12.3%	2.5%*	1.2%*	0.4%	0.2%	0.1%	0.1%
3D-vector	**150 s**	**14.7%**	**10.0%**	**1.4%***	**0.2%***	0.3%*	0.1%*	0.1%*	0.0%*
	300 s	**34.8%**	**29.0%**	**5.4%***	**1.3%***	**1.1%***	**0.2%***	0.4%*	0.1%*
	450 s	56.2%	50.4%	**12.1%***	**4.6%***	**2.6%***	**0.4%***	0.8%*	0.2%*
	600 s	**70.2%**	**57.7%**	**18.1%***	**7.0%***	**4.6%***	**0.7%***	1.4%*	0.3%*

Abbreviations: ERB = endorectal balloon; LR = left-right direction; AP = anterior-posterior direction; SI = superior-inferior direction.

Fig. 2 shows the graphs for the observed displacements in each direction for the ERB-group and No-ERB-group. Overall, no large differences in results between the different directions were observed, except for displacements <3 mm that occurred more frequently in the SI direction in both groups. Displacements >3 mm were rare, in particular for the ERB-group. Similar as observed for the 3D-vector displacements, displacements in the three directions were always smaller in the ERB-group than in the No-ERB-group, although significant differences were limited to AP displacements >1 mm (Table 2). The largest differences between the ERB-group and No-ERB-group were observed in the AP and LR directions for displacements >1 mm, with reductions from 9.3% to 3.3% in the LR direction and from 9.4% to 3.8% in the AP direction after 600 s. In particular in the AP direction, the ERB reduces large displacements. In addition, the variances of the cumulative percentage of displacements in the AP direction were significantly smaller in the ERB-group ($p < 0.02$). For the LR direction, this was only the case for the thresholds >1 mm and >3 mm, and for the SI direction only for the threshold >3 mm.

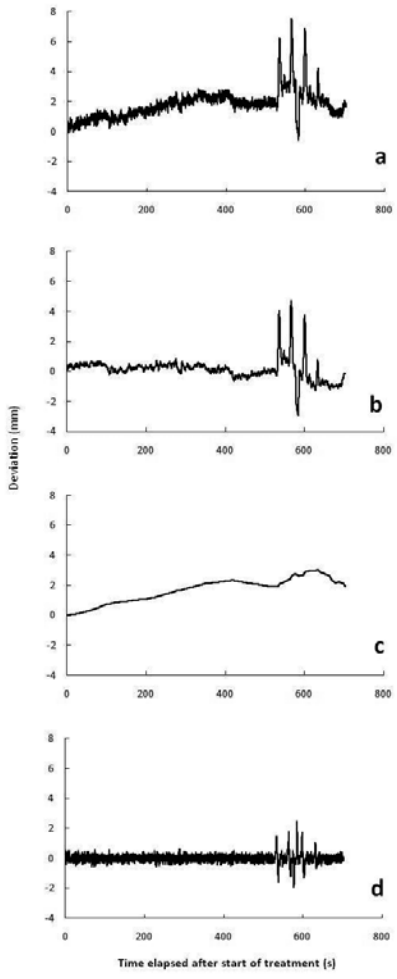
Fig. 2 Cumulative percentage of deviations >1 mm, >3 mm and >5 mm in three directions. Solid line: patients without ERB; dashed line: patients with ERB.



Different types of motion

An example of a track of one treatment fraction is shown in Fig. 3a. The decomposition of this track in transients, trends and spikes attributable to instrumental noise is displayed in Fig. 3b, 3c and 3d, respectively. Large variations were observed in the occurrence of these contributions, both between different tracks of the same patient, and between patients, and in the No-ERB-group as well as the ERB-group.

Fig. 3 Example of a track of one treatment fraction (**a**) with decomposition into transients (**b**), trends (**c**) and instrumental noise (**d**).



In Fig. 4 and 5, the contribution of both trends and transients to the deviations in three directions is shown. Trends constitute approximately 80% of all observed displacements and transients approximately 20%. LR displacements, however, are almost totally caused by trends. Application of an ERB diminishes both the trends and transients. Significant reductions in trends were observed for AP displacements >1 mm, in transients for AP displacements >1 mm and >3 mm.

Fig. 4 Cumulative percentage of trends >1 mm, >3 mm and >5 mm in three directions. Solid line: patients without ERB; dashed line: patients with ERB.

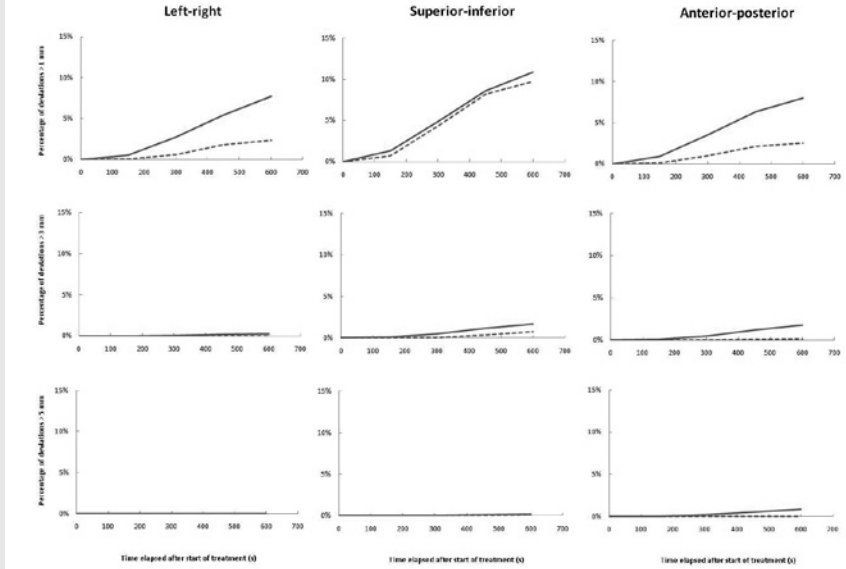
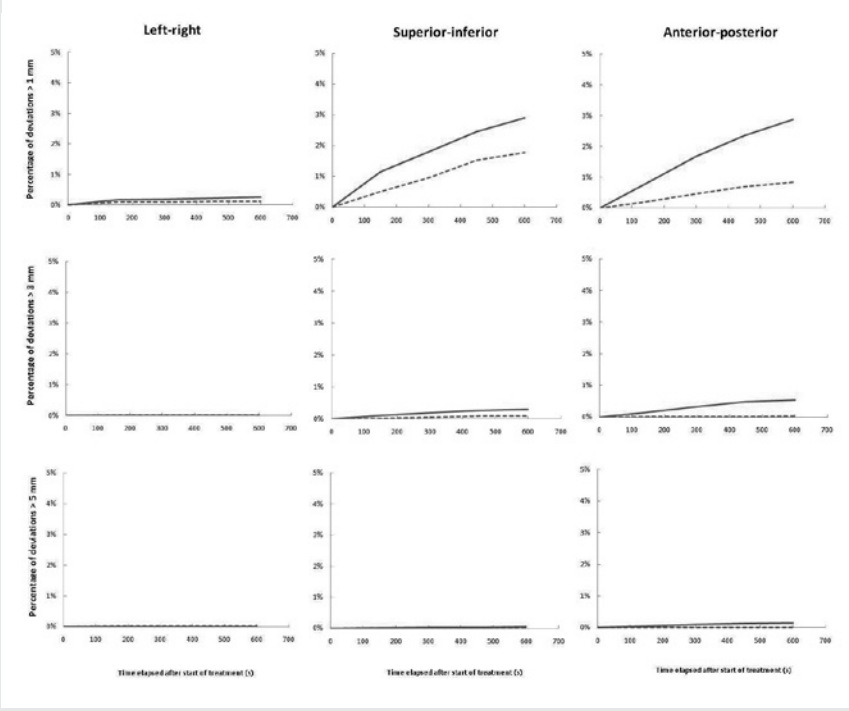


Fig. 5 Cumulative percentage of transients >1 mm, >3 mm and >5 mm in three directions. Solid line: patients without ERB; dashed line: patients with ERB.



Discussion

The results from the present study show that intrafraction displacements are negligible during the first 150 s of an average treatment fraction, but the percentage of prostate displacements increases with time. Application of an ERB reduces these displacements, in particular in the AP direction. In spite of the large variance of the occurrence of displacements within both groups, the reduction is significant for 3D displacements. However, for individual directions the reduction is only significant for displacements <3 mm in the AP direction. Interfraction setup deviations were not significantly different between patients treated with and without ERB.

Langen *et al.* found that, averaged over all patients, the prostate was displaced >3 mm and >5 mm in 13.6% and 3.3% of the total treatment time, respectively [14]. In the present study, for a similar group of patients treated without ERB at the same institute

and with the same protocol, we found percentages equal to 20.4% and 5.6% for these thresholds, respectively (Table 2). These differences can be explained by the large inter-patient and interfraction variation of the observed displacements with respect to the small number of patients included in both studies (17 and 15 patients, respectively). Even larger intrafraction deviations were observed by Kotte *et al.* [17]. A direct comparison of their results with the results from our study is difficult, because the timescale in their study was not quantified. However, after analyzing the data from our study in a similar way (data not shown), it was observed that in particular deviations >2 mm occurred considerably less frequent in the group treated without ERB than described by Kotte *et al.* Because the effect of the ERB is larger for larger displacements, it would therefore possibly be more pronounced in the latter population than in the present study.

Studies using cine-MRI to assess intrafraction motion without application of an ERB revealed that rectal filling was a predictor of prostate movements [18;19]. It was stated that a filled rectum is associated with mobile gas pockets, leading to rectal movements and hence prostate displacements. It seems unlikely that moving stool and mobile gas pockets also induce intrafraction motion when an ERB is applied, which is presumably the most important mechanism by which the ERB reduces intrafraction prostate movement. Other mechanisms may include fixation of the prostate by pushing it towards the pubic bone during treatment. All patients in this study were treated in a supine position, as it has been shown that this reduces prostate movements due to ventilation as compared to a prone position [20]. A recent study using the Calypso system showed a threefold decrease in prostate movements >3 mm and >5 mm [21].

In two other studies intrafraction motion was compared between patients with and without ERB. In the first study, D'Amico *et al.* concluded that an ERB reduced intrafraction motion, as repeated CT-imaging with 1 min time intervals showed a decrease in maximum prostate AP displacement from 4 mm to ≤1 mm [8]. Although intermittent imaging using this interval is not as sensitive as continuous real-time tracking [22], it confirmed the prostate immobilizing effect, as observed in the present study. Recently, the ERB-induced reduction in intrafraction prostate displacements has been confirmed in a second study, using cine-MRI [12]. Application of a 100 ml water-filled ERB was shown to reduce intrafraction prostate motion in both prone and supine patient position, as compared to 100 ml of water infused directly into the rectum in proton therapy. In that study, the scanning time was 240 s, in which a 3D prostate displacement of 3 mm was observed in approximately 5% of time, both with and without ERB. Smaller displacements were observed more frequently in patients without ERB. In the present study, patients without ERB had 3D displacements >3 mm

in 5.4% of time after 300 s, while this was significantly lower in patients treated with ERB: 1.3%. It should be noted, however, that these studies cannot be directly compared, because water-filled ERBs were used in the cine-MRI study, and water infused in the rectum in the control group. Both *et al.* recently reported on intrafraction prostate displacements, also measured with electromagnetic tracking, for a different type of ERB [13]. Small displacements were observed, and it was concluded that ERBs stabilize the prostate. Similar to the present study, correlations were observed between displacements and elapsed treatment time. In contrast to the present study, however, the data was not directly compared to patients treated without ERB. When comparing the displacements with ERB from both studies, those in the present study are somewhat smaller than in the study by Both *et al*, which might be caused by the use of a different ERB.

With regard to interfraction deviations, Wachter *et al.* observed maximum prostate AP displacements >5 mm in 2/10 patients treated with ERB, compared to 8/10 patients treated without ERB, using repeated CT-examinations, leading to the conclusion that an ERB reduces prostate movements during treatment [7]. Also other investigators observed only limited prostate motion with ERB application, using biweekly CT scans, with a maximum mean displacement (1 SD) of 0.98 (1.78) mm [9;23]. However, in both studies prostate displacements were measured based on CT scan comparison, and patient setup data were not mentioned. Results from the present study could confirm neither these small displacements, nor an ERB-induced reduction of interfraction displacements, which confirms the results from a previous study from our group using a slightly different ERB [11]. Another study by El-Bassiouni *et al.* confirmed that interfraction deviations are not reduced by ERB application [24]. An important contribution to interfraction variation of prostate position is the patient's body position after initial treatment setup and contraction or relaxation of musculature, which cannot be altered by application of an ERB. Furthermore, on planning CT scans, sporadically, stool proximal to the ERB and prostate is observed. This indicates that stool -when present- may get trapped at insertion of the ERB, and may give rise to interfraction variation of the prostate position, but, as stated before, does not induce intrafraction motion when an ERB is applied.

Application of tight CTV-to-PTV margins may be possible when prostate motion is tracked continuously, as has been suggested previously [25]. However, tight margins require a strict re-alignment or tracking protocol, potentially leading to an increased workload for radiotherapists. In this study, a repositioning threshold of 3 mm was used, leading to 88 and 207 corrections in the ERB-group and No-ERB-group, respectively. This means that usage of an ERB leads to less treatment interruptions, hence a decreased workload for radiotherapists. These corrections were retrospectively undone to analyze the actual displacements, showing that after 600 s (when most of the treatments had finished) in the No-ERB-group 18.1% of tracked data in 3D exceeded 3 mm, compared to 7.0% in the ERB-group (Table 2). This means that application of an isotropic CTV-to-PTV margin of 3 mm in patients without ERB theoretically leads to underdosage of the CTV in almost 20% of treatment time, when no intrafraction corrections are done. In case of a 5 mm uniform margin, this percentage decreases to 4.6%, compared to 0.7% with ERB, indicating that when using an ERB and 5 mm margins, even without intrafraction corrections, the CTV exceeds the PTV in <1% of time, suggesting this is a sufficient margin when on-line corrections are used to minimize interfraction variation. It should be noted, however, that in the present study, additional factors that might influence CTV-to-PTV margins, like seminal vesicle motion and prostate deformation, were not included in the analyses.

Real-time image guidance has been recommended for hypofractionated stereotactic body RT of the prostate to compensate for intrafraction motion >5 mm, to prevent an unacceptable reduction of CTV coverage [3]. Langen *et al.* also observed severe underdosage for some individual fractions in helical tomotherapy without ERB, although these had a small effect on the cumulative dose [26]. It should be emphasized, however, that these observations were specific for helical tomotherapy. As shown in the present study, with ERB application 3D deviations >5 mm are reduced to <1%, even after 600 s, indicating a negligible effect on the total dose.

As shown in Fig. 3, intrafraction prostate motion can be decomposed into three components: a slow trend, somewhat faster transients and spikes. The trend is thought to be a result from relaxation of the pelvic floor musculature or slowly moving stool, while the transient movements are probably caused by peristaltic motion or the passage of gas [14]. The spikes can most likely be attributed to instrumental noise. LR deviations are mainly caused by trends, suggesting that peristaltic motion has no influence on the lateral prostate displacements. AP and SI deviations, on the other hand, are composed of both trends and transients, the former constituting approximately 80% of the deviations. Both types of motion are decreased by ERB application. It has been suggested that waiting some time after ERB insertion might reduce intrafraction motion, due to patient relaxation after insertion [27]. The present study shows, however, that the cumulative percentage of time with prostate displacements increased linearly with time, both without and with ERB. Figures 4 and 5 show that in the plot of the trends, a kink appears after 150 s, which is not the fact for transients. Although it was not possible to determine whether this kink is a significant trend break considering the possibly not optimal division in trends and transients and the rather crude time interval used in the analysis, one could speculate that this kink is related to pelvic floor musculature relaxation.

In conclusion, an air-filled ERB significantly reduces intrafraction prostate motion, especially after 150 s, making it a potentially beneficial instrument to use during longer treatments, like stereotactic hypofractionated RT. Interfraction variation, however, was not influenced by ERB application.

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8

General Discussion

General Discussion

This thesis aims to identify anatomic structures involved in the development of fecal incontinence-related complaints after prostate radiotherapy (RT) and to investigate dose-effect relationships. Furthermore, the potential beneficial effect of endorectal balloons on anorectal wall doses and the development of toxicity are described.

Anorectal toxicity

Anorectal toxicity after prostate RT comprises different symptoms [1], and patients seem to be bothered most by incontinence-related complaints, such as fecal loss and urgency [2]. The first step in investigating its origin is a proper assessment of these complaints. There are many different instruments to assess radiation-induced anorectal toxicity, although it has been acknowledged that the use of general toxicity scales, such as the combined Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer toxicity scale, should not be used, as it may lead to the loss of information [3]. As mentioned in Chapter 5, at our department the Radiation-Induced Lower Intestinal Toxicity (RILIT) scoring system is used to record anorectal complaints during regular follow-up. This instrument investigates eight different complaints (anal blood loss, mucus loss, abdominal cramps, diarrhea, urgency, incontinence, frequency and anal pain), scored on a four or five point scale [1]. Although it specifically pays attention to incontinence-related complaints, it may still underestimate the actual toxicity rates, as physician-reported rates tend to underestimate both the frequency and severity of toxicity [4]. This suggests that the use of patient questionnaires should be encouraged. Therefore, nowadays patients at our department are asked to fill out the Expanded Prostate cancer Index Composite (EPIC) [5] at follow-up. However, when questionnaires are not applied, in our opinion, patients should always be actively asked for specific symptoms (*e.g.* loss of stools), rather than whether they do or do not have intestinal complaints, as these may then be underreported (*e.g.* due to embarrassment).

Given the differences in recording complaints, toxicity rates vary largely in the literature, and reported late anorectal toxicity rates after intensity-modulated radiotherapy vary from 5% to 65% [6;7]. The use of different scoring instruments makes direct comparison of toxicity data between studies very difficult [8], particularly of specific complaints, as in many studies general toxicity scales are used. We therefore advocate the use of specific scoring systems, enabling comparison of individual complaints between trials. Still, even when specific complaints are recorded, these may be scored differently by different observers, as is discussed in Chapter 6.

Pathophysiology

Results from Chapters 5 and 6 suggest that specific incontinence-related complaints arise from different anatomic subsites, confirming the statement that these complaints truly differ, and should be scored differently. It has been suggested previously, based on anorectal dose-surface map analysis, that anorectal complaints have specific sites of origin in the anorectal region, with dose-effect relationships for soiling and fecal incontinence in the anal region and lower rectum [9]. This is in concordance with our findings discussed in Chapter 5 and 6, as is the absence of dose-effect relationships for frequency. For urgency, however, no dose-effect relationship was observed in the previous study, while our results suggest an association with both anal and rectal dose-parameters. Potentially, differences in scoring, as described above, attribute to this discrepancy.

The multifactorial pathogenesis of incontinence has been confirmed by others [10;11], suggesting that a combination of anal and rectal factors are involved in the development of incontinence. Our anorectal manometry and barostat results showed a reduced anal resting pressure and lower tolerated rectal pressure in patients with incontinence and/or urgency, suggesting that these complaints are caused by a combination of reduced rectal capacity and impaired anal sphincter function. Others have reported comparable deteriorations of anorectal function after RT [11;12]. Further exploration of these complaints, which is described in Chapter 6, showed dose-effect relationships for urgency and incontinence with regard to individual pelvic floor muscles, suggesting that radiation-induced incontinence is associated with dysfunction of the external anal sphincter and puborectalis muscle, while in the development of urgency all investigated muscles seem to play a role. These observations lead to hypotheses about the anatomic origin of these complaints, but do not answer questions about the underlying pathophysiology. In previous histo-pathologic studies in patients with radiation-induced anorectal complaints smooth muscle hypertrophy and damage to the myenteric plexus has been observed [13], suggesting that these changes may play a role in its development.

The absence of dose-effect relationships for frequency with regard to the anorectum, despite significant reductions in rectal functions, as mentioned in Chapter 5, is somewhat surprising. Potentially, the observed rectal dysfunction is associated with other, non-investigated dose parameters, like the shape of the spatial dose distribution to the rectal mucosa. Recently, it has been shown that the lateral extent of the dose distribution is correlated with rectal bleeding, whereas longitudinal extent was associated with loose stools [14]. Possibly, the rectal wall is less compliant when the whole circumference received a high radiation dose, as it may lead to a more rigid rectum due to fibrosis.

The development of histological and functional changes after prostate RT is a dynamic process [11;15], indicating that these may be progressive over time. However, also spontaneous improvement of rectal wall damage has been described [16]. Anorectal manometry and barostat testing, as described in Chapter 5, were only performed once in each patient, and were used to show differences between patients with and without complaints. To get a good overview of the dynamics of anorectal damage, however, repeated function testing is needed.

Endorectal balloons

The results from Chapter 3 show that endorectal balloons (ERBs) significantly reduce doses to the anal wall, in addition to the known rectal wall sparing effect, described in Chapter 2. Furthermore, in post-prostatectomy RT also a beneficial effect of ERBs on anorectal doses was shown, in particular with regard to the anal wall (Chapter 4). Although these results were derived from planning studies, the observed decrease in anal wall and rectal wall doses may lead to lower toxicity rates, given the observed dose-effect relationships for both the anal wall and rectal wall [3;17]. Peeters *et al.* observed a hazard ratio for fecal incontinence of 1.039 for 1 Gy increase in anal wall mean dose [3]. As 12 Gy and 7.5 Gy reductions in anal wall mean doses were observed when ERBs were applied in 3D conformal RT (3D-CRT) and intensity-modulated RT (IMRT), respectively, application of an ERB might thus reduce the risk of fecal incontinence by a factor (1.039^{12} =) 1.58 and ($1.039^{7.5}$ =) 1.33 for the respective techniques. When these anal wall mean doses are used in the dose-effect model for urgency, as described in Chapter 6, for 3D-CRT, the risk of urgency would decrease from 29% (41 Gy) to 6% (29 Gy) with application of an ERB. For IMRT, the incidence would decrease from 5% to 1%. It should be noted, however, that this is a model-based assumption, based on a relatively small group of patients, in contrast to the abovementioned study by Peeters *et al.*, which included 641 patients.

The observed dosimetric advantages of ERBs were confirmed by data presented in Chapters 5 and 6. Patients who had been treated with ERB, had received significantly lower doses to the anorectum. Although these studies were not designed to investigate this difference, patients treated with ERB reported significantly less complaints than patients treated without ERB. The sum of the abovementioned results on ERB application, *i.e.* reduced anorectal wall doses and the observed dose-effect relationships for anorectal complaints, strongly suggests that the use of ERBs leads to reduced anorectal toxicity rates in prostate RT. The low toxicity rates, reported by patients treated with ERB, support this. A final conclusion on the effect of ERBs on toxicity, however, can only be drawn from a prospective trial, comparing patients treated with and without ERB. So far, only one study with such a design has been described in the literature, showing reduced late rectal mucosal changes on

repeated endoscopy, and reduced late rectal toxicity [15]. It is clear that more comparative studies are needed to confirm this.

In addition to the anorectal wall sparing effect, in Chapter 7 it is shown that ERBs significantly reduce intrafraction prostate motion. This effect was especially observed when the treatment lasts longer than 2.5 min, indicating that the use of an ERB may have a beneficial effect in long daily treatment sessions, like stereotactic body irradiation. Interfraction prostate variation, however, was not influenced by the ERB, which is consistent with a previous study from our group [18] and indicates that additional set-up and correction protocols are needed to minimize this. With ERB application and an on-line position verification system, an isotropic margin of 5 mm around the prostate may be sufficient in prostate IMRT, as the prostate then exceeds this margin in < 1% of treatment time. Clearly, when real-time electromagnetic tracking is used, such as the Calypso system described in Chapter 7, even smaller margins can be applied, as manual table corrections can be done during the actual treatment.

Delineation of organs at risk

In previous studies, when the rectum was delineated, this often included the anal canal [19;20]. Several investigators, however, have suggested that the anal region should be considered separately in RT planning to reduce fecal incontinence [3;21-23]. The different dose-effect relationships regarding anal wall and rectal wall doses for anorectal complaints, described in this thesis, support this statement to consider the anal canal and rectum to be separate organs. Because there is no consensus in the literature about the delineation method of the anal canal, we compared two methods in Chapter 3, both with and without ERB. It was shown that in both situations the anal wall can be delineated consistently. However, when separately contouring the pelvic floor muscles, considered to be involved in fecal continence, the continence apparatus proved to be thrice the volume of the suggested anal wall contour, as is described in Chapter 6. Given the observed dose-effect relationships for these specific muscles, it may be appropriate to delineate the total continence apparatus to be able to spare this in IMRT.

Based on the dose-effect curves in Chapter 6 the following constraints (mean dose) can be deduced for application in RT planning in order to minimize the risk of late fecal urgency and/or incontinence: anal wall < 30 Gy, rectal wall < 45 Gy, internal anal sphincter < 30 Gy, external anal sphincter < 10 Gy, puborectalis muscle < 50 Gy, levator ani muscles < 40 Gy.

It is important to note that in many studies, including those described in this thesis, dose evaluation with regard to the organs at risk is performed on the planning CT scan, which is actually a snapshot that might not be representative for the whole treatment. It has been shown that rectal wall doses exceed the set constraints in almost 30% of actual treatments, when daily CT images were compared to the planned dose on the planning CT, suggesting that adaptive RT with repeated delineation may be of benefit [24]. The same may apply to dose parameters obtained from the studies presented in this thesis. Daily CT imaging, *e.g.* using cone-beam CT, may be useful to further investigate this issue.

Future perspectives

At this moment, a prospective cohort study is being conducted at our department, in which 60 localized prostate cancer patients are followed 2 years after RT. At baseline, anorectal function testing is performed, which is repeated after 6, 12 and 24 months. Furthermore, patients fill out EPIC questionnaires at baseline and regular follow-up. Finally, after 24 months, an endoscopy is performed. This trial should give a better insight in the dynamics of anorectal dysfunction after prostate RT and its relation to dosimetric parameters and subjective complaints. As most of these patients are also enrolled in a randomized multicentre phase III trial on hypofractionation, comparing 2 Gy per fraction to 3.4 Gy per fraction, the effect of dose per fraction on anorectal function can also be explored.

Furthermore, as mentioned above, clinical studies on the application of ERBs are needed, preferably randomized trials. Based on the results from previous studies and from the studies mentioned in this thesis, in our institution ERBs are used in all prostate cancer patients. A multicentre study together with departments where ERBs are not routinely used may be an option to investigate its effect on late anorectal toxicity.

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9

Summary

Summary

In this thesis, several aspects of fecal incontinence-related complaints after prostate radiotherapy (RT) are discussed, in order to investigate its pathophysiology. Also, the role of endorectal balloons (ERBs) in the reduction of these bothering complaints is described.

In **Chapter 2**, the results of a literature review on the application of ERBs in prostate RT are presented. Overall, ERBs are tolerated well, although care must be taken in patients with pre-existing anorectal disease, who seem to have an increased risk of developing ERB-related toxicity. Several planning studies have shown a beneficial effect of ERBs on anorectal wall doses, which may lead to reduced toxicity rates. However, only one prospective study has been performed to compare late toxicity between patients treated with and without ERB, showing less rectal bleeding in the former group. More comparative trials are needed to investigate this issue. Finally, although some investigators have reported reduced interfraction and intrafraction prostate variation with ERB application, this has not been confirmed by others. Therefore, as potential pitfalls have been described in the use of ERBs, it is recommended to use additional set-up and correction protocols.

Chapter 3 shows that, in a planning study, an ERB reduces anal wall doses in both 3-field and 4-field three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT), planned to a total dose of 78 Gy. Because in the literature different methods of anal wall contouring are described, the effect of an ERB was tested using two different methods. It is shown that the anal wall can be delineated consistently on both the CT scans with ERB and those without ERB, leading to identical volumes. With ERB application, the mean dose to the anal wall is reduced by 12 Gy and 7.5 Gy in 3D-CRT and IMRT, respectively, irrespective of the method of anal wall delineation. Given the dose-effect relationships of fecal incontinence to the anal wall, these observations may lead to reduced anal toxicity.

In **Chapter 4**, the results of another planning study show that, in addition to a beneficial effect in definitive RT, an ERB reduces anorectal wall doses in post-operative RT as well. The largest advantage is observed for anal wall dose parameters, with a reduction of 6 Gy in mean dose. Also, several anal wall dose-volume parameters are reduced by the ERB. Regarding the rectal wall, dose-volume and dose-surface parameters in the intermediate dose range are significantly reduced. Since these parameters are predictive for late anorectal toxicity, application of an ERB may thus reduce this. However, like in the investigation presented in **Chapter 3**, clinical studies are needed to confirm this hypothesis.

As discussed in **Chapter 5**, differences in anal wall and rectal wall dosimetry, as well as in anorectal manometry and barostat testing imply that fecal incontinence, urgency and frequency after prostate RT arise from different anatomic substrates. Sixty patients, treated with RT for localized prostate cancer, were categorized according to the presence or absence of the abovementioned symptoms, and it is shown that patients with urgency or incontinence have an impaired anal squeeze pressure, as well as a lower tolerated pressure to the rectal wall. In addition, urgency seems associated with many anal and rectal wall dose parameters, while incontinence is only associated with some anal parameters. Patients with frequency, on the other hand, show a reduction on almost all rectal wall parameters, measured with barostat testing, without an association with any of the dosimetric parameters. This leads to the hypothesis that in the pathophysiology of urgency, and to a lesser degree incontinence, an impairment of both anal pressures and rectal capacity plays a role, while frequency may be caused by an impaired rectal capacity and sensory function. When treated patients, irrespective of complaints, are compared to a control group of untreated men, significantly lower anal resting pressures and tolerated rectal volumes are observed in the former group. Based on the observed associations between complaints and dose parameters, dose constraints for RT planning are suggested (*e.g.* anal wall mean dose < 38 Gy). Finally, although not a primary objective of the study, patients treated with ERB in this study showed significantly lower anal and rectal wall doses, and reported less complaints than patients treated without ERB.

A further exploration of potential anatomic structures, involved in the development of fecal incontinence-related complaints after prostate RT is presented in **Chapter 6**. In 48 patients treated with prostate RT, four individual pelvic floor muscles, considered to be involved in normal fecal continence, were delineated on the planning CT scans: the internal anal sphincter, external anal sphincter, puborectalis muscle and levator ani muscles. The mean, maximum and minimum doses to these muscles were retrieved from the treatment planning system. All patients were seen during regular follow-up and, like in **Chapter 5**, the absence or presence of urgency, incontinence and frequency was recorded. It is shown that the volume of the total continence apparatus exceeds the volume of the 'conventionally delineated' anal wall approximately by a factor three. Furthermore, urgency seems associated with doses to all four delineated muscles, while incontinence seems mainly associated with doses to the external anal sphincter and puborectalis muscle. As could be expected, based on the results from **Chapter 5**, no associations between frequency and any of the investigated dose parameters were observed. Based on the observed associations, dose-effect curves for the different structures were constructed and dose constraints for RT planning are formulated in this chapter. It is shown that less urgency and incontinence were reported in patients treated with ERB, and that this group received

significantly lower anal and rectal wall doses, as well as lower doses to all delineated muscles.

Finally, **Chapter 7** discusses the effect of an ERB on interfraction and intrafraction prostate deviations, by using continuous electromagnetic tracking. It is shown that application of an ERB has no effect on the magnitude of interfraction deviations. However, intrafraction motion is significantly decreased when an ERB is used, especially when the treatment lasts longer than 2.5 min. The largest reductions are observed in the anterior-posterior direction. Also, the number of corrections needed to re-align a patient during treatment is significantly lower in patients treated with ERB. These results suggest that when an on-line correction strategy is used to minimize the interfraction variation, an isotropic CTV-to-PTV margin of 5 mm may suffice to correct for intrafraction motion when an ERB is used, as in < 1% of time the CTV will not be covered by the predefined PTV. Based on these observations, ERBs may be beneficial in long daily treatment sessions (*e.g.* hypofractionated stereotactic RT).

In conclusion, specific fecal incontinence-related complaints after prostate RT seem to have a different pathophysiology, based on function testing and dosimetry, and the anorectum should not be considered one continuous organ in RT planning and dose evaluation. Instead, it should at least be separated in a rectal wall and anal wall. Endorectal balloons reduce doses to the anal wall, rectal wall and individual pelvic floor muscles in planning studies and retrospective analyses. Also, they reduce intrafraction prostate motion. These findings suggest that ERBs may reduce late anorectal toxicity. Comparative clinical trials, however, are needed to draw definite conclusions on this topic.

10

Summary in Dutch (Nederlandse Samenvatting)
Dankwoord
List of Publications
Curriculum Vitae

Summary in Dutch (Nederlandse Samenvatting)

Prostaatcarcinoom is in Nederland de meest gediagnosticeerde vorm van kanker bij mannen boven de 45 jaar, met een incidentie van meer dan 9.500 nieuwe patiënten per jaar. Eén van de curatieve behandelopties bij patiënten met een gelokaliseerd prostaatcarcinoom is uitwendige radiotherapie. Echter, doordat door set-up variaties gedurende de behandeling, zoals interfractie en intrafractie variatie van de prostaat, marges rondom de prostaat worden toegepast om onderdosering van de tumor te voorkomen, worden ook omliggende organen (deels) meebestraald, wat kan leiden tot het optreden van bijwerkingen. In het geval van prostaatradiotherapie moet hierbij worden gedacht aan anorectale klachten, mictieproblemen en erectiestoornissen. Wanneer deze klachten permanent zijn, blijkt met name anorectale toxiciteit een impact op de kwaliteit van leven te hebben, waarbij het van belang is te onderkennen dat dit uit verschillende klachten kan bestaan. Hiervan lijken vooral klachten met betrekking tot faecale incontinentie patiënten zorgen te baren.

Verschillende studies hebben uitgewezen, dat er een dosis-respons relatie bestaat bij radiotherapie voor prostaatcarcinoom, waardoor de tendens bestaat tot dosisescalatie. Echter, aangezien ook voor anorectale klachten dosis-effect relaties bekend zijn, is het van belang de radiatiedoses op het anorectum zo laag mogelijk te houden. In de afgelopen jaren hebben de ontwikkeling van 3D conformatie radiotherapie en later intensity-modulated radiotherapy (IMRT) het mogelijk gemaakt preciezer te bestralen, waardoor aan het doelgebied een hogere dosis kan worden gegeven, terwijl de omliggende structuren worden gespaard. Verder maakt de toepassing van image-guided radiotherapy, zoals het gebruik van portal imaging met behulp van goud-markers en cone-beam CT, prostaat positieverificatie en -correctie mogelijk, waardoor kleinere marges kunnen worden toegepast. Echter, zelfs na IMRT worden incidenties van late anorectale toxiciteit gemeld, variërend van 5% tot 65%.

Om het risico op anorectale toxiciteit verder te verlagen kan tijdens de bestralingsbehandeling gebruik gemaakt worden van dagelijks ingebrachte endorectale ballonnen, enerzijds omdat is gebleken dat deze de dosis op het rectum reduceren, anderzijds vanwege een verondersteld prostaat-immobiliserend effect. Het effect van deze ballonnen op klachten met betrekking tot faecale incontinentie is echter niet bekend. Teneinde anorectale klachten te kunnen voorkomen, is kennis van het ontstaansmechanisme noodzakelijk. Wanneer bekend is welke anatomische structuren betrokken zijn bij de ontwikkeling van deze klachten, kan met behulp van moderne bestralingstechnieken getracht worden deze te sparen. Een manier om hier meer inzicht in te krijgen is het identificeren van objectieve veranderingen bij patiënten met dergelijke klachten en deze te correleren met bestralingsdoses. Zo zijn bij patiënten met rectaal

bloedverlies veranderingen aan het rectumslijmvlies beschreven, alsmede verschillende dosis-volume en dosis-oppervlakte parameters, die predictief zijn voor het ontstaan hiervan. In het geval van hinderlijke klachten die samenhangen met faecale incontinentie is echter weinig bekend, behoudens dat patiënten na prostaatradiotherapie een verminderde anale sfincterfunctie en capaciteit van het rectum hebben vergeleken met daarvoor. Om kennis te verwerven over de relatie met bestralingsdosis, worden de te onderzoeken structuren ingetekend op planning CT-scans, waarna de verschillende dosisparameters worden berekend door een treatment planning systeem. In veel voorgaande studies is daartoe het anorectum als één orgaan ingetekend, terwijl naast dosis-effect relaties toxiciteit met betrekking tot het anorectum, deze ook zijn beschreven voor het anale kanaal alleen.

In dit proefschrift wordt een aantal studies besproken, waarin dieper ingegaan wordt op het mogelijke ontstaansmechanisme van anorectale klachten, met name met betrekking tot faecale incontinentie, en of deze klachten kunnen worden voorkomen door het gebruik van endorectale ballonnen.

In **Hoofdstuk 2** wordt een overzicht gegeven van de internationale literatuur over het gebruik van endorectale ballonnen bij prostaatradiotherapie. Het blijkt dat patiënten deze ballonnen goed verdragen, hoewel patiënten met preëxistente anorectale klachten, zoals hemorrhoïden, een verhoogd risico lopen op ballon-geïnduceerde toxiciteit. Verder blijkt uit verschillende planningsstudies dat toepassing van een endorectale ballon anorectale doses reduceert. Dit zou kunnen leiden tot minder toxiciteit, hoewel slechts één klinische studie dit voordeel heeft onderzocht en bevestigd. Meer vergelijkende studies zijn daarom noodzakelijk om dit effect definitief te kunnen bevestigen. Tot slot blijkt dat er geen consensus bestaat over het effect van endorectale ballonnen op interfractie en intrafractie variatie, waardoor wordt geadviseerd deze te combineren met set-up en correctieprotocollen.

Hoofdstuk 3 behandelt vervolgens een planningsstudie, waaruit blijkt dat endorectale ballonnen de dosis op het anale kanaal verlagen bij zowel 3D conformatie radiotherapie als IMRT, met een afname in de gemiddelde dosis van 12 Gy, respectievelijk 7,5 Gy. Gezien de bekende dosis-effect relatie van faecale incontinentie met betrekking tot het anale kanaal, zou dit kunnen leiden tot minder anale toxiciteit. Verder wordt in dit hoofdstuk een manier beschreven om het anale kanaal separaat van het rectum in te tekenen, aangezien dit in eerdere studies vaak als één orgaan is beschouwd. Het blijkt dat intekening van het anale kanaal op een consistente manier kan plaatsvinden op scans met en zonder endorectale ballon.

Naast een primaire bestralingsbehandeling, kunnen ook patiënten met een lokaal tumorrecidief na prostatectomie in opzet curatief worden bestraald. **Hoofdstuk 4** laat het effect zien van een endorectale ballon op doses op het rectum en het anale kanaal bij patiënten na prostatectomie. Het blijkt dat ook in deze situatie een reductie in anorectale doses optreedt, met name ten aanzien van het anale kanaal. Ook rectumdoses in het intermediaire dosisbereik worden hierdoor verlaagd. Aangezien deze parameters predictief zijn gebleken voor anorectale toxiciteit, zouden endorectale ballonnen het risico hierop dus kunnen verlagen. Echter, evenals geldt voor de resultaten uit **Hoofdstuk 3**, dient deze hypothese in een klinische studie te worden bevestigd.

Hoofdstuk 5 beschrijft de resultaten van een onderzoek, waarbij gebruik is gemaakt van anorectale manometrie en barostat onderzoek om anale drukken en rectale compliantie en sensibiliteit te kunnen meten. Bestraalde patiënten blijken een significant lagere rustdruk in het anale kanaal en verlaagde tolerantie van rectumvolumes te hebben dan een controlegroep van niet-behandelde patiënten. Voorts werden patiënten met faecale *incontinentie* (verlies van ontlasting), *urgency* (verhoogde aandrang) en *frequency* (toegenomen frequentie) na prostaatradiotherapie vergeleken met patiënten zonder deze klachten na bestraling. Het blijkt dat patiënten met *incontinentie* en *urgency* een significant lagere anale knijpkracht hebben, en een lagere rectumdruk tolereren, dan patiënten zonder deze klachten. Wanneer dosisparameters tussen deze groepen worden vergeleken, blijkt verder dat verschillende anale en rectale parameters geassocieerd zijn met *urgency*, terwijl enkele anale parameters predictief lijken voor *incontinentie*. *Frequency*, daarentegen, is niet geassocieerd met de onderzochte dosisparameters, maar patiënten met *frequency* scoorden wel significant lager op bijna alle functionele rectumparameters. Deze observaties leiden tot de hypothese, dat *urgency*, en in mindere mate *incontinentie*, worden veroorzaakt door een combinatie van anale en rectale dysfunctie, terwijl *frequency* vooral een probleem lijkt van een gestoorde rectumcompliantie en -sensibiliteit. Op basis van de geobserveerde dosis-effect relaties wordt een voorstel gedaan voor verschillende dosislimieten, die gebruikt kunnen worden bij de radiotherapieplanning. Tenslotte blijken patiënten, die bestraald zijn met ballon lagere doses op het anorectum te hebben gehad en tevens lijken deze patiënten minder klachten te rapporteren dan patiënten die zonder ballon zijn behandeld.

In navolging van **Hoofdstuk 5**, wordt in **Hoofdstuk 6** dieper ingegaan op mogelijke anatomische structuren, die geassocieerd zijn met het ontstaan van faecale incontinentie. Hiertoe werden vier bekkenbodemspieren, die beschouwd worden betrokken te zijn bij normale faecale continentie, separaat ingetekend: de interne anale sfincter, externe anale sfincter, musculus puborectalis en musculus levator ani.

Patiënten werden vergeleken op basis van de aan- of afwezigheid van dezelfde klachten als genoemd in **Hoofdstuk 5**, en het blijkt dat, terwijl *urgency* geassocieerd lijkt met alle ingetekende bekkenbodemspieren, dit voor *incontinentie* enkel geldt voor de externe anale sfincter en musculus puborectalis. *Frequency* was wederom niet geassocieerd met de onderzochte dosisparameters. Op basis van de gevonden associaties, zijn in **Hoofdstuk 6** verschillende dosis-effectcurves voor de individuele structuren geconstrueerd, leidend tot dosislimieten, die kunnen worden toegepast in radiotherapieplanning. Wederom bleken patiënten, bestraald met ballon, lagere doses op het anale kanaal, het rectum en de bekkenbodemspieren te hebben gekregen, alsmede minder *incontinentie* en *urgency* te rapporteren.

Hoofdstuk 7 tenslotte, laat het effect van endorectale ballonnen zien op interfractie en intrafractie prostaatverplaatsingen. Hiertoe is een studie gedaan in samenwerking met het M.D. Anderson Cancer Center in Orlando (V.S.), waarbij 30 patiënten vóór behandeling electromagnetische transponders in de prostaat geplaatst kregen, waarmee de prostaatpositie continu kan worden geregistreerd. De helft van deze patiënten werd vervolgens behandeld met endorectale ballon, de andere helft zonder. Het blijkt dat de ballon geen effect heeft op de interfractie variatie. Intrafractie bewegingen daarentegen, worden significant gereduceerd met gebruik van de ballon, vooral na 150 seconden. Tevens zijn bij toepassing van de ballon minder positioneringscorrecties nodig tijdens de bestraling. Op basis van deze resultaten kan, bij gebruik van een on-line correctieprotocol om de interfractie variatie te minimaliseren én een endorectale ballon, een marge van 5 mm rondom de prostaat volstaan om onderdoseringen te voorkomen. Met name bij de toepassing van lange dagelijkse behandelingen, zoals gehypofractioneerde stereotactische radiotherapie, kan een ballon van voordeel zijn.

Concluderend lijken verschillende klachten, gerelateerd aan faecale incontinentie, een verschillend ontstaansmechanisme te hebben, gebaseerd op de functionele metingen en dosimetrie, zoals beschreven in dit proefschrift. Het anorectum moet dan ook niet worden beschouwd als één orgaan, maar in ieder geval worden opgedeeld in een anaal kanaal en rectum. Verder reduceren endorectale ballonnen doses op het rectum, het anale kanaal en bekkenbodemspieren, alsmede de intrafractiebeweging van de prostaat. Deze observaties suggereren dat endorectale ballonnen het risico op anorectale toxiciteit verlagen, hoewel vergelijkende klinische studies noodzakelijk zijn om dit definitief te bevestigen.

Dankwoord

Aan het eind van dit proefschrift (hoewel het voor sommige lezers de eerste, en mogelijk enige, regels zullen zijn die gelezen worden) rest mij nog een woord van dank uit te spreken aan eenieder die het mogelijk heeft gemaakt dit hier vandaag in het openbaar te kunnen verdedigen. In eerste instantie betreft dit alle patiënten die hun medewerking hebben verleend aan de in dit proefschrift beschreven onderzoeken, en iedereen die in meer of mindere mate een bijdrage heeft geleverd aan de totstandkoming ervan. Met het risico iemand te vergeten, waarvoor alvast mijn excuses, wil ik een aantal personen in het bijzonder dank toezeggen.

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Klinisch fysici, in willekeurige volgorde: *ir. A.L. Hoffmann, beste Aswin,* dank voor je goede adviezen en je rol als sparring partner. Dankzij jouw kennis en kunde hebben we een aantal fysische vraagstukken naar tevredenheid kunnen oplossen. Ik hoop dat je in MAASTRO je ambities kunt verwezenlijken en dat we ondanks de afstand toch onze samenwerking nog eens kunnen voortzetten. *Dr. M. Kunze-Busch, beste Martina,* dank voor al je inspanningen bij de nauwkeurige herberekeningen en beoordeling van Hoofdstukken 4 en 5, alsmede voor je tomeloze optimisme en de altijd klaarstaande chocolaatjes, die al menig hypoglykemie hebben voorkomen. *Dr. R.J.W. Louwe, beste Rob,* dank voor de prettige samenwerking bij het totstandkomen van Hoofdstuk 7. Mede door jouw inspanningen en kennis van Matlab heeft ons Calypso-onderzoek in korte tijd geleid tot een mooie publicatie. Dank ook voor de reisverhalen en ik hoop dat je je plek hebt gevonden bij de Kiwi's. *Dr. K.M. Langen and dr. A.P. Shah,*

dear Katja and Amish, thank you for the pleasant cooperation on our project regarding Calypso measurements in patients treated with or without endorectal balloon at the M.D. Anderson Cancer Center Orlando.

Alle medewerkers van de afdeling Radiotherapie UMCN, artsen, verpleegkundigen, FT-groep, laboranten, ondersteunend personeel, en iedereen die niet in deze categorieen is te vangen, dank voor de prettige samenwerking de afgelopen 7 jaar. Een speciaal woord van dank aan *Peter van Kollenburg en Gill McColl. Beste Peter,* dank voor alle tijd die je hebt gestoken in het vele planningswerk voor Hoofdstukken 4 en 5. *Beste Gill,* dank voor het vervaardigen van de dose-surface maps en je uitleg aan mij over hoe ik deze zelf kon construeren. *AIOS Radiotherapie UMCN,* zowel degenen die hun opleiding reeds hebben afgerond als zij die nog in opleiding zijn, dank voor een prettige en gezellige opleidingstijd. Jullie begrip en interesse voor het doen van onderzoek tijdens de opleiding werkt motiverend en verdient een compliment.

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Paranimfen. Drs. B.F.L. van Nuenen, beste Bart, op de drempel van je eigen promotie kun je de ceremonie alvast eens van dichtbij meemaken en zien hoe het moet (of niet). Of het nu gaat om het lopen van de Vierdaagse, behoefte aan iemand om een biertje mee te drinken of een dag als vandaag, het is goed te weten dat er een goede vriend is om op terug te vallen, bedankt daarvoor! *Dr. J. Honings, beste Jimmie,* twee jaar na je eigen promotie zijn de rollen omgedraaid. Nu mag ik zweten en kun jij het water inschenken. Vandaag wordt ongetwijfeld weer een mooie herinnering om bij te schrijven naast vele andere, zoals Rembo&Rembo, St. Gallen en de Pret met de Fret Show. Dank voor dat alles! Mannen, ik vind het mooi dat jullie mij vandaag in

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Curriculum Vitae

Robert Jan Smeenk was born in Tubbergen on the 23rd of February 1980. After graduating from the Lorentz College in Arnhem in June 1998, he started medical school at the Catholic University Nijmegen (today Radboud University Nijmegen). On May 16th 2002, he received the Student award from the Catholic University Nijmegen, because of several extracurricular activities.

Robert Jan obtained his medical degree on March 18th 2005, and subsequently started as a resident at the Department of Radiation Oncology of the Radboud University Nijmegen Medical Centre with prof. dr. J.W.H. Leer. He started a PhD project on anorectal toxicity after prostate radiotherapy under supervision of prof. dr. J.H.A.M. Kaanders and dr. E.N.J.Th. van Lin. For this project he received a grant from the Dutch Cancer Society (KUN 2008-4239), which enabled him to spend one year full-time on research. In March and April 2009, he worked on a collaborative research project at the M.D. Anderson Cancer Center Orlando, FL, with dr. K.M. Langen and dr. P.A. Kupelian.

In August 2009, he continued his residency, which he finished in March 2012. Subsequently, he started as a radiation oncologist at the Department of Radiation Oncology of the Radboud University Nijmegen Medical Centre.

Color Figures

Fig. 2 Transverse (top) and sagittal (bottom) dose distribution of IMRT plans without (left) and with ERB (right) in place (prescribed dose 78 Gy). Contours: rectal wall (green), anal wall (purple) and PTV (blue).

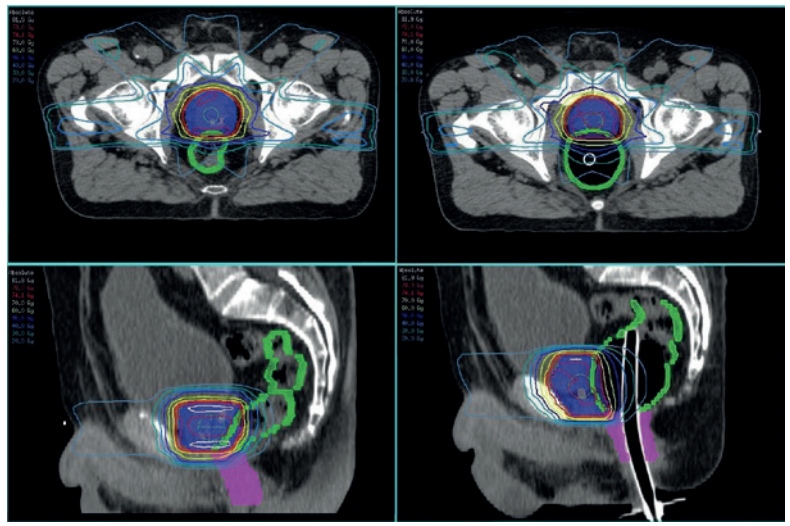


Fig. 2 Transversal (top), sagittal (middle) and frontal (bottom) view of delineated Rwall (green) and Awall (purple) for CT-scans without ERB (left column) and with ERB in place (right column).

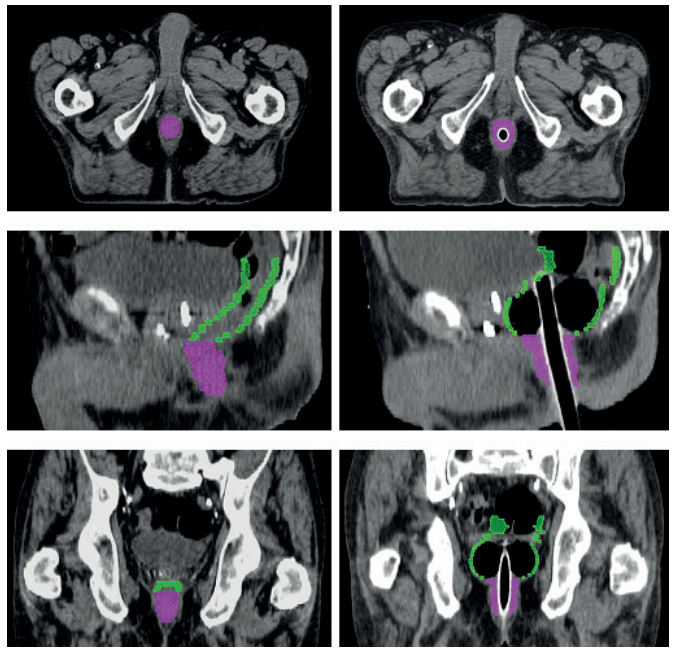


Fig. 3 Differences in dose distribution on the anal wall (purple contour) between 6 different plans within 1 patient (3-field technique without ERB (**a**), 3-field technique with ERB (**b**), 4-field technique without ERB (**c**), 4-field technique with ERB (**d**), IMRT without ERB (**e**), and IMRT with ERB (**f**), respectively. Blue area: planning target volume; green contour: rectal wall).

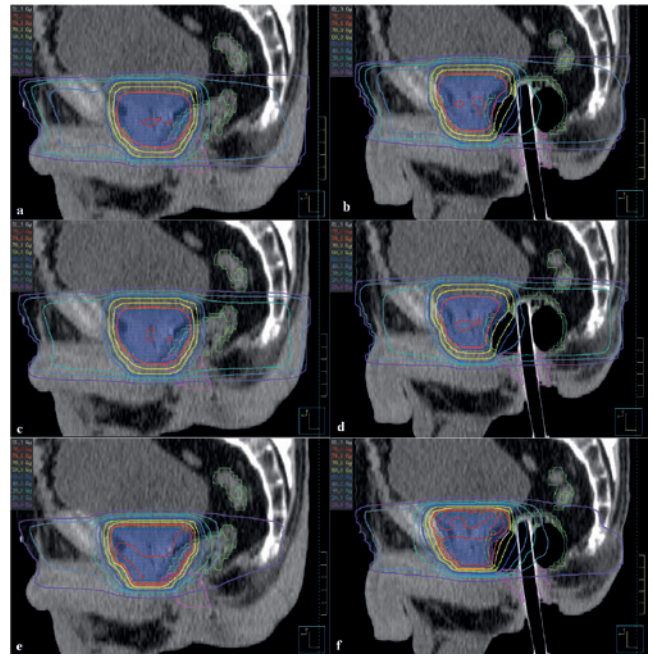


Fig. 2 Sagittal (**a**), transverse (**b**-**d**) and coronal (**e**-**g**) views of delineated CTV on CT-scans without endorectal balloon (left column) and with endorectal balloon (right column). Red contour: CTV; blue contour: PTV; green contour: rectal wall; purple contour: anal wall.

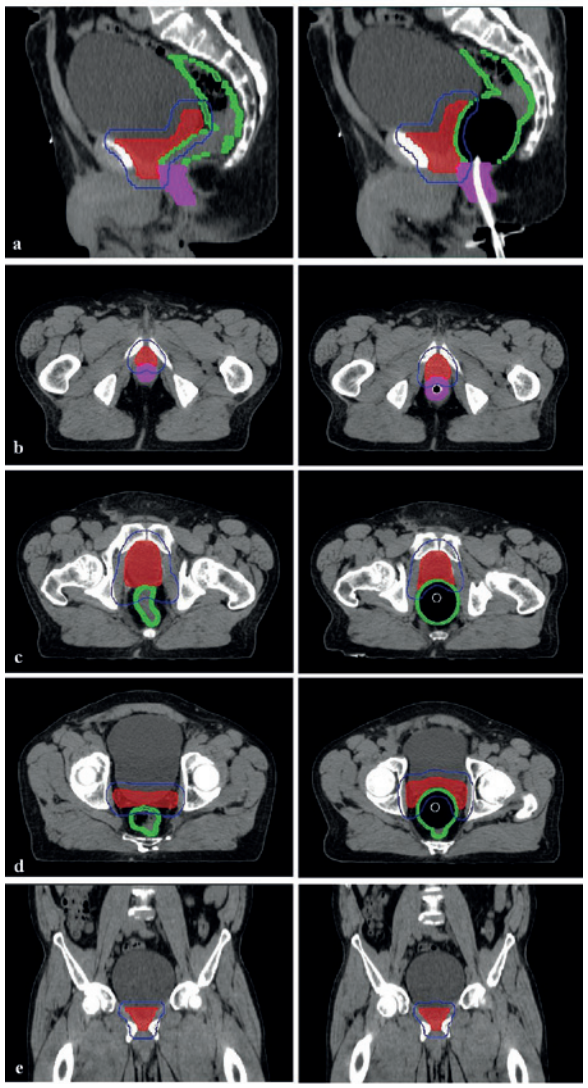


Fig. 2 Continued.

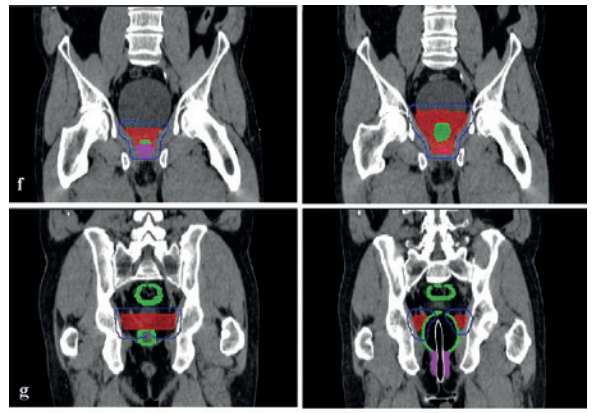


Fig. 3 Example of a relative rectal wall dose-surface map in a patient without endorectal balloon (left) and with endorectal balloon (right).

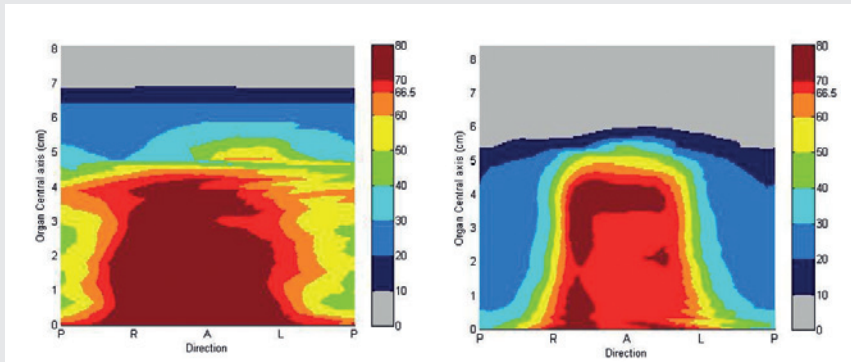
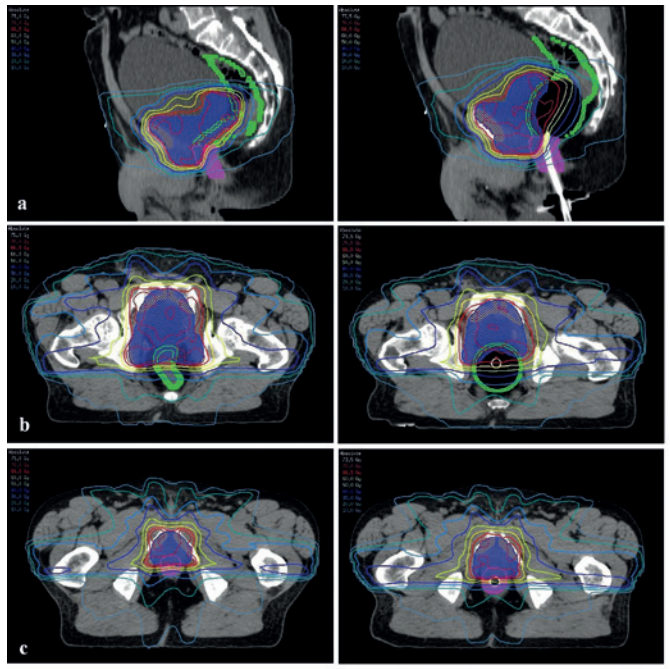


Fig. 4 Sagittal (**a**) and transverse (**b**-**c**) views of dose distributions in one patient without endorectal balloon (left) and with endorectal balloon (right). Contours as in Fig. 2.



Chapter 6

Fig. 1 Example of the delineated pelvic floor muscles in coronal (**a**), sagittal (**b**) and transverse (**c**-**e**) view in a patient with endorectal balloon inserted. Red contour: internal anal sphincter; green contour: external anal sphincter; blue contour: puborectalis muscle; yellow contour: levator ani muscles.

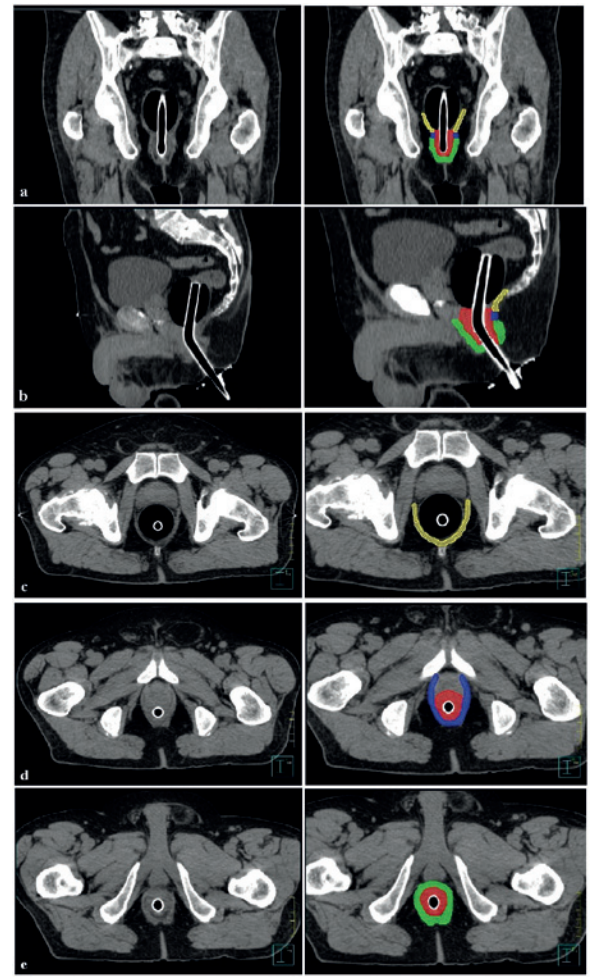


Fig. 2 Schematic image of the rectum, anal canal and individual pelvic floor muscles (I: internal anal sphincter; E: external anal sphincter; P: puborectalis muscle; L: levator ani muscles). Lines represent associations between complaints and subsites.