Reduction of rectal toxicity in prostate cancer radiation therapy by implantable rectum spacers

Citation for published version (APA):

Vanneste, B. G. L. (2018). *Reduction of rectal toxicity in prostate cancer radiation therapy by implantable rectum spacers*. [Doctoral Thesis, Maastricht University]. Maastricht University.
<https://doi.org/10.26481/dis.20180704bv>

Document status and date:

Published: 01/01/2018

DOI:

[10.26481/dis.20180704bv](https://doi.org/10.26481/dis.20180704bv)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

REDUCTION
OF
RECTAL
TOXICITY
IN
PROSTATE
CANCER
RADIATION
THERAPY
BY
IMPLANTABLE
RECTUM
SPACERS

Reduction of rectal toxicity in prostate cancer radiation therapy by implantable rectum spacers

B.G.L. Vanneste

COLOPHON

Cover : Tim Onderbeke, www.timonderbeke.com
Lay-out : Ilse Modder, www.ilsemodder.nl
Printed by : Gildeprint, www.gildeprint.nl
Photography : Tim Onderbeke, www.timonderbeke.com
ISBN/EAN : 978-94-6233-995-8

Reduction of rectal toxicity in prostate cancer radiation therapy by implantable rectum spacers PhD
thesis, Maastricht University, the Netherlands

© Copyright B.G.L. Vanneste, Maastricht, 2018, All rights reserved.

Copyrights of the following chapters belong to the publisher
and permission is obtained for inclusion in this thesis

Chapter 2 Biomed Res International vol 2016, Article ID 6829875 © copyright Hindawi Publishing Corporation
Chapter 3 Int J Colorectal Dis 2015 30:1293–1303 © copyright Springer Berlin Heidelberg
Chapter 4 Radiother Oncol 2015;114(2):276-81 © copyright Elsevier
Chapter 5 Radiother Oncol 2016;121(1):118-123 © copyright Elsevier
Chapter 6 Submitted to Phys Med Biol © copyright Institute of Physics Publishing
Chapter 7 IBJU 2017 Mar 24;43 © copyright ScholarOne Inc.
Chapter 8 Strahlentherapie und Onkologie 2018 Jan;194(1):31-40 © copyright Springer International
Publishing AG
Chapter 9 Technical innovations & Patients Support in Radiation Oncology 6 (2018) 1–4 © copyright Elsevier
Chapter 10 Radiother Oncol 2017 S0167-8140(17)32485-4 © copyright Elsevier
Chapter 11 Accepted to Acta Oncologica © copyright Taylor & Francis online

The research described in this thesis was performed at MAASTRO Clinic, Maastricht, the Netherlands.
The printing of this thesis is partially funded by Astellas, Eurocept homecare, Ipsen, QLRAD
International (Endorectal Balloon RectalPro), RT-IDea BV

Reduction of rectal toxicity in prostate cancer radiation therapy by implantable rectum spacers

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Universiteit Maastricht
op gezag van de rector magnificus Prof. Dr. Rianne M. Letschert
volgens het besluit van het college van Decanen,
in het openbaar te verdedigen
op woensdag 4 juli 2018 om 12:00uur.

door
Ben Guy Luc Vanneste

In memory of my oldest brother Sven

Promotor:

Prof. Dr. P. Lambin

Co-Promotoren:

Dr. E.N. van Lin, Praxis für Strahlentherapie, Goch, Duitsland

Dr. Ir. A.L. Hoffmann, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden,
Dresden, Duitsland

Manuscript commissie:

Prof. Dr. F. Verhaegen (*voorzitter*)

Prof. Dr. M. van Vulpen, Holland PTC, Delft

Dr. B. Pieters, AMC, Amsterdam

Prof. Dr. G. A. van Koeveringe

CONTENTS

General Introduction – Overview

Chapter 1	Introduction	12
Chapter 2	Prostate cancer Radiation Therapy: What does a clinician have to know? <i>Vanneste BGL, Van Limbergen EJ, van Lin EN, van Roermund J, Lambin P.</i> Biomed Res International vol. 2016, Article ID 6829875.	34
Chapter 3	Chronic radiation proctitis: tricks to prevent and treat. <i>Vanneste BGL, Van de Voorde L, de Ridder RJ, Van Limbergen E, Lambin P, Van Lin EN.</i> Int J Colorectal Dis 2015 30:1293–1303.	64

PART I – Modeling

Chapter 4	Spacers in Radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective? <i>Vanneste BGL, Pijls-Johannesma M, Van De Voorde L, van Lin EN, K van De Beek, van Loon J, Ramaekers BL, Lambin P.</i> Radiother Oncol. 2015;114(2):276-81.	92
Chapter 5	Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection <i>Vanneste BGL, Hoffmann A, van Lin E, Van de Voorde L, Schubert C, Pinkawa M, Lambin P.</i> Radiother Oncol. 2016;121(1):118-123.	108
Chapter 6	Anorectal wall dose-surface maps localize the dosimetric benefit of hydrogel rectum spacers in prostate cancer radiotherapy <i>Vanneste BGL, Buettner F, Pinkawa M, Lambin P, Hoffmann AL.</i> <i>Submitted to Phys Med Biol</i>	128

PART II – Clinical data

Chapter 7	Implantation of a biodegradable rectal balloon implant: Tips, tricks and pitfalls. <i>Vanneste BGL, Lutgens LC, van de Beek K, Lambin P.</i> IBJU. 2017 Mar 24;43.	148
-----------	--	-----

Chapter 8	Shrinkage of the rectal balloon implants: does it affect significantly rectal dose distribution and complication risk? <i>Vanneste BGL</i> , Van Wijk Y, Lutgens LC, Van Limbergen EJ, van Lin E, van de Beek K, Lambin P, Hoffmann A. <i>Strahlentherapie und Onkologie</i> 2018 Jan;194(1):31-40.	166
Chapter 9	A biodegradable rectal balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn disease <i>Vanneste BGL</i> , Van Limbergen EJ, van de Beek K, van Lin E, Lutgens LC, Lambin P. <i>Technical innovations & Patients Support in Radiation Oncology</i> 6 (2018) 1-4.	186

PART III – Future

Chapter 10	A novel prospective decision support method to estimate the value of a rectum spacer: 'Virtual Rectum Spacer'. Van Wijk Y, <i>Vanneste BGL</i> , van der Meer S, van Elmpt W, Pinkawa M, Lambin P. <i>Radiother Oncol</i> 2017 Aug 16: S0167-8140(17)32485-4.	200
Chapter 11	Development of an iso-toxic multifactorial model decision support system integrating genetic markers of toxicity for the implantation of a rectum spacer van Wijk Y, <i>Vanneste BGL</i> , Jochems A, Walsh S, Oberije C, Pinkawa M, Ramaekers B, Vega A, Lambin P. <i>Acta Oncologica (Accepted)</i>	222
Chapter 12	General Discussion and Future perspectives	244

Addenda

Chapter 13	Summary	264
	Nederlandse samenvatting	266
	Valorisation	269
	Acknowledgments	273
	Curriculum Vitae	275
	List of publications	276

LIST OF ABBREVIATIONS

ARW	AnoRectal wall
CE	Cost-effectiveness
CBCT	Cone Beam Computed Tomography
CRP	Chronic Radiation Proctitis
CT	Computed Tomography
CTV	Clinical Target Volume
DSH	Dose Surface Histogram
DSM	Dose Surface Map
DSS	Decision Support System
DVH	Dose Volume Histogram
EBRT	External Beam RadioTherapy
EQD2	Equivalent 2 Gy Dose
gEUD	Generalized Equivalent Uniform Dose
GI	Gastro-Intestinal
Gy	Gray
HGS	Hydrogel Spacer
IBD	Inflammatory Bowel Disease
ICER	Incremental Cost-Effectiveness Ratio
IMRT	Intensity Modulated RadioTherapy
IRS	Implantable Rectum Spacer
LAT	Lateral
LKB	Lyman-Kutcher-Burman
MAF	Minor Allele Frequency
MRI	Magnetic Resonance Imaging
NTCP	Normal Tissue Control Probability
OR	Odds Ratio
PCa	Prostate Cancer
PEG	Poly-Ethylene-Glycol
PDA	Patient Decision Aid
PSA	Prostate Specific Antigen
PTV	Planning Target Volume
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RBI	Rectal Balloon Implant
RESPECT	REctum Spacer for Prostate External beam Cancer Therapy
RT	RadioTherapy
SNP	Single Nucleotide Polymorphism

TCP	Tumour Control Probability
VAS	Visual Analyzing Score
V-IRS	Virtual Implantable Rectum Spacer

CHAPTER 1

General introduction

GENERAL INTRODUCTION

Prostate cancer: treatment options and outcome

Prostate cancer (PCa) is the most common cancer among males in the Western world, with more than 1.62 million new cases diagnosed in 2015, and 366,000 deaths worldwide [1,2,3] (Figure 1 and 2). The lifetime risk of developing PCa is 1 in 8 in the Western world [4]. Treatment options for localized PCa include active surveillance, radical prostatectomy (RP), and definitive radiotherapy (RT). The outcomes of RP and RT are similar according a recently published phase III randomized trial, but they differ significantly in terms of the side effects [5]. All these treatments provide a high cure rate: chances of surviving 5 years after diagnosis are good (98.9% based on data from 2004–10) [6], while 84% men diagnosed with PCa in the UK survived their disease for ten years or more [4]. Nevertheless, it is estimated that 92,300 European men died from prostate cancer in 2012 [4], most of them several years (>5) after initial treatment. Although PCa is associated with a reduced life expectancy after several years (5 to 10 years), the quality of life decreasing may occur prior to treatment and/or worsen after treatment, due to a lower sexual functioning, increased urinary incontinence, and changes in bowel function [7,8].

FIGURE 1: Incidence of the most common cancer types in 2016 in the Netherlands. Male cancers are presented on the left, female cancers on the right. Prostate cancer is the most common male cancer, with an incidence of 19.5% of all types of cancer. (Reprinted from www.iknl.nl).

FIGURE 2: The 10 most common causes of cancer death worldwide in 2012. (Reprinted from Cancer UK 2012).

Patient empowerment by shared decision-making using multiple decision support systems

In an era of individualized cancer treatment, patients should be empowered to balance the benefits and risks of informed treatment choices [9-11]. Paternalistic care needs to be replaced by a *shared decision-making* approach, where clinicians and patients make treatment decisions together, based on the patient's individual values, personal (risk-taking) preferences and disease characteristics. Stacey and colleagues recently published a systematic review based on 105 published randomized controlled trials, involving more than 31,000 participants, comparing decision aids to usual care. They concluded that decision aids significantly increase decision quality, improving decision-making processes and patients' knowledge of treatment options and outcomes, with lower decisional conflicts [10]. Hence, there is a need to develop decision aids that provide patients with balanced information on individual disease stage and associated treatment options, helping them to comprehend and clarify their personal treatment preferences [11]. Lack of awareness about all treatment options can result in decisions which are not in line with the individual values, resulting in decisional regret [12,13]. A recently published study demonstrated that one third of Dutch PCa patients were dissatisfied with the information provided, which affected their post-treatment quality of life [14].

FIGURE 3: Overview of the multifactorial clinical decision support systems integrating all available patient data, comparing the best outcomes of different treatment modalities personalized in terms of toxicity, cure rates, quality of life, and cost-effectiveness. DSS can be integrated in the multidisciplinary tumor board, and one step further at the level of the specialists. (Reprinted with permission from <https://vimeo.com/241154708>).

Furthermore, a randomized controlled trial of usual care versus decision aid in men eligible for both RP and RT showed that the treatment choice was influenced by the hospital they visited [15]. However, in curative PCa RT, physicians have problems predicting the preferences of patients empowered with a decision aid [16]. They tend to underestimate both the patient's decision-making preferences, as well as the patient's preference for less toxic treatments. Therefore, patients should be informed first – possibly by a decision aid – before discussing patient preferences.

We envision a paradigm shift from current population-based medicine to personalized and participative medicine. This transition will be supported by the development of multifactorial clinical decision support systems (DSS) (Figure 3). DSS are continuously updated software tools, integrating all available patient data (clinical, imaging, biological, genetic, and cost-effectiveness data), based on validated prediction models of treatment outcome. A DSS is constantly re-evaluated in different patient datasets in order to refine and re-optimize the models, ensuring the continuous utility of the models (Figure 3). DSS compare the best outcome of different personalized treatment modalities, in terms of toxicity, cure rates, quality of life, and cost-effectiveness. DSS can be integrated in the clinical workflow in two ways: in the multidisciplinary tumor board to support different treatment choices (e.g., radical prostatectomy versus radiotherapy), and at the level of the specialist (i.e., a radiation oncologist can evaluate whether an IRS would be beneficial or not).

External beam radiation therapy for PCa: advances in technology and outcome

RT can be administered using radiation sources that are either applied internally or externally. In the former case (brachytherapy), radioactive sealed sources are permanently or temporarily placed in proximity to the tumor. In the latter case (teletherapy), a linear accelerator device generates high-energy X-rays that are collimated to produce an external beam of ionising radiation, which is directed onto the tumor by means of a gantry that rotates around the patient. For PCa RT, brachytherapy and teletherapy are exploited clinically both separately as well as in combination, depending on the clinical staging, age, and performance (associated comorbidity, life expectancy, uroflowmetry) of the patient to be treated. The work described in this thesis is strictly limited to external beam RT with high-energy X-rays (EBRT); teletherapy using protons or carbon ions (particle therapy) is beyond the scope of this thesis.

An EBRT procedure consists of 2 consecutive parts (Figure 4). Firstly, in the preparatory “RT planning” phase, an optimal dose distribution needs to be designed for every individual patient being treated. Here, sophisticated computer-based treatment planning systems are used to optimize the design parameters (number of beams, beam angles, energy, and collimation, as well as the calculated monitor units) and simulate the three-dimensional dose distribution that will be

delivered to the patient. The dosimetric quality of the dose distribution is evaluated against pre-set dose-volume histogram objectives and constraints for both the tumor and organs at risk.

FIGURE 4: Diagram of an EBRT procedure (Reprinted with permission from [17]).

Once an optimal trade-off between (the often contradictory) objectives and constraints has been reached, the settings of the design parameters define what is referred to as the “treatment plan.” Secondly, in the “dose delivery” phase, a linear accelerator employs the treatment plan to deposit an energy distribution in the patient that mimics the planned dose distribution. EBRT is usually administered using multiple treatment fractions, delivered over several weeks (typically 4–8 weeks), depending on the dose-per-fraction and the total dose. Typically for PCa, a normofractionated treatment schedule is used, administering a curative dose of 78 Gy in 39 fractions of 2 Gy (once daily during weekdays over the course of 8 weeks). The nearly 2 months such a treatment course is inconvenient for patients. It is also costly for healthcare providers; especially for patients living at long distances from a treatment centre, or for those who have a poor support system, shortening the treatment course would be beneficial [18,19]. In a hypofractionated treatment regime substantially fewer fractions of a larger dose per fraction are used, usually given over a shorter total treatment time and with a lower total treatment dose. However, due to the larger fraction size, the biological effect is comparable to that of the normofractionated treatment [20]. For a moderately hypofractionated schedule, 19 to 28 fractions of 2.5 Gy to 3.4 Gy per fraction is traditionally performed. Several randomized phase III trials have revealed a slight increase in toxicity rates when compared to conventional schedules with comparable outcomes [21–23]. In extreme hypofractionation, which is also called stereotactic ablative radiotherapy (SABR), a small number of fractions of 6.5 to 10 Gy are administered. So far, for SABR for PCa only preliminary outcome data from non-randomized studies have been published [24–26]. Therefore, prospective randomized phase III trials with additional follow-up are required to further clarify the

benefits of SABR.

In multi-fraction EBRT for PCa, both inter- and intrafractional variations occur, due to patient setup inaccuracies and organ (i.e., rectum and bladder) filling dynamics that induce prostate motion relative to the bony anatomy. To compensate for such variations, safety margins are used around the prostate, generating a planning target volume (PTV) [27]. Application of these safety margins leads to a larger volume of surrounding healthy tissues and critical organ structures being irradiated, with consequently an increased risk of gastrointestinal (GI) toxicities. The probability of developing this injury is related to the volume of rectum irradiated, total RT dose, RT technique, and dose per fraction [28]. Individual patient factors can also influence the susceptibility to GI toxicities: comorbidity of vascular disease, diabetes, connective tissue disease or inflammatory bowel disease, specific conditions such as smoking, and concomitant chemotherapy [29]. RT side effects are divided in early (acute) and chronic (late) side effects. Acute side effects, by definition, occur up to 3 months after RT, and are usually self-limiting. Chronic side effects typically occur 3–6 months after RT, or even years later. Symptoms include bleeding, diarrhea, mucus discharge, urgency, and tenesmus [29].

Technological advances in EBRT for PCa have improved the accuracy and precision of dose delivery techniques over the last two decades, and facilitate dose escalation and hypofractionation, without compromising the organs at risk (rectum, bladder). Examples of improved RT techniques are 3D-conformal RT (3D-CRT), intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic ablative RT. Image-guided radiotherapy (IGRT) is used to accurately position the patient and localize the tumor prior to each treatment fraction. This allows the setup uncertainties and treatment margins to be reduced, which results in an improved sparing of surrounding healthy tissues without compromising dose coverage of the target volume. IGRT for PCa, based on intraprostatic implanted fiducial markers [30-31] and daily orthogonal kV imaging or cone-beam computed tomography (CBCT), has been shown to significantly reduce the setup error as compared to bony alignment [32-35]. These techniques allow for more conformal dose distributions to the target volume, and hence an improved sparing of surrounding healthy tissues (Figure 5).

FIGURE 5: Examples of color wash representation of a calculated dose distribution of a 3DCRT, an IMRT, and a VMAT treatment plan superimposed onto a transversal computed tomography slice of the same patient. The red line represents the PTV volume (prostate + margin). Spatial differences in high-dose (red), intermediate-dose (yellow), and low-dose (dark blue) regions are evident. Diagram of an EBRT procedure (Reprinted with permission from [17]).

Abbreviations: 3DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy.

EBRT for PCa: effectiveness, toxicity reduction, quality of life improvement

Several studies have shown that escalating the prescribed dose up to and beyond 78 Gy leads to improved loco-regional control, biochemical disease-free survival, distant metastasis-free survival, PCa specific mortality, and even overall survival in intermediate and high-risk PCa [36-42]. Despite significant technical advances to improve treatment precision and accuracy, there is still a potential risk of patients developing severe gastrointestinal (GI) toxicity. Dose escalation to 78 Gy in comparison with 68 Gy has raised the rates of acute and chronic Grade ≥ 2 rectal toxicity from 3% to 20%, and 5% to 21%, respectively [43-45]. This makes the rectum the dominant dose-limiting organ at risk in prostate EBRT. All side effects of the treatment can have a huge impact on the quality of life of the patient. To improve the quality of life in these patients, the side effects should be diminished [46-47].

Implantable rectum spacers

Since the ano-rectal complex is closely located to the prostatic gland, the PTV margin (at least) partially overlaps with the anterior ano-rectal wall (ARW), such that the latter is included in the high-dose volume. Several investigators have demonstrated that minimizing the radiation dose to this volume of the ano-rectal structure reduces the risk for late rectal bleeding. More precisely, when 20% and 15% of the ano-rectal volume receives a dose of at least 70 and 75 Gy (in 2 Gy fractions), the risk of developing Grade 2 and Grade 3 late rectal bleeding is <15% and <10%, respectively [48,49]. Despite the ability of modern dose delivery techniques to administer highly conformal dose distributions with very steep dose gradients at the rim of the PTV, this still remains a significant risk.

The PTV margin is required to account for setup inaccuracies and intra- and interfractional prostate motion (due to rectal and bladder filling dynamics). The inherent problem is that the high-dose volume of the PTV partially overlaps with the ano-rectum, no matter how steep the dose gradient is. Therefore, the only option to prevent rectal volumes from being exposed to high radiation doses is to artificially increase the distance between the prostate and the ano-rectal complex. Several devices have been developed to achieve improved sparing of the rectal structures. These devices can be divided into endo-rectal balloons (ERB) and relatively novel implantable rectum spacers (IRS) (Figure 6). The ERB increases the distance from the *dorsal* and *lateral* rectal wall (yellow arrow in Figure 6) to the PTV, whereas the *anterior* rectal wall is pushed towards the PTV. The IRS pushes the total rectal wall away from the PTV by increasing the total prostate-rectum distance (yellow arrow in Figure 6, Figure 7).

DEVICES TO SPARE RECTAL STRUCTURES:

ERB

IRS

FIGURE 6: Transversal T2-weighted magnetic resonance images of a prostate (between 2 green arrows) cancer patient with an endo-rectal balloon (ERB) and an implantable rectum spacer (IRS) in blue. The PTV margin (red) around the prostate and rectal wall (brown) are schematically depicted.

Abbreviations: PTV= planning target volume.

FIGURE 7: Color-wash representation of calculated dose distributions superimposed onto an axial computed tomography slice before (a) and after (b) IRS gel injection in the same patient. Prostate is illustrated in yellow contour, with in red contour the PTV margin. Without IRS, the high-dose region >75% (purple) overlaps with the anterior part of the rectum (brown contour), while with IRS in situ the high-dose region spans the IRS (black contour), and not the rectum. The 40% isodose contour (purple) overlaps the entire rectum in (a), whereas it overlaps the rectum partially in (b). (Reprinted with permission from [50])

Abbreviations: IRS = implantable rectum spacer.

FIGURE 8: Schematic illustration of prostate irradiation without (a) and with (b) implanted rectum spacer.

An ERB is inserted into the rectum before each treatment fraction to increase the distance from the dorsal and lateral rectal wall to the prostate. Although the anterior ARW is pushed towards the prostate (Figure 5), the overall net effect proved to be beneficial in 3D-CRT and IMRT [51]. Smeenk and colleagues showed an absolute reduction in the mean dose to the anus of 12 Gy and 7.5 Gy, for 3D-CRT and IMRT, respectively [52]. However, patients can experience discomfort due to daily insertion of the ERB.

An IRS is implanted as a biodegradable tissue filler between the prostate and the rectum to increase the distance from the anterior rectal wall to the prostate. In contrast to an ERB, where

the anterior part of the rectal wall is pushed into the high-dose region of the PTV while pushing the dorsal and lateral rectal wall away from the prostate, the IRS pushes the complete rectal structure away from the PTV (figures 7 and 8). Different types of IRS are available and have been applied clinically for EBRT for PCa: an absorbable hydrogel [53], a hyaluronic acid [54], a saline-filled rectal balloon implant (RBI) [55], or a collagen implant [56]. All types of IRS are implanted using a transperineal approach, which is usually guided by transrectal ultrasound. The main difference between these types of IRS is their chemical composition and their ability to allow for post-implant correction.

Hydrogels are injected as polyethylene liquids and polymerize *in situ* within a few seconds, following the mixture of two liquid hydrogel precursors [53]. This hydrogel is similar to products used in brain surgery, cardiology, and ophthalmology [57-59]. In 2011, Pinkawa and colleagues described a relative rectum dose reduction within the 76 Gy isodose of 67% in 3D-CRT, and 89% in IMRT dose distributions, respectively.

- Hyaluronic acid is a natural polysaccharide compound found in human tissues as connective and extracellular matrix [54]. Prada and colleagues (2007) reported on the use of this IRS in combination with brachytherapy. They showed a relative reduction of 28% in the maximum rectum dose, averaged over all patients in the cohort [54].
- An inflatable rectal balloon implant is made of poly(L-lactide-co-caprolactone). This is a co-polymer of polylactide acid and epsilon caprolactone, in a ratio of 70:30. It is a widely used, medically biodegradable material, and was specifically developed to be used as a tissue spacer [60]. Levy and colleagues demonstrated the proper functionality of the RBI capability to retain its inflated form during a certain period (e.g., patients' radiation session) from *in vitro* and *in vivo* studies in dogs, guinea pigs, and rabbits [60,61]. In 2013, the first clinical results showed a relative reduction by 82% of the rectal volume receiving 74 Gy [55].
- Human collagen is well known from injections into the perineum for treatment of urinary incontinence [62]. Noyes and colleagues (2012) reported a mean reduction in the rectal wall of 50% with an IRS.

The RBI is supposed to have some potential advantages over the other types of IRS. First of all, post-implant correction of the RBI position is possible; if the RBI is mispositioned, it can be easily deflated and replaced, whereas liquid spacers (hydrogels, hyaluronic acid, human collagen) do not permit any correction once injected. If a liquid spacer is accidentally implanted in the rectal wall, a chronic wound could form. As it takes 3 to 9 months for the spacer to dissolve, the start of radiation treatment needs to be delayed, since an immediate start of RT could increase the risk of fistula development. In case the RBI is mispositioned, it is possible to deflate it and stitch any wound that might have been created. In addition, a chemical reaction is required in hydrogels, which limits the implantation time. Furthermore, since the RBI inflates to a predetermined and

predictable shape, the learning curve involved to obtain an adequate implant is steeper than for hydrogels. In addition, an amount of iodine contrast medium can be added to the saline to enhance the visualization of the RBI on CT and CBCT scans. Moreover, because the RBI is a closed system, there is no risk of air or hydrogel injection into blood vessels (although incidences of these side effects have not yet been described).

The role of spacers in locally advanced prostate cancers or extended extra-prostatic disease extension (T3a/4) is unclear [63]. The possible negative influence of a spacer in cases with a dorsal prostate capsule infiltration is unknown, as tumor cells could be displaced from the high-dose region by the spacer [64]. More studies are therefore needed to evaluate the advantages and possible disadvantages of spacers in these patients.

Study rationale

In literature, there is general consensus that an IRS reduces ano-rectal doses due to the increased distance between the prostate and the anterior rectal wall. However, IRS implantation is a costly and invasive procedure. So far, no data on the cost-effectiveness of this innovative device exist. As the cost-effectiveness of newly introduced techniques and interventions has become increasingly important in an era of ever-rising healthcare expenses, there is an urgent need to investigate this topic for PCa patients undergoing EBRT.

Furthermore, the still significant risk for irradiated patients of developing Grade 2 or Grade 3 late rectal bleeding (<15% and <10%, respectively) requires a careful selection of those individuals who are at high risk for developing these GI toxicities. A second topic that needs to be studied is treatment individualization to avoid unbeneficial implantations, involving selecting those patients who are expected to benefit most from an IRS implantation.

Another issue is that the identification of patients who have the highest risk of developing rectal toxicity is based solely on clinical factors. This is insufficient since genetic and dosimetric factors also determine the risk for developing rectal toxicity. Therefore, there is a need for a decision support system that integrates these multivariable predictive factors to be able to select these high-risk patients for IRS implantation with the greatest possible accuracy.

Further, most clinical studies investigating the effect of IRS have focused on hydrogel and hyaluronic based spacers in small patient cohorts. For the RBI, clinical data is even scarcer. A method to implant an RBI has not been described. Clearly, there is a need to identify potential hazards during implantation and to formulate recommendations to optimize the implantation procedure, in order to guarantee a stable and well-positioned RBI over the whole treatment course of EBRT. A thorough assessment of the RBI's volume stability and potential dosimetric consequences of RBI deflation is required to quantify its rectum sparing effect.

Goals, objectives, and hypotheses of the thesis

In this thesis the following goals and objectives are addressed:

1. To motivate the need for an individualized approach in the treatment of PCa, a general overview of and comparison between different treatment modalities (e.g., surgery and radiation therapy) is given. The choice for a particular treatment modality mainly depends on a patient's individual preferences when weighing the risk of treatment-related toxicities. Here, a *shared decision-making* approach can facilitate the decision-making process. The aim of this thesis is to develop a patient decision aid that supports the treatment decision process and empowers patients to take a proactive role in their treatment pathway. The tool has been deployed to provide patients insight into their own preferences regarding the various treatment options, and to help them weigh the risks of treatment-related toxicities.
2. Radiation therapy for PCa is associated with a 15–20% risk of late Grade 2 or more chronic radiation proctitis (CRP). The optimal management of CRP has not been defined. The objective was to provide an overview of means and measures to prevent CRP, and to develop an algorithm for the treatment of CRP. The IRS will be introduced as a means for the prevention of CRP.
3. An IRS is not beneficial for all PCa patients undergoing EBRT. Methods are needed to identify those patients that are expected to benefit most from an IRS implantation. The aim was to develop methods to explore the benefit of an IRS prior to implantation using a model-based approach. In a first approach, decision rules based on clinical risk factors were used to select patients for IRS implantation. In a second approach, an IRS was simulated through the use of deformation fields to predict the geometric changes on computed tomography (CT) images prior to treatment planning. This “virtual IRS,” in combination with a normal-tissue complication probability (NTCP) model and a cost-effectiveness analysis, can serve as the basis for a decision support system for the IRS implantation.
4. An implanted IRS changes the shape and location of ano-rectal wall dose distributions. Such spatial information is currently disregarded in the assessment of treatment-related toxicity and for the optimization of treatment planning. The goal was to demonstrate significant differences in shape-based measures of rectal-wall dose surface maps between patients receiving IMRT with and without IRS, and to relate these differences to previously published NTCP models based on spatio-dosimetric information.
5. To facilitate a safe and easy clinical introduction of the RBI, potential pitfalls and hazards need to be identified. The goal was to report on the peri-operative side effects

experienced by the first patients to receive implants in our institution.

6. PCa patients with active inflammatory bowel disease (IBD) have an increased risk of developing severe GI toxicities following EBRT. The objective was to show that an RBI is a feasible and practical workaround to protect the rectum against high-dose exposure in a patient with active Crohn's disease undergoing EBRT of the prostate.

The following four hypotheses are tested in this thesis:

1. An IRS is a cost-effective tool in prostate cancer EBRT: it significantly reduces the risk of severe GI toxicity and the treatment costs associated with these side effects.
2. Prostate cancer patients who are expected to benefit most from IRS implantation can be identified prior to EBRT through decision rules based on clinical risk factors.
3. An RBI induced prostate-rectum separation of at least 1 cm throughout the whole course of image-guided, moderately hypofractionated VMAT reduces the risk of developing Grade 2 or higher GI toxicity.
4. The construction of a virtual IRS, in combination with a toxicity prediction model and a cost-effectiveness analysis, provides the basis for the development of a decision support tool for the implantation an IRS prior to EBRT for PCa.

Outline of the thesis

This thesis focuses on the reduction of GI toxicity in patients with PCa undergoing EBRT by means of an IRS, and on the identification of individual patients who are expected to benefit most from an IRS.

It consists of a general introduction (**Chapter 1**), which includes the clinical background for state-of-the-art prostate radiation therapy (**Chapter 2**), and an overview of the measures used to treat and prevent chronic radiation proctitis (**Chapter 3**). The rest of this thesis comprises three parts (Figure 9): I) modeling studies for treatment outcome prediction and assessment of cost-effectiveness; II) clinical implementation of the RBI; and III) development of a virtual IRS as a basis for a multifactorial decision support system for pre-implantation assessment of the effects on dosimetry, toxicity reduction, and cost-effectiveness of an IRS.

In **Part I**, hypotheses 1 and 2 are addressed by modeling studies investigating the clinical benefit of an IRS. In **Chapter 4**, the cost-effectiveness of toxicity reduction by an IRS is assessed for prostate IMRT. In **Chapter 5**, decision rules based on clinical risk factors are developed to select those patients who are expected to benefit most from an IRS. In **Chapter 6**, shape-based dosimetric information is used to quantify the reduction in the extent of high-dose areas on the ano-rectal wall by an IRS in PCa patients scheduled for IMRT.

Part II relates to the clinical implementation of the RBI. In **Chapter 7**, the potential hazards

for optimizing the procedure of the RBI are described, with the report of the perioperative complications of the first 15 patients to receive an implant at our institute. In **Chapter 8**, hypothesis 3 is tested. In **Chapter 9**, an RBI-based workaround for a patient with active IBD in need of PCa radiation treatment is presented.

In **Part III**, hypothesis 4 is addressed. To identify patients with a high risk of developing radiation-induced rectal toxicity *prior* to implantation of an IRS, in **Chapter 10** a multifactorial decision support system is developed based on the virtual implantation of an IRS in combination with an NTCP model and cost-effectiveness analysis. In **Chapter 11**, a proof-of-concept is presented for an iso-toxic virtual IRS model integrating validated genetic biomarkers of toxicity and previously published tumor control probabilities as a multifactorial decision support system for the implantation of an IRS.

In **Chapter 12**, a critical recapitulation of the advances in knowledge this work has produced is presented, as well a reflection on aspects that need further research efforts to integrate the IRS as a tool for future individualized radiation treatment of patients with prostate cancer.

FIGURE 9: Schematic overview of the outline of this thesis.

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM. et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *Global Burden of Disease Cancer Collaboration, JAMA Oncol.* 2017;3(4):524
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *European Journal of Cancer* (2013) 49, 1374-1403.
3. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-86.
4. Lifetime risk was calculated by the Statistical Information Team at Cancer Research UK, 2012.
5. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Neal DE; ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med.* 2016 Sep 14.
6. Wolff RF, Ryder S, Bossi A, Briganti A, Crook J, Henry A, Karnes J, Potters L, de Reijke T, Stone N, Burckhardt M, Duffy S, Worthy G, Kleijnen J. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. *Eur J Cancer.* 2015 Aug;51(16):2345-67.
7. Glass AS, Cowan JE, Fuldeore MJ, Cooperberg MR, Carroll PR, Kenfield SA, et al. Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era. *Urology* 2013;82(1):60–5.
8. Lardas M, Liew M, van den Bergh RC, De Santis M, Bellmunt J, Van den Broeck T, Cornford P, Cumberbatch MG, Fossati N, Gross T, Henry AM, Bolla M, Briers E, Joniau S, Lam TB, Mason MD, Mottet N, van der Poel HG, Rouvière O, Schoots IG, Wiegel T, Willemse PM, Yuan CY, Bourke L. Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review. *Eur Urol.* 2017 Jul 27. pii: S0302-2838(17)30535-3. doi: 10.1016/j.eururo.2017.06.035. [Epub ahead of print] Review.
9. Trifiletti DM, Sturz VN, Showalter TN, Lobo JM. Towards decision-making using individualized risk estimates for personalized medicine: A systematic review of genomic classifiers of solid tumors. *PLoS One.* 2017 May 9;12(5):e0176388.
10. Stacey D, Légaré F, Lewis KB. Patient Decision Aids to Engage Adults in Treatment or Screening Decisions. *JAMA.* 2017 Aug 15;318(7):657-658.
11. Lambin P, Zindler J, Vanneste BG, De Voorde LV, Eekers D, Compter I, Panth KM, Peerlings J, Larue RT, Deist TM, Jochems A, Lustberg T, van Soest J, de Jong EE, Even AJ, Reymen B, Rekers N, van Gisbergen M, Roelofs E, Carvalho S, Leijenaar RT, Zegers CM, Jacobs M, van Timmeren J, Brouwers P, Lal JA, Dubois L, Yaromina A, Van Limbergen EJ, Berbee M, van Elmpt W, Oberije C, Ramaekers B, Dekker A, Boersma LJ, Hoebbers F, Smits KM, Berlanga AJ, Walsh S. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev.* 2017 Jan 15;109:131-153.
12. Davison, B Joyce, So, Alan I, & Goldenberg, S Larry. (2007). Quality of life, sexual function and decisional regret at 1 year after surgical treatment for localized prostate cancer. *BJU international*,

- 100(4), 780-785.
13. Stacey D, Taljaard M, Smylie J, Boland L, Breau RH, Carley M, Jana K, Peckford L, Blackmore T, Waldie M, Wu RC, Legare F. Implementation of a patient decision aid for men with localized prostate cancer: evaluation of patient outcomes and practice variation. *Implement Sci.* 2016 Jul 2;11(1):87.
 14. Lamers, Romy ED, Cuypers, Maarten, Husson, Olga, Vries, Marieke, Kil, Paul JM, Ruud Bosch, JLH, & Poll-Franse, Lonneke V. (2015). Patients are dissatisfied with information provision: perceived information provision and quality of life in prostate cancer patients. *Psycho-Oncology*.
 15. van Tol-Geerdink JJ, Leer JW, van Oort IM, van Lin EJ, Weijerman PC, Vergunst H, Witjes JA, Stalmeier PF. Quality of life after prostate cancer treatments in patients comparable at baseline. *Br J Cancer.* 2013 May 14;108(9):1784-9. doi: 10.1038/bjc.2013.181. Epub 2013 Apr 23.
 16. Stalmeier PF, van Tol-Geerdink JJ, van Lin EN, Schimmel E, Huizenga H, van Daal WA, Leer JW. Doctors' and patients' preferences for participation and treatment in curative prostate cancer radiotherapy. *J Clin Oncol.* 2007 Jul 20;25(21):3096-100.
 17. Vanneste BGL, Van Limbergen EJ, van Lin EN, van Roermund J, Lambin P. Prostate cancer Radiation Therapy: What does a clinician have to know? *Biomed Res International* vol. 2016, Article ID 6829875.
 18. Brenner MJ, Kaplan ID. Is there any benefit from hypofractionation in external-beam irradiation for prostate cancer? *J Clin Oncol* 2014;32:1-2.
 19. Clemente S, Nigro R, Oliviero C, Marchioni C, Esposito M, Giglioli FR, Mancosu P, Marino C, Russo S, Stasi M, Strigari L, Veronese I, Landoni V. Role of the technical aspects of hypofractionated radiation therapy treatment of prostate cancer: a review. *Int J Radiat Oncol Biol Phys.* 2015 Jan 1;91(1):182-95.
 20. Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, Dielwart MF, Incrocci L, Lebesque JV. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008 Nov 15;72(4):980-8.
 21. Aluwini S, Pos F, Schimmel E, van Lin E, Krol S, van der Toorn PP, de Jager H, Dirks M, Alemayehu WG, Heijmen B, Incrocci L. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol.* 2015;16(3):274.
 22. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, Shah AB, D'Souza DP, Michalski JM, Dayes IS, Seaward SA, Hall WA, Nguyen PL, Pisansky TM, Faria SL, Chen Y, Koontz BF, Paulus R, Sandler HM. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. *J Clin Oncol.* 2016.
 23. Dearnaley DP, Syndikus I, Mossop H, Birtle AJ, Bloomfield DJ, Cruickshank C, et al. Comparison of hypofractionated high-dose intensity-modulated radiotherapy schedules for prostate cancer: results from the phase III randomized CHHiP trial (CRUK/06/016). *J Clin Oncol* 2016;34.
 24. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, Meier R, Wang J, Kupelian P, Steinberg M, Katz A. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol.* 2013 Nov;109(2):217-21.
 25. Yu JB, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic body radiation therapy

- versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *J Clin Oncol*. 2014 Apr 20;32(12):1195-201
26. King CR, Collins S, Fuller D, Wang PC, Kupelian P, Steinberg M, Katz A. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys*. 2013 Dec 1;87(5):939-45.
 27. Bel A, van Herk M, Lebesque JV. Target margins for random geometrical treatment uncertainties in conformal radiotherapy. *Med Phys*. 1996 Sep;23(9):1537-45.
 28. Talcott JA, Manola J, Clark JA, Kaplan I, Beard CJ, Mitchell SP, Chen RC, O'Leary MP, Kantoff PW, D'Amico AV (2003) Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol*. 21(21):3979–86.
 29. Shadad AK, Sullivan FJ, Martin JD, Egan LJ (2013) Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol* 14;19(2):185-98.
 30. Langenhuijsen JF, van Lin EN, Kiemeney LA, van der Vicht LP, McColl GM, Visser AG, Witjes JA. Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors. *Int J Radiat Oncol Biol Phys*. 2007 Nov 1;69(3):671-6.
 31. Fawaz ZS, Yassa M, Nguyen DH, Vavassis P. Fiducial marker implantation in prostate radiation therapy: complication rates and technique. *Cancer Radiother*. 2014 Dec;18(8):736-9
 32. Nederveen AJ, van der Heide UA, Dehnad H, van Moorselaar RJ, Hofman P, Lagendijk JJ. Measurements and clinical consequences of prostate motion during a radiotherapy fraction. *Int J Radiat Oncol Biol Phys* 2002;53:206-14.
 33. Khosa R, Nangia S, Chufal KS, Ghosh D, Kaul R, Sharma L. Daily online localization using implanted fiducial markers and its impact on planning target volume for carcinoma prostate. *J Cancer Res Ther*. 2010 Apr-Jun;6(2):172-8.
 34. Sveistrup J, af Rosenschöld PM, Deasy JO, Oh JH, Pommer T, Petersen PM, Engelholm SA. Improvement in toxicity in high risk prostate cancer patients treated with image-guided intensity-modulated radiotherapy compared to 3D conformal radiotherapy without daily image guidance. *Radiat Oncol*. 2014 Feb 4;9:44.
 35. Ariyaratne H, Chesham H, Pettingell J, Alonzi R. Image-guided radiotherapy for prostate cancer with cone beam CT: dosimetric effects of imaging frequency and PTV margin. *Radiother Oncol*. 2016 Oct;121(1):103-108.
 36. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, Bonfrer JM, Incrocci L, Lebesque JV. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol*. 2006;24(13):1990-6
 37. Dearnaley D, Sydes M, Graham J, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8(6):475-87.

38. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009 Aug;74(5):1405-18.
39. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010 Mar;28(7):1106-11.
40. Zelefsky MJ, Fuks Z, Hunt M, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001;166:876-81.
41. Kim M, Hoffman K, Levy L, et al. Improvement in prostate cancer survival over time: a 20-year analysis. *Cancer J* 2012;18(1):1-8.
42. Kalbasi A, Li J, Berman A, Swisher-McClure S, Smaldone M, Uzzo RG, Small DS, Mitra N, Bekelman JE. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. *JAMA Oncol*. 2015 Oct;1(7):897-906.
43. Al-Mamgani A, Heemsbergen WD, Peeters ST, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73(3):685-91.
44. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(4):1124-9.
45. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(1):67-74.
46. Glass AS, Cowan JE, Fuldeore MJ, Cooperberg MR, Carroll PR, Kenfield SA, et al. Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era. *Urology* 2013;82(1):60-5.
47. Fonteyne V, Ost P, Vanpachtenbeke F, Colman R, Sadeghi S, Villeirs G, Decaestecker K, De Meerleer G. Rectal toxicity after intensity modulated radiotherapy for prostate cancer: which rectal dose volume constraints should we use? *Radiother Oncol*. 2014 Dec;113(3):398-403
48. Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. *Radiother Oncol*. 2009;93(2):153-67.
49. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S123-9.
50. Vanneste BG, Hoffmann AL, van Lin EN, Van De Voorde L, Pinkawa M, Lambin P. Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. *Radiother Oncol*. 2016: S0167-8140(16)34290-6.
51. Smeenk RJ, Hoffmann AL, Hopman WP, van Lin EN, Kaanders JH. Dose-effect relationships for individual pelvic floor muscles and anorectal complaints after prostate radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012 Jun 1;83(2):636-44.
52. Smeenk RJ, van Lin EN, van Kollenburg P, Kunze-Busch M, Kaanders JH. Anal wall sparing effect of

- an endorectal balloon in 3D conformal and intensity-modulated prostate radiotherapy. *Radiother Oncol.* 2009 Oct;93(1):131-6.
53. Pinkawa M, Corral NE, Caffaro M. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol* 2011;100(3):436-41.
 54. Prada PJ, Fernández J, Martínez AA, de la Rúa A, Gonzalez JM, Fernandez JM, Juan G. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys* 2007;69(1):95-102.
 55. Melchert C, et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol* 2013;106(2):210-4.
 56. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82(5):1918-22.
 57. Garasic JM, Martin L, Anderson RD. Acute evaluation of the Mynx vascular closure device during arterial re-puncture in an ovine model. *J. Invasive Cardiol.* 2009; 21, 283–285.
 58. Garasic JM, Martin L, Anderson RD. Acute evaluation of the Mynx vascular closure device during arterial re-puncture in an ovine model. *J. Invasive Cardiol.* 21, 283–285 (2009).
 59. Bertolaccini L, Lyberis P, Manno E. Lung sealant and morbidity after pleural decortication: a prospective randomized, blinded study. *J Cardiothorac Surg.* 2010 May 28;5:45.
 60. Levy Y, Paz A, Yosef RB, Corn BW, Vaisman B, Shuhat S, Domb AJ. Biodegradable inflatable balloon for reducing radiation adverse effects in prostate cancer. *J Biomed Mater Res B Appl Biomater.* 2009 Nov;91(2):855-67.
 61. Ben-Yosef R, Paz A, Levy Y, Alani S, Muncher Y, Shohat S, Domb A, Corn B. A novel device for protecting rectum during prostate cancer irradiation: in vivo data on a large mammal model. *J Urol.* 2009 Mar;181(3):1401-6.
 62. Faerber GJ, Richardson TD. Long-term results of transurethral collagen injection in men with intrinsic sphincter deficiency. *Endourol.* 1997 Aug;11(4):273-7.
 63. G. Mok, E. Benz, J.-P. Vallee, R. Miralbell, and T. Zilli. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review, *International Journal of Radiation Oncology Biology Physics*, 2014, vol. 90, no. 2, pp. 278–288.
 64. G. Hatiboglu, M. Pinkawa, J.-P. Vallée, B. Hadaschik, and M. Hohenfellner. Application technique: placement of a prostate—rectum spacer in men undergoing prostate radiation therapy. *BJU International*, 2012, vol. 110, no. 11, pp. E647–E652.

CHAPTER 2

Prostate cancer Radiation Therapy: What does a clinician have to know?

ABSTRACT

Radiotherapy (RT) for prostate cancer (PCa) has steadily evolved over the last decades, with improving biochemical disease-free survival. Recently population based research also revealed an association between overall survival and doses ≥ 75.6 Gray (Gy) in men with intermediate- and high-risk PCa. Examples of improved RT techniques are image-guided RT, intensity-modulated RT, volumetric modulated arc therapy, and stereotactic ablative body RT, which could facilitate further dose escalation. Brachytherapy is an internal form of RT that also developed substantially. New devices such as rectum spacers and balloons have been developed to spare rectal structures. Newer techniques like protons and carbon ions have the intrinsic characteristics maximising the dose on the tumour while minimising the effect on the surrounding healthy tissue, but clinical data are needed for confirmation in randomised phase III trials. Furthermore, it provides an overview of an important discussion issue in PCa treatment between urologists and radiation oncologists: the comparison between radical prostatectomy and RT. Current literature reveals that all possible treatment modalities have the same cure rate, but a different toxicity pattern. We recommend proposing the possible different treatment modalities with their own advantages and side-effects to the individual patient. Clinicians and patients should make treatment decisions together (shared decision-making) while using patient decision aids.

1. INTRODUCTION

Prostate cancer (PCa) is the most common cancer among males in the Western world, with more than 1.11 million new cases diagnosed in 2012 and 307,000 deaths [1, 2]. The lifetime risk of developing PCa is 1 in 8 [3]. It is expected that the incidence will substantially increase in the coming decades due to the aging population, which makes it a huge health care problem. The total economic costs of PCa in Europe are estimated to exceed 8.43 billion [4]. One of the biggest challenges in the 21st century will be to offer the best individualised treatment at reasonable costs.

External-beam radiotherapy (EBRT) and brachytherapy (BT) are potentially curative therapies for PCa. RT has undergone tremendous improvements in the last decades. Dose escalation in prostate EBRT leads to improved locoregional control, biochemical disease-free survival (bDFS), distant metastasis-free survival, PCa specific mortality, and even overall survival in intermediate- and high-risk PCa [5–11]. However, dose escalation is limited by toxicity of surrounding healthy tissues, and therefore improved tumour control is expected to come at the cost of higher toxicity, greatly impacting patients' quality of life [12–14]. However, dose escalation is possible due to advances in different RT techniques, sophisticated computer-based treatment planning, and/or development of extra devices, avoiding increased dose delivery to the surrounding healthy tissue. The purpose of this article is to provide insight into the enormous improvements in RT techniques to practicing clinicians and primary care doctors and to develop a greater comfort level when referring patients to a radiation oncologist. Furthermore, it provides an overview of an important discussion issue concerning RT from a clinician's perspective: the comparison between operation and RT.

2. OVERVIEW OF EXTERNAL BEAM RADIATION TREATMENTS

In EBRT a dose of ionising radiation is generated by an external X-ray source. In the past this was a cobalt-60 source machine, but nowadays a high-tech tele-therapy unit is used for this purpose [15, 16]. Linear accelerators are the source of electronic induced irradiation. The radiation beam leaves the linear accelerator by a gantry. Different options of machines are commercially available: a traditional linear accelerator where the gantry can rotate around the patient (Arc therapy). Other possibilities are tomotherapy (=helical therapy) where the radiation dose is delivered slice-by-slice [17], or cyberknife (=a robotic radiosurgery system) where the location of the prostate is identified during treatment and active corrections are made for movements of the prostate during treatment delivery [18]. Evolving radiation techniques as protons and carbon ions are also introduced and are discussed below. Over the last 20 years the methods of delivering a dose of ionising radiation to a target area have changed incrementally. An EBRT procedure consists of 2 main parts (Figure 1).

FIGURE 1: Overview of an EBRT procedure.

First, in a preparatory phase an RT plan needs to be created. This process is referred to as RT planning. Secondly, the linear accelerator requires delivering this plan to a patient in an appropriate fashion: the RT dose delivery.

In the preparatory phase, images of the patient are acquired. On these scans the clinical target area is delineated to which the radiotherapy dose is prescribed. In the 90s this area was delineated on conventional planar 2D X-rays, on which the target area (the prostate and seminal vesicles) could only be assumed. Later, CT based planning was introduced [19]. On the latter the target areas are visualised and can be delineated directly leading to up to one-third less geographical miss of the

target [20]. Another advantage of CT based planning was that also critical structures like rectal wall and bladder around the target could be visualised and subsequently spared from radiation, by avoiding the X-ray beams to pass through them. Currently an MRI is being integrated more broadly into the planning process. MRI allows us to delineate the prostate more precisely from the pelvic diaphragm, and the base of the prostate can be differentiated more precisely from the seminal vesicles [21, 22]. An additional MRI changes the delineation of the clinical target volume in 18% to 20% of cases compared to CT based planning [23, 24]. Moreover, tumour extension in and outside of the prostate and invasion in the seminal vesicles are better visible on MRI and therefore more often included in the target volumes [24, 25]. Chang and colleagues reported significant volume changes with MRI delineation: extracapsular extension was significantly more incorporated into target volumes with the addition of MRI (40%) in comparison with CT (32%). The seminal vesicles are also more often included: 18% versus 3%, respectively. In addition, CT scans overestimate prostate volume by 10% to 45% [21, 22, 26–32]. Furthermore, an MRI revealed an important decrease of the interobserver delineation variation, especially at the prostatic apex [33]. We expect that a correct delineation of the target volume will result in better treatment outcome, with less toxicity, but until now this is not proven yet.

In addition to improved radiotherapy planning, developments were introduced to verify correct dose delivery during the whole course of RT over the several fractions delivered according to the radiotherapy plan. In earlier times patients were positioned on a linear accelerator using surrogate reference points: external reference points like skin lines or tattoo points or using bony landmarks visualised by conventional plain X-ray photographs taken on the linear accelerator. However, as it is known that the prostate and the seminal vesicles can move independently from these reference points this can be problematic because it could lead to off-target dose delivery, which in turn compromises tumour cure [34, 35]. In earlier times this problem was compensated by expanding the margins of the RT field to minimise the chance of a geographical miss. The downside of this approach was however that this approach leads to a higher volume of irradiation to the surrounding healthy tissues and critical structures. More recently, this problem is tackled by the placement of fiducials (markers) into the prostate before the RT treatment [36–38]. In this way the movement of the prostate can be monitored during treatment, and field setups can be adjusted in case of movement of the prostate ensuring correct dose delivery, even with small safety margins. A comparable methodology is implantation of electromagnetic transponders (Calypso®) [39]. Other image guidance strategies are used but are focused on visualisation of the prostate itself instead of a surrogate (marker): cone-beam computed tomography [40], MRI [41], and ultrasound imaging [42]. The most popular strategy is the use of fiducials because of the easy and quick performance. Disadvantages of the image guidance strategy directly focused on the organ are poor image quality (cone-beam computed tomography, ultrasound) and high costs (MRI). All this leads to the development of dose volume constraints to diminish the

chance on rectal and urinary toxicity [13, 43]. As delineation became more accurate and precise, consequently the necessity emerged for better shaping the dose around the target and avoiding the critical structures. In earlier techniques, like 3D-conformal RT, beams were shaped around the tumour contours with a collimator blocking gamma rays out of unwanted areas (i.e., healthy organs). The tumour was irradiated mostly using 4 fields opposed to each other (anteroposterior and lateral opposing fields). The result was a high-dose “box” in the overlap zone of the four bundles. Later, intensity-modulated radiotherapy (IMRT) techniques were introduced. Here the tumour was approached from additional angles, using mobile computer-controlled collimators, creating additional degrees of freedom to shape the high-dose region around the target.

Volumetric modulated arc therapy (VMAT) or rapid arc therapy is a relatively novel radiation technique. It is an advanced form of IMRT that delivers a 3D-dose distribution with a 360-degree rotation of the gantry in a single or multiarc treatment. This results in an improved target volume coverage and sparing of normal tissues compared with less modern techniques (Figure 2). VMAT has the advantage of favourable dose distributions. Furthermore, it reduced the monitor units required compared with IMRT and reduced treatment delivery time [44, 45].

FIGURE 2: Examples of dose distribution of a 3DCRT, IMRT-5, VMAT, PSPT, IMPT, and a BT treatment plan calculated on the same patient. The red surface represents the high-dose regions, the yellow surface the intermediate-high-dose regions, the dark blue surface the low-dose regions, and the azure blue surface the intermediate-dose regions. 3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; PSPT: passively scattered proton therapy; IMPT: intensity modulated proton therapy; BT: brachytherapy.

These improvements in delineation and more conformal RT technique but also treatment delivery verifications allowed for further dose escalation resulting in higher cure rates with similar or slightly higher toxicity [8, 46–53]. Standard RT uses a daily dose of 1.8 to 2.0 Gy for 39–45 fractions. The updated published randomised phase III trials of dose escalation are summarised in Table 1. The dose escalations revealed a 10 to 20% increase of bDFS. This advantage, however, did not translate into an improvement of overall survival. Besides, Kalbasi and colleagues demonstrated in a huge cohort of patients (42,481) of the National Cancer Data base that dose escalation up to ≥ 75.6 Gy is associated with improved overall survival in men with intermediate- and high-risk prostate cancer [11].

TABLE 1: Updated phase III randomised trials on dose escalation for prostate cancer. All results are statistically significant, except those marked with ^{n.s.}

	N	Median FU(yrs)	Dose (Gy)	Benefit bDFS (%)	Toxicity Gr2 GI (%)	Toxicity Gr2 GU (%)
<u>MD Anderson:</u>						
Kuban et al. 2008	301	8.7	70 vs 78	59 vs 78	13 vs 26	13 vs 8 ^{n.s.}
<u>MGH:</u>						
Michalski et al. 2015	1499	7	70.2 vs 79.2	57 vs 74	16 vs 22	10 vs 15
<u>Dutch Trial:</u>						
Heemsbergen et al. 2014	669	9.1	68 vs 78	61 vs 69	25 vs 35	40 vs 41 ^{n.s.}
<u>Royal Marsden:</u>						
Dearnaley et al. 2014	843	10	64 vs 74	43 vs 55	24 vs 33	8 vs 11 ^{n.s.}
<u>GETUG:</u>						
Beckendorf et al. 2011	306	5.1	70 vs 80	68 vs 76.5	14 vs 19.5	10 vs 17.5

Abbreviations: bDFS = biochemical Disease-Free Survival, ^{n.s.} = not significant

2.1. Hypofractionation

A total dose cannot be delivered in one fraction, since this would produce serious adverse reactions. Therefore, the total dose needs to be split into fractions. Healthy cells can recover themselves from the RT during the interfraction periods, whereas tumour cells are damaged. Hypofractionated (HF) EBRT means a larger dose per fraction with less fractionations, mainly given over a shorter time period, with a lower total dose. This lower total dose has a comparable effect with a higher standard dose in fractions of 2 Gy [54]. The damage is greater in larger fractionations and the total dose is lower for the same effect. To easily compare the different

RT schemas all RT schedules are recalculated in standard 2Gy fractions. Several tools are available to calculate different RT schedules with each other, for example, <http://rotoolbox.com/calculators/eqd2/>.

HF for PCa is traditionally performed in 19 to 28 fractions of 2.5Gy to 3.4Gy per fraction. HF has earned increasing attention as it has a higher therapeutic ratio (=the difference between treatment benefits and morbidity) than standard fractionated IMRT, which may theoretically lead to greater local cancer control [55, 56]. Furthermore, HF EBRT ameliorates logistical inconveniences for both patients and their providers. It is particularly useful for patients who benefit logistically from a shortened HF course like patients living at long distance from an RT centre or who have a poor support system [57, 58]. The results of three recently published phase III trials are summarised in Table 2 [59–61]. These trials revealed that HF is well tolerated, albeit with a slight increase in toxicity rates when compared to conventional schedules. No improvement on bDFS has been noticed; however, the follow-up period is possibly insufficient. Further evaluations and reports are expected in the coming years.

Table 2: Updated phase III randomised trials on hypofractionation for prostate cancer. All results are statistically significant, except those marked with ^{n.s.}

	N	Median FU (yrs)	Dose (Gy) Per fraction	Benefit bDFS (%)	Toxicity Gr2 GI (%)	Toxicity Gr2 GU (%)
<i>Dutch Trial:</i>						
Aluwini et al. 2015	820	5	39 x 2 vs 19 x 3.4	77 vs 80 ^{n.s.}	Equal; 13	22 vs 23
<i>RTOG 0415:</i>						
Lee et al. 2016	1092	5.8	41 x 1.8 vs 28 x 2.5	85.3 vs 86.3	11.4 vs 18.3	20.5 vs 26.2
<i>CHHiP:</i>						
Dearnaley et al. 2016	3163	5.1	37 x 2 vs 20 x 3 vs 19 x 3	88.3 vs 90.6 vs 85.9	Equal; 2 ^{n.s.}	11 vs 13 ^{n.s.}

Abbreviations: bDFS = biochemical Disease-Free Survival; CHHiP = Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer; ^{n.s.} = not significant; Gr2 = Grade 2 or more toxicity

2.2. Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) is an extreme form of HF. Stereotaxy refers to a precise method of target localisation using three-dimensional coordinates derived from medical imaging. SBRT for PCa is traditionally performed in 3–7 fractions of 6Gy to 10Gy per fraction. SBRT is delivered with even higher than standard precision procedures, for example, a customised body pillow formed by vacuum suction [62]. Just like in conventional EBRT there is an evolution with more dose guidance and higher precision (see above). The available literature consists mainly of several nonrandomised phase II trials. Recently, a large multi-institutional trial of 1100 patients was reported. Separate prospective phase 2 protocols of localised PCa patients from different

institutes treated between 2003 and 2011 were pooled for analysis [63]. With a median follow-up of 36 months, the five-year bDFS rate was 93%. As this series mostly consisted of low- and intermediate-risk patients and follow-up is still limited, this treatment is only recommended for selected low- and intermediate-risk patients with localised PCa. That the acute urogenital toxicity seemed higher than conventional EBRT [64] might pose a disadvantage. On the other hand, low late urinary and rectal toxicities after median follow-up of three years were reported [65]. Data from published prostate SBRT trials have shown late grade 3 GI and GU toxicities within the 3%. However, this data is preliminary and prospective randomised phase III trials and additional follow-up are required to further clarify the relative differences between both treatment modalities.

3. BRACHYTHERAPY

BT is an internal RT, where radiation comes from an implanted source, such as seeds or capsules. BT permits an extreme dose escalation far exceeding other RT modalities. Furthermore, no extra treatment margin is necessary for set-up errors. In general, two types of BT are clinically used: low-dose rate (LDR) and high-dose rate (HDR). In LDR radioactive sources are permanently implanted in the prostate, whereas at HDR temporary needles are placed in the prostate in which a radioactive source irradiates the prostate temporarily. Both modalities can be used either as a monotherapy or as a boost with EBRT. Monotherapies are generally used for low- and intermediate-risk PCa, whereas combined therapy usually is used for intermediate- and high-risk PCa [66]. The logistics are the main advantage of LDR: you can implant it with small shields, whereas HDR is applied in a specialised shielded room for radioprotection issue. LDR has the disadvantage that some extensions are difficult to cover, for example, seminal vesicle extension and extra capsular extension, which can be adequately covered by HDR.

3.1. Low-Dose Rate

Permanent seed implantation involves injecting approximately 50–125 radioactive seeds into the prostate depending on the volume [67]. General or spinal anaesthesia is required. The seed implantation is performed under TRUS guidance via the transperineal approach, with the patient placed in dorsal lithotomy position. LDR is accomplished in an outpatient single visit setting. Individual (loose) seeds or stranded seeds (seeds linked together in dissolvable suture material) are used in LDR [66]. Stranded seeds minimise seed migration and improve dose delivery [68, 69]. The planned RT dose is emitted over several months with an average dose rate of 0.1 Gy/h, depending on the specific isotope [70]. Iodine-125 (I-125) and palladium-103 (Pd-103) are mostly used. Pd-103 has a higher dose rate and is more frequently used in the United States. The prescription dose varies from 145 Gy for I-125 to 120 Gy for Pd-103. The BT alone is an option for patients with low- and intermediate-risk disease when there are only limited features, such as a serum PSA between 10 and 20 ng/mL or small volume Gleason score 7 [68, 70].

Grimm et al. conducted a comprehensive literature review to identify over 18,000 papers involving treatment of localised PCa published during 2000–2010 [71]. Selection criteria were made based on the following criteria: median follow-up of at least five years (which is still short for PCa); patient stratification into pretreatment risk; both clinical and pathological staging; accepted standard definitions for PSA failure; minimum patients number for each risk group which was accepted as 100 for low- and intermediate- and 50 for high-risk group; and results published in peer-review journals only. All the study outcomes were calculated for each risk group and suggested that BT alone, particularly seed implant, provides superior bDFS in low-risk patients. For the intermediate-risk group, combination RT (EBRT + BT) seems to be equal to BT alone. For high-risk patients combination RT with or without androgen deprivation therapy seems to be superior. Furthermore, in a recently reported randomised trial (ASCENDE-RT, NCT00175396),

a LDR boost was demonstrated to be much more effective than an EBRT boost in high-risk prostate cancer patients: a 9-year BRFS of 83% versus 63% [72]. However, these results should be interpreted with some caution because this is only published in an abstract form: no mention of image guidance or quality assurance is made, yet. Toxicity rates are also not clearly mentioned in this abstract. Although these results encourage choosing BT as an element of management, it should be remembered that selection bias may play a main role.

3.2. High-Dose Rate

With HDR BT, transperineal catheters are first inserted in the prostate under general or spinal anaesthesia. The hollow catheters are connected to an HDR “afterloader” with an isotope, mostly iridium-192 (Ir-192). The dose rate is at least 12 Gy/h. The afterloader machine loads the hollow catheters while the BT team is outside the shielded room for radioprotection issues. This machine pushes a wire connected to the radioactive source into each of the different catheters, one by one under computer-control, utilising stop positions and dwell times according to the plan. After treatment, the afterloader withdraws the sources. After the BT treatment the catheters are removed. No radioactive seeds are left in the body.

HDR is often used in a combination therapy with EBRT. Outcomes are superior to those achieved with EBRT alone [73–77]. One phase III trial is reported by Mount Vernon Hospital where they compared EBRT (55 Gy, 20x) with EBRT (37.5 Gy, 13x) and HDR boost (17 Gy, 2x) [73]. Hoskin et al. demonstrated a 7-year BRFS rate of 75% compared with 61%, respectively, with similar incidence of severe late urinary and rectal morbidity. An ongoing randomised trial (PROBACH, NTR3897) will further evaluate the value of HDR as a boost therapy in intermediate- and high-risk PCa.

Another older phase III trial is reported by Sathya and colleagues [78]. They proved that the combination of HDR plus EBRT was superior to EBRT alone for a 5 years BRFS of 71% compared with 39%. This is logic when comparing the total dose schedules to the prostate: the combination therapy was superior with 75 to 80 Gy (comparable with nowadays EBRT schedules) in comparison with EBRT only where the given dose was inferior with 66 Gy and with 2 cm safety margins.

Although the interest in monotherapy HDR is growing, no phase III trials are conducted. Several nonrandomised series are reported on the results of monotherapy HDR in multiple and in single fractions, which are promising.

4. NEW TECHNIQUES: PROTON THERAPY, CARBON ION

Newer RT techniques which utilise heavy particles such as protons and carbon ions have a potential dosimetric benefit of the so-called “Bragg” peak (Figure 3). This means that the maximum dose delivery occurs immediately before the particles come to rest. This means that the maximum effect on the tumour can be determined while minimising the impact on the surrounding healthy tissue. These approaches are currently in development [79–81].

FIGURE 3: The Bragg peak demonstrating the plots energy loss of ionising radiation during its travel through the body. Maximum energy deposition at the target area (tumour) without energy loss after the target (healthy organs).

Zietman et al. published the only randomised series currently available, comparing a high- to a low-proton boost, resulting in a significant increase in bDFS in the high-dose arm [8].

Carbon ions seem more efficient than protons which can be explained by the fact that carbon ion beams are twice to three times more effective than protons or photons [82, 83]. Habl and colleagues published an HF schedule using either carbon ions or protons resulting in comparable acute toxicities [84]. Long-term outcome data on these treatments are not yet available. However, until now, no evidence is shown to support the use of protons in preference to conventional RT for patients with prostate cancer; neither technique had been shown to give improved results over the others with respect to disease control or toxicity [85].

An ongoing multi-institutional phase III-randomised trial (PARTIQoL, NCT01617161) evaluates the value of protons in low- and intermediate-risk PCa in comparison with IMRT. This trial will probably shed light on the additional value of protons in comparison with conventional IMRT for PCa. In any event, we believe the future lies in multifactorial decision support systems calculating for each individual patient the outcome and the cost-effectiveness of the various treatments [86, 87].

5. NEW DEVICES: BALLOON/SPACER

Another way to reduce toxicity is to physically create some space between the healthy organ (rectum) and the targeted area (prostate). As ionising radiation decreases by the inverse square law, even a few millimetres of increased separation can lead to sparing the healthy organ for high doses of radiation.

To spare rectal structures several spacer devices are developed [88]. These can be divided into endorectal balloons and relatively novel rectum spacers. Endorectal balloons are placed into the rectum for each daily treatment. Although the ventral anorectal wall is pushed towards the prostate, the distance from the posterior rectal wall to the prostate is increased with an overall effect proved to be beneficial in RT [89].

Rectum spacers are implanted as a tissue filler into the anterior perirectal fat to separate the rectum from the prostate (Figure 4). Increasing the prostate-rectum distance displaces the rectal wall away from the prostate and out of the high-dose RT regions. The overall effect is a reduction in the total volume of irradiated rectum and the maximum dose to the rectum. The implantation of such rectum spacers is performed transperineally under real-time TRUS guidance. The insertion procedure can be performed under local, spinal, or general anaesthesia [90]. The implanted rectum spacer remains in place over the course of the RT treatment and the spacer biodegrades naturally within six months after implantation [91]. Different types of rectum spacers have been developed: an absorbable hydrogel, a hyaluronic acid, a collagen, and a saline-filled balloon [91, 92]. Although several studies are available on the acute outcome, dosimetry, and cost-effectiveness of a rectum spacer, the long-term outcomes are not yet clear [93–103]. If the spacer is combined with HF, BT, SBRT, or proton therapy, the reduction of toxicity could be even more expected. Very recently, decision rules based on clinical risk factors solely are identified for which patients a spacer implantation is predicted to be beneficial [104]. However, further research is needed to assess the predictive performance of these decision rules and to generate adequate decision support systems. The available results are encouraging for the design of further clinical trials.

FIGURE 4: Axial T2-weighted magnetic resonance images of a patient with a hydrogel spacer before injection (a) and after injection (b).

6. RT COMPARED TO SURGERY

The results of a well-balanced randomised phase III trial comparing RT with RP and active monitoring are very recently reported (PROTECT, NCT02044172) [105, 106]. Hamdy and colleagues compared all those treatments for low-risk localised prostate cancer with a median follow-up of 10 years (1643 patients). Only 17 prostate-cancer-specific mortalities were observed: 8 patients in the active-monitoring group, 5 men in the RP group, and 4 patients in the EBRT group. The differences among the groups were not significant. RP and EBRT were associated with lower incidences of disease progression than active monitoring, respectively, 46 incidences for active therapies compared with 112 men for active-monitoring ($p < 0.001$). Also metastases rates developed more in the active-monitoring group: 33 men in comparison with 13 and 16 for RP and EBRT, respectively ($p = 0.004$). Patient-reported outcomes are also reported: RP had the greatest negative effect on sexual function and urinary continence. EBRT had little effect on urinary continence (urinary voiding and nocturia); however, bowel function was worse. In the active-monitoring group sexual and urinary function declined gradually over years.

All treatments provide an extremely high cure rate. Recently, Lennernäs et al. published the first randomised trial comparing RP with EBRT + HDR [107]. Due to insufficient power and small series (89 patients) no conclusion could be drawn about the efficacy. Nonetheless, some observational data suggest that outcomes with RP lead to better overall and cancer-specific survival than RT [108–112]. Wallis and colleagues recently published a meta-analysis comparing RP with EBRT or BT [108]. They pooled 118,830 patients from 19 studies and concluded that overall and prostate cancer-specific mortality were higher for patients treated with RT compared with RP. Subgroup analyses by risk group, radiation regimen, time period, and follow-up length did not alter the results.

However, all those comparison trials have several limitations. First, patients with greater comorbidity tend to be treated with RT [113]. In addition, comorbidities that have been shown a major impact on survival are not always mentioned [114]. Further, some RT schedules in those trials are using inferior low-dose [115]. Also, a potential bias exists for unaccounted differences between risk groups [116]. Next, baseline characteristics are often different and have a profound impact as differences in the percentage of positive biopsies or Gleason 4 + 3 versus 3 + 4 tumours [116–118]. Furthermore, big meta-analyses are being criticised as the studies synthesised in such analyses do not all pose level 3 evidence [119, 120].

Other data suggest that even either EBRT or BT using adequate dosing schedules and conformal techniques are similar to RP when men with clinically localised PCa are stratified based upon clinical tumour stage, pretreatment serum Prostate Specific Antigen, and Gleason score [121, 122]. Kim et al. concluded that outcomes are not inferior to those of RP despite the fact that the EBRT group included more high-risk patients [122]. Grimm et al. conducted a comprehensive

literature review to identify all studies involving treatment of localised PCa. They even concluded that BT provides superior outcome in patients with low-risk and intermediate-risk disease. High-risk disease revealed the best outcome with combination therapy of EBRT and BT [71]. However, like all comparison trials those have several limitations [123]. First, the endpoint of bDFS is not fair because the definition is different for RP and RT. Further, it is difficult to determine bDFS as a surrogate of cancer-specific survival. Moreover, in the comprehensive literature review of Grimm many RP studies are excluded because they are based on pathology report after RP, which is not possible with RT. Next, many surgical factors can influence oncological outcome and are not reported as innovations in RP (robotic-assisted RP) and caseload volume per institute. Finally, the risk stratification (intermediate-risk group) was more varied amongst articles, thus reflected in significant differences in baseline risk for PSA failure between the treatment methods.

To conclude, one well-controlled randomised phase III trial (PROTECT) randomly assigned men with localised PCa to active monitoring, RT, or RP. This trial revealed comparable outcomes for each treatment, but with a different toxicity pattern.

Our belief is that a paradigm shift from current population-based medicine to personalised and participative medicine is underway. This transition is being supported by the development of multifactorial clinical decision support systems based on prediction models of treatment outcome and constantly reevaluated in different patient datasets in order to refine and reoptimise the models, ensuring the continuous utility of the models.

Nowadays, decisions on the most appropriate treatment for each patient are dependent on unique personal patient characteristics and preferences, clinician judgment, and resource availability. Therefore, to achieve the right treatment for each individual, we believe patients and clinicians should make decisions together: shared decision-making (SDM) [124, 125] to embrace truly participative medicine. SDM is an interactive process in which patients and clinicians collaborate in choosing health care, based upon the best available evidence [126–128]. Several studies have reported that patients involved in SDM experience less decisional conflict, improved compliance with treatment, and a greater quality of life with less comorbidities such as anxiety, fatigue, and depression [129]. This has been confirmed in a Cochrane study by Stacey and colleagues [130]. The health care system benefits, also in terms of reduced costs and fewer unnecessary/unwanted procedures [131]. However, the implementation of SDM remains a challenge in health care systems due to numerous barriers [132–134]. These barriers can be divided into patient, clinician, and organisational barriers. Patient barriers include age and attitudes. Older patients tend to prefer a paternalistic model in which treatment decisions are made by the doctor [132]. Of course, a significant part of patients opt for this model while the doctor chooses the ideal treatment for the particular patient. There are also barriers from the health care provider side,

such as the perception that SDM is too time-consuming or complicated to pursue [133, 134]. Furthermore, clinicians often unintentionally use jargon. Finally, organisational factors such as a lack of support, time, and resources are also commonly described barriers [133].

Patient decision aids (PDAs) have been developed to overcome these challenges [135]. PDAs supply patients with treatment options, treatment-specific information, and treatment comparison to help patients discover their personal preferences [136] (Figure 5, <http://www.treatmentchoice.info/decision-aid-tools.html>). PDAs are not developed to promote one option over another or to replace clinician consultation. Instead, they prepare patients to make informed, values-based individual decisions with clinicians (<http://ipdas.ohri.ca/>) [130, 137].

FIGURE 5: A summary of some screen shots of an interactive PDA for PCa (<http://www.treatmentchoice.info/>). The PDA provides information to the patient of the characteristics of his disease, the available treatments for his own situation, his individual preferences, and a comparison of the possible treatments. It offers a summarised advice based upon the information provided by the patient. The purpose of this is to inform the patient; a final decision is always taken together with the clinician.

7. CONCLUSION

During the past 20 years, RT in PCa has improved significantly in all areas, including treatment technique, planning, and quality control. Examples of improved RT techniques are image-guided RT, IMRT, VMAT, SBRT, LDR-HDR BT, and protons. Rectum spacers and balloons have been developed to diminish rectal toxicities. Further research is needed to define the value of all these promising new techniques. With those technical implementations the long-term bDFS are improved. We recommend dose escalation up to ≥ 75.6 Gy (calculated as standard fractionations of 2 Gy). Doses up to 75.6 Gy is associated with improved overall survival in men with intermediate- and high-risk prostate cancer. HF is an attractive therapeutic option, and the randomised phase III trials revealed a slight increase of toxicity rates in comparison to conventional schedules.

An important discussion issue between urologists and radiation oncologists is summarised: the comparison between RP and RT. The results of a well-balanced randomised phase III trial comparing RT with RP and active monitoring are very recently reported. The outcomes of RP and RT are similar, but they differ significantly in terms of the side-effects. We recommend proposing different treatment modalities to the individual patient characteristics and preferences. For each individual, we recommend that clinicians and patients should make decisions together, shared decision-making, while using patient decision aids.

REFERENCES

1. J. Ferlay, E. Steliarova-Foucher, J. Lortet-Tieulent et al., "Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012," *European Journal of Cancer*, vol. 49, no. 6, pp. 1374–1403, 2013.
2. J. Ferlay, I. Soerjomataram, R. Dikshit et al., "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012," *International Journal of Cancer*, vol. 136, no. 5, pp. E359–E386, 2015.
3. "Lifetime risk was calculated by the Statistical Information Team at Cancer Research UK," 2012, <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer>.
4. A. Heidenreich, P. J. Bastian, J. Bellmunt et al., "EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013," *European Urology*, vol. 65, no. 1, pp. 124–137, 2014.
5. S. T. H. Peeters, W. D. Heemsbergen, P. C. M. Koper et al., "Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy," *Journal of Clinical Oncology*, vol. 24, no. 13, pp. 1990–1996, 2006.
6. D. P. Dearnaley, M. R. Sydes, J. D. Graham et al., "Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial," *The Lancet Oncology*, vol. 8, no. 6, pp. 475–487, 2007.
7. G. A. Viani, E. J. Stefano, and S. L. Afonso, "Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled Trials," *International Journal of Radiation Oncology Biology Physics*, vol. 74, no. 5, pp. 1405–1418, 2009.
8. A. L. Zietman, K. Bae, J. D. Slater et al., "Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09," *Journal of Clinical Oncology*, vol. 28, no. 7, pp. 1106–1111, 2010.
9. M. J. Zelefsky, Z. Fuks, M. Hunt et al., "High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer," *Journal of Urology*, vol. 166, no. 3, pp. 876–881, 2001.
10. M. M. Kim, K. E. Hoffman, L. B. Levy et al., "Improvement in prostate cancer survival over time: a 20-year analysis," *Cancer Journal*, vol. 18, no. 1, pp. 1–8, 2012.
11. A. Kalbasi, J. Li, A. T. Berman et al., "Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer," *JAMA Oncology*, vol. 1, no. 7, pp. 897–906, 2015.
12. A. S. Glass, J. E. Cowan, M. J. Fuldeore et al., "Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era," *Urology*, vol. 82, no. 1, pp. 60–65, 2013.
13. V. Fonteyne, P. Ost, F. Vanpachtenbeke et al., "Rectal toxicity after intensity modulated radiotherapy for prostate cancer: which rectal dose volume constraints should we use?" *Radiotherapy and Oncology*, vol. 113, no. 3, pp. 398–403, 2014.

14. B. G. L. Vanneste, L. Van De Voorde, R. J. de Ridder, E. J. Van Limbergen, P. Lambin, and E. N. van Lin, "Chronic radiation proctitis: tricks to prevent and treat," *International Journal of Colorectal Disease*, vol. 30, no. 10, pp. 1293–1303, 2015.
15. F. W. George, C. E. Carlton Jr., R. F. Dykhuizen, and J. R. Dillon, "Cobalt-60 telecurietherapy in the definitive treatment of carcinoma of the prostate: a preliminary report," *Journal of Urology*, vol. 93, pp. 102–109, 1965.
16. A. Dal Pra and L. Souhami, "Prostate cancer radiation therapy: a physician's perspective," *Physica Medica*, vol. 32, no. 3, pp. 438–445, 2016.
17. S. Scobioala, C. Kittel, N. Wissmann et al., "A treatment planning study comparing tomotherapy, volumetric modulated arc therapy, Sliding Window and proton therapy for low-risk prostate carcinoma," *Radiation Oncology*, vol. 11, no. 1, 2016.
18. W. Kilby, J. R. Dooley, G. Kuduvali, S. Sayeh, and C. R. Maurer Jr., "The CyberKnife® robotic radiosurgery system in 2010," *Technology in Cancer Research and Treatment*, vol. 9, no. 5, pp. 433–452, 2010.
19. C. A. Perez and L. W. Brady, Chapter 51 Prostate, J. B. Lippincott & Co, Philadelphia, Pa, USA, 2nd edition, 1992.
20. N. N. Low, S. Vijayakumar, I. Rosenberg et al., "Beam's eye view based prostate treatment planning: is it useful?" *International Journal of Radiation Oncology, Biology, Physics*, vol. 19, no. 3, pp. 759–768, 1990.
21. M. Milosevic, S. Voruganti, R. Blend et al., "Magnetic resonance imaging (MRI) for localization of the prostatic apex: comparison to computed tomography (CT) and urethrography," *Radiotherapy and Oncology*, vol. 47, no. 3, pp. 277–284, 1998.
22. C. Rasch, I. Barillot, P. Remeijer, A. Touw, M. Van Herk, and J. V. Lebesque, "Definition of the prostate in CT and MRI: A Multi-observer Study," *International Journal of Radiation Oncology Biology Physics*, vol. 43, no. 1, pp. 57–66, 1999.
23. P. J. Horsley, N. J. Aherne, G. V. Edwards et al., "Planning magnetic resonance imaging for prostate cancer intensity-modulated radiation therapy: impact on target volumes, radiotherapy dose and androgen deprivation administration," *Asia-Pacific Journal of Clinical Oncology*, vol. 11, no. 1, pp. 15–21, 2015.
24. J. H. Chang, D. Lim Joon, B. T. Nguyen et al., "MRI scans significantly change target coverage decisions in radical radiotherapy for prostate cancer," *Journal of Medical Imaging and Radiation Oncology*, vol. 58, no. 2, pp. 237–243, 2014.
25. G. M. Villeirs and G. O. De Meerleer, "Magnetic resonance imaging (MRI) anatomy of the prostate and application of MRI in radiotherapy planning," *European Journal of Radiology*, vol. 63, no. 3, pp. 361–368, 2007.
26. M. Roach III, P. Faillace-Akazawa, C. Malfatti, J. Holland, and H. Hricak, "Prostate volumes defined by magnetic resonance imaging and computerized tomographic scans for three-dimensional conformal radiotherapy," *International Journal of Radiation Oncology Biology Physics*, vol. 35, no. 5, pp. 1011–

1018, 1996.

27. M. Debois, R. Oyen, F. Maes et al., "The contribution of magnetic resonance imaging to the three-dimensional treatment planning of localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 45, no. 4, pp. 857–865, 1999.
28. G. L. Sannazzari, R. Ragona, M. G. Ruo Redda, F. R. Giglioli, G. Isolato, and A. Guarneri, "CT-MRI image fusion for delineation of volumes in three-dimensional conformal radiation therapy in the treatment of localized prostate cancer," *British Journal of Radiology*, vol. 75, no. 895, pp. 603–607, 2002.
29. W. L. Smith, C. Lewis, G. Bauman et al., "Prostate volume contouring: a 3D analysis of segmentation using 3DTRUS, CT, and MR," *International Journal of Radiation Oncology Biology Physics*, vol. 67, no. 4, pp. 1238–1247, 2007.
30. B. Hentschel, W. Oehler, D. Strauß, A. Ulrich, and A. Malich, "Definition of the CTV prostate in CT and MRI by using CT-MRI image fusion in IMRT planning for prostate cancer," *Strahlentherapie und Onkologie*, vol. 187, no. 3, pp. 183–190, 2011.
31. L. Sander, N. C. Langkilde, M. Holmberg, and J. Carl, "MRI target delineation may reduce long-term toxicity after prostate radiotherapy," *Acta Oncologica*, vol. 53, no. 6, pp. 809–814, 2014.
32. T. Seppälä, H. Visapää, J. Collan et al., "Converting from CT- to MRI-only-based target definition in radiotherapy of localized prostate cancer: a comparison between two modalities," *Strahlentherapie und Onkologie*, vol. 191, no. 11, pp. 862–868, 2015.
33. G. M. Villeirs, K. Van Vaerenbergh, L. Vakaet et al., "Interobserver delineation variation using CT versus combined CT + MRI in intensity-modulated radiotherapy for prostate cancer," *Strahlentherapie und Onkologie*, vol. 181, no. 7, pp. 424–430, 2005.
34. J. Liang, Q. Wu, and D. Yan, "The role of seminal vesicle motion in target margin assessment for online image-guided radiotherapy for prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 73, no. 3, pp. 935–943, 2009.
35. E.-J. Rijkhorst, A. Lakeman, J. Nijkamp et al., "Strategies for online organ motion correction for intensity-modulated radiotherapy of prostate cancer: prostate, rectum, and bladder dose effects," *International Journal of Radiation Oncology Biology Physics*, vol. 75, no. 4, pp. 1254–1260, 2009.
36. J. F. Langenhuisen, E. N. J. T. van Lin, L. A. Kiemeny et al., "Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors," *International Journal of Radiation Oncology Biology Physics*, vol. 69, no. 3, pp. 671–676, 2007.
37. Z. S. Fawaz, M. Yassa, D. H. Nguyen, and P. Vavassis, "Fiducial marker implantation in prostate radiation therapy: complication rates and technique," *Cancer/Radiotherapie*, vol. 18, no. 8, pp. 736–739, 2014.
38. J. Sveistrup, P. M. af Rosenschöld, J. O. Deasy et al., "Improvement in toxicity in high risk prostate cancer patients treated with image-guided intensity-modulated radiotherapy compared to 3D conformal radiotherapy without daily image guidance," *Radiation Oncology*, vol. 9, no. article 44, 2014.
39. R. D. Foster, T. D. Solberg, H. S. Li et al., "Comparison of transabdominal ultrasound and electromagnetic transponders for prostate localization," *Journal of Applied Clinical Medical Physics*, vol. 11, no. 1, p.

2924, 2010.

40. M. Oldham, D. Létourneau, L. Watt et al., "Cone-beam-CT guided radiation therapy: a model for on-line application," *Radiotherapy & Oncology*, vol. 75, no. 3, pp. 271.e1–271.e8, 2005.
41. B. W. Raaymakers, J. J. W. Lagendijk, J. Overweg et al., "Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept," *Physics in Medicine and Biology*, vol. 54, no. 12, pp. N229–N237, 2009.
42. A. Y. C. Fung, K. M. Ayyangar, D. Djajaputra, R. M. Nehru, and C. A. Enke, "Ultrasound-based guidance of intensity-modulated radiation therapy," *Medical Dosimetry*, vol. 31, no. 1, pp. 20–29, 2006.
43. V. Carillo, C. Cozzarini, T. Rancati et al., "Relationships between bladder dose-volume/surface histograms and acute urinary toxicity after radiotherapy for prostate cancer," *Radiotherapy and Oncology*, vol. 111, no. 1, pp. 100–105, 2014.
44. E. A. Mellon, K. Javedan, T. J. Strom et al., "A dosimetric comparison of volumetric modulated arc therapy with step-and-shoot intensity modulated radiation therapy for prostate cancer," *Practical Radiation Oncology*, vol. 5, no. 1, pp. 11–15, 2015.
45. D. Palma, E. Vollans, K. James et al., "Volumetric modulated arc therapy for delivery of prostate radiotherapy: comparison with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy," *International Journal of Radiation Oncology Biology Physics*, vol. 72, no. 4, pp. 996–1001, 2008.
46. M. J. Zelefsky, E. J. Levin, M. Hunt et al., "Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 70, no. 4, pp. 1124–1129, 2008.
47. A. Pollack, G. K. Zagars, G. Starkschall et al., "Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial," *International Journal of Radiation Oncology Biology Physics*, vol. 53, no. 5, pp. 1097–1105, 2002.
48. D. A. Kuban, S. L. Tucker, L. Dong et al., "Long-term results of the M. D. anderson randomized dose-escalation trial for prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 70, no. 1, pp. 67–74, 2008.
49. J. M. Michalski, J. Moughan, and J. Purdy, "A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer," *Journal of Clinical Oncology*, vol. 33, supplement 7, abstract 4, 2015.
50. A. Al-Mamgani, W. L. J. van Putten, W. D. Heemsbergen et al., "Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 72, no. 4, pp. 980–988, 2008.
51. W. D. Heemsbergen, A. Al-Mamgani, A. Slot, M. F. H. Dielwart, and J. V. Lebesque, "Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival," *Radiotherapy and Oncology*, vol. 110, no. 1, pp. 104–109, 2014.
52. D. P. Dearnaley, G. Jovic, I. Syndikus et al., "Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial," *The Lancet*

- Oncology, vol. 15, no. 4, pp. 464–473, 2014.
53. V. Beckendorf, S. Guerif, E. Le Prisé et al., “70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 80, no. 4, pp. 1056–1063, 2011.
 54. M. C. Joiner and A. van der Kogel, *Basic Clinical Radiobiology*, Edward Arnold, London, UK, 4th edition, 2009.
 55. L. C. Cho, R. Timmerman, and B. Kavanagh, “Hypofractionated external-beam radiotherapy for prostate cancer,” *Prostate Cancer*, vol. 2013, Article ID 103547, 11 pages, 2013.
 56. S. Jabbari, V. K. Weinberg, K. Shinohara et al., “Equivalent biochemical control and improved prostate-specific antigen nadir after permanent prostate seed implant brachytherapy versus high-dose three-dimensional conformal radiotherapy and high-dose conformal proton beam radiotherapy boost,” *International Journal of Radiation Oncology Biology Physics*, vol. 76, no. 1, pp. 36–42, 2010.
 57. M. J. Brenner and I. D. Kaplan, “Is there any benefit from hypofractionation in external-beam irradiation for prostate cancer?” *Journal of Clinical Oncology*, vol. 32, no. 17, pp. 1851–1852, 2014.
 58. S. Clemente, R. Nigro, C. Oliviero et al., “Role of the technical aspects of hypofractionated radiation therapy treatment of prostate cancer: a review,” *International Journal of Radiation Oncology Biology Physics*, vol. 91, no. 1, pp. 182–195, 2015.
 59. S. Aluwini, F. Pos, E. Schimmel et al., “Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial,” *The Lancet Oncology*, vol. 16, no. 3, pp. 274–283, 2015.
 60. W. R. Lee, J. J. Dignam, M. B. Amin et al., “Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer,” *Journal of Clinical Oncology*, vol. 34, no. 20, pp. 2325–2332, 2016.
 61. D. P. Dearnaley, I. Syndikus, H. Mossop et al., “Comparison of hypofractionated high-dose intensity-modulated radiotherapy schedules for prostate cancer: RESULTS from the Phase III randomized CHHiP trial (CRUK/06/016),” *Journal of Clinical Oncology*, vol. 34, 2016.
 62. L. Wang, R. Jacob, L. Chen et al., “Stereotactic IMRT for prostate cancer: setup accuracy of a new stereotactic body localization system,” *Journal of applied clinical medical physics*, vol. 5, no. 2, pp. 18–28, 2004.
 63. C. R. King, D. Freeman, I. Kaplan et al., “Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials,” *Radiotherapy and Oncology*, vol. 109, no. 2, pp. 217–221, 2013.
 64. J. B. Yu, L. D. Cramer, J. Herrin, P. R. Soulos, A. L. Potosky, and C. P. Gross, “Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity,” *Journal of Clinical Oncology*, vol. 32, no. 12, pp. 1195–1201, 2014.
 65. C. R. King, S. Collins, D. Fuller et al., “Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 87, no. 5, pp. 939–945, 2013.

66. M. W. T. Chao, P. Grimm, J. Yaxley, R. Jagavkar, M. Ng, and N. Lawrentschuk, "Brachytherapy: state-of-the-art radiotherapy in prostate cancer," *BJU International*, vol. 116, pp. 80–88, 2015.
67. D. Ash, A. Flynn, J. Battermann, T. De Reijke, P. Lavagnini, and L. Blank, "ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer," *Radiotherapy and Oncology*, vol. 57, no. 3, pp. 315–321, 2000.
68. E. M. Tapen, J. C. Blasko, P. D. Grimm et al., "Reduction of radioactive seed embolization to the lung following prostate brachytherapy," *International Journal of Radiation Oncology Biology Physics*, vol. 42, no. 5, pp. 1063–1067, 1998.
69. W. R. Lee, A. F. deGuzman, S. K. Tomlinson, and D. L. McCullough, "Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy," *Radiotherapy & Oncology*, vol. 65, no. 2, pp. 123–127, 2002.
70. S. Nag, W. Bice, K. DeWyngaert, B. Prestidge, R. Stock, and Y. Yu, "The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis," *International Journal of Radiation Oncology Biology Physics*, vol. 46, no. 1, pp. 221–230, 2000.
71. P. Grimm, I. Billiet, D. Bostwick et al., "Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group," *BJU International*, vol. 109, supplement 1, pp. 22–29, 2012.
72. W. J. Morris, S. Tyldesley, H. H. Pai et al., "ASCENDE-RT: a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer," *Journal of Clinical Oncology*, vol. 33, supplement 7, abstract 3, 2015.
73. P. J. Hoskin, A. M. Rojas, P. J. Bownes, G. J. Lowe, P. J. Ostler, and L. Bryant, "Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer," *Radiotherapy and Oncology*, vol. 103, no. 2, pp. 217–222, 2012.
74. G. C. Morton, "High-dose-rate brachytherapy boost for prostate cancer: rationale and technique," *Journal of Contemporary Brachytherapy*, vol. 6, no. 3, pp. 323–330, 2014.
75. B. De Bari, A. Daidone, and F. Alongi, "Is high dose rate brachytherapy reliable and effective treatment for prostate cancer patients? A review of the literature," *Critical Reviews in Oncology/Hematology*, vol. 94, no. 3, pp. 360–370, 2015.
76. D. J. Demanes, D. Brandt, L. Schour, and D. R. Hill, "Excellent results from high dose rate brachytherapy and external beam for prostate cancer are not improved by androgen deprivation," *American Journal of Clinical Oncology*, vol. 32, no. 4, pp. 342–347, 2009.
77. D. J. Demanes, A. A. Martinez, M. Ghilezan et al., "High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 81, no. 5, pp. 1286–1292, 2011.
78. J. R. Sathya, I. R. Davis, J. A. Julian et al., "Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced

- cancer of the prostate,” *Journal of Clinical Oncology*, vol. 23, no. 6, pp. 1192–1199, 2005.
79. A. Zietman, “Proton beam and prostate cancer: an evolving debate,” *Reports of Practical Oncology and Radiotherapy*, vol. 18, no. 6, pp. 338–342, 2013.
 80. Y. Shioyama, H. Tsuji, H. Suefuji et al., “Particle radiotherapy for prostate cancer,” *International Journal of Urology*, vol. 22, no. 1, pp. 33–39, 2015.
 81. B. S. Hoppe, C. Bryant, and H. M. Sandler, “Radiation for prostate cancer: intensity modulated radiation therapy versus proton beam,” *Journal of Urology*, vol. 193, no. 4, pp. 1089–1090, 2015.
 82. D. Georg, J. Hopfgartner, J. Gøra et al., “Dosimetric considerations to determine the optimal technique for localized prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-rate or low-dose-rate brachytherapy,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 88, no. 3, pp. 715–722, 2014.
 83. K. C. Schiller, G. Habl, and S. E. Combs, “Protons, photons, and the prostate—is there emerging evidence in the ongoing discussion on particle therapy for the treatment of prostate cancer?” *Frontiers in Oncology*, vol. 6, article 8, 2016.
 84. G. Habl, M. Uhl, S. Katayama et al., “Acute toxicity and quality of life in patients with prostate cancer treated with protons or carbon ions in a prospective randomized phase II study—the IPI trial,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 95, no. 1, pp. 435–443, 2016.
 85. “Proton therapy for prostate cancer: time for evidence,” *The Lancet Oncology*, vol. 15, no. 8, p. 775, 2014.
 86. Q. Cheng, E. Roelofs, B. L. Ramaekers et al., “Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer—comparison of dose, toxicity and cost-effectiveness,” *Radiotherapy and Oncology*, vol. 118, no. 2, pp. 281–285, 2016.
 87. S. Walsh, E. Roelofs, P. Kuess et al., “A validated tumor control probability model based on a meta-analysis of low, intermediate, and high-risk prostate cancer patients treated by photon, proton, or carbon-ion radiotherapy,” *Medical Physics*, vol. 43, no. 2, pp. 734–747, 2016.
 88. R. J. Smeenk and E. N. J. T. van Lin, “Application of anorectal sparing devices in prostate radiotherapy,” *Radiotherapy & Oncology*, vol. 106, no. 2, pp. 155–156, 2013.
 89. E. N. J. T. van Lin, J. Kristinsson, M. E. P. Philippens et al., “Reduced late rectal mucosal changes after prostate three-dimensional conformal radiotherapy with endorectal balloon as observed in repeated endoscopy,” *International Journal of Radiation Oncology Biology Physics*, vol. 67, no. 3, pp. 799–811, 2007.
 90. G. Hatiboglu, M. Pinkawa, J.-P. Vallée, B. Hadaschik, and M. Hohenfellner, “Application technique: placement of a prostate—rectum spacer in men undergoing prostate radiation therapy,” *BJU International*, vol. 110, no. 11, pp. E647–E652, 2012.
 91. G. Mok, E. Benz, J.-P. Vallee, R. Miralbell, and T. Zilli, “Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review,” *International Journal of Radiation Oncology Biology Physics*, vol. 90, no. 2, pp. 278–288, 2014.
 92. M. Pinkawa, “Spacer application for prostate cancer radiation therapy,” *Future Oncology*, vol. 10, no.

- 5, pp. 851–864, 2014.
93. P. J. Prada, J. Fernández, A. A. Martínez et al., “Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients,” *International Journal of Radiation Oncology * Biology * Physics*, vol. 69, no. 1, pp. 95–102, 2007.
 94. R. B. Wilder, G. A. Barne, R. F. Gilbert et al., “Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 77, no. 3, pp. 824–830, 2010.
 95. R. C. Susil, T. R. McNutt, T. L. DeWeese, and D. Song, “Effects of prostate-rectum separation on rectal dose from external beam radiotherapy,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 76, no. 4, pp. 1251–1258, 2010.
 96. W. R. Noyes, C. C. Hosford, and S. E. Schultz, “Human collagen injections to reduce rectal dose during radiotherapy,” *International Journal of Radiation Oncology Biology Physics*, vol. 82, no. 5, pp. 1918–1922, 2012.
 97. M. Pinkawa, N. E. Corral, M. Caffaro et al., “Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer,” *Radiotherapy & Oncology*, vol. 100, no. 3, pp. 436–441, 2011.
 98. M. Uhl, B. Van Triest, M. J. Eble, D. C. Weber, K. Herfarth, and T. L. De Weese, “Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial,” *Radiotherapy and Oncology*, vol. 106, no. 2, pp. 215–219, 2013.
 99. C. Melchert, E. Gez, G. Bohlen et al., “Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study,” *Radiotherapy & Oncology*, vol. 106, no. 2, pp. 210–214, 2013. D. Y. Song, K. K. Herfarth, M. Uhl et al., “A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes,” *International Journal of Radiation Oncology Biology Physics*, vol. 87, no. 1, pp. 81–87, 2013.
 100. T. J. Strom, R. B. Wilder, D. C. Fernandez et al., “A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy ± intensity modulated radiation therapy,” *Radiotherapy and Oncology*, vol. 111, no. 1, pp. 126–131, 2014.
 101. B. G. L. Vanneste, M. Pijls-Johannesma, L. Van De Voorde et al., “Spacers in radiotherapy treatment of prostate cancer: is reduction of toxicity cost-effective?” *Radiotherapy and Oncology*, vol. 114, no. 2, pp. 276–281, 2015.
 102. N. Mariados, J. Sylvester, D. Shah et al., “Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 92, no. 5, pp. 971–977, 2015.

103. B. G. Vanneste, A. L. Hoffmann, E. N. van Lin, L. Van De Voorde, M. Pinkawa, and P. Lambin, "Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection," *Radiotherapy and Oncology*, vol. 121, no. 1, pp. 118–123, 2016.
104. F. C. Hamdy, J. L. Donovan, J. A. Lane et al., "10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer," *The New England Journal of Medicine*, vol. 375, no. 15, pp. 1415–1424, 2016.
105. J. L. Donovan, F. C. Hamdy, J. A. Lane et al., "Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer," *New England Journal of Medicine*, vol. 375, no. 15, pp. 1425–1437, 2016.
106. B. Lennernäs, K. Majumder, J.-E. Damber et al., "Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: a swedish multicenter randomized trial with patient-reported outcomes," *Acta Oncologica*, vol. 54, no. 6, pp. 875–881, 2015.
107. C. J. D. Wallis, R. Saskin, R. Choo et al., "Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis," *European Urology*, vol. 70, no. 1, pp. 21–30, 2016.
108. P. Sooriakumaran, T. Nyberg, O. Akre et al., "Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes," *British Medical Journal*, vol. 348, Article ID g1502, 2014.
109. F. Petrelli, I. Vavassori, A. Coinu, K. Borgonovo, E. Sarti, and S. Barni, "Radical prostatectomy or radiotherapy in high-risk prostate cancer: a systematic review and metaanalysis," *Clinical Genitourinary Cancer*, vol. 12, no. 4, pp. 215–224, 2014.
110. K. Akakura, H. Suzuki, T. Ichikawa et al., "A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months," *Japanese Journal of Clinical Oncology*, vol. 36, no. 12, pp. 789–793, 2006.
111. J. Y. Lee, K. S. Cho, J. K. Kwon et al., "A competing risk analysis of cancer-specific mortality of initial treatment with radical prostatectomy versus radiation therapy in clinically localized high-risk prostate cancer," *Annals of Surgical Oncology*, vol. 21, no. 12, pp. 4026–4033, 2014.
112. S. Houterman, M. L. G. Janssen-Heijnen, A. J. M. Hendrikx, H. A. Van Den Berg, and J. W. W. Coebergh, "Impact of comorbidity on treatment and prognosis of prostate cancer patients: a population-based study," *Critical Reviews in Oncology/Hematology*, vol. 58, no. 1, pp. 60–67, 2006.
113. M. Roach III and K. Thomas, "Overview of randomized controlled treatment trials for clinically localized prostate cancer: implications for active surveillance and the United States preventative task force report on screening?" *Journal of the National Cancer Institute. Monographs*, vol. 2012, no. 45, pp. 221–229, 2012.
114. A. Rane, "Surgery or radiotherapy for prostate cancer?" *British Medical Journal*, vol. 348, Article ID g1580, 2014.
115. M. Roach III, "Radical prostatectomy v radiation: only a randomised trial can provide the answer,"

- British Medical Journal, vol. 348, Article ID g2266, 2014.
116. S. H. Giordano, Y.-F. Kuo, Z. Duan, G. N. Hortobagyi, J. Freeman, and J. S. Goodwin, "Limits of observational data in determining outcomes from cancer therapy," *Cancer*, vol. 112, no. 11, pp. 2456–2466, 2008.
 117. J. B. Eifler, E. B. Humphreys, M. Agro, A. W. Partin, B. J. Trock, and M. Han, "Causes of death after radical prostatectomy at a large tertiary center," *The Journal of Urology*, vol. 188, no. 3, pp. 798–801, 2012.
 118. C. J. Wallis, R. Saskin, R. Choo et al., "Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis," *European Urology*, vol. 70, no. 1, pp. 21–30, 2016, *European Urology*, vol. 70, no. 1, pp. e15-6, 2016.
 119. C. J. Wallis, R. Saskin, R. Choo et al., "Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis," *European Urology*, vol. 70, no. 1, pp. 21–30, 2016.
 120. R. F. Wolff, S. Ryder, A. Bossi et al., "A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer," *European Journal of Cancer*, vol. 51, no. 16, pp. 2345–2367, 2015.
 121. Y.-J. Kim, K. H. Cho, H. R. Pyo et al., "Radical prostatectomy versus external beam radiotherapy for localized prostate cancer: comparison of treatment outcomes," *Strahlentherapie und Onkologie*, vol. 191, no. 4, pp. 321–329, 2015.
 122. P. Sooriakumaran, M. Spahn, and P. Wiklund, "Apples and oranges: comparison of treatment methods for prostate cancer using biochemical recurrence as an endpoint," *BJU International*, vol. 110, no. 4, pp. 477–478, 2012.
 123. P. Lambin, J. Zindler, B. G. Vanneste et al., "Decision support systems for personalized and participative radiation oncology," *Advanced Drug Delivery Reviews*, 2016.
 124. P. Lambin, J. Zindler, B. Vanneste et al., "Modern clinical research: how rapid learning health care and cohort multiple randomised clinical trials complement traditional evidence based medicine," *Acta Oncologica*, vol. 54, no. 9, pp. 1289–1300, 2015.
 125. F. Légaré, D. Stacey, N. Brière et al., "A conceptual framework for interprofessional shared decision making in home care: protocol for a feasibility study," *BMC Health Services Research*, vol. 11, article no. 23, 2011.
 126. G. Elwyn, A. O'Connor, D. Stacey et al., "International Patient Decision Aids Standards (IPDAS) Collaboration. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process," *British Medical Journal*, vol. 333, no. 7565, p. 417, 2006.
 127. G. Elwyn, S. Laitner, A. Coulter, E. Walker, P. Watson, and R. Thomson, "Implementing shared decision making in the NHS," *BMJ*, vol. 341, Article ID c5146, 2010.
 128. J. D. Tariman, D. L. Berry, B. Cochrane, A. Doorenbos, and A. D. Schepp, "Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review," *Annals of Oncology*, vol. 21, no. 6, pp. 1145–1151, 2009.
 129. D. Stacey, F. Légaré, N. F. Col et al., "Decision aids for people facing health treatment or screening decisions," *The Cochrane Database of Systematic Reviews*, no. 1, Article ID CD001431, 2014.

130. E. O. Lee and E. J. Emanuel, "Shared decision making to improve care and reduce costs," *The New England Journal of Medicine*, vol. 368, no. 1, pp. 6–8, 2013.
131. H. L. Kane, M. T. Halpern, L. B. Squiers, K. A. Treiman, and L. A. McCormack, "Implementing and evaluating shared decision making in oncology practice," *CA: A Cancer Journal for Clinicians*, vol. 64, no. 6, pp. 377–388, 2014.
132. F. Légaré, S. Ratté, K. Gravel, and I. D. Graham, "Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions," *Patient Education and Counseling*, vol. 73, no. 3, pp. 526–535, 2008.
133. K. Gravel, F. Légaré, and I. D. Graham, "Barriers and facilitators to implementing shared decision-making in clinical practice: a systematic review of health professionals' perceptions," *Implementation Science*, vol. 1, article 16, 2006.
134. A. M. O'Connor, A. Rostom, V. Fiset et al., "Decision aids for patients facing health treatment or screening decisions: systematic review," *British Medical Journal*, vol. 319, no. 7212, pp. 731–734, 1999.
135. J. D. Harrison, L. Masya, P. Butow et al., "Implementing patient decision support tools: moving beyond academia?" *Patient Education and Counseling*, vol. 76, no. 1, pp. 120–125, 2009.
136. D. Stacey, F. Légaré, A. Lyddiatt et al., "Translating evidence to facilitate shared decision making: development and usability of a consult decision aid prototype," *The Patient*, vol. 9, no. 6, pp. 571–582, 2016.

CHAPTER 3

Chronic radiation proctitis:
tricks to prevent and treat

Int J Colorectal Dis 2015 30:1293–1303

© Copyright Springer Berlin Heidelberg

Vanneste BGL, van de Voorde L. de Ridder RJ, van Limbergen E, Lambin P, van Lin EN.

ABSTRACT

Objective

The purpose of this study was to give an overview of the measures used to prevent chronic radiation proctitis (CRP) and to provide an algorithm for the treatment of CRP.

Methods

Medical literature databases including PubMed and Medline were screened and critically analyzed for relevance in the scope of our purpose.

Results

CRP is a relatively frequent late side effect (5–20%) and mainly dependent on the dose and volume of irradiated rectum. Radiation treatment (RT) techniques to prevent CRP are constantly improving thanks to image-guided RT and intensity-modulated RT. Also, newer techniques like protons and new devices such as rectum spacers and balloons have been developed to spare rectal structures. Biopsies do not contribute to diagnosing CRP and should be avoided because of the risk of severe rectal wall damage, such as necrosis and fistulas. There is no consensus on the optimal treatment of CRP. A variety of possibilities is available and includes topical and oral agents, hyperbaric oxygen therapy, and endoscopic interventions.

Conclusions

CRP has a natural history of improving over time, even without treatment. This is important to take into account when considering these treatments: first be conservative (topical and oral agents) and be aware that invasive treatments can be very toxic.

Keywords

Radiotherapy, Radiation proctitis, Prevention, Treatment

INTRODUCTION

Radiation injury to the rectum represents a feared complication of radiotherapy (RT) in urological, gynecological, and gastrointestinal malignancies (prostate, urinary bladder, cervix, uterus, and anus). Chronic radiation proctitis (CRP) is a relatively frequent late (after 3–6 months) side effect that affects 5–20 % of cancer patients [1–3]. The probability of developing the injury is related to the volume of rectum irradiated, total RT dose, RT technique, and dose per fraction [4]. Also, individual patient factors can influence the susceptibility to CRP: comorbidity of vascular disease, diabetes, connective tissue disease or inflammatory bowel disease, specific conditions such as smoking, and concomitant chemotherapy [5, 6]. Published nomograms based on patient risk factors (use of anti-coagulants, hormonal therapy, or anti-hypertensives; presence of diabetes or hemorrhoids, and a history of pre-RT abdominal surgery) have been predictive for CRP in prostate cancer [7, 8].

Until now, no optimal management has been defined for CRP. A variety of therapeutic modalities is available ranging from oral agents to endoscopic interventions. The aim of this article is to summarize the measures being developed for the prevention of CRP and to present a practical algorithm for the treatment of CRP based on a review of the literature.

SYMPTOMS

RT can cause both early (acute) and late (chronic) side effects [9]. Acute side effects by definition occur up to 3 months after RT and are usually self-limiting. Chronic side effects occur 3–6 months after RT or even years later. The side effects of RT are scored in five groups (see Table 1) according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 (CTCAE) [10]. Acute side effects include diarrhea, mucus discharge, urgency, tenesmus, and uncommonly bleeding [5]. Similar symptoms are seen in patients with chronic CRP, but bleeding is the most common symptom, with potential iron-deficiency anemia that requires blood transfusions. In addition, patients may have symptoms of obstructed defecation due to strictures with symptoms of constipation, rectal pain, urgency, and, rarely, fecal incontinence due to overflow [5]. In a series of studies, Andreyev et al. identified 23 different symptoms that develop after pelvic RT [11–13].

TABLE 1: Radiation proctitis according to the ‘common toxicity criteria’, version 4

Grade CRP	Symptoms
1	Rectal discomfort; intervention not indicated
2	Symptoms (rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated.
5	Death

PATHOGENESIS

CRP results from progressive epithelial atrophy and fibrosis associated with obliterative endarteritis, chronic mucosal ischemia, submucosal fibrosis, and new vessel formation, which have been shown to lead to clinical symptoms [14]. This is not further discussed here because they go beyond the scope of this article and can be found elsewhere [14, 15].

DIAGNOSIS

CRP should be suspected in any patient who has had pelvic RT and presents with the symptoms mentioned above, even if the radiotherapy took place years ago. Diagnosis by endoscopy is important to exclude other causes of proctitis (infectious colitis, inflammatory bowel disease, diversion colitis, ischemic colitis, diverticular colitis) and a second malignancy [15].

Endoscopy is also important to determine the extent and severity of CRP. There are three main forms of endoscopic findings in CRP: inflammation predominant form (I-CRP) (edema, mucosal pallor, and ulcer), bleeding predominant form (B-CRP) (friability, spontaneous hemorrhage, and telangiectasia), and a mixed form (with features from both I-CRP and B-CRP) (Figure 1a-d) [15–17]. The endoscopic classification of CRP is usually analyzed by the Vienna Rectoscopy Score (VRS) to describe rectal mucosa [18]. The VRS divides the inner rectal mucosa into 12 mucosal areas. Furthermore, each area is scored on the presence and grading of telangiectasia (Grade 0–3), congested mucosa (Grade 0–3), ulceration (Grade 0–4), stricture (Grade 0–4), and necrosis (Grade 0–1). However, other scoring systems also exist [19].

FIGURE 1: Endoscopic features illustrating the different grades of CRP at the anterior rectum wall. **a** shows CRP with edematous and multiple non-confluent telangiectatic lesions, **b** demonstrates a predominantly bleeding form of CRP, **c** illustrates necrosis with multiple confluent telangiectatic lesions, and **d** shows an ulcer

Rectal wall biopsies should be avoided as they may initiate chronic, poorly healing wounds. A number of studies have also described fistula formation over the prostate following rectal biopsies [20–22]. Therefore, a biopsy is only justified if a malignancy is suspected or in case of important therapeutic consequences. In these cases, biopsies should be taken from the posterior and lateral rectal walls to avoid the anterior irradiated high-dose areas [20]. In conclusion, biopsies do not really contribute to the diagnosis of CRP and should be avoided.

PREVENTION

Excluding the rectum from the irradiation fields to prevent CRP has a high priority in RT. Optimizing the RT planning by using planning constraints reduces the irradiated rectal volume and consequently decreases the risk of rectal toxicity [23].

There is increasing evidence supporting the role of genetic variants in the development of RT-induced toxicity [24]. Recently, the first replicated genetic associations for adverse reactions to RT were reported [25]. Active research to identify high-risk patients is based on genetic biomarkers [26] that could allow radiotherapists to select patients for which extra care should be taken to decrease the dose to the rectum.

Different RT techniques

The use of modern RT techniques (intensity-modulated RT) and the use of implanted fiducial markers into the prostate (image-guided RT) minimize the dose of radiation to the rectum while maximizing the dose to the prostate [27–29].

Newer RT techniques which utilize heavy particles such as protons and carbon ions are currently being developed and tested to improve outcomes with reduced toxicity [30, 31]. Carbon ions seem to be better protective than protons which can be explained by the steeper dose gradients achieved by heavier particles [32]. Although these methods have the potential to deliver optimal doses of radiation to the tumor with only minimal exposure to the surrounding normal tissues, the long-term outcomes are not yet clear.

Medication

The use of medical therapy (amifostine, sucralfate, 5-aminosalicylic acid, or sulphasalazine) to prevent the development of CRP has only a minimal effect and is not widely used [33–36]. Placebo-controlled phase III trials have shown no benefit from either topical or oral sucralfate [37]. However, higher doses of amifostine are described as tolerable and as having a better protective effect against the early and late short-term effects of RT [38].

Newer insights have revealed that synbiotics and microbiotics can be used to manipulate the intestinal flora to prevent and treat CRP [39, 40]. Further research is needed to *confirm those preliminary data*.

Rectum spacer

Devices have been developed to spare rectal structures [41]. These can be divided into endorectal balloons and relatively novel rectum spacers. Endorectal balloons are inserted into the rectum for each daily treatment fraction to increase the distance from the dorsal rectal wall to the prostate.

Although the anterior anorectal wall is pushed towards the prostate, the overall effect proved to be beneficial in 3D-conformal RT and intensity-modulated RT [42]. Rectum spacers are implanted as a tissue filler into the anterior perirectal fat to separate the rectum from the prostate (Figure 2). Increasing the prostate-rectum distance displaces the rectal wall away from the prostate and out of the regions of high-dose RT. The overall effect is a reduction in the maximum dose to the rectum and the total volume of irradiated rectum. The implantation of such rectum spacers is typically performed transperineally under real-time transrectal ultrasound guidance. The insertion procedure can be performed under local (with or without sedation), spinal, or general anesthesia [43]. The implanted rectum spacer remains in place over the course of the RT treatment, and the spacer biodegrades naturally within 6 months after implantation [44]. Different types of rectum spacers have been developed: an absorbable hydrogel, a hyaluronic acid, a collagen, and a saline-filled balloon [44–46]. Several studies are available on the dosimetry, acute outcome, and cost-effectiveness of a rectum spacer; however, no long-term results are available yet [47–56].

FIGURE 2: Axial T2-weighted magnetic resonance images of a patient with a hydrogel spacer before injection (**a**) and after injection (**b**)

TREATMENT

A wide variety of interventions have been tried for treating CRP. There have been no large controlled randomized trials to evaluate the treatment of CRP. Also, several studies have resulted in ambiguous outcome measurements, showing no structured outcome measurement to describe and compare the findings from different trials. Some studies used the VRS scoring system to evaluate treatments; others used different clinical outcomes. Thus, experience is derived mostly from small clinical trials, expert opinions, and case reports [57, 58]. Interventions can broadly be categorized into medical therapies, endoscopic therapies, and surgical interventions. Medical therapy is the main stay of treatment for I-CRP. Endoscopy is the main treatment modality for B-CRP if the bleeding is affecting quality of life [15]. It is very important to realize, when considering invasive treatments, that CRP can improve over time without any active treatment [59].

In patients with CRP, treatment should be based upon the pattern and severity of symptoms and experience at the treatment center. A treatment algorithm is presented in Figure 3 for this purpose. For patients with minor symptoms that do not affect their quality of life, no treatment may be indicated because CRP has a natural history of improving over time without treatment. For patients with I-CRP, Andreyev et al. published a treatment guide that recommends loperamide, fibers, stool-bulking agents, and corticosteroids [13]. Patients with B-CRP and physical complaints of anemia (dyspnoea, effort, palpitations, fatigue) should be monitored for anemia and where appropriate given iron supplements or blood transfusion. If necessary, endoscopic treatment is also indicated [60]. B-CRP is the most common form, and therefore, most studies have concentrated and published on B-CRP.

Medical treatment of B-CRP

Medical treatments with level I evidence of benefits in small randomized trials are listed here: sucralfate enema [61, 62], metronidazole [63], vitamin A [64], and hyperbaric oxygen therapy (HOT) [65].

Sucralfate enema

Sucralfate is an aluminum salt that adheres to mucosal cells and stimulates prostaglandin production, producing cytoprotective effects. It has been used in the treatment of peptic ulcers [66]. In a prospective randomized trial, Kochhar et al. reported 37 patients with RT-induced CRP who were assigned to a 4-week course of sulfasalazine (3 g/day) plus prednisolone enemas (20 mg 2×/day) or sucralfate enemas (2 g 2×/day) [61].

Kochhar et al. subsequently reported in a prospective study on 26 patients with moderate to severe CRP who were treated with 20-ml sucralfate enemas twice daily until bleeding stopped or failure of therapy was acknowledged. Response to the therapy was considered good when the severity of bleeding improved by two grades. This was observed in 77 % of patients [62]. Kochhar et al.

concluded that sucralfate enemas give a better clinical response and are better tolerated.

Although placebo-controlled randomized trials are needed to fully assess efficacy, sucralfate is recommended as the preferred mode of short-term treatment.

FIGURE 3: Algorithm for treatment of CRP

Metronidazole

Anti-microbial agents could be effective in CRP because of their immune-modulatory effects [67] and selective toxicity to microorganisms that contribute to the pathogenesis of CRP [68].

Cavcic et al. reported on 60 patients with CRP who received mesalazine (1 g 3×/day) and a betamethasone enema (1/day during 4 weeks) with or without oral metronidazole (400 mg 3×/day) [63]. The addition of metronidazole was associated with a reduction in rectal bleeding, diarrhea, and ulcers at 4 weeks, 3 months, and 12 months. This trial suggested that metronidazole can improve symptoms and mucosal healing in combination with anti-inflammatory treatments.

Vitamin A/E/C

Antioxidants were suggested to have cytoprotective effects by reducing cellular oxidative stress following radiation injury to intestinal tissue [69].

Ehrenpreis et al. reported on a prospective double-blind trial including 19 patients with CRP 6 months after RT who were randomized to receive oral vitamin A (10,000 IU 2×/day, during 90 days) or a placebo. Vitamin A significantly reduced rectal symptoms of CRP [64].

Kennedy et al. reported on 20 patients treated for symptomatic CRP with oral vitamin E (400 IU 3×/day) and vitamin C (500 mg 3×/day). Bleeding resolved in 4 of 11 patients, and diarrhea resolved in 50 % of patients [70].

Hyperbaric oxygen therapy

HOT involves patients breathing pure oxygen in a pressurized room or tube. In a HOT chamber, the air pressure is increased to three times higher than normal air pressure [71]. Under these conditions, the lungs can gather more oxygen than at normal air pressure. This higher oxygenated blood may be beneficial because it inhibits bacterial growth and stimulates the release of growth factors and stem cells, which promotes wound healing. It may even reverse progressive changes caused by RT and may improve other symptoms such as urinary problems [72, 73].

Clarke [65] performed a controlled randomized trial with groups that were randomized to HOT at 2.0 atm absolute or air at 1.1 atm absolute. HOT significantly improved the healing responses in patients with refractory CRP, generating an absolute risk reduction of 32 % (number needed to treat, 3) [65]. A Cochrane review revealed a significantly increased chance of improvement or cure following HOT for CRP (RR 1.72; 95 % CI 1.0 to 2.9, p 0.04) [74].

Unfortunately, hyperbaric oxygen facilities are not always available, so patients may need to travel long distances to their nearest unit, and treatments are time-consuming (60–120 min for 30–70 sessions) and expensive [75].

Endoscopic treatment

A variety of endoscopic therapies is available for rectal bleeding caused by CRP including argon plasma coagulation (APC), topical formalin, laser, heater, and bipolar probes. There is no

level I evidence of benefit in randomized trials. The goal of endoscopic treatments of CRP is to control bleeding. Endoscopic treatments may require multiple procedures and can have very significant adverse effects [60]. Due to a known high-potential risk of fistulas and ulcerations in the first 2 years after RT, we advise that all endoscopic treatments should be performed by an experienced gastroenterologist with particular awareness of post-RT rectal injury in close collaboration with a pelvic radiation oncologist [76].

Argon plasma coagulation

APC is a form of electrocautery, in which a monopolar diathermy is transmitted to the target tissue through an ionized gas in a non-contact fashion (0.8–3.0 mm from the target) [77]. APC is considered by many gastroenterologists as the treatment of choice for CRP [78–81]. However, it should be used with caution in this patient group. Complications such as bowel explosions following the use of APC in inadequately prepared bowels have been described but are preventable [82]. Other severe side effects, such as the occurrence of deep ulceration [83, 84], fistulation [85], stricture formation [86–88], bleeding [83, 84, 89], perforation [83], and severe and sometimes chronic pain [80, 89, 90], reflect the risk of any therapy in chronically ischemic tissues. Rectal ulcers after APC when used for CRP are observed in approximately 26 % of patients, in one series, even up to 52 % [91–93]. Together with restricting argon flow rates and wattage, a very precise and brief application of the argon catheter could potentially reduce complication rates [94]. In specialist centers, serious complications of previous APC treatment in this patient group continue to be seen regularly [60].

Swan et al. presented a complete resolution of bleeding in 72 % of 50 patients who had bleeding CRP [79]. Thirty-four percent of the patients experienced short-term, self-limiting complications; 2 % experienced a long-term complication. The setting was a tertiary referral hospital, where only dedicated and experienced gastroenterologists were involved in post-RT rectal injury.

Topical formalin

Formalin seals fragile neovasculature in radiation-damaged tissues to prevent further bleeding through chemical cauterization [95, 96]. This treatment is simple to perform, but a severe disadvantage is a chemical burn to the skin if there is spillage [60].

There are several small retrospective studies on the use of formalin. These studies used a variety of formalin application techniques, from irrigation to direct application, and formalin concentrations, from 3.6 to 10 % [97]. The short-term success rate of this technique ranged from 60 to 100 % [98–109]. However, the procedure is not risk free and may induce major complications such as acute colitis [110].

Yeoh et al. showed that APC and topical formalin had comparable efficacy in the durable control of rectal bleeding associated with CRP but had no beneficial effect on anorectal dysfunction

[111]. However, more authors reported that APC may be more effective in treating CRP as compared with formalin therapy [58, 89, 112].

Laser

The argon and neodymium/yttrium aluminum garnet (Nd:YAG) laser has been used to coagulate bleeding vessels throughout the gastrointestinal tract [113]. A study that included 65 patients treated with an Nd:YAG laser found an improvement in symptoms in 78 % of patients (range, 58 to 87 %) [114]. However, the laser is expensive and not widely available.

Assessing the effectiveness of these interventions is complicated by the small number of patients included in many trials, the lack of a control arm, and the fact that the natural history of CRP is to improve over time without treatment.

Surgery

Surgery is considered as a last resort for patients with CRP and should be reserved for those who are found to have a stricture, permanent bleeding, perforation, or a fistula that is not responsive to the medical and endoscopic approaches [15, 115]. Surgical treatment options include excision, urinary and fecal diversion (diverting stoma), and reconstruction of a coloanal J reservoir [116]. Severe postoperative complications can occur such as sepsis, wound dehiscence, bowel obstruction, and de novo rectal fistula [76]. Yegappan et al. reported a 3 % postoperative mortality rate [117].

Fischer et al. concluded that 51 % of their participants had a fair outcome, 34 % had slight or moderate symptoms, and 14 % had disabling symptoms [118]. Lane et al. revealed that good outcomes can be expected in properly selected patients [119]. Turina et al. determined that the best results were found in patients presenting with colorectal anastomotic and primary bowel strictures as their main complication, while most patients with severe CRP and very distal strictures required permanent diversion [120].

CONCLUSION

CRP is a commonly observed late side effect of pelvic RT and can occur even years after treatment. First of all, care should be taken to minimize the risk of CRP by improving RT techniques (IMRT, IGRT) or to implement new devices to spare the rectum (spacers, balloons). On the basis of the available knowledge, we constructed a practical management algorithm (Figure 3). The literature generally recommends a flexible endoscopy to determine the cause. Biopsy, and especially anterior rectal biopsy, within the first years of RT should be avoided, because this augments the risk of a fistula and is not likely to provide any relevant information.

There are three main forms of CRP: I-CRP, B-CRP, and a mixed form. I-CRP responds well to loperamide, fibers, stool-bulking agents, and corticosteroids. B-CRP is often self-limiting and responds well to conservative management; it is advisable to stop anti-coagulants, if possible, and start with antioxidants (vitamin A, E, C) and/or antibiotics (metronidazole). If no response is observed, patients should be started on sucralfate enemas. In severe cases, with persistent bleeding, chemical (formalin) or thermal (coagulation) treatments are successful. If HOT is available, it may also be a good option. Surgery should be considered as the last resort and is only indicated if fistulas and strictures are not healing. Although surgery can lead to significant improvements, it also bears an increased risk of postsurgical complications. Based on the frequency of CRP, prospective controlled and larger studies are advised to increase our knowledge about both the prevention and treatment of CRP.

REFERENCES

1. Garg AK, Mai WY, McGary JE, Grant WH, 3rd, Butler EB, Teh BS. Radiation proctopathy in the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys*. 2006;66(5):1294–1305. doi: 10.1016/j.ijrobp.2006.07.1386.
2. Kuku S, Fragkos C, McCormack M, Forbes A. Radiation-induced bowel injury: the impact of radiotherapy on survivorship after treatment for gynaecological cancers. *Br J Cancer*. 2013;109(6):1504–1512. doi: 10.1038/bjc.2013.491.
3. Krol R, Smeenk RJ, van Lin EN, Yeoh EE, Hopman WP. Systematic review: anal and rectal changes after radiotherapy for prostate cancer. *Int J Color Dis*. 2014;29(3):273–283. doi: 10.1007/s00384-013-1784-8.
4. Talcott JA, Manola J, Clark JA, Kaplan I, Beard CJ, Mitchell SP, Chen RC, O'Leary MP, Kantoff PW, D'Amico AV. Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol*. 2003;21(21):3979–3986. doi: 10.1200/JCO.2003.01.199.
5. Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol*. 2013;19(2):185–198. doi: 10.3748/wjg.v19.i2.185.
6. Theis VS, Sripadam R, Ramani V, Lal S. Chronic radiation enteritis. *Clin Oncol (R Coll Radiol)*. 2010;22(1):70–83. doi: 10.1016/j.clon.2009.10.003.
7. Valdagni R, Rancati T, Fiorino C, Fellin G, Magli A, Baccolini M, Bianchi C, Cagna E, Greco C, Mauro FA, Monti AF, Munoz F, Stasi M, Franzone P, Vavassori V. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1065–1073. doi: 10.1016/j.ijrobp.2007.11.037.
8. Valdagni R, Kattan MW, Rancati T, Yu C, Vavassori V, Fellin G, Cagna E, Gabriele P, Mauro FA, Baccolini M, Bianchi C, Menegotti L, Monti AF, Stasi M, Giganti MO, Fiorino C. Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1957–1966. doi: 10.1016/j.ijrobp.2011.03.028.
9. Dörr W. Radiobiology of tissue reactions. *Ann ICRP*. 2015
10. National Cancer Institute (2013) Common Terminology Criteria for Adverse Events (CTCAE) 4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed 18 May 2015
11. Gami B, Harrington K, Blake P, Dearnaley D, Tait D, Davies J, Norman AR, Andreyev HJ. How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol Ther*. 2003;18(10):987–994. doi: 10.1046/j.1365-2036.2003.01760.x.
12. Gillespie C, Goode C, Hackett C, Andreyev HJ. The clinical needs of patients with chronic gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol Ther*. 2007;26(4):555–563. doi: 10.1111/j.1365-2036.2007.03405.x.
13. Andreyev HJ, Benton BE, Lalji A, Norton C, Mohammed K, Gage H, Pennert K, Lindsay JO. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. *Lancet*. 2013;382(9910):2084–2092. doi: 10.1016/S0140-6736(13)61648-7.

14. Leiper K, Morris AI. Treatment of radiation proctitis. *Clin Oncol (R Coll Radiol)* 2007;19(9):724–729. doi: 10.1016/j.clon.2007.07.008.
15. Wu XR, Liu XL, Katz S, Shen B. Pathogenesis, diagnosis, and management of ulcerative proctitis, chronic radiation proctopathy, and diversion proctitis. *Inflamm Bowel Dis.* 2015;21(3):703–715. doi: 10.1097/MIB.0000000000000227.
16. Moore EM, Magrino TJ, Johnstone PA. Rectal bleeding after radiation therapy for prostate cancer: endoscopic evaluation. *Radiology.* 2000;217:215–218. doi: 10.1148/radiology.217.1.r00oc24215.
17. Reichelderfer M, Morrissey JF. Colonoscopy in radiation colitis. *Gastrointest Endosc.* 1980;26:41–43. doi: 10.1016/S0016-5107(80)73265-0.
18. Wachter S, Gerstner N, Goldner G, Potzi R, Wambersie A, Potter R. Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma. *Radiother Oncol.* 2000;54(1):11–19. doi: 10.1016/S0167-8140(99)00173-5.
19. Chi KD, Ehrenpreis ED, Jani AB. Accuracy and reliability of the endoscopic classification of chronic radiation-induced proctopathy using a novel grading method. *J Clin Gastroenterol.* 2005;39(1):42–46.
20. Chrouser KL, Leibovich BC, Sweat SD, Larson DW, Davis BJ, Tran NV, Zincke H, Blute ML. Urinary fistulas following external radiation or permanent brachytherapy for the treatment of prostate cancer. *J Urol.* 2005;173(6):1953–1957. doi: 10.1097/01.ju.0000158041.77063.ff.
21. Theodorescu D, Gillenwater J, Koutrouvelis P. Prostatourethral-rectal fistula after prostate brachytherapy. *Cancer.* 2000;89:2085–2091. doi: 10.1002/1097-0142(20001115)89:10<2085::AID-CNCR8>3.0.CO;2-Q.
22. Thornhill JA, Long RM, Neary P, O'Connor HJ, Ryan B, Fraser I. The pitfalls of treating anorectal conditions after radiotherapy for prostate cancer. *Ir Med J.* 2012;105:91–93.
23. Fonteyne V, De Neve W, Villeirs G, De Wagter C, De Meerleer G. Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: the need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. *Radiother Oncol.* 2007;84(2):156–163. doi: 10.1016/j.radonc.2007.06.013.
24. West C, Azria D, Chang-Claude J, Davidson S, Lambin P, Rosenstein B, De Ruyscher D, Talbot C, Thierens H, Valdagni R, Vega A, Yuille M. The REQUITE project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors. *Clin Oncol (R Coll Radiol)* 2014;26(12):739–742. doi: 10.1016/j.clon.2014.09.008.
25. Fachal L, Gómez-Caamaño A, Barnett GC, Peleteiro P, Carballo AM, Calvo-Crespo P, Kerns SL, Sánchez-García M, Lobato-Busto R, Dorling L, Elliott RM, Dearnaley DP, Sydes MR, Hall E, Burnet NG, Carracedo Á, Rosenstein BS, West CM, Dunning AM, Vega A. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. *Nat Genet.* 2014;46(8):891–894. doi: 10.1038/ng.3020.
26. West CM, Barnett GC. Genetics and genomics of radiotherapy toxicity: towards prediction. *Genome Med.* 2011;3(8):52. doi: 10.1186/gm268.
27. Zelefsky MJ, Fuks Z, Hunt M, Yamada Y, Marion C, Ling CC, Amols H, Venkatraman ES, Leibel SA.

- High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys.* 2002;53:1111–1116. doi: 10.1016/S0360-3016(02)02857-2.
28. De Meerleer GO, Fonteyne VH, Vakaet L, Villeirs GM, Denoyette L, Verbaeys A, Lummen N, De Neve WJ. Intensity-modulated radiation therapy for prostate cancer: late morbidity and results on biochemical control. *Radiother Oncol.* 2007;82:160–166. doi: 10.1016/j.radonc.2006.12.007.
 29. Wortel RC, Incrocci L, Pos FJ, Lebesque JV, Witte MG, van der Heide UA, van Herk M, Heemsbergen WD. Acute toxicity after image-guided intensity modulated radiation therapy compared to 3D conformal radiation therapy in prostate cancer patients. *Int J Radiat Oncol Biol Phys.* 2015;91(4):737–744. doi: 10.1016/j.ijrobp.2014.12.017.
 30. Zietman A. Proton beam and prostate cancer: an evolving debate. *Rep Pract Oncol Radiother.* 2013;18(6):338–342. doi: 10.1016/j.rpor.2013.06.001.
 31. Shioyama Y, Tsuji H, Suefuji H, Sinoto M, Matsunobu A, Toyama S, Nakamura K, Kudo S. Particle radiotherapy for prostate cancer. *Int J Urol.* 2015;22(1):33–39. doi: 10.1111/iju.12640.
 32. Georg D, Hopfgartner J, Gora J, Kuess P, Kragl G, Berger D, Hegazy N, Goldner G, Georg P. Dosimetric considerations to determine the optimal technique for localized prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-rate or low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2014;88(3):715–722. doi: 10.1016/j.ijrobp.2013.11.241.
 33. Stellamans K, Lievens Y, Lambin P, Van den Weyngaert D, Van den Bogaert W, Scalliet P, Hutsebaut L, Haustermans K. Does sucralfate reduce early side effects of pelvic radiation? A double-blind randomized trial. *Radiother Oncol.* 2002;65(2):105–108. doi: 10.1016/S0167-8140(02)00281-5.
 34. Athanassiou H, Antonadou D, Coliarakis N, Kouveli A, Synodinou M, Paraskevaidis M, Sarris G, Georgakopoulos GR, Panousaki K, Karageorgis P, Throuvalas N, Oncology Hellenic Group Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. *Int J Radiat Oncol Biol Phys.* 2003;56(4):1154–1160. doi: 10.1016/S0360-3016(03)00187-1.
 35. Jahraus CD, Bettenhausen D, Malik U, Sellitti M, St Clair WH. Prevention of acute radiation-induced proctosigmoiditis by balsalazide: a randomized, double-blind, placebo controlled trial in prostate cancer patients. *Int J Radiat Oncol Biol Phys.* 2005;63(5):1483–1487. doi: 10.1016/j.ijrobp.2005.04.032.
 36. Simone NL, Ménard C, Soule BP, Albert PS, Guion P, Smith S, Godette D, Crouse NS, Sciuto LC, Cooley-Zgela T, Camphausen K, Coleman CN, Singh AK. Intrarectal amifostine during external beam radiation therapy for prostate cancer produces significant improvements in quality of life measured by EPIC score. *Int J Radiat Oncol Biol Phys.* 2008;70(1):90–95. doi: 10.1016/j.ijrobp.2007.05.057.
 37. Kneebone A, Mameghan H, Bolin T, Berry M, Turner S, Kearsley J, Graham P, Fisher R, Delaney G. Effect of oral sucralfate on late rectal injury associated with radiotherapy for prostate cancer: a double-blind, randomized trial. *Int J Radiat Oncol Biol Phys.* 2004;60(4):1088–1097. doi: 10.1016/j.ijrobp.2004.04.033.
 38. Koukourakis MI, Kyrgias G, Panteliadou M, Papadopoulou A, Tsiarkatsi M, Papachristou E, Bebeli M.

- Dose escalation of amifostine for radioprotection during pelvic accelerated radiotherapy. *Am J Clin Oncol.* 2013;36(4):338–343. doi: 10.1097/COC.0b013e318248d882.
39. Ferreira MR, Muls A, Dearnaley DP, Andreyev HJ. Microbiota and radiation-induced bowel toxicity: lessons from inflammatory bowel disease for the radiation oncologist. *Lancet Oncol.* 2014;15(3):e139–e147. doi: 10.1016/S1470-2045(13)70504-7.
 40. Nascimento M, Aguilar-Nascimento JE, Caporossi C, Castro-Barcellos HM, Motta RT. Efficacy of synbiotics to reduce acute radiation proctitis symptoms and improve quality of life: a randomized, double-blind, placebo-controlled pilot trial. *Int J Radiat Oncol Biol Phys.* 2014;90(2):289–295. doi: 10.1016/j.ijrobp.2014.05.049.
 41. Smeenk RJ, van Lin ENJT. Application of anorectal sparing devices in prostate radiotherapy. *Radiother Oncol.* 2013;106(2):155–156. doi: 10.1016/j.radonc.2013.02.004.
 42. Van Lin EN, Kristinsson J, Philippens ME, de Jong DJ, Van DV, Kaanders JH, Leer JW, Visser AG. Reduced late rectal mucosal changes after prostate three-dimensional conformal radiotherapy with endorectal balloon as observed in repeated endoscopy. *Int J Radiat Oncol Biol Phys.* 2007;67:799–811. doi: 10.1016/j.ijrobp.2006.09.034.
 43. Hatiboglu G, Pinkawa M, Vallee JP, Hadaschik B, Hohenfellner M. Application technique: placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. *BJU Int.* 2012;110:e647–e652. doi: 10.1111/j.1464-410X.2012.11373.x.
 44. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys.* 2014;90(2):278–288. doi: 10.1016/j.ijrobp.2014.06.044.
 45. Pinkawa M. Spacer application for prostate cancer radiation therapy. *Future Oncol.* 2014;10(5):851–864. doi: 10.2217/fon.13.223.
 46. Schutzer ME, Orio PF, Biagioli MC, Asher DA, Lomas H, Moghanaki D. A review of rectal toxicity following permanent low dose-rate prostate brachytherapy and the potential value of biodegradable rectal spacers. *Prostate Cancer Prostatic Dis.* 2015;18(2):96–103. doi: 10.1038/pcan.2015.4.
 47. Prada PJ, Fernández J, Martínez AA, de la Rúa A, Gonzalez JM, Fernandez JM, Juan G. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys.* 2007;69(1):95–102. doi: 10.1016/j.ijrobp.2007.02.034.
 48. Wilder RB, Barne GA, Gilbert RF, et al. Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2010;77(3):824–830. doi: 10.1016/j.ijrobp.2009.05.069.
 49. Susil RC, McNutt TR, DeWeese TL, et al. Effects of prostate-rectum separation on rectal dose from external beam radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;76:1251–1258. doi: 10.1016/j.ijrobp.2009.07.1679.
 50. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;82(5):1918–1922. doi: 10.1016/j.ijrobp.2011.02.034.

51. Pinkawa M, Corral NE, Caffaro M, et al. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol.* 2011;100(3):436–441. doi: 10.1016/j.radonc.2011.09.005.
52. Uhl M, van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. *Radiother Oncol.* 2013;106(2):215–219. doi: 10.1016/j.radonc.2012.11.009.
53. Melchert C, Gez E, Bohlen G, et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol.* 2013;106(2):210–214. doi: 10.1016/j.radonc.2013.01.007.
54. Song DY, Herfarth KK, Uhl M, et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys.* 2013;87:81–87. doi: 10.1016/j.ijrobp.2012.12.019.
55. Strom TJ, Wilder RB, Fernandez DC, et al. A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy±intensity modulated radiation therapy. *Radiother Oncol.* 2014;111:126–131. doi: 10.1016/j.radonc.2014.02.011.
56. Vanneste BG, Pijls-Johannesma M, Van De Voorde L, van Lin EN, van de Beek K, van Loon J, Ramaekers BL, Lambin P. Spacers in radiotherapy treatment of prostate cancer: is reduction of toxicity cost-effective? *Radiother Oncol.* 2015;114(2):276–281. doi: 10.1016/j.radonc.2015.01.005.
57. Denton A, Andreyev J, Forbes A, Maher EJ. Non-surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev.* 2002;1
58. Hanson B, MacDonald R, Shaikat A. Endoscopic and medical therapy for chronic radiation proctopathy: a systematic review. *Dis Colon Rectum.* 2012;55(10):1081–1095. doi: 10.1097/DCR.0b013e3182587aef.
59. Mendenhall WM, McKibben BT, Hoppe BS, Nichols RC, Henderson RH, Mendenhall NP. Management of radiation proctitis. *Am J Clin Oncol.* 2014;37(5):517–523. doi: 10.1097/COC.0b013e318271b1aa.
60. Andreyev HJN, Davidson SE, Gillespie C, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. *Gut.* 2012;61(2):179–192. doi: 10.1136/gutjnl-2011-300563.
61. Kochhar R, Patel F, Dhar A, Sharma SC, Ayyagari S, Aggarwal R, Goenka MK, Gupta BD, Mehta SK. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. *Dig Dis Sci.* 1991;36(1):103–107. doi: 10.1007/BF01300096.
62. Kochhar R, Sriram PV, Sharma SC, Goel RC, Patel F. Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. *Dig Dis Sci.* 1999;44(5):973–978. doi: 10.1023/A:1026612731210.
63. Cavcic J, Turcic J, Martinac P, et al. Metronidazole in the treatment of chronic radiation proctitis: clinical

- trial. *Croat Med J*. 2000;41:314–318.
64. Ehrenpreis E, Jani A, Levitsky J, et al. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. *Dis Colon Rectum*. 2005;48:1–8. doi: 10.1007/s10350-004-0821-7.
 65. Clarke RE, Tenorio LM, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys*. 2008;72:134–143. doi: 10.1016/j.ijrobp.2007.12.048.
 66. Szabo S, Vattay P, Scarbrough E, et al. Role of vascular factors, including angiogenesis, in the mechanisms of action of sucralfate. *Am J Med*. 1991;91:S158–S160. doi: 10.1016/0002-9343(91)90469-E.
 67. Hanauer SB. Inflammatory bowel disease revisited: newer drugs. *Scand J Gastroenterol Suppl*. 1990;25(s175):97–106. doi: 10.3109/00365529009093133.
 68. Goodman LS, Gilman A. The pharmacological basis of therapeutics. 9. New York: McGraw-Hill; 1996. pp. 995–998.
 69. Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: prevention and treatment. *World J Gastroenterol*. 2013;19(2):199–208. doi: 10.3748/wjg.v19.i2.199.
 70. Kennedy M, Bruninga K, Mutlu EA, Losurdo J, Choudhary S, Keshavarzian A. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. *Am J Gastroenterol*. 2001;96:1080–1084. doi: 10.1111/j.1572-0241.2001.03742.x.
 71. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea Hyperb Med*. 2002;29:4–30.
 72. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg*. 1983;41:351–357. doi: 10.1016/S0278-2391(83)80005-6.
 73. Marx RE, Ehler WJ, Tayapongsak P, et al. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *Am J Surg*. 1990;160:519–524. doi: 10.1016/S0002-9610(05)81019-0.
 74. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev*. 2012;5
 75. Kishan AU, Kupelian PA. Late rectal toxicity after low-dose-rate brachytherapy: incidence, predictors, and management of side effects. *Brachytherapy*. 2015;14(2):148–159. doi: 10.1016/j.brachy.2014.11.005.
 76. Phan J, Swanson DA, Levy LB, Kudchadker RJ, Bruno TL, Frank SJ. Late rectal complications after prostate brachytherapy for localized prostate cancer: incidence and management. *Cancer*. 2009;115(9):1827–1839. doi: 10.1002/cncr.24223.
 77. Farin G, Grund KE. Technology of argon plasma coagulation with particular regard to endoscopic applications. *Endosc Surg Allied Technol*. 1994;2:71–77.
 78. Tjandra JJ, Sengupta S. Argon plasma coagulation is an effective treatment for refractory hemorrhagic radiation proctitis. *Dis Colon Rectum*. 2001;44(12):1759–1765. doi: 10.1007/BF02234451.
 79. Swan MP, Moore GT, Sievert W, et al. Efficacy and safety of single session argon plasma coagulation in the management of chronic radiation proctitis. *Gastrointest Endosc*. 2010;72:150–154. doi: 10.1016/j.

- gie.2010.01.065.
80. Villavicencio RT, Rex DK, Rahmani E. Efficacy and complications of argon plasma coagulation for hematochezia related to radiation proctopathy. *Gastrointest Endosc.* 2002;55(1):70–74. doi: 10.1067/mge.2002.119877.
 81. Karamanolis G, Triantafyllou K, Tsiamoulos Z, Polymeros D, Kalli T, Misailidis N, Ladas SD. Argon plasma coagulation has a long-lasting therapeutic effect in patients with chronic radiation proctitis. *Endoscopy.* 2009;41(6):529–531. doi: 10.1055/s-0029-1214726.
 82. Soussan BE, Mathieu N, Roque I, Antonietti M. Bowel explosion with colonic perforation during argon plasma coagulation for hemorrhagic radiation-induced proctitis. *Gastrointest Endosc.* 2003;57(3):412–413. doi: 10.1067/mge.2003.131.
 83. Taieb S, Rolachon A, Cenni JC, et al. Effective use of argon plasma coagulation in the treatment of severe radiation proctitis. *Dis Colon Rectum.* 2001;44(12):1766–1771. doi: 10.1007/BF02234452.
 84. Canard JM, Védrenne B, Bors G, et al. Long term results of treatment of hemorrhagic radiation proctitis by argon plasma coagulation. *Gastroenterol Clin Biol.* 2003;27(5):455–459.
 85. Dees J, Maarten AC, Meijssen MA, Kuipers EJ. Argon plasma coagulation for radiation proctitis. *Scand J Gastroenterol Suppl.* 2006;41(s243):175–178. doi: 10.1080/00365520600664300.
 86. Fenwick JD, Khoo VS, Nahum AE, Sanchez-Nieto B, Dearnaley DP. Correlations between dose-surface histograms and the incidence of long-term rectal bleeding following conformal or conventional radiotherapy treatment of prostate cancer. *Int J Radiat Oncol Biol Phys.* 2001;49(2):473–480. doi: 10.1016/S0360-3016(00)01496-6.
 87. Rotondano G, Bianco MA, Marmo R, et al. Long-term outcome of argon plasma coagulation therapy for bleeding caused by chronic radiation proctopathy. *Dig Liver Dis.* 2003;35(11):806–810. doi: 10.1016/S1590-8658(03)00454-7.
 88. Tam W, Moore J, Schoeman M. Treatment of radiation proctitis with argon plasma coagulation. *Endoscopy.* 2000;32(9):667–672. doi: 10.1055/s-2000-9020.
 89. Zinicola R, Rutter MD, Falasco G, Brooker JC, Cennamo V, Contini S, Saunders BP. Haemorrhagic radiation proctitis: endoscopic severity may be useful to guide therapy. *Int J Color Dis.* 2003;18(5):439–444. doi: 10.1007/s00384-003-0487-y.
 90. Venkatesh KS, Ramanujam P. Endoscopic therapy for radiation proctitis-induced hemorrhage in patients with prostatic carcinoma using argon plasma coagulator application. *Surg Endosc.* 2002;16(4):707–710. doi: 10.1007/s00464-001-8164-0.
 91. Ravizza D, Giancarla F, Trovato C, Crosta C. Frequency and outcomes of rectal ulcers during argon plasma coagulation for chronic radiation-induced proctopathy. *Gastrointest Endosc.* 2003;57(4):519–525. doi: 10.1067/mge.2003.144.
 92. Andreyev HJ. Argon plasma coagulation in chronic radiation proctitis: Postgate et al. *Endoscopy.* 2007;39(8):751–752. doi: 10.1055/s-2007-966772.
 93. Andreyev HJ. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *Lancet Oncol.* 2007;8(11):1007–1017. doi: 10.1016/S1470-

- 2045(07)70341-8.
94. Sebastian S, O'Connor H, O'Morain C, et al. Argon plasma coagulation as first-line treatment for chronic radiation proctopathy. *J Gastroenterol Hepatol*. 2004;19(10):1169–1173. doi: 10.1111/j.1440-1746.2004.03448.x.
 95. Haas EM, Bailey HR, Farragher I. Application of 10 percent formalin for the treatment of radiation-induced hemorrhagic proctitis. *Dis Colon Rectum*. 2007;50(2):213–217. doi: 10.1007/s10350-006-0707-y.
 96. Parikh S, Hughes C, Salvati EP, Eisenstat T, Oliver G, Chinn B, Notaro J. Treatment of hemorrhagic radiation proctitis with 4 percent formalin. *Dis Colon Rectum*. 2003;46(5):596–600. doi: 10.1007/s10350-004-6614-1.
 97. Henson C. Chronic radiation proctitis: issues surrounding delayed bowel dysfunction post-pelvic radiotherapy and an update on medical treatment. *Ther Adv Gastroenterol*. 2010;3(6):359–365. doi: 10.1177/1756283X10371558.
 98. Seow-Chen F, Goh H, Eu K, Ho Y, Tay S. A simple and effective treatment for hemorrhagic radiation proctopathy using formalin. *Dis Colon Rectum*. 1993;36(2):135–138. doi: 10.1007/BF02051168.
 99. Biswal B, Lal P, Rath G, Shukla N, Mohanti B, Deo S. Intrarectal formalin application, an effective treatment for grade III haemorrhagic radiation proctitis. *Radiother Oncol*. 1995;35(3):212–215. doi: 10.1016/0167-8140(95)01565-X.
 100. Saclarides T, King D, Franklin J, Doolas A. Formalin installation for refractory radiation-induced hemorrhagic proctitis. *Dis Colon Rectum*. 1996;39(2):196–199. doi: 10.1007/BF02068075.
 101. Roche B, Chauterns R, Marti M. Application of formaldehyde for treatment of hemorrhagic radiation-induced proctitis. *World J Surg*. 1996;20(8):1092–1095. doi: 10.1007/s002689900166.
 102. Counter S, Froese D, Hart M. Prospective evaluation of formalin therapy for radiation proctitis. *Am J Surg*. 1999;177(5):396–398. doi: 10.1016/S0002-9610(99)00072-0.
 103. Luna-Pérez P, Rodríguez-Ramírez SE. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. *J Surg Oncol*. 2002;80(1):41–44. doi: 10.1002/jso.10095.
 104. de Parades V, Etienney I, Bauer P, Bourguignon J, Meary N, Mory B, Sultan S, Taouk M, Thomas C, Atienza P. Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis—an effective but not risk-free procedure: a prospective study of 33 patients. *Dis Colon Rectum*. 2005;48(8):1535–1541. doi: 10.1007/s10350-005-0030-z.
 105. Raman RR. Two percent formalin retention enemas for hemorrhagic radiation proctitis: a preliminary report. *Dis Colon Rectum*. 2007;50(7):1032–1039. doi: 10.1007/s10350-007-0241-6.
 106. Sharma B, Kumar R, Singh KK, Chauhan V. Intrarectal application of formalin for chronic radiation proctitis: a simple, cheap and effective treatment. *Trop Gastroenterol*. 2010;31(1):37–40.
 107. Nelamangala Ramakrishnaiah VP, Javali TD, Dharanipragada K, Reddy KS, Krishnamachari S. Formalin dab, the effective way of treating haemorrhagic radiation proctitis: a randomized trial from a tertiary care hospital in South India. *Color Dis*. 2012;14(7):876–882. doi: 10.1111/j.1463-1318.2012.03008.x.
 108. Sánchez HA, del Vicente Sánchez MP, Arteta Jiménez M. Formalin for haemorrhagic radiation-induced

- proctitis. *Int J Color Dis.* 2012;27(5):683–685. doi: 10.1007/s00384-011-1268-7.
109. Pironi D, Panarese A, Vendettuoli M, Pontone S, Candioli S, Manigrasso A, De Cristofaro F, Filippini A (2013) Chronic radiation-induced proctitis: the 4 % formalin application as non-surgical treatment. *Int J Color Dis* 28(2):261–266. doi:10.1007/s00384-012-1571-y
 110. Pikarsky AJ, Belin B, Efron J, Weiss EG, Nogueras JJ, Wexner SD. Complications following formalin installation in the treatment of radiation-induced proctitis. *Int J Color Dis.* 2000;15(2):96–99. doi: 10.1007/s003840050240.
 111. Yeoh E, Tam W, Schoeman M, Moore J, Thomas M, Botten R, Di Matteo A. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys.* 2013;87(5):954–959. doi: 10.1016/j.ijrobp.2013.08.034.
 112. Alfadhli AA, Alazmi WM, Ponich T, Howard JM, Prokopiw I, Alaqeel A, Gregor JC. Efficacy of argon plasma coagulation compared with topical formalin application for chronic radiation proctopathy. *Can J Gastroenterol.* 2008;22(2):129–132.
 113. De Palma GD. Confocal laser endomicroscopy in the “in vivo” histological diagnosis of the gastrointestinal tract. *World J Gastroenterol.* 2009;15(46):5770–5775. doi: 10.3748/wjg.15.5770.
 114. Taylor JG, Disario JA, Bjorkman DJ. KTP laser therapy for bleeding from chronic radiation proctopathy. *Gastrointest Endosc.* 2000;52(4):353–357. doi: 10.1067/mge.2000.107726.
 115. Do NL, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterol Res Pract.* 2011;2011:1–9. doi: 10.1155/2011/917941.
 116. Lucarotti M, Mountford R, Bartolo D. Surgical management of intestinal radiation injury. *Dis Colon Rectum.* 1991;34(10):865–869. doi: 10.1007/BF02049698.
 117. Yegappan M, Ho YH, Nyam D, Leong A, Eu KW, Seow C. The surgical management of colorectal complications from irradiation for carcinoma of the cervix. *Ann Acad Med Singap.* 1998;27(5):627–630.
 118. Fischer L, Kimose HH, Spjeldnaes N, Wara P. Late progress of radiation-induced proctitis. *Acta Chir Scand.* 1990;156(11–12):801–805.
 119. Lane BR, Stein DE, Remzi FH, Strong SA, Fazio VW, Angermeier KW. Management of radiotherapy induced rectourethral fistula. *J Urol.* 2006;175(4):1382–1387. doi: 10.1016/S0022-5347(05)00687-7.
 120. Turina M, Mulhall AM, Mahid SS, Yashar C, Galandiuk S. Frequency and surgical management of chronic complications related to pelvic radiation. *Arch Surg.* 2008;143(1):46–52. doi: 10.1001/archsurg.2007.7.

PART I Modeling

Triangulation

Path Image 1

Path Image 2

CHAPTER 4

Spacers in Radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective?

Radiother Oncol 2015;114(2):276-81

© Copyright Elsevier

Vanneste BGL, Pijls-Johannesma M, Van De Voorde L, Van Lin EN, Van De Beek K, Van Loon J, Ramaekers BL, Lambin P.

ABSTRACT

Background and purpose

To compare the cost-effectiveness of treating prostate cancer patients with intensity-modulated radiation therapy and a spacer (IMRT+S) versus IMRT-only without a spacer (IMRT-O).

Materials and methods

A decision-analytic Markov model was constructed to examine the effect of late rectal toxicity and compare the costs and quality-adjusted Life Years (QALYs) of IMRT-O and IMRT+S. The main assumption of this modeling study was that disease progression, genito-urinary toxicity and survival were equal for both comparators.

Results

For all patients, IMRT+S revealed a lower toxicity than IMRT-O. Treatment follow-up and toxicity costs for IMRT-O and IMRT+S amounted to €1604 and €1444, respectively, thus saving €160 on the complication costs at an extra charge of €1700 for the spacer in IMRT+S. The QALYs yielded for IMRT-O and IMRT+S were 3.542 and 3.570, respectively. This results in an incremental cost-effectiveness ratio (ICER) of €55,880 per QALY gained. For a ceiling ratio of €80,000, IMRT+S had a 77% probability of being cost-effective.

Conclusion

IMRT+S is cost-effective compared to IMRT-O based on its potential to reduce radiotherapy-related toxicity.

Keywords

Prostate cancer, Radiotherapy, Toxicity-reduction, Spacer, Cost-effectiveness

INTRODUCTION

In the past decade, intensity-modulated radiation therapy (IMRT) has become a widely used treatment for localized prostate cancer. Although IMRT enables highly conformal dose distributions, there is still a potential risk of patients developing severe gastro-intestinal (GI) toxicity [1]. Various devices have been developed to spare rectal structures [2]. These can be divided into endo-rectal balloons (ERBs) that increase the distance from the dorsal rectal wall to the prostate and relatively novel spacers that separate the anterior rectal wall from the prostate by injecting an absorbable hydrogel or saline-filled balloon that naturally biodegrades within 6 months after implantation (Figure 1). Several studies have confirmed both a decrease in calculated rectal dose and a decrease in clinically observed rectal toxicity [3–8] when using a spacer.

FIGURE 1: Axial T2 magnetic resonance images of a patient with a spacer before injection (a) and after injection (b).

Although pilot studies and clinical studies are available on the dosimetric and outcome effects of a spacer, no cost-effectiveness analyses have been conducted so far. Due to ever-expanding health care expenses, knowledge about the cost of treatments is continuously gaining importance. Particularly knowledge on how extra costs are related to the additional gain in health related outcome of treatments, which might be either a gain in overall survival, or a benefit in quality of life. This study aims to provide insight into the cost-effectiveness of a spacer, relating the extra costs to the gain in quality of life through reduction in rectal side effects in patients with prostate cancer.

The objective of this modeling study is to look at the cost-effectiveness of a toxicity-reducing spacer for prostate cancer patients by comparing IMRT therapy with a spacer (IMRT+S) versus IMRT-only without a spacer (IMRT-O). It gives an overview of the economic consequences before introducing this new approach into standard practice.

MATERIALS AND METHODS

Decision-model: Markov model

To assess whether the additional spacer costs are justified given the expected reduction in toxicity, a decision-analytic Markov model was constructed to compare the expected costs and effects of IMRT-O with IMRT+S. Toxicity (i.e., grade ≥ 2 late rectal bleeding) and associated costs were modeled over a 5 year time horizon, because the incidence of events occurring after 5 years is small. In this model, a hypothetical cohort of prostate cancer patients moves between mutually exclusive health states according to a set of transition probabilities. The cycle length of the model was set to one year.

Markov model input

The inputs for the Markov model are based on a published nomogram that relates dose–volume histogram to the risk of rectal bleeding [9] and studies published on complications-related costs and quality of life [10] (Table 1). Health states were based on whether patients were alive and had mild or no side-effects and whether they had grade ≥ 2 late rectal bleeding (Figure 2). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 (CTCAE) [11]. The final absorbing state was ‘death’, either due to cancer or other causes. The Markov model was built and analyzed in Microsoft Office Excel 2007.

FIGURE 2: Diagrammatic representation of the Markov model

Transition probabilities

Transition probabilities were derived from the literature for each cycle; the input parameters are listed in Table 1. Considering that the percentage volume of rectum receiving >75 Gy (V75rectum) is one of the inputs in the nomogram for predicting radiation-induced toxicity in prostate cancer

patients, we used the Valdagni nomogram to estimate the risk of late rectal bleeding [9]. The prediction model of Valdagni is based on patients enrolled in 2002–2004. The mean percentages of 5.5% and 1.2% for V75rectum after IMRT-O and IMRT+S were derived from the literature [12].

TABLE 1: Input parameters for base case Markov model

	IMRT+S	IMRT-O	Source
Effectiveness			
Rectum V75%	1.2%	5.5%	[12]
Total probability at 5 years of GI grade 2 or higher	6%	10%	[9]
Utilities			
Prostate cancer without treatment-related toxicity	0.9		[14]
Prostate cancer with severe late GI toxicity (grade ≥ 2)	0.727		[10]
Costs (in euros)			
Cost follow-up prostate cancer without treatment-related toxicity	€323		See details in Supplementary Table 1 (2010)
Cost late grade 2 GI toxicity	€478		See details in Supplementary Table 1 (2010)
Cost late grade 3 GI toxicity	€4104		See details in Supplementary Table 1 (2010)
Proportion grade 2 (of all grade 2 and 3)	0.75		[19]
Spacer treatment (material and implantation)	€1700	–	See details in Table 2

Effects and costs

Quality of life

The use of utility scores allows for the calculation of Quality Adjusted Life Years (QALYs) and cost per QALY ratios. The model uses health-related quality of life in terms of utility scores as an outcome measure. Utility scores provide a single index value for health status, ranging from 0 (representing death) to 1 (representing perfect health) [13]. Utility scores were derived from the literature and are listed in Table 1. The utility for prostate cancer patients was derived by using the EuroQol (EQ-5D) instrument before and 6 months after completion of radiation [14]. The future effects were discounted to their present value by a rate of 1.5%, according to Dutch guidelines [15].

Costs

As there is no standard treatment for late GI toxicity, the following assumptions were based on expert opinion. Grade 2 is mostly treated with low cost items such as diets or medication. Patients with grade 3 toxicity have on average 2 flexible sigmoidoscopies and blood transfusions.

Some patients with more severe cases of GI toxicity may need more procedures such as laser treatment: it was assumed that patients with grade 3 toxicity would have on average 2 laser therapy sessions. The average monitoring and treatment costs for the treatment of all late GI toxic effects was calculated using the proportions of patients with grade 2 and 3 toxic effects. The proportion of grade 3 toxicity of all grade 2 and 3 effects was 25%. All costs were reported in euros (€) and are listed in detail in Table 2. Price indices were used to convert costs to the 2012 price level. Where possible, unit costs were based on the Dutch manual for cost research [16]. Since the costs of IMRT in both treatment strategies are similar, once-only treatment costs solely consisted of spacer costs (i.e., the application of the spacer plus the cost of the spacer itself). In addition, the calculation took into account the cost of standard follow-up and treatment-related complications over the modeled period (Supplementary Table 1). Future costs were discounted to their present value by a rate of 4% [15].

TABLE 2: Cost-effectiveness analyses results

	IMRT+S	IMRT-O	Incremental
Life years gained (95% CI)	4.189 (4.187–4.191)	4.189 (4.187–4.191)	0.000
QALY gained (95% CI)	3.570 (3.126–3.855)	3.542 (3.119–3.817)	0.028 (0.006–0.05)
Spacer treatment costs*	€1700	€0	€1700
Radiotherapy follow-up and toxicity costs (95% CI)	€1444 (€1032–€1853)	€1604 (€1290–€1947)	–€160
Total cost (95% CI)	€3144	€1604	€1540 (€1239–€1838)
Incremental cost per QALY gained (95% CI)			€55,880 (€27,796–€212,895)

Abbreviations: CI = confidence interval; LY = life year; QALY = quality-adjusted life year.
Compromises the cost of the spacer itself: €1300. The rest is an estimation of the use of an ultrasound and template, the collaboration with an urologist, materials, care on department, eventually extra imaging. Minimum €1300, maximum €2100.
Comprises the cost components: follow-up (€323 annually), late grade 2 GI toxicity (€478 annually) and late grade 3 GI toxicity (€4104 annually) assuming a proportion grade 2 (of all grade 2 and 3) of 0.75.

Markov model analysis

Over a 5 year time horizon, the expected mean costs, occurrence of toxicity, and QALYs were estimated for all comparators. Subsequently, the incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the costs of an additional QALY gained when comparing two strategies. Whether a treatment

strategy is considered cost-effective depends on how much society is willing to pay per gained QALY, which is referred to as the ceiling ratio. We adopted a ceiling ratio of €80,000, which is the informal ceiling ratio for a high burden of disease in the Netherlands [17].

To illustrate the results of the simulation, a cost-effectiveness acceptability curve (CEAC) was calculated [18]. A CEAC shows the probability that a treatment has the highest net monetary benefit, and thus is cost-effective, given different ceiling ratios. It simultaneously shows the probability that the 'wrong' decision will be made by implementing the treatment that, based on the currently available evidence, appears to be the most cost-effective.

Markov model assumptions

The main assumption was that the disease progression and survival rates were equal for the two treatments. A conservative assumption was made that the utility decrement related to severe late GI toxicity (grade ≥ 2) was independent on other toxicities (genito-urinary (GU) toxicity (all grades), GI grade 1 toxicity and erectile dysfunction) and progression. No PSA survival difference was assumed because it was considered that in both arms the received radiotherapy dose was similar and equivalent to 78 Gy. The late GI toxicity was modeled as irreversible, which implied that some form of post-treatment intervention is necessary. Since the occurrence of complications due to the spacer is expected to be very low and data were lacking on this parameter, complications were ignored in the base case (the reference case).

IMRT techniques for both treatment strategies were assumed to be 'equal' in terms of costs, that is, to have the same fractionation schedule, dose delivery and treatment planning technique. Finally, we assumed that 75% of the total rectal toxicity (grade 2 and 3) would be grade 2 [19].

Sensitivity analyses

Sensitivity analyses were performed to handle the uncertainty around the economic analysis [20]. One-way sensitivity analyses were conducted to determine the parameters to which the ICER is most sensitive. One-way sensitivity analyses were performed by varying selected model parameters based on the 95% confidence interval (CI) of the base-case estimate, where available, while keeping all other parameters constant. Results are shown in tornado diagrams, illustrating the impact of the range of each variable on the model's outcome. The variables are ordered with those with the broadest range of impact on the top. Variables with progressively narrower ranges of impact are placed below, giving an appearance similar to that of a tornado. CIs were not available for the costs used in the model. Hence, all other costs were modeled using the minimum and maximum values specified in Supplementary Table 1.

RESULTS

Cost-effectiveness of IMRT+S versus IMRT-O

The combined follow-up and toxicity costs were estimated at €1444 and €1604 for IMRT+S and IMRT-O, respectively, thus saving €160 on the complication costs in favor of IMRT+S. Adding the spacer costs of €1700 resulted in a total cost of €3144 for IMRT+S.

The QALYs yielded were 3.542 and 3.570 for IMRT-O and IMRT+S, respectively. IMRT+S thus produces 0.028 QALYs more than IMRT-O. When all costs and effects are discounted by 4% and 1.5% respectively, IMRT+S costs an additional €1540 per patient. Hence, IMRT+S is more expensive than IMRT-O, but the former produces 0.028 additional QALYs.

This results in an ICER of €55,880 per QALY gained. For the ceiling ratio of €80,000, IMRT+S had a high probability of being cost-effective (77%). The cost-effectiveness acceptability curve is presented in Figure 3.

FIGURE 3: Cost-effectiveness acceptability curve (CEAC) for IMRT with and without a spacer, showing that the probability of a spacer being cost-effective based on a willingness to pay of €80,000 per QALY is 77%. The vertical line represents the ceiling ratio that was adopted in our analyses (€80,000/QALY).

Sensitivity analyses

The one-way sensitivity analyses are presented using a Tornado diagram (Figure 4). The results revealed that IMRT+S remained cost-effective in most scenarios, given a ceiling ratio of €80,000 is adopted. Further analyses found IMRT+S to be cost-effective if the utility of healthy patients was more than 0.845 and if the GI toxicity utility was less than 0.78. The model was most sensitive to variations in the healthy utility, with no GI toxicity; the net benefit varied from €35.414 to €127.963. The model was the least sensitive to variations in overall survival, in which the net

benefit ranged from €55.444 to €55.507. The model stayed cost-effective to variations of cost of spacer and implementation procedure (range from €1300 to €2100).

FIGURE 4: A Tornado diagram showing the sensitivity analysis, using the 95% CI of all the input factors of the model. Each bar depicts the overall effect on net benefits as that input is varied across the indicated range of values, while other input variables are held constant. The vertical line indicates the base case. *Range is used instead of 95%CI.

DISCUSSION

To our knowledge, this is the first study to examine the cost-effectiveness of spacers for a GI toxicity-reducing strategy in IMRT therapy for prostate cancer.

The external beam RT for localized prostate cancer has evolved as a result of the introduction of IMRT. Still, GI toxicity does occur and its resulting reduction of quality of life cannot be ignored. Dose-escalated IMRT beyond 78 Gy prescription dose has raised the rates of acute and chronic grade ≥ 2 rectal toxicity from 3% to 20% and 5% to 21%, respectively [21–23]. The risk of rectal toxicity depends on the volume of the rectum that receives a high radiation dose [24]. In a large prospective series, the percentage volume of rectum receiving >70 Gy (V70rectum) correlated with the occurrence of chronic rectal toxicity. Grade ≥ 2 chronic rectal toxicity occurred in 54% and 13% of patients in whom the V70rectum was $>26.2\%$ and $\leq 26.2\%$, respectively [25]. It is therefore important to implement techniques that prevent these high rectal volume doses. As the prostate is directly adjacent to the rectal wall, the anterior rectal wall cannot be spared completely from the high dose region irrespective of the radiation technique.

In the past decade several research groups have investigated physically separating the rectum from the prostate (e.g., by injecting a hydrogel) to reduce the rectal dose and improve quality of life after treatment. Tests have previously been carried out in which the space between the prostate and rectum was injected with hyaluronic acid, human collagen or PEG-based hydrogel [3–8]. All studies confirmed a decrease of the rectal dose when using an absorbable spacer: Prada et al. and Wilder et al. [3,4] reported no rectal bleeding with the use of spacers versus no spacers. Noyes et al. and Uhl et al. [5,6] showed a 50% and 60.3% dose reduction of the rectal wall, respectively. Pinkawa et al. [7] found a 59% decrease in rectal V70. A multi institutional trial resulted in ≥ 7.5 -mm prostate-rectal separation in 95.8% of patients; 95.7% had decreased rectal V70 of $\geq 25\%$, with a mean reduction of 8.0 Gy [12].

No side effects were described due to the application. Results from a simulation study with IMRT planning of cadaveric specimens showed that a prostate-rectum separation of 10 mm was sufficient to reduce the mean rectal V70 by 83.1% ($p < 0.05$) [26]. These results confirm a decrease of rectal dose when using an absorbable spacer and a decrease of rectal toxicity. The results presented in this paper are valuable for decision-making in terms of policy making and future research. If all the assumptions are correct, IMRT+S is less toxic and more effective than IMRT-O for all prostate cancer patients. Sensitivity analysis revealed that the model was robust to changes in individual parameters and IMRT+S remained cost-effective in most scenarios given a ceiling ratio of €80,000 is adopted.

The main research implication is that the applied study method is a feasible and informative method to explore the potential cost-effectiveness of the spacer in individual patients and

different RT techniques, such as stereotactic body RT (SBRT).

If we acknowledge patient heterogeneity and we can select a population of patients with a high risk of late rectal complications (e.g., re-irradiation, inflammatory bowel disease, diabetes mellitus [27] or anticoagulantia [28]), the cost-effectiveness of the spacer will most likely improve because those patients will benefit even more from the use of a spacer.

This study has several limitations, inherent to its design, worth mentioning. As all early economic studies of new techniques, including this one, it is limited by clinical data comparing those two treatment modes. The procedures for placing the spacer could have some disadvantages. Potential side effects could occur such as pain, rectal perforation and abscess, although not reported so far. These risk factors are not yet fully described and are estimated to be very low (<5%) [4]. The costs incurred with these risk factors have not been included. As discussed by Vordermark et al. [29], the side effects of the injection must be followed prospectively.

A longer follow-up is needed to obtain a larger patient cohort to assess how a rectal dose reduction will impact on late rectal toxicity in patients undergoing spacer insertion. Next, it is important to note that the available prediction model developed by Valdagni et al. [9] was used to predict the occurrence of toxicity. As with all prediction models, these models can possibly be optimized to achieve more accurate predictions. The prediction model of Valdagni is based on patients enrolled in 2002–2004, using an older technique. Newer radiation techniques, as image-guided radiation therapy or volumetric arc therapy, enable dose painting around the prostate with a consequent enhancement of non-dosimetric predictors of rectal toxicity.

The ceiling of €80,000 per QALY is a basis for debate: willingness-to-pay values per QALY gained differ across countries. In the UK £20,000–£30,000 per QALY has been accepted as the threshold to decide whether or not the National Institute for Health and Clinical Excellence (NICE) should recommend use of a new healthcare technology [30].

In the US, the threshold of \$50,000–\$100,000 per QALY often is mentioned in medical literature. The Australian Pharmaceutical Benefits Advisory Committee was unlikely to recommend a drug or treatment for listing if the ICER exceeded AU \$76,000. This uncertainty of threshold levels has an impact on the implications of cost-effectiveness results.

Finally, GU toxicity and erectile dysfunction were not modeled. Weber et al. [31] have shown that administering a spacer may increase the delivered dose to the bladder by displacing the prostate gland anteriorly. However this increase in dose–volume metrics is non-significant in a majority of cases. Also, given the lack of dose–volume data, it is doubtful that the modified dosimetry after spacer injection could lead to an increase in GU toxicity. This is confirmed by Song et al. [12], who showed that the V70 of the bladder is lower with the use of a spacer than without.

In conclusion, the current paper demonstrates that, according to the Dutch health costs and based on the applied assumptions are correct, the spacer can be cost-effective for prostate

cancer patients due to less severe toxicity and a reduction in treatment costs associated with these side effects. The incremental cost-effectiveness ratio of IMRT+S versus IMRT-O was €55,880 per QALY gained. IMRT+S has a 77% probability of being cost effective at a willingness-to-pay value of €80,000 per QALY gained. The cost-effectiveness of the spacer is expected to increase if patient heterogeneity is acknowledged.

SUPPLEMENTARY TABLE 1: Detailed follow-up cost after treatment

Cost Health States	Cost (2012)	Volume/y	Range (min- max)	Mean	Source
No/mild toxicity					
Consultation Radiotherapist	€97.17	2-4/y	€194.34	€388.69	€291.52 Hakkaart-van Roijen L, et al. 2010
PSA measurement	€10.36	2-4/y	€20.72	€41.44	€31.08 Hakkaart-van Roijen L, et al. 2010
Total healthy:			€215.06	€430.13	€322.60
Grade 2 late GI					
Medication for diarrhea (fe. Salofalk/Arestal)	€15.65	4-6 weeks/y	€62.60	€93.90	€234.75 Health Care Insurance Board 2012
Consultation Radiotherapist	€97.17	1-4x/y	€97.17	€388.69	€242.93 Hakkaart-van Roijen L, et al. 2010
Total grade 2:			€159.77	€482.59	€477.68
Grade ≥ 3 late GI					
Medication for diarrhea (fe. Salofalk/Arestal)	€15.65	4-12 weeks/y	€62.60	€187.80	€375.60 Health Care Insurance Board 2012
Argon plasma coagulation	€501.53	1-3x/y	€501.53	€1,504.58	€1,003.05 Hakkaart-van Roijen L, et al. 2010
Blood transfusion	€749.53	1-3x/y	€749.53	€2,248.60	€1,499.07 Hakkaart-van Roijen L, et al. 2010
Consultation specialist (Gastroenterologist)/ academic hospital	€203.13	1-4x/y	€203.13	€812.52	€507.82 Hakkaart-van Roijen L, et al. 2010
Sigmoidoscopy	€359.42	1-3x/y	€359.42	€1,078.26	€718.84 Hakkaart-van Roijen L, et al. 2010
Total grade ≥ 3:			€1,876.21	€5,831.75	€4,104.38

REFERENCES

1. Talcott JA, Manola J, Clark JA, et al. Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol*. 2003;21(21):3979–86.
2. Smeenk RJ, van Lin ENJT. Application of anorectal sparing devices in prostate radiotherapy. *Radiother Oncol*. 2013;106(2):155–6.
3. Prada PJ, Fernández J, Martínez AA, et al. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys*. 2007;69(1):95–102.
4. Wilder RB, Barne GA, Gilbert RF, et al. Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(3):824–30.
5. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1918–22.
6. Uhl M, van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. *Radiother Oncol*. 2013;106(2):215–19.
7. Pinkawa M, Corral NE, Caffaro M. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol*. 2011;100(3):436–41.
8. Melchert C, Gez E, Bohlen G, et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol*. 2013;106(2):210–4.
9. Valdagni R, Kattan MW, Rancati T, et al. Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1957–66.
10. Hummel SR, Stevenson MD, Simpson EL, Staffurth J. A model of the cost-effectiveness of intensity-modulated radiotherapy in comparison with three-dimensional conformal radiotherapy for the treatment of localised prostate cancer. *Clin Oncol (R Coll Radiol)*. 2012;24(10):e159–67.
11. Common Terminology Criteria for Adverse Events 4.0 (CTCAE). (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
12. Song DY, Herfarth KK, Uhl M, et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys*. 2013;87(1):81–7.
13. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press; 2005.
14. Hodges JC, Lotan Y, Boike TP, et al. Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: an emerging initial radiation treatment option for organ-confined prostate cancer. *J Oncol Pract*. 2012;8(3):31–7.
15. Health Care Insurance Board. *Guidelines for pharmaco-economic research (in Dutch)*. Diemen: Health care insurance Board; 2012.

16. Hakkaart-van Roijen L, Tan S, Bouwmans C, et al. Manual for Costing Research (in Dutch). Amstelveen: College voor zorgverzekering [Health Care Insurance Board]; 2010.
17. Council for Public Health and Health Care. Sensible and sustainable care. Zoetermeer: Council for Public Health and Health Care; 2006.
18. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ* 1994;3:309–19.
19. Zelefsky MJ, Fuks Z, Leibel SA. Intensity-modulated radiation therapy for prostate cancer. *Semin Radiat Oncol* 2002;12(3):229–37.
20. Briggs A: Handling uncertainty in economic evaluation and presenting the results, in Drummond MM (ed): *Economic Evaluation in Health Care*. Oxford, United Kingdom, Oxford University Press, 2001, 173-214.
21. Al-Mamgani A, Heemsbergen WD, Peeters ST, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73(3):685–91.
22. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(4):1124–9.
23. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(1):67–74.
24. Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. *Radiother Oncol*. 2009;93(2):153–67.
25. Huang EH, Pollack A, Levy L, et al. Late rectal toxicity: Dose–volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;54(5):1314–21.
26. Susil RC, McNutt TR, DeWeese TL, Song D. Effects of prostate-rectum separation on rectal dose from external beam radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;76(4):1251–8.
27. Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: a predictor of late radiation morbidity. *Int J Radiat Oncol Biol Phys* 1999;43(3):475–9.
28. Willett CG, Ooi CJ, Zietman AL, et al. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. *Int J Radiat Oncol Biol Phys*. 2000;46(4):995–8.
29. Vordermark D, Guckenberger M, Baier K, Markert K. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity-modulated brachytherapy or EBRT for prostate cancer patients: in regard to Prada et al. (*Int J Radiat Oncol Biol Phys* 2007;69:95–102) *Int J Radiat Oncol Biol Phys* 2008;71(1):316–7.
30. NICE 2004. Guide to the Methods of Technology Appraisal.
31. Weber DC, Zilli T, Vallee JP, Rouzaud M, Miralbell R, Cozzi L. Intensity modulated proton and photon therapy for early prostate cancer with or without transperineal injection of a polyethylen glycol spacer: a treatment planning comparison study. *Int J Radiat Oncol Biol Phys*. 2012;84(3):e311–8.

CHAPTER 5

Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection

Radiother Oncol 2016;121(1):118-123

© Copyright Elsevier

Vanneste BGL, Hoffmann A, van Lin E, van de Voorde L, Schubert C, Pinkawa M, Lambin P.

ABSTRACT

Background and purpose

Previous studies confirmed that implantable rectum spacers (IRS) decreased acute gastrointestinal (GI) toxicity in a significant percentage of prostate cancer patients undergoing intensity modulated radiation therapy (IMRT). We developed decision rules based on clinical risk factors (CRFs) to select those patients who are expected to benefit most from IRS implantation.

Materials and methods

For 26 patients dose distributions with (IMRT + IRS) and without (IMRT – IRS) IRS were calculated. Validated nomograms based on CRFs and dosimetric criteria (anorectal $V_{40\text{Gy}}$ and $V_{75\text{Gy}}$) were used to predict probabilities for grade 2–3 (G2–3) acute GI toxicity, G2–3 late rectal bleeding (LRB), G3 LRB, and G2–3 faecal incontinence (FI) for IMRT + IRS and IMRT – IRS. All permutations of CRFs were generated to identify most benefit scenarios (MBS) in which a predicted toxicity reduction of $\geq 5\%$ points in $\geq 25\%$ of the cohort was present due to IRS implantation.

Results

IMRT + IRS revealed a significant reduction in $V_{40\text{Gy}}$ ($p = 0.0357$) and $V_{75\text{Gy}}$ ($p < 0.0001$) relative to IMRT – IRS. For G2–3 acute GI toxicity and G2–3 LRB, the predicted toxicity rates decreased in 17/26 (65%) and 20/26 (77%) patients, and decision rules were derived for 22/32 (69%) and 12/64 (19%) MBS, respectively. From the decision rules, it follows that diabetes status has no impact on G2–3 acute toxicity, and in absence of pre-RT abdominal surgery, the implantation of an IRS is predicted to show no clinically relevant benefit for G2–3 LRB.

Conclusions

Prostate cancer patients who are expected to benefit most from IRS implantation can be identified prior to IMRT based on their CRFs profile.

Keywords

Prostate cancer, Radiotherapy, Rectum spacer, Patient selection, Toxicity prediction.

INTRODUCTION

Despite recent improvements, image-guided radiotherapy and highly-conformal dose delivery techniques for prostate cancer are still associated with severe gastro-intestinal (GI) toxicity. As a result, a significant percentage of patients suffer from a negative impact on their quality of life [1–3]. Various temporary or long-term implantable medical devices have been developed to spare rectal structures by excluding them from high-dose radiation exposure. Endo-rectal balloons are used to increase the distance from the dorsal rectal wall to the prostate [4]. Implanted rectum spacers (IRS) are used to separate the anterior rectal wall from the prostate by injecting an absorbable hydrogel or hyaluronic acid, or by placing a saline-filled balloon or collagen implant [5–8].

Several studies have confirmed that an IRS decreases the rectal dose and consequently also the acute rectal toxicity to such an extent that the costs of IRS placement are justified [5–14]. A better selection of patients with a decision support system to implant an IRS would further enhance cost-effectiveness, an issue that is becoming increasingly important due to ever-expanding expenses in health care [14,15]. Since the follow-up interval of the studies conducted is still too short, no long-term late toxicity scores have been reported yet. Instead, validated multifactorial nomograms based on clinical risk factors and dosimetric data can be exploited to predict toxicity scores [16,17].

In the current study, we used such nomograms to test the hypothesis that implanting a hydrogel IRS in patients with prostate cancer undergoing intensity modulated radiation therapy (IMRT + IRS) reduces the predicted grade 2–3 (G2–3) acute and late rectal toxicities in comparison to patients undergoing IMRT without IRS (IMRT – IRS). Furthermore, we identified scenarios of clinical risk factors for which implantation of an IRS is predicted to significantly reduce G2–3 acute and late rectal toxicity rates in a sufficiently large proportion of patients. Finally, we generate decision rules for the toxicity end-points covering these sets of scenarios, making it possible to select those patients who are expected to benefit most from an IRS implantation prior to treatment planning for IMRT.

MATERIALS AND METHODS

Patient characteristics

This study included 26 patients with localized prostate cancer who had signed an informed consent form, after approval by the ethics committee of the University Hospital RWTH Aachen, where these patients were treated. Patients for this study were consecutively selected in 2011 [5,18]. The patient and tumour characteristics are summarized in Table 1. Prognostic risk-group stratification of the patients was defined according to the D’Amico classification [19].

TABLE 1: Patient (N = 26) and tumour characteristics.

Age (years; median [range])	73 [56–82]
Prognostic risk group*: (No. of patients)	
1. Low-risk	8 (31%)
2. Intermediate-risk	11 (42%)
3. High-risk	7 (27%)
Prostate volume: (cm ³ ; median [range])	
PTV	50 [25–130]
Clinical risk factors for nomograms: (No. of patients)	
Diabetes	4
Haemorrhoids	2
Previous abdominal surgery	2
Anticoagulant drugs	7
Hormonal therapy	7
Anti-hypertensives	11

Abbreviation: PTV = planning target volume.

* Low-risk: no risk factors: PSA < 10 ng/ml; Gleason score < 7; cT-stage < 2b; Intermediate-risk: one risk factor: PSA 10–20 ng/ml or Gleason score = 7 or cT-stage = 2b/c; High-risk: two risk factors or PSA > 20 ng/ml or Gleason score > 7 or cT-stage > 2b/c.

Rectum spacer implantation

In these patients, a 10 cm³ IRS gel (SpaceOAR™ System, Augmenix Inc., Waltham, MA) was injected in the recto-prostatic space prior to IMRT planning and dose delivery. This IRS implantation technique has been described previously by Pinkawa et al. [5].

Image acquisition and organ delineation

Every patient underwent two computed tomography (CT) scans in supine position with a slice thickness of 5 mm: one CT scan prior to IRS implantation and one 3–5 days after IRS implantation. In total, 52 CT scans were imported into the Pinnacle³ radiation treatment planning system (Version 8.0 m, Philips Medical Systems, Fitchburg, WI) to calculate clinically acceptable dose

distributions for IMRT – IRS and IMRT + IRS (Figure 1). For accurate target volume delineation, T2-weighted magnetic resonance imaging (MRI) scans were additionally performed after IRS implantation. After registration with the corresponding CT scans the prostate, the adjacent rectal wall, and the IRS gel (for volumetric analysis) were contoured.

FIGURE 1: Color-wash dose distribution in an axial plane before (a) and after (b) IRS gel injection in the same patient, with prostate (yellow) and PTV (red). Without IRS, the high-dose region > 75% (red) overlaps with the anterior part of the rectum (brown), while with IRS in situ the high-dose region spans the IRS (black), and not the rectum. The 40% isodose contour (purple) overlaps the entire rectum in (a), whereas it overlaps the rectum partially in (b). Abbreviation: IRS = implantable rectum spacer.

Depending on the prognostic risk group, the clinical target volume (CTV) was defined as the prostate only (CTV1), the prostate including the proximal 2–4 slices of the seminal vesicles depicted on CT (CTV2), or the prostate with the entire seminal vesicles (CTV3) [20]. To generate the planning target volume (PTV), the CTV was expanded by 8 mm in lateral–anterior, 5 mm in superior–inferior and 4 mm in posterior direction, as described in an earlier study [5,12]. Moreover, the bladder, femoral heads, anus, rectum and the outer anorectal wall contour (anal canal up to the recto-sigmoid flexure) were contoured as organs at risk on the CT scans. To allow for intercomparison between IMRT – IRS and IMRT + IRS planned dose distributions, the delineated cranio-caudal distance was chosen to be identical for each patient and for every pre- and post- IRS-implant CT scan, resulting in the same anal and rectal length per patient. Two independent observers (MP and BV) performed the delineations.

Treatment planning technique

All IMRT – IRS and IMRT + IRS treatment plans were designed by inverse planning using a direct

machine parameter optimization (DMPO) algorithm for step-and-shoot IMRT with 5 coplanar 15 MV photon beams (gantry angles: 45°, 105°, 180°, 255°, 315°) [21]. The dose grid included the PTV, organs at risk, and an additional 4–5 cm of tissue in both the cranial and caudal directions. The prescribed dose to the PTV was 78 Gy in 2 Gy fractions, requiring at least 99% of the volume to receive 95% of the prescribed dose within the –5% to +7% ICRU uniformity criteria [22]. The same dosimetric constraints were used for both IMRT – IRS and IMRT + IRS treatment planning, based on the relevant maximum tolerance doses (indicated as $D_{\max}$) and the maximum allowed relative volumes to be exposed to a certain dose level (indicated as $V_{xx\text{Gy}}$), as published by the Radiation Therapy Oncology Group (RTOG) for rectum and bladder [23]: $V_{50\text{Gy}}(\text{rectum}) \leq 50\%$, $V_{70\text{Gy}}(\text{rectum}) \leq 20\%$, $D_{\max}(\text{rectum}) \leq 76$ Gy, $V_{55\text{Gy}}(\text{bladder}) \leq 50\%$, and $V_{70\text{Gy}}(\text{bladder}) \leq 30\%$. The mean anorectal dose (MARD), mean anal dose (MAD), and mean rectal dose (MRD) were evaluated for statistical analysis.

Multifactorial nomograms for NTCP prediction

Validated nomograms based on clinical risk factors (use of anticoagulants, hormonal therapy, or anti-hypertensives; pelvic node irradiation; presence of diabetes or haemorrhoids; and a history of pre-RT abdominal surgery) and dosimetric parameters of the anorectum ($V_{40\text{Gy}}$ and $V_{75\text{Gy}}$) were used to predict for each *individual* patient the normal tissue complication probability (NTCP) for G2–3 acute GI toxicity, G2–3 late rectal bleeding (LRB), G3 LRB, and G2–3 faecal incontinence (FI) for both the IMRT – IRS and IMRT + IRS treatment plans [16,17].

Identification of beneficent scenarios

To identify scenarios of clinical risk factors predicting a significant reduction in GI toxicity scores for a sufficiently large proportion of patients, we first considered the most favourable and the most unfavourable scenarios, being defined as the binary permutation of clinical risk factors producing the most positive and the most negative predicted NTCPs, respectively. From the regression coefficients of the nomograms it appeared that ‘use of anticoagulants’ and ‘hormonal therapy’ positively affected the predicted NTCPs. On the other hand ‘presence of diabetes’, ‘presence of haemorrhoids’, ‘pelvic node irradiation’, and ‘previous abdominal surgery’ negatively affected the predicted NTCPs. Consequently, the most unfavourable scenario represents the combination of ‘presence of diabetes’, ‘presence of haemorrhoids’, ‘pelvic node irradiation’, and ‘previous abdominal surgery’ in absence of ‘use of anticoagulants’ and ‘hormonal therapy’. The most favourable scenario represents the combination of ‘use of anticoagulants’ and ‘hormonal therapy’ in absence of ‘presence of diabetes’, ‘presence of haemorrhoids’, ‘pelvic node irradiation’, and ‘previous abdominal surgery’. To assess the decrease in predicted NTCPs between IMRT + IRS and IMRT – IRS for both scenarios, the corresponding permutations of risk factors were applied to all individual patients in the cohort, while leaving the variation in dosimetric risk factors unchanged. From the resulting distribution of predicted changes in NTCPs, the proportion having an NTCP

reduction of at least 5% and 10% points was assessed for both scenarios. Furthermore, we considered all possible scenarios by generating the remaining binary permutations of clinical risk factors (in total: 32 for G2–3 acute toxicity, 64 for G2–3 LRB, Gr3 LRB, and G2–3 FI) to identify the set of scenarios yielding a predicted NTCP reduction of at least 5% points in at least 25% of the patients. Finally, a Boolean expression² for this set of scenarios was generated to establish a decision rule per toxicity end-point.

Statistical analysis

The statistical analyses were performed using the Statistics and Machine Learning Toolbox™ from MATLAB-software (Version 10.0, MathWorks, Inc., Natick, MA). The Wilcoxon's signed rank test was applied to test for a significant decrease in predicted toxicity rates between IMRT + IRS and IMRT – IRS. All statistical tests were one-sided, with $p < 0.05$ considered to be statistically significant.

RESULTS

Dosimetric plan performance with and without IRS

The median implanted IRS volume was 10.6 cc [range: 8.3–20.4 cc]. No statistically significant difference was observed between the prostate (CTV) and the PTV volumes in IMRT + IRS and IMRT – IRS ($p = 0.269$ and $p = 0.603$, respectively). The median anorectum $V_{40\text{Gy}}$ was reduced from 53.4% for IMRT – IRS to 47.6% for IMRT + IRS ($p = 0.0357$). The median $V_{75\text{Gy}}$ was significantly reduced from 3.9% for IMRT – IRS to 0.4% for IMRT + IRS ($p < 0.0001$). The median MARD for IMRT – IRS and IMRT + IRS was 38.7 Gy and 34.9 Gy, respectively, yielding a significant reduction ($p < 0.001$). A significant reduction in the median MAD from 34.3 Gy for IMRT – IRS to 24.8 Gy for IMRT + IRS ($p < 0.001$) was observed. The median MRD was significantly reduced from 39.0 Gy for IMRT – IRS to 35.5 Gy for IMRT + IRS ($p = 0.009$).

Predicted NTCP reduction

First, NTCP estimates were calculated for IMRT + IRS and IMRT – IRS based on the clinical risk factors as given for the individual patients. The pair-wise comparison of predicted NTCPs revealed significantly lower predicted G2–3 acute and late rectal toxicity rates for IMRT + IRS than for IMRT – IRS; the decrease was not significant for FI (Table 2). For G2–3 acute toxicity and for G3 LRB, a decrease in predicted toxicity for both endpoints was present in 17/26 (65%) patients. For G2–3 LRB, a decrease in predicted NTCP was expected in 20/26 (77%) patients. For 23/26 patients (88%) no decrease in G2–3 FI was revealed.

TABLE 2: Median [range] predicted acute and late toxicity rates in the entire cohort (N = 26)

	NTCP _{IMRT+IRS} (%)	NTCP _{IMRT-IRS} (%)	Δ NTCP (%)	p value
Nomacu	20 [8–33]	22 [11–32]	3 [–3 to 15]	<0.001
3 yr G2–3 LRB	5 [4–11]	6 [4–13]	1 [–1 to 5]	<0.0001
3 yr G3 LRB	3 [3–10]	4 [4–11]	1 [–1 to 2]	<0.002
G2–3 LFI	1 [0–5]	2 [0–6]	1 ^{n.s.} [0–2]	0.006 ^{n.s.}

Abbreviations: Nomacu = acute RTOG Grade 2 to Grade 3 lower gastro-intestinal toxicity; 3 yr G2–3 LRB = 3 years of Grade 2 to Grade 3 late rectal bleeding; 3 yr G3 LRB = 3 years of Grade 3 late rectal bleeding; G2–3 LFI = chronic Grade 2 to Grade 3 late faecal incontinence; IRS = implantable rectum spacer. ^{n.s.}Not significant.

In Table 3, the statistics of the predicted NTCPs for both the most unfavourable and most favourable scenarios are presented. For the most unfavourable scenario, the G2–3 acute toxicity rate decreased in 17/26 (65%) patients. For G2–3 LRB, G3 LRB, and G2–3 FI a decrease in predicted toxicity was present in 22/26 (85%) patients, 21/26 (81%) patients, and in 13/26 (50%) patients, respectively. For the most favourable scenario, the G2–3 acute toxicity rate decreased in 17/26 (65%) patients. For G2–3 LRB, G3 LRB, and G2–3 FI a decrease in predicted toxicity was

present in 17/26 (65%) patients, 13/26 (50%) patients, and in 1/26 (4%) patients, respectively.

TABLE 3: Median [range] predicted acute and late toxicity rates stratified by scenario

	Scenario	NTCP _{IMRT+IRS} (%)	NTCP _{IMRT-IRS} (%)	Δ NTCP (%)	p value	Δ NTCP $\geq$ 5% (%)	Δ NTCP $\geq$ 10% (%)
Nomacu	MU	45 [33–54]	48 [39–59]	5 [–4 to 20]	<0.001	50	12
	MF	10 [6–14]	11 [8–16]	2 [–2 to 8]	<0.001	4	0
3yr G2–3 LRB	MU	17 [13–21]	22 [15–30]	5 [–4 to 16]	<0.0001	50	12
	MF	4 [3–4]	5 [4–6]	1 [–1 to 3]	<0.0001	0	0
3yr G3 LRB	MU	13 [11–16]	17 [12–22]	3 [–2 to 10]	<0.0001	19	0
	MF	3 [2–3]	3 [3–4]	1 [0–2]	0.02	0	0
G2–3 LFI	MU	12 [7–17]	13 [9–19]	1 [–3 to 12]	0.03	12	4
	MF	0 [0–1]	1 [0–1]	0 [0–1]	0.06 ^{n.s.}	0	0

Abbreviations: MU = most unfavourable scenario; MF = most favourable scenario; NTCP_{IMRT+IRS} = normal-tissue complication probability for IMRT plans with IRS gel; NTCP_{IMRT-IRS} = normal-tissue complication probability for IMRT plans without IRS gel; Δ NTCP $\geq$ x% = percentage of patients in study cohort having an NTCP decrease of at least x% points; IRS = implantable rectal spacer; Nomacu = acute RTOG Grade 2 to Grade 3 lower gastro-intestinal toxicity; 3 yr G2–3 LRB = 3 years of Grade 2 to Grade 3 late rectal bleeding; 3 yr G3 LRB = 3 years of Grade 3 late rectal bleeding; G2–3 LFI = chronic Grade 2 to Grade 3 late faecal incontinence; IRS = implantable rectum spacer. ^{n.s.}Not significant.

Decision rules

Regarding G2–3 acute toxicity, in 22/32 (69%) scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients (Table S1, Supplementary Data). The Boolean decision rule that describes these 22 scenarios was found to be:

NOT (A OR E) OR (C AND D) OR (AX OR E) AND (CX OR D)

where A = use of anticoagulants; B = diabetes; C = presence of haemorrhoids; D = pelvic node irradiation; E = hormonal therapy, F = previous abdominal surgery.

Among these 22 scenarios, the most unfavourable scenario and 5/31 additional scenarios had a median NTCP-reduction of at least 5%.

For G2–3 LRB, in 12/64 (19%) scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients (Table S2, Supplementary Data). The Boolean decision rule that describes these 12 scenarios was found to be:

F AND (NOT (A) AND ((B OR C) AND (D AND E) OR NOT (D OR E))) OR (NOT (C)AND D AND

NOT (E) OR (C AND D AND NOT (E))

where A = use of anticoagulants; B = diabetes; C = presence of haemorrhoids; D = pelvic node irradiation; E = hormonal therapy, F = previous abdominal surgery.

For G3 LRB and G2–3 FI an NTCP-decrease of at least 5% points was not predicted to occur in at least 25% of the patients.

DISCUSSION

This is the first study to assess the benefits of an IRS for reducing GI toxicity in prostate cancer patients scheduled for IMRT prior to implantation of such a device. We identified combinations of clinical risk factors for which IRS implantation is predicted to be beneficial. For two clinically relevant toxicity end-points, we generated decision rules to identify patients who are expected to benefit most from the implantation of an IRS, based solely on their clinical risk profiles and not on dosimetric or genetic factors. The probability of developing GI toxicity is not only related to the dose and the volume of the anorectum receiving a high radiation dose, but also depends on clinical risk factors and genetic profiles. GI toxicity is a concern in EBRT of prostate cancer and its adverse effect on the quality of life cannot be ignored. Dose-escalated IMRT up to a dose of 78 Gy has raised the rates of acute and chronic Grade ≥ 2 rectal toxicity compared with lower doses (e.g., 68 Gy) from 3% to 20% and 5% to 21%, respectively [24–28]. Keeping the volume fraction of the anorectum receiving more than 75 Gy ($V_{75\text{Gy}}$) below 5% has been demonstrated to be predictive of late rectal bleeding [29]. Therefore, it is important to use techniques that prevent rectal volumes from being exposed to high doses. Implantation of an absorbable IRS between the prostate and the anterior rectal wall artificially increases the distance between the prostate and the anterior rectal wall, and hence reduces the dose delivered to the anorectum [30,31]. Besides dosimetric factors, several clinical risk factors have been shown to predict for radiation-induced GI toxicity in prostate cancer patients. Based on combinations of scenarios of clinical risk factors, we developed the first set of decision rules to predict the estimated toxicity reduction of an IRS prior to implantation. This introduces the opportunity to better select patients for IRS implantation, avoid unbeneficial implantations and possible complications, enhance quality of life, and consequently improve the cost-effectiveness of the treatment. In addition to dosimetric and clinical factors, the prediction could possibly be further improved by including genetic biomarkers to select those patients having increased risk factors for increased rectal toxicity [32–34]. Recently the first replicated genetic associations were reported for adverse reactions to EBRT [35]. A next step could therefore be to incorporate genetic risk in those models [34].

The multifactorial nomograms by Valdagni et al. were used in our study to predict acute and late toxicity rates [16,17]. In our patient group, these nomograms revealed a significant decrease in G2–3 acute and late GI toxicity. When we compared the most unfavourable with the most favourable scenario, a most unfavourable scenario was predicted to be beneficial with IMRT + IRS, while the benefit in the most favourable scenario was minimal. Between those two extreme scenarios, multiple other scenarios were identified yielding a predicted NTCP reduction of at least 5% points in at least 25% of patients. To select patients for IRS implantation, the concept of late rectal toxicity as a consequential late effect arising from acute RT injury is important [36]. This implies that the decision rule we developed to predict a clinically relevant reduction of acute toxicity in a sufficiently large proportion of patients after implantation of an IRS, could be used to select optimal candidates for implantation of an IRS, and hence reduce acute and consequently

late toxicities. Regarding G2–3 acute toxicity, in 22 scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients (Table S1). The interpretation of the corresponding decision rule covering these scenarios is as follows: first, the conjunction of absence of ‘use of anticoagulants’ and absence of ‘hormonal therapy’ represents 8 scenarios that correspond to the Boolean expression $\text{NOT } (A \text{ OR } E)$ (Table S1). Secondly, 6 additional scenarios are provided by the conjunction of both ‘presence of haemorrhoids’ and ‘pelvic node irradiation’. This corresponds to the Boolean expression $(C \text{ AND } D)$. The remaining 8 scenarios are described by the presence of either ‘use of anticoagulants’ or ‘hormonal therapy’, in conjunction with either ‘presence of haemorrhoids’ or ‘pelvic node irradiation’. This corresponds to $(A \text{ XOR } E) \text{ AND } (C \text{ XOR } D)$. These 3 expressions are combined in a disjunctive way to establish the full decision rule. From this decision rule, it follows that diabetes status has no impact on the decision rule. For G2–3 LRB, in 12 scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients. From the corresponding rule, it follows that in absence of pre-RT abdominal surgery, the implantation of an IRS is predicted to show no clinically relevant benefit for G2–3 LRB.

The present study has several limitations. First, the confidence intervals of the regression coefficients in the logistic regression model of the nomograms were not incorporated in our analysis. Hence, confidence intervals for the predicted NTCPs have not been computed, possibly leading to an over- or underestimation. Furthermore, the nomograms used were gathered from clinical data acquired between 2002 and 2004, an era of less conformal dose delivery techniques compared to modern IMRT. Nowadays, IMRT with daily image-guided set-up correction enables accurate dose delivery, thus possibly enhancing the non-dosimetric predictors of rectal toxicity. Moreover, the two decision rules we developed are based on different clinical risk factors, and not on dosimetric factors. Further, the nomograms used are only internally validated, and stand in need of external clinical prospective validation. Next, as far as the predictive performance of the decision rules is concerned, their sensitivity, specificity, and calibration have to be assessed in an independent test-population. Finally, other prediction models exist with other clinical factors that might influence acute and late GI toxicity [37,38]. Hamstra et al. reported that patient age, a history of myocardial infarction, and congestive heart failure are predictors for G3 GI toxicity [37]. However, they concluded that the use of anticoagulants increased toxicity independent of age and comorbidity. The use of anticoagulants is already included in the nomograms of Valdagni et al. Tucker et al. also reported that patients with cardiovascular disease had a significantly higher incidence of late rectal toxicity [38]. Those risk factors have not been included in the nomogram of Valdagni et al. This is therefore a limitation of their prediction model.

In the present study, we evaluated differences in predicted NTCP due to the implantation of an absorbable hydrogel spacer. We investigated combinations of clinical risk factors to generate

decision rules in order to predict clinical scenarios in which patients are expected to benefit most from spacer implantation. Wolf et al. recently published a study comparing the dosimetric differences between various spacing methods, showing that balloon spacers had a more pronounced effects than hydrogel spacers [39]. At the time of planning, balloon spacers revealed a 63% reduction of the rectum surface encompassed by the 95% isodose-line, in comparison to 38% for the hydrogel. However, they were unable to demonstrate any clinically relevant difference in acute GI toxicity. The relevant scenarios of clinical risk factors that were identified in our study are based on treatment plans with and without an implanted hydrogel. Our method could also be applied to patients with an implanted balloon spacer. According to the nomograms, balloon spacers would probably not decrease acute toxicity more than hydrogel spacers, because of similar mean rectal dose. However late toxicity is expected to decrease with balloon spacers due to a lower $V_{75\text{Gy}}$ in comparison to hydrogel spacers. Further research is needed to test this hypothesis.

The results presented in this paper are also valuable for policy making by health care insurance companies. Currently, there is no reimbursement for IRS implantation in the Netherlands. Only new treatment modalities with level I–II scientific evidence are approved for reimbursement. A reliable patient-selection tool may fundamentally change this procedure. A model-based approach could possibly be instrumental for this, since such an approach was also employed for the introduction of proton therapy in the Netherlands. According to guidelines of the Dutch National Society of Radiotherapy Oncology, a predicted reduction of 10% of grade 2, 5% of grade 3 and 2% of grade 4–5 complications would be required to justify the increased costs for such treatment [40]. If we apply these thresholds, we estimate that approximately 20% of the localized prostate cancer patients would benefit from an IRS, and consequently should have its placement reimbursed. If the IRS is combined with brachytherapy, proton therapy, or stereotactic radiotherapy, the toxicity reduction may even be more pronounced due to the steep dose gradients of these techniques. However, this hypothesis needs to be clinically validated.

The next step will be to implement the cost-effectiveness model to obtain a four-level decision support system with complete integration of dose, toxicity, cost-effectiveness, and genetic input [41,42].

In conclusion, the implantation of an IRS is predicted to reduce the G2–3 acute and late rectal toxicity rates in prostate cancer patients undergoing IMRT. Scenarios of clinical risk factors were identified for which implantation of an IRS is predicted to significantly reduce G2–3 acute and late rectal toxicity rates with IMRT prior to implantation of the IRS. Decision rules were developed to support the physician in selecting those patients who will benefit most from IRS implantation prior to IMRT planning. A prospective follow-up study in an independent patient cohort is needed to assess the predictive performance of the decision rules.

SUPPLEMENTARY FILES

TABLE S1: All 32 binary permutations of clinical risk factors for G2-3 acute toxicity. Permutations 1–10 define the set of scenarios yielding a predicted toxicity reduction of at least 5% points in less than 25% of patients. Permutations 11–32 define the set of scenarios yielding a predicted toxicity reduction of at least 5% points in at least 25% of patients. For the latter set the Boolean decision rule was derived: the conjunction of absence of ‘use of anticoagulants’ and absence of ‘hormonal therapy’ represents 8 scenarios (*marked in yellow*). Furthermore, 6 additional scenarios are provided by conjunction of both ‘presence of haemorrhoids’ and ‘pelvic node irradiation’ (*marked in green*). The remaining 8 scenarios are described by the presence of either ‘use of anticoagulants’ or ‘hormonal therapy’ in conjunction with either ‘presence of haemorrhoids’ or ‘pelvic node irradiation’ (*marked in blue*).

	Use of anticoagulants	Diabetes	Presence of haemorrhoids	Pelvic node irradiation	Hormonal therapy	Δ NTCP $\geq$ 5% [%]
1*	1	0	0	0	1	4
2	0	0	0	0	1	12
3	1	0	0	0	0	12
4	1	0	0	1	1	12
5	1	0	1	0	1	12
6	1	1	0	0	1	12
7	1	1	0	0	0	15
8	1	1	1	0	1	15
9	1	1	0	1	1	19
10	0	1	0	0	1	23
11	0	0	0	0	0	27
12	0	0	0	1	1	27
13	0	0	1	0	1	27
14	1	0	0	1	0	27
15	1	0	1	0	0	27
16	1	0	1	1	1	27
17	1	1	1	0	0	38
18	0	0	1	0	0	42
19	0	1	0	0	0	42
20	0	1	0	1	1	42
21	0	1	1	0	1	42
22	1	0	1	1	0	42
23	1	1	0	1	0	42
24	1	1	1	1	1	42
25	0	0	0	1	0	46
26	0	0	1	1	1	46

TABLE S1 CONTINUED:

	Use of anticoagulants	Diabetes	Presence of haemorrhoids	Pelvic node irradiation	Hormonal therapy	$\Delta\text{NTCP} \geq 5\%$ [%]
27	0	0	1	1	0	50
28	0	1	0	1	0	50
29	0	1	1	0	0	50
30**	0	1	1	1	0	50
31	0	1	1	1	1	50
32	1	1	1	1	0	50

Abbreviations: $\Delta\text{NTCP} \geq 5\%$ = percentage of patients in study cohort having a predicted normal-tissue complication probability decrease of at least 5% points; * = most favourable scenario; ** = most unfavourable scenario.

TABLE S2: The 12 binary permutations of clinical risk factors defining the set of scenarios yielding a predicted G2-3 LRB toxicity reduction of at least 5% points in at least 25% of patients

	Use of anticoagulants	Diabetes	Presence of haemorrhoids	Pelvic node irradiation	Hormonal therapy	Previous abdominal surgery	$\Delta\text{NTCP} \geq 5\%$ [%]
1	0	1	0	0	0	1	27
2	0	0	1	0	0	1	31
3	0	0	1	1	1	1	31
4	0	1	0	1	1	1	31
5	1	0	1	1	0	1	31
6	0	0	0	1	0	1	35
7	0	1	0	1	0	1	42
8	0	1	1	0	0	1	42
9	0	1	1	1	1	1	42
10	1	1	1	1	0	1	42
11	0	0	1	1	0	1	45
12*	0	1	1	1	0	1	50

Abbreviations: $\Delta\text{NTCP} \geq 5\%$ = percentage of patients in study cohort having a predicted normal-tissue complication probability decrease of at least 5% points; * = most unfavourable scenario.

REFERENCES

1. Fonteyne V, Ost P, Vanpachtenbeke F, et al. Rectal toxicity after intensity modulated radiotherapy for prostate cancer: which rectal dose volume constraints should we use? *Radiother Oncol*. 2014;113(3):398-403.
2. Musunuru HB, Quon H, Davidson M, et al. Dose-escalation of five-fraction SABR in prostate cancer: Toxicity comparison of two prospective trials. *Radiother Oncol*. 2016;118(1):112-7.
3. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis*. 2015;30(10):1293-303.
4. Smeenk RJ, Van Lin ENJT. Application of anorectal sparing devices in prostate radiotherapy. *Radiother Oncol* 2013;106(2):155-6
5. Pinkawa M, Corral NE, Caffaro M. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer *Radiother Oncol* 2011;100(3):436-41.
6. Melchert C, Gez E, Bohlen G et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol* 2013;106(2):210-4.
7. Prada PJ, Fernández J, Martínez AA et al. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys* 2007;69(1):95-102.
8. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82(5):1918-22.
9. Wilder RB, Barne GA, Gilbert RF et al. Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;77(3):824-30.
10. Uhl M, Van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. *Radiother Oncol* 2013;106(2):215-19.
11. Song DY, Herfarth KK, Uhl M et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys* 2013;87(1):81-7.
12. Strom TJ, Wilder RB, Fernandez DC et al. A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy ± intensity modulated radiation therapy. *Radiother Oncol* 2014;111(1):126-31.
13. Mariados N, Sylvester J, Shah D, et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys*. 2015;92(5):971-7.
14. Vanneste BG, Pijls-Johannesma M, Van De Voorde L et al. Spacers in radiotherapy treatment

- of prostate cancer: Is reduction of toxicity cost-effective? *Radiother Oncol* 2015;114(2):276-81.
15. Lambin P, van Stiphout RG, Starmans MH, et al. Predicting outcomes in radiation oncology-multifactorial decision support systems. *Nat Rev Clin Oncol*. 2013;10(1):27-40.
 16. Valdagni R, Rancati T, Fiorino C et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys* 2008;71(4):1065-73.
 17. Valdagni R, Kattan MW, Rancati T et al. Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys* 2012;82(5):1957-66.
 18. Pinkawa M, Piroth MD, Holy R et al. Quality of life after intensity-modulated radiotherapy for prostate cancer with a hydrogel spacer. Matched-pair analysis. *Strahlenther Onkol* 2012;188(10):917-25.
 19. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-74.
 20. Makarov DV , Trock BJ, Humphreys EB et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007;69:1095-101.
 21. Bratengeier K, Meyer J, Flentje M. Pre-segmented 2-Step IMRT with subsequent direct machine parameter optimisation - a planning study. *Radiat Oncol* 2008;3:38.
 22. Pollack A, Zagars G, Starkschall G et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53(5):1097-105.
 23. Lawton C, Michalski J, El-Naqa I et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;74:383-7.
 24. Al-Mamgani A, van Putten WL, Heemsbergen WD, et al. Update of Dutch multicenter dose escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72(4):980-988.
 25. Zelefsky MJ, Levin EJ, Hunt M et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(4):1124-9.
 26. Kuban DA, Tucker SL, Dong L et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(1):67-74.
 27. Ghadjar P, Jackson A, Spratt DE et al. Patterns and predictors of amelioration of genitourinary toxicity after high-dose intensity-modulated radiation therapy for localized prostate cancer: implications for defining postradiotherapy urinary toxicity. *Eur Urol* 2013;64(6):931-8.
 28. Aluwini S, Pos F, Schimmel E et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol* 2015;16(3):274-83.

29. Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. *Radiother Oncol* 2009;93(2):153-67.
30. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys* 2014;90(2):278-88.
31. Pinkawa M. Spacer application for prostate cancer radiation therapy. *Future Oncol* 2014;10(5):851-64.
32. West C, Azria D, Chang-Claude J et al. The REQUITE project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors. *Clin Oncol (R Coll Radiol)* 2014;26(12):739-42.
33. West CM, Barnett GC. Genetics and genomics of radiotherapy toxicity: towards prediction. *Genome Med* 2011;3(8):52.
34. van Gisbergen MW, Voets AM, Starmans MH et al. How do changes in the mtDNA and mitochondrial dysfunction influence cancer and cancer therapy? Challenges, opportunities and models. *Mutat Res Rev Mutat Res*. 2015;764:16-30
35. Fachal L, Gómez-Caamaño A, Barnett GC et al. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. *Nat Genet* 2014;46(8):891-4.
36. Dörr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol* 2001;61:223-31.
37. Hamstra DA, Stenmark MH, Ritter T, et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1246-53.
38. Tucker SL, Dong L, Bosch WR, et al. Late rectal toxicity on RTOG 94-06: analysis using a mixture Lyman model. *Int J Radiat Oncol Biol Phys*. 2010;78(4):1253-60.
39. Wolf F, Gaisberger C, Ziegler I, et al. Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. *Radiother Oncol*. 2015;116(2):221-5.
40. Langendijk JA, Lambin P, De Ruyscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. *Radiother Oncol*. 2013;107(3):267-73.
41. Lambin P, Zindler J, Vanneste BG, et al. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev*. 2016 Jan[Epub ahead of print].
42. Cheng Q, Roelofs E, Ramaekers BL, et al. Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer - Comparison of dose, toxicity and cost-effectiveness. *Radiother Oncol*. 2016;118(2):281-

CHAPTER 6

Anorectal wall dose-surface maps localize the dosimetric benefit of hydrogel rectum spacers in prostate cancer radiotherapy

Submitted to Phys Med Biol

© Copyright Institute of Physics Publishing

Vanneste BGL, Buettner F, Pinkawa M, Lambin P, Hoffmann AL.

ABSTRACT

Background and Purpose

To evaluate spatial differences in dose distributions of the ano-rectal wall (ARW) using dose-surface maps (DSMs) between prostate cancer patients receiving intensity-modulated radiation therapy with and without implantable rectum spacer (IMRT+IRS; IMRT-IRS, respectively), and to correlate this with late gastro-intestinal (GI) toxicities using validated spatial and non-spatial normal-tissue complication probability (NTCP) models.

Materials and Methods

For 26 patients DSMs of the ARW were generated. From the DSMs various shape-based dose measures were calculated at different dose levels: lateral extent, longitudinal extent, and eccentricity. The contiguity of the ARW dose distribution was assessed by the contiguous-DSH (cDSH). Predicted complication rates between IMRT+IRS and IMRT-IRS plans were assessed using a spatial NTCP model and compared against a non-spatial NTCP model.

Results

Lateral extent, longitudinal extent and cDSH were significantly lower in IMRT+IRS than for IMRT-IRS at high-dose levels. Largest significant differences were observed for cDSH at dose levels >50Gy, followed by lateral extent at doses >57Gy, and longitudinal extent. Significant decreases ($p = 0.01$) in median rectal and anal NTCPs were predicted when using an IRS.

Conclusions

Dose surface maps are generated for prostate radiotherapy using an IRS. The IRS reduces the lateral and longitudinal extent of high-dose areas (>50 Gy) in anterior and superior-inferior directions. The spatial NTCP model predicts a significant decrease in Gr 2 late rectal bleeding and subjective sphincter control. Differences in predicted GI toxicity rates between spatial and non-spatial NTCP models needs further investigation. In future, these spatial dose distribution information with the predicted toxicities can be explored to create decision support models that may select patients for IRS implantation, or not.

INTRODUCTION

Gastro-intestinal (GI) toxicity is a common side-effect of external beam radiation therapy (EBRT) for prostate cancer and has a negative impact on the quality of life even many years after the EBRT [1-3]. Various devices have been introduced to spare ano-rectal structures [4]. Endo-rectal balloons are being used to increase the distance from the dorsal and lateral rectal wall to the prostate, whereas implantable rectum spacers (IRS) separate the anterior rectal wall from the prostate by injection of an absorbable hydrogel [5], a hyaluronic acid [6], a saline-filled balloon [7], or a collagen implant [8]. Several studies have confirmed that an IRS decreases the rectal dose and consequently the acute rectal toxicity rate [9-14]. Furthermore, it has been established that an IRS decreases the late rectal toxicity rates [15, 16], leading to an increased cost-effectiveness [17]. Until now, the dosimetric impact of an IRS has been assessed quantitatively by dose-volume histograms (DVHs) obtained from the planned 3D dose distributions. From these studies, consensus exists that an IRS significantly reduces the dose exposure to the ano-rectal wall (ARW). However, spatial dosimetric information of the 3D dose distribution is lost by analysing DVHs or dose-surface histograms (DSHs), and therefore hampers to investigate the correlation between the shape and location of the ARW dose distribution with clinical outcome measures. Extraction of shape-based dose measures such as spatially correlated DSHs or contiguous-dose surface histograms (cDSHs) from dose-surface maps (DSMs) has been suggested as a valuable tool for advanced dose-response studies and to support a better selection of patients likely to benefit from the IRS [18-22]. Buettner et al. [23] quantified correlations between measures describing the shape and location of the dose distribution and different outcomes. Furthermore, inclusion of such spatio-dosimetric features into normal-tissue complication probability (NTCP) models has been shown to increase the predictive power over models based on DVH parameters solely [24,25]. Hence better insights into the relationship between the ano-rectal dose distribution and (late) GI toxicity in EBRT of prostate cancer can be obtained.

The primary aim of the current study was to test the hypothesis that shape-based measures of the ARW surface dose distribution reveal a significant change in size, shape and location of the local surface dose distribution in patients undergoing intensity modulated radiation therapy with an IRS (IMRT+IRS) and without IRS (IMRT-IRS). To this end, spatial features from ARW DSMs and cDSHs were compared between these two groups. Furthermore, shape-based DSM parameters were used in combination with previously published spatial NTCP models to test the hypothesis that predicted complication rates for Grade 2 GI toxicity decrease for IMRT+IRS relative to IMRT-IRS. Finally, these results were compared with Grade 2 GI toxicity decrease derived from validated NTCP models based on DVH data solely.

MATERIALS AND METHODS

Patient selection and rectum spacer implantation

After approval by the local ethics committee, 26 consecutive patients with localized prostate cancer treated between January 2011 and June 2011 were included in this study. All patients had signed an informed consent. The patient and tumour characteristics are summarized in Table 1. Prognostic risk-group stratification of the patients was defined according to the D’Amico classification [26].

An IRS gel (SpaceOAR™ System, Augmenix Inc., Waltham, MA) was injected in these patients between the prostate and the rectum prior to EBRT. The injection method has been described previously [5]. The amount of injected hydrogel was limited to 10 cm³ in all patients (only the first patient received 15 cm³). It maintains space for approximately 3 months and is compression resistant. The hydrogel is cleared in approximately 6 months via renal filtration [5].

TABLE 1: Patient (N = 26) and tumour characteristics.

Age (years; median [range])	73 [56–82]
Prognostic risk group*: (no. of patients)	
1- Low-risk	8 (31%)
2- Intermediate-risk	11 (42%)
3- High-risk	7 (27%)
Prostate volume: (cm ³ ; median [range])	
PTV	50 [25–130]

Abbreviations: PTV = planning target volume.

* Low-risk: no risk factors: PSA <10 ng/ml; Gleason score <7; cT-stage <2b; Intermediate-risk: one risk factor: PSA 10–20 ng/ml or Gleason score =7 or cT-stage = 2b/c; High-risk: two risk factors or PSA >20 ng/ml or Gleason score >7 or cT-stage >2b/c.

Target volume definition and organ at risk delineation

Each patient underwent two computed tomography (CT) scans in supine position with a slice thickness of 5 mm; one prior to IRS implantation and one 3–5 days after IRS implantation. The resulting 52 CT scans were imported into the Pinnacle³ treatment planning system (Version 8.0m, Philips Medical Systems, Fitchburg, USA) to design dose distributions for IMRT-IRS and IMRT+IRS (Figure 1). Additionally, a T₂-weighted transversal magnetic resonance imaging (MRI) scan was acquired after implantation for image registration with the post-implant CT-scan to enable soft tissue delineation of the prostate, the adjacent rectal wall and the IRS. The CT images were rigidly registered with the T₂-weighted MRI scans by auto matching based on soft tissue landmarks A knee and ankle rest was used to create a reproducible setup of the leg position both for the CT and the MRI scans. Patients were asked to have a fully bladder for both the planning CT scan and MRI scan. Treatment plans for IMRT-IRS and IMRT+IRS were planned on the respective CT scans to allow for dosimetric comparison.

Depending on the prognostic risk group the clinical target volume (CTV) was defined as the prostate only (CTV1), the prostate with the base of the seminal vesicles (CTV2) corresponding to the proximal 2-4 seminal vesicle slices, or the prostate with the whole seminal vesicles (CTV3) [27].

For the planning target volume (PTV), 8 mm lateral-anterior, 5 mm superior-inferior and 4 mm posterior margins were added to the CTV, as described in an earlier study [5]. On relevant CT image slices, the bladder, femoral heads, rectum and anal-canal were delineated. The ano-rectum structure consists of the rectum and the anal-canal. The rectum was delineated from the top of the anal-canal up to the recto-sigmoid flexure. The anal-canal was considered as the distal 3 cm of the ano-rectum [28]. Only when the last 3 cm was obviously in the lumen of the rectum, the cranial boundary was adapted as the section below the lowest section with a visible rectum lumen [29]. In order to facilitate intra-patient comparison, the contours in the treatment plans for IMRT+IRS and IMRT-IRS were delineated over the same length in superior-inferior direction. Two independent observers performed the delineations (MP and BV).

FIGURE 1: Color-wash dose distribution in an axial plane before (a) and after (b) IRS gel injection in the same patient, with prostate (yellow) and PTV (red). Without IRS, the high-dose region >75% (yellow) overlaps with the anterior part of the rectum (brown), while with IRS in situ the high-dose region spans the IRS (black), and not the rectum. The 40% isodose contour (purple) overlaps the entire rectum in (a), whereas it overlaps the rectum partially in (b).

Abbreviations: PTV = planning target volume; IRS = implantable rectum spacer.

Treatment planning technique

All IMRT-IRS and IMRT+IRS plans were designed by inverse treatment planning using a direct machine parameter optimization (DMPO) algorithm for step-and-shoot IMRT with 5 coplanar 15 MV photon beams (gantry angles: 45°, 105°, 180°, 255°, 315°) [30]. The treatment planning technique has been described previously [5]. The prescribed dose to the PTV was 78 Gy in 2 Gy fractions [30], requiring at least 99% of the volume to receive 95% of the prescribed dose. The same dosimetric constraints were used for IMRT-IRS and IMRT+IRS plans, based on the relevant maximum tolerance dose (indicated as $D_{\max}$) and the maximum allowed relative volume receiving a certain dose level of xx Gy (indicated as $V_{xx\text{Gy}}$), as published by the Radiation Therapy Oncology Group (RTOG) for rectum and bladder [32]: $V_{40\text{Gy}}(\text{rectum}) \leq 60\%$, $V_{75\text{Gy}}(\text{rectum}) \leq 5\%$, $D_{\max}(\text{rectum}) \leq 76$ Gy, $V_{55\text{Gy}}(\text{bladder}) \leq 50\%$, $V_{70\text{Gy}}(\text{bladder}) \leq 30\%$, $V_{50\text{Gy}}(\text{femoral heads}) \leq 5\%$. Since the $V_{40\text{Gy}}$ and $V_{75\text{Gy}}$ are well-known DVH parameters that are predictive for late rectal toxicity these measures were used to assess the plan quality [28,33,34].

Spatial analysis of the ano-rectal dose distribution

For each individual patient, DSMs for both the anal-canal wall and the rectum wall were generated from the 3D dose distributions of the IMRT-IRS and IMRT+IRS treatment plans by virtual unfolding of these structures, as previously described by Buettner and colleagues [23]. A DSM represents the 2D maps dose distribution over the surface of the ARW (Figure 2). In the current work, DSMs were produced by first extracting the dose to the surface of the ARW contour at 100 equiangular points on every CT slice of the surface of the ARW contour and subsequent virtually cutting of this contour at its most posterior location. This was implemented using an in-house developed MATLAB software tool (The MathWorks, Natick, MA, USA).

FIGURE 2: Dose-surface maps of rectal wall (a,b) and anal wall (c,d) (in Gy) without IRS (a,c) and with IRS (b,d) in the same patient. The vertical axis corresponds to the superior-inferior direction, whereas the horizontal axis represents circumferential the direction: P, R, A, L.

Abbreviations: IRS = implantable rectum spacer, P = posterior (P), right (R), anterior (A), left (L).

Shape-based dose measures were extracted from the DSMs following Buettner et al [23]. The algorithm first generated binary DSMs by thresholding the primary DSMs at 38 dose levels ranging from 5–79 Gy into dose clusters. At each dose level an ellipse was fitted to the largest dose cluster. Lateral (LAT) extent in posterior-anterior-posterior direction and longitudinal (LONG) extent in superior-inferior direction were quantified by projecting the major and minor axes of this ellipse to the main axes of the DSMs. The non-circularity of the dose clusters was described by the eccentricity (ECC) of the ellipse. Furthermore, the algorithm assessed the contiguity of the single largest ARW area of the cDSH, by determining the single largest contiguous area of the DSM, as function of the dose threshold at a given dose level of xx Gy ($cDSH_{xxGy}$).

Differences in LAT extent, LONG extent, ECC and $cDSH_{xxGy}$ between DSMs and cDSHs from IMRT+IRS and IMRT-IRS plans were compared statistically with a one-sided paired Wilcoxon signed rank test. The statistical analyses were performed using the Statistics and Machine

Learning Toolbox from MATLAB software (Version 10.0, MathWorks, Inc., Natick, USA). LAT extent of 55 Gy, 67 Gy, and 71 Gy were compared because previous studies showed these parameters to be highly predictive for late rectal bleeding [24,25]. The significance levels were established using a permutation test accounting for multiple testing, as described in previous work [21,23-25]. Box plots were used to visualise the summary statistics as well as the individual and group differences. Each pair of dots linked by a dotted line represents a single patient from the study cohort, allowing for a two-level comparison of the differences in dosimetric measure. A p -value < 0.05 was considered statistically significant. Shown p values were corrected for multiple testing.

In order to correct for multiple testing, a free step-down resampling algorithm was applied, taking advantage of the dependence structure between the cut-points [35]. The same framework was used in previously analysis, and further details on the method can be found in previously published work [23].

NTCP prediction

Previously published models to predict the NTCP based on shape-based features of the 3D dose distribution to the ARW were shown to have a higher predictive power for late GI toxicity than NTCP models based on DVHs [24,25]. From these studies it was found that the LAT extent at 53 Gy and 55 Gy was one of the strongest predictor for subjective sphincter control and Grade 2 (Gr 2) late rectal bleeding, respectively [24,25]. Furthermore LAT extent of 67 Gy and 71 Gy were compared because previous studies showed these parameters are highly predictive for late rectal bleeding [24,25]. In the present analysis, we exploited these spatial NTCP models to assess differences in predicted complication rates between IMRT+IRS and IMRT-IRS plans. These differences were compared against predictions based on the Lyman-Kutcher-Burman (LKB) NTCP model with parameters by Rancati et al. ($n = 0.24$, $m = 0.14$, $TD_{50} = 75.7$ Gy) taking solely the DVH data into account [40,41].

Observed Toxicity Assessment

The complications were recorded in terms of the Expanded Prostate Cancer Index Composite (EPIC) Questionnaire to analyze quality-of-life (QoL) changes. The questionnaire consists of 50 items concerning urinary, bowel, sexual, and hormonal domains. The multi-item scale was transformed linearly to a 0 to 100 scale, with high scores representing better health-related QoL. They were scored at the end of EBRT, 2 months, 2 and – if possible – 6 years after treatment completion. In accordance with the literature, mean QoL changes below 5 points can be defined as clinically not significant, 5 to 10 as small changes, 10 to 20 as moderate changes, and > 20 as large changes.

RESULTS

Dosimetric plan evaluation with and without IRS

The median implanted IRS volume determined on the post-implant CT scan was 10.6 cc [range: 8.3–20.4 cm³]. The median ano-rectum $V_{40\text{Gy}}$ and $V_{75\text{Gy}}$ significantly reduced between IMRT-IRS and IMRT+IRS from 53.4% to 47.6% ($p = 0.036$), and from 3.9% to 0.4% ($p < 0.001$), respectively.

DSM analysis

For the rectal wall, LAT extent, LONG extent as well as cDSH areas were significantly lower in IMRT+IRS than in IMRT-IRS at high-dose levels (Figure 3a). The largest significant differences were observed for cDSH areas at dose levels >50 Gy, followed by LAT and LONG extent at doses >57 Gy. For these three features, no significant differences were observed for dose levels <50 Gy. For LONG extent no significant differences were found for some high dose levels (Figure 3a). For ECC no significant differences were found over the whole dose range (Figure 3a). For the anal wall, LAT extent, ECC as well as cDSH areas were significantly lower in IMRT+IRS than in IMRT-IRS at high-dose levels (Figure 3b). The largest significant differences were observed for LAT extent at doses >60 Gy. The box plots shown in Figure 4 illustrate the summary statistics and density traces for LAT extent of 55 Gy, 67 Gy, and 71 Gy of the IMRT+IRS and IMRT-IRS plans. All box plots revealed a wide spectrum of values without apparent sub-group differentiation, but still a significantly lower LAT extent of 55 Gy, 67 Gy, and 71 Gy for IMRT+IRS than IMRT-IRS,

respectively $p = 0.046$, $p = 0.002$, $p < 0.001$.

FIGURE 3: Significance level of differences in geometrical measures between IMRT+IRS and IMRT-IRS plans as function of the dose threshold levels for the rectum (a) and the anal (b) wall. Statistically significant differences are shown in red, black points are not significant. The horizontal dotted line represents the significance level of 0.05.

Abbreviations: cDSH = contiguous-dose-surface histograms; Ecc = Eccentricity; Lat = Lateral (posterior-anterior-posterior)

extent; Long = longitudinal (superior-inferior) extents.

FIGURE 4: Box plots comparing the relative lateral extent for dose levels of 55, 67 and 71 Gy for IMRT+IRS versus IMRT-IRS. The lines denote to paired observations between the same patient +/- IRS.

NTCP prediction

The box plots shown in Figure 5 illustrate the predicted spatial NTCP rates for Gr 2 anal and Gr 2 rectal toxicity of IMRT-IRS and IMRT+IRS. A significant decrease in median rectal NTCP and in median anal NTCP is observed from 12% to 8.5% ($p = 0.01$) and from 13% to 11% ($p = 0.01$), respectively, when using an IRS. The median rectal NTCP for Gr 2 late rectal bleeding using the LKB-parameters were 2.9% (range: 0.3–10.1) versus 0.7% (range: 0–8.8) for IMRT-IRS and

IMRT+IRS, respectively.

FIGURE 5: Box plot comparing the predicted Grade 2 or more rectal toxicity rates (a) and Grade 2 or more anal toxicity rates (b) for IMRT+IRS versus IMRT-IRS using spatial NTCP models.

Observed Toxicities

At the last day of EBRT uncontrolled leakage of feces, and more than once bloody stools during the last 4 weeks before the consult are observed in 12% and 19%, respectively. Two months after EBRT, these complaints are reported in 9% and 4%, respectively. Overall, after 2 and 6 years, no such problems are reported. The median scores of the bowel domain functions were 80, 96, 98, 96 at the last day of EBRT, 2 months, 2 years, and 6 years after EBRT, respectively (minimal score

changes of 2 points for late toxicities).

DISCUSSION

In this study we showed that an IRS significantly changes the size, shape and location of the local surface dose distribution over ano-rectal structures in prostate cancer patients undergoing intensity modulated radiation therapy. We identified that an IRS particularly reduces the LAT and LONG extent of high-dose areas (>50 Gy) in anterior and superior-inferior directions. A correlation of these shape-based dose measures with predicted toxicity rates based on previously published NTCP models, showed that the IRS is expected to decrease the toxicity rates for Gr 2 late rectal bleeding and subjective sphincter control.

Several investigators demonstrated that minimising the volume of the ano-rectum receiving more than 70 Gy below 20% to be predictive of a very low incidence of Gr 2 late rectal bleeding [33,40]. Therefore, it is useful to prevent rectal volumes from being exposed to high radiation doses. Implantation of an IRS increases the distance between the prostate and the anterior rectal wall, and hence reduces the dose delivered to the ano-rectum [42,43]. The current study is the first to systematically investigate shape-based differences in the ano-rectal wall dose distribution between prostate IMRT plans with and without IRS. Furthermore these spatial features were used to predict the expected NTCP reduction between IMRT+IRS and IMRT-IRS, and these were compared with the expected NTCP reduction based on DVH data solely.

A recently published prospectively randomized trial demonstrated the safety and effectiveness of a hydrogel IRS implantation in 149 consecutive patients [14]. This study showed that patients experienced 10-point declines in bowel quality of life at 15 months 11.6% and 21.4% of spacer and control patients, respectively. In contrast to this, Habl et al. reported the occurrence of 2 fistulas out of 91 patients [12]. However, there is a growing body of literature on prospective studies that supports the safety of IRSs in combination with EBRT, when practiced in experienced hands [13].

Previous studies investigated correlations between spatial 3D dose distributions to sub-regions of the ARW and (acute and late) GI toxicity [19-22]. However, so far no comparative study has been performed in patients with an implanted IRS. Heemsbergen et al. described clinical evidence for a dose-effect relationship for bleeding and mucus loss within the dose to the upper 70-80% part of the ARW [19]. For soiling and faecal incontinence, they found a strong association within the dose to the inferior 40-50% to the ARW. As demonstrated in this study, an IRS reduces the dose-volume in the anterior upper and anterior inferior region of the ARW, and reduces the predicted late Gr 2 GI toxicity rates. Furthermore, Buettner et al. reported the strongest correlations between rectal bleeding and LAT extent at doses between 50 Gy and 60 Gy [25]. This confirms the importance of an IRS to reduce the LAT extent in high-dose areas. In addition, Mumbodh et al. obtained a relation between late rectal toxicity and irradiation of the upper part of the rectum [20]. An IRS decreases anterior extents in superior-inferior directions. Furthermore, Wortel et al. recently demonstrated significant relationships between acute rectal toxicity and the

cranial-posterior rectal site [22], which, as we have shown in the current analysis, is decreased by an IRS.

DSM analysis is a well-known tool for advanced dose-response studies in prostate radiotherapy, which has successfully been applied to analyse radiation-induced rectal toxicity [36-39]. Different algorithms exist to generate DSMs from the 3D dose distribution of the ARW. One of the restrictions of the used model is the fact that the DSM is constructed by cutting the rectum at the most posterior location point. However this most posterior rectum point could by chance be a long way to the left or the right of the centre of the contour, jumping between slices. This could give rise to discontinuities in the DSM. This could be corrected by using the cutting point as the point on the contour surface directly posterior to the centre of mass the centre of mass [45]. DSMs in general have some well-known limitations [23]. First, to unfold the ARW, different algorithms exist [37,38], so the same dose distribution can result in different DSMs. We used a slice-wise unfolding algorithm which has already been successfully used to examine the shape of the dose-distribution to the ARW [21,23,25]. Second, the DSMs were constructed on a single planning CT scan before treatment. This can lead to mismatch due to large inter-individual variations [45]. Motion of the ARW during treatment is a source of uncertainty that was not taken into account in the current study. However, we observed that in some patients a worsening of the rectal dosimetry occurred for IMRT+IRS, with consequently a worse NTCP prediction. It is well known that the rectum changes position, volume, and shape between treatment fractions. This is mainly caused by changes in rectal filling due to inclusion of gas bubbles and stool [48,49]. In this case the distance between the prostate and ano-rectum is still increased due to IRS implantation, but the distance between the more cranial part of the rectum (above the IRS) decreased incrementally, as a consequence of which the latter part received a higher dose than the former part. Fenwick et al. concluded that setup-errors and ARW movement have only a slight impact on fits of NTCP models for a whole treatment period [46]. Furthermore, Thor and colleagues revealed a strong association with rectal morbidity at high doses (>55 Gy), for the planned and the simulated dose distributions including in particular random rectal motion [47]. Next, concerning the treatment planning technique: it is possible to reduce intermediate dose levels (30–50 Gy) in the ARW-region by an arc-therapy with an avoidance-region near the rectum or by using strictly lateral beams to diminish the LAT and LONG extent, with consequently a decrease of Gr 2 late rectal bleeding [5]. Finally, the models used for the spatial and non-spatial NTCP differ: a fair comparison between them is hindered by the fact that their were not derived for the same patient cohort. Nevertheless, both models have been published earlier and are used for NTCP prediction in literature. Currently, there is not enough clinical outcome data to compare the predicted and observed toxicity rates and to calibrate the models for patients who received an IRS. It is a topic of further research to find out whether the NTCP parameters derived from a patient cohort without IRS can be used for a cohort with IRS.

By using spatial NTCP models (Buettner) that were previously shown to have a higher predictive power than NTCP models based on DVH data (LKB model) [24], the current study predicts a statistically significant gain in NTCP when using an IRS in prostate cancer patients receiving IMRT. Comparing the NTCP predictions based on shape-based dose measures against those based on DVH measures a less pronounced decrease in toxicity rate was observed for the latter. This may be due to the fact that the LKB-model is more sensitive for high-dose than for intermediate-dose levels, and the relative volume receiving a high dose is smaller for the volume of the solid ano-rectum than for the 2D shape-based dose measures of the ARW (Buettner). This could explain the difference between the both models. Follow-up data are needed to compare the predicted and observed toxicity rates to calibrate the NTCP models, which is beyond the scope of the current study.

Recently, decision rules were generated to support the clinician in selecting patients who are expected to benefit most from IRS implantation prior to IMRT planning [50]. This can be helpful for selecting patients for an IRS. Further systematic evaluations of dose, clinical and even genetic parameters are needed to evaluate which features are predictive to improve the benefit of an IRS, such that future treatments can be individually tailored to patients who will benefit most from IRS implantation [34,50,51,52]. Spatial dose distributions in combination with the predicted GI toxicities can add extra information to be incorporated in more accurate decision support systems to further individualise prostate cancer radiotherapy treatment. Such investigations are mandatory to define the definitive role of an IRS in prostate cancer radiotherapy. Furthermore, patient decision aids can be developed with integration of the choice of an IRS to fulfil the complete personalized and participative medicine [52,53,54].

In conclusion, we demonstrated statistically significant shape-based differences in ARW DSMs between IMRT+IRS and IMRT-IRS. An IRS reduces the LAT and LONG extent of high-dose areas (>50 Gy) in anterior and superior-inferior directions in 78 Gy IMRT plans. An IRS decreases the predicted toxicity rates for Gr 2 late rectal bleeding and subjective sphincter control. The extra spatial information can be added in decision support systems to optimise the decision to implant an IRS or not. The predictive power of spatial and non-spatial NTCP models has yet to be completely established for patients receiving IMRT with an IRS.

REFERENCES

1. Glass AS, Cowan JE, Fuldeore MJ, Cooperberg MR, Carroll PR, Kenfield SA, Greene KL. Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era. *Urology*. 2013;82(1):60-5.
2. Krol R, Smeenk RJ, van Lin EN, Hopman WP. Impact of late anorectal dysfunction on quality of life after pelvic radiotherapy. *Int J Colorectal Dis*. 2013;28(4):519-26.
3. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis*. 2015;30(10):1293-303.
4. Smeenk RJ, Van Lin ENJT. Application of anorectal sparing devices in prostate radiotherapy. *Radiother Oncol* 2013;106(2):155-6.
5. Pinkawa M, Corral NE, Caffaro M. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer *Radiother Oncol* 2011;100(3):436-41.
6. Prada PJ, Fernández J, Martínez AA, de la Rúa A, Gonzalez JM, Fernandez JM, Juan G. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys* 2007;69(1):95-102.
7. Melchert C, et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol* 2013;106(2):210-4.
8. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82(5):1918-22.
9. Vanneste BG, van De Beek K, Lutgens L, Lambin P. Implantation of a biodegradable rectum balloon implant: tips, Tricks and Pitfalls. *Int Braz J Urol*. 2017 Mar 24;43.
10. Song DY, et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys* 2013;87(1):81-7.
11. Strom TJ, et al. A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy $\pm$ intensity modulated radiation therapy. *Radiother Oncol* 2014;111(1):126-31.
12. Habl G, et al. Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective Randomized Phase II Study-The IPI Trial. *Int J Radiat Oncol Biol Phys*. 2016;95(1):435-43.
13. Fagundes M, Han-Chih Chang J, Michalski J, Soffen E, Davis B, Pisansky T. In Regard to Habl et al. *Int J Radiat Oncol Biol Phys*. 2016;96(1):241-2.
14. Mariados N, et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys*. 2015;92(5):971-7.
15. Hamstra DA, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. *Int J Radiat Oncol Biol Phys*. 2017;97(5):976-985.

16. Pinkawa M, Berneking V, König L, Frank D, Bretgeld M, Eble MJ. Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. *Strahlenther Onkol* 2017; 193(1):22-28.
17. Vanneste BG, Pijls-Johannesma M, Van De Voorde L, van Lin EN, van de Beek K, van Loon J, Ramaekers BL, Lambin P. Spacers in radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective? *Radiother Oncol* 2015;114(2):276-81.
18. Hoogeman MS, van Herk M, de Bois J, Muller-Timmermans P, Koper PC, Lebesque JV. Quantification of local rectal wall displacements by virtual rectum unfolding. *Radiother Oncol*. 2004;70(1):21-30.
19. Heemsbergen WD, Hoogeman MS, Hart GA, Lebesque JV, Koper PC. Gastrointestinal toxicity and its relation to dose distributions in the anorectal region of prostate cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;61(4):1011-8.
20. Munbodh R, Jackson A, Bauer J, Schmidtlein CR, Zelefsky MJ. Dosimetric and anatomic indicators of late rectal toxicity after high-dose intensity modulated radiation therapy for prostate cancer. *Med Phys* 2008;35:2137–50.
21. Buettner F, Gulliford SL, Webb S, Partridge M. Using dose-surface maps to predict radiation-induced rectal bleeding: a neural network approach. *Phys Med Biol*. 2009;54(17):5139-53.
22. Wortel RC, Witte MG, van der Heide UA, Pos FJ, Lebesque JV, van Herk M, Incrocci L, Heemsbergen WD. Dose-surface maps identifying local dose-effects for acute gastrointestinal toxicity after radiotherapy for prostate cancer. *Radiother Oncol*. 2015;117(3):515-20.
23. Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M. Assessing correlations between the spatial distribution of the dose to the rectal wall and late rectal toxicity after prostate radiotherapy: an analysis of data from the MRC RT01 trial (ISRCTN 47772397). *Phys Med Biol*. 2009;54(21):6535-48.
24. Buettner F, Gulliford SL, Webb S, Partridge M. Modeling late rectal toxicities based on a parameterized representation of the 3D dose distribution. *Phys Med Biol*. 2011;56(7):2103-18.
25. Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M. The dose-response of the anal sphincter region--an analysis of data from the MRC RT01 trial. *Radiother Oncol*. 2012;103(3):347-52.
26. D'Amico AV, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-74.
27. Makarov DV, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007;69:1095-101.
28. Peeters ST, Lebesque JV, Heemsbergen WD, van Putten WL, Slot A, Dielwart MF, Koper PC. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1151-61.
29. Vordermark D, Schwab M, Ness-Dourdoumas R, Sailer M, Flentje M, Koelbl O. Association of anorectal dose-volume histograms and impaired fecal continence after 3D conformal radiotherapy for carcinoma of the prostate. *Radiother Oncol*. 2003;69(2):209-14.
30. Bratengeier K, Meyer J, Flentje M. Pre-segmented 2-Step IMRT with subsequent direct machine

- parameter optimisation - a planning study. *Radiat Oncol* 2008;3:38.
31. Pollack A, Zagars G, Starkschall G, Antolak JA, Lee JJ, Huang E, von Eschenbach AC, Kuban DA, Rosen I.. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53(5):1097-105.
 32. Lawton C, Michalski J, El-Naqa I et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;74:383-7.
 33. Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. *Radiother Oncol* 2009;93(2):153-67.
 34. Valdagni R, et al. Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys* 2012;82(5):1957-66.
 35. P.H. Westfall and S. S. Young, *Resampling-Based Multiple Testing: Examples and Methods for p-Value Adjustment* Wiley, New York, 1993
 36. Meijer GJ, van den Brink M, Hoogeman MS, Meinders J, Lebesque JV. Dose-wall histograms and normalized dose-surface histograms for the rectum: a new method to analyze the dose distribution over the rectum in conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;45:1073-80.
 37. Sanchez-Nieto B, Fenwick JF, Nahum AE, Dearnaley DP. Biological dose surface maps: evaluation of 3D dose data for tubular organs. *Radiother Oncol* 2001;61 (Suppl 1): S52.
 38. Tucker SL, Zhang M, Dong L, Mohan R, Kuban D, Thames HD. Cluster model analysis of late rectal bleeding after IMRT of prostate cancer: a case-control study. *Int J Radiat Oncol Biol Phys* 2006;64:1255-64.
 39. van Lin ENJT, Kristinsson J, Philippens MEP, Philippens ME, de Jong DJ, van der Vicht LP, Kaanders JH, Leer JW, Visser AG. Reduced late rectal mucosal changes after prostate three-dimensional conformal radiotherapy with endorectal balloon as observed in repeated endoscopy. *Int J Radiat Oncol Biol Phys* 2007;67:799-811.
 40. Rancati T, et al. Fitting late rectal bleeding data using different NTCP models: Results from an Italian multi-centric study (AIROPROS0101). *Radiother Oncol* 2004;73:21-32.
 41. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S123-9.
 42. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys* 2014;90(2):278-88.
 43. Pinkawa M. Spacer application for prostate cancer radiation therapy. *Future Oncol* 2014;10(5):851-64.
 44. Shelley LEA, Scaife JE, Romanchikova M, Harrison K, Forman JR, Bates AM, Noble DJ, Jena R, Parker MA, Sutcliffe MPF, Thomas SJ, Burnet NG. Delivered dose can be a better predictor of rectal toxicity than planned dose in prostate radiotherapy. *Radiother Oncol*. 2017 Jun;123(3):466-471.
 45. Dréan G, Acosta O, Ospina JD, Simon A, Haigron P, Lafond C, de Crevoisier R. Identification of a rectal subregion highly predictive of rectal bleeding in prostate cancer IMRT. *Radiother Oncol*.

- 2016;119(3):388-97.
46. Fenwick JD. Impact of dose-distribution uncertainties on rectal ntcp modeling. II: Uncertainty implications. *Med Phys*. 2001;28(4):570-81.
 47. Thor M, Apte A, Deasy JO, Karlsdóttir Å, Moiseenko V, Liu M, Muren LP. Dose/volume-response relations for rectal morbidity using planned and simulated motion-inclusive dose distributions. *Radiother Oncol*. 2013;109(3):388-93.
 48. Huang TC, Chou KT, Yang SN, Chang CK, Liang JA, Zhang G. Fractionated changes in prostate cancer radiotherapy using cone-beam computed tomography. *Med Dosim*. 2015;40(3):222–5.
 49. Chen Z, Yang Z, Wang J, Hu W. Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. *Radiat Oncol*. 2016 Aug 2;11:103.
 50. Vanneste BG, Hoffmann AL, van Lin EN, Van De Voorde L, Pinkawa M, Lambin P. Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. *Radiother Oncol*. 2016: S0167-8140(16)34290-6.
 51. West C, et al. The REQUITE project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors. *Clin Oncol (R Coll Radiol)* 2014;26(12):739-42.
 52. van Wijk Y, Vanneste BGL, Walsh S, van der Meer S, Ramaekers B, van Elmpt W, Pinkawa M, Lambin P. Development of a virtual spacer to support the decision for the placement of an implantable rectum spacer for prostate cancer radiotherapy: Comparison of dose, toxicity and cost-effectiveness. *Radiother Oncol*. 2017: S0167-8140(17)32485-4.
 53. Stacey D, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2014 Jan 28;(1):CD001431.
 54. Lambin P, et al. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev*. 2016 Jan 14. Epub ahead of print.

PART II Clinical Data

Trigonometric

Path Image 1

Path Image 2

CHAPTER 7

Implantation of a biodegradable rectal balloon implant: Tips, tricks and pitfalls

ABSTRACT

Introduction

A rectum balloon implant (RBI) is a new device to spare rectal structures during prostate cancer radiotherapy. The theoretical advantages of a RBI are to reduce the high radiation dose to the anterior rectum wall, the possibility of a post-implant correction, and their predetermined shape with consequent predictable position.

Objective

To describe, step-by-step, our mini-invasive technique for hands-free transperineal implantation of a RBI before start of radiotherapy treatment.

Materials and Methods

We provide step-by-step instructions for optimization of the transperineal implantation procedure performed by urologists and/or radiation oncologists experienced with prostate brachytherapy and the use of the real-time bi-plane transrectal ultrasonography (TRUS) probe. A RBI was performed in 15 patients with localised prostate cancer. Perioperative side-effects were reported.

Results

We provide 'tips and tricks' for optimizing the procedure and proper positioning of the RBI. Please watch the animation, see video in <https://vimeo.com/205852376/789df4fae4>.

The side-effects included mild discomfort to slight pain at the perineal region in 8 out of 15 patients. Seven patients (47%) had no complaints at all. Two patients developed redness of the skin, where prompt antibiotic regimen was started with no further sequelae. One patient revealed a temporary urine retention, which resolved in a few hours following conservative treatment. Further no perioperative complications occurred.

Conclusion

This paper describes in detail the implantation procedure for an RBI. It is a feasible, safe and very well-tolerated procedure

INTRODUCTION

Prostate cancer radiotherapy can develop limiting anorectal toxicity [1-3]. It is therefore important to implement techniques to spare rectal structures [3].

Several devices have been established to spare anorectal structures by excluding them from high radiation dose exposure. Endo-rectal balloons are used to increase the distance from the dorsal rectal wall to the prostate [3], and implanted rectum spacers (IRS) are designed to separate the anterior rectal wall from the prostate by injecting a biodegradable material. Four types of IRS have been developed: hyaluronic acid [4], absorbable hydrogel [5], collagen implants [6], or a saline-filled balloon [7]. In the past decade, research groups have investigated the use of a prostate IRS (Figure 1), with hyaluronic acid and poly-ethylene-glycol (PEG)-based hydrogel [4, 5, 8-12]. All reported a decrease of the rectal dose (Figure 2).

This paper describes in detail the implantation procedure for a (saline-filled) rectum balloon implant (RBI) (Figure 3). It provides step-by-step instructions, identifying the potential hazards and 'tips and tricks' for optimising the procedure as well as proper positioning of the RBI. Furthermore, we report the perioperative complications of the first 15 patients implanted in our institute

MATERIALS AND METHODS

After approval by the local ethics committee and institutional review board, 15 consecutive patients with localised prostate cancer (cT1-2 N0) treated between June 2015 and March 2016 were included in this feasibility study. Gleason scores > 7 and high PSA-values were not exclusion criteria. Extended extra-prostatic disease extension (T3a/4) was an exclusion criterion, as were distant metastatic disease and previous pelvic EBRT. All patients signed an informed consent document. The RBI (BioProtect Ltd, Israel) implantation was demonstrated in a video review to illustrate a clinically useful stepby-step technique see video in <https://vimeo.com/205852376/789df4fae4>. All patients were assessed immediately post-injection, 4 to 7 days after implantation. The possible complications were recorded in terms of Common Terminology Criteria for Adverse Events (Version 4.0) [13]. Pain was scored 1 hour, 8 hours, and 24 hours after implantation using the visual analogue scale (VAS), ranging from 0 to 10.

FIGURE 1: A schematic illustration (www.bioprotect.co.il) (a) and an MRI image (Balanced fast field Echo-sequence) (b) of a biodegradable rectum balloon implant (RBI) between the anterior rectum wall (R) and the prostate (P), creating space between the two organs.

FIGURE 2: Isodose distribution in an axial CT plane before (a) and after rectum balloon implant (RBI) implantation (b) in the same patient. The image on the left shows the high-dose region >80% (green) overlapping the entire part of the rectum (brown), whereas with the RBI in situ the high-dose region is not in the rectum. The 65% isodose contour (blue) overlaps the entire rectum in (a), whereas there is no overlap in the rectum in (b).

FIGURE 3: The RBI kit, with the needle with the dilatator (blue) and sheath (white) above, and the rectum balloon implant (rolled up) deployer (RBID) below. note the line on the RBID: when the RBID is inserted through the sheath up to this mark it means the tip of the deployer is at the end of the sheath. Retract the sheath while holding the RBID in place.

RESULTS

Step-by-step description of application technique

Precautions - medications

Anticoagulation should be stopped before this minimally invasive procedure because bleeding can disturb transrectal ultrasound (TRUS) vision. The timing of therapy stop and re-initiation depends on the specific drug used. In contrast to transrectal biopsies, the transperineal RBI implantation yields a lower infection risk after careful skin preparation. Nevertheless, an antibiotic prophylaxis is recommended to reduce the risk of infection by the implant [12]. A rectal enema will empty the rectum and improve the conditions for TRUS [14]. We use oral ciprofloxacin (500 mg, bid, for three days) and Colex Klysma (100mL, one hour before procedure).

Positioning - material

The RBI implantation is performed under TRUS guidance using the transperineal approach, with the patient placed in the dorsal lithotomy position (Figure 4). This setup is similar to the implantation procedure for prostate brachytherapy [9]. A brachytherapy stepper unit is used to stabilise the TRUS probe and allows the operator to use both hands for the implantation.

A bi-plane TRUS probe (Pro Focus 2202 - BK Medical; transducer type 8848) is used with a US contrast gel-filled condom to improve visibility of the prostate, the Denonvilliers' fascia (DF) and the anterior rectal wall.

Anaesthesia

The implantation procedure can be performed under local, spinal or short general anaesthesia. A short general anaesthesia is preferred at the MAASTRO Clinic.

Procedure

First, a Foley balloon is inserted to empty the bladder so there is no resistance when the RBI is fully deployed, and to provide anatomical landmarks of the central plane, which consequently aids the central and effective positioning of the RBI.

Careful skin disinfection is performed with chlorhexidine solution (1%) 10mg/mL, and sterile drapes are used to cover the patient's legs.

Fiducial intraprostatic markers are implanted for image-guided external beam prostate irradiation. These gold markers could pierce and deflate the RBI; to avoid this, we implant the fiducials via the transperineal (instead of transrectal) route simultaneous with the RBI implantations, as described by Gez et al. [15]. We start implantation of the markers just before RBI implantation.

FIGURE 4: The setup: patient is placed in dorsal lithotomy position, with brachytherapy stepper unit and TRUS probe.

Hydrodissection

A hydrodissection using saline is performed to create tissue planes and facilitate correct placement of the RBI between the DF and the anterior rectal wall. A 20mL syringe is filled with saline. The needle is introduced through the perineum in the midline, ± 1.5 cm above the TRUS probe (little finger width) (Figure 5). This can easily be viewed on the axial TRUS view. Next, the needle must be introduced parallel to the probe (or slightly angled) into the prostate apex (switch to sagittal TRUS view).

The hydrodissection is performed between the DF and the rectal fascia while advancing the needle within this space up to the prostate base. The DF is a fibromuscular structure, fused with the posterior prostate and seminal vesicles. Lowering the probe (dorsal) without pressure on the prostate (in contrast with brachytherapy procedure) before starting hydrodissection may help to open the space. The saline is injected slowly. As the space opens, the needle is advanced until it reaches mid-gland [4,6,7,14]. This manoeuvre must be monitored on axial and sagittal TRUS views. The three layers of the rectum (mucosa, muscle, fascia) must be visually inspected to ensure that no rectal fascia is caught by the needle (Figure 6).

FIGURE 5: Transperineal insertion of the needle, with the dilatator (blue) and the sheath (white).

Balloon insertion

A 20 ml syringe is filled with warm (35-40°C), bubble-free saline to fill the RBI. The saline is combined with 1.5 cc contrast iodine to visualise the RBI on the planning CT and cone-beam CT scans. If the patient is allergic to contrast iodine, the RBI should be filled with saline only. The saline should be at body temperature to ensure adequate RBI expansion. Just superior of the needle, 1.5 cm above the anus, a longitudinal skin incision of the perineum is made that is 1 cm in width and 1.5 cm deep. The dilatator is advanced with a sheath to the tip of the needle. Axial view is used to check that the dilatator and the sheath are in the central plane ('D-line', or plane of the urethral catheter). A switch to sagittal view is then made to advance the dilatator and sheath over the needle. The needle is shifted to check that the rectum wall is free. If it is not clear, a palpation is performed to check and feel if the rectum wall is free. When the sheath has advanced to the prostate base, the needle and the dilatator are removed while the sheath is firmly held in place. The RBI deployer (RBID) is inserted through the sheath up to the line marked on the RBID: the tip of the RBID will now be at the end of the sheath.

The sheath is retracted while the RBID is held in place. The RBI is exposed and slowly inflated to the specified (15-20cc) volume, approximately 3ml every 3-5 seconds, while the inflation of the RBI is carefully checked on axial and sagittal views (Figures 6 and 7).

FIGURE 6: A hydrodissection is performed to separate the tissue planes with saline, helping to create space for the RBI between the Denonvilliers' fascia and the anterior rectal wall. Be mindful of the three layers of the rectum: fascia (f), muscle (Ms) and mucosa (Mc). The vertical white line is the base of the prostate. Most of the prostate is not clearly visible because of the acoustic shadow of the needle. note the foley balloon catheter (Bc) in the bladder and the catheter in the urethra, indicating that you are in the midline.

Lowering the probe (dorsal) without placing pressure on the prostate may help to open the space and easily fill the RBI. The RBI must be in the midline between the prostate and rectum from base to apex. The three layers of the rectum (mucosa, muscle, fascia) must be visually inspected to ensure that no rectal fascia is caught by the needle (Figures 6 and 7). The TRUS probe is progressively moved down as far as possible, and a check is performed to verify that the rectum wall is free, in order to avoid rectum perforation. The RBID is detached from the RBI and left sealed *in situ* [7,16]. Axial and sagittal TRUS views are used to verify that the RBI is properly positioned (Figure 8). The rectal integrity and RBI position inflation are checked using rectal palpation. The skin incision is sutured using dissolvable stitches. Finally, the catheter is removed.

Perioperative side-effects

No grade 3 or 4 toxicities were reported in the week after implantation. The implantation procedure revealed no thrombosis and no perforation of bladder or rectum, and no anti-allergic shock reaction occurred. No penile bleeding was observed. One patient experienced a temporary urine retention, which resolved within a few hours following conservative treatment.

There was a slight increase of redness of the skin in two patients, where a prompt antibiotic regimen was started with no subsequent episodes of infection.

FIGURE 7: Axial ultrasound image: rectum balloon implant (RBI) being filled with saline between the prostate (p) and the rectum (R). note the urinary catheter (c) in the central plane, or ‘D-line’.

FIGURE 8: sagittal ultrasound image of patient with a rectum balloon implant (RBI) in situ between the prostate (p) and the rectum (R). The view is in the central plane with the urinary catheter (c) and the foley balloon catheter (Bc) visible in the bladder.

The major side effect included pain in the perineal region (range from 1-3, according to VAS) in 5 out of 15 patients, which was easily addressed with paracetamol or nonsteroidal anti-inflammatory drugs. Three additional patients felt slight discomfort. Dysuria occurred in five patients. Ecchymosis in the transperineal region and tenesmus occurred in two patients and one patient, respectively. Seven patients (47%) were free of complications.

DISCUSSION

The RBI separates the anterior rectal wall from the prostate, facilitating reduction of the high radiation dose to the anterior rectum wall. The potential failure modes, possible complications or pitfalls and corrective actions for this implantation procedure are described in Table 1.

Several types of spacers are available: hyaluronic acid, PEG-based hydrogel, human collagen, and biodegradable balloon. The advantage of the inflatable RBI system is that it allows for post-implant correction of the RBI position, whereas liquid spacers (hydrogels, hyaluronic acid, human collagen) do not permit any correction once injected [7]. Furthermore, if such a liquid spacer is injected in the rectum wall, a rectum fistula can occur; this was recently mentioned by Habl et al., whereby they stopped using this promising technique [17]. Next, the biodegradable RBI inflates to a predetermined and predictable shape, meaning a learning curve is probably less important. Pinkawa et al. reported a learning curve of 64 implantations to fully implement and optimise rectum hydrogel spacer placement [18]. Therefore, we choose to use the RBI. However, a possible disadvantage is early volume loss of the RBI before the end of the radiation treatment, as recently published by Wolf et al. [19]. Further research is needed to evaluate and quantify this volume loss.

The implantation of rectum spacers is well tolerated. No severe grade 3-4 complications occurred in our series. In the literature, severe complications have been documented, but in very low numbers [8, 9]. Perforation of the bladder or rectum are reported in 3 out of 23 cases (13%) in procedures performed without hands-free TRUS guidance [5,8]. According to the authors, these complications resolved with no further sequelae. After protocol modifications and introduction of TRUS guidance, no perforations or other severe complications have occurred, as in our series. We observed 1 out of 15 cases (7%) of temporary urinary retention, probably provoked by the use of general anaesthesia. The literature reported this in 1 out of 11 cases (9%) and 3 out of 26 cases (12%), respectively [6, 15].

TABLE 1: List of hazards adapted to RBI implantation and corrective actions.

Potential failure mode	Corrective action
Bad TRus view:	
Stool	Rectal cleansing
Bubbles	Wait a few minutes
Prostate calcifications	Not reliable
Hydrodissection:	
needle is not advanced:	
in the midline	Check relation on TRUS axial view and the D-line/central plane with the urinary catheter
to the prostate base	Palpate with finger to check if rectum wall is free
Not performed in the proper plane	Check on TRUS axial view and perform again
Hydrodissection is not possible due to	
incorrect position of the needle, e.g. in the rectum wall or in the prostate	Reposition the needle
adhesions or patient anatomy	Lowering the probe before starting may help to open the space; if this is not possible, it is recommended to abort the procedure
Dilator:	
is difficult to insert	Make a deeper incision
is not advanced to the prostate base	Check on TRUS and reposition
Balloon:	
cannot be inflated	Remove the sheath sufficiently
	Push the balloon deeper, so it does not interfere with pelvic muscles
is partially inflated and accidentally sealed	Remove RBI or detach it
is inflated in a suboptimal position (wrong cleavage)	Deflate RBI (percutaneous)
is sealed and spontaneously deflates	Completely deflate RBI, be mindful of perforation
Post-procedure:	
Infection	Prophylactic antibiotic pre-procedure
	Quick start of antibiotic regimen
Bleeding	Stop antiplatelet therapy in advance
Urinary retention	Urinary catheter
Rectal perforation	Deflate RBI, suture, and post-operative antibiotics
Balloon is deflated	Implant transperineal fiducial markers before RBI implantation

Most of the current literature is limited to spacer implantation in patients with low-risk localised (intra-capsular) prostate cancer. So far, the role of spacers in locally advanced and high-risk prostate cancers is unclear [8]. The possible negative influence of a spacer in cases with a dorsal prostate capsule rupture is yet unknown, as tumour cells could be displaced out of the high-dose region by the spacer [14]. Studies are therefore needed to evaluate the advantages and possible disadvantages of spacers in these patients.

Each RBI is handmade and has a variable maximum volume of 15-20cc (BioProtect Ltd, Israel).

The volume must not exceed the specific amount indicated on the individual balloon label in order to preserve RBI function and prevent bursting (with consequent loss of function). In practice, we correlate the volume of the RBI with the volume of the prostate: small prostates (<35cc) do not need not the maximum RBI volume for sufficient space (at least 1cm). According to Pinkawa et al., a volume of 10mL is enough to ensure a distance of around 1cm (20).

Further clinical studies are required to define the place of an RBI in the treatment of prostate cancer radiotherapy. We believe that in the future, RBI should be prescribed on the basis of an individualised risk assessment with a validated predictive model and a decision support system to identify *a priori* whether individual patients will benefit from an RBI [21, 22]. Prospective follow-up studies in independent patient cohorts are needed to assess the benefits of such an RBI.

CONCLUSIONS

This paper provides detailed step-by-step instructions for the safe implantation of an RBI. This procedure should be performed by urologists and/or radiation oncologists who are experienced in prostate brachytherapy and the use of TRUS. The RBI implantation is a safe and very well tolerated procedure with only slightly increased discomfort, and in some cases pain in the perineal region, which is easily addressed with mild pain medication. The theoretical advantages of RBI include reducing the high radiation dose to the anterior rectum wall, the possibility of a post-implant correction, and the implant's predetermined shape with consequent predictable position, meaning a learning curve is probably less important.

Acknowledgements

The authors thank E. Van Lin, P. Roman, S. Delbressine and S. Walsh for their helpful collaboration in the preparation of this manuscript.

REFERENCES

1. Budäus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol.* 2012;61:112-27.
2. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis.* 2015;30:1293-303.
3. Vanneste BG, Van Limbergen EJ, van Lin EN, van Roermund JG, Lambin P. Prostate Cancer Radiation Therapy: What Do Clinicians Have to Know? *Biomed Res Int.* 2016;2016:6829875.
4. Prada PJ, Fernández J, Martínez AA, de la Rúa A, Gonzalez JM, Fernandez JM, et al. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys.* 2007;69:95-102.
5. Uhl M, van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using na absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. *Radiother Oncol.* 2013;106:215-9.
6. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;82:1918-22.
7. Melchert C, Gez E, Bohlen G, Scarzello G, Koziol I, Anscher M, et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol.* 2013;106:210-4.
8. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys.* 2014;90:278-88.
9. Pinkawa M. Spacer application for prostate cancer radiation therapy. *Future Oncol.* 2014;10:851-64.
10. Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2015;92:971-7.
11. Vanneste BG, Pijls-Johannesma M, Van De Voorde L, van Lin EN, van de Beek K, van Loon J, et al. Spacers in radiotherapy treatment of prostate cancer: is reduction of toxicity costeffective? *Radiother Oncol.* 2015;114:276-81.
12. Strom TJ, Wilder RB, Fernandez DC, Mellon EA, Saini AS, Hunt DC, et al. A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy±intensity modulated radiation therapy. *Radiother Oncol.* 2014;111:126-31.
13. Common Terminology Criteria for Adverse Events 4.0 (CTCAE). (Accessed in June 21, 2016. Available at. <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>)
14. Hatiboglu G, Pinkawa M, Vallée JP, Hadaschik B, Hohenfellner M. Application technique: placement of

- a prostate-rectum spacer in men undergoing prostate radiation therapy. *BJU Int.* 2012;110:E647-52.
15. Gez E, Cytron S, Ben Yosef R, London D, Corn BW, Alani S, et al. Application of an interstitial and biodegradable balloon system for prostate-rectum separation during prostate cancer radiotherapy: a prospective multi-center study. *Radiat Oncol.* 2013;8:96.
 16. Kouloulas V, Kalogeropoulos T, Platoni K, Georgakopoulos J, Matsopoulos G, Chaldeopoulos D, et al. Feasibility and radiation induced toxicity regarding the first application of transperineal implementation of biocompatible balloon for high dose radiotherapy in patients with prostate carcinoma. *Radiat Oncol.* 2013;8:82.
 17. Hahl G, Uhl M, Katayama S, Kessel KA, Hatiboglu G, Hadaschik B, et al. Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective Randomized Phase II Study--The IPI Trial. *Int J Radiat Oncol Biol Phys.* 2016;95:435-43.
 18. Pinkawa M, Klotz J, Djukic V, Schubert C, Escobar-Corral N, Caffaro M, et al. Learning curve in the application of a hydrogel spacer to protect the rectal wall during radiotherapy of localized prostate cancer. *Urology.* 2013;82:963-8.
 19. Wolf F, Gaisberger C, Ziegler I, Krenn E, Scherer P, Hruby S, et al. Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. *Radiother Oncol.* 2015;116:221-5.
 20. Pinkawa M, Bornemann C, Escobar-Corral N, Piroth MD, Holy R, Eble MJ. Treatment planning after hydrogel injection during radiotherapy of prostate cancer. *Strahlenther Onkol.* 2013;189:796-800.
 21. Lambin P, Zindler J, Vanneste B, van de Voorde L, Jacobs M, Eekers D, et al. Modern clinical research: How rapid learning health care and cohort multiple randomised clinical trials complement traditional evidence based medicine. *Acta Oncol.* 2015;54:1289-300.
 22. Vanneste BG, Hoffmann AL, van Lin EN, Van De Voorde L, Pinkawa M, Lambin P. Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. *Radiother Oncol.* 2016 Oct;121(1):118-123.

CHAPTER 8

Shrinkage of the rectal balloon implants:
does it affect significantly rectal dose distribution
and complication risk?

Strahlentherapie und Onkologie 2018 Jan;194(1):31-40

© Copyright Springer International Publishing AG

Vanneste BGL, van Wijk Y, Lutgens LC, van Limbergen EJ, van Lin E, van de Beek K, Lambin P, Hoffmann A.

ABSTRACT

Purpose

To assess the effect of a shrinking rectal balloon implant (RBI) on the anorectal dose and complication risk during the course of moderately hypofractionated prostate radiotherapy.

Methods

In 15 patients with localized prostate cancer, an RBI was implanted. A weekly kilovolt cone-beam computed tomography (CBCT) scan was acquired to measure the dynamics of RBI volume and prostate–rectum separation. The absolute anorectal volume encompassed by the 2 Gy equieffective 75 Gy isodose (V75Gy) was recalculated as well as the mean anorectal dose. The increase in estimated risk of grade 2–3 late rectal bleeding (LRB) between the start and end of treatment was predicted using nomograms. The observed acute and late toxicities were evaluated.

Results

A significant shrinkage of RBI volumes was observed, with an average volume of 70.4% of baseline at the end of the treatment. Although the prostate–rectum separation significantly decreased over time, it remained at least 1 cm. No significant increase in V75Gy of the anorectum was observed, except in one patient whose RBI had completely deflated in the third week of treatment. No correlation between mean anorectal dose and balloon deflation was found. The increase in predicted LRB risk was not significant, except in the one patient whose RBI completely deflated. The observed toxicities confirmed these findings.

Conclusions

Despite significant decrease in RBI volume the high-dose rectal volume and the predicted LRB risk were unaffected due to a persistent spacing between the prostate and the anterior rectal wall.

Keywords

Volumetric, modulated arc therapy, Radiotherapy, Rectum, Volume stability, Toxicity

INTRODUCTION

External beam radiation therapy (EBRT) is an effective curative treatment option for patients with localized adenocarcinoma of the prostate compared to surgery [1]. Increasing radiation dose is associated by increased control; however, this is correlated with an increased potential risk of gastrointestinal (GI) toxicity, with possibly a decrease in the quality of life [2, 3, 4]. Despite the development of advanced treatment techniques like intensity-modulated radiation therapy, volumetric arc therapy, and image-guided radiotherapy, sparing of the rectal wall is a prerequisite for safe delivery of high doses to the prostate. This makes the rectum the dominant dose-limiting organ at risk in prostate EBRT. To spare the rectum, artificial spacing material has been used for insertion into the retroprostatic space. Implantable rectum spacers (IRS) separate the anterior rectal wall from the prostate by creating an artificial distance between these organs. As such they reduce the dose exposure to the rectum, consequently decreasing the risk of GI toxicity. Different types of IRS exist, all of which are implanted through a transperineal approach. Hyaluronic acid [5] and collagen implants [6] are physiological compounds made of substances that are naturally present in the human body. Potential side effects for transmission of infectious agents or immunological reactions have been reported [7]. Therefore, commercially available spacers based on polyethylene glycol (PEG) hydrogels [8] and biodegradable saline-filled rectal balloon implants (RBI) [9] have been developed. Recently Wolf et al. [10] compared PEG and RBI spacer technologies in 59 prostate cancer patients undergoing radiation treatment and concluded that the RBI was superior in reducing rectum dose, whereas the PEG hydrogel spacer had a better volume consistency with respect to the duration of treatment. They reported an early and sudden RBI volume decline in 4 out of 16 patients, and an average volume loss of >50% in the remaining 12 patients during the full course of treatment over 8 weeks of a normofractionated radiotherapy regimen comprising 41 fractions.

The aim of our study was to evaluate the RBI volume stability and the dosimetric effect of RBI volume shrinkage on the anorectum and to estimate the 3-year risk of grade 2–3 late rectal bleeding (LRB) during the course of a moderately hypofractionated EBRT regimen comprising 28 fractions. We tested the hypotheses that despite of an expected RBI volume decrease over time there is no significant increase in the absolute anorectal volume encompassed by the 2 Gy equieffective dose of 75 Gy (V75Gy) and in the mean anorectal dose, both of which are considered relevant parameters for predicting LRB. We also tested the hypothesis that there is no correlation between RBI deflation and mean anorectal dose. In addition, we hypothesized that the predicted increase in risk of LRB resulting from the volume decrease of the RBI is insignificant. Furthermore, we postulated that this predicted status quo of LRB risk can be explained by a persistent prostate–rectum separation of at least 1 cm during the whole course of treatment. Finally, we reported the observed acute and—as far as possible—late toxicities.

MATERIALS AND METHODS

Patient selection

After approval by the institutional review board (number 14-38-03/09-internal-6335), 15 consecutive prostate cancer patients were prospectively included in this study between June 2015 and March 2016. Patients with a histologically confirmed, localized adenocarcinoma of the prostate were enrolled in this study to receive an RBI (BioProtect Ltd, Israel). All patients had signed an informed consent form. The patient and tumor characteristics are summarized in Table 1. Patients who had been classified as intermediate risk were prescribed additional neoadjuvant hormonal therapy for 6 months [11]. The high-risk patients were offered an additional 1.5 years hormonal therapy as an extension of the 6-month neoadjuvant therapy after EBRT. All patients underwent magnetic resonance imaging (MRI) to exclude extraprostatic spread. Dorsal extraprostatic disease extension (stage T3a/4) was an exclusion criteria, as well as distant metastatic disease, inflammatory bowel disease and previous pelvic EBRT.

TABLE 1: Patient (N = 15) and tumor characteristics

Age (years; median [range])	72 [63–77]
Prognostic risk groups*: (no. of patients)	
1 – Low risk	1 (7%)
2 – Intermediate risk	5 (33%)
3 – High risk	9 (60%)

*Low risk: no risk factors: PSA <10ng/ml; Gleason score <7; cT stage <2b; Intermediate risk: PSA 10–20ng/ml and/or Gleason score = 7 or cT stage = 2b/c; High risk: PSA >20ng/ml or Gleason score >7 or cT stage >2b/c

RBI implantation procedure

An RBI was implanted in these patients between the prostate and the anterior rectal wall 7–10 days prior to the start of EBRT. The injection technique has been previously described in detail [12]. A short general anesthesia is preferred at our department. However, the implantation procedure can be also performed under local or spinal anesthesia. First, four fiducial markers (PolyMark™, CIVCO, Orange City, IA, USA) were implanted intraprostatically for daily position verification. The RBI was implanted transperineally under biplane transrectal ultrasonography guidance. A bubble-free (sterile) saline solution was used to fill and inflate the RBI. The saline solution was mixed with approximately 1.5cm³ iodinated contrast medium to enhance the visualization of the RBI on computed tomography (CT) scans. The injected volume was varied, depending on the volume of the prostate. Because the RBI should not be filled to achieve a prostate–rectum separation larger than 30mm, we adapted the volume of the RBI to the volume of the prostate: small prostates (<35 ml) do not need the maximum RBI volume to guarantee a prostate–rectum separation of at least 1 cm, which is considered as a conclusive spread [13].

Target volume definition, dose prescription, and treatment planning

Each patient underwent a CT scan and MRI scan 5–7 days after RBI implantation in supine position with a slice thickness of 3 mm for treatment planning and target volume delineation purposes, respectively. One hour prior to image acquisition, patients were instructed to first empty their bladder, then drink 300 ml of water to have a full bladder, and empty their bowel. No use of laxative was recommended. The CT and MRI scans (balanced turbo field echo sequence with isotropic 0.5 mm in-plane resolution) were coregistered based on the fiducial markers.

Delineation of the prostate (CTV = clinical target volume) was performed on the T2-weighted MRI scan, while the RBI and the organs at risk were delineated on the CT scan (Figure 1). In case the CT and MR images showed different prostate shapes and volumes (e.g., due to differences in rectal filling), the MR imaging was repeated. The first planning target volume (PTV1) was constructed according to the institutional protocol by expanding the CTV with 10, 7 and 6 mm in cranial–caudal, anterior–posterior, and left–right direction, respectively. A second PTV (PTV2) was defined as a 5 mm isotropic expansion of the CTV, with exclusion of the anorectum and bladder. All treatment plans were designed for dose delivery with a volumetric modulated arc technique (VMAT) using 10 MV photon beams (Eclipse Version ICD-10, Varian Medical Systems Inc., Palo Alto, CA, USA). The prescribed dose to PTV1 and PTV2 was 65.8 and 70 Gy, in 28 fractions of 2.35 and 2.5 Gy, respectively [14]. With $\alpha/\beta = 3$ Gy for late rectal toxicity, the maximum 2 Gy equieffective dose (EQD₂) in the anorectum for this type of plan is 77 Gy [15]. No density override for the iodine-containing RBI was performed because it was assumed that the contrast medium that was present in the RBI at the time of CT scanning and treatment planning remained present during treatment delivery. The overall treatment time was 7 weeks, at 4 fractions a week. The dose–volume constraints fulfilled the institutional protocol, which is based on the QUANTEC guidelines [16]. All patients underwent daily X-ray based position verification and repositioning based on the intraprostatic fiducial markers.

FIGURE 1: Color-wash isodose distribution projected on an axial CT slice before (a) and after RBI implantation (b) in the same patient with the planning target volume in red. Without RBI (a), the high-dose region >80% (green isodose) overlaps with the entire ventral part of the rectum (black line), whereas with the RBI in situ (b) the rectum is exposed to a dose <65% (blue isodose)

RBI volume and distance dynamics

To assess the volume stability of the RBI over time, a weekly kilovolt cone beam computed tomography (CBCT) scan was acquired in treatment position prior to irradiation, respectively at fractions 1, 7, 11, 15, 19, 23, and 27. The resulting 105 CBCT scans were imported into the treatment planning system for delineation and subsequent 3D volumetry of the RBI. Furthermore, the minimum distance between the prostate and the anterior rectal wall was measured at midprostate level in anterior–posterior direction. Two observers independently delineated the RBI (RG and BV) and the anorectum (DH and BV). The anorectal structure consists of the rectum and the anal canal. The rectum was delineated from the top of the anal canal up to the rectosigmoid flexure. The anal canal was considered as the distal 3 cm of the anorectum. Six to nine months after RBI implantation, an MRI scan was acquired to evaluate the biodegradability of the RBI.

Anorectal dose estimation

To assess the dosimetric consequences of RBI shrinkage on the anorectum, the planned dose distribution of the three patients with the largest observed RBI volume reduction was recalculated on the weekly acquired CBCT images, while keeping all planning parameters (e.g., beam arrangement, field size, fluence maps, monitor units) the same as for the initial, CT-based treatment plan. The dose–volume histogram (DVH) for the anorectum obtained from the treatment plan was converted into EQD₂ using the Withers formula [17]:

$$EQD2 \alpha/\beta = D \cdot d + \alpha \beta^2 + \alpha \beta, \quad EQD2 \alpha/\beta = D \cdot d + \alpha \beta^2 + \alpha \beta,$$

where $\alpha/\beta = 3 \text{ Gy}$ for late rectal toxicity, D is the total dose, and d is the dose per fraction. All dose–volume parameters were obtained from the EQD₂-converted DVH. The absolute V75Gy of the anorectum was compared between the CT and CBCT plans: in the 3 cases with the largest RBI volume decrease the weekly CBCT images were compared. For the remaining patients, only

the CBCT images of the last week (CBCT27) were used for comparison of the anorectal V75Gy against the CT-based plan. The EQD₂-converted mean anorectal dose was calculated for the planning CT and the final CBCT for all patients.

Complication risk estimation

To assess the effect of the RBI volume decrease on the 3-year risk of grade 2–3 LRB, a set of previously published multifactorial nomograms were used [18]. These nomograms use clinical parameters (use of anticoagulants, hormonal therapy, or antihypertensives; pelvic node irradiation; presence of diabetes or hemorrhoids; and a history of pre-RT abdominal surgery), in addition to dosimetric parameters (mean rectal dose and the percentage of the anorectum volume receiving at least an EQD₂ of 75Gy) to predict the risk of late rectal bleeding. The nomograms were applied to the initial treatment plans and the plans performed on the final CBCT images for each patient. The results were used to estimate the largest change in predicted complication risk due to shrinkage of the RBI.

Observed toxicity assessment

The complications were recorded in terms of Common Terminology Criteria for Adverse Events (Version 4.03) [19]. Acute gastrointestinal (GI) and genitourinary (GU) toxicities were scored in the 2nd, 4th, 6th week of treatment and 3 months after its completion. Late toxicities were scored in the 6th, 9th, and—in case if possible—12th, and 18th months after treatment completion.

Statistical analysis

The statistical analyses were carried out using the Statistics Toolbox of MATLAB (Version 10.2, The MathWorks, Natick, MA, USA) software. The paired-samples Wilcoxon signed rank test was applied to test for a significant decrease in volume of the RBI on weekly acquired CBCT scans, and for a significant decrease in distance between prostate and rectum. This test was also applied to test for a significant increase in predicted complication risk between the first and last fraction. All statistical tests were one-sided, with $P < 0.05$ considered to be statistically significant.

RESULTS

RBI volume and distance stability

The median injected and delineated RBI volumes were 17.0cm³ (range 9–17 cm³) and 20.0cm³ (range 12.9–22.6cm³), respectively. Volume differences are explained by the fact that the delineated RBI structure comprises both the injected saline solution and the RBI envelope. Two patients were excluded from the stability analysis because in one patient CBCT scans were missing due to a protocol violation and in another patient the RBI had disappeared on CBCT in the third week of treatment as no contrast medium could be detected. For the remaining 13 patients, the descriptive statistics of the RBI volume dynamics are summarized in Table 2 and depicted in Figure 2. The median RBI volumes at fractions 1, 15, and 27 were 19.6 (range 12.8–21.7), 15.6 (range 11.7–20.6), and 11.9 cm³ (range 6.3–19.8cm³), respectively. The weekly decrease in absolute RBI volume was significant for all time points, with an average volume loss of 29.6% at fraction 27 relative to baseline. The largest relative volume decrease occurred during the first week (i. e., between fraction 1 and 7), and after fraction 19 (Figure 2). The median volume loss relative to baseline was 25% (range 5.7–54.9%). The descriptive statistics of the prostate–rectum distance dynamics are also summarized in Table 2. Although the weekly decrease of minimum prostate–rectum distance was significant for all time points, this distance remained greater than 1 cm at all times.

TABLE 2: RBI volume and minimum prostate–rectum distance dynamics

	RBI volume (cm ³ ; median [range])	Prostate–rectum distance (cm; median [range])
Planning CT	20.0 [12.9–22.6]	2.3 [1.9–2.9]
CBCT 1	19.6 [12.8–21.7]	2.2 [1.8–2.8]
CBCT 7	16.0 [12.8–20.7]	2.0 [1.7–2.5]
CBCT 11	15.8 [11.7–20.7]	1.9 [1.6–2.4]
CBCT 15	15.6 [11.7–20.6]	1.9 [1.5–2.4]
CBCT 19	14.5 [11.3–20.0]	1.9 [1.3–2.4]
CBCT 23	14.0 [9.6–19.8]	1.7 [1.1–2.3]
CBCT 27	11.9 [6.3–19.8]	1.4 [1.1–2.3]

RBI rectal balloon implant, CBCT cone-beam computed tomography

FIGURE 2: A box and whisker plot of the delineated rectal balloon implant (RBI) volumes during a full treatment course of 28 fractions in 13 patients (grey dashed lines) observed by weekly cone-beam computed tomography (CT) images

RBI resorption

Six to nine months after completion of EBRT a residual rest of the RBI envelope was visible on T2-weighted MRI in only 1 out of 15 (7%) patients; no contrast medium or saline solution could be observed. Neither space-occupying effects nor complications (infections, perforations, fibrosis) were observed in any of the patients.

Anorectal dosimetry

In the patient whose RBI had disappeared on the CBCT scan in the third week of treatment, the V75Gy of the anorectum significantly increased from 0 to 4.3 and 5.9 cm³ at fraction 1, 11, and 27, respectively (patient 9, Figure 3.) In the other two patients (numbers 5 and 12) exhibiting the largest RBI volume decrease (45 and 52% of the original volume, respectively) a significant increase in absolute V75Gy of the anorectum was only observed in the CBCT scan of fraction 23 (patients 5 and 12, Figure 3). Furthermore, the RBI deflation did not lead to significant increase in V75Gy ($p = 0.577$). Among the remaining patients there was only one patient who showed an increase of V75Gy from 0 cm³ on the CT plan to 3.6 cm³ on the CBCT27 plan (Table 3). In 2 out of 11 patients, the V75Gy remained 0 for both the CT and CBCT27 scans. In 6 patients, even a slight decrease of V75Gy was determined. The increase in V75Gy for all patients except the

one of whom the RBI disappeared was not significant ($P = 0.57$). The increase in mean anorectal dose was significant ($P = 0.02$); however, no correlation was found between the mean anorectal dose and the volume of the RBI ($P = 0.3$). The correlation between the anorectal volume and the anorectal mean dose was significant ($P = 0.005$).

FIGURE 3: Relative volume dynamics of rectal balloon implant during a full treatment course of 28 fractions in 13 patients (grey dashed lines) observed by weekly cone-beam computed tomography (CT) images. The mean values (dark blue) with the standard deviations (light blue) are presented.

TABLE 3: Descriptive statistics for treatment plans based on the planning CT scan and the CBCT scan of fraction 27

	Planning CT median [range]	CBCT27 median [range]
Rectal volume (cc)	88.7 [56.1–187.4]	68.65 [45.3–200.8]
Mean rectal dose (Gy)	26.2 [10.9–34.6]	33.9 [19.3–38.7]
V75Gy (cc)	0.1 [0.0–1.6]	0.7 [0.0–5.9]
Complication risk (%)	4.1 [3.8–11.9]	4.5 [3.9–11.6]

CT computed tomography, CBCT cone-beam computed tomography, V75Gy volume receiving at least a 2Gy equieffective dose (EQD2₃) of 75 Gy, Mean rectal dose mean EQD2₃ dose in the anorectum

Risk of late rectal bleeding

In the patient whose RBI had completely deflated in the third week of treatment (patient 9), the risk of LRB was predicted to increase from 4.0 to 9.8%. For the two patients with the largest observed RBI shrinkage (patients 5 and 12) the predicted increase in LRB risk was 0 and 0.2%, respectively (Figure 4). The largest increase in complication risk predicted for the remaining patients was 3.4%, resulting from a RBI volume decrease of 32%. The difference between the predicted risk of LRB at the start of treatment and the end of treatment, excluding the patient with the deflated RBI, was not significant ($P = 0.07$) (Figure 5).

FIGURE 4: Dynamics of estimated absolute anorectal volume encompassed by the biological equivalent 75 Gy isodose during a full treatment course of 3 patients (numbers 5, 9, 12) exhibiting the largest volume decrease of the implanted rectal balloon. Patient 9 had the complete rectal balloon implant (RBI) shrinkage on cone-beam computed tomography (CBCT) of fraction 11: the V75Gy increased significantly. In the other two patients (5 and 12) a significant increase in absolute V75Gy of the anorectum was observed in only one CBCT scan (fraction 23) over the total treatment course.

Observed toxicities

No acute grade 3 or 4 toxicities were reported during treatment or 3 months after completion. Overall, 5 patients (33%) experienced no toxicity, 6 patients (40%) had grade 1 GU toxicities, and 4 patients (27%) had grade 2 GU toxicities. During the course of therapy, in 4 patients (27%)

grade 1 GI toxicity was observed, but no grade 2 or more acute GI toxicities.

No late grade 3 GI toxicity has been reported. Late grade 2 GI toxicity was observed in 1 patient: the rectal bleeding started at 9 months after radiation. This was the patient whose RBI had completely deflated in the third week of treatment. Grade 1 GI and GU late toxicities were reported in 2 patients.

DISCUSSION

This study provides the first evaluation of RBI volume stability that is based on weekly CBCT measurements during the full course of EBRT. As previously reported in literature, an RBI volume decrease was expected over time. We analyzed the dosimetric consequences of this phenomenon and predicted the increase in risk of 3-years grade 2–3 late rectal bleeding resulting from a shrinking RBI to assess its potential clinical impact. Moreover, the observed acute and early late toxicities were adjusted.

GI toxicity is the major treatment-related side effect in prostate cancer radiotherapy: the rates of acute and chronic grade ≥ 2 rectal toxicity has increased by dose-escalated EBRT (up to a dose of 78 Gy) compared with lower doses (e.g., 68 Gy) from 3 to 20% and from 5 to 21%, respectively [20, 21, 22, 23, 24]. Therefore, it is advantageous to push the rectal wall out of high-dose regions by implantation of an IRS device [25, 26]. So far, most studies in the literature have reported on the use of a PEG hydrogel as an IRS [27, 28, 29, 30, 31]. The RBI has some practical advantages [9]. First of all postimplant correction of the RBI position is possible; if the RBI is dispositioned, it can be easily deflated and replaced, whereas liquid spacers (PEG hydrogels, hyaluronic acid, human collagen) do not permit any correction once being injected [9, 12]. In addition, a chemical reaction is required to occur in PEG hydrogels, which limits the implantation time. Furthermore, since the RBI inflates to a predetermined and predictable shape, the learning curve to obtain an adequate implant is less steep than for PEG hydrogels. In addition, due to the defined shape and homogenous hypodense signal, the RBI has an excellent CT visibility, which is most advantageous for treatment planning and CBCT-based evaluations. Besides, some amount of iodine contrast can be added to the saline to enhance the visualization of the RBI on CT and CBCT scans (Figure 1). Moreover, because the RBI is a closed system, there is no risk of air or hydrogel injection into vessels.

Nevertheless, disadvantages of the RBI have also been reported. Recently Wolf et al. [10] described an early deflation effect. They reported an average volume loss of $>50\%$ during a full treatment course of 37–41 fractions (8 weeks). The volumes they estimated were mainly based on measurements of the diameters of the RBI on two orthogonal X-ray images and calculations by the volume formula for an ellipsoid cylinder. The measurements were only performed on CBCT scans of fractions 20 and 38. Data on the dynamics of the prostate–rectum separation over time are missing in their study. Wolf et al. only recalculated one treatment plan on a CBCT scan for a single patient whose RBI showed a significant volume loss of 58%, and reported an increase of 9.2 cm^2 for the rectum volume encompassed by the 95% isodose. We measured 3D volume changes on weekly CBCT scans and observed that a prostate–rectum separation of at least 1 cm is maintained during the full treatment course, except in the patient where the RBI deflated. The persistent spread of at least 1 cm means that also for other RT techniques like 3D conventional EBRT, intensity-modulated radiotherapy, or proton therapy, the sustained spread is considered

as enough for protecting the anorectal structures [13].

By evaluating the dose on the anorectal structure, we observed that the V75Gy of the anorectum steadily increased only in one patient whose RBI disappeared completely in the third week of treatment. In the 2 remaining patients where the RBI shrank most, the V75Gy changed significantly in only two CBCT scans during the whole treatment course, but not in the last CBCT scan. This effect was caused by a difference in rectal filling (inclusion of gas bubbles and/or stool). The distance between the prostate and anorectum was still enlarged due to the presence of the RBI. However, the distance between the prostate and anorectum at the level of the cranial part of the rectum (above the RBI) could decrease incrementally. This is especially the case when the rectal filling is increased dramatically, and when seminal vesicles are irradiated. In this situation, the cranial part of the rectum above the RBI anorectum could receive a higher dose. Furthermore, the RBI could exert pressure on the rectum and thereby decrease the rectal volume being exposed to an intermediate and a high dose and increase the volume being exposed to low doses, with unknown clinical consequences. To reduce the low- and intermediate-dose levels, a different treatment planning technique using either an arc technique with an avoidance region near the rectum or using strictly anterior and lateral beams would be required.

By applying multifactorial nomograms on the initial treatment plan and on the final treatment plan, the predicted increase in risk of late rectal bleeding was analyzed. This showed that for the patient with the deflated RBI, the risk considerably increased, emphasizing the effect of the device. For the patient whose RBI had completely deflated, a significant increase in the risk of late rectal bleeding was predicted by the nomogram (Figure 5). This was confirmed by the late rectal bleeding event 9 months after treatment. For the remaining patients, there was no significant increase in predicted complication risk, suggesting that the decrease in RBI volume has little impact on the effectiveness of the RBI. Some fluctuations in predicted toxicity risk can be seen, but these are likely also due to the rectal filling. Indeed, besides the distance between the rectal wall and the prostate, the rectum size could be a possible predictor of GI toxicity [32, 33, 34, 35]. A previous study reported a sudden complete deflation of the RBI in 4 out of 16 patients three weeks after implantation [10]. In our series, one patient experienced such a sudden complete deflation three weeks after implantation. A possible explanation was a nonoptimal positioning: the RBI was positioned more caudally than the others, with the tip of the RBI in the pelvic muscle. Because of this positioning, an excessive force was required to inflate the RBI, which could have damaged the sealing mechanism. Another possible explanation of early deflation could be an excessive filling of the RBI (i.e., prostate–rectum separation larger than 30 mm) with bursting and consequent loss of function: each RBI is handmade, and one has to be sure not to exceed the maximum volume allowed that is indicated on the label of the product.

A limitation of this study is the small number of patients included. As this was a feasibility study, only

15 patients were included. Furthermore, there was no prior consensus on the level and window settings of the CBCT scans, which might have influenced the volumetric results. In addition, the CBCT scans were acquired at different time points and, hence, revealed different bladder and rectum filling, thus, adding extra uncertainty to the comparison performed. Furthermore, the nomograms used are not validated for patients treated with a RBI. More research is needed in larger patient cohorts to obtain more evidence. Finally, we evaluated weekly time points, and not daily, which later could be more representative for the whole treatment.

The RBI was successfully implanted in all 15 patients. The mean RBI volumes revealed an average volume of 70.4% of baseline at the end of treatment. Despite the weekly RBI shrinkage to be significant, neither significant increase in absolute V75Gy of the anorectum nor in predicted LRB risk were observed over the full treatment course of our moderately hypofractionated EBRT regimen. Although the minimum prostate–rectum distance showed a significant decrease, it was at least 1 cm during the full treatment course, indicating that such spacing is sufficient to reduce the anorectal V75Gy of a treatment plan delivered by a volumetric modulated arc technique. In patients experiencing a complete deflation of the RBI, the absolute V75Gy of the anorectum is expected to increase significantly, and so is the predicted risk of late rectal bleeding, and the observed toxicity. We advise to acquire imaging by CBCT scans at regular times during the course of treatment to assess deflation dynamics of the RBI. Only when the prostate–rectum distance decreases to less than 1 cm is a treatment plan adaptation recommended.

FIGURE 5: Increase in predicted probability (percentage points) of late rectal bleeding between the planning computed tomography (CT) and the last cone-beam CT (CBCT) scan (fraction 27) for each of the patients

Acknowledgements

The authors thank Renee Granzier, Debbie Herfs, Janneke Bovendeerd, and Marlies Lendfers for their help with the delineations and treatment planning on the cone-beam CT scans.

REFERENCES

1. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P et al (2016) 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med* 375(15):1415-1424.
2. Fonteyne V, Ost P, Vanpachtenbeke F, et al (2014) Rectal toxicity after intensity modulated radiotherapy for prostate cancer: which rectal dose volume constraints should we use? *Radiother Oncol* 113(3):398-403.
3. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN (2015) Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis* 30(10):1293-303.
4. Musunuru HB, Quon H, Davidson M, et al (2016) Dose-escalation of five-fraction SABR in prostate cancer: Toxicity comparison of two prospective trials. *Radiother Oncol* 118(1):112-7.
5. Prada PJ, Fernández J, Martínez AA et al (2007) Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys* 69(1):95-102.
6. Noyes WR, Hosford CC, Schultz SE (2012) Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys* 82(5):1918-22.
7. Prendes BL, Yung KC, Likhterov I, et al (2012) Long-term effects of injection laryngoplasty with a temporary agent on voice quality and vocal fold position. *Laryngoscope* 122(10):2227-33.
8. Pinkawa M, Corral NE, Caffaro M (2011) Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol* 100(3):436-41.
9. Melchert C, Gez E, Bohlen G et al (2013) Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol* 106(2):210-4.
10. Wolf F, Gaisberger C, Ziegler I, et al (2015) Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. *Radiother Oncol* 116(2):221-5.
11. Denham JW, Steigler A, Tai KH, Joseph D, Matthews J, Atkinson C, Spry NA, Turner S, North J, Christie D, Wynne C, Lamb DS (2013) Paradoxical metastatic progression following 3 months of neo-adjuvant androgen suppression in the TROG 96.01 trial for men with locally advanced prostate cancer. *Radiother Oncol* 107(2):123-8.
12. Vanneste BG, van de Beek K, Lutgens L, Lambin P (2017) Implantation of a biodegradable rectum balloon implant: Tips, tricks and pitfalls. *International Braz J Ur* 2017 Mar 24;43. [Epub ahead of print]
13. Susil RC, McNutt TR, DeWeese TL, Song D (2010) Effects of prostate-rectum separation on rectal dose from external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 76(4):1251-8.
14. Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A (2007) Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys* 1;68(5):1424-30.
15. Bentzen SM, Dörr W, Gahbauer R, Howell RW, Joiner MC, Jones B, Jones DT, van der Kogel AJ, Wambersie A, Whitmore G (2012) Bioeffect modeling and equieffective dose concepts in radiation

- oncology--terminology, quantities and units. *Radiother Oncol* 105(2):266-8.
16. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO (2010) Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 76(3 Suppl):S123-9.
 17. Withers HR, Thames HD, Peters LJ (1983) A new isoeffect curve for change in dose per fraction. *Radiother Oncol* 1:187-91.
 18. Valdagni R, Kattan MW, Rancati T et al (2012) Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome. *Int J Radiat Oncol Biol Phys* 82(5):1957-66.
 19. Common Terminology Criteria for Adverse Events 4.03 (CTCAE). Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
 20. Al-Mamgani A, van Putten WL, Heemsbergen WD, et al (2008) Update of Dutch multicenter dose escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 72(4):980-988.
 21. Zelefsky MJ, Levin EJ, Hunt M et al (2008) Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 70(4):1124-9.
 22. Kuban DA, Tucker SL, Dong L et al (2008) Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 70(1):67-74.
 23. Ghadjar P, Jackson A, Spratt DE et al (2013) Patterns and predictors of amelioration of genitourinary toxicity after high-dose intensity-modulated radiation therapy for localized prostate cancer: implications for defining postradiotherapy urinary toxicity. *Eur Urol* 64(6):931-8.
 24. Aluwini S, Pos F, Schimmel E et al (2015) Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol* 16(3):274-83.
 25. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T (2014) Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys* 90(2):278-88.
 26. Pinkawa M (2014) Spacer application for prostate cancer radiation therapy. *Future Oncol* 10(5):851-64.
 27. Uhl M, Van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL (2013) Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. *Radiother Oncol* 106(2):215-19.
 28. Song DY, Herfarth KK, Uhl M et al (2013) A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys* 87(1):81-7.
 29. Strom TJ, Wilder RB, Fernandez DC et al (2014) A dosimetric study of polyethylene glycol hydrogel in 200 prostate cancer patients treated with high-dose rate brachytherapy ± intensity modulated radiation therapy. *Radiother Oncol* 111(1):126-31.
 30. Mariados N, Sylvester J, Shah D, et al (2015) Hydrogel Spacer Prospective Multicenter Randomized

Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys* 92(5):971-7.

31. Pinkawa M, Berneking V, König L, Frank D, Bretgeld M, Eble MJ (2017) Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. *Strahlenther Onkol* 193(1):22-28.
32. Hoogeman MS, van Herk M, de Bois J, Lebesque JV (2005) Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. *Radiother Oncol* 74(2): 177-85.
33. Huang TC, Chou KT, Yang SN, Chang CK, Liang JA, Zhang G (2015) Fractionated changes in prostate cancer radiotherapy using cone-beam computed tomography. *Med Dosim.* 40(3):222–5.
34. Chen Z, Yang Z, Wang J, Hu W (2016) Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. *Radiat Oncol* 2;11:103.
35. Hedrick SG, Fagundes M, Case S, Renegar J, Blakey M, Artz M, Chen H, Robison B, Schreuder N (2017) Validation of rectal sparing throughout the course of proton therapy treatment in prostate cancer patients treated with SpaceOAR. *J Appl Clin Med Phys* 18: 82–89.

CHAPTER 9

A biodegradable rectal balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn disease

Technical innovations & Patients Support in Radiation Oncology 6 (2018) 1–4

© Copyright Elsevier

Vanneste BGL, van Limbergen EJ, van de Beek K, van Lin E, Lutgens LC, Lambin P.

ABSTRACT

Background

Radiotherapy in patients with active inflammatory bowel disease (IBD) is usually considered an absolute exclusion criterion for prostate cancer radiotherapy treatment.

There are no reports available on the use of a biodegradable rectal balloon implantation (RBI) in patients with active IBD for prostate cancer radiotherapy.

Case presentation

We report on a patient with high-risk prostate cancer with the comorbidity of an active IBD with pancolitis location. He was treated with neo-adjuvant hormonal therapy and high-dose external beam radiotherapy to the prostate and the seminal vesicles. Before radiotherapy treatment, a biodegradable RBI was implanted between the prostate and the anterior rectal wall to push the rectum outside of the high-dose area. This patient at high-risk for rectal toxicity was successfully irradiated to his prostate with only a grade I urinary toxicity, no acute rectal toxicity or toxicity flare of the IBD.

Conclusions

This case describes the use of a RBI implantation in patients with active IBD for prostate cancer radiotherapy. The use of a biodegradable RBI proved to be a promised solution for such patients, and have to be further investigated.

Keywords

Prostate cancer, Radiotherapy, Rectal Balloon Implant, Inflammatory Bowel Disease

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal (GI) tract in individuals with a genetic predisposition, who have been exposed to environmental risk factors, without an infectious cause [1]. IBD refers to a disease comprising two major disorders: ulcerative colitis and Crohn's disease. Active and medically controlled IBD are generally considered to be absolute or relative contraindications for using ionising radiation because of the severely increased risk of GI toxicity, with reported grade ≥ 3 late GI complications attributable to external beam radiation therapy (EBRT), up to as much as 73% using conventional EBRT techniques [2,3].

The current standard of care for locally advanced prostate cancer is high-dose EBRT and/or brachytherapy or radical prostatectomy [4,5]. EBRT for prostate cancer may lead to GI toxicity as a common side-effect, which has a negative impact on the quality of life even many years after the EBRT [6,7]. Several devices have been developed to spare anorectal structures [8]. Implantable rectum spacers (IRS) push the anterior rectal wall away from the prostate by injection of an absorbable hydrogel [9], a hyaluronic acid [10], a saline-filled balloon [11], or a collagen implant [12]. Several studies have confirmed that an IRS decreases the rectal dose leading to decreasing acute and late rectal toxicity, and consequently increasing cost-effectiveness [13-15].

In this report, we present a patient with a high-risk cT2N0 Gleason 4+5 prostate cancer treated with neo-adjuvant hormonal therapy and concurrent EBRT using volumetric-modulated arc therapy (VMAT). A biodegradable rectal balloon implant (RBI) was applied before the start of EBRT to protect and push the anterior rectal wall out of the irradiation field. This case report illustrates a possible workaround for the problem of active IBD for a patient in need of prostate cancer radiotherapy.

CASE PRESENTATION

A 73-year-old man was diagnosed with a Gleason 4+5=9 adenocarcinoma of the prostate by a routine blood measurement (PSA 9.2 ng/ml). Transrectal ultrasound-guided biopsies of the prostate revealed a Gleason 4+5 prostate cancer, 6/6 in the right side in 30 to 80% of the biopsies. Left side was negative. The patient was in good condition, with a World Health Organization (WHO) performance status of 0, but with active IBD status (Crohn's). Crohn's-associated ulcerative lesions were reported over the whole colon-rectum, with approximately monthly exacerbations. The patient reported more than four stools a day, with loss of mucus, and urgency. He was on sustained medical treatment (golimumab 100 mg), adjusted with prednisone 15 mg for an exacerbation. Magnetic resonance imaging (MRI) revealed a tumour in the right side of the prostate with dubious extra-prostatic spread to the apex (Figure 1). No suspected lymph nodes or seminal vesicles invasion were observed. A bone scan revealed no metastases. Clinical staging was a high-risk cT2-3a (dubious MRI) N0 prostate cancer.

FIGURE 1: Axial T2-weighted MRI of a patient with an RBI before (a) and after implantation (b)
Abbreviation: MRI = Magnetic Resonance Image; RBI = Rectal Balloon Implant.

The patient was discussed at a multi-disciplinary tumour board. In light of the patient's relatively young age and good life expectancy, a curative treatment was recommended. Brachytherapy as monotherapy was not considered because of the high Gleason score and the high-volume disease. Radical prostatectomy was not considered due to the high Gleason score, the dubious extra-prostatic spread to the apex, and the possible adhesions. The risk of a positive section margin was assumed to be very high, with consequentially the need for salvage EBRT with associated high rectal toxicity. Moreover, radical prostatectomy would preclude the implantation

of an RBI to decrease GI toxicity. Therefore, primary neo-adjuvant hormonal therapy for six months was suggested to attempt a possible downstage of the prostate cancer and to diminish the activity of the Crohn's disease, followed with high-dose EBRT in combination with an RBI.

We started with neo-adjuvant hormonal therapy for six months to downstage [16]. After three months, the PSA had decreased to 0.4 ng/ml, with testosterone at castration level (<0.3 nmol/L). The IBD was relatively stable with one flare during these three months. After approximately six months the preparations for EBRT were started: First, fiducial markers were implanted intra-prostatically. Secondly, an RBI was implanted between the prostate and the anterior rectal wall. The RBI was implanted transperineally under bi-plane transrectal ultrasonography guidance. The injection technique has been described previously [17]. A bubble-free (sterile) saline solution was used to fill and inflate the RBI. The saline solution was mixed with approximately 1.5 cm^3 iodinated contrast medium to enhance the visualisation of the RBI on computed tomography (CT) scans and cone-beam CT scans. The volume of the prostate was adequately decreased with hormonal therapy ($<35\text{ cm}^3$), and therefore a 12 cm^3 of saline liquid was as enough to guarantee a prostate-rectum separation of at least 1 cm [17].

The implantation procedure was tolerated well, without complications. No pain or discomfort in the perineal region (according to Visual Analogue Scale (VAS)) was reported in the week after the implantation. The perineal region showed no signs of infection.

A CT scan and an MRI scan (Figure 1) were performed 7 days after RBI implantation in supine position with a slice thickness of 3 mm for treatment planning and delineation purposes, respectively. A filled bladder was asked for the planning scans and every treatment fraction. The CT and MRI scans were co-registered on the fiducial markers.

Delineation of the prostate (: CTV = clinical target volume) was performed on the T2-weighted MRI scan, while the RBI, the base of the seminal vesicles (according to the prognostic Partin risk group) and the organs at risk were delineated on the CT scan [18]. The planning target volume (PTV1) was constructed according to the institutional protocol (CTV + 10 mm cranial - caudal, + 7 mm anterior - posterior, + 6 mm left - right).

This patient was treated using VMAT radiotherapy to a dose of 70 Gray (Gy) [19] (28 fractions of 2.5 Gy) with 10 MV photon beams (Eclipse Version ICD-10, Varian Medical Systems Inc., Palo Alto, USA) (Figure 2). The overall treatment time was 7 weeks, at 4 fractions a week. The irradiation plan revealed a V65 (relative volume of rectum receiving 65 Gy or more) of 0.2 %, a V54 of 8.4 % and a maximum point dose on the rectum of 66.5 Gy.

The EBRT treatment was very well tolerated: the patient only had a slight difference in urinary

excretion reported as a grade I according to the Common Terminology Criteria for Adverse Events (Version 4.0) [20]. The acute urinary side effects consisted only of slightly raised frequency with nocturia 2 to 3 times a night. No acute rectal toxicity, pain or urgency were reported by the patient. No additional medication was prescribed. Three weeks after EBRT, the patient reported no complaints at all. The IBD was unremarkable, and no exacerbation was observed during and after the EBRT. Ten months after EBRT, the PSA had dropped to an undetectable level and the patient reported no complaints.

FIGURE 2: Color-wash isodose distribution in an axial (a) and sagittal (b) CT plane after RBI (yellow) implantation, with prostate PTV1 (green), PTV2 (red). The prescribed dose to PTV1 and PTV2 was 65.8 and 70 Gy, in 28 fractions of 2.35 and 2.5 Gy, respectively. Image (a) shows the high-dose region >70% (blue) with nearly no overlap in the rectum (brown). The high-dose region >85% (green) reveals no overlap at all within the rectum. In image (b) at the more cranial part there is minimal overlap observed.

Abbreviation: RBI = Rectal Balloon Implant; PTV = Planning Target Volume.

DISCUSSION

In the literature, an (active) IBD has long been considered to be a relative (or even absolute) contraindication for the use of ionising radiation therapy to sites including bowel structures, because of the extremely increased risk of GI toxicity (grade 3 up to 73% using conventional EBRT techniques) [2,3]. A few papers have been published on the use of EBRT in IBD patients. Willett et al. found a 46% incidence of serious acute, and 21% incidence of late side effects [2]. They observed a five-year late toxicity of 73% with conventional EBRT techniques, compared to 23% using specialised techniques ($p=0.02$).

In a review, Tolia et al. reported that the grade ≥ 3 acute and late GI complications attributable to EBRT ranged between 20 to 21%, and 8 to 29%, respectively [3]. They observed that the location and the activity status of the IBD in combination with the EBRT bowel dose and volume are related to the severity of post-irradiation morbidity.

Recently, Murphy et al. analysed the acute GI toxicity exacerbation in patients on concomitant medical therapy for IBD during an EBRT treatment: 57% with medication versus 8% without (absolute difference of 49%; 95% CI 10 to 89%, $p=0.03$) [21]. The five-year risk of late GI toxicity was relatively low with no significant differences. However, caution should be taken because of consequential late damage [22]. They concluded that EBRT should not be recommended for patients who are in an active flare of an IBD or had an acute flare in the year before treatment. Furthermore, White et al. evaluated the association of the use of modern radiation techniques in patients with decreased acute toxicity: acute grade ≥ 2 toxicity occurred in 28% of patients treated with intensity-modulated radiotherapy (IMRT) versus 100% of patients treated with 3D-conventional RT ($p=0.01$). They concluded that modern EBRT techniques diminish the risk of GI toxicity in IBD patients [23].

Song et al. reported an 21% incidence of acute grade ≥ 3 toxicity effects. All patients who had grade ≥ 3 had received concurrent chemotherapy ($p=0.04$) [24].

The reported studies are difficult to interpret, because of the limited sample size with a very low number of events and the retrospective designs. Furthermore, wide confidence intervals are given, which indicates the need for careful selection to identify patients who are expected to face GI exacerbation from EBRT.

Given the fact that IBD comprises GI mucosal inflammation, the concern for using irradiation therapy is reasonable [23]. Caution should be taken when exposing a considerable volume of bowel structures to significant doses of radiation, either through EBRT or brachytherapy. High-dose ionising radiation (EBRT and/or brachytherapy) is therefore usually avoided for this patient population. As a result, the outcome and survival may be compromised for these patients. In

case of IBD, the risk of radiation-related bowel toxicity constitutes an enormous problem. To our knowledge, no radioprotective agents are available to circumvent this serious side effect and, consequently, excluding the sensitive structures from the high-dose region seems to be the only reasonable solution. This is the first case describing a successful RBI implantation for dose-escalated EBRT in a patient with active IBD to decrease the radiation dose at the rectal wall.

Some limitations of the proposed workaround are important to take into consideration. First, the follow-up period (ten months) is relatively short to evaluate a complete late toxicity report.

Secondly, an additional potential concern regarding the placement of an RBI in patients with Crohn's disease could be submucosal inflammation and scarring, complicating the placement of such a device. To avoid this problem, a hydrodissection using saline is performed to create tissue planes and facilitate correct placement of the RBI between the Denonvilliers' fascia and the anterior rectal wall. Susil et al. demonstrated on a histologic basis that Denonvilliers' fascia could be accurately injected: a prostate-rectum separation of 10 mm was demonstrated as sufficient to reduce the mean rectal volume receiving 70 Gy by 83.1% ($p < 0.05$) [25] .

Next, perforation in the rectal wall is earlier reported by Fisher-Valuck and colleagues in 9 out of 149 cases (6%). However they observed no correlation between rectal wall infiltration and patient complications till now [26], the ramifications of rectum perforations are not yet described when a patient has active IBD. More clinical studies are needed to prove the safety of this procedure in this category of patients.

Finally, most research of the use of spacers is limited in patients with low-and intermediate-risk prostate cancer. The role of spacers in locally advanced and high-risk prostate cancers regarding potential rectal wall invasion is not yet clear. Villers and co-authors reported in their series of 243 prostatectomy specimens that prostate cancer invaded the Denonvilliers' fascia in 19% of cases [27]. They observed in no cases tumour invasion completely through the full thickness of this structure. The possible negative influence of a spacer in cases with a dorsal prostate capsule rupture (cT3a) is unclear, as tumour cells could be displaced out of the high-dose region by the spacer [28]. Future studies are therefore mandatory to evaluate the role of spacers in these patients.

CONCLUSION

An active IBD under active medical therapy for IBD, would generally be regarded as an absolute contraindication for EBRT, based on the data from the literature discussed above. This case report illustrates a possible workaround for the problem of active IBD for a patient in need of prostate cancer radiotherapy. In our opinion, this treatment strategy using EBRT in combination with an IRS should be considered in this specified high-feature patient population to obtain the best outcome and survival.

REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142(1):46-54.
2. Willett CG, Ooi CJ, Zietman AL, et al. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. *Int J Radiat Oncol Biol Phys* 2000;46(4):995-8.
3. Tolia M, Zygogianni A, Kouvaris JR, et al. Irradiation Toxicity and Inflammatory Bowel Diseases (IBD): Review. *Rev Recent Clin Trials* 2014;9(1):31-6.
4. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med* 2016;375(15):1415-1424.
5. Vanneste BG, Van Limbergen EJ, van Lin EN, van Roermund J, Lambin P Prostate cancer Radiation Therapy: What does a clinician have to know? *Biomed Res International*, 2016,Article ID 6829875.
6. Krol R, Smeenk RJ, van Lin EN, Hopman WP. Impact of late anorectal dysfunction on quality of life after pelvic radiotherapy. *Int J Colorectal Dis* 2013;28(4):519-26.
7. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis* 2015;30(10):1293-303.
8. Smeenk RJ, Van Lin EN. Application of anorectal sparing devices in prostate radiotherapy. *Radiother Oncol* 2016;106(2):155-6.
9. Pinkawa M, Corral NE, Caffaro M. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol* 2011;100(3):436-41.
10. Prada PJ, Fernández J, Martínez AA et al. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys* 2007;69(1):95-102.
11. Melchert C, Gez E, Bohlen G et al. Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study. *Radiother Oncol* 2013;106(2):210-4.
12. Noyes WR, Hosford CC, Schultz SE. Human collagen injections to reduce rectal dose during radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82(5):1918-22.
13. Mariados N, Sylvester J, Shah D et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015;92(5):971-7.
14. Hamstra DA, Mariados N, Sylvester J et al. Continued Benefit to Rectal Separation for Prostate RT: Final Results of a Phase III Trial. *Int J Radiat Oncol Biol Phys* 2017;97(5):976-85.
15. Vanneste BG, Pijls-Johannesma M, Van De Voorde L et al. Spacers in radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective? *Radiother Oncol* 2015;114(2):276-81.
16. Denham JW, Steigler A, Tai KH, et al. Paradoxical metastatic progression following 3 months of neo-adjuvant androgen suppression in the TROG 96.01 trial for men with locally advanced prostate cancer. *Radiother Oncol*. 2013;107(2):123-8.
17. Vanneste BG, van de Beek K, Lutgens L, Lambin P. Implantation of a biodegradable rectum balloon

implant: Tips, tricks and pitfalls. *International Braz J Ur* 2017(article in press).

18. Makarov DV , Trock BJ, Humphreys EB et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007;69:1095-101.
19. Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys* 2007;68(5):1424-30.
20. Common Terminology Criteria for Adverse Events 4.0 (CTCAE). Available at:http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
21. Murphy CT, Heller S, Ruth K, et al. Evaluating toxicity from definitive radiation therapy for prostate cancer in men with inflammatory bowel disease: Patient selection and dosimetric parameters with modern treatment techniques. *Pract Radiat Oncol* 2015;3(3):215-22.
22. Dörr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol* 2001;61:223–31.
23. White EC, Murphy JD, Chang DT, Koong AC. Low Toxicity in Inflammatory Bowel Disease Patients Treated With Abdominal and Pelvic Radiation Therapy. *Am J Clin Oncol* 2015;38(6):564-9.
24. Song DY, Lawrie WT, Abrams RA, Kafonek DR, Bayless TM, Welsh JS, DeWeese TL. Acute and late radiotherapy toxicity in patients with inflammatory bowel disease. *Int J Radiat Oncol Biol Phys*. 2001;51(2):455-9.
25. Susil RC, McNutt TR, DeWeese TL, Song D. Effects of prostate-rectum separation on rectal dose from external beam radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;76(4):1251-8.
26. Fischer-Valuck BW, Chundury A, Gay H, Bosch W, Michalski J. Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall. *Pract Radiat Oncol*. 2017; 7(3):195-202.
27. Villers A, McNeal JE, Freiha FS, Boccon-Gibod L, Stamey TA. Invasion of Denonvilliers' fascia in radical prostatectomy specimens. *J Urol*. 1993;149(4):793-8.
28. Hatiboglu G, Pinkawa M, Vallee JP, Hadaschik B, Hohenfellner M. Application technique: placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. *BJU Int*. 2012;110:647-652.

PART III Future

Triangulation

Path Image 1

Path Image 2

CHAPTER 10

A novel prospective decision support method
to estimate the value of a rectum spacer:
'Virtual Rectum Spacer'

Radiother Oncol 2017 S0167-8140(17)32485-4

© Copyright Elsevier

Van Wijk Y, **Vanneste BGL**, Walsh S, van der Meer S, Ramaekers B, van Elmpt W, Pinkawa M,
Lambin P.

ABSTRACT

Introduction

Previous studies have shown that the implantable rectum spacer (IRS) is not cost-effective for all patients. A virtual IRS (V-IRS) was constructed to help identify the patients for whom it is cost-effective to implant an IRS, and its viability as a tool to tailor the decision of an IRS implantation to be beneficial for the specified patient was assessed. Please watch animation: (<https://www.youtube.com/watch?v=tDlagSXMkqw>)

Materials and Methods

The V-IRS was tested on 16 patients: 8 with a rectal balloon implant (RBI) and 8 with a hydrogel spacer. A V-IRS was developed using 7 computed tomography (CT) scans of patients with a RBI. To examine the V-IRS, CT scans before and after the implantation of an IRS were used. IMRT plans were made based on CT scans before the IRS, after IRS and with the V-IRS, prescribing 70 Gray (Gy) in 28 fractions of 2.5 Gy to the planning target volume (biological dose of 80 Gy). Toxicity was assessed using externally validated normal tissue complication probability (NTCP) models, and the cost-effectiveness was analyzed using a published Markov model.

Results

The rectum volume receiving 75 Gy (V75) were improved by both the IRS and the V-IRS with on average 4.2% and 4.3% respectively. The largest NTCP reduction resulting from the IRS and the V-IRS was 4.0% and 3.9% respectively. The RBI was cost-effective for 1 out of 8 patient, and the hydrogel was cost-effective for 2 out of 8 patients, and close to effective for a third patient. The classification accuracy of the model, regarding cost-effectiveness, was 100%.

Conclusion

The V-IRS approach in combination with a toxicity prediction model and a cost-effectiveness analyses is a promising basis for a decision support tool for the implantation of either a hydrogel spacer or a rectum balloon implant.

Keywords

Prostate cancer, Radiotherapy, Implantable rectum spacer, NTCP models, Cost-effectiveness, Decision support

INTRODUCTION

For patients with prostate cancer, intensity modulated radiotherapy (IMRT) is one of the curative treatment options. Dose-escalation has revealed to improve tumor control and overall survival in intermediate and high-risk prostate cancer [1-3]. However, this also leads to increased risk of gastro-intestinal (GI) toxicity which negatively impacts the quality of life (QoL) [4, 5]. The proximity between the prostate and the anterior rectal wall causes part of the high radiation-dose region (>90%) to overlap with the rectum, the primary organ at risk (Figure 1A).

FIGURE 1: A) The prostate (blue) and rectum (brown) before placement of an Internal Rectum Spacer and B) after the placement of the Spacer. The green contour is the iso-dose at 90% of the target dose.

To spare the rectum, two commercially available implantable rectum spacers (IRS) have been developed: one type based on polyethylene glycol hydrogels (SpaceOAR™ System, Augmenix Inc.) [6] and the other is a biodegradable saline-filled rectal balloon implant (BioProtect Ltd, Israel) [7, 8]. These devices have been designed to increase the distance between the anterior rectal wall and the prostate, and pushing the rectal wall out of the high-dose region (Figure 1B). Several studies have shown that this technique results in lower dose within the rectum, resulting in lower toxicity levels [9, 10]. However, the IRS has not shown significant improvements for all patients, and is a costly and invasive procedure [11-13].

To identify the patients that are expected to benefit most from an IRS, we developed a novel method to explore *a priori* the benefit of the IRS. The method simulates an IRS through the use of deformation fields and predicts the geometric result of an IRS before the start of treatment: a so-called virtual implantable rectum spacer (V-IRS). This results in a comparison between computed tomography (CT) scans of the patient with a V-IRS (prior to the start of the treatment), and one without IRS. To this end, a comparison of dose gain distributions, predicted

normal tissue complication probabilities (NTCP) and a cost-effectiveness (CE) analysis between these two treatment plans can be performed (Figure 2). The developed method is based on the multifactorial decision support system developed in [14] and may be used to support the decision on the implantation of an IRS for individual patients [15, 16]. In this study, we evaluated the V-IRS' performance in helping the decision support to implant an IRS or not for patients with prostate cancer. We did this by comparing the V-IRS to the real IRS on the three different levels: dose, NTCP, and CE.

FIGURE 2: An overview of the decision support system for which the virtual internal rectum spacer (IRS) would be a basis. The image shows the input to be a treatment plan for a patient without the IRS, a treatment plan for a patient with the virtual IRS and relevant clinical information. The input data are then split into two different pipelines: one for without IRS and one for with IRS, and a three level analyses is performed. The two pipelines come together in a third pipeline, where comparison is made which can help support the decision to place a spacer or not. NTCP = normal tissue complication probability.

MATERIAL AND METHODS

Patient characteristics

This study included 23 patients with localized prostate cancer who have signed informed consent. We placed a rectal balloon implant (RBI) in 15 of these patients and 8 patients had a hydrogel IRS implanted. All patients were included after approval by the local ethics committee.

Image acquisition and organ delineation

Each patient was scanned in supine position using standard CT imaging. The patients with a hydrogel IRS all underwent two CT scans: one prior to the IRS implantation, and one several days after implantation. The slice thickness of these scans was 5mm, with a pixel size of approx. 1 mm. Of the 15 patients who received a RBI, 8 were scanned prior to implantation as well as several days after, and 7 only after implantation. The slice thickness for these scans was 3 mm with a pixel size of 1 mm.

The clinical target volume (CTV) in the patients who received a RBI was defined as the prostate only, and for the patients with a hydrogel it was defined as the prostate with seminal vesicles, according the risk of involvement of the seminal vesicles.

The planning target volume (PTV) was obtained by expanding the CTV by 6 mm in all directions to account for geometrical uncertainties (daily setup variability and internal organ motion).

V-IRS

To predict the geometrical changes which occur after implantation of an IRS, a virtual CT image was created using image deformation.

The precise shape of an IRS after implementation varied from patient to patient, which is why a model of an IRS was used as the basis for the deformation. The model of the RBI was obtained using the CT scans of 7 of the patients with RBI. The method used is visualized in Figure 3.

The model IRS was inserted into the CT image by applying a deformation field, shown in Figure 4, to a CT image of a patient prior to the implantation of an IRS. Several assumptions were made during the development of the deformation field. First, the deformation was assumed to only take place along the direction in which the IRS inflates. Though a small amount of deformation took place along the other axes, this effect was assumed minimal compared to the inflation direction. Second, the deformation was assumed to affect up to 2 cm of tissue. After this, the deformation fades due to compression. Last, due to the stiffness of the prostate and the rectum, the organs didn't align perfectly around the IRS. This effect was simulated using a parabolic distribution. The field was applied to the CT image and contours using the "field_application" function from the REGGUI software for MATLAB® [17], placing the center of the field between the middle of the prostate and the rectum. A comparison between the shape of the real IRS and organs is compared to the shape of the V-IRS and organs in Figure 5 and Table 1.

FIGURE 3: The implantable rectum spacer (IRS) model was developed using seven delineations of rectal balloon implants (RBI) and converting these into bit masks. These masks were overlapped, summed and normalized to obtain a probability map for the shape of the IRS. To obtain a mask of the model IRS, this probability map is converted to a binary image by thresholding it at 0.6. At value 1, all IRS's overlap, at value 0, no delineations of IRS's were found at all. This threshold was chosen so that the model IRS would have a volume similar to the average IRS (12 cm³).

FIGURE 4: The deformation field assumed only deformation along the axis through both the prostate and the rectum. After 2 cm the deformation field is 0. The spacer is assumed to have deformation effect in a hyperbolic distribution along the other axes. The top left image shows the prostate and rectum before deformation. The top right shows the deformation field. The bottom image shows the result of the deformation field.

FIGURE 5: An overlap of the structures one of the images with the real implantable rectum spacer (IRS) and with the virtual IRS. On the left side the structures of the real image are that of a rectum balloon implant, on the right side the real structures are of a hydrogel spacer.

TABLE 1: Overview of the distances between the rectum and the prostate at mid-prostate level and the PTV overlap with the rectum after placement of an RBI or hydrogel spacer and after application of the V-IRS.

Property	RBI	V-IRS	P-value
Median Distance (cm) [range]	1.37 * [0.98-1.90]	1.50* [0.72-1.82]	0.64
Minimum Distance (cm) [range]	0.56** [0.0-1.14]	0.92** [0.17-1.44]	0.1
PTV overlap with Rectum (cm ³) [range]	0.05 [0.0-0.74]	0.0 [0.0-0.58]	1
Property	Hydrogel	V-IRS	P-value
Median Distance (cm) [range]	0.93* [0.48-1.57]	1.83* [1.54-2.18]	0.008
Minimum Distance (cm) [range]	0.31** [0.1-0.49]	0.81** [0.1-1.41]	0.30
PTV overlap with Rectum (cm ³) [range]	0.16 [0.0-3.25]	0.0 [0.0-1.58]	1

RBI: rectum balloon implant, V-IRS: virtual implantable rectum spacer, CI: confidence interval, PTV: planning target volume

*The median of the median distance between the rectum and the prostate over all patients

** The median of the minimum distance between the rectum and the prostate over all patients

Dose distribution

A certified technician applied a treatment plan on the CT scan prior to IRS implementation, with IRS, and on the virtual image. All treatment plans were designed for dose delivery with a volumetric modulated arc technique with 10 MV photon beams (Eclipse Version ICD-10, Varian Medical Systems Inc., Palo Alto, USA). The treatment plans included 28 fractions of 2.5 Gray (Gy), resulting in a total dose of 70 Gy [18] (Table 2). The equivalent 2 Gy dose (EQD2) for this type of plan is 77 Gy [19] for an α/β ratio of 3 Gy for late rectal toxicity [20], and 80 Gy with an α/β ratio of 1.5 Gy for a prostate tumor.

The Dose Volume Histogram (DVH) of the dose within the rectum was used for dose comparison between the plan without IRS to the plan with IRS. To test the V-IRS, three treatment plans were made for each patient; one on the scan before IRS insertion, one on the scan with the IRS, and one on the scan with the V-IRS.

To check that all plans were comparable, the equivalent uniform dose (EUD) in the CTV was calculated for each plan.

TABLE 2: An overview of the constraints set during treatment planning (given dose)

Structures	Constraints	
Planning Target Volume	V70 > 95%	V77 < 3%
Rectum Volume	V70 = 0%	
Anal Canal Volume	V74 = 0%	Mean dose < 40 Gy
Anorectum Volume	V54 < 50%	V65 <20%
Bladder Volume	V70 = 0%	

Gy: Gray, Vxx: percentage of volume receiving more than xx Gy

Toxicity model

To indicate whether the IRS results in significant improvement in GI toxicity for a given patient, the DVH alone is not sufficient. Clinical differences between patients result in variations in predicted toxicity even when the dose distribution is similar. In order to predict the GI toxicity resulting from the treatment plan in combination with certain clinical parameters, a validated NTCP model was used (Table 3). The chosen model is a multivariate logistic regression model that uses the mean rectal dose, the percentage of the volume of the rectum receiving more than 75 Gy (V75) and several clinical parameters as predictors for late rectal bleeding [21, 22]. The concordance indices for this model were 0.62 and is the same NTCP model used in [11]. The IRS is expected to improve the NTCP predicted by this model, because the IRS increases the distance between the rectum and the prostate, thus reducing the V75 in the rectum.

Cost-effectiveness model

The system is expanded with a published Markov model that analyses the CE of the implantation of the IRS by comparing the gain from the IRS in quality of life with the increased costs associated with the IRS [13]. The Markov model calculates the incremental net monetary benefit (iNMB) between the two treatment options: IMRT with IRS (IMRT+IRS) and IMRT without IRS (IMRT-IRS). The NMB is obtained by multiplying the number of quality adjusted life years (QALY) with a willingness to pay (WTP) threshold and subtracting the treatment costs. The iNMB is obtained by subtracting the NMB of IMRT-IRS from the NMB of IMRT+IRS. If the iNMB is positive, the implantation of an IRS is considered cost-effective. In this study a WTP threshold of €80,000 is used, which is the informal ceiling ratio for a high burden of disease in the Netherlands [23]. The WTP varies strongly per country (£20,000-£30,000 in the UK and \$50,000-\$100,000 in the USA), and is a variable input parameter in the model. The other parameters used in the Markov model are described in Table 4. Whether or not the IRS was effective or not in a given patient strongly depends on the decrease in NTCP resulting from the IRS. A reduced NTCP results in more QALY's, but also lower follow-up costs resulting from toxicity.

Statistics

We used two-tailed Wilcoxon signed rank tests to determine whether the differences between the plans without IRS and the plans with IRS were significant. P-values of less than 0.05 were considered significant.

TABLE 3: Overview of the NTCP models used.

Probability G2-G3 acute rectal bleeding (N = 1132)	Coefficient	SE
Constant	-2.489	0.5243
Use of anticoagulants (0/1)	-0.4702	0.2034
Diabetes (0/1)	0.2445	0.2543
Hemorrhoids (0/1)	0.4066	0.1796
Irradiation of pelvic nodes (0/1)	0.4455	0.2821
Hormonal therapy (0/1)	-0.4252	0.2079
Mean rectal dose (Gy)	0.0339	0.0096
Probability G2-G3 late rectal bleeding (N = 718)	Coefficient	SE
Constant	-3.5082	0.7000
Prediction of acute G2-G3 late rectal bleeding (%)	0.0258	0.0173
Surgery prior to treatment	0.7465	0.4175
V75 in rectum (%)	0.0571	0.0215

G2-G3: grade 2-grade 3 standard RTOG/EORTC scores, RTOG: Radiation therapy oncology group, EORTC: European organization for research and treatment of cancer, Gy: Gray, V75: volume percentage receiving more than 75 Gy, SE: standard error.

TABLE 4: An overview of the values used in the Markov CE model for the cost-effectiveness of the IRS

Utilities	Value	SE
Prostate cancer without treatment-related toxicity	0.9	0.05
Prostate cancer with severe late GI toxicity (grade $\geq$ 2)	0.727	0.04
Costs	Value	CI
Yearly costs prostate cancer without toxicity	€323	€215-€430
Yearly costs late grade 2 GI toxicity	€481	€160-€482
Yearly costs late grade 3 GI toxicity	€4,051	€1,876-€5,832
Proportion grade 2 (of all grade $\geq$ 2)	0.75	0.652-0.848
Cost IRS treatment	€1,700	€1,300-€2,100

IRS: implantable rectum spacer, GI: gastro-intestinal, SE: standard error, CI: confidence interval

RESULTS

Rectum Balloon Implant results

The implantation of a RBI resulted in a minor reduction of the mean rectal dose: 1.5 Gy [-14.9-12.4] average ($p = 0.383$) for the RBI and 5 Gy [2.3-8.4] for the V-IRS ($p = 0.008$) (Table 5). Large differences were observed in rectal volumes in IMRT+IRS and IMRT+V-IRS: in one patient the rectal volume before RBI implantation was 215.5 cm³, and 33.1 cm³ after RBI implantation. The EUD in the CTV for all these plans was between 79 and 80.5 Gy.

The mean reduction in V75 was 3.2% [0.4-8.6] ($p = 0.008$) resulting from the RBI and 3.2% [1.0-7.8] from the V-IRS. The largest difference between the V75 of the plans on the CT's after the implantation of an RBI and those with a V-IRS was 0.9%.

The NTCP reduction resulting from the RBI was on average 1.0% [-0.6-3.9], and 1.1% [0.3-3.5] resulting from the V-IRS. The decrease in NTCP resulting from the RBI and from the V-IRS is shown in Figure 6A. Note that the NTCP for patient 7 was lower than before the IRS was implanted. This resulted in an average iNMB of -€1158 and -€1032 for the RBI and the V-IRS respectively, showing that the implantation of an IRS is not cost-effective when performed on all 8 patients. The iNMB's for each of the patients that received a RBI are shown in Figure 7A. For all these patients, the V-IRS predicts correctly whether or not the implantation of an IRS is cost-effective. For one patient among these eight the implantation is expected to be cost-effective.

TABLE 5: Overview of results for the Rectum Balloon implants (RBI) and the virtual implantable rectum spacer (V-IRS).

	Before RBI	After RBI	V-IRS
Mean Rectal Dose (EQD2 Gy)	20.8	19.3	15.8*
[range]	[10.5–39.9]	[10.2–31.3]	[7.9–32.9]
V75 in Rectum (%)	3.4	0.2*	0.2*
[range]	[1.1–9.0]	[0–0.7]	[0–1.2]
NTCP (%)	4.9	3.9	3.8
[range]	[3.8–8.5]	[3.5–4.8]	[3.2–5.2]
iNMB		-€1158	-€1032
[range]		[-€2049–€481]	[-€1497–€328]
Mean Rectal Dose (EQD2 Gy)	31.9	26.3	25.6*
[range]	[25.2–41.0]	[18.9–32.9]	[19.8–33.8]
V75 in Rectum (%)	6.2	1.0*	0.8*
[range]	[1.9–9.8]	[0–3.6]	[0–4.7]
NTCP (%)	6.2	4.4	4.3
[range]	[4.8–8.2]	[3.6–5.8]	[3.7–4.8]
iNMB		-€669	-€567
(range)		[-€2308–€526]	[-€1525–€542]

RBI: rectal balloon implant, V-IRS: virtual implantable rectum spacer, EQD2: Equivalent 2 Gy Dose, V75: Volume percentage receiving at least 75 Gy, NTCP: Normal tissue complication probability, iNMB: incremental Net Monetary Benefit.

*Two-tailed Wilcoxon signed rank test: significant difference in dose at 5% from the plan before hydrogel.

FIGURE 6: The decrease in normal tissue complication probability (iNTCP) as a result of the implantable rectum spacer (IRS). The results for the rectum balloon implants (RBI) is shown in A, and those for the Hydrogel spacer in B. These decreases are compared to those caused by the virtual IRS (V-IRS).

Hydrogel results

The mean rectal dose was reduced by 5.6 Gy [-7.8-7.0] after the implantation of a hydrogel IRS ($p = 0.055$), and by 6.3 Gy [1.8-4.0] with the V-IRS ($p = 0.008$) (Table 5). For this set of patients large differences in rectal volume were found as well, one with 263 cm³ before the implantation of the hydrogel IRS and 156 cm³ after. The implantation of the hydrogel IRS resulted in a mean V75 reduction of 5.2% [-1.7-9.8] ($p = 0.0156$), and the V-IRS predicted a reduction of 5.4% [0.9-9.8] ($p = 0.008$). The largest difference between the V75 of the plans on the CT's after the implantation of a hydrogel and those with a V-IRS was 3.7%. The EUD in the CTV for all these plans was between 79.5 and 81 Gy.

FIGURE 7: The incremental net monetary benefits for each of the patients with a Rectum balloon implant in A, and with a Hydrogel Spacer in B. If the iNMB is negative, the implantation of an IRS is not cost-effective.

The NTCP was 1.8% [-1-3.8] lower, on average, after the implantation of a hydrogel IRS than before, and 1.9% [0.4-3.9] lower with V-IRS. The decrease in NTCP resulting from the Hydrogel and from the V-IRS is shown in Figure 6B. Note that the NTCP for patient 8 was lower than before the IRS was implanted. The resulting iNMB was -€669 and -€567 for the hydrogel IRS and the V-IRS, respectively, showing that the implantation of the hydrogel is also not cost-effective when applied to all patients. Figure 7B shows the iNMB's for each of the patients with a hydrogel spacer. For this set of patients the V-IRS classifies the cost-effectiveness correctly when compared to the real IRS. Patient 4 and 5 appear to be cost-effective, though patient 4 with only a small gain, and patient 2 is close to cost-effective.

DISCUSSION

In this study, we have developed a V-IRS which can be used to support the decision for the implantation of an IRS for a specified patient or not.

Our method has two main strengths. The first is that a CT of a patient with an IRS can be generated and made available for treatment planning purposes without the real implantation of the IRS itself. This means that the benefit of the IRS for the specified patient can be estimated without having to put the patient through the discomfort of the operation, and without the additional costs of the placement of the IRS. The second is that instead of only looking at the improved dose reduction by implanting the IRS, the NTCP reduction and the CE are also taken into consideration. This allows for a decision based not only on dose reduction, but also on the health gain and the costs associated with the health gain.

The V-IRS gives a good approximation of NTCP and of the cost-effectiveness when compared to an IRS for both commercial systems: the RBI and the hydrogel IRS. The differences between the health gain predicted by the V-IRS and achieved by the RBI were small for 7 of the 8 patients. For the hydrogel these differences were larger, especially when the NTCP was smaller than 2.5%. However, at higher NTCP values, the V-IRS made more accurate predictions. On CE level, the V-IRS performed well: each time the real IRS was expected not to be cost-effective, the V-IRS had the same conclusion, and vice versa. The differences in iNMB between the V-IRS and the RBI were small, showing that the V-IRS is an excellent approximation of the RBI. The differences in iNMB between the hydrogel IRS and the V-IRS were larger, but not enough to cause a classification error.

The V-IRS was based on the RBI, which, as a closed system, inflates to a predetermined shape, which is not the case for the hydrogel IRS. This could cause errors in the predicted iNMB for the hydrogel spacer, but due to the variability of the shape of the hydrogel, a V-IRS based on a hydrogel is not likely to be more predictive than the one used in this study (Figure 8). However, the volume of the hydrogel was often lower than the V-IRS, possibly overestimating its effectiveness. This could be solved by decreasing the V-IRS volume when applied to hydrogels.

The results presented in this study showed that the patients who were to be implanted with a hydrogel spacer had higher NTCP's than the patients to be implanted with a RBI. This was because all patients in the hydrogel spacer group had the seminal vesicles included in the CTV, while the patients with in the RBI group didn't. This is kept consistent with the V-IRS, and did not visibly influence its performance.

FIGURE 8: 18 delineations of gel spacers were used to create a probability map for the shape of the IRS. At value 18, all IRS's overlap, at value 0, no delineations of IRS's were found at all. There is very little overlap between the hydrogel spacers (less than 0,5 cm³ has overlap between 14 or more hydrogels).

One of the main limitations of the study was the small amount of patients included. Though they were sufficient for a first proof of concept, a more elaborate study including a larger amount of patients is required for validation of the method.

Further, the deformation field used to create the images with the V-IRS was arbitrarily chosen. Though the field appeared to perform well, improvement is possible. Image registration could be used to develop a deformation field once a larger amount of patients becomes available which could be updated every time a new patient is treated. Other methods should be considered as well, such as a simple shift in the anterior rectal wall, rather than a deformation field around a model IRS. Additionally, options for directly shifting the dose map, and thus eliminating the need to perform treatment planning on the CT with the V-IRS should be explored.

Next, the mean rectal dose has been shown to be a predictor for acute rectal bleeding, which, on its turn, is a predictor for late rectal bleeding (consequential late effect). Although the mean rectal dose is dependent on the overlap between the rectal wall and the high-dose region, it is mainly affected by the rectum volume, which varies strongly [24, 25]. This change in rectal volume cannot be predicted by the model, and might influence the decision on whether or not to place an IRS.

For 2 patients, patient 7 with a RBI, and patient 8 with a hydrogel, this even led to an increase in predicted NTCP. Future works should include models that use the dose surface histogram (DSH), rather than the DVH in the rectum, as this is much less affected by the rectal volume [26].

During this study the only NTCP taken into account was for late rectal bleeding. Late fecal incontinence, erectile dysfunction, and urinary symptoms are not calculated, but do have an effect on the patients QoL. An appropriate expansion to the system would be to include NTCP models for these types of toxicities. The possible complications after placement of the IRS (pain, rectal perforation) were not taken into account, as the risk of these factors is low (<5%) [27], and are not yet fully described.

Furthermore, the nomograms on which the NTCP model is based are from 2002-2004, where now outdated dose delivery techniques were conformal. The performance of a decision support system based on a V-IRS is partially dependent on the accuracy of the NTCP models. This must be taken into account during further development of the system, by using newer models when these become available.

The current model is isodosimetric which shows the toxicity for both the CT images before the IRS and after the IRS assuming both receive the same dose within the target volume. However, some patients could have improved tumor control probability when treated with higher target dose, which would improve the cost-effectiveness of the IRS (Table 6). Future studies should include an analyses of an isotoxic version of the model, which would analyze how much dose escalation is possible while still maintaining low NTCP values for each of the different situations. Including genetic markers into the NTCP model would also improve the decision support on whether or not to place an IRS in a prostate cancer patient [28].

TABLE 6: An overview of the iNMB of the RBI and the hydrogel spacer after rescaling of the treatment plan to a target dose of 80 Gy in 32 fractions.

	RBI	V-IRS
iNMB original plan	-€1158	-€1032
[range]	[-€2049–€481]	[-€1497– €328]
iNMB scaled plan	-€442	-€379
[range]	[-€1878–€3873]	[-€1476–€3631]
	Hydrogel Spacer	Virtual IRS
iNMB original plan	-€669	-€567
[range]	[-€2308–€526]	[-€1525–€542]
iNMB scaled plan	€376	€619
[range]	[-€2769–€2057]	[-€1210–€2333]

RBI: Rectal Balloon implant, V-IRS: Virtual Implantable Rectum Spacer, iNMB: incremental Net Monetary Benefit.

CONCLUSION

The implantation of an IRS is not cost-effective for all patients, so individual patient assessment is needed. The V-IRS approach in combination with a NTCP model and a CE analysis can serve as the basis for a decision support system for the implantation of either a hydrogel IRS or a rectum balloon implant.

Acknowledgements

Marlies Lendfers is gratefully acknowledged for her help in developing the treatment plans used in this study.

REFERENCES

1. Zelefsky, M.J., X. Pei, J.F. Chou, M. Schechter, M. Kollmeier, B. Cox, et al., *Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes*. Eur Urol, 2011. **60**(6): p. 1133-9.
2. Kalbasi, A., J. Li, A. Berman, S. Swisher-McClure, M. Smaldone, R.G. Uzzo, et al., *Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer*. JAMA Oncol, 2015. **1**(7): p. 897-906.
3. Ben G.L.Vanneste, E.J.V.L., Emile N. van Lin, Joep G.H. van Roermund, and Philippe Lambin, *Prostate Cancer Radiation Therapy: What Do Clinicians Have to Know?* BioMed Research International, 2016. **2016**: p. 14.
4. Vanneste, B.G., L. Van De Voorde, R.J. de Ridder, E.J. Van Limbergen, P. Lambin, E.N. van Lin, *Chronic radiation proctitis: tricks to prevent and treat*. Int J Colorectal Dis, 2015. **30**(10): p. 1293-303.
5. Glass, A.S., J.E. Cowan, M.J. Fuldeore, M.R. Cooperberg, P.R. Carroll, S.A. Kenfield, et al., *Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era*. Urology, 2013. **82**(1): p. 60-5.
6. Pinkawa, M., N.E. Corral, M. Caffaro, M.D. Piroth, R. Holy, V. Djukic, et al., *Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer*. Radiother Oncol, 2011. **100**(3): p. 436-41.
7. Wolf, F., C. Gaisberger, I. Ziegler, E. Krenn, P. Scherer, S. Hruby, et al., *Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency*. Radiother Oncol, 2015. **116**(2): p. 221-5.
8. Gez, E., S. Cytron, R. Ben Yosef, D. London, B.W. Corn, S. Alani, et al., *Application of an interstitial and biodegradable balloon system for prostate-rectum separation during prostate cancer radiotherapy: a prospective multi-center study*. Radiat Oncol, 2013. **8**: p. 96.
9. Hamstra, D.A., N. Mariados, J. Sylvester, D. Shah, L. Karsh, R. Hudes, et al., *Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial*. Int J Radiat Oncol Biol Phys, 2016.
10. Mariados, N., J. Sylvester, D. Shah, L. Karsh, R. Hudes, D. Beyer, et al., *Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy*. Int J Radiat Oncol Biol Phys, 2015. **92**(5): p. 971-7.
11. Vanneste, B.G., A.L. Hoffmann, E.N. van Lin, L. Van De Voorde, M. Pinkawa, P. Lambin, *Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection*. Radiother Oncol, 2016.
12. Hutchinson, R.C., V. Sundaram, M. Folkert, Y. Lotan, *Decision analysis model evaluating the cost of a temporary hydrogel rectal spacer before prostate radiation therapy to reduce the incidence of rectal complications*. Urol Oncol, 2016. **34**(7): p. 291 e19-26.
13. Ben G.L. Vanneste , M.P.-J., Lien Van De Voorde, Emile N. van Lin,, J.v.L. Kees van de Beek, Bram L. Ramaekers, Philippe Lambin, *Spacers in radiotherapy treatment of prostate cancer: Is reduction of*

- toxicity cost-effective? Radiotherapy and Oncology, 2015. **114**(2015): p. 276–281.
14. Cheng, Q., E. Roelofs, B.L. Ramaekers, D. Eekers, J. van Soest, T. Lustberg, et al., *Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer - Comparison of dose, toxicity and cost-effectiveness*. Radiother Oncol, 2016. **118**(2): p. 281-5.
 15. Lambin, P., E. Roelofs, B. Reymen, E.R. Velazquez, J. Buijsen, C.M. Zegers, et al., *'Rapid Learning health care in oncology' - an approach towards decision support systems enabling customised radiotherapy*. Radiother Oncol, 2013. **109**(1): p. 159-64.
 16. Lambin, P., R.G. van Stiphout, M.H. Starmans, E. Rios-Velazquez, G. Nalbantov, H.J. Aerts, et al., *Predicting outcomes in radiation oncology--multifactorial decision support systems*. Nat Rev Clin Oncol, 2013. **10**(1): p. 27-40.
 17. Janssens, G., L. Jacques, J. Orban de Xivry, X. Geets, B. Macq, *Diffeomorphic registration of images with variable contrast enhancement*. Int J Biomed Imaging, 2011. **2011**: p. 891585.
 18. Kupelian, P.A., T.R. Willoughby, C.A. Reddy, E.A. Klein, A. Mahadevan, *Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience*. Int J Radiat Oncol Biol Phys, 2007. **68**(5): p. 1424-30.
 19. Barton, M., *Tables of equivalent dose in 2 Gy fractions: a simple application of the linear quadratic formula*. Int J Radiat Oncol Biol Phys, 1995. **31**(2): p. 371-8.
 20. Marzi, S., B. Saracino, M.G. Petrongari, S. Arcangeli, S. Gomellini, G. Arcangeli, et al., *Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional versus hypofractionated scheme for localized prostate cancer*. J Exp Clin Cancer Res, 2009. **28**: p. 117.
 21. Valdagni, R., M.W. Kattan, T. Rancati, C. Yu, V. Vavassori, G. Fellin, et al., *Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? Building the first set of nomograms for late rectal syndrome*. Int J Radiat Oncol Biol Phys, 2012. **82**(5): p. 1957-66.
 22. Valdagni, R., T. Rancati, C. Fiorino, G. Fellin, A. Magli, M. Baccolini, et al., *Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT*. Int J Radiat Oncol Biol Phys, 2008. **71**(4): p. 1065-73.
 23. *Sensible and sustainable care* W.a.S. the Council for Public Health and Health Care to the Minister of Health, Editor. 2006: Zoetermeer.
 24. de Crevoisier, R., S.L. Tucker, L. Dong, R. Mohan, R. Cheung, J.D. Cox, et al., *Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy*. Int J Radiat Oncol Biol Phys, 2005. **62**(4): p. 965-73.
 25. Hoogeman, M.S., M. van Herk, J. de Bois, J.V. Lebesque, *Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer*. Radiother Oncol, 2005. **74**(2): p. 177-85.
 26. Meijer, G.J., M. van den Brink, M.S. Hoogeman, J. Meinders, J.V. Lebesque, *Dose-wall histograms and normalized dose-surface histograms for the rectum: a new method to analyze the dose distribution over the rectum in conformal radiotherapy*. Int J Radiat Oncol Biol Phys, 1999. **45**(4): p. 1073-80.
 27. Vanneste, B.G., K. van De Beek, L. Lutgens, P. Lambin, *Implantation of a biodegradable rectum balloon*

- implant: tips, Tricks and Pitfalls*. Int Braz J Urol, 2017. **43**.
28. Fachal, L., A. Gomez-Caamano, G.C. Barnett, P. Peleteiro, A.M. Carballo, P. Calvo-Crespo, et al., *A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1*. Nat Genet, 2014. **46**(8): p. 891-4.

CHAPTER 11

Development of an iso-toxic multifactorial model decision support system integrating genetic markers of toxicity for the implantation of a rectum spacer

Acta Oncologica (Accepted)

van Wijk Y, **Vanneste BGL**, Jochems A, Walsh S, Oberije C, Pinkawa M, Ramaekers B, Vega A, Lambin P.

ABSTRACT

Introduction

Previous studies revealed that dose escalated radiotherapy for prostate cancer patients leads to higher tumour control probabilities (TCP) but also to higher rectal toxicities. An isotoxic model was developed to maximize the given dose while controlling the toxicity level. This was applied to analyse the effect of an implantable rectum spacer (IRS) and extended with a genetic test of normal tissue radio-sensitivity. A virtual IRS (V-IRS) was tested using this method. We hypothesized that the patients with increased risk of toxicity would benefit more from an IRS.

Materials and Methods

16 localised prostate cancer patients implanted with an IRS were included in the study. Treatment planning was performed on Computed Tomography (CT) images before and after the placement of the IRS and with a V-IRS. The normal tissue complication probability (NTCP) was calculated using a QUANTEC reviewed model for Grade $\geq$ 2 late rectal bleeding and the number of fractions of the plans were adjusted until the NTCP value was under 5%. The resulting treatment plans were used to calculate the TCP before and after placement of an IRS. This was extended by adding the effect of two published genetic single nucleotide polymorphisms (SNP's) for late rectal bleeding.

Results

The median TCP resulting from the optimized plans in patients before the IRS was 75.1% [32.6-90.5%]. With IRS, the median TCP is significantly higher: 98.9% [80.8-99.9%] ($P<0.01$). The difference in TCP between the V-IRS and the real IRS was 1.8% [0.0-18.0%]. Placing an IRS in the patients with SNP's improved the TCP from 49.0% [16.1-80.8%] and 48.9% [16.0-72.8%] to 96.3% [67.0-99.5%] and 90.1% [49.0-99.5%] ($P<0.01$) respectively for either SNP.

Conclusion

This study was a proof-of-concept for an isotoxic model with genetic biomarkers with a V-IRS as a multifactorial decision support system for the decision of a placement of an IRS.

Keywords

Prostate cancer radiotherapy, implantable rectum spacer, isotoxic model, NTCP and TCP models, multifactorial decision support

INTRODUCTION

Intensity modulated radiotherapy (IMRT) is one of the primary curative treatments for patients with prostate cancer. Studies have revealed that dose escalation leads to better biochemical progression free survival [1,2]. However, the proximity between the anterior rectal wall and the prostate allows for limited dose escalation without resulting in severe gastro-intestinal (GI) toxicity [3,4,5].

The implantable rectum spacer (IRS) is a device developed to spare the rectum by increasing the distance between the anterior rectal wall and the prostate, thus reducing the overlap between the rectal wall and the high dose region [6,7,8,9]. Recent studies have shown that this device significantly reduces the dose in the rectum, thus reducing the risk of complications, for approximately 20% of the patients [5]. For these patients, the IRS would allow for same radiation dose and cure rate with decreased rectal toxicity rates. There is increasing evidence supporting the role of several genetic variants in the development of radiation-induced toxicity to distinguish the patients having increased risk factors for severe rectal and urinary toxicity [10,11]. We hypothesize that the patients with increased risk of radiation-induced rectal toxicity would benefit more from an IRS. Furthermore, the use of IRS in prostate cancer patients allows for more dose escalation, with consequently improving their prospective therapeutic ratio.

In this proof-of-concept study we developed a method to determine the amount of possible dose escalation with the resulting tumour control probability (TCP) without exceeding the set of boundaries for the complication risks: the so-called “isotoxic dose escalation” approach [12,13]. This method is applied to compare the possible dose escalation on patients with plans available before and after the placement of an IRS. This model is combined with a so-called ‘virtual IRS’ (V-IRS) [14]. This method uses image deformation to obtain CT images of patients with a predicted IRS position without having to place one (watch the animation: <https://www.youtube.com/watch?v=tDlagSXMkqw>). Furthermore, this method helps identify the patients for whom significantly higher TCP is possible by placing an IRS.

To further individualize the predictions done for patients, the patients radio-sensitivity needs to be taken into account. Studies have shown that the difference in radio-sensitivity between patients are likely due to common genetic variants, such as single nucleotide polymorphisms (SNPs). We applied the developed method to compare the results for patients using the model including and not including the genetic biomarker.

MATERIAL AND METHODS

Patient characteristics

For this study, 16 patients with localized prostate cancer who had signed an informed consent were included. Two different commercial types of IRS's are used: 8 had received a rectum balloon implant (RBI) (BioProtect Ltd, Israel) [9] and 8 had a hydrogel spacer (HGS) (SpaceO-ARTM System, Augmenix Inc., Waltham, MA) placed [7]. Patient characteristics are projected in table 1. The hydrogel and RBI patients included in this study were consecutively selected in 2011 and 2015, respectively. Both studies were approved by their local ethics committees.

Table 1: Patient characteristics

Characteristic	Subgroup	Number of patients (%)
Risk group	Low	2 (12.5%)
	Intermediate	7 (43.75%)
	High	7 (43.75%)
IRS	Balloon	8 (50%)
	Hydrogel	8 (50%)

IRS: Implantable rectum Spacer
Risk group: Low-risk: no risk factors: PSA <10 ng/ml; Gleason score <7; cT-stage <2b; Intermediate-risk: one risk factor: PSA 10–20 ng/ml or Gleason score =7 or cT-stage = 2b/c; High-risk: two risk factors or PSA >20 ng/ml or Gleason score >7 or cT-stage >2b/c.

Imaging and treatment planning

Standard Computed tomography (CT) imaging was performed twice on all patients while they were in supine position: once before and once after placement of an IRS. These images had a slice thickness of 5 mm for the patients with a HGS, and 3 mm for those with a RBI. The pixel size was 1 mm for all images.

The clinical target volume (CTV) was defined as the prostate for 8 patients, and the prostate including seminal vesicles for the rest and the planning target volume (PTV) was obtained by extending the CTV with 6 mm in all directions to account for uncertainties in planning an treatment delivery. The rectum volumes were delineated as a solid organ, including the rectum as well as the anal canal. The same experienced radiation oncologist (BV) did all delineations.

Plans were performed by a certified technician on all CT images, yielding two treatment plans for each patient (one without IRS, one with IRS). The treatment plans were designed for dose delivery with a volumetric modulated arc technique with 10 MV photon beams (Eclipse Version ICD-10, Varian Medical Systems Inc., Palo Alto, USA). Dose delivery was planned to be done in 28 fractions of 2.5 Gray (Gy) [15]. Dose constraints held during treatment planning are shown in table 2.

Table 2: An overview of the planning constraints set during treatment planning.

Structures	Constraints	
Planning Target Volume	V70 > 95%	V77 < 3%
Rectum Volume	V70 = 0%	
Anal Canal Volume	V74 = 0%	Mean dose < 40 Gy
Anorectum Volume	V54 < 50%	V65 < 20%
Bladder Volume	V70 = 0%	

Gy: Gray, Vxx: percentage of volume receiving more than xx Gy

Isotoxic model

Dose calculations

Treatment planning was performed in fractions of 2.5 Gy instead of 2 Gy, which is the case for the treatment plans on which the NTCP model was based. For this reason, the equivalent 2 Gy dose (EQD2) in the rectum resulting from the treatment plan is calculated and used as input for the model. This is done using the Withers equation [16]:

$$EQD2 = D \cdot \frac{(d + \alpha/\beta)}{(2 + \alpha/\beta)}.$$

Here D is the total dose, d is the fraction dose and α/β represent the fractionation sensitivity of the organ. For late rectal toxicity, the α/β ratio has been estimated to be 3 Gy [17].

NTCP model

The NTCP model used is the Lyman-Kutcher-Burman (LKB) model [18] that was reviewed by the QUANTEC group (quantitative analysis of normal tissue effects in the clinic). This model is described by the equations shown below:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx$$

$$t = \frac{gEUD - TD50}{m \cdot TD50}$$

$$gEUD = \left(\sum_i v_i d_i^{1/n} \right)^n$$

where $gEUD$ stands for generalized equivalent uniform dose, is the number of the DVH bin, is the volume of the bin and is the dose. The LKB model is a dose response curve that uses the $gEUD$ as a dose parameter, which is obtained using the DVH, and a parameter, which determines which part of the DVH is statistically most important. The curve is dependent on the dose required for an NTCP of 50% ($TD50$) and the steepness of the curve (n). The QUANTEC-recommended parameters are $TD50 = 76.9$, $n = 0.09$ and $m = 0.13$ for grade ≥ 2 late rectal toxicity.

Single Nucleotide Polymorphisms

This NTCP model was expanded as a proof-of-concept with genetic markers of rectal toxicity, for which we used published results of a meta-analysis of GWASs (Genome Wide Association Study) for genetic markers of late toxicity, in prostate cancer patients treated with radiotherapy [11]. The two SNPs most associated with rectal bleeding, that approach meta-analysis significance, were selected for the initial proof-of-concept: rs141044160 (SNP 1) with an odds ratio of 2.68 ($P = 2.26 \times 10^{-6}$) and rs7432328 (SNP 2), with an odds ratio of 3.36 ($P = 3.32 \times 10^{-6}$). The SNP's were incorporated into the dose response curve using a published mathematical method [19].

In order to incorporate a SNP into the LKB model, the dose response curve was split into two different dose response curves: one for the population with the SNP and one without. The dosimetric factor used by the LKB is the gEUD, and the parameters which determine the shape of the dose response curve are the TD50, which is the gEUD needed for a 50% response, and m, which is inversely proportional to the gradient at TD50. In order to split the LKB curve into two, we need to determine the new TD50 and the new m for both curves. For this, we need to know the relationship of the response of the curve without SNP and with SNP, p_0 and p_1 respectively, to the original curve p .

The prevalence factor of the SNP can be calculated using the minor allele frequency (MAF) as shown in equation:

$$s = 2 \cdot MAF + MAF^2 \approx 2 \cdot MAF$$

Where s is the prevalence. Because the total probability of toxicity needs to remain the same over the whole populations, the relationship of the two new curves to the original can be described as shown in equation:

$$p = s \cdot p_1 + (1 - s)p_0$$

The odds ratio (OR) can be described as function of p_0 and p_1 as shown in equation:

$$OR = \frac{\frac{p_1}{1-p_1}}{\frac{p_0}{1-p_0}}$$

Which allows us to describe equation $p = s \cdot p_1 + (1 - s)p_0$ as follows

$$p = s \frac{OR \cdot p_0}{p_0(OR-1)+1} + (1 - s)p_0$$

Since the OR of each SNP is reported, as well as the MAF, we can now use the method reported in Appelt & Vogelius [19] to find the correct values for TD50 and m corresponding to the low and high risk curves.

In this method, clinical parameters are incorporated into a dose response by separating the curve for the overall population into two curves: one for the population with the SNP risk allele and one for the population without. This is done using the odds ratio and the proportion between the population with and without the risk factor. The proportion of the population with the SNP risk allele can be calculated using the minor allele frequency. For this study, we demonstrated the effects of the SNPs on the NTCP model by applying it on the patient cohort, assuming they were carriers for either SNP risk allele were considered.

TCP model

The used TCP model [20] was built to predict the clinical response to external beam radiotherapy in patients with low, intermediate and high risk prostate cancer, and is available on <http://predictcancer.org/Main.php?page=TCPprostateModel>. This model utilizes realistic radio biologically input parameters and works for a wide range of treatment strategies [21]. The inputs to the TCP model are the number of fractions, the fraction dose, the treatment modality and the risk group of the patient [20]. The prostate-specific antigen (PSA), TNM and Gleason score are the input factors to the classification of the risk group: low, medium or high (table1).

The TCP model utilizes realistic radio biologically input parameters and works for a wide range of treatment strategies [19]. The model is described using equation:

$$TCP = \left(\frac{1}{k}\right) \sum_{i=1}^k (\exp(-N_0 S(D)_i))$$

where represents groups of patients with separate radiosensitivity, k is the initial clonogen sum and is the surviving fraction of a population of cells irradiated by a total uniform dose . To evaluate the result of dose escalation, only the fraction dose is varied in this study to test the amount of dose escalation possible without exceeding NTCP limits.

Isotoxic method

The proposed model uses an optimized treatment plan for a patient, calculates the DVH in the organs at risk and scales this DVH by changing the fraction dose used during treatment planning. The fraction dose is varied in order to obtain a maximum TCP value without exceeding the cut-off value set for the NTCP value, which, for this paper, is arbitrarily chosen to be 5% (Figure 1). The fraction dose for a plan with 28 fractions advised by the model can

vary between 1.5 and 3.5 Gy. These limits are chosen because a plan with 28 fractions with less than 1.5 Gy, resulting TCP was modelled to always be lower than 25%, and more than 3.5 fractions was to always result in a TCP higher than 95%. In reality 1.5 Gy in 28 fractions would not be for curative treatment, but in this study these plans are calculated for theoretical comparison.

Figure 1. A flowchart of the isotoxic model. The model loads a treatment plan made by an expert and increases or decreases the fraction dose. Each time fraction dose is increased or decreased, the normal tissue complication probability (NTCP) is recalculated until a set cut-off value is reached. The tumour control probability (TCP) is then calculated.

The method only takes into account rectal toxicity, but as the bladder is also an organ at risk, we added a constraint to the bladder dose [22], as is shown in figure 2. To prevent the dose from escalating too much in the bladder, we limited the bladder dose in agreement with published constraints [22]. The percentage of the volume receiving more than 80 Gy (V80%), should be no more than 15%, the V75% no more than 25%, the V70% no more than 35%, and the V65 no more than 50%.

To use the method to select patients for whom the placement of an IRS is beneficial, a minimum increase in TCP should be chosen. For this study, two cut-off values were used for the increase in TCP as a result of the placement of an IRS: 25% and 50%.

Virtual Spacer

In order to use the isotoxic model to predict the improvement of the IRS in a specified patient, CT images of a patient are needed before the placement of the IRS. To this end, a previously developed V-IRS was used [14]. This V-IRS uses a model IRS derived from 7 delineations of a RBI and uses image deformation to insert the model into a CT image of a patient without an IRS, thus creating a virtual image of the patient with an IRS. This virtual image is then subjected to treatment planning, and the isotoxic model is used to calculate the highest possible TCP without exceeding the NTCP limit. In this study we test the V-IRS by comparing the results of the isotoxic model to those of the actual IRS.

Figure 2: The V80%, V75%, V70% and V65% for each of the patients included in the study after the dose was optimised by the isotoxic model. It can be noted that the dose in the bladder is higher for the patients with implantable rectum spacer (IRS) and V-IRS, which is because the dose given to the planning target volume (PTV) can be increased more in patients with an IRS without exceeding the constraints on the rectum toxicity. It can also be noted that the bladder dose remains within the given limits.

Statistics

We used two-tailed Wilcoxon signed rank tests to determine whether the increase in optimal TCP for the plans without IRS and with IRS was significant. The test was also applied to test if the difference between the NTCP values before and after placement was significant. P-values of less than 0.05 were considered significant.

RESULTS

Dose escalation

Giving more dose per fraction increases both the TCP and the NTCP predictions for a given patient (Figure 3). The original plans (before applying the isotoxic method) consisted of 28 fractions of 2.5 Gy, which, for this set of patients corresponds to a median TCP of 80.8% with a range of [51.8-92.0%]. The median fraction dose allowed by the model without exceeding the NTCP constraint before the placement of an IRS was 2.5 Gy [2.4-2.7 Gy] (Table 3), and corresponds to 75.1% [32.6-90.5%] TCP. The TCP for the patients when given a conformal treatment plan of 2 Gy in 35 fractions corresponds to a TCP of 60.8% [26.3-80.9%]. Figure 3 shows that to obtain a median TCP of at least 90%, the dose needs to be escalated further to 2.7 Gy per fraction for a treatment plan with 28 fractions, which was possible for 2 of the 16 patients while holding to the pre-set accepted toxicity rates. For 5 of the patients 2.6 Gy per fraction could be given, and for the remaining patients, no dose escalation was possible.

Table 3: An overview of the fraction dose, the NTCP grade $\geq$ 2 late rectal bleeding and the TCP results. All plans are calculated for 28 fractions.

	Before IRS <i>Median [range]</i>	After IRS <i>Median [range]</i>	V-IRS <i>Median [range]</i>
EUD (Gy)	58.5 [57.2–60.4]	59.0 [57.6–60.3]	59.0 [57.5–60.2]
Fraction dose (Gy)	2.5 [2.4–2.7]	2.8 [2.5–3.4]	3.1 [2.5–3.9]
NTCP late rectal bleeding (%)	3.5 [2.5–5.2]	3.7 [2.7–5.1]	3.6 [2.6–4.8]
TCP (%)	75.1 [32.6–90.5]	98.9 [80.8–99.9]	99.3 [80.8–100.0]

IRS: Implantable Rectum Spacer; V-IRS: virtual IRS, EUD: equivalent uniform dose in rectum with $n=0.09$, TCP: Tumor Control Probability, NTCP: Normal Tissue Complication Probability

IRS gain

The placement of an IRS resulted in an increase in advised fraction dose of 0.4 Gy [-0.1-0.9 Gy] on average for all patients. Note that the minimum increase is negative, which means this is a decrease. This results in an absolute increase in TCP of 21.1% [-8.9-57.9%] which is statistically significant ($P < 0.01$) (Figure 4). Patient specific outcomes have been plotted in a similar manner in Figure 5. In only one patient the TCP after the placement of an IRS is lower than before placement. For this patient, the rectum volume had decreased after the placement of an IRS (from 268.9 cm³ to 156.1 cm³).

Figure 3. The median tumour control probability (TCP) and the median normal tissue complication probability (NTCP) is plotted against the fraction dose for the patients without implantable rectum spacer (IRS) and with IRS.

Figure 4. The median tumour control probability (TCP) and range, as well as the median normal tissue complication probability (NTCP) and range, for the patients without implantable rectum spacer (IRS), with IRS and with the virtual IRS (V-IRS) is shown.

The difference in the NTCP resulting from the optimized plan for the patients without IRS and with IRS is 0.15% and is not significant ($P = 0.47$). We performed an analyses for different NTCP limits in Figure 6. Per group, the NTCP limit of the iso-toxic model is set to be 2.5, 5 and 10%. It can be observed that even when the NTCP limit is 2.5%, the patients with spacers perform well regarding the TCP, with median values of 95% and 99% for the actual IRS and the V-IRS respectively. When the NTCP limit is 10%, the improvement found by the IRS has less impact (90% to 99%). The V-IRS performs reasonably well for different ranges, though with the tight NTCP limit of 2.5%, the real IRS predicts a lower median TCP than the V-IRS (95% as opposed to 99%).

Figure 5. The normal tissue complication probability (NTCP) predictions as function of the fraction dose for each individual patient is projected before and after the placement of an implantable rectum spacer (IRS). The first 8 patients received a rectum balloon implant (RBI) and the second 8 received a hydrogel spacer.

Figure 6. The NTCP limit of the isotoxic model is changed to different numbers: 2.5, 5 and 10%. The median tumour control probability (TCP) and range, as well as the specific median normal tissue complication probability (NTCP) and range, for the patients without implantable rectum spacer (IRS), with IRS and with the virtual IRS (V-IRS).

If an increase in TCP of 25% is taken as a threshold for the decision to place an IRS, then 7 of the 16 patients would be selected by the model for the placement of an IRS. Two patients even had an increased TCP of 50% resulting from the IRS.

Performance V-IRS

The difference in fractionation result between the V-IRS and the real IRS was a median of 0.3 Gy [0.0-0.8 Gy], which translates to a median TCP difference of 1.8% [0.0-18.0%] (Figure 4 and 6). The difference between the optimized TCP for the real IRS and the V-IRS was not significant ($P = 0.2$). There were two patients for whom the difference in TCP between the V-IRS plan and the IRS plan was 18%, and in both patients the rectum volume had changed significantly (57.9% and 58.1% volume decrease in the image after the IRS).

When considering a minimum increase in TCP of 25% for the placement of an IRS, then 6 of the 16 patients would be selected by the model using the V-IRS, in contrary to the 7 selected using the actual IRS. The increase predicted by the V-IRS was underestimated compared to the real IRS in one patient, with an increase of 13.7% versus 27.7%. The two patients who had an increased TCP of 50% resulting from the real IRS, had the same increase predicted by the V-IRS.

Figure 7. The median tumour control probability (TCP) and the mean normal tissue complication probability (NTCP) is plotted against the fraction dose for the patients with SNP's (a: rs141044160 and b: rs7432328) without implantable rectum spacer (IRS) and with IRS.

The median NTCP for the original plan (28 fractions of 2.5 Gy) was 11.2% [2.2-19.6%] and 13.1% [2.7-22.5%] for SNP 1 and SNP 2 respectively, which is reduced significantly ($P < 0.01$) when using the isotoxic method. The results show (Table 4) that if the patients are carriers of

the chosen SNPs, the TCP while restraining the NTCP would be 49.0% for SNP 1, and 48.9% for SNP 2. The placement of an IRS resulted in significantly better TCP values ($P<0.01$), with a median of 96.3% [67.0-99.5%] and 90.1% [49.0-99.5%] for SNP 1 and SNP 2 respectively, which was significantly higher than without IRS ($P<0.01$) for both SNP's. Four other SNP's were found to be near significant for late rectal bleeding; results for these SNP's are shown in Figure 8. We performed a sensitivity analyses on a range of odds ratios to show the possible effects of different SNP's for late rectal bleeding in Figure 9.

Table 4. An overview of the hypothetical fraction dose, the NTCP grade $\geq$ 2 late rectal bleeding and the TCP results if the patients were carrier of the risk alleles for either of the selected SNP's. All plans are calculated for 28 fractions.

SNP 1	Before IRS <i>Median [range]</i>	After IRS <i>Median [range]</i>	V-IRS <i>Median [range]</i>
EUD (Gy)	53.9 [52.1–55.1]	54.1 [52.7–55.2]	53.9 [53.0–54.9]
Fraction dose (Gy)	2.4 [2.2–2.6]	2.7 [2.4–3.2]	2.9 [2.3–3.7]
NTCP late rectal bleeding (%)	3.8 [2.5–4.9]	3.9 [2.8–4.9]	3.8 [3.0–4.6]
TCP (%)	49.0 [16.1–80.8]	96.3 [67.0–99.5]	96.4 [48.9–100.0]
SNP 2	Before IRS <i>Median [range]</i>	After IRS <i>Median [range]</i>	V-IRS <i>Median [range]</i>
EUD (Gy)	53.2 [51.0–54.4]	52.9 [51.5–54.1]	53.3 [51.3–54.3]
Fraction dose (Gy)	2.3 [2.2–2.5]	2.6 [2.3–3.2]	2.9 [2.3–3.7]
NTCP late rectal bleeding (%)	3.8 [2.3–5.0]	3.8 [2.6–5.2]	4.1 [2.5–5.2]
TCP (%)	48.9 [16.0–72.8]	90.1 [49.0–99.5]	96.4 [49.0–100.0]

IRS: Implantable Rectum Spacer, V-IRS: virtual IRS, EUD: equivalent uniform dose in rectum with $n=0.09$, TCP: Tumor Control Probability, NTCP: Normal Tissue Complication Probability, SNP: Single-Nucleotide Polymorphism, SNP 1: rs141044160, SNP 2: rs7432328

Figure 8: The SNP's shown in the paper are the two SNP's that had the most effect on the NTCP, but six close to significant SNP's for late rectal bleeding were found. The results from these others SNP's without implantable rectum spacer (IRS) are shown in figure (a). In figure (b) the results are shown with IRS. Only the SNP's with rsID rs141044160 and rs7432328 were used in the paper. Note that rs4804134 and rs12497518 had odds ratios of 0.6, and thus lowered the risk of late rectal bleeding. Also note that though they had the same odds ratio, the curves differ. This is due to the difference in minor allele frequency (0.31 and 0.47 respectively).

Figure 9: To demonstrate the effect of the odds ratios (ORs) single nucleotide polymorphisms (SNPs), the OR's of the SNPs were artificially varied between 0.5 and 10, and the resulting normal tissue complication probability (NTCP) was calculated for the different fraction doses. Since the tumour control probability (TCP) is not effected by the SNPs, this remains the same. The figure (a) shows the results without implantable rectum spacer (IRS). The Minor Allele Frequency for all these ORs was assumed to be 0.05. The results are shown for the patients with IRS in figure (b). SNPs with an OR lower than 1 have a protective effect on the rectum. Patients with these SNPs have a lower risk of late rectal toxicity, and can safely be considered for more dose escalation.

DISCUSSION

In this study, we have developed an isotoxic method integrating genetic markers of rectal radio-sensitivity combined with a V-IRS which can be used to support the decision for the implantation of an IRS for a specified patient or not. The method applies image deformation to a CT image of a patient without IRS, and creates a virtual CT image with IRS. The method calculates the maximum dose per fraction that can be given without exceeding an upfront determined limit for the NTCP value for late rectal bleeding.

The results show that a higher prescribed dose should be given to improve TCP, and can be safely given when combined with an IRS. This method can be used as the basis of a multifactorial DSS, which can be used as a meta-treatment planning system [23] to decide in which patients to place an IRS, as well as advise on how much dose escalation is possible to apply for a specified patient [24, 25]. This method also allows for shared decision making, taking into account the patients priorities, such as cure rate or risk of toxicity.

Our method has two main strengths. Firstly, the method uses NTCP prediction values to predict the amount of dose escalation possible while keeping rectal toxicities under control. Applying this method in the clinic would allow dose escalation to be used more safely and improve outcomes for patients [26]. Secondly, treatment planning with an IRS can be applied to a CT of a patient without the real implantation of the IRS itself. This means that the increase in TCP with the IRS for the specified patient can be estimated without having to put the patient through the discomfort of the implantation, and without the additional costs of the placement of the IRS, before it has been established that an IRS will be beneficial.

The results showed that the system would advise further dose escalation even without the placement of an IRS, which would result in better outcomes for these patients. The system foresees a gain in TCP for 7 of the 16 patients, showing the model can be used as to identify patients for whom an IRS is beneficial. Using the V-IRS, 6 of the 7 patients for whom the spacer would be significantly effective could be identified. The patient not identified had very different rectal fillings before and after IRS placement. This demonstrates that this DSS has the potential to identify patients who benefit most from an IRS. This improves the cost-effectiveness of the IRS by only placing it in patients who would benefit from it, while also improving their survival and quality of life.

During this study, SNP's were incorporated into the NTCP model and tested on the patient cohort, assuming all were heterogeneous for either SNP. Because the toxicity risk of a carrier is larger than for a non-carrier, these patients could normally be considered for alternative treatments, such as surgery. However, the method presented here has the potential to identify patients with this SNP who could be treated safely with radiotherapy after placement

of an IRS. This would be beneficial, since placing an IRS is less invasive and has a very low to no impact on the quality of life, especially in comparison with surgery [8]. This would also be beneficial for patients who don't want an operation or who are not candidates for surgery. One of the main limitations of the study was the small amount of patients included. Though they were sufficient for a first proof-of-concept, a more elaborate study including a larger amount of patients is required for internal validation of the method, and additional data sets are required for external validation.

Furthermore, the LKB model uses the entire DVH as a predictor for late rectal bleeding, which is partly effected by the rectal volume, a factor which varies strongly over time [27]. The model cannot predict these changes in rectal volume, and for some patients this may influence the outcome. For two patients, this difference in volume was as much as 150 cm³, and for one patient this resulted in a large overestimation of the NTCP by the V-IRS. For another patient the decrease in rectal volume even resulted in an increased NTCP after the placement of the IRS. A possible solution to this problem is to submit patients with very full rectums to rescanning, or for patients to be given a laxative prior to scanning. For future validation of the V-IRS, only CT scans with similar rectal filling before and after IRS placement should be used, as only then a fair comparison can be made. Finally, concerning optimising the treatment planning technique: it is possible to reduce intermediate dose levels (30–50 Gy) in the rectum region by an arc-therapy with an avoidance-region near the rectum.

Another possible error in both the TCP and the NTCP model is the α/β ratio, which varies between prostate, rectum and bladder. In order to fully understand the effect possible errors in the α/β ratio have on the calculated outcome, a sensitivity analyses should be done.

The V-IRS used in this study was based on a RBI, a closed system which has a predictable shape, while 8 of the patients were implanted with a HGS, which has a highly variable shape [28]. However, patients with a large increase in TCP resulting from a hydrogel spacer can still be identified using the V-IRS, and therefore it still has potential as the basis of the DSS, even for the hydrogel spacer. The V-IRS has been published in a proof-of-concept study and has not been validated yet.

The integration of the SNPs is theoretical in this study, as none of the patients were sequenced and tested for the SNPs, and as the MAF is low (0.05 and 0.06), it is not likely any of them would be carriers. An improved method would be to build an NTCP model on a large patient cohort for whom sequencing has been done and for whom outcome data has been collected. Also, though SNPs have been identified that are significant for rectal toxicity in general, currently no SNPs have been found to be significant for late rectal bleeding specifically [11].

To date, six SNPs have been associated with rectal bleeding (11), of which two were used in this study. These SNPs approaching statistical significance in a meta-analysis ($P < 5 \times 10^{-6}$). Further validation in larger studies are needed before incorporate these SNPs in NTCP models. Once significant SNPs are identified, these can be incorporated into NTCP models. The NTCP model is dependent on the DVH in the rectum; however, during treatment this DVH might vary depending on day-to-day variability of rectum filling. This could influence the accuracy of the NTCP model. In order to fully demonstrate the effect this has on the NTCP prediction, the real administered rectal dose should be computed. Also, the NTCP model used in this study only uses the DVH as a predictor for late rectal bleeding, however, studies have shown that several clinical parameters (diabetes, abdominal surgery, etc.) are also strong predictors. In future work, we intend to include NTCP models using clinical predictors into the model as well as fully integrate multiple SNPs. We also want to validate the method of combining published SNP's with NTCP models on a dataset for which sequencing was done, and for which outcomes were known.

Including different endpoints for the toxicity models, such as incontinence, erectile dysfunction and urinary toxicity would serve to further improve patient specific decision making. Another good expansion of the model would be to add a cost-effectiveness analyses, which would enhance the cost-effectiveness of the IRS, a topic that is becoming increasingly important due to ever-expanding expenses in health care [29, 30]. Another development would be to focus on hypofractionation as well. Possibilities for extreme hypofractionation, such as stereotactic radiotherapy, single fraction high dose rate brachytherapy or single shot proton therapy could be explored. This would serve to further increase patient prospects as well as cost-effectiveness.

Analyses should be done on how easily prescription dose can be adjusted, and whether variation in fraction dose or number of fractions would be most effective.

The isotoxic model integrating genetic markers for rectal toxicity developed in this study can be used to evaluate a treatment plan, and test how much dose can be given without causing excessive damage to the rectum. Thus sparing the organs at risk at a chosen described level while optimizing the TCP. In combination with the V-IRS, this method can serve as the basis for a DSS for the implantation of an IRS.

REFERENCES

1. Kalbasi A, Li J, Berman A, et al. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. *JAMA Oncol.* 2015;1:897-906.
2. Zelefsky MJ, Pei X, Chou JF, et al. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. *Eur Urol.* 2011;60:1133-9.
3. Glass AS, Cowan JE, Fuldeore MJ, et al. Patient demographics, quality of life, and disease features of men with newly diagnosed prostate cancer: trends in the PSA era. *Urology.* 2013;82:60-5.
4. Vanneste BG, Van De Voorde L, de Ridder RJ, et al. Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis.* 2015;30:1293-303.
5. Vanneste BG, Hoffmann AL, van Lin EN, et al. Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection. *Radiother Oncol.* 2016;121:118-23.
6. Gez E, Cytron S, Ben Yosef R, et al. Application of an interstitial and biodegradable balloon system for prostate-rectum separation during prostate cancer radiotherapy: a prospective multi-center study. *Radiat Oncol.* 2013;8:96.
7. Pinkawa M, Corral NE, Caffaro M, et al. Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. *Radiother Oncol.* 2011;100:436-41.
8. Vanneste BG, van De Beek K, Lutgens L, et al. Implantation of a biodegradable rectum balloon implant: tips, Tricks and Pitfalls. *Int Braz J Urol.* 2017;43.
9. Vanneste BGL, van Wijk Y, Lutgens LC, et al. Dynamics of rectal balloon implant shrinkage in prostate VMAT : Influence on anorectal dose and late rectal complication risk. *Strahlenther Onkol.* 2017.
10. Fachal L, Gomez-Caamano A, Barnett GC, et al. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. *Nat Genet.* 2014;46:891-4.
11. Kerns SL, Dorling L, Fachal L, et al. Meta-analysis of Genome Wide Association Studies Identifies Genetic Markers of Late Toxicity Following Radiotherapy for Prostate Cancer. *EBioMedicine.* 2016;10:150-63.
12. Zindler JD, Thomas CR, Jr., Hahn SM, et al. Increasing the Therapeutic Ratio of Stereotactic Ablative Radiotherapy by Individualized Isotoxic Dose Prescription. *J Natl Cancer Inst.* 2016;108.
13. De Ruyscher D, van Baardwijk A, Steevens J, et al. Individualised isotoxic accelerated radiotherapy and chemotherapy are associated with improved long-term survival of patients with stage III NSCLC: a prospective population-based study. *Radiother Oncol.* 2012;102:228-33.
14. van Wijk Y, Vanneste BGL, Walsh S, et al. Development of a virtual spacer to support the decision for the placement of an implantable rectum spacer for prostate cancer radiotherapy: Comparison of dose, toxicity and cost-effectiveness. *Radiother Oncol.* 2017;125:107-12.
15. Kupelian PA, Willoughby TR, Reddy CA, et al. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys.* 2007;68:1424-30.
16. Withers HR, Thames HD, Jr., Peters LJ. A new isoeffect curve for change in dose per fraction. *Radiother Oncol.* 1983;1:187-91.
17. Marzi S, Saracino B, Petrongari MG, et al. Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional versus hypofractionated scheme for localized prostate cancer. *J Exp Clin Cancer Res.*

- 2009;28:117.
18. Michalski JM, Gay H, Jackson A, et al. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys.* 2010;76:S123-9.
 19. Appelt AL, Vogelius IR. A method to adjust radiation dose-response relationships for clinical risk factors. *Radiother Oncol.* 2012;102:352-4.
 20. Walsh S, van der Putten W. A TCP model for external beam treatment of intermediate-risk prostate cancer. *Med Phys.* 2013;40:031709.
 21. Stewart RD, Li XA. BGRT: biologically guided radiation therapy-the future is fast approaching! *Med Phys.* 2007;34:3739-51.
 22. Viswanathan AN, Yorke ED, Marks LB, et al. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys.* 2010;76:S116-22.
 23. Chetty IJ, Martel MK, Jaffray DA, et al. Technology for Innovation in Radiation Oncology. *Int J Radiat Oncol Biol Phys.* 2015;93:485-92.
 24. Lambin P, Zindler J, Vanneste B, et al. Modern clinical research: How rapid learning health care and cohort multiple randomised clinical trials complement traditional evidence based medicine. *Acta Oncol.* 2015;54:1289-300.
 25. Lambin P, Roelofs E, Reymen B, et al. 'Rapid Learning health care in oncology' - an approach towards decision support systems enabling customised radiotherapy'. *Radiother Oncol.* 2013;109:159-64.
 26. Reymen B, van Baardwijk A, Wanders R, et al. Long-term survival of stage T4N0-1 and single station IIIA-N2 NS-CLC patients treated with definitive chemo-radiotherapy using individualised isotoxic accelerated radiotherapy (INDAR). *Radiother Oncol.* 2014;110:482-7.
 27. Hoogeman MS, van Herk M, de Bois J, et al. Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. *Radiother Oncol.* 2005;74:177-85.
 28. Pinkawa M, Klotz J, Djukic V, et al. Learning curve in the application of a hydrogel spacer to protect the rectal wall during radiotherapy of localized prostate cancer. *Urology.* 2013;82:963-8.
 29. Lambin P, Zindler J, Vanneste BG, et al. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev.* 2017;109:131-53.
 30. Vanneste BG, Pijs-Johannesma M, Van De Voorde L, et al. Spacers in radiotherapy treatment of prostate cancer: is reduction of toxicity cost-effective? *Radiother Oncol.* 2015;114:276-81.

CHAPTER 12

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Given the improvements in clinical outcome that image-guided external beam radiation therapy of prostate cancer (PCa) has achieved through dose escalation during the last decades, the quality of life of these patients is now gaining more attention. As gastrointestinal (GI) toxicity is nowadays considered to be the main limitation in EBRT for PCa, efforts have been undertaken to achieve improved sparing of the ano-rectal complex, and consequently decrease the risk of GI toxicity. One approach to prevent rectal volumes from being exposed to high doses is to artificially increase the distance between the prostate and the ano-rectal wall using a novel technique: with an implantable rectum spacer (IRS).

The aim of the research work presented here is to implement the IRS in prostate EBRT, and to determine under which conditions an IRS significantly reduces the risk of developing high-grade (i.e., Grade 2 or higher) GI toxicities.

The main hypotheses of this thesis are:

1. An IRS is a cost-effective tool in prostate cancer EBRT: it significantly reduces both the risk of severe GI toxicity, as well as the treatment costs associated with these side effects.
2. PCa patients who are expected to benefit most from IRS implantation can be identified through decision rules solely based on clinical risk factors, prior to EBRT and IRS implantation.
3. An RBI induced prostate-rectum separation of at least 1 cm, throughout the whole course of image-guided, moderately hypofractionated VMAT, reduces the risk of developing Grade 2 or higher GI toxicity.
4. The construction of a virtual IRS, in combination with a toxicity prediction model and a cost-effectiveness analysis, provides the basis for developing a decision support tool regarding implanting an IRS prior to EBRT for PCa.

In this chapter, a motivated view of the methods, the advances in knowledge in the field, the implications for patient care, and a critical reflection of the results obtained will be presented. Furthermore, limitations of the research described in this thesis are discussed.

With a shared decision-making approach towards personalized and participative medicine

Chapter 2 provides a general overview of prostate RT and describes the first objective of the thesis. As the clinical outcome of different treatment options for PCa (i.e., surgery, external beam radiation therapy, brachytherapy, active surveillance) is already at a very high level, quality of life plays a prominent role in the post-treatment period, which can be both functional (urinary, gastrointestinal, and erectile side effects) as well as psychological (post-treatment decisional regret). To optimize quality of life, a *shared decision-making* approach is presented, for which the author has developed and introduced a *patient decision aid* (PDA) in the clinic (<http://www.treatmentchoice.info/decision-aid-tools.html>). A paradigm shift from the currently population-

based medicine towards a participatory and less paternalistic approach is presented. Previously, several studies showed that approximately 70% of the patients want to be actively involved when an important medical decision has to be made [1,2]. Stacey and colleagues revealed Level I evidence that patients exposed to decision aids either during or in preparation for a consultation with a clinician feel more knowledgeable, better informed, and clearer about their values, as well as probably having a more active role in decision-making and more accurate risk perceptions. Nowadays, decisions on the most appropriate treatment for each patient are dependent on unique individual patient characteristics and preferences, clinician judgment, and resources availability. The PDA tool provides evidence-based information (updated with the recently published randomized phase III trial, PROTECT [3,4]) about the different treatment options. The pros and cons of treatment-specific complications and treatment comparison for the individual patient are set out in a clear and easily understandable way, without medical jargon. A knowledge test has also been included in the PDA to assess whether a patient has understood the impact of every treatment modality and its specific advantages and disadvantages. Furthermore, the individual preferences of a patient are included: they decide what is important for them, for example absolutely avoiding incontinence problems, or running absolutely no risk of rectal injury. Finally, a comparison of all the possible treatments is presented to patients, such that they can make the best individual decision that best complies with their preferences in balancing the risks and benefits. With this PDA, physicians can understand the needs of their patients better. The aim is to provide patients with objective, evidence-based information about the possible treatment options. Only in that way are patients able to participate in making decisions about their treatment.

To fine-tune, implement, and evaluate the impact of the developed PDA, a prospective study (PRODECA, NCT03278197) has recently started at MAASTRO Clinic in cooperation with the Maastricht University Medical Center (MUMC) and the Zuyderland hospitals. This study comprises 3 phases with the following aims.

Firstly, a *development phase*: to assess the decisional needs of both patients and clinicians. It will also test the patients' and clinicians' comprehension, and the acceptability and usability of the "alpha version" of the tool (first draft with treated patients and clinicians according to the IPDAS criteria (<http://ipdas.ohri.ca>; IPDAS: International Patient Decision Aids Standards). The development phase will continue with a value clarification: a Delphi study with former prostate cancer patients to determine the most important patient preferences and value clarification aspects the decision aid should include.

Secondly, an *implementation phase*: to develop an implementation and dissemination plan for shared decision-making which is based on the evaluation of barriers and facilitators with regard to the use of patient decision aid tools in clinical practice.

Thirdly, the *evaluation phase*: to establish the impact of the shared decision-making process. Here, the extent to which clinicians involve patients in the decision-making process will be evaluated. Furthermore, the decisional conflict will be assessed using the Decisional Conflict Scale (DCS), to measure personal perceptions of: a) uncertainty in choosing options; b) factors contributing to uncertainties, such as feeling uninformed, unclear about personal values, and unsupported in decision-making; and c) effective decision-making, such as feeling the choice is informed, values-based, and likely to be implemented, and expressing satisfaction with the choice [5,6]. The DCS comprises 16 statements related to feeling informed, decisional uncertainty, clear values, support, and quality of decisions. Each of these statements is scored on a five-point Likert scale, from 1 (strongly agree) to 5 (strongly disagree) [5,6].

For the reasons mentioned above, using PDAs can help increase a patient's quality of life. However, its use can also entail possible restrictions.

Firstly, patients can find it stressful and problematic to be empowered to decide about their treatment [7].

Secondly, a treatment choice should ideally be a reflection of a well-balanced evaluation of the side effects and the benefits of each treatment modality. However, in reality treatment decisions are indisputably very subjective, depending on the personal contact with the primary attending physician, and the knowledge of family or friends diagnosed with PCa and their relevant treatment [8]. Sommers and colleagues concluded that the strongest predictor of treatment choice remains the type of clinician seen at the first visit, mainly based on the preferences and expectations of the patients, rather than on the biases of the treating clinician [9]. In addition, van Tol and colleagues reported on the influence of the treatment choice by the hospital the patients visited [10].

Thirdly, the choice to become involved in the treatment decision process is of course an individual one, but is also culturally dependent [11,12]. Although scientific evidence is lacking, it is the author's personal experience that men living in the northern Netherlands are more willing to be involved and to be in charge of their own treatment decision those living in the southern Netherlands. The latter seem to be more at home with the paternalistic model in which treatment decisions are solely made by the physician.

Fourthly, several trials reported on the higher satisfaction level of patients, with a trend to less regret, and a higher quality of life of these individuals who are involved in their treatment process [13,14]. However, patients who – generally speaking – are prone to respond to surveys, are more likely to be well educated, affluent, motivated, and interested, and therefore these patients are biased, as opposed to a random selection taken from the entire population.

In the next step of our study, the shared decision-making process will be integrated in the clinical workup of PCa patients at the Department of Urology of MUMC and at MAASTRO Clinic. To maximize the integration and the benefit of the multi-disciplinary team, in future, joint consultations

by the urologist and radiation oncologist should be implemented for PCa patients who are to be treated in our institutions.

Prevention and treatment of anorectal toxicity

In **Chapter 3**, measures to reduce the risk of CRP by sophisticated RT techniques (intensity-modulated RT, volumetric arc RT, image-guided RT) and the implementation of new rectum-sparing devices have been determined. Since there is no consensus on the optimal treatment of CRP in the literature, we have developed a practical algorithm for the treatment of CRP, which is based on a review of the literature. This forms the basis for a short operating procedure that has been implemented for the treatment of CRP in the Department of Gastroenterology of the MUMC. However, the proposed treatments are neither based on a systematic literature review nor on a meta-analysis. Furthermore, the data were mostly acquired from small prospective phase II randomized trials. However, the series are small and no randomized phase III trials have been published.

PART I – MODELLING STUDIES

The importance of cost-effectiveness analysis of IRS for healthcare providers

The first hypothesis of this thesis was that an IRS is a cost-effective tool in prostate EBRT related to less severe GI toxicity, with a reduction in treatment costs associated with these GI side effects. Worldwide, there is increasing concern about the growing costs of cancer care [15]. Medical scientists must explore the “beneficial effects” of new therapies, devices, and technologies, and answer the question whether the extra costs are justified by the increased benefits. Due to ever-expanding healthcare expenses, knowledge about the cost of treatments is continuously gaining importance, in particular knowledge on how extra costs are related to the additional gain in health-related outcome. An economic evaluation of the trade-off between these costs and side effects of new treatments is a very attractive approach to implement new modalities in the clinic.

Chapter 4 demonstrates that the extra costs are cost-effective of the gain in quality of life obtained through a reduction in rectal side effects in patients with prostate cancer undergoing EBRT while using an IRS. Whether a new strategy is considered cost-effective depends on how much a society is willing to pay per gained Quality Adjusted Life Year (QALY). This is referred as the ceiling ratio. In the Netherlands, a ceiling ratio of EUR 80,000 per gained QALY is adopted as a cost-effective treatment. If the ceiling ratio is below EUR 80,000, the new treatment is deemed cost-effective and could be reimbursed for most patients based on this information. At the start of the study, there were intensive discussions with healthcare insurance companies about reimbursing the IRS in PCa radiotherapy, but without success for every patient. Instead, an agreement has been reached with some insurance companies to reimburse the IRS for patients who are at very high risk of developing rectal injuries. Additionally, internal and external funding was obtained to cover the expenses for the supplementary costs to implant an IRS in these high-risk patients.

Cost-effectiveness analyses are important examinations but have several limitations. Firstly, for the implementation of new therapies or devices such analyses are not based on data from phase III randomized clinical trials, but on small planning studies and expert opinions. This is inherent to cost-effective analysis of new innovations, because no “level one” evidence (i.e., evidence that is based on at least one randomized phase III trial) is available. However, recently a phase III randomized control trial has been performed by Hamstra and colleagues, who reported with a median of 3 year follow-up a decrease of Grade ≥ 2 GI toxicities of 5.7% and 0%, for the treatment without IRS and with IRS (IMRT-IRS and IMRT+IRS), respectively [16]. Grade ≥ 1 urinary toxicity was reduced from 15% for IMRT-IRS to 4% for IMRT+IRS ($p=0.46$). They concluded that men in the IMRT+IRS arm had less bowel toxicity with consequently fewer decreases in both urinary and bowel quality of life compared to the IMRT-IRS group. Based on these insights, performing a new analysis – one that includes the reported GI toxicities, the additional genitourinary toxicities, and the improvements in quality of life – is recommended, to be able to more accurately predict

the cost-effectiveness of the IRS.

Secondly, the ceiling ratio of EUR 80,000 per QALY is decisive for the analysis. However, the willingness-to-pay values per QALY gained differ across continents and countries; for example, in the UK the threshold of GBP 20,000–30,000 per QALY is accepted, whereas in the US the threshold of USD 50,000–100,000 per QALY or even more is mentioned, while in Australia AUD 76,000 is the recommended QALY. These differences in threshold levels have a huge impact on the implications of all cost-effectiveness results worldwide. It depends on what the society is willing to pay to be cost-effective.

Thirdly, normal-tissue complication models are used as input factors for these analyses. However, these models are (mostly) based on dosimetric data only, and lack clinical, individual, and genetic information. Validated multivariable NTCP models integrating this information should therefore be used for future cost-effectiveness analyses.

Finally, normal-tissue complication models are known to be RT-technique dependent. Models that have been developed and validated for 3D-CRT cannot be applied to IMRT or even proton therapy, because the normal-tissue dose heterogeneity obtained by the latter techniques is usually much larger than for the former technique. Hence, judicious use and validation of the NTCP models for clinical decision-making is indicated for each technique.

Patient heterogeneity of PCa radiotherapy induced rectal toxicity

The second hypothesis of this thesis was that decision rules based on clinical risk factors can identify PCa patients with a high risk of developing radiation-induced rectal toxicity prior to IRS implantation. As an IRS is not even beneficial for all PCa patients undergoing EBRT, the implication of this hypothesis is that patients who are expected to benefit most from IRS implantation can be identified *prior* to implantation (**Chapter 5**). As a direct consequence, the cost-effectiveness of IRS implantation is expected to increase.

To introduce new techniques in the Netherlands, the Royal Netherlands Academy of Arts and Sciences (KNAW) distributed a comprehensive foresight study of the methodology that should be applied to generate relevant evidence for implementing new technologies in health care [17]. An example of such a methodology is the *model-based approach*, which has been applied for the approval of proton therapy facilities, and consequently the introduction and validation of the clinical benefit of proton therapy in the Netherlands. Recently, the Health Council of the Netherlands (Gezondheidsraad) delivered a report directing that this model-based approach should adopt the use of a decision support system to be able to select patients for proton therapy when the reduction of toxicity forms the primary indication for using this technology [18–20]. According to guidelines of the Dutch Society of for Radiotherapy and Oncology (NvRO), a predicted reduction of 10% of Grade 2 complications, 5% of Grade 3 complications, and 2% of Grade 4 and Grade 5 complications would be required to justify the increased costs for such

treatments. Dutch proton therapy centers are required to test the benefit of proton therapy in advance for individual patients using such decision rules. Only if the expected toxicity reduction exceeds the aforementioned thresholds, will treatments be reimbursed. Such a model-based approach should be also applied for the implementation and wide-spread use of an IRS.

The two decision rules generated in **Chapter 5** can be expanded to include patients who have a very high risk of developing rectal toxicity due to, for example, re-irradiation, inflammatory bowel disease, or dosimetric high burden. The cost-effectiveness of the IRS is expected to improve since those patients will benefit more from an IRS than others. If the national toxicity reduction guidelines of the NvRO are applied, it is estimated that approximately 15% of the localized prostate cancer patients would benefit from an IRS, and consequently should have its implantation reimbursed. Further discussions with health insurance companies are required to effectuate this.

A model-based approach to select PCa patients who are expected to benefit most from IRS implantation prior to EBRT shows promise. However, conscientious and judicious use of this approach is needed, due to the fact that flaws in the models reported in Part I of this thesis exist (**Chapter 5** and **Chapter 6**).

Firstly, how often the side effects predicted by dose–response models will occur is not completely understood. These models consider only severe complications, such as bleeding or fistulas. Yet more common complications, such as fecal incontinence and urgency, are not included in these models, and are known to also compromise the quality of life in PCa patients undergoing EBRT. Secondly, the NTCP models used in this work have been initially validated for cohorts of patients where no IRS had been implanted.

Thirdly, the NTCP models by Valdagni and colleagues and Buettner and colleagues have only been internally validated. These models need external validation in an independent patient cohort. Fourthly, both the nomograms by Valdagni and colleagues and the dose-surface maps by Buettner and colleagues were based on data from dose distributions that are less conformal than those being delivered by modern IMRT techniques with daily image-guided setup correction methods having improved the precision of dose delivery. This possibly could enhance the non-dosimetric predictors for rectal toxicity.

Fifthly, statistical uncertainty in these models has not been taken into account, which could have lead to an over- or underestimation of the complication probabilities.

Sixthly, other clinical factors than those which were included in the nomograms by Valdagni and colleagues might influence acute and late GI toxicity. Further research is required to investigate this.

PART II – CLINICAL IMPLEMENTATION OF IRS: THE RBI

A persistent prostate-rectum separation throughout the full treatment course provides sufficient rectal sparing

We started to study the use of an RBI for PCa radiotherapy because of its potential advantages over other types of IRS, as was mentioned in the **General introduction** of this thesis. To test the alleged advantages of an RBI and to assess its potential disadvantages, 15 consecutive patients were prospectively implanted with an IRS between June 2015 and February 2016, as described in **Chapter 7**. The advances in knowledge obtained from this first patient series include a better insight into the potential hazards of RBI implantation and the corrective actions these require. Furthermore, the acute toxicities have been reported. In **Chapter 9**, a possible workaround is presented for IRS implantation in PCa patients with active inflammatory bowel diseases, where the risk of radiation-related bowel toxicity constitutes an enormous problem, with an up to nearly 75% chance of Grade 3 GI toxicities. As a result, the outcome and survival may be compromised for these patients. The proposed workaround has an implication on clinical patient care, and could be a safe solution for such patients. Further research is needed to confirm these results.

The third hypothesis has been confirmed in **Chapter 8**. It was reported that the distance between the prostate and rectum decreased during a moderate hypofractionated EBRT regimen as a result of RBI deflation. However, the distance remained at least 1 cm throughout the full treatment course, indicating that such spacing is sufficient to reduce the ano-rectal volume receiving 75 Gy or more. The results confirm an RBI-induced reduction of predicted and observed Grade 2 or higher GI toxicity.

Wolff and colleagues also observed the phenomenon of an RBI deflating early on, at the beginning of a course of radiation therapy [21]. They reported an average volume loss of >50% during a full course of treatment of 37–40 fractions (8 weeks). In our series, the RBI volume changes were measured with weekly three-dimensional CBCT scans, instead of with a mathematical calculation using 2D images. A significant spread of at least 1 cm between prostate and rectum was observed. In one patient a sudden complete deflation of the RBI was observed, after 3 weeks of implantation. This early deflation severely compromises the rectal sparing effect. Monitoring the RBI volume decrease during the course of treatment is therefore recommended, preferably using weekly CBCT scans. Adapting the treatment plan if the minimum prostate-rectum separation becomes less than 1 cm is also recommended.

PART III – MULTIFACTORIAL DECISION SUPPORT SYSTEM USING A VIRTUAL SPACER

The fourth hypothesis is tested in **Chapter 10**. A “virtual” IRS (useful for both RBI and hydrogel spacer) is generated using a model that is based on a CT scan without IRS. This model was used to create a deformation field (e.g., virtual IRS) on CT scans of patients without IRS. Predictions of the gain in dose and toxicity reduction can consequently predict if the IRS is cost-effective for the specified patient. This is a very attractive approach since the benefit for an individual patient can be estimated without implanting the IRS. This means no extra discomfort for the patient due to the operation, and no additional costs for IRS placement. However, caution should be exercised before such a decision support system is integrated into clinical practice, taking the following into consideration.

Firstly, as this decision support system is a proof-of-concept, it has been based on a small patient cohort. To establish the internal validation, the system should be tested in a clinical trial on a larger cohort of patients. Furthermore, an external validation should be performed to assess its performance in an independent patient cohort and to adapt or re-calibrate the prediction model if required.

Secondly, irradiated rectal volumes are predictive for acute and late GI toxicity. However, volume changes due to rectal filling (e.g., stool and gas) cannot be predicted by this model. The predictions are based on dose-volume histogram data, where spatial information on the 3D dose distribution is lost. Dose surface maps (**Chapter 6**) provide information on the shape and location of the ano-rectal wall dose distribution, with consequently increased predictive power compared to models based solely on DVH parameters [22,23]. Recently, Shelly and colleagues reported that accumulated DSMs revealed stronger correlations with clinically observed rectal bleeding and proctitis than the DSMs obtained from the planned dose distribution [24]. Hence, it is expected that incorporation of daily DSM information will improve the performance of the DSS. Thirdly, individual genetic factors were not included in the proof-of-concept version of the DSS. However, in **Chapter 11**, the first genetic factors were included in the system. In the future, more single nucleotide polymorphism is expected to be discovered, which can help to fine-tune the decision support system.

Fourthly, a DSS needs to meet the essential requirements of all relevant medical device directives: CE marking (CE: Conformité Européene) or FDA approval (FDA: U.S. Food and Drug Administration). Only then can it be implemented in clinical practice.

There are other possibilities to reach an “isotoxic” approach, that is, maximizing the gain in dose while maintaining the toxicity level; this can also be achieved with other techniques, such as simultaneous integrated boost techniques, using ERB, or different IRSs.

Simultaneous integrated boost techniques are being investigated in the FLAME trial, where the

benefits of an ablative boost of a focal lesion are examined [25]. The dose to the dominant intraprostatic lesion is, however, limited to 95 Gy, which is lower than what can be achieved with an IRS. If this boost technique could be used in combination with an IRS, even higher doses could be approached.

The comparison of an IRS with an ERB showed that the spacer gel outperformed the ERB in the majority of the examined and relevant dosimetric rectal-sparing parameters in a stereotactic radiotherapy [26]. The ERB did not outperform the gel spacer in any measured rectal dose parameter. The ventral rectal wall is pushed into the high-dose using an ERB. Other IRSs have similar rectal dosimetric advantages. There are no significant differences in implantation procedures between the different compounds.

FUTURE PERSPECTIVES

More clinical studies investigating the use of an IRS are needed. Based on the results from previous studies and from the studies mentioned in this thesis, the IRS is being deployed in our institution for those PCa patients who are expected to benefit most from its implantation. A prospective study is currently being conducted at MAASTRO Clinic, which is based on a combination of the clinical decision rules described in **Chapter 5**. The set of decision rules has been expanded to include patients who have a very high risk to develop rectal toxicity due to, for example, re-irradiation and inflammatory bowel disease. Furthermore, if the relevant dose-volume threshold of the rectal volume is exceeded (e.g., $V_{65\text{ Gy}} > 15\%$), the patient is also considered to be a candidate for IRS implantation. Results of this study are pending.

The development of more sophisticated DSSs can help to improve the patient selection for IRS implantation. The proposed method for virtual spacer reconstruction will be examined in a prospective controlled trial to implement this cost-effectiveness model to obtain the three-level DSS with complete integration of dose, toxicity, and cost-effectiveness. To further optimize the DSS, the fourth-level with genetic input will be incorporated. A grant proposal has been submitted to realize this project in a proof-of-principle institutional stratified non-randomized observational study: RESPECT-1 (a prospective study of REctum Spacer for Prostate External beam Cancer Therapy). This will be a part of the European TAILORED-trial, which is a European consortium investigating a personalized risk-adapted approach for stratifying cancer patients. The goal is to tailor treatments to each patient's unique biology.

The use of an IRS can be further explored in PCa patients in combination with other radiotherapy techniques, like brachytherapy, stereotactic radiotherapy, or particle therapy. As all of these techniques have the ability to deliver highly conformal dose distributions with a sharp dose fall-off at the rim of the target volume in the proximity of the rectum, they could be of interest to better spare the rectal structures in PCa patients being irradiated. Only few studies have recently reported on the use of an IRS in combination with these techniques.

For brachytherapy in the primary setting, using an IRS is of relatively low importance since no additional PTV margins are necessary for setup uncertainties. However, in a re-irradiation setting, the additional doses are gaining importance, as discussed by Guimas and colleagues regarding a series of 18 patients: in 8 out of 10 patients who had whole gland salvage therapy a hyaluronic acid IRS was used, whereas 8 patients were treated with focal prostate salvage brachytherapy [27]. He reported that the median 0.1 cc dose delivered to the rectum was 83.9 Gy without IRS, in comparison to 63.3 Gy with IRS, respectively ($p=0.04$). No differences were observed between focal or whole-gland plans while using the IRS. In the meantime, comparing whole gland versus partial gland therapy revealed cumulative prostate and rectum biological effective doses higher in patients treated with whole-gland salvage therapy than in patients treated with focal salvage

therapy (258.1 Gy vs. 172.6 Gy; $p < 0.01$, respectively).

Mahal and colleagues also reported on a series of 11 patients in a re-irradiation setting using a hydrogel as IRS [28]. They concluded that implantation of an IRS was feasible in most patients with prior irradiation. In 3 patients, IRS implantation failed because of fibrosis and adhesions. For the 8 patients in whom spacing was accomplished, the median space between the prostate and rectum was 10.9 mm (patients with prior EBRT) vs. 7.7 mm (patients with prior brachytherapy), $p=0.048$.

For proton therapy, Chung and colleagues demonstrated a significant decrease in rectal dose and predicted Grade ≥ 2 rectal toxicity in PCa patients treated *in silico* with proton therapy [29]. They reported that at least 9 mm space between prostate and rectum resulted in a decrease for Grade ≥ 2 rectal toxicity from 13.5% without IRS, to 4.19% with IRS, respectively. Hedrick and colleagues recently demonstrated the consistency of rectal sparing of a hydrogel using three consecutive CT scans in PCa patients undergoing proton therapy [30]. For scanned carbon ion therapy for PCa, Rucinski and colleagues showed dosimetric benefit of an increased distance between prostate and rectum using a gel spacer [31,32]. However, a prospective randomized phase II trial investigating the safety and feasibility of proton therapy versus carbon ion therapy in hypofractionated treatment, reported that in 2 out of 92 patients the insertion of a gel spacer was stopped due to the occurrence of gel in the rectal wall and the consecutive occurrence of rectal fistulas [33].

For stereotactic radiotherapy for PCa, Jones and colleagues compared the rectal-sparing capabilities of ERBs versus injectable spacer gels in patient samples obtained from 2 multi-institutional prospective trials using a schedule of 45 Gy in 5 fractions [26]. This study showed that the spacer gel outperformed the ERB in the majority of the examined and relevant dosimetric rectal-sparing parameters. The ERB did not outperform the gel spacer in any measured rectal dose parameter.

Extreme hypofraction schedules for prostate cancer are traditionally given in 3 to 5 fractions [34]. Ultra-extreme hypofractionation in theoretically 1 or 2 fractions could be very attractive and safely performed while using an IRS. Since no reports on this topic are currently available in the literature, this should be further investigated. In terms of cost-effectiveness, this could be a very attractive approach, comparing 1 or 2 fractions with a standard schedule of 39, or a moderate hypofractionation schedule of 28 fractions. For such extreme hypofractionation schedules geographical misses should be avoided, and hence it is of utmost importance to detect any volumetric changes in IRS prior to or during treatment. Image-guidance is therefore absolutely mandatory.

Including the genetic signature of the tumor to identify who will benefit most from dose escalation will be interesting to investigate in the future. These patients are highly predictive for biochemical recurrence. Selecting these high-risk patients for the highest dose escalation in combination with an IRS, will be possible without exceeding the limits for complication risks. This additional information can be added in the multiple DSS to re-optimize the models, ensuring the continuous improvement of the utility of these models.

Since literature on the application of an IRS for the aforementioned RT techniques is still scarce, and the number of patients studied is small, future clinical studies are needed to determine the observed toxicity reduction and the cost-effectiveness for these forms of dose delivery techniques.

Besides being successfully used in PCa radiotherapy, the IRS also promises to be able to be incorporated in other pathologies where it is necessary to create distance between a target volume and abutting organs at risk, thus diminishing the risk of radiation-induced toxicities. This has recently been investigated in cadaveric models for head and neck, pancreas, and cervical cancers. Rao and colleagues demonstrated that spacing of the contralateral submandibular gland using a hydrogel spacer enables substantial reduction in both irradiated volume and dose delivered to the gland, thereby reducing the risk of xerostomia [35]. Furthermore, the same group showed the feasibility and theoretical advantages of an injectable hydrogel to increase the space between the head of the pancreas and the duodenum in a human cadaveric model [36]. For cervical brachytherapy, Damato and colleagues were able to realize a clinically meaningful rectal dose reduction, due to the injection of a hydrogel between the cervix, rectum, and bladder in human cadavers [37]. Future studies may provide additional supporting evidence and need to evaluate the safety, efficacy, and cost-effectiveness of IRS implantation for these indications, to reduce toxicity and improve the patients' quality of life.

Concluding remarks

The work described in this thesis has focused on prostate cancer external beam radiation therapy and the avoidance of the gastrointestinal side effects. The feasibility and benefit of an implantable rectum spacer application have been described as a clear and safe method, which has proven to be a cost-effective way of reducing the risk of gastrointestinal toxicity. However, to further increase the cost-effectiveness, the identification of patients who have the highest risk to develop rectal toxicity – and hence would benefit most from an implantable rectum spacer implantation – needs to be improved. The developed prediction models for patient selection have to be validated in clinical studies with larger patient populations.

REFERENCES

1. Stacey D, Légaré F, Lewis KB. Patient Decision Aids to Engage Adults in Treatment or Screening Decisions. *JAMA*. 2017 Aug 15;318(7):657-658. doi: 10.1001/jama.2017.10289.
2. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2017 Apr 12;4:CD001431.
3. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Neal DE; ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 375(15):1415-1424.
4. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, Blazeby JM, Peters TJ, Holding P, Bonnington S, Lennon T, Bradshaw L, Cooper D, Herbert P, Howson J, Jones A, Lyons N, Salter E, Thompson P, Tidball S, Blaikie J, Gray C, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Davis M, Turner EL, Martin RM, Neal DE; ProtecT Study Group*. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*. 2016 Oct 13;375(15):1425-1437.
5. O'Connor AM. Validation of a decisional conflict scale. *Med Decis Making*. 1995 Jan-Mar;15(1):25-30.
6. Légaré F, Leblanc A, Robitaille H, Turcotte S. The decisional conflict scale: moving from the individual to the dyad level. *Z Evid Fortbild Qual Gesundheitswes*. 2012;106(4):247-52. Epub 2012 Mar 28.
7. Gwede CK, Pow-Sang J, Seigne J, et al. Treatment decision-making strategies and influences in patients with localized prostate carcinoma. *Cancer*. 2005;104:1381-90.
8. Aning JJ, Wassersug RJ, Goldenberg SL. Patient preference and the impact of decision-making aids on prostate cancer treatment choices and post-intervention regret. *Curr Oncol*. 2012 Dec;19(Suppl 3):S37-44.
9. Sommers BD, Beard CJ, D'Amico AV, Kaplan I, Richie JP, Zeckhauser RJ. Predictors of patient preferences and treatment choices for localized prostate cancer. *Cancer*. 2008;113:2058-67.
10. van Tol-Geerdink JJ, Leer JW, van Oort IM, van Lin EJ, Weijerman PC, Vergunst H, Witjes JA, Stalmeier PF. Quality of life after prostate cancer treatments in patients comparable at baseline. *Br J Cancer*. 2013 May 14;108(9):1784-9. doi: 10.1038/bjc.2013.181. Epub 2013 Apr 23.
11. Bastiaens H, Van Royen P, Pavlic DR, Raposo V, Baker R. Older people's preferences for involvement in their own care: a qualitative study in primary health care in 11 European countries. *Patient Educ Couns*. 2007;68(1):33-42.
12. Feldman-Stewart D, Capirci C, Brennenstuhl S, et al. Information for decision making by patients with early stage prostate cancer: a comparison across 9 countries. *Med Decis Making*. 2011;31:754-66.
13. van Tol-Geerdink JJ, Willem Leer J, Weijerman PC, van Oort IM, Vergunst H, van Lin EN, Alfred Witjes J, Stalmeier PF. Choice between prostatectomy and radiotherapy when men are eligible for both: a randomized controlled trial of usual care vs decision aid. *BJU Int*. 2013 Apr;111(4):564-73.
14. van Tol-Geerdink JJ, Leer JW, Wijkstra CJ, van Oort IM, Vergunst H, van Lin EJ, Witjes JA, Stalmeier PF.

- Does a decision aid for prostate cancer affect different aspects of decisional regret, assessed with new regret scales? A randomized, controlled trial. *Health Expect*. 2016 Apr;19(2):459-70.
15. Meropol NJ, Schrag D, Smith TJ, et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. *J Clin Oncol* 2009;27:3868-74.
 16. Hamstra DA, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. *Int J Radiat Oncol Biol Phys*. 2017;97(5):976-985.
 17. Royal Dutch Academy of Sciences. Evaluation of new technology in health care. In need of guidance for relevant evidence. Available at: https://www.knaw.nl/en/news/publications/evaluation-of-new-technology-in-health-care-1?set_languageZen. Accessed November 1, 2015.
 18. Health Council of the Netherlands. Proton radiotherapy. Horizon scanning report. The Hague: Health Council of the Netherlands; 2009. Available at: <http://www.gezondheidsraad.nl/en/publications/optimale-gezondheidszorg/proton-radiotherapy>. Accessed November 1, 2015.
 19. Lambin P, van Stiphout RG, Starmans MH, et al. Predicting outcomes in radiation oncology multifactorial decision support systems. *Nat Rev Clin Oncol* 2013;10:27-40.
 20. Widder J, van der Schaaf A, Lambin P, Marijnen CA, Pignol JP, Rasch CR, Slotman BJ, Verheij M, Langendijk JA. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. *Int J Radiat Oncol Biol Phys*. 2016 May 1;95(1):30-6.
 21. Wolf F, Gaisberger C, Ziegler I, et al (2015) Comparison of two different rectal spacers in prostate cancer external beam radiotherapy in terms of rectal sparing and volume consistency. *Radiother Oncol* 116(2):221-5.
 22. Buettner F, Gulliford SL, Webb S, Partridge M. Modeling late rectal toxicities based on a parameterized representation of the 3D dose distribution. *Phys Med Biol*. 2011;56(7):2103-18.
 23. Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M. The dose-response of the anal sphincter region--an analysis of data from the MRC RT01 trial. *Radiother Oncol*. 2012;103(3):347-52.
 24. Shelley LEA, Scaife JE, Romanchikova M, Harrison K, Forman JR, Bates AM, Noble DJ, Jena R, Parker MA, Sutcliffe MPF, Thomas SJ, Burnet NG. Delivered dose can be a better predictor of rectal toxicity than planned dose in prostate radiotherapy. *Radiother Oncol*. 2017 Jun;123(3):466-471.
 25. Lips IM, van der Heide UA, Haustermans K, van Lin EN, Pos F, Franken SP, Kotte AN, van Gils CH, van Vulpen M. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. *Trials*. 2011 Dec 5;12:255. doi: 10.1186/1745-6215-12-255.
 26. Jones RT, Hassan Rezaeian N, Desai NB, Lotan Y, Jia X, Hannan R, Kim DWN, Hornberger B, Dubas J, Laine AM, Zelefsky MJ, Timmerman RD, Folkert MR. Dosimetric comparison of rectal-sparing capabilities of rectal balloon vs injectable spacer gel in stereotactic body radiation therapy for prostate cancer: lessons learned from prospective trials. *Med Dosim*. 2017 Jul 31. pii: S0958-3947(17)30067-5.
 27. Guimas V, Quivrin M, Bertaut A, Martin E, Chambade D, Maingon P, Mazoyer F, Cormier L, Créhange G. Focal or whole-gland salvage prostate brachytherapy with iodine seeds with or without a rectal spacer for postradiotherapy local failure: How best to spare the rectum? *Brachytherapy*. 2016 Jul-

Aug;15(4):406-11.

28. Mahal BA, Ziehr DR, Hyatt AS, Neubauer-Sugar EH, O'Farrell DA, O'Leary MP, Steele GS, Niedermayr TR, Beard CJ, Martin NE, Orio PF, D'Amico AV, Devlin PM, Nguyen PL. Use of a rectal spacer with low-dose-rate brachytherapy for treatment of prostate cancer in previously irradiated patients: Initial experience and short-term results. *Brachytherapy*. 2014 Sep-Oct;13(5):442-9.
29. Chung H, Polf J, Badiyan S, Biagioli M, Fernandez D, Latifi K, Wilder R, Mehta M, Chuong M. Rectal dose to prostate cancer patients treated with proton therapy with or without rectal spacer. *J Appl Clin Med Phys*. 2017 Jan;18(1):32-39.
30. Hedrick SG, Fagundes M, Case S, Renegar J, Blakey M, Artz M, Chen H, Robison B, Schreuder N. Validation of rectal sparing throughout the course of proton therapy treatment in prostate cancer patients treated with SpaceOAR®. *J Appl Clin Med Phys*. 2017 Jan;18(1):82-89.
31. Ruciński A, Bauer J, Campbell P, Brons S, Unholtz D, Habl G, Herfarth K, Debus J, Bert C, Parodi K, Jäkel O, Haberer T. Preclinical investigations towards the first spacer gel application in prostate cancer treatment during particle therapy at HIT. *Radiat Oncol*. 2013 Jun 6;8:134.
32. Rucinski A, Brons S, Richter D, Habl G, Debus J, Bert C, Haberer T, Jäkel O. Ion therapy of prostate cancer: daily rectal dose reduction by application of spacer gel. *Radiat Oncol*. 2015 Feb 27;10:56. doi: 10.1186/s13014-015-0348-1.
33. Habl G, Uhl M, Katayama S, Kessel KA, Hatiboglu G, Hadaschik B, Edler L, Tichy D, Ellerbrock M, Haberer T, Wolf MB, Schlemmer HP, Debus J, Herfarth K. Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective Randomized Phase II Study--The IPI Trial. *Int J Radiat Oncol Biol Phys*. 2016 May 1;95(1):435-43.
34. De Bari B, Arcangeli S, Ciardo D, Mazzola R, Alongi F, Russi EG, Santoni R, Magrini SM, Jereczek-Fossa BA; on the behalf of the Italian Association of Radiation Oncology (AIRO). Extreme hypofractionation for early prostate cancer: Biology meets technology. *Cancer Treat Rev*. 2016 Nov;50:48-60.
35. Rao AD, Coquia S, De Jong R, Gourin C, Page B, Latronico D, Dah S, Su L, Clarke S, Schultz J, Rosati LM, Fakhry C, Wong J, DeWeese TL, Quon H, Ding K, Kiess A. Effects of biodegradable hydrogel spacer injection on contralateral submandibular gland sparing in radiotherapy for head and neck cancers. *Radiother Oncol*. 2017 Oct 3. pii: S0167-8140(17)32584-7.
36. Rao AD, Feng Z, Shin EJ, He J, Waters KM, Coquia S, DeJong R, Rosati LM, Su L, Li D, Jackson J, Clark S, Schultz J, Hutchings D, Kim SH, Hruban RH, DeWeese TL, Wong J, Narang A, Herman JM, Ding K. A Novel Absorbable Radiopaque Hydrogel Spacer to Separate the Head of the Pancreas and Duodenum in Radiation Therapy for Pancreatic Cancer. *Int J Radiat Oncol Biol Phys*. 2017 Aug 14. pii: S0360-3016(17)33711-2.
37. Damato AL, Kassick M, Viswanathan AN. Rectum and bladder spacing in cervical cancer brachytherapy using a novel injectable hydrogel compound. *Brachytherapy*. 2017 Sep - Oct;16(5):949-955.

CHAPTER 13

Addenda

SUMMARY

This thesis focuses on gastrointestinal (GI) toxicity caused by prostate cancer external beam radiotherapy (RT), and gives an overview to introduce an implantable rectum spacer (IRS) implantation, and to improve patient selection for IRS implantation in order to reduce GI toxicity in those patients that are expected to benefit most from IRS implantation.

In Chapter 2, the results of a literature overview on prostate cancer radiotherapy are presented. Overall, technical advances have led to maximizing the radiation dose to the tumor, while minimizing the dose to healthy tissues, with improved biochemical disease-free survival and overall survival. Current literature reveals that all possible treatment modalities have the same cure rate, but a different toxicity pattern. We recommend explaining the possible different treatment modalities, each with their own advantages and side effects, to the individual patients. Clinicians and patients should make treatment decisions together (*shared decision-making*) while using patient decision aids.

Chapter 3 describes the GI toxicity of prostate cancer RT. A well-known complication of RT is called chronic radiation proctitis (CRP). The chapter provides a literature review of the optimal prevention and treatment of CRP. This is a relatively frequent late (3–6 months after RT) side effect that affects 5–20% of RT treated cancer patients. Symptoms include diarrhea, constipation, mucus discharge, urgency, spasms, cramps, bleeding, and rectal pain. Bleeding can be so dominant that blood transfusions are required. CRP is mainly dependent on the dose and volume of irradiated rectum. RT techniques to prevent CRP are constantly improving, thanks to image-guided RT and intensity-modulated RT. Also, newer techniques like protons and new devices such as implantable rectum spacers (IRS) and balloons have been developed to spare rectal structures. Biopsies do not contribute to diagnosing CRP and should be avoided because of the risk of severe rectal wall damage, such as necrosis and fistulas. Furthermore, an algorithm is provided for the treatment of CRP.

Chapter 4 is a cost-effectiveness analysis of an IRS. This investigation revealed how the costs of spacers are related to the reduction in rectal side effects in patients with prostate cancer. If all the assumptions of the used model are correct, IMRT+IRS is less toxic and more effective than IMRT-IRS for all prostate cancer patients. The spacer is cost-effective for prostate cancer patients, due to less severe toxicity and a reduction in treatment costs associated with these side effects. If we acknowledge patient heterogeneity and we can select a population of patients with a high risk of late rectal complications, the cost-effectiveness of the spacer will most likely improve since those patients will benefit even more from the use of a spacer.

Chapter 5 is about discovering which patients are expected to benefit most from IRS implantation. Scenarios of clinical risk factors were identified for which implantation of an IRS is

predicted to significantly reduce Grade 2 and Grade 3 acute and late rectal toxicity rates with IMRT prior to implantation of the IRS. This introduces the opportunity to better select patients for IRS implantation, avoid unbeneficial implantations and possible complications, enhance quality of life, and consequently improve the cost-effectiveness of the treatment.

In **Chapter 6**, the results of a planning study revealed the most beneficial location of an IRS on the anal and rectal wall by spatially analyzing the 3D dose distributions dose surface maps. An IRS significantly reduces the lateral and longitudinal extent of high-dose areas (>50 Gy) in anterior and superior-inferior directions in high-dose IMRT, and consequently decreases the predicted NTCP for late rectal bleeding and sphincter control.

Chapter 7 is a summary of an easy introduction of an IRS: step-by-step instructions for optimization of the transperineal implantation procedure. For a safe implantation of an RBI, such a procedure should be performed by urologists and/or radiation oncologists who are experienced with prostate brachytherapy and the use of TRUS. The theoretical advantages of rectal balloon implants are discussed. Perioperative side effects are reported as low to absent.

Chapter 8 is a feasibility trial of the rectal balloon implant. The maintenance of an RBI is proven with low acute toxicities, resolving 3 to 6 months after treatment.

Chapter 9 is an illustration of a possible workaround for the problem of active IBD for a patient in need of prostate cancer radiotherapy. We conclude that the treatment strategy of using EBRT in combination with an IRS should be considered in this specified high-feature patient population to obtain the best outcome and survival.

In **Chapter 10** and **Chapter 11**, two new decision support systems are developed: a novel method to predict the dose gain, toxicity reduction, and the cost-effectiveness of an IRS by implanting a “virtual” IRS based on a CT scan without an IRS. Further, an iso-toxic model with integrated genetic biomarkers is produced to predict the gain of an IRS in a certain patient before the real implantation of an IRS.

SAMENVATTING (NEDERLANDS)

Prostaat kanker is in Nederland de meest gediagnosticeerde kanker bij mannen: meer dan 11.000 nieuwe patiënten per jaar. **Hoofdstuk 2** beschrijft de evolutie die radiotherapie de laatste 20 jaar heeft doorgemaakt, meer toegespitst op de prostaat bestraling. Radiotherapie (inwendig en uitwendig) is één van de mogelijk genezende behandelingen voor lokaal prostaatkanker, naast een operatie en een actief volgen beleid. Alle behandelingen hebben dezelfde, heel hoge genezingskans (> 90%), echter de bijwerkingen zijn verschillend. Een bestralingsbehandeling wordt bijna altijd over een periode van verschillende dagen toegediend en elke toediening wordt een 'fractie' genoemd. Tijdens iedere behandel fractie kan de prostaat bewegen en ook tussen iedere fractie onderling kan de prostaat zich op een andere positie bevinden. Er worden daarom marges rond de prostaat ingecalculeerd om de prostaattumor voldoende goed te bestralen. Hierdoor kunnen echter ook omliggende organen bestraald worden, waardoor er bijwerkingen kunnen optreden: plasklachten, defecatie klachten en erectiestoornissen. Deze klachten zijn meestal van voorbijgaande aard, maar soms ook blijvend (5-20%), dewelke de kwaliteit van het leven erg negatief kunnen beïnvloeden. Verder wordt in **hoofdstuk 2** verwezen naar een gezamenlijke therapie beslissing door middel van een patiënten keuzehulp, die mede ontwikkeld is door de auteur van dit proefschrift (<http://www.treatmentchoice.info/decision-aid-tools.html>). Gezamenlijke therapie beslissing is een manier van werken waarbij arts en patiënt samen tot een beleid komen dat het beste aanleunt bij de individuele keuzes en voorkeuren van een patiënt. Bij gezamenlijke besluitvorming wordt er expliciet rekening gehouden met de persoonlijke omstandigheden van de patiënt. Daardoor levert dit meer patiënttevredenheid op, minder comorbiditeit en draagt dit bij tot een betere arts-patiëntrelatie.

Hoofdstuk 3 richt zich voornamelijk op de rectale (endeldarm) bijwerkingen van een radiotherapie behandeling: rectaal bloedverlies, diarree, constipatie, slijm afscheiding, krampen, rectale pijn, toegenomen frequentie, fecale urgentie (drang) en incontinentie (verlies van ontlasting). Het bloeden kan zo fulminant zijn dat bloedtransfusies noodzakelijk zijn. Biopsies dragen niet bij tot een diagnose en moeten absoluut vermeden worden vanwege het risico op initiatie van ernstige rectumwand schade, met desbetreffende iatrogene necrose (celdood) en fistelvorming (niet natuurlijk kanaal tussen 2 lichaamsholten) tot gevolg. Een overzicht van de mogelijkheden ter preventie en een behandeling algoritme voor die klachten zijn ontwikkeld, dewelke nu als standaard gehanteerd wordt. Eén van de preventie mogelijkheden is een implanteerbare rectum 'spacer' (IRS). Met een IRS wordt de afstand tussen de prostaat en het rectum vergroot. Dit kan door een rectale ballon of een hydrogel 'spacer' te implanteren in het vetweefsel tussen de endeldarm en de prostaat. Ander beschreven producten zijn collageen en hyaluronzuur implantaten.

Deel II bestaat voornamelijk uit modellering en individualisering van de IRS. **Hoofdstuk 4** behandelt een kosten-batenanalyse van een IRS implantatie bij prostaat kanker over de gehele

populatie. Dit onderzoek toont aan hoe de kosten van een IRS zich verhouden tegenover de beperking van de kosten van de behandeling van deze darm bijwerkingen. Als alle aannames correct zijn is een radiotherapie behandeling met IRS minder toxisch en effectiever dan een radiotherapie behandeling zonder IRS. Een IRS heeft 77 % waarschijnlijkheid om kosteneffectief te zijn bij een grens van €80.000,- per gewonnen levensjaar in een perfecte gezondheid. Deze grens werd door de Gezondheidsraad in Nederland vastgelegd in 2006. Deze afkapwaarde wordt toegepast om een nieuw medicijn of behandeling te evalueren op zijn kosteneffectiviteit. Als we uit de patiëntenpopulatie een selectie kunnen maken van patiënten met een hoger risico op late rectale complicaties, zal de kosteneffectiviteit van de IRS nog verhogen.

Hoofdstuk 5 onderzoekt welke patiënten het meest zouden profiteren van een IRS implantatie. Klinische risicofactoren zijn geïdentificeerd waarvoor een implantatie van een IRS de graad 2-3 acute en late rectale bijwerkingen vermindert. Het gevolg hiervan is een betere selectie met desbetreffend het vermijden van onnodige implantaties en mogelijke complicaties.

Hoofdstuk 6 stipuleert de resultaten van een planningsstudie, waaruit blijkt dat een bestraling met een IRS een lagere bestralingsdosis heeft op zowel het anale (kringspier) kanaal als de rectumwand tegenover een bestraling zonder IRS. Dit is bestudeerd door een ruimtelijke analyse van de 3D dosisverdelingen met zogenaamde dosis oppervlakte mappen. Een IRS vermindert de laterale en longitudinale hoge dosis gebieden (> 50 Gy) in het anterieure deel van de endeldarm. Derhalve zijn de voorspelde late bijwerkingen voor rectaal bloedverlies minder, en verbetert de controle over de sluitspier.

Deel III behandelt de klinische implementatie van een rectaal ballon implantaat (RBI).

Hoofdstuk 7 is een samenvatting van een introductie van een RBI: het is een stap voor stap handleiding voor een optimale implantatie procedure. Voor een veilige implantatie van een RBI, wordt geadviseerd dat een dergelijke procedure uitgevoerd wordt door urologen en / of radiotherapeut oncologen die ervaring hebben met prostaat brachytherapie en het gebruik van transrectale echografie. De theoretische voordelen van een RBI worden besproken. De perioperatieve bijwerkingen zijn laag.

Hoofdstuk 8 is een haalbaarheidsstudie van RBI bij 15 patiënten die bestraald werden. Het behoud van het volume van een RBI is er toegelicht met een laag voorkomen van acute toxiciteit, en een lage predictieve en geobserveerde late toxiciteit.

Hoofdstuk 9 is een mogelijke oplossing voor een prostaatkanker patiënt met een actieve IBD. Een behandelstrategie van EBRT met een RBI wordt er beschreven.

Deel IV is een blik naar de toekomst. In **hoofdstuk 10** is een geïntegreerd systeem ontwikkeld (en gepatenteerd door de auteur) voor het ontwikkelen van een virtuele IRS: een CT-scan wordt voor de behandeling genomen. Een virtuele IRS wordt gereconstrueerd. Daarop kan een

kosteneffectiviteit en bijwerkingen voorspelling op uitgevoerd worden zonder dat de IRS effectief geïmplantéerd is. Hierdoor kan voorspeld worden of de IRS inderdaad kosten effectief zal zijn bij deze specifieke patiënt vooraleer de IRS geïmplantéerd is. Daarenboven wordt in **hoofdstuk 11** een proefconcept beschreven van zogenaamde iso-toxische behandeling: er wordt berekend hoeveel bestraling moet toegediend worden zonder het rectum overmatige schade toe te brengen.

VALORIZATION

Prostate cancer is the most common type of cancer among males in the Western world, and the second deadliest cancer for men, with an estimated 1,620,000 new cases every year, and an expected 366,000 related deaths on an annual basis worldwide [1-3]. In the Netherlands, there were approximately 11,000 new cases in 2015 [4]. It is expected that the incidence will substantially increase in the coming decades, due to the growth of the aging population and screening, which makes it an enormous healthcare problem. Furthermore, some prostate cancers grow very slowly, so some elderly men die *with* – rather than *of* – their prostate cancer, even without treatment [5]. Therefore, treatment differentiation and individualization is becoming ever more important. The total economic costs of PCa in Europe is estimated to exceed EUR 8.43 billion [6]. One of the biggest challenges in the 21st century will be to offer the best individualized treatment at reasonable costs to maintain our socioeconomic healthcare system.

EBRT is a well-known potentially curative therapy for PCa besides performing surgery [7]. RT has undergone huge improvements in the last decades, and is in no way comparable with the RT of the past. Dose escalation in prostate EBRT leads to improved loco-regional control and PCa-specific mortality [8-14]. However, dose escalation is limited by toxicity for surrounding healthy tissues, and improved tumor control might come at the cost of higher toxicity, with great impact on patients' quality of life. The Dutch healthcare system attaches great importance to improving quality of care (improved therapeutic results, and/or reduced toxicity), within a reasonable control of costs (ICER of EUR 80,000 per QALY), within a shared decision-making atmosphere [15,16]. All these subjects are part of the content in this thesis.

In this thesis a new technique – the implantable rectum spacer – is introduced, which causes less toxicity, at a reasonable cost, while improving quality of life. In the first part of the thesis, the cost-effectiveness of an IRS is proven: due to less severe toxicity, with a reduction in the treatment costs associated with these side effects, the cost of an IRS itself was outweighed. Further studies presented in this thesis have proven that decision rules are reliable, and a reproducible method for selecting a population of patients with a high risk of late rectal complications. This will consequently increase the cost-effectiveness of the IRS, since those patients will benefit even more from the use of an IRS. Dose surface maps are generated to obtain more insight into the best location for an IRS on the ARW.

Furthermore, a detailed description is given of the implantation procedure for an RBI, which can be used to introduce this technique in every department. The procedure is described as safe and well tolerated. Moreover, a system has been developed to predict *a priori* the gain of such an IRS, which is the perfect base for tailoring and individualization of a PCa RT treatment. The principle of predicting the benefit of an IRS has been shown to be feasible. This model-based approach has very recently been adapted for the introduction of proton therapy in the Netherlands. Dutch

proton therapy centers must reveal the estimated benefit of a proton therapy in advance [17]. Only if the expected benefit exceeds a certain threshold, will treatments be reimbursed. We want to implement the IRS in prostate cancer EBRT in a similar way.

In the future, we postulate that IRS can become an important cornerstone of EBRT in certain specified prostate cancer patients. In future, we want to further explore the possibilities in clinical practice by using those differentiating prediction models in the clinic. There is an increasing amount of evidence to support the role of clinical and genetic variants in the development of radiation-induced GI toxicity. Further systematic evaluations of dose, clinical, and genetic parameters are warranted, in order to evaluate whether all those features could improve the predictive gain of an IRS. Developed models could give a more accurate NTCP prediction for each individual undergoing EBRT for prostate cancer. Radiation oncologists would consequently be better able to select those patients with potential high risk for rectal toxicity. We postulate that in the future this will lead to individualized treatment with a selective discrimination of only those patients for whom extra care should be taken to decrease the dose to the rectum. These are topics for future investigation to define the definitive role of the IRS. The use of such individualized risk assessment models allows us to focus only on those patients who have a high chance to benefit from it. This is important for healthcare providers' ability to prioritize the available resources for the patients who need this. This is different from the "one size fits all" recommendations in most international guidelines. According to us, the next step will be to implement the cost-effectiveness model to acquire a four-level decision support system with complete integration of dose, toxicity, cost-effectiveness, and genetic input. Prospective follow-up studies are therefore required. Identifying patients who are at high risk of GI toxicity may help restrict the implantation of an IRS to those most likely to benefit, and promote the personalized approach to prostate cancer radiotherapy. The multiple decision support systems needs to meet the essential requirements of all relevant medical device directives: a CE marking (Conformité Européene) or FDA (Food and Drug Administration) approval. Only then can DSS be implemented in clinical practice.

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *Global Burden of Disease Cancer Collaboration, JAMA Oncol.* 2017;3(4):524
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *European Journal of Cancer* (2013) 49, 1374-1403.
3. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-86.
4. <http://www.cijfersoverkanker.nl>
5. Riihimäki M, Thomsen H, Brandt A, et al. What do prostate cancer patients die of? *Oncologist* 2011;16:175-181.
6. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol.* 2013 Nov;14(12):1165-74.
7. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Neal DE; ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 375(15):1415-1424.
8. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;70(1):67-74.
9. Michalski JM, Moughan J, Purdy J. A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer. *J Clin Oncol* 2015;33. (suppl 7; abstr 4)
10. Al-Mamgani A, van Putten WL, Heemsbergen WD, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:980-988.
11. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol.* 2014;110(1):104-9.
12. Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, Aird EG, Bottomley D, Huddart RA, Jose CC, Matthews JH, Millar JL, Murphy C, Russell JM, Scrase CD, Parmar MK, Sydes MR. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol.* 2014 Apr;15(4):464-73.
13. Beckendorf V, Guerif S, Le Prisé E, Cosset JM, Bougnoux A, Chauvet B, Salem N, Chapet O, Bourdain S, Bachaud JM, Maingon P, Hannoun-Levi JM, Malissard L, Simon JM, Pommier P, Hay M, Dubray B, Lagrange JL, Luporsi E, Bey P. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys.* 2011 Jul 15;80(4):1056-63.
14. Kalbasi A, Li J, Berman A, Swisher-McClure S, Smaldone M, Uzzo RG, Small DS, Mitra N, Bekelman JE. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. *JAMA Oncol.* 2015 Oct;1(7):897-906.

15. Health Council of the Netherlands. Proton radiotherapy. Horizon scanning report. The Hague: Health Council of the Netherlands; 2009. Available at: <http://www.gezondheidsraad.nl/en/publications/optimale-gezondheidszorg/proton-radiotherapy>. Accessed November 1, 2015.
16. Lambin P, Zindler J, Vanneste BG, De Voorde LV, Eekers D, Compter I, et al. Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev.* 2016 Jan 14.
17. Widder J, van der Schaaf A, Lambin P, Marijnen CA, Pignol JP, Rasch CR, Slotman BJ, Verheij M, Langendijk JA. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. *Int J Radiat Oncol Biol Phys.* 2016 May 1;95(1):30-6.

ACKNOWLEDGMENTS

Completing this doctoral thesis was made possible with the cooperation and support of many people. I would like to thank everyone who contributed to this work or who helped with its completion, in particular the following individuals.

I would like to thank my patients, who were willing to collaborate in developing new, innovative treatments, and had the courage to participate in this in such a difficult period in their lives.

I would like to thank Philippe Lambin for supporting this work. It is a pity that you are (too) often abroad or away, but you have brilliant ideas, and it was an honor to work with you together on this project. I still wonder at and am amazed by how you put MAASTO clinic on the map, making it one of the “important radiotherapy research institutes” that it is today. Nowadays, you are working at MUMC with your D-Lab. I’m certain that this project will become a success as well. I hope that in the future we can work together on new ventures.

I would like to thank Aswin Hoffmann for critical revisions, always pushing for another, better iteration. Your extremely precise revisions always set me a step further towards attempting to do better. Although at times things seemed to go slowly for me, I learned a lot from you about physics, statistics and more. I really appreciated your punctuality, something I always prefer in a clinical physicist and researcher. I hope we will work together on other projects in the future.

I would like to thank Emile van Lin for being a critical and extremely discerning supervisor, sometimes very straightforward, but that’s how I like it. Thank you for teaching me the details of having my work published without a problem and for always putting your finger on the right spot. It was a pity that our work in clinical practice was limited to such a very short time. Nevertheless, I still learned a lot from you.

I would like to thank Prof. Frank Verhaegen, Prof. Marco van Vulpen, Dr. Bradley Pieters and Prof. Gommert van Koeveringe for examining this work.

I would like to thank all my teachers and my co-authors – with regard to this work and earlier published work – for all your contributions. When working on all these manuscripts, I learnt a lot from everyone.

I would like to thank M. Pinkawa, especially for sharing your hydrogel spacer data so easily, and for your quick responses.

I would like to thank my colleague medical doctors (Ludy, Danielle and Evert) of the BRUG team (BRachy-Uro-Gyn) for creating a wonderful working atmosphere, and acting as such a coherent

team. You guys are great to work with and we are the A-team! The report of the international site visit described us at end of 2015 as follows: “Urology is ahead of the rest with their innovation agenda. This is a good example for the other groups.”

I would also like to thank the other members of our team: Physician's Assistant Debbie Herfs, the radiation technicians especially Marlies Lendfers and Janneke Bovendeerd, doctor's assistants, the secretary, etc.

I would like to thank Lien Van De Voorde and Judith van Loon, for being my seconds (paranimfs).

I would like to thank Tim Onderbeke, an artist from Ghent, who painted the cover of this thesis and delivered the photography, and Ilse Modder, a graphic designer, who created this work in its current format.

I would like to thank my parents and my brothers: thanks to you I'm standing here today, and I am who I am. Mom and dad, you taught me a lot and always motivated me in what I did. Thanks for being my family.

And finally, of course I would like to thank Magali Goesaert: for being a wonderful partner, and for being the best mom ever to our son and daughter, Louis and Victoire. You are always positive minded, always encouraging me in what I do. Together we are a tandem in perfect balance who are pushing and stimulating each other to higher ends.

CURRICULUM VITAE

Ben Guy Luc Vanneste was born on September 10th, 1981 in Ronse, Belgium. He graduated from the Gymnasium at the Sint-Jozefinstituut in Kortrijk in June 1999. Like his two older brothers, he started medical school at the Catholic University of Leuven, Campus Kortrijk (Kulak) in September 1999 and graduated in June 2006, with honours (*cum laude*).

In September 2006, he started his radiotherapy-oncology residency at the University of Antwerp (Prof. D. Van den Weyngaert). In May 2008, he continued at the NKI-AvL (Nederlands Kanker Instituut-Antoni van Leeuwenhoek instituut) in Amsterdam, the Netherlands. He remained working at this internationally recognized center of excellence in cancer care until December 2012 under the supervision of Prof. M. Verheij. There he was given

plenty of opportunities to become involved in all new radiation techniques and to gain experience in several other leading European clinics. From January 2011 until May 2011 he worked at the AMC (Academisch Medisch Centrum Amsterdam) with Dr B. Pieters, to become fully introduced to brachytherapy. From November 2011 until May 2012, he fulfilled a fellowship in brachytherapy at the internationally well-known Institut Gustave Roussy in Villejuif, France (IGR), working with Dr C. Haie-Meder to further establish these skills.

Finally, he started work as a staff member with a focus on urology, gynecology, and brachytherapy at the MAASTRO Clinic, from January 2013 until the present day. He started a PhD project focusing on prostate cancer and HDR, under supervision of Prof. P. Lambin. In 2014 the subject was switched to Implantable Rectum Spacers. In addition, he is the principal MD involved in urology and brachytherapy research at MAASTRO-Clinic: he is the co-developer of a prostate decision aid, and co-developer and co-inventor of a virtual spacer implantation tool and decision support system. At present, he is co-chair of the brachytherapy, urology, and gynecology unit at the MAASTRO Clinic.

He is co-author of over 30 peer-reviewed scientific publications, is a member of several professional societies (ESTRO, ASTRO, ABRO/BVRO, NVRO), and has been a reviewer for various international scientific journals since 2015.

LIST OF PUBLICATIONS

1. **Vanneste BGL**, van wijk Y, Lutgens LC, Van Limbergen EJ, van Lin EN, van de Beek K, Lambin P, Hoffmann AL.
Dynamics of rectal balloon implant shrinkage do not affect anorectal dose and late rectal complication risk in prostate VMAT.
Strahlentherapie und Onkologie 2018 Jan;194(1):31-40.
2. **Vanneste BGL**, Van Limbergen EJ, van de Beek K, van Lin E, Lutgens LC, Lambin P.
A biodegradable rectal balloon implant to protect the rectum during prostate cancer radiotherapy for a patient with active Crohn disease
TIPS-RO 2018 (6);1-4
3. Camps S, Fontanarosa D, de With P, Verhaegen F, **Vanneste BGL**
The use of ultrasound imaging in external beam radiation therapy workflow of prostate cancer patients
BioMed Research Internationals Vol. 2018, Article ID 7569590, 16 pages, 2018.
4. Camps SM, Verhaegen F, **Vanneste BGL**, de With PHN, Fontanarosa D
CT scan based patient-specific transperineal ultrasound probe setups for image guided radiotherapy procedures for prostate cancer patients
Med Phys. 2018 May 14. doi: 10.1002/mp.12972. [Epub ahead of print]
5. Walsh S, Roelofs E, Kuess P, van Wijk Y, **Vanneste BGL**, Dekker A, Lambin P, Jones B, Georg D, Verhaegen F
Towards a clinical decision support system for external beam radiation oncology prostate cancer patients: proton vs photon radiotherapy? A radiobiological study of robustness and stability.
Cancers (Basel) 2018;10(2).
6. Groot HJ, Lubberts S, de Wit R, Witjes AJ, Kerst JM de Jong IE,
Groenewegen G, Van den Eertwegh AJM, Poortmans PM, Klumpen H, van den Berg HA, Hulshof MCCM, Smilde TJ, **Vanneste BGL**, Aarts MJ, Incrocci L, van den Bergh ACM, Jóźwiak K, van den Belt-Dusebout ACW, Horenblas S, Gietema JA, Leeuwen FE, Schaapveld M
Second cancer risk after treatment for testicular germ cell cancer: a case-cohort study
JCO Accepted.

7. van Wijk Y, **Vanneste BGL**, Jochems A, Walsh S, Pinkawa M, Lambin P.
Development of an iso-toxic model integrating validated genetic markers of toxicity and tumour control probability: a multifactorial decision support system for prostate cancer radiotherapy to support the decision to place an implantable rectum spacer
Acta Oncologica Accepted

8. **Vanneste BGL**, Lutgens LC, van de Beek K, Lambin P.
Implantation of a biodegradable rectum balloon implant: Tips, tricks and pitfalls.
IBJU 2017 Mar 24;43.

9. van Wijk Y, **Vanneste BGL**, Walsh S, van der Meer S, Ramaekers B, van Elmpt W, Pinkawa M, Lambin P
Development of a Decision Support System for an Implantable Rectum Spacer during prostate cancer radiotherapy: Comparison of dose, toxicity and cost-effectiveness.
Radiother Oncol 2017 Aug 16: S0167-8140(17)32485-4.

10. Alitto AR, Gatta R, **Vanneste BGL**, Meldolesi E, Damiani A, Lanzotti V, Frascino V, Masciocchi C, Dekker A, Lambin P, Valentini V, Mantini G
PR.O.DI.GE.: PRedictions models in prOstate cancer for personalized meDIcine challenGE
Future Oncology 2017 Oct;13(24):2171-2181.

11. Fonseca G, Podesta M, Bellezzo M, van den Bosch M, Lutgens L, **Vanneste BGL**, Voncken R, Van Limbergen E, Reniers B, Verhaegen F
Online pretreatment verification of high-dose rate brachytherapy using an imaging panel
Phys Med Biol. 2017 Jul 7;62(13):5440-5461.

12. **Vanneste BGL**, Van Limbergen EJ, van Lin EN, van Roermund J, Lambin P.
Prostate cancer Radiation Therapy: What does a clinician have to know?
Biomed Res International vol. 2016, Article ID 6829875, 14 pages, 2016.
Special issue "Advances in Localized Prostate Cancer Management"

13. **Vanneste BGL**, Hoffmann A, van Lin E, Van De Voorde L, Pinkawa M, Lambin P.
Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection.
Radiother Oncol. 2016;121(1):118-123.

14. Vanneste BGL

Chronic radiation proctitis: prevention better than cure?
Atlas of Science – March 2016.

15. Vanneste BGL, Lopez-Yurda M, Tan IB, Balm AJ, Borst GR, Rasch CR.

Irradiation of localized squamous cell carcinoma of the nasal vestibule.
Head Neck. 2016 Apr;38 Suppl 1:E1870-5.

16. van der Meer S, Vanneste BGL, Herfs D, van Elmpt W, Schubert C, Pinkawa M, Lambin P
A novel method to predict a priori the toxicity reduction of a prostate-rectum spacer: Virtual Rectum Spacer
Radiother Oncol. 2016 Volume 118, Supplement 1, Pages S105–S106.

17. Lambin, Zindler, Vanneste, et al.
Decision Support Systems for Personalized and Participative Radiation Oncology
Advanced Drug Delivery 2016 Review.

18. van der Meer S, Camps S, van Elmpt W, Podesta M, Sanches P, Vanneste BGL, Fontanarosa D, Verhaegen F.
Simulation of daily CT images based on deformable image registration of daily ultrasound images: a proof of concept.
Med Phys. 2016;43(4):1913.

19. Vanneste BGL, M Pijls-Johannesma, L Van De Voorde, EN Van Lin, K Van De Beek, J van Loon, BL Ramaekers, P Lambin.
Spacers in Radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective?
Radiother Oncol. 2015;114(2):276-81.

20. Vanneste BGL

Spacers in Radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective?
- “Beyond the Abstract”
Berkeley, Ca - UroToday.com - June 2015.

21. Vanneste BGL, Van de Voorde L, de Ridder RJ, Van Limbergen E, Lambin P, Van Lin EN.
Chronic Radiation Proctitis: Prevention and Algorithm for treatment.
Int J Colorectal Dis (2015) 30:1293–1303.

22. Van De Voorde L, **Vanneste B**, Houben R, et al.
Image-guided stereotactic ablative radiotherapy for the liver: A safe and effective treatment.
Eur J Surg Oncol. 2015;41(2):249-56.

23. Lambin, Zindler, **Vanneste**, et al.
Modern clinical research: How rapid learning health care and cohort multiple randomised clinical trials complement traditional evidence based medicine.
Acta Oncol. 2015 Sep 23:1-12.

24. Heidemans-Hazelaar C, Avenarius J, Jonkman A, **Vanneste B**, Stalpers L, Dorresteijn L
Insufficiëntiefracturen van het sacrum na radiotherapie.
Tijdschrift Neurologie & neurochirurgie 2015;116:108-112.

25. Van De Voorde L, Janssen L, Larue R, Houben R, Buijsen J, Sosef M, **Vanneste B**, Schraepen MC, Berbée M, Lambin P.
Can metformin improve 'the tomorrow' of patients treated for oesophageal cancer?
Eur J Surg Oncol. 2015 Jun 6

26. Van De Voorde L, Larue R, Persoon L, Öllers M, Nijsten S, Bosmans G, Berbée M, Swinnen A, van Elmp W, **Vanneste B**, Verhaegen F, Lambin P.
The influence of gastric filling instructions on dose delivery in patients with oesophageal cancer: A prospective study.
Radiother Oncol. 2015 Sep 10.

27. **Vanneste BGL**, Meijnen P, Hammerstein CS, Bijker N, van Os RM, Stalpers LJ, Pieters BR.
Postoperative brachytherapy for endometrial cancer using a ring applicator.
Brachytherapy. 2014;14(2):273-8.

28. Van De Voorde L, **Vanneste B**, Borger J, Troost E, Werner P.
Rapid decline of follicular lymphoma-associated chylothorax after low dose radiotherapy to retroperitoneal lymphoma localization.
Case Reports in Hematology.
Volume 2014 (2014), Article ID 684689.

29. Van De Voorde L, Larue RT, Pijls M, Buijsen J, Troost EG, Berbée M, Sosef M, van Elmp W, Schraepen MC, **Vanneste B**, Oellers M, Lambin P.
A qualitative synthesis of the evidence behind elective lymph node irradiation in oesophageal cancer.
Radiother Oncol. 2014 Nov;113(2):166-174.

30. **Vanneste BGL**, van Tienhoven G, Kloen P, Stalpers LJA.
Insufficiëntie fracturen van het bekken na radiotherapie.
Nederlands Tijdschrift van Oncologische Geneeskunde. 2013;10:20-4.
31. Mazon R, Gilmore J, Dumas I, Champoudry J, Goulart J, **Vanneste B**, Tailleux A, Morice P, Haie-Meder C.
Adaptive 3D image-guided brachytherapy: a strong argument in the debate on systematic radical hysterectomy for locally advanced cervical cancer.
The Oncologist. 2013;18(4):415-22.
32. **Vanneste BGL**, Borst GR, van den Heuvel M, Belderbos JS.
Diagnose en behandeling van radiatiepneumonitis.
Nederlands Tijdschrift van Oncologische Geneeskunde. 2012;9:344-9.
33. **Vanneste BGL**, Haas RL, Bard MP, Rijna H, Váldes Olmos RA, Belderbos JS.
Involved field radiotherapy for locally advanced non-small cell lung cancer: isolated mediastinal nodal relapse.
Lung Cancer. 2010 Nov;70(2): 218-20.

Submitted:

34. **Vanneste BGL**, Buettner F, Pinkawa M, Lambin P, Hoffmann AL.
Added value of hydrogel spacers to prostate IMRT: where is the benefit for the ano-rectal wall?
Phys Med Biol.
35. Groot HJ, Gietema GJ, Aleman BMP, Incrocci L, de Wit R, Witjes AJ, Groenewegen G, de Brouwer P, Meijer OWM, Hulshof MCM, van den Berg HA, Smilde TJ, **Vanneste BGL**, Aarts MJ, van den Bergh ACM, van den Belt-Dusebout ACW, Lubberts S, Jóźwiak K, Horenblas S, van Leeuwen FE, Schaapveld M
Risk of Diabetes Mellitus after para-aortic radiation for testicular cancer
Annals of Oncology.

36. Groot HJ, Leeuwen FE, Lubberts S, Horenblas S, de Wit R, Witjes AJ, Groenewegen G, Poortmans PM, Hulshof MCCM, Meijer OWM, de Jong IE, van den Berg HA, Smilde TJ, **Vanneste BGL**, AartsMJ, JóźwiakK, vandenBelt-DuseboutACW, GietemaJA, SchaapveldM Cause-specific mortality among testicular cancer patients treated in the Netherlands since 1976. JNCI.
37. **Vanneste BGL**, Van Limbergen EJ, van Roermund JGH, Lutgens LC, Lambin P, Oelke M. A Treatment Algorithm for Radiation Cystitis and Urethritis World Journal of Urology.