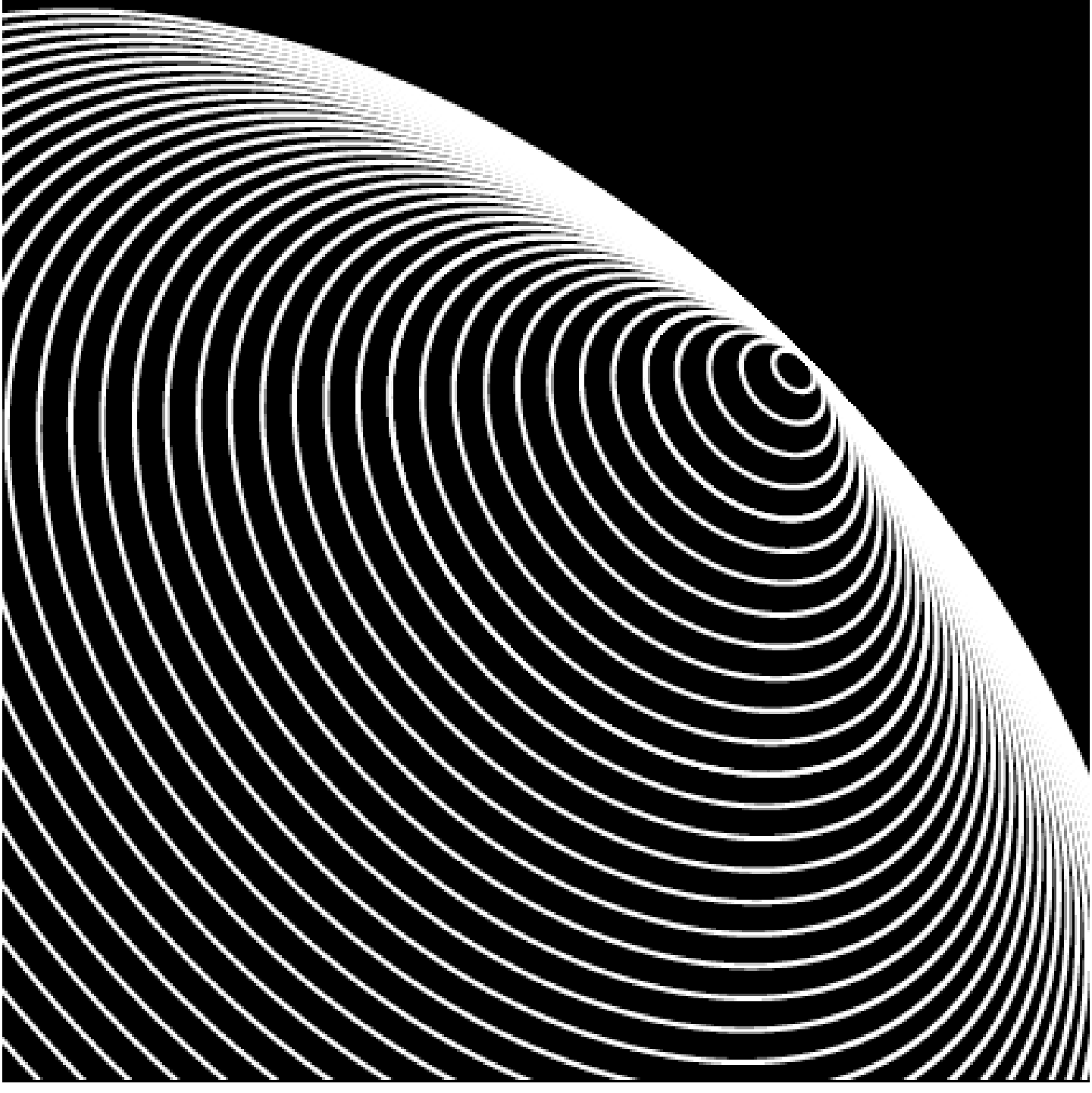
PROSTATE CANCER RADIOTHERAPY:
A FIELD IN MOTION

Ruud C. Wortel



PROSTATE CANCER RADIOTHERAPY:
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Prostate Cancer Radiotherapy: A Field in Motion

Proefschrift

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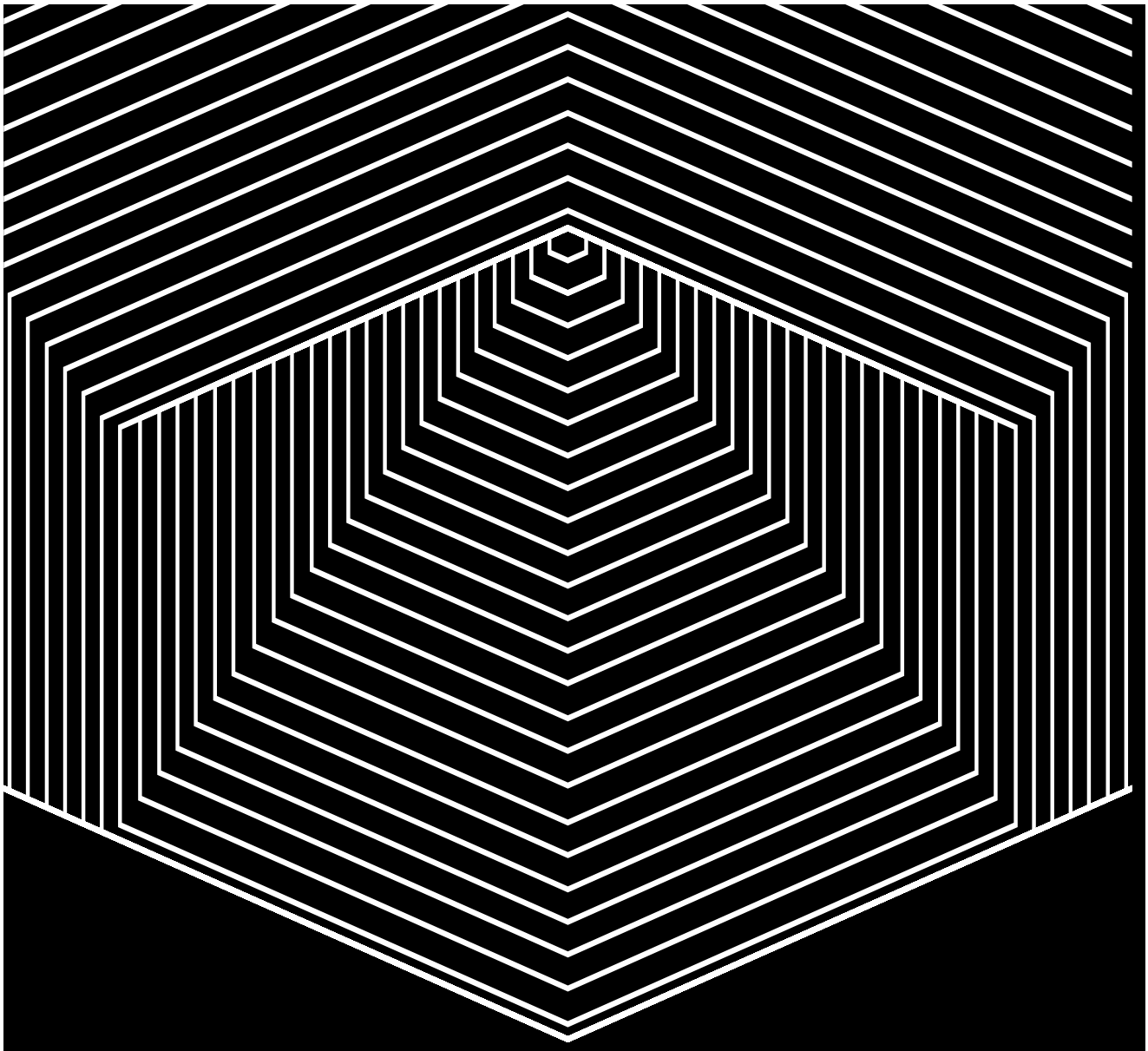
Voor mijn ouders

TABLE OF CONTENTS



“I MEAN, HOW DO YOU KNOW WHAT YOU’RE GOING TO DO ‘TILL YOU DO IT? THE ANSWER IS, YOU DON’T.”

J.D. Salinger, The Cather in the Rye

CHAPTER 01

General introduction and outline of the thesis

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Prostate cancer

Prostate cancer is the second most common cancer in the male population worldwide and the fifth most common cause of cancer-related death (1). In 2012, an estimated 1.1 million new cases (15.0% of all cancers diagnosed in males) and over 300,000 deaths (6.6% of cancer-related death among males) were reported globally (1). In the Netherlands, over 11,000 patients are diagnosed annually (2), which is a two-fold increase since the introduction of prostate specific antigen (PSA) screening assays into clinical practice in the 1980s and 1990s (3). In case of clinical suspicion, prostate cancer is generally diagnosed by means of transrectal image-guided biopsy of the prostate. Approximately half of all patients are aged 70 years or higher at the time of diagnosis (2).

Prostate cancer treatment

The majority of patients are diagnosed with localized disease and can be offered curative treatment options including radical prostatectomy, brachytherapy and external beam radiotherapy (EBRT). A radical prostatectomy is an operation to remove the prostate gland, which can either be performed via an open, laparoscopic or a robot-assisted approach. Brachytherapy either uses radioactive wires which are temporarily placed in the prostate before removing them, or radioactive seeds, which slowly release radiation after being placed in the prostate permanently. In external beam radiotherapy (EBRT), an external source is used to deliver ionizing radiation beams to the prostate.

The choice of treatment is generally based on patient preference, risk profile (4), expected treatment efficacy (5), and patient characteristics such as age, comorbidity profile, and pretreatment symptoms. In the Netherlands, brachytherapy is generally used in patients with favorable tumor characteristics, whereas EBRT and to a somewhat lesser extent radical prostatectomy can also be applied in intermediate- or high-risk prostate cancer patients with higher risk of subclinical tumor extension beyond the prostate gland.

External beam radiotherapy

In modern EBRT, radiation beams are delivered using a medical linear accelerator. A linear accelerator generates high-energy X-rays (photons) which are subsequently aimed at the region of interest. During treatment, the patient lies on a treatment bench, while the linear accelerator rotates around the patient and delivers radiation from multiple angles in order to shape the radiation beams to the contour of the tumor. In prostate cancer treatment, the overall treatment dose is divided into multiple smaller fractions, which are generally delivered daily during weekdays over a period of several weeks. Fractionated treatment delivery improves treatment efficacy, and also reduces the risk of radiation-induced toxicity of adjacent healthy

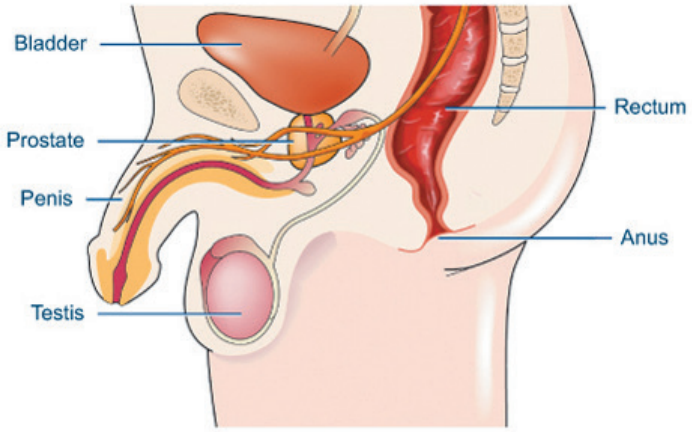
organs (6). The reductions in radiation-induced toxicity are achieved because healthy organs have effective self-repair mechanisms which enable them to repair radiation-induced DNA damage between subsequent fractions (7-9).

Treatment techniques

In the era of 2-dimensional (2D) conventional radiotherapy, radiation beams were only matched to the height and width of the tumor, thus exposing surrounding tissue to high radiation doses (10). The clinical implementation computed tomography (CT) scans and advanced EBRT treatment planning systems enabled the introduction of 3-dimensiontal (3D)-conformal radiotherapy (3D-CRT) in the late 1980s (10). The use of 3D images in the process of treatment planning enabled 3D-CRT to deliver radiation beams matched to the shape of the tumor, while sparing surrounding healthy tissues.

The introduction of intensity modulated radiotherapy (IMRT) as a further development of 3D-CRT represents one the most important advances in radiotherapy of the last decades (10,11). In addition to 3D-CRT, IMRT radiation beams are divided into smaller segments and the intensity of each beam can be modulated during treatment using a multi-leaf collimator. This technique is of specific use in treatment of complex shapes with close proximity to radiosensitive healthy structures, such as the bladder, rectum and anus (Figure 1) (10).

Figure 1. Schematic overview of the lower male genitourinary tract



Planning studies demonstrated that IMRT can significantly reduce the dose to normal tissues as compared to 3D-CRT, without compromising coverage of the planning target volume (i.e. prostate with or without seminal vesicles) (Figure 2) (12-15).

Figure 2. Dose color-wash of IMRT (upper panels: A-C) and 3D-CRT (lower panels: D-F) treatment plan.

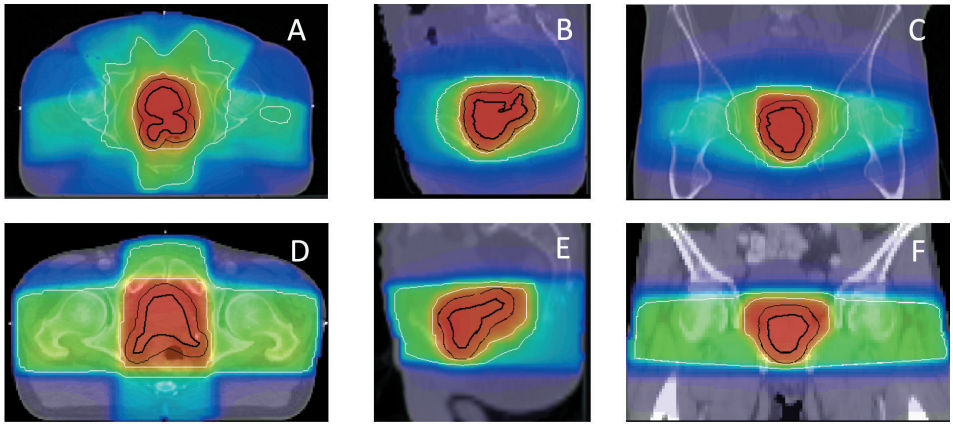


Figure Legend: Clinical target volume (prostate and seminal vesicles) and planning target volume are contoured in black. Dose wash demonstrates smaller high-dose region (red) for IMRT (upper panels: A-C) as compared to 3D-CRT (lower panels: D-F).

Image-guidance (IG) techniques further increased the precision of prostate cancer treatment. Fiducial markers implanted into the prostate and in-room cone-beam CT-imaging facilitated daily prostate localization and alignment before each fraction. These techniques replaced previous protocols which used bony anatomy landmarks for daily localization and alignment. Safety margins around the target volume, which are needed to account for uncertainties in delineation and intra-fraction prostate motion, could be reduced from approximately 10 mm for 3D-CRT to 5 mm using IG-IMRT.

Dose-escalation

Before 3D-CRT was implemented in clinical practice, 2D-conventional EBRT for prostate cancer was typically delivered in 32-35 fractions of 1.8-2.2 Gray (Gy) up to total treatment doses of 64-70 Gy (16-18). A randomized study by Dearnaley and colleagues conducted between 1988 and 1995 demonstrated that 3D-CRT up to 64 Gy in 32 fractions significantly lowered the risk of late radiation-induced rectal toxicities as compared to previous 2-D conventional treatment delivering similar radiation doses (19). Until that moment, rectal toxicity had been considered

the major dose-limiting factor. These data formed the basis for clinical trials exploring higher treatment doses to improve treatment efficacy.

After the study by Dearnaley and colleagues (19) was published, several other randomized phase 3 trials have demonstrated the clinical benefit of treatment to 74-78 Gy as compared to previous schedules of 64-70 Gy in terms of relapse-free survival (16-18). The Dutch CKTO 96-10 dose-escalation trial randomized 669 patients with low- to high-risk localized prostate cancer between 68 Gy in 34 fractions and 78 Gy in 39 fractions (16). At 5-year follow-up, dose-escalation to 78 Gy resulted in superior relapse-free survival, especially in patients with intermediate- and high-risk disease (16). Based on these findings, treatment to 78 Gy in 39 fractions of 2 Gy has been widely introduced in the Netherlands from 2006 onwards.

Radiation-induced side effects

Dose-escalated EBRT up to 74- 78 Gy was, however, associated with substantial toxicity levels (17,18,20). For example, 3-year cumulative incidences of rectal side effects after EBRT up to 78 Gy in the CKTO 96-10 trial included rectal discomfort requiring medication in 10%, rectal bleeding requiring blood transfusion or laser treatment in 10%, increased frequency of stools (≥6/day) in 10%, and use of incontinence pads in 9% (20). Frequent urinary symptoms included nocturia (≥4 times/night) in 22%, and dysuria requiring medication in 14% (20). Such radiation-induced side effects can be graded according to the Radiation Therapy Oncology Group and European Organization of Research and Treatment of Cancer (RTOG-EORTC) scoring criteria for acute and later toxicity (21). Non-lethal genitourinary or gastrointestinal toxicities are graded from 1 (mild) up to 4 (severe) (21). Grade 2 toxicities frequently require medical treatment, whereas grade 3 or 4 toxicities necessitate hospital admission for adequate management. In the CKTO 96-10 trial, the 3-year cumulative risk of late RTOG-EORTC gastrointestinal grade ≥2 toxicity was 23.2 % for 68 Gy vs. 26.5% for 78 Gy, whereas the risk of genitourinary grade ≥2 toxicity was 28.5% vs. 30.2% after 68 Gy and 78 Gy, respectively (20).

Another common side effect of radiation therapy is erectile dysfunction. In literature, the reported incidence of erectile dysfunction following EBRT varies between 6% and 84% (22). Such rate discrepancies decrease the clinical interpretability and might result from differences in expertise between treatment centers, differences in study populations, means of data collection and data presentation. It has been shown that patients' quality of life related to sexual function is significantly associated with treatment satisfaction in patients and their partners (23). Patients frequently seek medical treatment for radiation-induced erectile dysfunction, which primarily consists of prescription of phosphodiesterase type 5 inhibitors such as sildenafil (Viagra©) or tadalafil (Cialis©) (24,25).

Hypofractionated radiotherapy

Even though the technical improvements associated with IMRT and image-guidance further improved treatment accuracy, dose-escalation above overall treatment doses of 80 Gy using conventional 2 Gy fractions remains impeded due to the risk of severe radiation-induced toxicities. In addition, current dose-escalated EBRT treatments of 74-78 Gy are delivered at five days per week over 7-8 weeks. Further increasing the treatment dose would even prolong the overall treatment time, which already has paramount impact on the quality of life of patients.

Several radiobiological studies suggest that hypofractionation might be applicable to increase the radiobiological tumor dose without increasing toxicity (7,8). Hypofractionated radiotherapy literally means a reduction in the number of treatment fractions. In hypofractionated EBRT, a reduction in the number of fractions is compensated for by increasing the radiation dose per fraction. Brenner and Hall (9) were the first to suggest that hypofractionation can be used to safely increase the radiobiological tumor dose. The interest in hypofractionated radiotherapy for prostate cancer is based on the unusual slow proliferation rate of prostate cancer cells which differs from most other cancers (9). In general, conventional fractionation induces accumulation of DNA damage, causing apoptosis, mitotic catastrophe, or senescence (26). The slow proliferation rate of prostate cancer cells results in high repair abilities of radiation-induced damage between fractions, with subsequent suboptimal outcome of treatment (26). Such slowly proliferating cells are sensitive to larger fraction doses, as they cause more immediate DNA double-stand breaks. In radiobiology, the sensitivity of tissues to changes in fractionation is expressed by the α/ß ratio (9). The α/ß ratio for prostate cancer as suggested by Brenner and Hall (9) is uniquely low, and approximated at 1.5 Gy. This indicates that prostate cancer cells require larger fraction doses for effective treatment than surrounding normal tissues, which have suggested α/ß ratios between 4-6 Gy (27-29). Others have recently confirmed the proposed low α/ß ratio for prostate cancer based on data from large clinical data sets (7,8).

Theoretically, hypofractionation could be used to increase the efficacy of treatment, while normal tissues should not be equally affected by larger fractions doses, and therefore toxicity levels should remain similar. In addition, hypofractionation being delivered in fewer fractions positively affects patients convenience and deployment of hospital resources.

The HYPRO trial

Between 2007 and 2010, the randomized, phase 3, multicenter HYpofractionated irradiation for PROstate cancer (HYPRO) trial for patients with intermediate- and high-risk prostate cancer was conducted in the Netherlands. Its aim was to investigate whether hypofractionated EBRT (19 fractions of 3.4 Gy) would increase relapse-free survival without increasing radiation-induced toxicity, compared with conventionally fractionated EBRT (39 fractions of 2 Gy) (30,31). The hypofractionated regimen was chosen based on the assumed α/ß ratio for prostate cancer

of 1.5 and calculations using the Linear Quadratic model. Using this model, the dose to tumor and normal tissue applied in hypofractionation schemes can be calculated in conventional 2 Gy fractions (32). Hypofractionation would achieve a bio-equivalent total dose of 90.4 Gy in 2 Gy fractions, corresponding to a dose-escalation of 12.4 Gy in 2 Gy fractions as compared to the conventionally fractionated schedule of 78 Gy in 39 fractions of 2 Gy.

The primary endpoint was 5-year relapse-free survival. Relapse-free survival was defined as biochemical relapse, locoregional relapse, distant relapse, or start of hormone therapy, whichever occurred first. Additional key endpoints were cumulative incidence of grade 2 or higher acute (Table 1) and late (Table 2) genitourinary and gastrointestinal toxicity according to the RTOG-EORTC scoring criteria (21,30,31).

Table 1. Acute gastrointestinal and genitourinary complication according to the RTOG morbidity scale

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
GI	Increased frequency or change in quality of bowel habits not requiring medication; rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs; mucous discharge not necessitating sanitary pads; rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support; severe mucous or blood discharge necessitating sanitary pads; abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
GU	Frequency of urination or nocturia twice pre-treatment habit; dysuria or urgency not needing medication	Frequency of urination is less frequent than every hour *(day: 12-16 times; Nocturia 5-8 times)*; dysuria, urgency, bladder spasm requiring local anaesthetic	Frequency of urination is more frequent than every hour *(day: >16 times; nocturia: >8 times);* dysuria, bladders spasm, urgency requiring frequent regular narcotic; gross hematuria; *complaints requiring permanent or suprapubic catheter*	Hematuria requiring transfusion/ obstruction not due to clots; ulceration; necrosis

Table Legend: Adaptations from (21) in italic
Table Abbreviations: RTOG= Radiation Therapy Oncology Group, GI= gastrointestinal, GU= genitourinary

Table 2. Late gastrointestinal and genitourinary complication according to the RTOG/EORTC morbidity scale

	Grade 1	Grade 2	Grade 3	Grade 4
GI	Mild diarrhea; mild cramping; bowel movements 2-5 per day; slight rectal discharge or bleeding	Moderate diarrhea; intermittent, severe cramping; bowel movements > 5 per day; *moderate* excessive, rectal discharge; intermittent, *frequent* bleeding -> *single laser treatment and/or transfusion*	*Watery diarrhea*; obstruction requiring surgery; bleeding requiring surgery or *≥2 laser treatments and/or transfusions*	Necrosis; perforation; fistula; *abdominal pain or tenesmus requiring tube decompression or bowel diversion*
GU	*Frequency during* day 1 per 1-2h; nocturia 2-3/night; slight dysuria *or microscopic hematuria* requiring no medication*; slight epithelial atrophy, minor telangiectasia;* bladder capacity > 300 cc	*Frequency during day:* 1 per ½-1h; nocturia 4-6/night*;* moderate dysuria *or intermittent* (mild, moderate) *hematuria* requiring medication.*; moderate telangiectasia;* bladder capacity: 150-300 cc	*Frequency during day* >1 per ½h; nocturia >6/night; *severe dysuria; frequent* (severe) *hematuria*; severe telangiectasia; bladder capacity: *100*-150 cc*; benign urethral strictures, requiring a TURP, dilation, suprapubic or permanent catheter*	Necrosis; severe hemorrhagic cystitis; bladder capacity: < 100 cc

Table Legend: Adaptations from (21) in italic

Table Abbreviations: RTOG= Radiation Therapy Oncology Group, EORTC= European Organization of Research and Treatment of Cancer, GI= gastrointestinal, GU= genitourinary

Secondary endpoints were erectile function and quality of life. The HYPRO trial was powered (n= at least 820 patients) to demonstrate an absolute increase in relapse-free survival of 10% with hypofractionated treatment, as compared to conventionally fractionated treatment (30,31). We hypothesized non-inferiority of hypofractionation for acute and late gastrointestinal and genitourinary toxicity (30,31).

Outline of the thesis

This thesis reports on research concerning the effects and side effects of novel treatment techniques and treatment schedules in radiotherapy for prostate cancer. The thesis is divided in three parts. Part I focusses on radiation-induced gastrointestinal and genitourinary side effects

associated with novel treatments. Part II focusses on treatment efficacy of hypofractionated radiotherapy. In Part III, quality of life and sexual function after modern EBRT are studied.

PART I: RADIATION-INDUCED TOXICITY

In the Netherlands, IG-IMRT has now replaced 3D-CRT in the treatment of prostate cancer. Despite convincing evidence in planning studies favoring IG-IMRT over 3D-CRT (12-15), prospective comparative clinical studies addressing these benefits have not been conducted (33-38).

In **Chapter 2** we study acute toxicity in patients treated to 78 Gy in 39 fractions either using 3D-CRT or IG-IMRT. Patients were selected from the experimental high-dose arm of the Dutch CKTO 96-10 dose-escalation trial (20) and the reference arm of the recent HYPRO trial (30,31). The treatment schedules in both prospective cohorts were virtually identical apart from applied treatment techniques. Patient-reported data were used to investigate the hypothesized benefits of IG-IMRT in terms of dose reductions to normal tissues and toxicity levels. In **Chapter 3** these patient populations are again used to evaluate anorectal dose distribution and its relation to acute rectal toxicity using dose-surface maps (39). Spatial information derived from dose-surface maps could serve as a basis for subsequent dose-effect modeling, improving dose constraints in clinical practice. A comparison of late side effects in both prospective cohorts is reported in **Chapter 4.** In **Chapter 5** we analyze the effects of the use of an endorectal balloon, magnetic resonance imaging (MRI)-based contouring and variation in applied safety margins on late rectal toxicities within the HYPRO trial.

PART II: TREATMENT EFFICACY

In **Chapter 6** we present the 5-year efficacy results from the HYPRO trial. In **Chapter 7** we provide an overview of the currently available results of hypofractionation trials.

PART III: QUALITY OF LIFE AND SEXUAL FUNCTION

In **Chapter 8** we report patient-reported outcomes on quality of life from the HYPRO trial. In **Chapter 9** we report on sexual function outcomes from the HYPRO trial. In **Chapter 10** we

review representative literature on erectile function after radiotherapy for prostate cancer in order to identify the cause of discrepancies in the reported erectile dysfunction rates in modern literature. We highlighted the strengths and weaknesses of current literature and made general recommendations in order to improve clinical interpretability and increase homogeneity between reports.

In **Chapter 11** we present the results of studies that were conducted at Memorial Sloan Kettering Cancer Center in New York. They previously demonstrated that treatment with sildenafil (Viagra©) during radiotherapy and up to six months after completion resulted in significantly better sexual function outcomes than placebo treatment did (40). They also suggested that radiation-induced erectile dysfunction is mainly the result of arteriogenic erectile dysfunction as a result of endothelial dysfunction (41). We have conducted *in vivo* studies on bovine endothelial cells to study whether sildenafil protects endothelial cells from endothelial dysfunction and unravel the pathway by which such protection takes place.

The general discussion of this thesis and future research perspectives are presented in **Chapter 12.** A summary of this thesis is provided in English and Dutch in **Chapter 13.**

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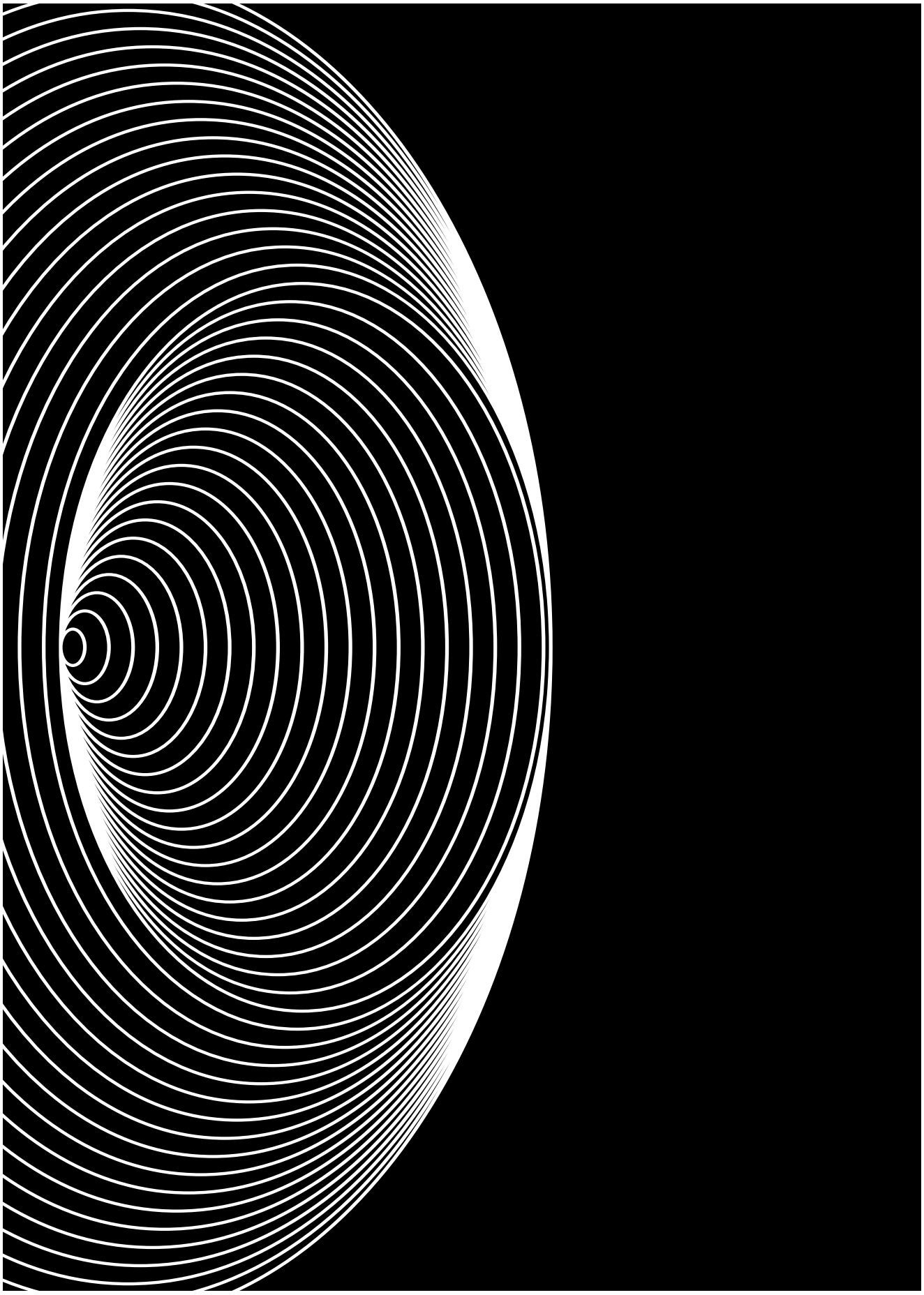
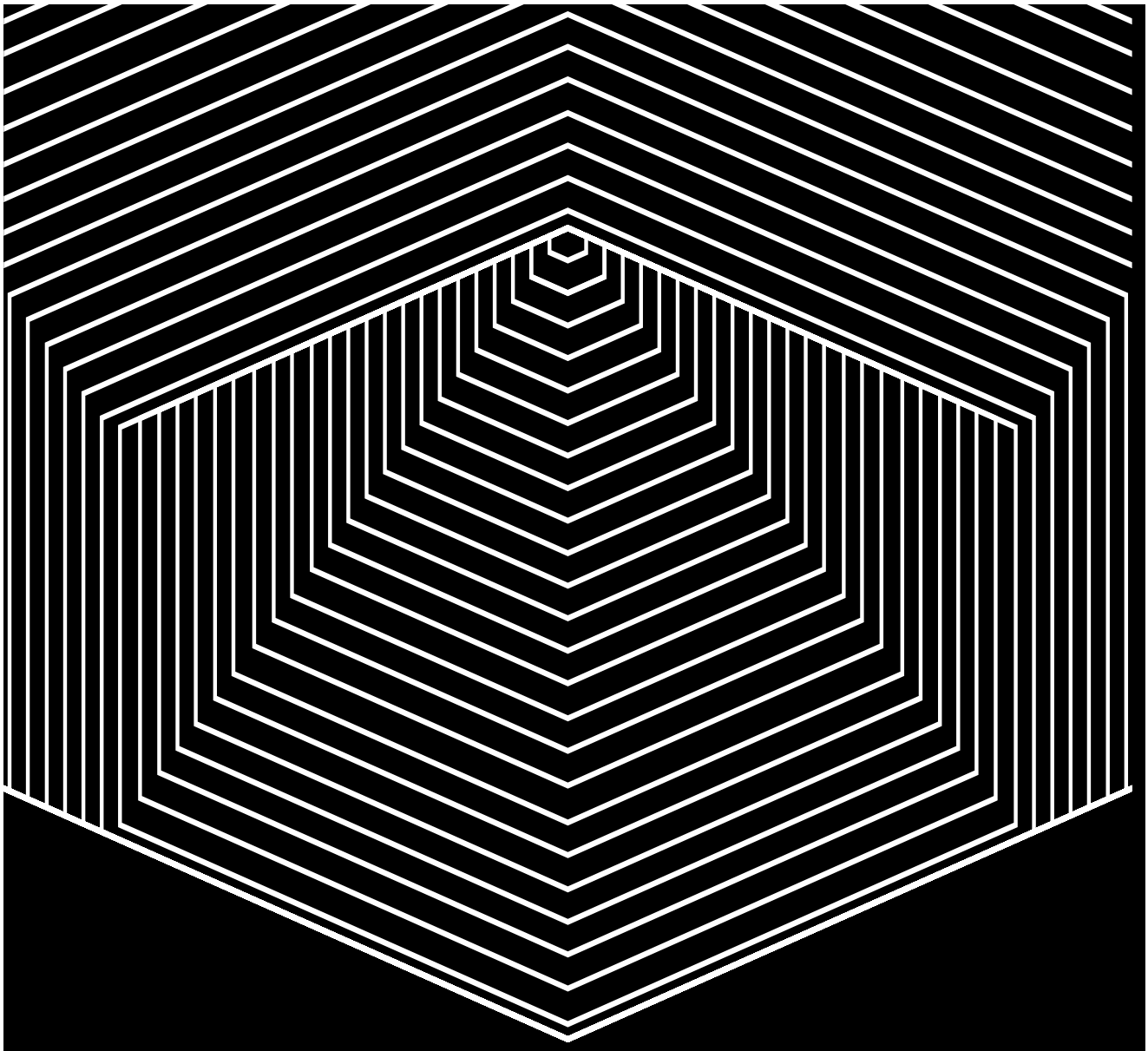


PART I

Radiation-induced toxicity



“INNOCENCE ABOUT SCIENCE IS THE WORST CRIME TODAY.”

Sir Charles Percy Snow

CHAPTER 02

Acute toxicity after image-guided intensity-modulated radiation therapy (IG-IMRT) compared to 3D-conformal radiation therapy (3D-CRT) in prostate cancer patients

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ABSTRACT

Purpose

The introduction of image-guided intensity modulated radiotherapy (IG-IMRT) allowed significant dose reductions to organs at risk in prostate cancer patients. However, clinical data identifying the benefits of IG-IMRT in daily practice are scarce. The purpose was to compare dose distributions to organs at risk and acute gastrointestinal (GI) and genitourinary (GU) toxicity levels of patients treated to 78 Gy with either IG-IMRT or 3D-CRT.

Methods and materials

Patients treated with 3D-CRT (n=215) and IG-IMRT (n=260) receiving 78 Gy in 39 fractions within two randomized trials were selected. Dose surface histograms of anorectum, anal canal and bladder were calculated. Identical toxicity questionnaires were distributed at baseline, at fraction 20 and 30 and 90 days after treatment. Radiation Therapy Oncology Group (RTOG) grade ≥1, grade ≥2 and ≥3 endpoints were derived directly from questionnaires. Univariate and multivariate binary logistic regression was applied.

Results

The median volumes receiving 5-75 Gy were significantly lower (all p values <0.001) with IG-IMRT for anorectum, anal canal and bladder. The mean dose to the anorectum was 34.4 Gy vs. 47.3 Gy ($p<0.001$), 23.6 Gy vs. 44.6 Gy for the anal canal ($p<0.001$) and 33.1 Gy vs. 43.2 Gy for the bladder ($p<0.001$). Significantly lower grade ≥2 toxicity was observed for proctitis, stool frequency ≥6/day and urinary frequency ≥12/day. IG-IMRT resulted in significantly lower overall GI grade ≥2 RTOG toxicity (29% vs. 49%, $p=0.002$) and overall GU grade ≥2 toxicity (38% vs. 48%, $p=0.009$).

Conclusions

A clinically meaningful reduction in dose to organs at risk and acute toxicity levels was observed in IG-IMRT patients, as a result of improved technique and tighter margins. Therefore, reduced late toxicity levels can be expected as well; additional research is needed to quantify such reductions.

INTRODUCTION

In the last two decades, intensity modulated radiotherapy (IMRT) has been developed as an evolution of three-dimensional conformal radiotherapy (3D-CRT). IMRT produces highly conformal dose distributions using beams of non-uniform radiation intensity and enables dose-escalation to irregularly shaped tumors with decreased dose to organs at risk (OAR). In addition, image guidance using cone-beam computed tomography (CBCT) and implanted fiducial markers further increased the precision of radiotherapy. Image-guided radiotherapy is applied most commonly in genitourinary malignancies and incremental costs related to online image-guided treatment strategies are acceptable (1,2). Planning studies on prostate cancer have demonstrated that IMRT treatment can reduce the dose to OAR compared to 3D-CRT, without a reduction of planning target volume (PTV) coverage (3-6). Acute toxicity is an independent predictor of late toxicity (7-10). Literature identifying the benefits of the clinical introduction of IG-IMRT for patients is scarce, especially regarding the potential reduction of acute toxicity levels (11,12).

The aim of the current study was to compare dose distributions to OAR (i.e. bladder, anal canal, anorectum) and acute toxicity rates of patients treated with IG-IMRT versus a 3D conformal technique in two randomized trials with comparable prospective data collection, identical treatment dose and fractionation, and identical patient questionnaires. For this purpose, patients were selected from two prospective randomized trials: the dose-escalation trial (CKTO 96-10), in which patients were randomized to 68 Gy or 78 Gy with mainly 3D-CRT and 10-mm margins (13), and the hypofractionation trial (CKTO 2006-08) comparing patients treated with mainly IG-IMRT and 5-8-mm margins to either 78 Gy or a hypofractionated treatment of 64.6 Gy (19x 3.4 Gy) (14). We hypothesized that GI dose distributions and toxicity rates would be lower with IG-IMRT due to the superior technique allowing reduced margins (10 mm for 3D-CRT vs. 5-8 mm for IG-IMRT). We expected comparable GU toxicity rates with both techniques since the prostatic urethra and part of the bladder neck lie within the PTV and likely receive similar or only slightly decreased dose with IG-IMRT despite the use of more advanced techniques.

PATIENTS AND METHODS

Patient population

We selected patients treated to 78 Gy (39 fractions) with IG-IMRT from the standard arm of the hypofractionation trial (14), and patients treated to 78 Gy with a 3-field 3D-CRT from the high-dose arm of the dose-escalation trial (68 Gy vs. 78 Gy) (13). In the latter group, patients for whom dose was reduced to 68-76 Gy prior to treatment due to rectal dose constraints (n=7)

or during radiotherapy because of toxicity (n=10), were included in this study as well. We only included patients for whom at least a baseline toxicity questionnaire and ≥1 questionnaire during the acute phase was available.

Included 3D-CRT patients (n=215) from the dose-escalation trial (1997-2003) had stage T1b-T4 localized prostate cancer (low- to high-risk) with an initial prostate-specific antigen (iPSA) <60 µg/l. The patients excluded from the 78 Gy arm of the current study were either treated with a four-field technique (n=35) or with non-image-guided IMRT (n=41) (Figure 1). Characteristics of this trial have been previously described in more detail elsewhere (13,15).

Figure 1. Flowchart of study

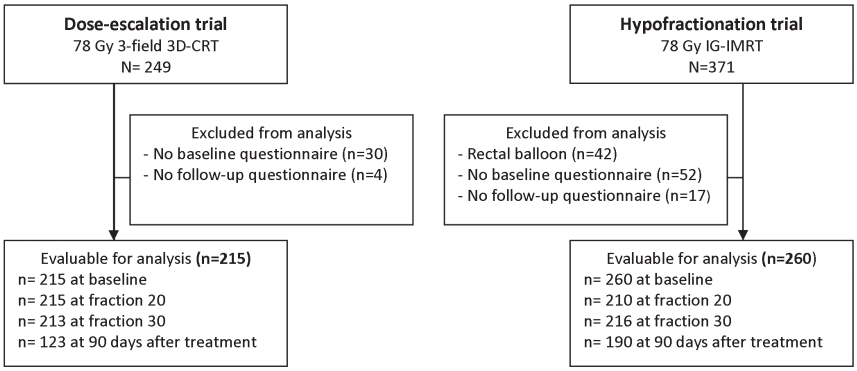


Figure Abbreviations: 3D-CRT=3D-conformal radiotherapy; IG-IMRT= Image-guided intensity modulated radiotherapy.

The included IG-IMRT patients from the hypofractionation trial (2007-2010), comparing standard fractionation (39x2 Gy) with hypofractionated treatment (19x3.4 Gy) (14), consisted of intermediate or high-risk localized adenocarcinoma of the prostate, defined by the single factor definition proposed by Chism *et al.* (16), and an iPSA <60 µg/l. Patients from the standard arm of the hypofractionation trial that were treated with volumetric modulated arc therapy (VMAT) (n=7), four-field 3D-CRT (n=13) or treated with a rectal balloon (n=42), were excluded (Figure 1). In both trials, application of hormonal treatment varied between the participating institutions, depending on local clinical protocols.

Treatment and contouring

Details concerning treatment planning have been previously reported (13-15). Briefly, all patients were prescribed 78 Gy to the prostate whereas dose prescriptions to the seminal vesicles (SVs) were different between both trials. Depending on the estimated probability of SV involvement, prescribed dose was 0 Gy, 50 Gy, 68 Gy, or 78 Gy in the dose-escalation trial, and 0 Gy, 70 Gy, or 78 Gy in the hypofractionation trial. Distribution of SV dose for both arms is summarized in Table 1.

Image-guided daily on-line set-up verification and correction with implanted fiducial markers and CBCT was used in 96% of all patients treated with IG-IMRT. For the remaining 4%, an off-line image-guided protocol using kilo-voltage CBCT imaging was used for prostate matching (17). Offline bony anatomy matching with electronic portal imaging was used for 3D-CRT.

Dose prescription was according to the International Commission on Radiation Units and Measurements guidelines, delivered five days per week in 2 Gy fractions. A full bladder protocol was applied for all patients and rectal emptying was stimulated for scanning.

The anorectum was delineated from the ischial tuberosities to the anal verge, whereas the anal canal was defined as the caudal 3 cm of the anorectum (in craniocaudal direction) (18, 19). The outer bladder wall was delineated on the planning CT scan. Applied dose constraints for 3D-CRT were the percentage of the rectum receiving ≥74 Gy ≤40%, and small bowel dose ≤68 Gy. For IG-IMRT the rectal volume receiving ≥65 Gy should not exceed 50%, whereas the mean anal dose should not exceed 60 Gy.

Acute toxicity scoring

For the current study, toxicity scores were derived directly from the selected questionnaires (baseline, fraction 20, fraction 30 and 90 days after treatment). The patient self-assessment questionnaire contains questions on GI and GU complaints and was comparable to the ones used by Tait *et al.* (20). Any patient-reported rectal discomfort or change in quality of bowel habits (Table 2) was scored as grade ≥1 toxicity, which is in line with the Radiation Therapy Oncology Group (RTOG) scoring system (21). GI grade ≥2 and grade 3 endpoints were scored as applied in the hypofractionation trial (Table 2). These endpoints were based on the RTOG scoring system, which was modified as follows: increased bowel frequency (>=6) was scored as grade 2 conform RTOG scoring system for late toxicity (21). Furthermore, proctitis grade 2 was scored in case there was moderate to severe mucous or blood loss or in case of mild mucous/blood loss combined with at least 2 other complaints: diarrhea, incontinence, tenesmus, cramps, or pain. The RTOG scoring system only addresses mucous loss.

Table 1. Patient and treatment characteristics

Variable	3D-CRT (n=215)	IG-IMRT (n=260)
Mean age (SD) (y)	68.9 (6.3)	70.5 (6.0)
T stage		
1	36 (16.7)	40 (15.4)
2	97 (45.1)	89 (34.2)
3a	53 (24.7)	102 (39.2)
3b	29 (13.5)	28 (10.8)
4	0	1 (0.4)
Gleason score		
2-6	106 (49.3)	75 (28.8)
7	81 (37.7)	119 (45.8)
8-10	28 (13.0)	66 (25.4)
Median PSA µg/L (range)	11.3 (0.4-57.0)	15.0 (1.8-59.6)
Risk category		
Low	34 (15.8)	0
Intermediate	72 (33.5)	75 (28.8)
High	109 (50.7)	185 (71.2)
Seminal Vesicle Dose		
0 Gy	43 (20.0)	50 (19.2)
50 Gy	35 (16.3)	0
68 Gy	101 (47.0)	0
70 Gy	0	125 (48.1)
78 Gy	36 (16.7)	85 (32.7)
Planning Margins		
5 mm	0	107 (41.3)
6-8 mm	0	151 (58.3)
10 mm	215 (100)	1 (0.4)
Hormonal Therapy	42 (19.5)	174 (66.9)
TURP	24 (11.2)	28 (10.8)
Diabetes Mellitus	12 (5.6)	29 (11.2)
Abdominal surgery	57 (26.5)	65 (25.0)
Smoking	34 (15.8)	28 (15.0)

Table Abbreviations: SD= Standard deviation; PSA=Prostate specific antigen; TURP= Transurethral resection of prostate.

All GU complaints on the questionnaire related to increased frequency and dysuria were scored according to RTOG (Table 2) (21). Incontinence was added as grade ≥1 toxicity. GI and GU endpoints concerning prescribed medication could not be derived from the questionnaire. Overall RTOG toxicity scores (including medication scores) from the original dose-escalation trial and the hypofractionation trial were available for comparison.

Comparison of dose distributions to OAR

Relative surfaces receiving ≥5 Gy- 80 Gy were calculated in dose steps of 5 Gy for anorectum and anal canal. Absolute dose-surface data were used for the bladder, because the variation is less with changes in bladder filling compared to relative dose data (22). Dose-surface histograms (DSHs) and mean doses to anorectal surface, anal surface and bladder surface were compared between IG-IMRT and 3D-CRT.

Statistical analysis

Dose distributions were compared using the Mann-Whitney U test. Endpoints were compared between IG-IMRT and 3D-CRT using binary logistic regression (univariate (UV) and multivariate (MV) analyses). At MV analysis, we adjusted for SV dose (continuous), baseline grade ≥2 complaints (GI and GU separately) as assigned in both original trials (yes/no), neo-adjuvant hormonal treatment (yes/no), age (<75/>75), previous transurethral resection of the prostate (TURP) (yes/no), previous abdominal surgery (yes/no) and smoking (yes/no). The variables IG-IMRT (yes/no) and baseline grade ≥2 complaints were included in all MV-models, as were all other variables per endpoint with a p-value<0.10 at UV-analysis. Urinary function of patients with a transurethral catheter during treatment (n=7) was not evaluable, therefore they were excluded from analyses regarding GU toxicity. Statistical analyses were performed using SPSS (version 20, SPSS Inc., Chicago). An α of 0.05 (two sided) was considered the limit of significance.

RESULTS

General characteristics

Patients treated with 3D-CRT returned on average 2.6 out of 3 follow-up questionnaires compared to 2.4 in the IG-IMRT arm. Conform the treatment schedule of five fractions per week, the questionnaires prior to fraction 20 and 30 were returned at 28 days (SD 1.9 days) and 42 days (SD 2.1 days) after the first fraction, respectively. The 3-months questionnaire was returned at a mean of 92 days after treatment (SD 19.6 days). Patient and treatment characteristics are reported in Table 1. In line with the inclusion criteria of both trials, low-risk patients were only included in the 3D-CRT group (15.8%). The prescribed dose to the SVs was

on average somewhat higher in the IG-IMRT group with comparable numbers receiving 0 Gy (19% versus 20%).

Dose-surface parameters

Figure 2 shows a summary of the DSHs. The average surface receiving at least a certain dose at each dose level is depicted with the corresponding 10th- and 90th percentile, with relative (%) surfaces for anorectum and anal canal, and absolute surfaces for the bladder. The median V5-V75 Gy was significantly lower (all p values <.001) with IG-IMRT for anorectum, anal canal and bladder. The largest differences were observed for the anal canal and the smallest differences are observed for the bladder.

Figure 2. Summary of dose-surface histograms to organs at risk with image-guided-IMRT and 3D-conformal radiotherapy

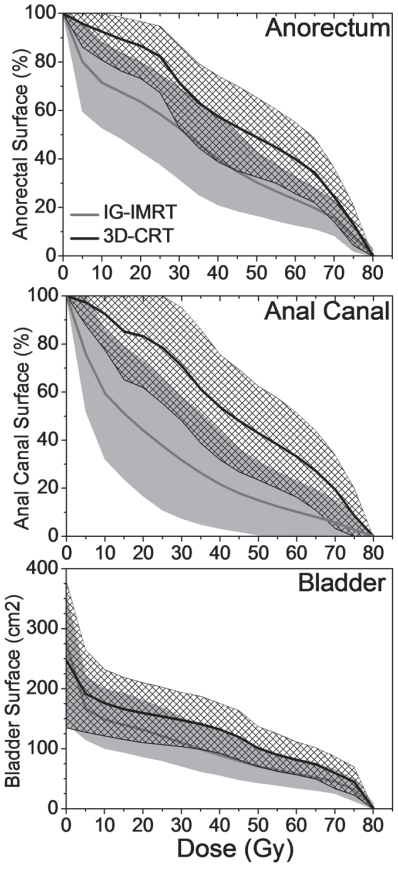


Figure Legend: Mean dose and 10th-90th percentile for image-guided-IMRT (grey) and 3D-conformal radiotherapy (black) of a) relative anorectal surface; b) relative anal canal surface; c) absolute bladder surface.

The mean dose to the anorectum was 34.4 Gy (SD 7.2 Gy) for IG-IMRT compared to 47.4 Gy (SD 6.6 Gy) for 3D-CRT (p<0.001). The anal canal received a significantly lower (p<0.001) mean dose of 23.6 Gy (SD 10.3 Gy) with IG-IMRT compared to 44.5 Gy (SD 9.0 Gy) with 3D-CRT. The mean dose to the bladder surface was significantly lower as well (p<0.001) for IG-IMRT compared to 3D-CRT (33.1 Gy, SD 10.9 Gy vs. 43.2 Gy, SD 12.5 Gy).

Acute toxicity endpoints

At MV analysis (Table 2), IG-IMRT significantly reduced abdominal cramps, tenesmus, mucous discharge, grade ≥2 proctitis, stool frequency ≥6/day, and urinary frequency ≥12/day (p values varying between 0.008 and 0.028). No MV analyses were performed for grade 3 complaints due to the low incidence of these endpoints. Baseline GI grade ≥2 complaints significantly predicted abdominal cramps (p=0.019, OR=5.03), incontinence (p=0.014, OR=4.53), blood loss (p=0.038, OR=3.70) and stool frequency ≥6/day (p=0.001, OR=8.49). As for GU, a previous TURP significantly reduced urinary pain (p=0.002, OR=0.36), straining (p=<0.001, OR=0.24) and nocturia ≥5/night (p=0.015, OR=0.32), whereas baseline GU grade ≥2 complaints significantly predicted incontinence (p=0.024, OR=1.86), frequency ≥12/day (p<0.001, OR=4.14) and nocturia ≥5/night (p<0.001, OR=3.40). Hormonal treatment significantly reduced urinary pain (p=0.005, OR=0.54).

The incidence of grade ≥2 complaints as a function of time is presented in Figure 3. The baseline incidence of all endpoints was comparable between both techniques, except for “urinary frequency ≥12/day,” which was significantly greater for 3D-CRT (6.8% vs. 2.0%, p=0.012).

RTOG overall toxicity scores

According to original trial records of the selected patients, GI grade >=2 toxicity was 34% (IG-IMRT) versus 60% (3D-CRT), whereas current GI scores (lacking medication endpoints) added up to 29% versus 49% (MV p-value=0.002, OR=0.49), respectively. Regarding GU, originally assigned grade >=2 scores were 53% versus 58%, and current scores were 38% (IG-IMRT) and 48% (3D-CRT) (MV p-value=0.009, OR=0.59).

Table 2. Univariate (UV) and multivariate (MV) binary logistic regression analyses for acute gastrointestinal (GI) and genitourinary (GU) toxicity

	IG-IMRT (n=260)	3D-CRT (n=215)	UV	MV	OR*
GI					
Painful defecation (G≥1)	28%	40%	0.007	0.177	0.74
Cramps (G≥1)	34%	46%	0.007	**0.028**	0.65
Tenesmus (G≥1)	49%	62%	0.006	**0.022**	0.65
Mucous discharge (G≥1)	47%	64%	<0.001	**0.002**	0.55
Incontinence (G≥1)	27%	27%	0.995	0.822	0.95
Blood loss (G≥1)	12%	20%	0.023	0.084	0.64
Diarrhea (G≥1)	14%	14%	0.987	0.976	0.99
Proctitis (G≥2)	27%	44%	<0.001	**0.008**	0.54
Stool frequency ≥6/day (G≥2)	8%	19%	<0.001	**0.012**	0.43
Proctitis (G≥3)	4%	2%	0.469	n.a.	n.a.
Overall grade ≥2	29%	49%	<0.001	**0.002**	0.49
GU					
Painful urination (G≥1)	50%	58%	0.123	0.979	0.99
Straining (G≥1)	57%	62%	0.260	0.165	0.76
Incontinence (G≥1)	34%	28%	0.129	0.410	1.19
Frequency ≥12/day (G≥2)	19%	30%	0.006	**0.009**	0.45
Nocturia ≥5/night (G≥2)	23%	27%	0.391	0.058	0.64
Macroscopic hematuria (G≥3)	3%	3%	0.720	n.a.	n.a.
Frequency ≥17/day (G≥3)	4%	7%	0.273	n.a.	n.a.
Nocturia ≥8/night (G ≥3)	4%	6%	0.271	n.a.	n.a.
Overall grade ≥2	38%	48%	0.034	**0.009**	0.59

Table Legend: * Odds ratio for MV analysis

Table Abbreviations: IG-IMRT= Image-guided intensity modulated radiotherapy; 3D-CRT=3D-conformal radiotherapy; OR= Odds ratio, UV= univariate, MV= multivariate, n.a.= not applicable

Figure 3. Incidence and standard-error of; Stool frequency ≥6/day; and proctitis grade ≥2/grade 3 (left column); and urinary frequency grade ≥2/grade 3; and nocturia grade ≥2/grade 3 (right column)

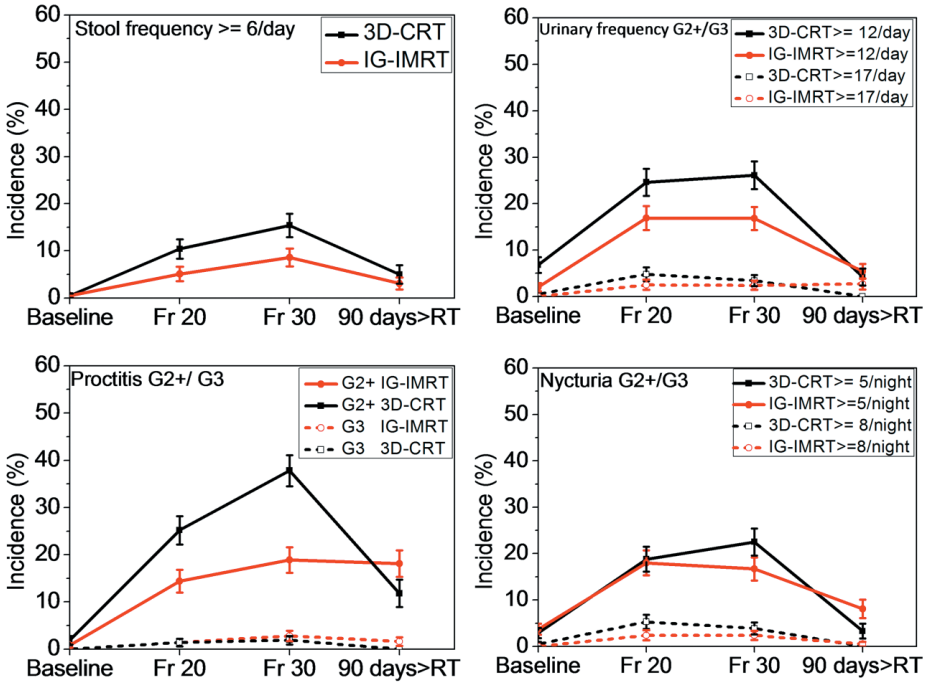


Figure Abbreviations: 3D-CRT=3D-conformal radiotherapy, IG-IMRT=image-guided intensity modulated radiotherapy

DISCUSSION

To our knowledge, this is the first paper quantifying differences in dose to OARs and acute toxicity levels between IG-IMRT and 3D-CRT, derived from clinical data in a prospective setting. The median V5-V75 Gy were significantly lower (all p values <.001) with IG-IMRT for all OAR, resulting in less treatment-induced acute toxicity. At MV analysis grade 2 endpoints "proctitis" "frequency of stools ≥6/day" and "urinary frequency ≥12/day" were scored significantly less in patients treated with IG-IMRT compared to 3D-CRT. IG-IMRT resulted in significantly lower incidences of assigned overall grade ≥2 GI and GU toxicity scores. The underlying local dose-effect relations in these patients are the subject of further investigations.

Two recent papers addressed acute toxicity in patients treated with either IMRT or 3D-CRT at an equal dose. Al-Mamgani *et al.* (12) compared 41 patients treated to 78 Gy with IMRT with

a group of 37 treated with 3D-CRT, and found that IMRT resulted in a significant decrease in acute GI Grade ≥2 toxicity but not in acute GU toxicity. Michalski *et al.* (11) reported a significant decrease in acute grade ≥2 GI and/or GU combined toxicity in 491 and 257 patients treated to 79.2 Gy with 3D-CRT and IMRT, respectively. However, no significant differences were found in GI or GU toxicity separately. The incidence of grade ≥2 GI and/or GU toxicity reported by Michalski *et al.* was low, with 9.7% for IMRT and 15.1% for 3D-CRT. It should however be noted that Michalski *et al.* used the National Cancer Institute's Common Toxicity Criteria version 2.0 (23) to score acute toxicity, making a comparison with our study difficult. Goldner *et al.* (24) stated that patients' self-reported toxicity questionnaires should be used together with doctors' reports in order to evaluate the true incidence of radiation-induced toxicity. If only data from doctors' reports are taken into account, as Michalski *et al.* did, the incidence of toxicity could be underestimated.

Dose constraints for 3D-CRT stipulated that small bowel dose should not exceed 68 Gy and ≤40% of the rectum should receive ≥74 Gy. The introduction of IG-IMRT facilitated that dose constraints could be adjusted in the hypofractionation trial and rectal volume receiving ≥65 Gy was not allowed to exceed 50%. This contributed to significantly lower median anorectal V65 in IG-IMRT patients and a reduction in the incidence of acute blood loss. Anal dose constraints (i.e. mean anal dose ≤60 Gy) were introduced for IG-IMRT treatment because anal dosimetric variables were associated with late incontinence (25). Even though the mean anal dose was significantly lower with IG-IMRT, the incidence of acute incontinence was comparable.

No bladder dose constraints were applied during treatment with both techniques. Mean bladder doses were significantly lower with IG-IMRT, resulting in a significantly lower incidence of urinary frequency ≥12/day. The fact that other GU RTOG grade ≥1 endpoints were comparable probably results from the dose to the bladder neck and prostatic urethra, which are included in the PTV with both techniques. A TURP prior to radiotherapy resulted in significantly less acute GU complications, in accordance with Peeters *et al.* and Schultheiss *et al.* (13,26). Baseline GU complaints might be decreased due to a previous TURP and a nonobstructed (prostatic) urethra might also be less prone to GU complaints resulting from radiation-induced edema.

Several investigators reported that acute GI toxicity is an independent significant predictor for late toxicity, a phenomenon called consequential late effect. Jereczek *et al.* (7) and Zelefsky *et al.* (8) both reported that acute rectal toxicity was a significant predictor for late GI toxicity. Heemsbergen *et al.* (9) demonstrated that acute mucous discharge and acute proctitis were predictors for late "overall toxicity," "intermittent bleeding," "use of pads" and "frequency of stools ≥6/day". Vargas *et al.* (10) reported that acute diarrhea and tenesmus were predictors for late GI toxicity. Because acute toxicity as well as delivered dose to OARs are predictors of

late toxicity, we expect this will eventually translate in lower late toxicity levels with IG-IMRT. Late toxicity evaluation will be the subject of a future study.

The current questionnaire-based study on toxicity endpoints resulted in a fair comparison between both techniques. Even though it remains a limitation that medication endpoints could not be included, we were able to estimate the degree of underestimation because we compared the current grade ≥2 scores with the original trial data. It should however be noted that changing policies to prescribe medication could have influenced a comparison of medication-related endpoints. Nowadays, prescription of alpha-blockers during treatment, which is usually scored as a grade 2 toxicity, is common practice and leads to a substantial increase in grade ≥2 toxicity even without self-reported toxicity. In order to avoid this, Pollack *et al.* (27) modified the coding criteria and alpha-blockers or occasional non-narcotic medication for dysuria were coded as grade 1.

Only intermediate- or high-risk prostate cancer patients were included in the hypofractionation trial and they might have more cancer related complaints prior to and during treatment. We are well aware that treatment groups were not completely comparable but if these factors did somewhat influence the outcomes of our study, it would have been a disadvantage for the IG-IMRT group and therefore only strengthen the conclusion that IG-IMRT leads to lower acute toxicity rates.

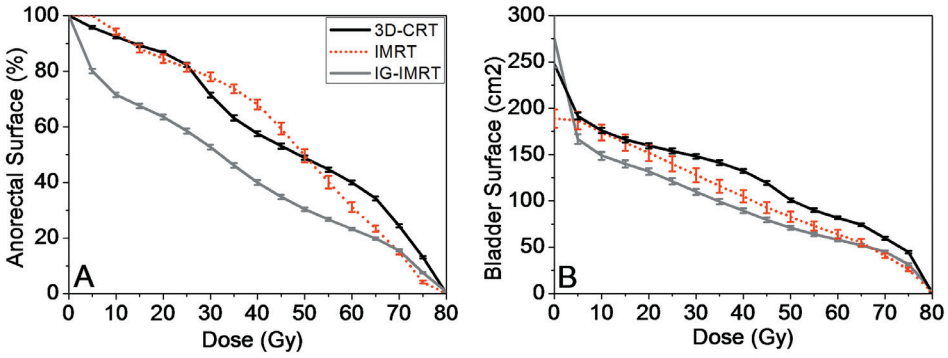
The introduction of IMRT and image-guidance with reduced margins improved the therapeutic ratio by allowing more stringent dose constraints and smaller irradiated volumes of normal tissue. In order to estimate the separate contribution of 1) IMRT and 2) smaller margins to the observed reduction in dose to the organs at risk, we plotted the average anorectum and bladder DSH (with standard error) of 41 IMRT patients who were irradiated with identical margins as the 3D-CRT group and without image-guidance (Figure 4).

This patient group was treated within the dose-escalation trial and has been previously prescribed by Al-Mamgani *et al.* (12). Figure 4a shows that the reduction of dose to the anorectal region in general is mainly the result of smaller margins, whereas the reduction of the high-dose region can be achieved by the IMRT technique only. Figure 4b shows that both technique and margins contribute about equally to the reduction in bladder dose. Note that the average absolute bladder surface was smaller in the IMRT group; this does however not affect the comparison of absolute bladder surfaces receiving doses in the range of 30 – 80 Gy.

In conclusion, treatment with IG-IMRT leads to a significant reduction in mean dose to anorectum, anal canal and bladder due to tighter margins, improved technique and improved dose constraints. This has led to a clinically meaningful reduction of side effects. Based on

these results reduced late toxicity levels can be expected as well; additional research is needed to quantify such reductions.

Figure 4. Summary of average dose-surface histograms (with standard error) for (A) anorectum and (B) bladder with image-guided-IMRT, IMRT and 3D-Conformal radiotherapy.



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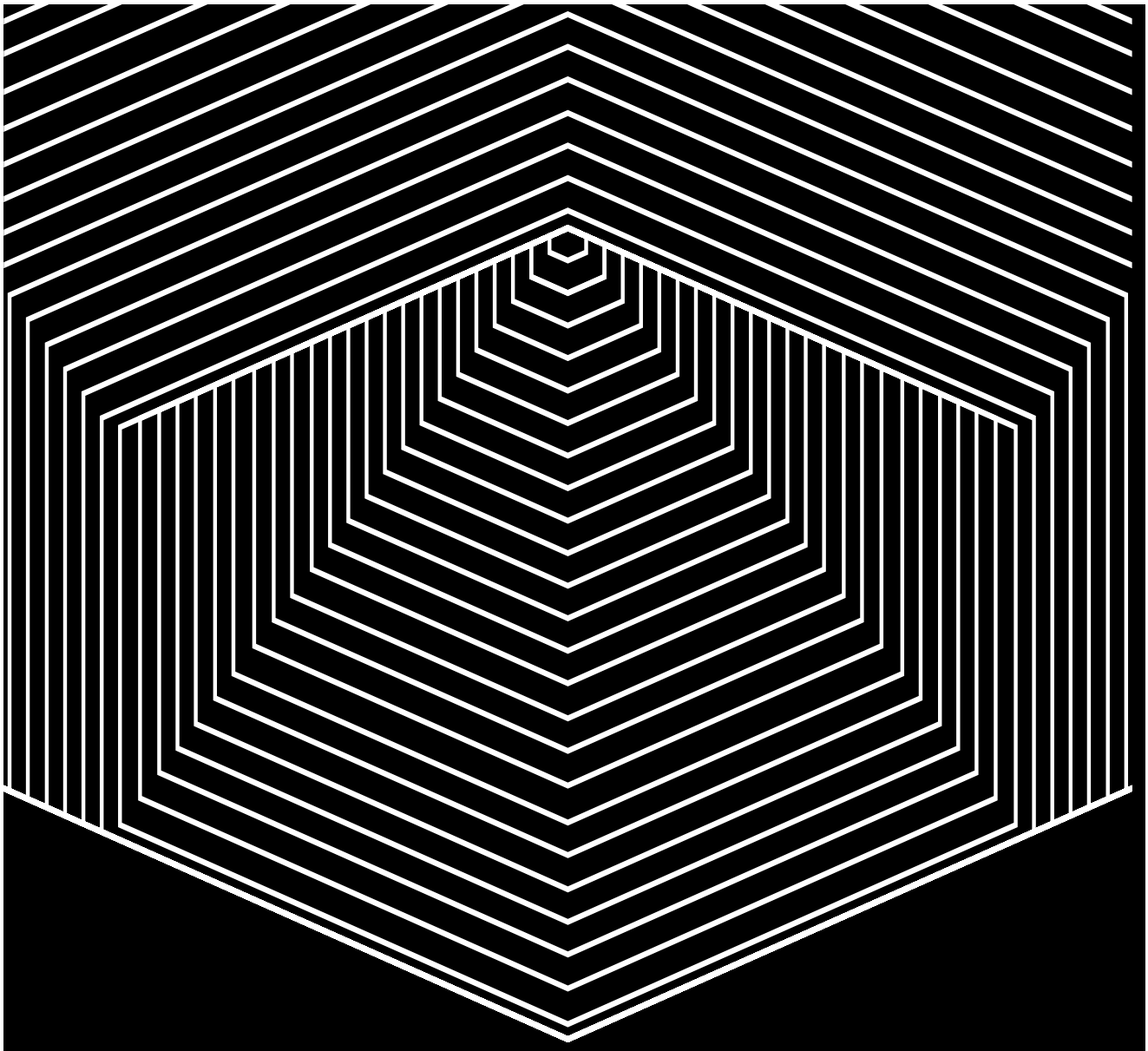

“I HAVE TO REMIND MYSELF THAT SOME BIRDS AREN’T MEANT TO BE CAGED. THEIR FEATHERS ARE JUST TOO BRIGHT.”

Morgan “Red” Freeman, The Shawshank Redemption

CHAPTER 03

Dose-surface maps identifying local dose-effects for acute gastrointestinal toxicity after radiotherapy for prostate cancer

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ABSTRACT

Background and purpose

We evaluated dose distributions in the anorectum and its relation to acute gastrointestinal toxicities using dose surface maps in an image-guided (IG) IMRT and 3D-conformal radiotherapy (3D-CRT) population.

Material and methods

For patients treated to 78 Gy with IG-IMRT (n=260) or 3D-CRT (n=215), for whom acute toxicity data was available, three types of surface maps were calculated: 1) total anorectum using regular intervals along a central axis with perpendicular slices, 2) the rectum next to the prostate, and 3) the anal canal (horizontal slicing). For each toxicity, an average dose map was calculated for patients with and without the toxicity and subsequently dose difference maps were constructed, 3D-CRT and IG-IMRT separately. P-values were based on permutation tests.

Results

Dose distributions in patients with grade ≥2 acute proctitis were significantly different from dose distributions in patients without toxicity, for IG-IMRT and 3D-CRT. At the cranial and posterior rectal site, in areas receiving moderate dose levels (≈25 – 50 Gy), dose differences up to 10 Gy were identified for IG-IMRT. For pain, cramps, incontinence, diarrhea and mucus loss significant differences were found as well.

Conclusions

We demonstrated significant relationships between acute rectal toxicity and local dose distributions. This may serve as a basis for subsequent dose-effect modeling in IG-IMRT, and improved dose constraints in current clinical practice.

INTRODUCTION

With new technologies like image-guided intensity modulated radiotherapy (IG-IMRT), reduced planning target volumes are achieved in modern radiotherapy. A more precise irradiation of the tumor has resulted in decreased dose levels to the organs at risk, and lower toxicity levels (1). We have demonstrated this previously for acute toxicity in prostate cancer patients treated with IG-IMRT compared to 3D-conformal radiotherapy (3D-CRT) (1). However, gastrointestinal (GI) toxicity remains a relatively common side-effect due to the anatomical proximity of the rectum to the prostate (2,3).

Many studies have described dose-effect relationships for the anorectum which has led to the clinical implementation of evidence-based rectal and anal canal dose constraints, in order to limit risks of late rectal bleeding and fecal incontinence (4-7). In 2010, a normal tissue complication (NTCP) model was recommended in a QUANTEC review (8). Such models are mainly based on data obtained from dose-volume histograms of the anorectum in historical patient cohorts treated with 3D-CRT and do not account for spatial information and (IG)-IMRT dose distributions (8).

IG-IMRT and related Volumetric Modulated Arc Therapy (VMAT) techniques offer more options to shape dose distributions compared to previous 3D-CRT techniques. By critically analyzing the details of dose distributions and healthy tissue response in more recent patient populations, dose constraints can be refined. Dose mapping is a suitable method to compare spatial patterns of local dose distributions between prostate cancer patients with and without toxicity. Hoogeman *et al* (9) created dose surface maps (DSM) of the anorectum by unfolding the rectal wall virtually and projecting the dose distribution onto a two-dimensional map. A limited number of studies constructed similar anorectum DSMs for various toxicity endpoints (10,11). Buettner *et al* (12) constructed DSMs of the anal sphincter region and correlated 3D dose distributions with various late side-effects.

In the current study, we evaluated dose distributions in the anorectum and its relation to acute toxicity in both an IG-IMRT and a 3D-CRT patient population. Acute GI side effects, especially proctitis-related symptoms like bleeding, mucus loss, pain, and cramps, are still encountered after modern treatment (1), and it has been demonstrated that these symptoms are in part associated with late damage through the mechanism of consequential damage (13). We constructed dose maps of the anorectum as well as two alternative types, focusing more on a) the anal canal separately and b) the intermediate-high dose region surrounding to the prostate. For this purpose, prospectively collected data from two clinical trials were available, representing a patient population treated with a 3D-CRT technique and a more recent population treated with IG-IMRT.

MATERIALS AND METHODS

Patient population

For this analysis, we included 215 low- to high-risk prostate cancer patients (14) treated to 78 Gy in 39 fractions with 3-field 3D-CRT and 10-mm margins from the high-dose arm of a dose-escalation trial (CKTO 96-10, 1997-2003), and 260 intermediate-high risk patients treated to 78 Gy with IG-IMRT and 5-8-mm margins from the standard arm of a hypofractionation trial (CKTO 2006-08, 2007-2010). The patient population has been described previously (1,15).

Treatment and contouring

The prescribed prostate dose was 78 Gy for all patients, whereas the seminal vesicle (SV) dose depended on the estimated probability of SV involvement (2,15). Daily online localization with fiducial markers and cone-beam computed tomography (CBCT) was used in 96% for IG-IMRT, whereas 4% was treated with an offline image-guided protocol for prostate matching using kilo-voltage CBCT imaging (16). Electronic portal imaging was used for offline bony anatomy matching and setup corrections in patients treated with 3D-CRT (17).

The outer anorectal wall contours were outlined on planning CT scans from the anal verge to the ischial tuberosities. In the 3D-CRT group, interpretation of the protocol was slightly different for some patients: delineation was discontinued in case the rectum was no longer adjacent to the sacrum. The anal canal was defined as the lowest three centimeters (18,19). A full bladder protocol was applied and rectal emptying was stimulated for scanning. For 3D-CRT, the percentage of the anorectum receiving >= 74 Gy was limited to 40%, the small bowel dose was limited to 68 Gy. As for IG-IMRT, the anorectal volume receiving ≥65 Gy was limited to 50% and mean anal dose was restricted to 60 Gy.

Toxicity endpoints

Acute toxicity data were derived directly from identical self-assessment patient questionnaires at fraction 20, 30, and 3 months after the end of treatment and were available for 215 3D-CRT patients and 260 IG-IMRT patients (1). Our primary endpoint was moderate to severe proctitis (grade ≥2), as applied in our previous study on acute toxicity differences between IG-IMRT and 3D-CRT (1,15). The definition is as follows: moderate to severe mucus or blood loss, or mild mucus/blood loss combined with at least 2 other complaints (diarrhea, incontinence, tenesmus, cramps, pain). Other evaluated endpoints were the presence of any (grade ≥1) blood loss, mucus loss, diarrhea, incontinence, tenesmus, cramps, pain (on at least one of the questionnaires of the acute phase). Incidences are reported in Table 1.

Dose-surface map: anorectum

We constructed an anorectum DSM for each patient by computing the central axis through the anorectum as contoured on planning CT, and constructed a fixed number of equally spaced planar cross-sections perpendicular to this axis (9,11). These cross-sections were subsequently unfolded at the dorsal side and the associated dose was projected onto a two-dimensional map. Finally, the length of the anorectum was normalized to 100%. A schematic representation is shown in Supplement 1. The standard anorectum map visualizes the complete anorectum. However, because anorectal length was normalized to 100%, high-dose regions are not perfectly matched between all patients and the anatomical function of the anal canal is ignored. This could limit the ability to identify areas of significant differences in local dose using this mapping method.

Dose-surface map: rectum

We therefore defined a rectum mapping aiming at matching high-dose regions at the level of the prostate. This mapping intersects the central axis at fixed intervals, while placing the axis' origin at mid-height of the delineated prostate. From prostatic mid-height, this map visualizes 3 cm along the central axis in cranial direction and 4cm in caudal direction (Supplement 1). Both the anorectum map and rectum map consisted of 45 intervals in circumferential direction and 50 intervals along the central axis.

Dose-surface map: anal canal

The anus mapping visualizes the most caudal 3 cm using fixed intervals and horizontal intersection planes, and places the origin at the lowest delineated contour. This mapping was performed with 2mm resolution along the central axis and represents a specific anatomic region of interest (20).

The upper parts of anus maps do not necessarily directly adjoin the bottom of rectum maps, because of inter-patient variation in the distance from prostatic mid-height (origin of rectum map) to the cranial edge of the anal canal.

Dose difference maps and significance testing

After constructing each DSM for each patient, we calculated average DSMs for groups of patients. First, we created average anorectum, rectum and anal canal DSMs for the 3D-CRT and IG-IMRT group to illustrate differences in dose delivery between both techniques. Subsequently, for 3D-CRT and IGI-MRT separately, average DSMs were calculated for patients with and without a specific toxicity endpoint to generate dose difference maps (toxicity minus no toxicity).

Finally, the significance of each dose difference map was determined using permutation testing (12,21). As previously described (21), the dose difference at each voxel was normalized to the

local standard deviation over all patients, resulting in a normalized dose difference map. The maximum value on this map summarizes the dose discrepancy between the toxicity groups, and does not suffer from a multiple testing issue. Subsequently, 10.000 random permutations of the patients over the toxicity groups were generated, and for each permutation the normalized maximum dose difference was computed. A p-value for the observed difference followed as the proportion of permutations that yielded a higher maximum normalized dose distribution than observed. To locate significant dose differences, the permutation for which 5% of permutations yielded a higher value was determined, and its maximum normalized dose difference was read out. On the observed map, contours were drawn around regions with normalized dose differences larger than this.

RESULTS

Patient characteristics are reported in Supplement 2. The volume of the delineated prostate was on average 64cm3 (33cm3 SD) for 3D-CRT compared to 58cm3 (28cm3 SD) for IG-IMRT. The significant difference (p=0.03) in volume between the two techniques was associated with the higher number of patients in the IG-IMRT group receiving adjuvant hormonal therapy (67% vs. 20%, respectively). The length of the delineated anorectum was on average 13.8cm (1.4cm SD) for 3D-CRT and 15.4cm (1.7cm SD) for Ig-IMRT (p<0.001). The differences in anorectum length resulted from slightly different methods of contouring. The mean dose maps demonstrated smaller intermediate to high dose regions on the anorectal, rectal and anal surface for IG-IMRT patients (Figure 1). Local standard deviations in the mean dose maps varied roughly from 5 to 25 Gy and were smallest around the rectal area surrounding the prostate (5-10 Gy) and largest at the caudal and cranial part of the anorectum (15-25 Gy).

Anorectal DSMs

Figure 2 shows the averaged anorectal DSMs for IG-IMRT patients with (Figure 2A) and without acute proctitis (Figure 2B). Figure 2C shows the dose difference map (2A minus 2B). For the endpoints incontinence (Figure 2D), cramps (Figure 2E), pain (Figure 2F), blood loss (Figure 2G), and mucus loss (Figure 2H) only the dose difference maps are shown. The corresponding figure for the 3D-CRT patients was added as a supplement (Supplement 3). The dose difference map for proctitis demonstrated an effect around the anorectal circumference around 60-70% of the central axis (Figure 2C). In this area receiving moderate dose levels (≈25 – 50 Gy), dose differences up to 10 Gy were identified for IG-IMRT. We found comparable patterns for incontinence, cramps, pain, blood loss (Figure 2D-G), and tenesmus (data not shown). Anorectal average dose- and dose difference maps for 3D-CRT revealed similar patterns, however 3D-CRT dose difference maps demonstrated less dose difference on the anterior anorectum wall cranial

Figure 1. IG-IMRT and 3D-CRT dose maps

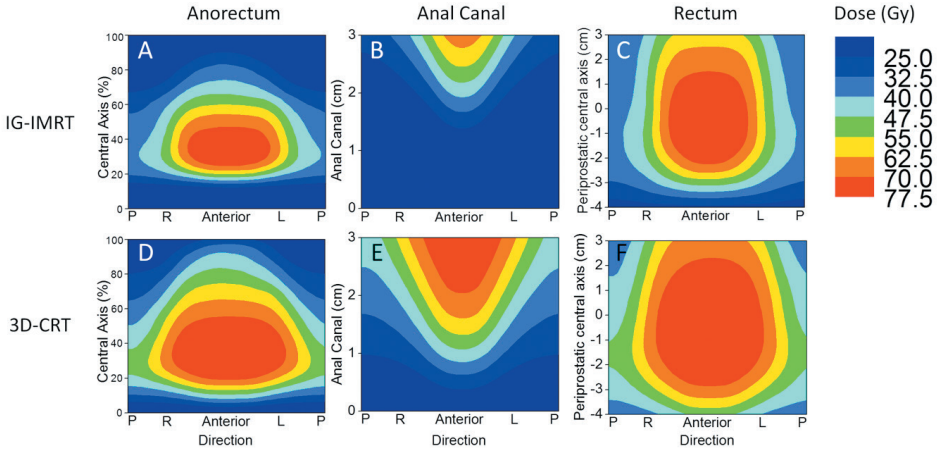

Figure Legend: Dose maps with distance along central axis (vertical) against location along circumference axis (horizontal). Upper panels (a-c) represent mean dose maps (anorectum, anus, rectum) of IG-IMRT patients, lower panels (d-f) for 3D-CRT patients.

Figure Abbreviations: P=posterior, R= Right, L=Left, IG-IMRT= Image-guided intensity modulated radiotherapy, 3D-CRT= 3-dimensional conformal radiotherapy

Figure 2. Dose maps (anorectum) for IG-IMRT subgroups.

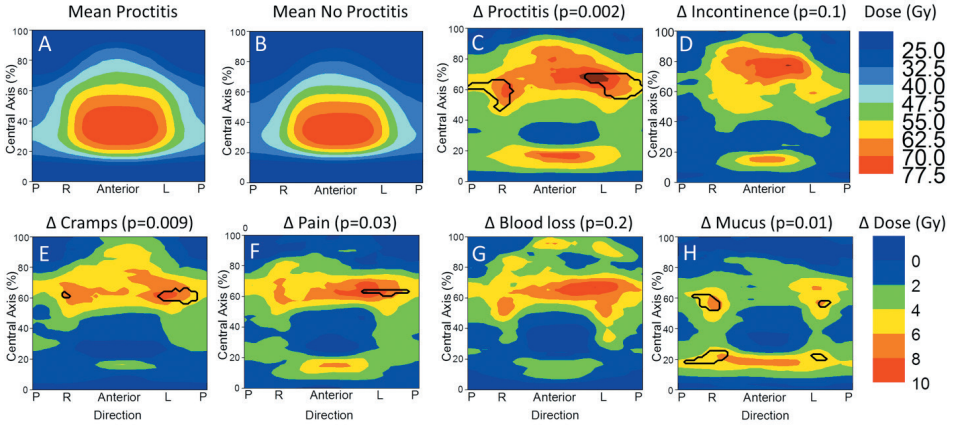

Figure Legend: The distance along the central axis (vertical) is plotted against the location along the circumference axis (horizontal). Upper panels represent: a) mean dose map for patients with acute proctitis, b) without acute proctitis, c) the corresponding dose difference map (toxicity minus no toxicity), d) dose difference map incontinence. Lower panels represent dose difference maps for e) cramps, f) pain, g) blood loss, h) mucus loss. p=0.05 contours are based on permutation tests.

Figure Abbreviations: P=posterior, R= Right, L=Left, IG-IMRT= Image-guided intensity modulated radiotherapy

Table 1. Toxicity endpoints within 3D-CRT and IG-IMRT groups including the corresponding incidence, and the p values obtained from the permutation tests for each type of dose mapping (anus, rectum, anorectum)

Acute toxicity	3D-CRT (n=215)				IG-IMRT (n=260)			
	Incidence	Anus	Rectum	Anorectum	Incidence	Anus	Rectum	Anorectum
Pain	40%	0.014	0.1	0.056	28%	0.1	0.041	0.03
Cramps	46%	0.5	0.7	0.7	34%	0.4	0.020	0.009
Tenesmus	62%	0.3	0.057	0.083	49%	0.062	0.056	0.1
Mucus	64%	0.008	0.006	0.007	47%	0.020	0.029	0.01
Incontinence	27%	0.044	0.037	0.2	27%	0.4	0.1	0.1
Blood loss	20%	0.4	0.096	0.2	12%	0.4	0.4	0.2
Diarrhea	14%	0.2	0.1	0.2	14%	0.034	0.041	0.2
Proctitis	44%	0.009	0.1	0.019	27%	0.048	0.003	0.002

Table Abbreviations: 3D-CRT= 3-dimensional conformal radiotherapy, IG-IMRT= mage-guided intensity-modulated radiotherapy

Figure 3. Acute diarrhea dose difference maps.

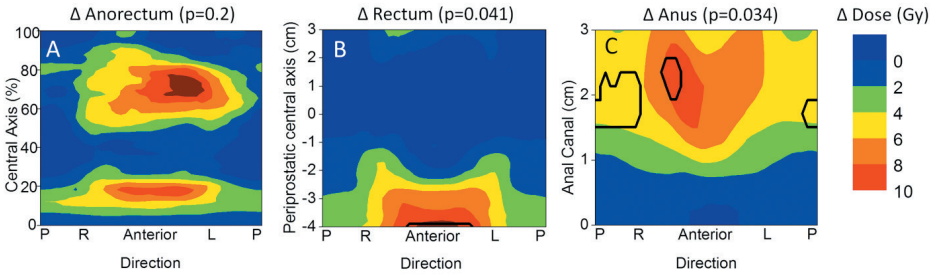

Figure Legend: Acute diarrhea dose difference maps (toxicity minus no toxicity) for IG-IMRT: a) anorectum, b) rectum, c) anus. Distance along central axis (vertical) against location along circumference axis (horizontal). p=0.05 contours are based on permutation tests.

Figure Abbreviations: P=posterior, R= Right, L=Left, IG-IMRT= mage-guided intensity modulated radiotherapy

to the prostate (Supplement 3). In each dose difference map, we indicated where significant differences (p=0.05 contours) were located. Corresponding p values are summarized in Table 1.

Rectum DSMs

Using the rectum mapping we found significant dose differences for IG-IMRT-induced proctitis, cramps, mucus loss, and diarrhea. These significant regions surrounding the prostate were also identified on the anorectal maps for proctitis (Figure 2C), cramps (Figure 2E), and mucus loss (Figure 2H), but not for diarrhea (Figure 3A). The rectum mapping for diarrhea (Figure 3B) covered the intermediate-high dose region around the prostate, and demonstrated a significantly higher local dose (p=0.041) towards the anus. This effect was best visualized using the anus mapping (Figure 3C) suggesting a circumferential effect (p=0.034).

Anal canal DSMs

The IG-IMRT anal canal maps demonstrated significant results for proctitis, diarrhea and mucus loss (Table 1). These significant regions within the anal canal were also identified on the anorectal mapping for mucus loss (Figure 2H), but not for proctitis (Figure 2C) and diarrhea.

DISCUSSION

In this study we explored the relationship between local dose distribution and development of acute GI toxicity in prostate cancer patients treated to 78 Gy with 3D-CRT and IG-IMRT. For this purpose, we studied relative anorectum maps and introduced two alternative types of surface mapping of the rectum and anal canal. We demonstrated that for various GI toxicity endpoints local dose-effects exist which are not taken into account in current clinical guidelines for treatment planning. This information is useful for the development of NTCP models limiting acute damage and therefore consequential late toxicities, as an extension of current NTCP models which aim mainly at limiting (late) rectal bleeding and fecal incontinence and are developed on 3D-CRT data.

All areas of significant local dose difference that were identified with the anorectum mapping method, were also identified by either the anus or rectum map (Table 1). As demonstrated for diarrhea (Figure 3), however, anus and rectum maps can identify additional areas of significance that are not registered using anorectal maps. These additional mapping methods are therefore useful in addition to the anorectum maps. By projecting the dose differences on normalized maps, we were able to demonstrate that in the area of intermediate dose levels on the cranial and posterior side of the rectum, IG-IMRT patients with acute grade ≥2 proctitis received on average more dose. For the endpoint diarrhea we found a significant area in the lower rectum

and upper anal canal which might be associated with more frequent stools, partial loss of sphincter control, or mucus loss, since diarrhea is in general more related to irradiation of the bowels.

We based our toxicity endpoints on patient-reported symptoms. A similar score list was published by Goldner et al in 2003 (22), and the setup resembles the EORTC Quality of Life Prostate Cancer module (QLQ-PR25) (23). Patient-reported symptoms have been qualified as a more valid source for toxicity scoring than the doctors report in case of mild to moderate toxicities (22), which was also discussed in the QUANTEC paper by Jackson et al (7).

We investigated two different prostate cancer populations treated in two different eras, for whom prescribed dose to the clinical target volume (CTV) was identical (39 x 2 Gy). The populations and its treatment differed in a number of aspects: different CTV-PTV margins and setup strategies were applied, planned dose to the seminal vesicles was not identical, and more patients in the IG-IMRT group were treated with adjuvant hormonal therapy (20 % vs 67%) which has been described as a predictive factor for acute GI toxicity (2,24). From this we can conclude that the results as described for the IG-IMRT patients have more clinical relevance since the setting is closer to current daily practice.

Dose differences between patients with and without acute toxicity were in general more pronounced for IG-IMRT patients, especially cranial to the prostate. (Figure 2, Supplement 3). This might be partly explained by the difference in patient setup: for IG-IMRT patients the planned dose in the rectum close to the prostate that we used for the mapping procedure, will be closer to the true delivered dose during treatment because of the prostate matching procedure. Furthermore, the area of the rectum included in the PTV, with no dose variation between patients, will be smaller in IG-IMRT patients because of the tighter margins, and dose variation is a prerequisite for identifying dose differences in the first place.

Clinical and dosimetric predictors for acute GI toxicity have been previously described (2,24), and include neo-adjuvant hormonal therapy (associated with less toxicity), SV dose, hemorrhoids, use of anticoagulants, and various dose parameters at intermediate – high dose levels (e.g. mean rectal dose, volume receiving ≥60 Gy). Peeters *et al*. also described relative and absolute rectal length parameters in the range of 5 – 30 Gy as predictive for overall grade ≥2 acute GI toxicity (25).

Correlations between the spatial 3D dose distributions in (parts of) the anorectum and acute toxicity have not previously been described; for late toxicity endpoints correlations with DSM parameters were reported from several studies. Buettner *et al.* (12) previously described significant correlations between DSM parameters derived from anal sphincter mapping and late subjective sphincter control whereas for urgency, loose stools, stool frequency, proctitis,

bleeding, and sphincter control management no significant correlations were identified. In an earlier study they reported on rectal dose shapes derived from surface maps as being more predictive for some late toxicity endpoints (bleeding, loose stools) than dose-volume parameters (26). Heemsbergen *et al.* constructed relative anorectal dose maps and found late bleeding and mucus loss to be related to the upper part of the GI tract, whereas late incontinence was related the lower part (11). Mumbodh *et al.* found a relation between late rectal toxicity and irradiation of the upper part of the rectum in an IMRT population (10). Our current findings add more knowledge about the development of radiation-induced damage in the rectum for patients treated with 3D-CRT and IG-IMRT techniques.

In order to obtain valid and clinically optimal relevant dose-effect relationships for IG-IMRT, further modeling has to be done for this treatment modality since discrepancies of model parameters are present between 3D-CRT and IG-IMRT (27). This implies that we have to take baseline complaints and comorbidity into account as potential effect-modifying factors. DeFraene *et al.* (28) demonstrated for late gastrointestinal toxicity endpoints that comparable prediction models were obtained with Lyman-Kutcher-Burman (LKB), Relative Seriality and logistic Normal Tissue Complication (NTCP) models, and that including clinical factors improved the predictive power of all models significantly.

Current modeling and definition of dose constraints are mainly based on dose-volume or dose-surface information, and spatial information is not taken into account. An example of such a model from the current IG-IMRT data is shown in Figure 4. A significantly higher mean dose ($p=0.002$), as reflected by the area under the curves in Figure 4A, was received by patients with acute proctitis (mean dose 36.7 Gy) than for patients without (mean dose 33.6 Gy). Figure 4B shows the probability of developing acute proctitis as a function of the surface receiving ≥40 Gy, when applying a straightforward univariate logistic regression model. A further systematic evaluation of dose parameters, spatial information, and clinical parameters, is needed to evaluate whether adding spatial dose information (e.g. dose-circumference parameters) could improve the predictive power of such models, which is beyond the scope of the current study.

In conclusion, significant differences in the local dose to rectal and anal surfaces were found between patients with or without various acute GI toxicities, especially for proctitis-related complaints like pain, cramps, mucus loss and diarrhea. These findings are clinically relevant and could be translated into practical dose constraints limiting these side effects as much as possible, and further improving the therapeutic ratio for prostate cancer.

Figure 4. a) Dose-surface histogram for IG-IMRT patients with and without proctitis with corresponding standard deviations, b) probability of acute proctitis is plotted as function of anorectal surface receiving 40 Gy or more.

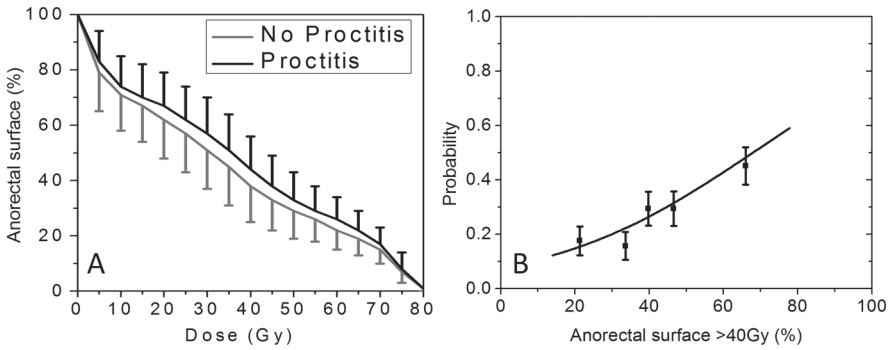

Figure Legend: The corresponding actual incidence is plotted in solid squares with corresponding error bars (standard error), for dose bins of approximately 51 patients each.

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SUPPLEMENTARY FILES

Supplementary File 1. Schematic representation of construction of dose maps demonstrating a) anorectum and anal canal, b) method of virtually unfolding anorectum, and c) normalized anorectum map, rectum map with origin at prostatic mid-height and anus map (most caudal 3cm)

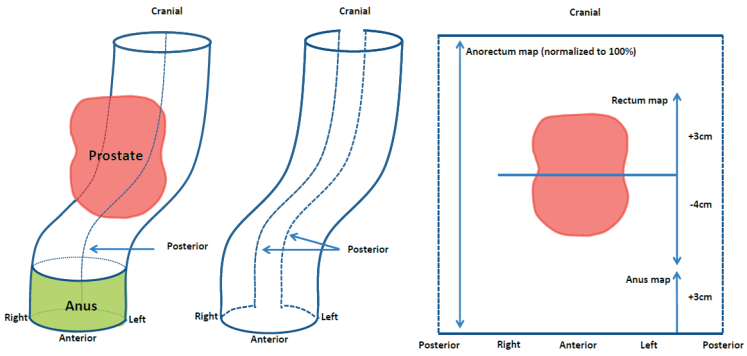


Figure Legend: The resolution of the dose maps was chosen based on the appearance of dose gradients in the mapped surfaces, and effectively slightly exceeded the 4mm dose grid resolution. In the circumferential direction 45 pixels were taken, i.e. every 8 degrees. In the axis direction of anorectum maps 50 pixels were taken, which would effectively cover a 15cm long rectum at 3mm resolution. The rectum mapping was also done using 50 pixels along the 7cm axis direction, i.e. using a 1.5mm resolution. The anus mapping was performed using 2mm spacing in the axis direction.

Supplementary File 2. Patient and treatment characteristics

Variable	3D-CRT (n=215)	IG-IMRT (n=260)
Age	69 (6.3)	71 (6.0)
Prostate volume (cm3)	65 (33)	58 (28)
Adjuvant hormonal therapy	42 (19.5)	174 (66.9)
Risk category		
Low	34 (15.8)	0
Intermediate	72 (33.5)	75 (28.8)
High	109 (50.7)	185 (71.2)
Seminal Vesicle Dose		
0 Gy	43 (20.0)	50 (19.2)
50 Gy	35 (16.3)	0
68 Gy	101 (47.0)	0
70 Gy	0	125 (48.1)
78 Gy	36 (16.7)	85 (32.7)
Planning Margins		
5 mm	0	107 (41.3)
6-8 mm	0	151 (58.3)
10 mm	215 (100)	1 (0.4)
Delineated anorectum length	13.8 (1.4)	15.4 (1.7)

Table Legend: Data are n (%) or mean (SD).

Table Abbreviations: 3D-CRT: 3D-conformal radiotherapy, IG-IMRT: image-guided intensity-modulated radiotherapy

Supplementary File 3. Dose maps (anorectum) for 3D-CRT subgroups.

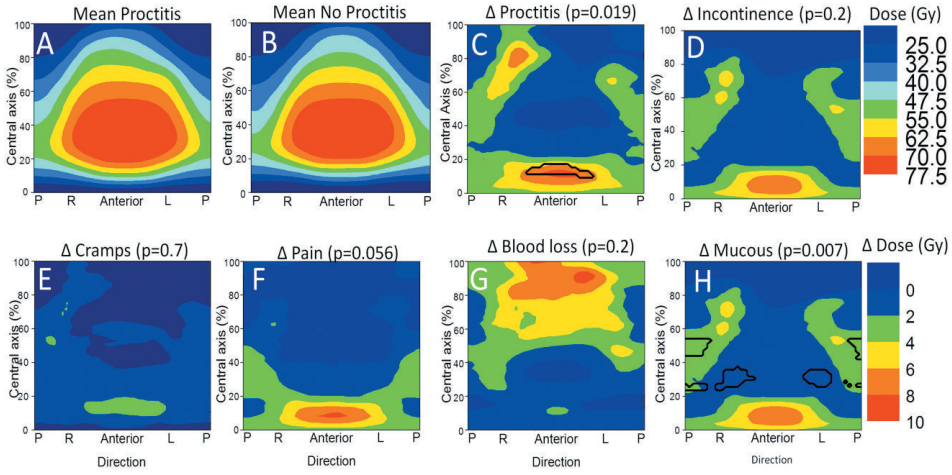
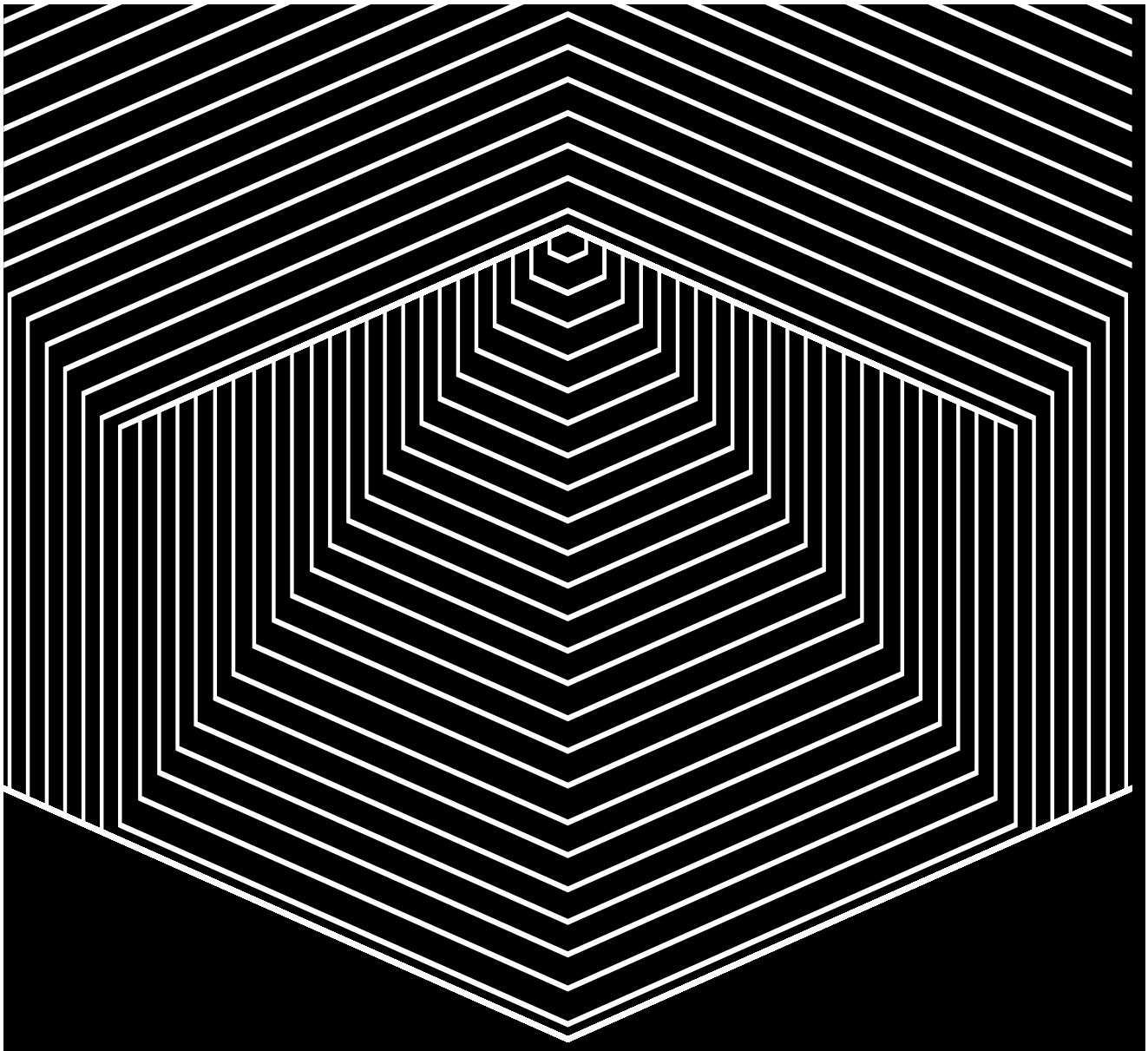


Figure Legend: The distance along the central axis (vertical) is plotted against the location along the circumference axis (horizontal). Upper panels represent: a) mean dose map for patients with acute proctitis, b) without acute proctitis, c) the corresponding dose difference map (toxicity minus no toxicity), d) dose difference map incontinence. Lower panels represent dose difference maps for e) cramps, f) pain, g) blood loss, h) mucus loss. p=0.05 contours are based on permutation tests.

Figure Abbreviations: P=posterior, R= Right, L=Left, 3D-CRT= 3-dimensional conformal radiotherapy



“NO ACTION IS WITHOUT ITS SIDE EFFECTS.”

Barry Commoner

CHAPTER 04

Late side effects after image-guided intensity modulated radiation therapy compared to 3D-conformal radiation therapy for prostate cancer: results from two prospective cohorts

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ABSTRACT

Purpose

Technical developments in the field of external beam radiotherapy enabled the clinical introduction of Image-Guided Intensity Modulated Radiotherapy (IG-IMRT), which improved target conformity and allowed reduction of safety margins. Whether this had an impact on late toxicity levels compared to previously applied three-dimensional conformal radiation techniques (3D-CRT) is currently unknown. We analyzed late side effects after treatment with IG-IMRT or 3D-CRT, evaluating two prospective cohorts of men treated for localized prostate cancer, in order to investigate the hypothesized reductions in toxicity.

Materials and methods

Patients treated with 3D-CRT (n=189) or IG-IMRT (n=242) to 78 Gy in 39 fractions were recruited from two Dutch randomized trials with identical toxicity scoring protocols. Late toxicity (>90 days after treatment) was derived from self-assessment questionnaires and case report forms, according to RTOG-EORTC scoring criteria. Grade ≥2 endpoints included gastrointestinal (GI) rectal bleeding, increased stool frequency, discomfort, rectal incontinence, proctitis, and genitourinary (GU) obstruction, increased urinary frequency, nocturia, urinary incontinence, and dysuria. The Cox proportional hazards regression model was used to compare grade ≥2 toxicities between both techniques, adjusting for other modifying factors.

Results

The five-year cumulative incidence of grade ≥2 GI toxicity was 24.9% for IG-IMRT and 37.6% following 3D-CRT (adjusted HR=0.59, p=0.005), with significant reductions in proctitis (HR=0.37, p=0.047) and increased stool frequency (HR=0.23, p<0.001). GU grade ≥2 toxicity levels at 5 years were comparable with 46.2% and 36.4% following IG-IMRT and 3D-CRT, respectively (adjusted HR=1.19, p=0.33). Other strong predictors (p<0.01) of grade ≥2 late toxicities were baseline complaints, acute toxicity, and age.

Conclusions

Treatment with IG-IMRT reduced the risk of late grade ≥2 complications, whereas GU toxicities remained comparable. This clinically relevant observation demonstrates that IMRT and image-guidance should therefore be the preferred treatment option, provided that margin reduction is implemented with caution.

INTRODUCTION

Patients with localized prostate cancer have a variety of curative treatment options. The risks of treatment-induced side effects influence patients' treatment choice considerably. Late side effects following treatment modalities are frequently compared (1,2), even though external beam radiotherapy (EBRT) cannot be considered a homogeneous group due to large differences in applied techniques of treatment delivery.

The introduction of intensity-modulated radiotherapy (IMRT) and image-guidance, using implanted fiducial markers and cone-beam computed tomography (CBCT), enabled reductions of safety margins. These margins around the target volume are needed to account for delineation uncertainties and prostate motion. Image-guidance enables prostate localization and alignment before each fraction, replacing previous protocols applying bony anatomy localization and alignment. Several studies demonstrated that by reducing the uncertainties in daily prostate position, margins can be reduced while maintaining the same level of tumor coverage and decreasing dose to normal tissues (3,4). Furthermore, IMRT planning systems with inverse planning algorithms generate a combination of beams of non-uniform intensity to achieve the specified objectives and dose constraints. Subsequently, IMRT enables delivery of more conformal dose distributions with sharp radiation dose gradients that facilitate enhanced organ sparing compared to 3D-CRT (5). Therefore, it is hypothesized that IG-IMRT should lower acute and late toxicity risks, however, randomized controlled trials demonstrating a beneficial effect of IG-IMRT over previous techniques, are lacking (6).

We previously demonstrated in two prospective cohorts that with IG-IMRT significant dose reductions to normal tissues were achieved compared to a 3D conformal radiotherapy (3D-CRT) population, resulting in significantly decreased acute peak gastrointestinal (GI) and genitourinary (GU) toxicity (7).

In the current study, we compared late toxicity in patients treated with IG-IMRT or 3D-CRT, using the same dose of 78 Gy in 39 fractions. For this purpose, we analyzed prospectively collected data from two randomized multicenter trials: one dose escalation trial representing a 3D-CRT reference population (8), and a recent IG-IMRT population from a hypofractionation trial (9). We hypothesized that improvements in imaging techniques and treatment delivery translated into lower levels of late toxicity following IG-IMRT compared to 3D-CRT.

PATIENTS AND METHODS

Patient population

We included patients from two Dutch prospective trials, in which identical patient questionnaires and case report forms regarding late toxicity were applied. Prostate cancer patients treated with IG-IMRT between 2007-2010 in the standard arm of a recent hypofractionation trial (9) were included (n=242) as long as they returned their baseline questionnaire, ≥1 questionnaire on acute- and ≥2 questionnaires on late toxicity. Patients were excluded if they received radiotherapy with a rectal balloon. As a reference population, we included 189 patients from the high-dose arm of a dose escalation trial (1997-2003), applying identical criteria for inclusion (8). A study flow-chart is provided as Supplementary File.

All patients had histologically confirmed stage T1b-T4NX-0MX-0 prostate cancer and an initial prostate-specific antigen (iPSA) concentration <60 µg/L. The 3D-CRT group included low-risk patients (T1-T2a, and Gleason score ≤6 and PSA <10 µg/L) according to the classification as proposed by Chism *et al* (Table 1) (10), whereas all IG-IMRT patients had intermediate-high risk disease. Application of androgen deprivation therapy (ADT) depended on local clinical protocols and was more often prescribed to the IG-IMRT group (67% vs. 21%, Table 1) (9,11). In general, a luteinizing hormone-releasing hormone analogue was preceded by an anti-androgen. In some, anti-androgen monotherapy was prescribed. ADT was generally started between 0-7 months before start of radiotherapy.

Treatment and contouring

For both cohorts, the prescribed dose to the prostate was 78 Gy in daily fractions of 2 Gy with an overall treatment time of eight weeks. Dose to the seminal vesicles (SVs) depended on the estimated probability of SV involvement (9,11,12). Elective lymph node irradiation was not applied.

The bladder wall and anorectal wall were delineated on planning CT scan; the most caudal 3 cm of the anorectum was defined as anus (7). Mandatory dose constraints for avoidance of normal tissues were defined. For 3D-CRT the small bowel dose was not exceed 68 Gy, whereas the rectal surface receiving ≥74 Gy was not to exceed 40%. As for IG-IMRT: the rectal volume receiving ≥65 Gy was to be below 50%, and the mean anal dose was to not exceed 60 Gy (8,9). Further treatment optimization was performed according local guidelines.

In the 3D-CRT group offline bony anatomy setup verification and correction was performed. As for IG-IMRT, implanted fiducials were used for online localization in 96%, in the remaining 4% a prostate setup correction protocol using kilo-voltage CBCT image-guidance was applied (4). Isotropic margins of 10mm and 5-8mm were added to the clinical target volume to yield the

planning target volume for 3D-CRT and IG-IMRT, respectively. During the boost, these margins were reduced to 5mm (3D-CRT) and 3-5mm (IG-IMRT) in all directions, except for the interface between the prostate and the rectum where no margin was used.

Late toxicity scoring

We calculated late toxicity based on both the scores on the original trial case report forms and the patient-reported symptoms (9,11). For that purpose, we selected patient questionnaires at six and 12 months, and annually thereafter until five years. Remaining questionnaires were ignored, in order to have an equal level of information between patients and treatment groups.

Table 1. Baseline characteristics

Variable	IG-IMRT (n=242)	3D-CRT (n=189)
Follow-up length (months)	57 (48-62)	62 (46-66)
Age (years)	71 (67-75)	70 (65-73)
T stage		
1	37 (15)	30 (16)
2	81 (34)	86 (46)
3a	96 (40)	46 (24)
3b	27 (11)	27 (14)
4	1 (<1)	0
Gleason score		
2-6	71 (29)	96 (51)
7	109 (45)	67 (35)
8-10	62 (26)	26 (14)
Initial PSA (µg/L)	15·0 (9.9-23.9)	11.4 (8.1-19.5)
Risk category (Chism *et al*) (10)		
Low	0	30 (16)
Intermediate	69 (29)	63 (33)
High	173 (71)	96 (51)
Seminal vesicle dose		
0 Gy	48 (20)	37 (20)
50 Gy	0	32 (17)
68 Gy	0	87 (46)
70 Gy	113 (47)	0
78 Gy	81 (33)	33 (17)

Table 1. Continued

Variable	IG-IMRT (n=242)	3D-CRT (n=189)
Planning margins		
5-6 mm	167 (69.0)	0
6-8 mm	75 (31.0)	0
10 mm	0	189 (100)
Androgen deprivation therapy		
No	81 (34)	149 (79)
≤6 months	40 (16)	10 (5)
12-36 months	121 (50)	30 (16)
TURP	26 (11)	16 (9)
Abdominal surgery	57 (24)	54 (29)
Acute RTOG-EORTC grade ≥2 toxicity*		
Gastrointestinal	69 (29)	96 (51)
Genitourinary	91 (38)	95 (50)
Hospital		
A	109 (45)	152 (80)
B	53 (22)	37 (20)
C	22 (9)	0
D	20 (8)	0
E	38 (16)	0

Table Legend: Data are n (%) or median (interquartile range), *according to RTOG-EORTC scoring criteria (13)
Table Abbreviations: IG-IMRT=image-guided IMRT, 3D-CRT= 3D Conformal radiotherapy, PSA= prostate specific antigen, TURP= transurethral resection of prostate, RTOG= Radiation Therapy Oncology Group, RTOG-EORTC= Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer

In the current study, maximum follow-up was set at 66 months (5.5 years). Patients with clinical relapse were censored from that point onwards, since distinction between treatment-related and relapse-related symptoms can be difficult. Events occurring beyond 90 days after the end of treatment were defined as late toxicity, according to a slightly modified version of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria (11,13).

The following grade ≥2 late GI endpoints were recorded: increased stool frequency (≥6/day), proctitis requiring use of steroids, pain with urge or cramps requiring medication, rectal

bleeding requiring laser treatment or transfusion, and use of incontinence pads >2 days/week for rectal loss of blood, mucus or stools. Grade ≥3 endpoints were watery diarrhea requiring medication more than twice per day, bleeding requiring ≥2 laser treatments or transfusions, and obstruction requiring surgery.

Grade ≥2 GU endpoints were nocturia (≥4/night), increased urinary frequency (≥16/day), dysuria requiring medication, hematuria requiring laser treatment or transfusion, and use of pads >2 days/week for urinary incontinence. As for grade ≥3 endpoints: nocturia (≥6/night), urinary frequency (≥32/day), hematuria requiring ≥2 transfusions or laser treatments, and urinary obstruction requiring treatment (transurethral resection of prostate, dilatation or (suprapubic) catheterization) (11).

Patient-reported outcomes

All patients recorded symptoms on questionnaires similar to the urinary and bowel items of the EORTC quality of life questionnaire for prostate cancer (EORTC-QLQ-PR25) (14). Reported were bowel frequency and urinary frequency (day and night), whereas other symptoms were graded on a four-point scale. Evaluated grade ≥1 GI symptoms were any blood loss, moderately increased stool frequency (≥4/day), any pain or urge or cramps, and any incontinence. Evaluated grade ≥1 GU symptoms were moderate nocturia (≥3/night), moderately increased urinary frequency (≥10/day), any dysuria, and any incontinence.

Normal tissue dose

For both cohorts, dose information for the anorectum-, anus- and bladder dose was available from treatment plans. Dose-surface histograms and dose-surface maps, comparing both groups, have been previously published (7,15). In the current study we compared dose levels to normal tissues between IG-IMRT and 3D-CRT within subgroups based on the prescribed SV dose (i.e. 0 Gy, 50-70 Gy and 78 Gy). Evaluated dose parameters were mean dose, relative surface receiving >= 60 Gy (anorectum, anal canal), and the absolute bladder surface receiving ≥ 60 Gy.

Statistical analysis

Cumulative incidences of grade ≥2 toxicity were calculated using the Kaplan-Meier method. Time was calculated from the last radiotherapy fraction. Patients were censored at 5-year follow-up, at clinical relapse, or at last follow-up (including 22 IG-IMRT patients and 16 3D-CRT patients who passed away < 5-years). The Cox proportional hazards regression (PHR) model was used to calculate the hazard ratios (HR) of IG-IMRT versus 3D-CRT and to adjust for other clinical factors. First, a crude HR was estimated for all grade ≥2 endpoints. Second, we determined the HR of each clinical factor in a baseline model with treatment group and overall grade ≥2 toxicity as the endpoint (GI and GU separately). Finally, a final MV model was created, including treatment group and all clinical factors with $p<0.2$ in the baseline model. This final model

Figure 1. Upper panels: Average dose to anorectum (A), anus (B) and bladder (C) as a function of seminal vesical dose. Lower panels: Relative anorectum surface (D), anus surface (E) and absolute bladder surface (F) receiving high dose above 60 Gy.

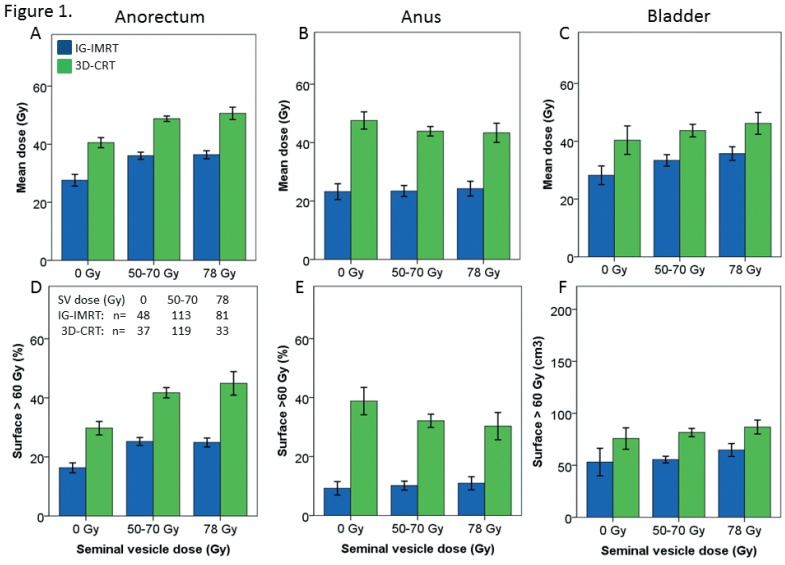


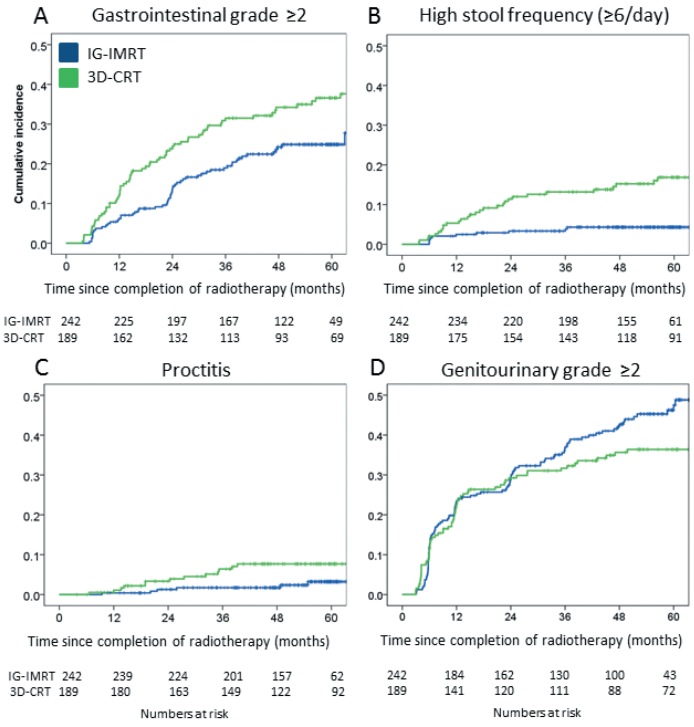
Figure Legend: Error bars represent 95% confidence interval

was also used to calculate adjusted HRs for the other grade ≥2 endpoints. The assumption of proportional hazards was visually checked by comparing the Kaplan-Meier curves of both groups. The proportions of patients with reported symptoms between both groups were compared with a Chi-square test. The two-sample t-test was used to compare dose parameters. Statistical analyses were performed using the SPSS 21.0 software (SPSS, Chicago, IL). A two-sided α of 0.05 was considered the limit of significance.

RESULTS

Median follow-up was 57 months (range 6.9- 66) for IG-IMRT and 62 months (range 6.2-66) for 3D-CRT. No low-risk patients (10) were treated with IG-IMRT and 66% in this group received androgen deprivation therapy (ADT) compared to 21% for 3D-CRT (Table 1). The mean prostate volume in IG-IMRT patients (58cm3, SD 27.6) was somewhat smaller compared to 3D-CRT (64.2 Cm3, SD 33.2), probably as a result of downsizing due to ADT. Within both groups 20% had no dose prescribed to the seminal vesicles (SVs), whereas the prescribed dose for the remaining 80% was 70-78Gy in the IG-IMRT group and 50-78Gy for 3D-CRT.

Figure 2. Kaplan-Meier curves of (A) overall grade ≥2 gastrointestinal toxicity, (B) high stool frequency ≥6/day, (C) proctitis requiring corticosteroids, and (D) overall grade ≥2 genitourinary toxicity



Dose to normal tissues

IG-IMRT resulted in significantly lower average dose (all p values <0.001) to the anorectal surface (34.5 Gy vs. 47.5 Gy; - 27%), anal canal surface (23.7 Gy vs. 44.5 Gy; -47%), and bladder surface (33.2 Gy vs. 43.5 Gy; -24%). Stratifying for prescribed SV dose (Figure 1a-f), a consistent reduction in average mean dose and high-dose volumes was observed with IG-IMRT (all p values <0.001).

Late gastrointestinal toxicity

The 5-year cumulative incidence of overall grade ≥2 GI toxicity was significantly lower for IG-IMRT compared to 3D-CRT (24.9% vs. 37.6%) (Table 2), with an adjusted HR of 0.59 (p=0.005). Clinical factors included in the final model were abdominal surgery, prescribed SV dose, diabetes, and baseline complaints (Table 3). Grade ≥2 GI toxicity increased mainly during the first three years followed by relative stabilization (Figure 2a). The incidences of all GI endpoints, except rectal incontinence and diarrhea, were lower with IG-IMRT (Table 2). Significant differences between IG-IMRT and 3D-CRT were found for high stool frequency (HR=0.23, p<0.001) and proctitis

(HR=0.37, p=0.047) (Figure 2b-c). Grade ≥3 GI events (rectal bleeding n=7, diarrhea n=1, surgery n=2) occurred during the first three years only and were present in 2.8% and 2.2% after 3D-CRT and IG-IMRT, respectively.

Late genitourinary toxicity

The 5-year cumulative incidences of grade ≥2 GU toxicity were 46.2% and 36.4% following IG-IMRT and 3D-CRT, respectively (adjusted HR= 1.19, p=0.33) (Figure 2d, Table 2). For all individual toxicity endpoints, comparable levels at five years were observed. Predictive factors included in the final model were baseline grade ≥2 complaints, abdominal surgery, ADT, and age (Table 3).

The 5-year cumulative incidences of GU grade ≥3 toxicity were 11.7% and 16.1% following IG-IMRT and 3D-CRT, respectively (HR=0.81, p=0.52). Grade ≥3 events included nocturia (9x IG-IMRT vs. 17x 3D-CRT), obstruction (15x vs. 10x), urinary frequency (3x vs. 2x) and hematuria (1x vs. 1x).

Patient-reported outcomes

The incidence of patient-reported symptoms throughout the years show that radiation-induced GI side effects are quite persistent (Figure 3). All GI complaints significantly increased post treatment, in both groups. In the IG-IMRT group the incidence of rectal bleeding diminished after three years whereas this was not the case for 3D-CRT. Rectal incontinence and discomfort remained at significant persistent higher levels compared to baseline, with both techniques. Comparing the treatment groups, significantly lower incidences for IG-IMRT were found for increased stool frequency, rectal blood loss and rectal discomfort (Figure 3a-c). The incidence of patient-reported GU symptoms increased only marginally after treatment with either technique.

Baseline incidences of GU symptoms were higher than for GI symptoms. Especially the baseline incidence of moderate nocturia (≥3/night) was relatively high and remained high during follow-up (Figure 3g).

Comparing both techniques for GU items, dysuria and moderate frequency (≥10/day) complaints (Figure 3e-f) were comparable throughout the years. A significantly larger proportion of IG-IMRT patients reported moderate nocturia at six months, and urinary incontinence at twelve months (Figure 3g-h), whereas no significant differences were observed beyond 12 months.

Table 2. Cumulative 3- and 5- year incidences for gastrointestinal and genitourinary grade ≥2 endpoints including the results of univariate and multivariate cox proportional hazards regression analyses.

	Cumulative incidence (%)							
	3 year		5 year		HR IG-IMRT vs. 3D-CRT			
	IG-IMRT (SE)	3D-CRT (SE)	IG-IMRT (SE)	3D-CRT (SE)	Crude	p	Adjusted (95% CI)	p
Gastrointestinal endpoints								
RTOG-EORTC Grade ≥2*	19.0 (2.6)	30.9 (3.4)	24.9 (3.0)	37.6 (3.7)	0.62	0.010	0.59 (0.41-0.85)	0.005
RTOG-EORTC Grade ≥3*	2.2 (1.0)	2.9 (1.3)	2.2 (1.0)	2.9 (1.3)	0.76	0.66	0.77 (0.22-2.72)	0.69
Pain with urge and cramps (requiring medication)	4.3 (1.3)	10.3 (2.3)	6.3 (1.7)	11.9 (2.5)	0.58	0.11	0.60 (0.30-1.17)	0.13
Proctitis (requiring steroids)	1.7 (0.9)	6.4 (1.9)	3.2 (1.4)	7.7 (2.1)	0.35	0.033	0.37 (0.14-0.99)	0.047
Rectal incontinence (pads >2days/week)	11.8 (2.1)	10.1 (2.3)	15.0 (2.4)	13.3 (2.6)	1.06	0.82	0.96 (0.56-1.64)	0.87
High stool frequency (≥6/day)	3.3 (1.2)	13.2 (2.5)	4.3 (1.3)	16.9 (2.9)	0.26	<0.001	0.23 (0.11-0.47)	<0.001
Rectal bleeding (laser/transfusion)	3.5 (1.2)	5.3 (1.7)	4.1 (1.4)	5.9 (1.8)	0.68	0.40	0.64 (0.25-1.61)	0.34
Diarrhea (medication >2/week)	1.3 (0.7)	0.6 (0.6)	3.3 (1.4)	1.5 (1.1)	3.42	0.13	3.08 (0.60-15.8)	0.18
Genitourinary endpoints								
RTOG-EORTC Grade ≥2*	36.0 (3.1)	31.7 (3.5)	46.2 (3.5)	36.4 (3.6)	1.29	0.11	1.19 (0.84-1.69)	0.33
RTOG-EORTC Grade ≥3*	9.5 (1.9)	8.6 (2.1)	11.7 (2.2)	16.1 (3.0)	0.81	0.44	0.81 (0.42-1.56)	0.52
Dysuria (requiring medication)	6.8 (1.7)	12.6 (2.5)	15.8 (2.9)	12.6 (2.5)	0.96	0.87	1.21 (0.65-2.25)	0.55
Hematuria (laser/transfusion)	0.9 (0.6)	0.6 (0.6)	0.9 (0.6)	0.6 (0.6)	2.75	0.39	2.64 (0.22-31.6)	0.44
Urinary incontinence (pads >2 days/week)	8.3 (1.8)	4.5 (1.6)	11.9 (2.3)	8.7 (2.3)	1.44	0.28	1.41 (0.67-2.95)	0.37
Urinary obstruction (requiring treatment)	4.7 (1.4)	2.2 (1.1)	6.0 (1.6)	6.6 (2.1)	1.04	0.93	2.03 (0.77-5.36)	0.15
High urinary frequency during day (≥16/day)	1.3 (0.7)	4.0 (1.5)	3.3 (1.0)	6.9 (2.0)	0.43	0.099	0.68 (0.20-2.25)	0.53
Nocturia (≥4/night)	25.6 (2.8)	24.3 (3.2)	29.9 (3.2)	27.1 (3.4)	1.18	0.37	0.93 (0.61-1.42)	0.74

Table Abbreviations: IG-IMRT= image-guided intensity modulated radiotherapy, 3D-CRT= 3D-conformal radiotherapy, RTOG-EORTC= radiation therapy oncology group and European organization for research and treatment of cancer, HR= Hazard ratio, CI= Confidence interval, SE= Standard error, * according to RTOG-EORTC scoring criteria (13)

Figure 3. Prevalence of patient-reported gastrointestinal and genitourinary symptoms.

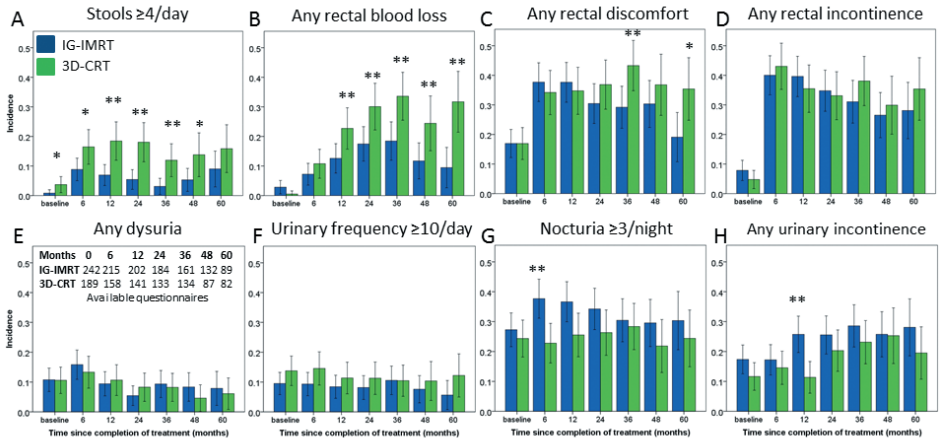


Figure Legend: Error bars represent 95% confidence interval. Statistically significant differences between IG-IMRT and 3D-CRT are indicated with * (p<0.05) or ** (p<0.01).

Late toxicity in acute toxicity subgroups

We previously reported on acute toxicity scores, directly derived from the self-assessment questionnaires, in the current study population (7). The proportion with peak acute grade ≥2 GI toxicity was 29% (n= 69) following IG-IMRT versus 51% (n=96) after 3D-CRT, and toxicity was mainly proctitis-related (bleeding and/or mucous loss in combination with pain, cramps and/or diarrhea) (Table 1) (7).

IG-IMRT patients who experienced acute GI grade ≥2 toxicity had a 2.94 fold (95% CI 1.74-4.97, p<0.001) increase in risk of developing late grade ≥2 complaints. Highest HRs were 7.29 for developing pain with urge and cramps (95% CI 2.32-22.9, p=0.001) and 2.98 for grade ≥2 rectal incontinence (95% CI 1.50-5.90, p=0.002). For 3D-CRT, rectal incontinence was also strongly associated with acute grade ≥2 complaints (HR 3.85, 95% CI 1.44-10.3, p=0.007), whereas a 2.41 fold (95% CI 1.43-4.06, p=0.001) increased risk of developing late overall grade ≥2 toxicity was present. As for GU toxicity, IG-IMRT patients with acute grade ≥2 complaints had a 1.90 fold (95% CI 1.29-2.78, p=0.001) increase of risk of late GU grade ≥2 toxicity, compared to 2.29 (95% CI 1.38-3.80, p=0.001) for 3D-CRT. Acute toxicity was particularly associated with nocturia in IG-IMRT (HR 2.56, 95% CI 1.60-4.09, p<0.001), as well as 3D-CRT (HR 2.75, 95% CI 1.50-5.04, p=0.001).

Table 3. Results of multivariate Cox proportional hazards analysis for gastrointestinal and genitourinary RTOG-EORTC grade ≥2 toxicity.

	Gastrointestinal grade ≥2 toxicity				Genitourinary grade ≥2 toxicity			
	Baseline model		Final model		Baseline model		Final model	
Factor	HR	p	HR (95% CI)	p	HR	p	HR (95% CI)	p
Baseline symptoms (grade ≥2 vs. grade <2)	5.07	<0.001	4.93 (1.90-12.9)	0.001	2.54	<0.001	2.42 (1.54-3.81)	<0.001
Abdominal surgery (yes vs. no)	1.47	0.050	1.37 (0.92-2.05)	0.12	1.29	0.12	1.29 (0.92-1.80)	0.14
Diabetes (yes vs. no)	1.53	0.15	1.39 (0.77-2.53)	0.27	1.36	0.22		
Androgen deprivation therapy (yes vs. no)	1.08	0.71			1.25	0.18	1.33 (0.95-1.88)	0.10
Duration of androgen deprivation therapy (12-36 vs. 0-6 months)	1.04	0.87			1.12	0.51		
Seminal vesicle dose (per 10 Gy)	1.08	0.041	1.10 (1.02-1.18)	0.013	1.01	0.63		
Risk group (continuous)	1.14	0.40			0.94	0.6		
Age (>70/ ≤70)	1.22	0.28			1.58	0.004	1.62 (1.18-2.21)	0.003
Transurethral resection of the prostate (yes/no)	1.08	0.79			1.21	0.44		
Prostate volume (per 10 cm3)	0.99	0.90			1.00	1		
Number of follow-up questionnaires (continuous)	1.00	0.99			0.98	0.71		
Treatment group (IG-IMRT vs. 3D-CRT)	0.62	0.010	0.59 (0.41-0.85)	0.005	1.29	0.11	1.19 (0.84-1.69)	0.33

Table Legend: Each clinical factor was tested in a baseline model with treatment group as a second covariate. In the final model, all clinical factors with p<0.2 were included.

Table Abbreviations: HR= hazard ratio, CI= confidence interval, IG-IMRT=image-guided intensity modulated radiotherapy, 3D-CRT= 3D-conformal radiotherapy.

DISCUSSION

External beam radiotherapy for prostate cancer has a negative impact on anorectal function (16), and is therefore a major point of concern for both treating physicians and patients. Our study demonstrated significant reductions in late GI toxicity among patients treated with IG-IMRT compared to 3D-CRT. Observed toxicity incidences with IG-IMRT were comparable with previously reported GI toxicity rates in 3D-CRT patients treated to 68 Gy (17).

Furthermore, we showed that GI symptoms are quite persistent throughout the years, with consistently lower incidences in the IG-IMRT group. These clinical improvements likely resulted from less exposure of anorectal tissue to radiation, as achieved by IMRT planning, margin reduction, and image-guidance resulting in more precise radiation of the target. We have previously demonstrated that the reduction in rectal dose is predominantly the result of image-guidance and margin reduction whereas the IMRT technique mainly causes a shift from high dose exposure to intermediate dose levels (7). The applied margins in the IG-IMRT group were heterogeneous and varied from 5 to 8 mm. Whether safety margins as low as 5 mm are sufficient for adequate dose coverage of the prostate has not yet been confirmed in tumor control data from large prospective studies. The current IG-IMRT population with margins varying between 5 to 8 mm was derived from the standard arm of a hypofractionation trial, demonstrating a fair 5-year relapse-free survival of 77% (18).

We observed no significant differences in grade≥2 GU toxicities between both cohorts, despite significant reductions in average bladder dose with IG-IMRT. Urinary function impairment also depends on high-dose irradiation of parts of the trigone, bladder neck or prostatic urethra, which were included in the planning target volume with both techniques (19). This might in part explain why we observed no reduction in GU toxicity. Furthermore, the effect of aging, baseline complaints, prescription of ADT, and symptoms caused by an obstructive prostate, might obscure dose-effects.

A limitation of this study that should be taken into account is the fact that both cohorts were treated in different eras, which could introduce cohort effects. It cannot be excluded that slightly different policies in treating side effects were present. It does however not influence toxicities like increased stool frequency, rectal bleeding, obstructions, or patient-reported symptoms. In addition, the IG-IMRT group included patients with more advanced disease, however risk group was no significant modifying factor in the Cox PHR baseline model. The unbalance in ADT prescription between both groups was also accounted for in the multivariate analysis because ADT has been associated with increased GU toxicity (9,11). Finally, IG-IMRT patients had a somewhat higher prescribed dose to the SVs, which we also adjusted for in the multivariate analysis.

To our knowledge, no prospective study exists comparing patients receiving prostate radiotherapy to similar doses using 3D-CRT and IG-IMRT (20,21). Several investigators have reported on late toxicity after 3D-CRT compared to IMRT, but IMRT was delivered without daily online image-guidance (22-25). Michalski *et al* reported comparable GU toxicity levels and a non-significant reduction in late grade ≥2 GI toxicity following IMRT compared to 3D-CRT in the high-dose arm (79.1 Gy) of a prospective trial (22). Patient-reported outcomes of the same trial revealed no differences between both techniques (23). In general, our reported toxicity rates were higher than reported in other studies (6). Toxicity scores are often based on case report forms only, whereas we used both case report forms and self-assessment questionnaires. Combining both is the preferred method to find the true incidence of radiation-induced toxicity (26)

In agreement with literature, we found higher levels of late GI and GU toxicity in patients with acute grade ≥2 toxicity (24,27,28). The underlying mechanism may be partly explained by dose-response (higher dose to normal tissue is related to both acute and late toxicity) and partly by a consequential aspect (acute toxicity is an independent risk factor for late damage). Genetic predisposition might play a role as well; patients more sensitive for radiation damage are at higher risk for both acute and late damage.

In contrast to our expectations, we found comparable late fecal incontinence rates after 3D-CRT and IG-IMRT, in spite of a significant and large reduction of dose to the anal canal using IG-IMRT (7). Several studies have previously identified dose-effect relationships between anal canal dose and fecal incontinence (16,29). Hence, dose constraints for treatment planning have been implemented in clinical practice, and were applied in the current IG-IMRT group. From quality of life studies it is known that fecal incontinence following pelvic radiotherapy significantly bothers patients (30). Further research is needed to clarify the observed fecal incontinence rates.

In conclusion, IG-IMRT was associated with significant and clinically relevant reductions in late GI toxicity. This resulted from high-precision and highly conformal radiotherapy as achieved by IMRT planning, image-guidance and margin reduction. These data provide evidence that IG-IMRT is indeed beneficial for the patient, suggesting that IMRT and image-guidance should be the preferred technique.

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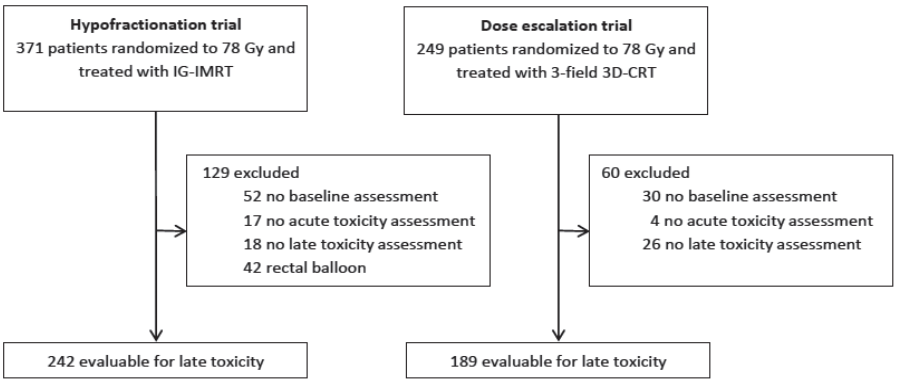
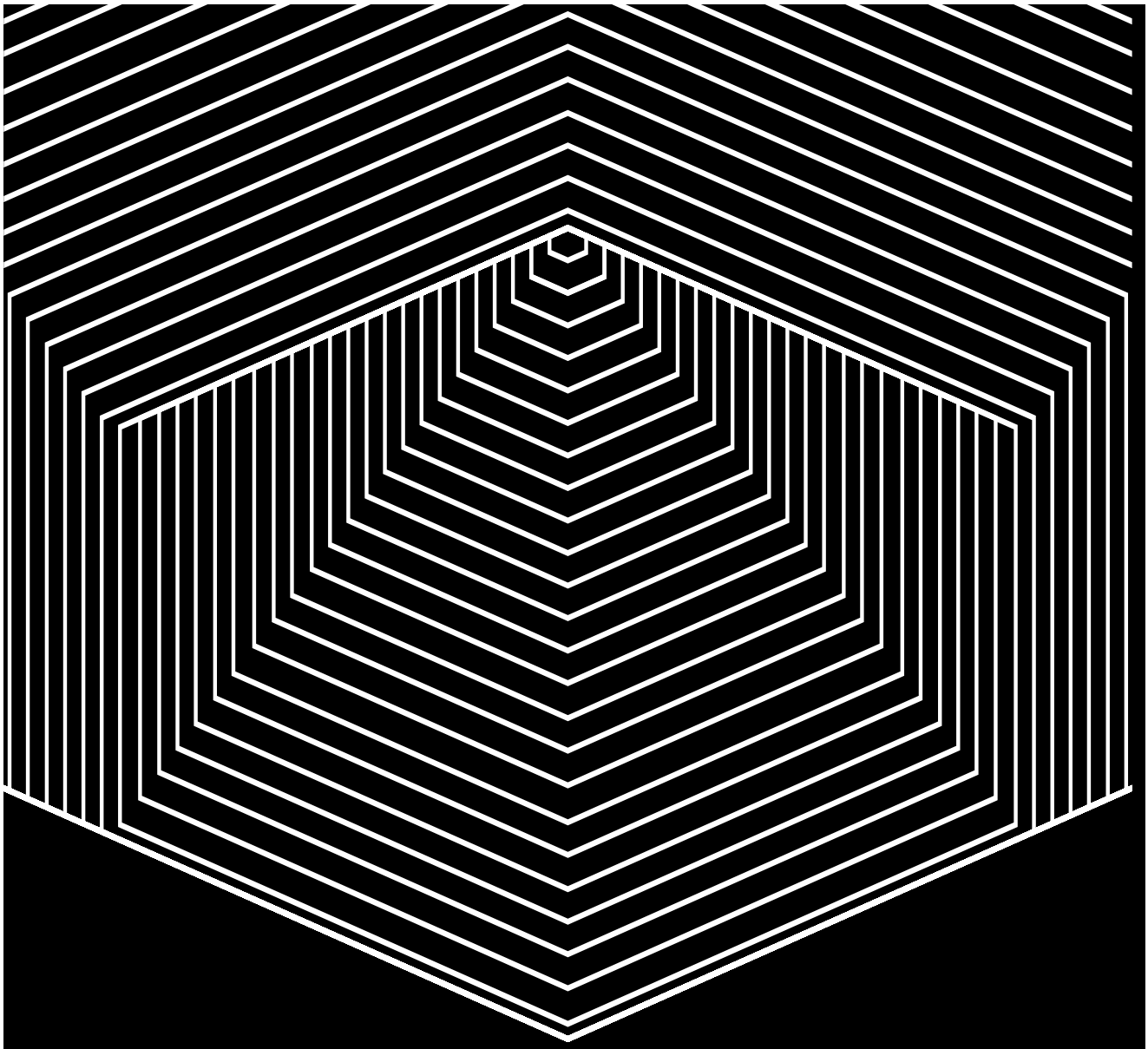
SUPPLEMENTARY FILES

Supplementary File 1. Study Flow chart





“RUIMTE SCHEIDT DE LICHAMEN,

NIET DE GEESTEN.”

Erasmus

CHAPTER 05

Local protocol variations for image-guided radiotherapy in the multicenter Dutch hypofractionation (HYPRO) trial: impact of rectal balloon and MRI delineation on anorectal dose and gastrointestinal toxicity levels

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ABSTRACT

Purpose

The phase 3 HYPRO trial randomized intermediate to high-risk localized prostate cancer patients to conventionally fractionated (78Gy/39fr) or hypofractionated radiotherapy (64.6Gy/19fr). Differences in techniques and treatment protocols were present between participating centers. This study aimed to compare dose parameters and patient-reported gastrointestinal symptoms between these centers.

Methods and materials

From the trial population we selected patients (n=572) from four treatment centers who received image-guided-IMRT (IG-IMRT). Center A (n=242) applied planning target volume (PTV) margins of 5-6mm and was considered the reference center. In center B (n=170, 7mm margins), magnetic resonance imaging (MRI) was integrated in treatment planning. An endorectal balloon (ERB) was applied in center C (n=85, 7mm margins). Center D (n=75) applied the largest PTV-margins of 8mm. The study protocol provided identical dose constraints for rectum and anal canal and local protocols were applied for further treatment optimization. Anorectal dose-surface histograms were compared applying t-tests. Rectal complaints during follow-up (6 months-4 years) were compared in a generalized linear model, adjusting for age, follow-up, treatment arm, and hormone therapy.

Results

Favorable anorectal dose distributions were found for center B (MRI delineation) and C (ERB application) as compared to center A and D. This was associated with significantly lower incidences of patient-reported complaints of rectal incontinence, use of incontinence pads, and rectal discomfort in these centers. Furthermore, lower incidences of increased stool frequency (≥4/day) and mucous loss were observed for center C.

Conclusions

Despite comparable IG-IMRT techniques and predefined dose constraints, pronounced differences in dose distributions and toxicity rates were observed. MRI delineation and ERB application were associated with favorable rectal dose parameters and toxicity profiles, whereas a 2-3mm difference in PTV-margins did not translate into observed differences. We conclude that choices for treatment optimization of IG-IMRT are important and clinically relevant for patients since these affect symptoms experienced in daily life.

INTRODUCTION

Modern image-guided intensity-modulated radiotherapy (IG-IMRT) techniques for prostate cancer treatment are nowadays implemented in daily clinical practice, since they are associated with favorable dose distributions and toxicity risks as compared to older 3D-conformal radiotherapy techniques (1,2). IG-IMRT techniques were also used by the majority of treatment centers that participated in the Dutch multicenter phase 3 HYpofractionated irradiation for PROstate cancer trial (HYPRO) (3-5). The HYPRO trial (2007-2010) was conducted to establish whether hypofractionated radiotherapy of 64.6 Gy in 19 fractions of 3.4 Gy would increase relapse-free survival as compared to conventionally fractionated treatment of 78 Gy in 39 fractions of 2 Gy (5), while establishing non-inferiority with respect to toxicity (3,4).

Although the study protocol provided dose constraints for rectum and anal canal, there were still some distinct differences in local treatment protocols allowed and present, since one center implemented magnetic resonance imaging (MRI) for prostate delineation, and another center applied an endorectal balloon (ERB). Furthermore, locally applied planning target volume (PTV) margins varied between centers, as were local treatment optimization procedures. MRI based delineation of the prostate has been introduced in the clinic by several radiotherapy institutes because of the improved soft tissue contrast especially for the apex (6). In planning studies, MRI-derived delineation achieved significantly reduced clinical target volumes (CTVs) and reduced the amount of irradiated rectal wall as compared to computed tomography (CT) based treatment plans (7,8). Studies on the ERB, which is inserted prior to each fraction, showed a reduction in intrafraction prostate motion and dose reduction to the posterior anorectal wall (9-11). Such differences in radiotherapy techniques and planning protocols with related potential dose reductions could have a significant impact on the toxicity risks for the patient.

In the current study, we compared the planned dose distributions to the anorectum and the patient-reported anorectal symptoms between four radiotherapy centers that have participated in the HYPRO trial. In this setting we are able to study the effects of MRI-based delineation, application of an ERB, and differences in PTV margins, on dose distributions and patient-reported rectal toxicities after image-guided (IG) IMRT for prostate cancer. We hypothesized that MRI-delineation, application of an ERB and reduced PTV margins were associated with reductions in anorectal dose and patient-reported rectal toxicities.

MATERIALS AND METHODS

Trial design and patient selection

Between March 2007 and December 2010, 820 men aged 44-85 years with histologically confirmed stage T1b-T4NX0MX0 localized prostate cancer were recruited (3-5). Trial inclusion and exclusion criteria have been previously reported (3-5). In brief, patients with intermediate- or high risk prostate cancer (12), an initial prostate-specific antigen (PSA) concentration of 60 µg/L or lower and a WHO performance status of 0-2 were eligible for inclusion, and were subsequently randomized to 78 Gy in 39 fractions or 64.6 Gy in 19 fractions.

For the current study, we selected patients (n=572) receiving IG-IMRT who returned at least one follow-up questionnaire (Table 1). We included those centers with profound differences in applied techniques and protocols that included at least 75 eligible patients (four of the seven centers that participated in the HYPRO trial) (Table 2). The study protocol was approved by the Medical Ethics Committee of Erasmus MC, Rotterdam, the Netherlands. All patients provided written informed consent.

Procedures

Conventionally fractionated radiotherapy was applied in 39 fractions of 2 Gy up to 78 Gy (five fractions per week during eight weeks), whereas hypofractionation of 64.6 Gy was delivered in 19 fractions of 3.4 Gy (three fractions per week during 6.5 weeks). Three fractions per week were applied for hypofractionation in order to avoid an excess in acute toxicity.

We considered an α/ß ratio in the range of 4-6 Gy for late toxicity when designing this trial. This resulted in bio-equivalent doses in 2 Gy fractions (EQD2) values of the hypofractionation schedule between 75.9-79.7 Gy, which approximated 78 Gy for conventional fractionation. (3). The CTV consisted of the prostate with or without SVs. The seminal vesicle (SV) dose was based on the risk of SV involvement (13). Patients in group 1 (risk of SV involvement lower than 10%) received no dose to the SV's (3-5). In group 2 (risk of involvement between 10–25%), the SV's received a reduced dose. With conventionally fractionated treatment, the treatment dose was administered with either a sequential boost technique, delivering 34 fractions of 2 Gy to the prostate plus vesicles and a boost of five fractions of 2 Gy to the prostate only, or using a simultaneously integrated boost technique, delivering 39 fractions of 1.85 Gy to the prostate plus SV's and an integrated boost of 39 fractions of 2 Gy to the prostate only (5).

With hypofractionated treatment, radiation was delivered in 16 fractions of 3.4 Gy to the the prostate plus SV's and a sequential boost of 3 fractions to the prostate only, or 19 fractions of 3.04 Gy to the prostate and SV's and a simultaneously integrated boost of 19 fractions to the prostate only (5). In group 3 (risk of SV involvement >25%), SV's received the full prescribed dose

Table 1. Patient (n=572) and treatment characteristics

Age (years)	70	(65-74)
Follow-up (months)	49	(35-54)
T Stage (%)		
T1	85	(14.9%)
T2	197	(34.4%)
T3a	222	(38.8%)
T3b	62	(10.8%)
T4	6	(1.0%)
Gleason Score (%)		
2-6	171	(29.9%)
7	256	(44.8%)
8-10	572	25.3%)
PSA Concentration (µg/L)	15.0	(9.4-26.0)
Risk Group (%)		
Intermediate	160	(28.0%)
High	412	(72.0%)
Abdominal Surgery (%)	147	(25.7%)
Diabetes Mellitus (%)	77	(13.5%)
ADT (%)	372	(65.0%)
Duration of ADT (months)	36	(6-36)
Treatment (%)		
CF (39x2 Gy)	281	(49.1%)
HF (19x 3.4 Gy)	291	(50.9%)
Treatment Center (%)		
A	242	(42.3%)
B	170	(29.7%)
C	85	(14.8%)
D	75	(13.1%)
PTV Margins (mm)		
5-6	242	(42.3%)
7	255	(44.6%)
8-10	75	(13.1%)

Table Legend: Data are presented as n (%) or median (interquartile range).

Table Abbreviations: PSA= prostate specific antigen, CF= conventional fractionation, HF=hypofractionation, PTV= planning target volume, ADT= androgen-deprivation therapy.

of 64.6 Gy for hypofractionation and 78 Gy for conventional fractionation. No elective lymph node irradiation was performed. Each center was free to use their own protocol for androgen deprivation therapy (ADT), which had to be prescribed equally in both treatment arms.

Treatment centers

Centers that participated in the HYPRO trial were to some extent free to use their own specific treatment techniques and protocols, which were to be applied equally within both treatment arms. In center A (n=242), isotropic PTV margins of 5-6mm were added to the CTV to yield the PTV. In center B and C, PTV margins of 7mm were used. In center B (n=170), magnetic resonance imaging (MRI) was used for treatment planning. A 3-tesla MRI was used and T1 and T2-weighed sequences were always included. In-house software (Worldmatch) was applied for CT-MRI matching. Matching was based on mutual information of grey values, with the prostate being the region of interest. For this procedure, markers are not specifically required. Treatment center C (n=85) inserted an ERB prior to each fraction in order to achieve rectal wall sparing (Figure 1, previously published by Smeenk et al (14)).

For this study, an air-filled (80-100cm3) ERB (QLRAD B.V., Dalfsen, the Netherlands) was applied daily. Center D (n=75) applied the largest PTV margins of 8mm. During the boost, all centers

Figure 1. Example of differences in anorectal dose distributions between treatment planning with and without an endorectal balloon.

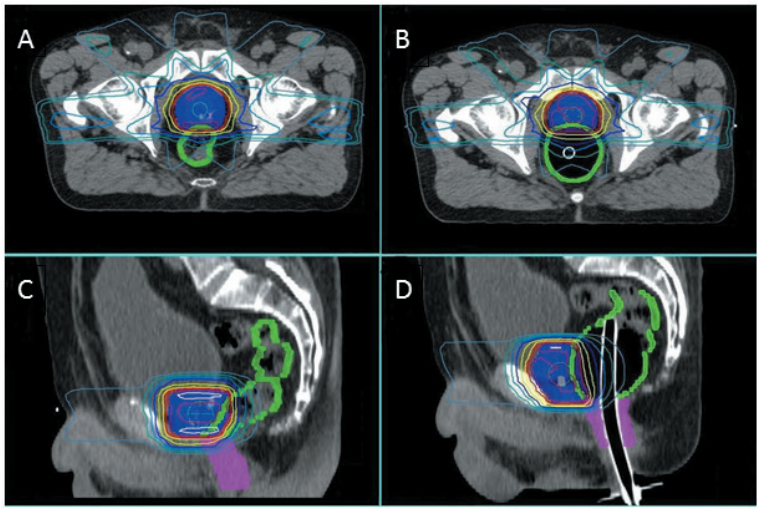


Figure Legend: Upper panels: Transverse section of planning CT with dose distribution of patient without (A) and with (B) inserted endorectal balloon. Lower panels: Sagittal section of planning CT with dose distribution of patient without (C) and with (D) inserted endorectal balloon

reduced PTV margins to 3-5mm in all directions except towards the rectum (0mm). All four centers used implanted fiducial markers for image-guidance. In center B, 38 patients were treated without fiducial markers. In these patients, an off-line image-guided protocol using kilovoltage cone-beam CT imaging was used for daily prostate matching (15).

Dose distributions of anorectum

Mandatory study dose constraints were applied in all centers. The rectal volume receiving ≥65 Gy was to be below 50%, and the mean anal dose was to not exceed 60 Gy (3). The outer anorectal wall contours were delineated from the ischial tuberosities to the anal verge (16). For this study, relative surfaces receiving 5-80 Gy were calculated for the anorectum. Relative dose surface histograms (DSHs) were generated per treatment arm and compared between centers.

Toxicity assessment

We evaluated rectal symptoms as indicated on the patient study questionnaires, which were comparable to the questionnaires used by Goldner and colleagues (17) and Litwin and colleagues (18), and identical to the questionnaire used by Peeters and colleagues in the CKVO 96-10 trial (19). Patient questionnaires were selected at baseline, at week 6 of treatment, and at 6, 12, 24, 36, and 48 months after completion of radiotherapy (3,19). Patients were censored from further analyses at the date of clinical relapse, as distinction between symptoms related to disease relapse or primary radiotherapy would have been difficult. Patient questionnaires completed between 5-8 weeks after the first fraction were selected for the time point at 6 weeks. Patient questionnaires completed within intervals of +/- 3 months after the last fraction were included for the 6- and 12-month time point. For other time points, forms returned within a 6-months window before or after the designated time point were included. In case multiple forms were completed within the same interval the one closest to the designated follow-up time was selected for analysis.

Patient-reported toxicity was evaluated according to slightly modified grade ≥1 Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria (20). We evaluated the following gastrointestinal symptoms: moderately increased stool frequency (≥4/day), any mucous loss, any rectal discomfort (pain, cramps, or tenesmus), any incontinence, any rectal blood loss, and any use of incontinence pads.

Statistical analysis

Center A included the largest number of eligible patients (n=242) and was therefore considered the reference center. Visual inspection of the distribution of variables was performed for assessing normality. Median delineated prostate volumes were compared between centers using the Mann Whitney U test, whereas mean anorectal dose between centers was compared using the independent t-test. Acute rectal toxicity (during RT) was compared between centers using the chi square test. Incidences of late rectal toxicity (from 6 months up to 4 years) were compared using a mixed model for binary outcomes with random intercept and fixed effects of center and the covariates follow-up period, age at start of radiotherapy, treatment arm, and duration of androgen deprivation therapy (generalized linear model (GLM) procedure). Statistical analyses were done with SPSS version 21 (SPSS Inc., Chicago, USA). A two-sided α of 0.01 was considered the limit of significance. This trial is registered at www.controlled-trials.com (ISRCTN85138529).

RESULTS

General characteristics

Patient and treatment characteristics are presented in Table 1. The median age of all patients (n=572) was 70 years (interquartile range 65-74). Within each treatment center, included patients were evenly distributed between treatment arms (Table 2). ADT for 6-36 months was prescribed to 372 patients (65%), being most frequently prescribed in center B (i.e. 88%) and least frequently in center A (i.e. 51%). Median duration of prescribed ADT varied between 36 months (IQR 36-36) in center A and D, to 6 months (IQR 6-36) for center B and C. ADT was prescribed at a median of 90 days before the first fraction (IQR 72-100) in center A, as compared to 54 days (IQR 34-86) for center B, 183 days (IQR 173-196) for center C, and 25 days (IQR 7-55) for center D.

Table 2. Treatment characteristics per treatment center

	A	B	C	D
Patients (%)	242	170	85	75
Conventional treatment	121 (50%)	81 (48%)	42 (49%)	37 (49%)
Hypofractionated treatment	121 (50%)	89 (52%)	43 (51%)	38 (51%)
Seminal vesicle dose group (%)				
1	46 (19%)	35 (21%)	25 (29%)	12 (16%)
2	126 (52%)	85 (50%)	39 (46%)	32 (43%)
3	70 (29%)	50 (29%)	21 (25%)	31 (41%)
ADT (%)				
No ADT	119 (49%)	21 (12%)	42 (51%)	19 (25%)
6 months	7 (3%)	79 (46%)	37 (43%)	7 (9%)
12-24 months	4 (2%)	0	4 (5%)	0
36 months	104 (43%)	66 (39%)	2 (2%)	47 (63%)
Unknown	8 (3%)	4 (2%)	0	2 (3%)
Days between start of ADT and first fraction (median, IQR)	90 (72-100)	54 (34-86)	183 (173-196)	25 (7-55)
Treatment planning imaging modality	CT	CT+ MRI	CT	CT
Fiducial Markers	Yes	Yes*	Yes	Yes
Delineated prostate volume (cm3) (median, IQR)	56.8 (43.8-75.4)	39.3 (29.9-52.5)	42.3 (33.7-60.0)	59.6 (46.9-71.5)
Delineated prostate volume in ADT-naïve patients (cm3) (median, IQR)	66.3 (51.7-93.7)	45.2 (34.8-54.6)	52.7 (40.7-66.7)	63.7 (52.7-74.9)
PTV margins (mm)	5-6	7	7	8
PTV margins seminal vesicles (mm)	8-10	7	7	8-10
Rectal balloon	No	No	Yes	No
Selected questionnaires per patient (median, IQR)	7 (6-7)	5 (4-6)	7 (6-7)	5 (4-6)
Completed questionnaires				
Baseline	233 (96%)	156 (92%)	85 (100%)	59 (79%)
During RT	227 (94%)	129 (76%)	83 (98%)	60 (80%)
6 months	234 (97%)	147 (86%)	84 (99%)	64 (85%)
12 months	227 (94%)	129 (76%)	85 (100%)	52 (69%)
24 months	214 (88%)	82 (48%)	79 (93%)	44 (59%)
36 months	195 (76%)	72 (42%)	70 (82%)	42 (56%)
48 months	175 (72%)	66 (39%)	69 (81%)	35 (47%)

Table Legend: *38 of 170 patients (22.3%) in center B were treated with off-line protocol using cone-beam CT imaging for prostate matching instead of fiducials.

Table Abbreviations: CT= computed tomography, MRI= magnetic resonance imaging, IQR= interquartile range, SD= standard deviation, ADT= androgen deprivation therapy, PTV= planning target volume

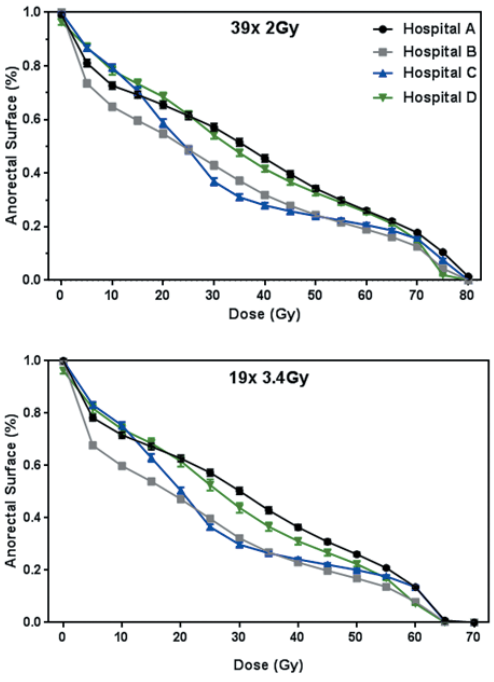
The delineated prostate volumes in center B (median 39.3 cm3, IQR 29.9-52.5) and center C (42.3 cm3, IQR 33.7-60.0) were statistically significantly smaller (Mann Whitney U, p<0.001) than in reference center A (56.8 cm3,

IQR 43.8-75.4). As ADT prescription varied among treatment centers, the delineated prostate volumes of hormone-naïve patients only were also compared between centers in order to exclude the effects of ADT in terms of prostate downsizing. These delineated prostate volumes demonstrated similar differences between centers as present in the total patient group (Table 2).

Dose distributions of anorectum

Figure 2 shows DSHs for each center, stratified for treatment. The average relative anorectal surface receiving at least a certain dose is shown for each dose level (in steps of 5 Gy). In general, center B (MRI-delineation and 7mm margins) and center C (ERB and 7mm margins) showed favorable dose distributions as compared to the reference center A (5-6mm margins). For conventional treatment of 78 Gy in 39 fractions, the mean anorectal dose in center B (29.5 Gy, SD 5.9, p<0.001) and center C (31.2 Gy, SD 4.6Gy, p<0.001) was significantly lower than in reference center A (36.4 Gy, SD 10.3). No significant difference was found for center D (34.8 Gy,

Figure 2. Average relative anorectal dose-surface histogram for each treatment center. A) Conventional treatment arm of 39 fractions of 2 Gy. B) Hypofractionated treatment arm of 19 fractions of 3.4 Gy



SD 5.9 Gy), which applied 8mm margins. As for hypofractionated treatment of 19 fractions of 3.4 Gy, center B (mean dose 21.8 Gy, SD 6.5) and center C (25.7 Gy, SD 3.2) again had significantly lower (p values <0.001) mean planned dose to the anorectum as compared to center A (30.1 Gy, SD 7.5 Gy). Again, no significant difference was found for center D (27.4 Gy, SD 8.3).

Patient-reported rectal toxicity

In general, the incidence of patient-reported gastrointestinal complaints at baseline were very low (Figure 3). Acute rectal complaints substantially increased during the course of treatment. Incidences of acute rectal complaints (at week 6 of radiation) were compared between treatment center A versus each of the other centers, and significant differences (chi square $p<0.01$) were only found between treatment center A vs. C for mucous loss (28.3% vs 16.8%, $p<0.001$) and rectal discomfort (59.9% vs 41.0%, $p=0.003$).

Late rectal complaints (6 months- 48 months) were analyzed using the generalized linear model (Table 3). For blood loss, we observed a positive significant trend ($\beta= 0.18$, $p<0.001$), indicating that complaints progressed over time. Increased stool frequency ($\beta=-0.24$, $p=0.001$), mucous loss ($\beta=-0.24$, $p<0.001$), and rectal discomfort ($\beta=-0.10$, $p=0.008$) all had a significant negative trend over time, indicating that complaints decreased between 6 months and 48 months follow-up. For incontinence and use of pads, no significant trends were observed over time, and complaints remained relatively stable during follow-up. Profound differences in symptom rates were observed between treatment centers at specific time points (Figure 3). For example, the incidence of rectal incontinence at 36 months was 23.4% for center A vs. 7.2% for center B, and 10.4% and 14.3% for center C and D, respectively. The incidences of all observed toxicity rates are reported in Supplementary File 1.

In the generalized linear model for late toxicity, we observed lower incidences of patient-reported toxicity for center B and C after adjusting for age at start of treatment, treatment arm, follow-up period, and duration of androgen deprivation therapy (ADT). Significantly lower incidences of patient-reported complaints of rectal incontinence, use of incontinence pads, and rectal discomfort were found for both center B and C, whereas a lower incidence of increased stool frequency (≥4/day) and mucous loss was observed for center C only (Table 3).

Figure 3. Incidence of patient-reported gastrointestinal toxicities per treatment center.

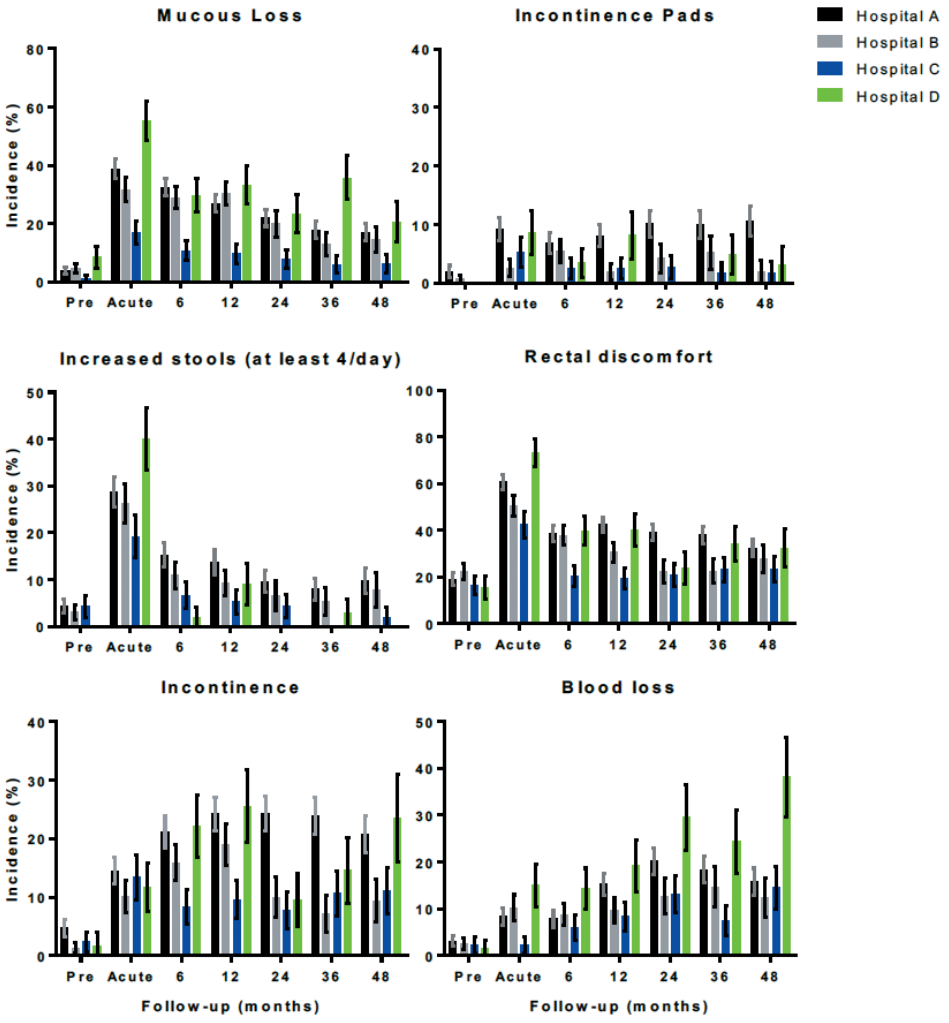


Figure Legend: Error bars represent standard error of proportion.

Figure Abbreviations: Pre= indicence at baseline, Acute= incidence during week 6 of treatment.

Table 3. Results of generalized linear model analyses for late rectal complaints (6 months-48 months)

Endpoint	Follow-up (period)		Center A vs. B		Center A vs. C		Center A vs. D	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Stools (≥4/ day)	-0.24 (-0.39- -0.09)	0.001	-0.41 (-0.82-0.005)	0.053	-1.24 (-1.85- -0.63)	<0.001	-1.40 (-2.24- -0.55)	0.001
Incontinence	-0.05 (-0.15- 0.04)	0.25	-0.63 (-0.93--0.33)	<0.001	-0.95 (-1.34- -0.56)	<0.001	-0.24 (-0.60- 0.12)	0.20
Pads	0.049 (-0.10- 0.20)	0.53	-0.88 (-1.43- -0.32)	0.002	-1.18 (-1.94- -0.42)	0.002	-0.59 (-1.31- 0.13)	0.11
Mucous Loss	-0.24 (-0.34- -0.15)	<0.001	-0.07 (-0.33- 0.19)	0.58	-1.28 (-1.69- -0.87)	<0.001	0.22 (-0.11- 0.54)	0.19
Rectal Discomfort	-0.10 (-0.18- -0.03)	0.008	-0.38 (-0.62- -0.14)	0.002	-0.68 (-0.97- -0.38)	<0.001	-0.18 (-0.48- 0.13)	0.25
Blood Loss	0.18 (0.08- 0.28)	<0.001	-0.30 (-0.63- 0.04)	0.09	-0.40 (-0.81- 0.01)	0.051	0.57 (0.21- 0.92)	0.002

Table Legend: estimated β with 95% confidence interval (95% CI) and p values for the covariates follow-up period and treatment center. Adjusted for age at start of treatment, treatment arm and duration of androgen deprivation therapy (months)

DISCUSSION

We evaluated anorectal dose distributions and gastrointestinal toxicity levels between four centers that participated in the prospective phase 3 HYPRO trial. Our study demonstrated that patients treated in the center who used MRI-based prostate delineation and patients treated in the center using an ERB had on average favorable anorectal dose distributions and favorable gastrointestinal toxicity levels, compared to the other two centers. Reductions in anorectal dose were most pronounced in the range of 5- 60 Gy for MRI delineation, and 20- 55 Gy for ERB application. Significantly lower incidences were observed for the endpoints incontinence, rectal discomfort, and use of incontinence pads in the center applying MRI-based delineation, and incontinence, rectal discomfort, use of incontinence pads, and mucous loss for the center applying an ERB. Such observed differences are clinically relevant and could impact quality of life.

MRI based delineation of the prostate

We observed favorable dose distributions and toxicity rates in the center applying MRI-based delineation. MRI-based delineation is associated with smaller delineated prostate volumes (21,22), which was also the case in this center: -31% compared to the other centers with CT-based delineation. These observations are in line with other studies demonstrating that CT-

derived prostate volumes were on average 1.3-1.4 times larger than MR derived volumes, especially toward the SVs and the prostatic apex (21,22). In the current study, other differences between the center applying MRI and the other centers were present as well, which could also have affected the comparison of volume, dose, and toxicity. Therefore, we should interpret these results carefully. For instance, ADT was more frequently prescribed in center B applying MRI delineation (88%) than in center A (51%). ADT results in prostate downsizing and could thus affect CTV, however we found similar differences in delineated prostate volumes between centers when analyzing hormone-naïve patients only, excluding the effects of ADT as an explanation for the observed differences in delineated prostate volume between treatment centers. (Table 2).

In our study, MRI-derived delineation was associated with smaller delineated prostate volumes, lower mean anorectal dose, and lower toxicity rates. A recent study by Sander and colleagues analyzed radiation-induced toxicity in 145 patients treated to 78 Gy either using CT- or MR-based delineation (23). Despite a 21.5% reduction in delineated prostate volumes using MRI, no reductions in overall rectal toxicity were found after follow-up of 36 months (1.4% for MRI vs. 4.2% for CT). Unfortunately, no comparison of planned rectal dose distributions was made between the CT and MRI group. Given the low rectal toxicity rates that were found, the authors conclude that a larger patient population might be required to demonstrate a difference between groups (23).

Endorectal balloon

In center C applying the ERB, significantly smaller prostate volumes were contoured (-26%) as compared to reference center A. In hormone-naïve patients, this reduction was only 20%. This indicates that reduction in delineated prostate volume could in part have been related to ADT, as this was initiated at a median of 183 days (IQR 173-196) before radiotherapy in the ERB-center as compared to 90 days (IQR 72-100) for reference center A. In addition, the observed differences could have been related to changes in prostate shape associated with introduction of an ERB. Heijmink and colleagues observed that ERB insertion significantly changed the prostate shape and reduced the volume (9).

In our study, the center applying an ERB demonstrated favorable anorectal dose distributions and anorectal toxicities despite somewhat larger PTV margins than applied in the reference center (7mm vs. 5-6mm). In a planning study by Smeenk and colleagues (24) introduction of an ERB was associated with a significant anal wall sparing effect. To our knowledge, only one comparative study reporting on clinical toxicity outcomes has been conducted so far. Van Lin and colleagues (25) studied 48 patients receiving 3D-CRT up to 67.5 Gy with or without ERB and found the ERB to be associated with a reduction in relative rectal wall volumes exposed

to intermediate-high doses and significantly less severe rectal mucosal damage on repeated rectosigmoidoscopies.

We have not analyzed whether daily insertion of the ERB itself caused discomfort in patients. Bastasch and colleagues however studied the effects of ERB insertion (100cm, air-filled) in 396 patients treated with IMRT to 77Gy in 35 fractions. (26). None of the patients declined the ERB during treatment, and only in 3 of 396 patients (0.8%) a reduction in the volume of the balloon was required. The vast majority of patient (393 of 396, 99.2%) tolerated the ERB during the entire course of treatment, which suggests the ERB is patient-friendly.

PTV margins

We found similar anorectal dose distributions and toxicity outcomes between center D (8mm margins) and reference center A (5-6mm margins), despite evidence that reduced PTV margins have a beneficial effect on rectal normal tissue complication probability (NTCP) (27). This indicates that other treatment optimization procedures are relevant as well. Clinical data addressing margin reduction are scarce. Crehange and colleagues compared 165 patients treated to 78 Gy using IG-IMRT with either 5mm margins or 10mm margins. It should be noted that the margins towards posterior were 5mm in both groups (28). With a median follow-up of more than 3 years, no significant differences in genitourinary or gastrointestinal radiation-induced toxicity according to the Common Toxicity Criteria Adverse Events version 3 (CTCAE v.3.0) morbidity grading scale were found (28).

IG-IMRT

We previously compared patient-reported rectal symptoms in patients treated to 78 Gy with IG-IMRT (without rectal balloon) versus patients treated to 78 Gy with 3D conformal techniques within a previous study (2). In that study, we observed no differences in patient-reported incontinence rates between the two techniques despite anorectal dose reductions in the IG-IMRT group. However, in the current study we do observe significant variations between centers applying IG-IMRT. The current results strongly suggest that a reduction in rectal incontinence rates is possible but strongly depends on choices for treatment planning and optimization in IG-IMRT.

Study limitations and future directions

The main objective of this study was to compare the impact of different local treatment planning protocols on anorectal dose distributions and patient-reported toxicity levels. In general, observed toxicity rates in our study were higher than present in the current body of publication on radiation-induced rectal toxicity. Two possible explanations are present for this finding; first, our data were derived from patient-reported questionnaires only. Physician-reported toxicity as scored according to the Radiation Therapy Oncology Group (RTOG) and European Organization

for Research and Treatment of Cancer (EORTC) toxicity criteria on the original case report forms were not evaluated. The differences between centers and physicians in the level of *reporting* toxicity would give a potential bias in the interpretation of relationships between toxicity levels, dose parameters, and local protocols. Most other studies provide physician-reported data, which according to studies by Goldner and colleagues, and Sonn and colleagues represent a profound underestimation of the patient-reported incidence of rectal toxicities (17,29). Second, the endpoints reported in this study represent slightly modified grade ≥1 toxicities according to the RTOG/EORTC scoring criteria (20). Most studies report grade ≥2 toxicities, which obviously are observed less frequently. As we choose patient-reported data as the basis for this study, further specification to grade 2 and grade 3 toxicity was not possible, because patients only reported on symptoms and not on interventions. Estimations of RTOG/EORTC grade ≥2 and grade ≥3 endpoints would also be uncertain (with associated large standard errors) duo to the relatively small subgroups.

A second limitation of the study is that the inclusion of SVs was not perfectly balanced between treatment centers. This might have affected the dose to OARs and could have introduced a potential bias. However, we have previously demonstrated that for IG-IMRT the SV dose only had minor influence on anorectal dose (2).

Finally, we might have overlooked other relevant differences in local treatment planning procedures at time of the recruitment phase of the HYPRO trial. Furthermore, the favorable dose distributions and toxicity rates that we observed for MRI delineation and ERB application do not definitely prove that this association is a causal relationship.

In future studies of the HYPRO trial we will investigate the relationship between individual dose variations to the rectum and anal canal, and toxicity endpoints. Investigating such dose-effect relationships will might offer valuable information, especially for patients treated with hypofractionated radiotherapy, as such data are scarce at present.

In conclusion, variations in local treatment protocols for IG-IMRT had a significant and clinically relevant effect on anorectal dose distributions and anorectal toxicity rates in prostate cancer patients, despite the use of similar techniques and identical trial protocol prescriptions. MRI delineation and ERB application were associated with favorable rectal dose parameters and toxicity profiles. Furthermore, we observed that a 2-3 mm difference in PTV margins did not translate into more favorable dose distributions, which indicates that other unspecified factors are relevant as well, probably related to plan optimization procedures.

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SUPPLEMENTARY FILES

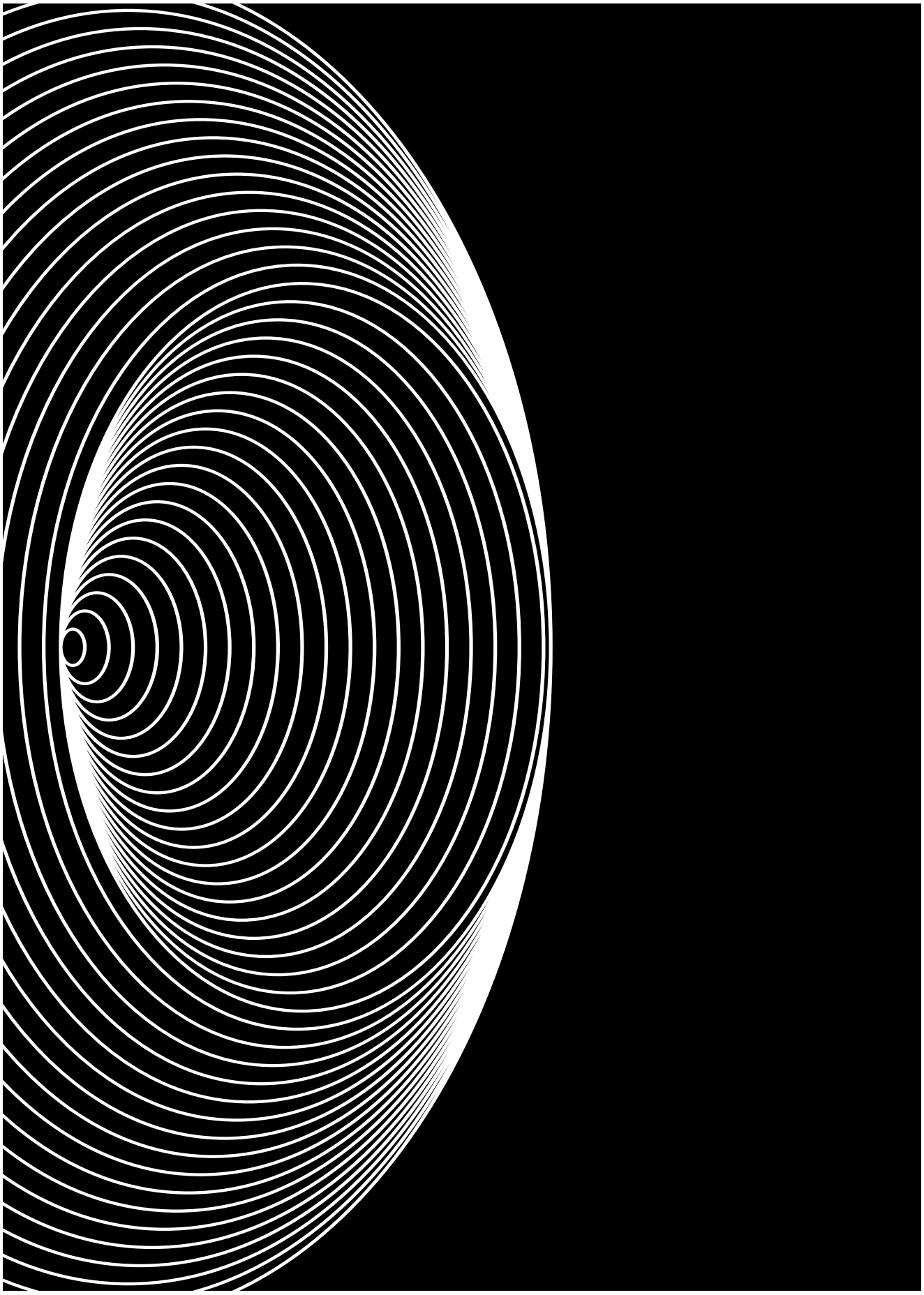
Supplementary File 1. Incidence of patient-reported gastrointestinal toxicities per treatment center

	Center A		Center B		Center C		Center D	
	%	S.E.	%	S.E.	%	S.E.	%	S.E.
Mucous Loss								
Baseline	3.9	1.3	4.5	1.7	1.2	1.2	8.5	3.7
During RT (week 6)	38.3	3.2	31.0	4.1	16.9	4.1	53.3	6.5
6 months	31.8	3.1	28.6	3.7	10.7	3.4	29.7	5.8
12 months	26.7	3.0	30.2	4.1	9.6	3.3	32.7	6.6
24 months	21.6	2.9	19.8	4.5	7.7	3.0	22.7	6.4
36 months	17.4	2.8	13.0	4.1	6.0	2.9	35.7	7.5
48 months	16.5	2.9	14.1	4.4	6.3	3.1	20.0	6.9
Incontinence Pads								
Baseline	1.7	0.9	0.6	0.6	0.0	0.0	0.0	0.0
During RT (week 6)	8.4	1.8	2.3	1.3	4.8	2.4	8.3	3.6
6 months	6.0	1.6	4.8	1.8	2.4	1.7	3.1	2.2
12 months	7.1	1.7	1.6	1.1	2.4	1.7	7.7	3.7
24 months	8.8	2.0	3.7	2.1	2.6	1.8	0.0	0.0
36 months	8.7	2.1	4.3	2.5	1.5	1.5	4.8	3.3
48 months	9.1	2.3	1.6	1.6	1.6	1.6	2.9	2.9
Stools (≥4/day)								
Baseline	3.4	1.2	2.6	1.3	3.5	2.0	0.0	0.0
During RT (week 6)	26.0	2.9	23.3	3.7	18.1	4.2	36.7	6.3
6 months	12.4	2.2	8.8	2.3	6.0	2.6	1.6	1.6
12 months	11.1	2.1	7.9	2.4	4.8	2.4	7.7	3.7
24 months	7.8	1.9	4.9	2.4	3.8	2.2	0.0	0.0
36 months	6.0	1.8	4.3	2.5	0.0	0.0	2.4	2.4
48 months	7.9	2.1	6.3	3.0	1.6	1.6	0.0	0.0
Rectal Discomfort								
Baseline	18.9	2.6	21.2	3.3	16.5	4.0	15.3	4.7
During RT (week 6)	59.9	3.3	49.6	4.4	41.0	5.4	73.3	5.8
6 months	36.9	3.2	36.1	4.0	20.2	4.4	39.1	6.1
12 months	40.9	3.3	30.2	4.1	19.3	4.4	38.5	6.8
24 months	37.3	3.4	21.0	4.6	20.5	4.6	22.7	6.4
36 months	35.3	3.5	21.7	5.0	22.4	5.1	33.3	7.4
48 months	29.3	3.6	25.0	5.5	22.2	5.3	31.4	8.0

Supplementary File 1. Incidence

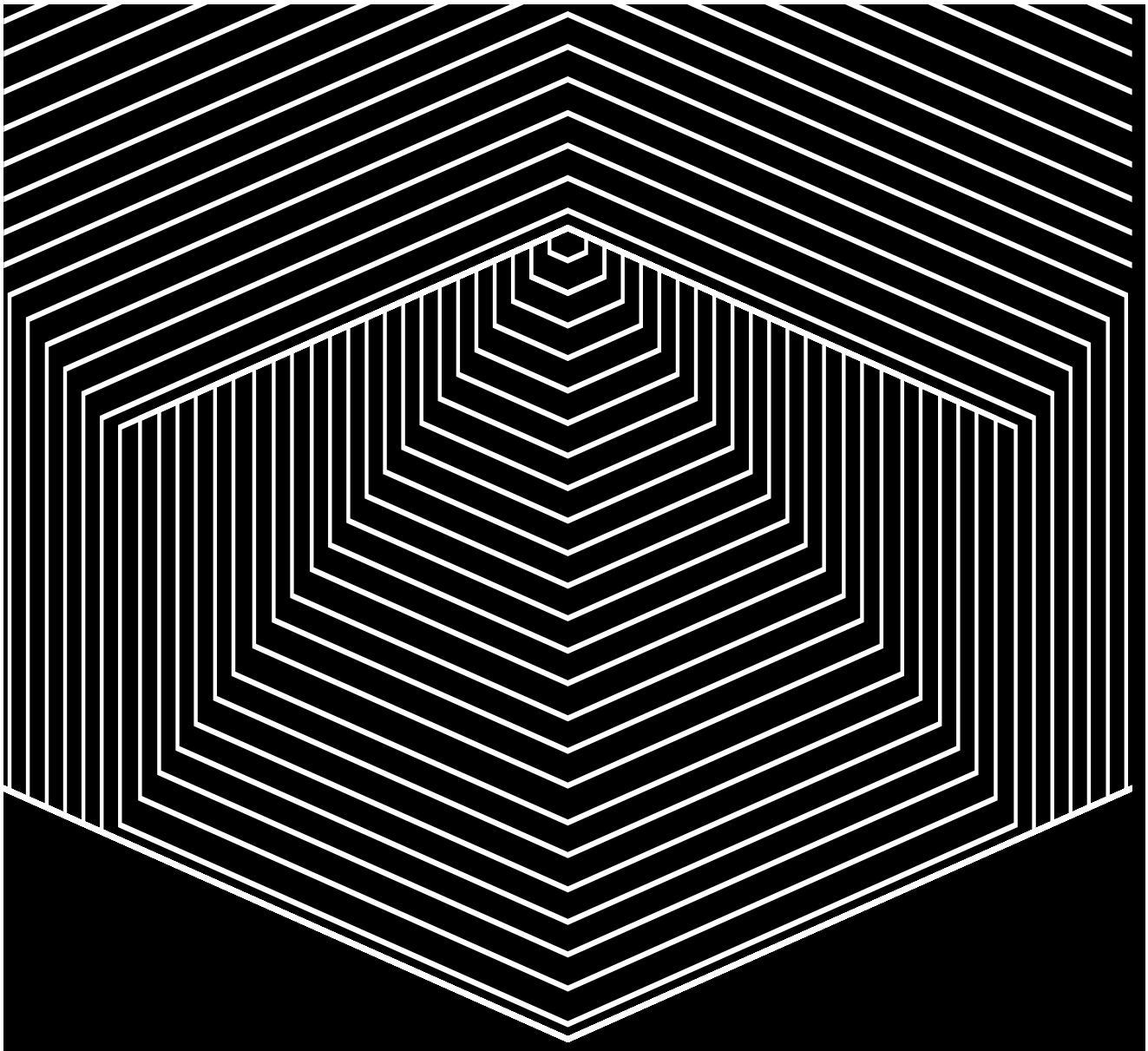
	Center A		Center B		Center C		Center D	
	%	S.E.	%	S.E.	%	S.E.	%	S.E.
Incontinence								
Baseline	4.7	1.4	1.3	0.9	2.4	1.7	1.7	1.7
During RT (week 6)	14.5	2.3	10.1	2.7	13.3	3.7	11.7	4.2
6 months	21.0	2.7	15.6	3.0	8.3	3.0	21.9	5.2
12 months	24.0	2.9	19.0	3.5	9.6	3.3	25.0	6.1
24 months	24.0	3.0	9.9	3.3	7.7	3.0	9.1	4.4
36 months	23.4	3.1	7.2	3.1	10.4	3.8	14.3	5.5
48 months	20.7	3.2	9.4	3.7	11.1	4.0	22.9	7.2
Blood Loss								
Baseline	3.0	1.1	2.6	1.3	2.4	1.7	1.7	1.7
During RT (week 6)	8.4	1.8	10.1	2.7	2.4	1.7	15.0	4.6
6 months	7.7	1.8	8.8	2.3	6.0	2.6	14.1	4.4
12 months	15.1	2.4	9.5	2.6	8.4	3.1	19.2	5.5
24 months	19.6	2.8	12.3	3.7	12.8	3.8	29.5	7.0
36 months	17.4	2.8	14.5	4.3	7.5	3.2	23.8	6.7
48 months	15.2	2.8	12.5	4.2	14.3	4.4	37.1	8.3

Table Legend: S.E.= Standard error of proportion, RT= radiotherapy



PART II

Treatment efficacy



“THE MOST DANGEROUS PHRASE IN THE LANGUAGE IS ‘WE’VE ALWAYS DONE IT THIS WAY’.”

Grace Hopper

CHAPTER 06

Hypofractionated versus conventionally fractionated radiotherapy for patients with localized prostate cancer (HYPRO): final efficacy results from a randomized, multicenter, open-label, phase 3 trial

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ABSTRACT

Background

Studies have reported a low α/ß ratio for prostate cancer, suggesting that hypofractionation could enhance the biological tumor dose without increasing genitourinary and gastrointestinal toxicity. In the multicenter phase 3, HYpofractionated irradiation for PROstate cancer (HYPRO) trial, hypofractionated radiotherapy was compared with conventionally fractionated radiotherapy for treatment of prostate cancer. We have previously reported acute and late incidence of genitourinary and gastrointestinal toxicity; here we report protocol-defined 5-year relapse-free survival outcomes.

Methods

We did an open-label, randomised, phase 3 trial at seven Dutch radiotherapy centers. We enrolled patients with intermediate-risk to high-risk T1b–T4NX–N0MX–M0 localized prostate cancer, a prostate-specific antigen concentration of 60 µg/L or less, and a WHO performance status of 0–2. We used a web-based application to randomly assign (1:1) patients to either hypofractionated radiotherapy of 64.6 Gy (19 fractions of 3.4 Gy, three fractions per week) or conventionally fractionated radiotherapy of 78.0 Gy (39 fractions of 2.0 Gy, five fractions per week). Based on an estimated α/ß ratio for prostate cancer of 1.5 Gy, the equivalent total dose in fractions of 2.0 Gy was 90.4 Gy for hypofractionation compared with 78.0 Gy for conventional fractionation. The primary endpoint was relapse-free survival. All analyses were done on an intention-to-treat basis in all eligible patients. The HYPRO trial completed recruitment in 2010 and follow-up is ongoing. This trial is registered with ISRCTN, number ISRCTN85138529.

Findings

Between March 19, 2007, and Dec 3, 2010, 820 patients were enrolled, of whom 804 were eligible and assessable for intention-to-treat analyses. Of these, 407 were assigned hypofractionated radiotherapy and 397 were allocated conventionally fractionated radiotherapy. 537 (67%) of 804 patients received concomitant androgen deprivation therapy for a median duration of 32 months (IQR 10–44). Median follow-up was 60 months (IQR 51–69). Treatment failure was reported in 169 (21%) of 804 patients, 80 (20%) in the hypofractionation group and 89 (22%) in the conventional fractionation group. 5-year relapse-free survival was 80.5% (95% CI 75.7–84.4) for patients assigned hypofractionation and 77.1% (71.9–81.5) for those allocated conventional fractionation (adjusted hazard radio 0.86, 95% CI 0.63–1.16; log-rank p=0.36). There were no treatment-related deaths.

Interpretation

Hypofractionated radiotherapy was not superior to conventional radiotherapy with respect to 5-year relapse-free survival. Our hypofractionated radiotherapy regimen cannot be regarded as the new standard of care for patients with intermediate-risk or high-risk prostate cancer.

INTRODUCTION

Dose-escalated external beam radiotherapy significantly improves relapse-free survival compared with treatment doses of 72.0 Gy and lower in patients with localized prostate cancer (1-3). Treatment up to 78.0 Gy in 39 fractions of 2.0 Gy has been introduced widely in the Netherlands after findings of a dose-escalation trial showed superior results with that schedule compared with 34 fractions of 2.0 Gy (1). The associated increase in radiation-induced toxic effects, however, restricts options for further dose escalation using conventional fractionation (2-4). Radiobiological models suggesting a low α/ß ratio for prostate cancer have sparked interest in hypofractionation as a means to increase the radiobiological tumor dose without increasing treatment-induced toxic effects (5-8). Moreover, hypofractionated radiotherapy is delivered in fewer fractions, improving patients' convenience, hospital logistics, and possibly reducing health-care costs.

Between 2007 and 2010, the HYpofractionated irradiation for PROstate cancer (HYPRO) trial - a randomized, phase 3, multicenter trial for intermediate-risk and high-risk localized prostate cancer - was conducted in the Netherlands to investigate whether hypofractionated external beam radiotherapy (19 fractions of 3.4 Gy) improves relapse-free survival without increasing toxic effects, compared with conventionally fractionated radiotherapy (39 fractions of 2.0 Gy). The hypofractionated regimen was chosen based on the assumption of an α/ß ratio for prostate cancer of 1.5 Gy (7,8), achieving dose escalation in 2.0 Gy fractions of 12.4 Gy up to an equivalent total dose of 90.4 Gy in 2.0 Gy fractions for hypofractionated treatment. We have previously reported the acute and late toxicity results from this trial; the postulated non-inferiority of hypofractionation compared with conventional fractionation was not shown (9,10). Here, we present pre-specified relapse-free survival outcomes after 5 years.

MATERIALS AND METHODS

Study design and participants

We did an open-label, randomized, phase 3 trial at seven radiotherapy centers in the Netherlands (Appendix Table 1). We recruited patients aged 44–85 years with histologically confirmed stage T1b–T4NX–N0MX–M0 localized prostate cancer (11), an initial prostate-specific antigen (PSA) concentration of 60 µg/L or lower, and a WHO performance status of 0-2 (9). Patients with low-risk disease (stage T1b–T2a, Gleason score of 6 or lower, or PSA <10 µg/L), according to the single-factor definition proposed by Chism and colleagues (11), were not eligible for inclusion (9). Therefore, we only included patients with high-risk prostate cancer (stage T3–T4, Gleason score ≥8, or PSA >20 µg/L) or intermediate-risk prostate cancer (defined as no low-risk or high-

risk disease). Patients with a PSA concentration less than 20 µg/L and Gleason score lower than 8 could be included without a work-up for metastases. Exclusion criteria were previous pelvic radiotherapy or radical prostatectomy, evidence of pelvic nodal disease (assessed by pelvic CT), or presence of distant metastases (assessed by bone scintigraphy). Every center applied its own protocol for androgen deprivation therapy, which was implemented equally for both treatment groups.

The medical ethics committee of Erasmus MC (Rotterdam, Netherlands) approved the HYPRO trial. All patients provided written informed consent. The Department of Radiation Oncology and the Clinical Trial Center at Erasmus MC coordinated and managed the trial. The protocol is available online.

Randomization and masking

We randomly allocated patients (1:1) to either hypofractionated radiotherapy or conventionally fractionated radiotherapy, using a minimization procedure (9,10). The Clinical Trial Center at Erasmus MC did the randomization procedure independently, via a web-based application. For logistical reasons, we did randomization at least 4 weeks before radiotherapy. We did not define a maximum interval between randomization and start of treatment, although the interval could be shorter if processing proceeded quickly. We used biased coin randomization to ensure overall balance and within each stratum of the stratification factors (treatment center and risk group [intermediate risk vs high risk]) (9–11). Local investigators received immediate notification of the assigned treatment via email or fax. Patients and investigators were not masked to treatment allocation.

Procedures

For patients assigned hypofractionation, we administered 64.6 Gy of radiation in 19 fractions of 3.4 Gy over 6.5 weeks (three fractions per week) (9,10) Hypofractionated radiotherapy was delivered as three fractions per week to avoid excessive acute toxic effects (9). For patients allocated conventional fractionation, we administered 78.0 Gy of radiation in 39 fractions of 2.0 Gy over 8 weeks (five fractions per week).

We assumed an α/ß ratio of 10.0 Gy for acute gastrointestinal and genitourinary toxic effects; therefore, the equivalent total dose in 2.0 Gy fractions for weekly and total acute toxic effects was 11.4 Gy and 72.1 Gy, respectively, for hypofractionation versus 10.0 Gy and 78.0 Gy, respectively, for conventional fractionation. We assumed an α/ß ratio of 4.0–6.0 Gy for late toxic effects when designing this trial, resulting in an equivalent total dose in 2.0 Gy fractions for the applied hypofractionation schedule of 75.9–79.7 Gy, which approximates to 78.0 Gy for conventional fractionation (9).

The clinical target volume consisted of the prostate with or without seminal vesicles. Based on the risk of seminal vesicle involvement according to the updated Partin tables for T stages of 2c or lower (12), and the previous tables for T stages higher than 2c (13), we defined three dose groups. Patients in group 1 (risk of seminal vesicle involvement <10%) received no dose to the seminal vesicles. In group 2 (risk of seminal vesicle involvement 10–25%), seminal vesicles received a reduced dose. With hypofractionation, the seminal vesicles received 16 fractions of 3.4 Gy (sequential boost technique) or 19 fractions of 3.04 Gy (simultaneously integrated boost). With conventional fractionation, this dose was administered with either a sequential boost technique, delivering 34 fractions of 2.0 Gy to the prostate-plus vesicles and a boost of five fractions of 2.0 Gy to the prostate only, or a simultaneously integrated boost technique, delivering 39 fractions of 1.85 Gy to the vesicles and 39 fractions of 2.0 Gy to the prostate. In group 3 (risk of seminal vesicle involvement >25%), seminal vesicles received the full prescribed dose of 64.6 Gy for hypofractionation and 78.0 Gy for conventional fractionation. We did not allow elective irradiation of the pelvic lymph nodes. Depending on the set-up verification and correction strategy at every center, we added 3–10 mm margins to the clinical target volume, yielding the planning target volume (9,10). For the boost, we reduced margins to 3–5 mm, except towards the rectum (0 mm). The planning CT or MRI was done 2 weeks before start of radiotherapy. Androgen deprivation therapy was prescribed at the discretion of the investigator, and every treatment center had its own protocol for treatment, which was identical for both treatment groups. In general, a luteinising hormone-releasing hormone analogue was preceded by an antiandrogen agent for 1–2 weeks.

After treatment, we assessed tumor response by measurement of PSA at follow-up visits scheduled every 3 months during the first 2 years after treatment, twice a year during years 3–5, and annually thereafter, until 10 years. If we suspected tumor recurrence or metastases based on complaints or clinical signs, we did transrectal ultrasound of the prostate, pelvic CT, and bone scintigraphy, at the discretion of the treating clinician.

We assessed toxic effects using case report forms and self-assessment questionnaires, and we scored them according to Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria (9). We assessed baseline gastrointestinal and genitourinary disorders before treatment. We scored toxic effects at 3, 6, and 12 months during the first year and annually thereafter. We reported and monitored adverse events in accordance with Dutch regulations (details in the study protocol) (9,10). Briefly, adverse events were recorded in the patient's chart. The treating clinicians assessed and recorded whether adverse events were related to treatment. The Clinical Trial Center forwarded all reports within 24 h of receipt to the study coordinator and study central data manager. Results regarding acute and late toxic effects have been published (9,10).

Outcomes

The primary endpoint was 5-year relapse-free survival, defined from randomization as biochemical relapse, clinical relapse, loco-regional or distant relapse, or start of hormone therapy, whichever occurred first (9,10). We defined biochemical relapse as a PSA concentration greater than the nadir, which was the lowest PSA value since treatment, plus 2 µg/L (14). We did a central review of the primary endpoint. We censored patients who died without evidence of previous relapse, and those whose death was not due to treatment-related toxic effects, atthe date of death. For the current analysis, we assessed overall survival as a post-hoc endpoint.

Additional protocol-defined key endpoints, which have been reported previously (9,10), were cumulative incidence of grade 2 or higher acute and late genitourinary and gastrointestinal toxic effects. We defined acute and late toxic effects as key endpoints, since relapse-free survival data cannot be interpreted without taking into account radiation-induced side-effects. Secondary endpoints were quality of life and erectile function, which will be reported separately.

Statistical analysis

We based power calculations on an absolute increase in relapse-free survival of 10% (from 70% to 80%) at 3 years with hypofractionation, compared with conventional fractionation (based on results of the Dutch dose-escalation trial) (4). We further assumed that most relapses would occur within the first 3 years and that relapse-free survival at 5 years with conventionally fractionated radiotherapy would be approximately 68%. With accrual of 400 patients per treatment arm over 4 years, and with additional follow-up of 3 years, we expected a total of 214 events, which would provide 92% power, with a two-sided α of 0.05. Assuming a dropout of 20 patients, we calculated a sample size of 410 individuals per treatment arm. We planned the final analysis at 3 years after inclusion of the last patient. We based our analyses on the intention-to-treat principle and restricted it to eligible patients.

We applied the Kaplan-Meier method to estimate survival curves and used the log-rank test to compare curves between treatment arms. We used Cox regression, assuming proportional hazards, to compare the primary endpoint of relapse-free survival and the post-hoc endpoint of overall survival between treatment arms. We tested the proportionality assumption in the Cox proportional hazards model with the Schoenfeld residuals (Appendix Table 2). We estimated hazard ratios (HRs) and 95% confidence intervals (CIs). We adjusted these analyses for the stratification factor of risk group. We applied post-hoc univariate and multivariate analyses to ascertain the prognostic value on relapse-free survival of age, PSA, Gleason score, T stage, seminal vesicle dose group, prostate volume, and androgen deprivation therapy. We did not impute missing data for covariates. We did post-hoc subgroup analyses to investigate the effects of treatments by comparing subgroup incidences of disease relapse and calculating HRs with 95% CIs. We tested the interaction effect of risk factors - including age, PSA, T stage, Gleason

score, prostate volume, risk group, seminal vesicle dose group, and androgen deprivation therapy - with treatment, to assess subgroup heterogeneity of the treatment effect. We did not correct for multiple testing and all p values were based on two-sided tests. We judged an α less than 0.05 as significant. We used Stata version 13.1 for analyses. This trial is registered with ISRCTN, number ISRCTN85138529.

Role of the funding source

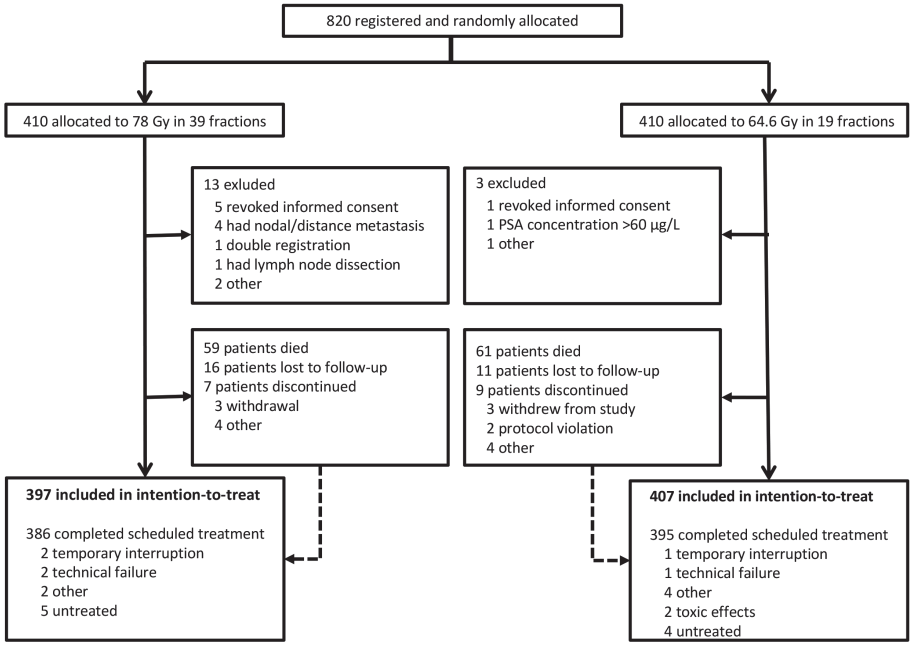
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between March 19, 2007, and Dec 3, 2010, 820 patients were randomized to radiotherapy with hypofractionation (n=410) or conventional fractionation (n=410). The median time from randomization to start of treatment was 34 days (IQR 22–49). Among the 820 registered patients, 16 (2%) were not eligible for the study (three allocated hypofractionation and 13 assigned conventional fractionation) and, therefore, they were excluded from the intention-to-treat analysis of relapse-free survival (Figure 1). The database was locked on July 14, 2015, at which the median follow-up for all patients alive (684 of 804 patients) was 60 months (IQR 51–69) from the date of randomization (61 months [51–68] for hypofractionation and 60 months [51–70] for conventional fractionation).

Baseline characteristics were distributed evenly between treatment groups (Table 1). Androgen-deprivation therapy was prescribed to 537 (67%) of 804 patients, and prescriptions were balanced evenly between treatment groups. Median duration of androgen deprivation therapy was 32 months (IQR 10–44; Appendix Table 3). Goserelin was the most frequent treatment given and was prescribed to 97 (36%) of 270 patients receiving androgen deprivation therapy in the hypofractionation group and 106 (40%) of 267 patients in the conventionally fractionated group. In general, at most centers, androgen deprivation therapy was prescribed for at least 24 months in patients with stage T3 and T4 tumors (124 [58%] of 214 patients in the hypofractionation group and 121 [59%] of 206 patients in the conventional fractionation group) and for 6–24 months in those with a Gleason score of 8 or higher, PSA concentrations greater than 20 µg/L, or both of these (60 [66%] of 91 patients in the hypofractionation group and 54 [62%] of 86 patients in the conventional fractionation group).

Figure 1. Trial flowchart



Intensity-modulated radiotherapy was used in 761 (95%) of 804 patients (385 in the hypofractionation group and 376 in the conventional fractionation group) and 753 (94%) patients received implanted fiducial markers for daily online image-guidance (381 in the hypofractionation group and 372 in the conventional fractionation group). Deviations in treatment delivery occurred for 14 patients and comprised: temporary interruption in three patients (one hypofractionation, two conventional fractionation); discontinuation due to toxic effects in two patients assigned hypofractionation; technical failure in three patients (incorrect delivery of one intensity-modulated radiotherapy field in two [one hypofractionation, one conventional fractionation], and under-dosage of 5% at dorsal side of the prostate in one assigned conventional fractionation); treatment according to the other treatment group in three patients (two hypofractionation, one conventional fractionation); an additional 2.0 Gy fraction because of delay in one patient assigned conventional fractionation; no treatment of seminal vesicles in one patient assigned hypofractionation; and interrupted treatment because of unrelated medical problems in one patient assigned hypofractionation (Figure 1). Furthermore, nine patients were not treated: one because of non-compliance with treatment immediately after randomization (assigned conventional fractionation); one who had radical prostatectomy (assigned conventional fractionation); four who withdrew from the study (one hypofractionation, three conventional fractionation); two who had advanced cardiac or

Table 1. Baseline patient and tumor characteristics

	Conventional Fractionation (n=397)		Hypofractionation (n=407)	
Age (years)	71	(67-75)	70	(66-74)
PSA concentration (µg/L)	14.6	(9.7-23.8)	14.0	(9.2-21.3)
T stage				
T1	59	(15%)	58	(15%)
T2a	45	(11%)	50	(12%)
T2b	38	(10%)	35	(9%)
T2c	49	(12%)	50	(12%)
T3a	164	(41%)	158	(39%)
T3b	38	(10%)	49	(12%)
T4	4	(1%)	7	(2%)
Gleason score				
≤6	120	(30%)	122	(30%)
7	182	(46%)	183	(45%)
8	57	(14%)	61	(15%)
9	34	(9%)	38	(9%)
10	4	(1%)	3	(1%)
Prostate volume (cm3)				
≤50	188	(45%)	184	(45%)
>50	197	(51%)	207	(51%)
Unknown	12	(4%)	16	(4%)
Risk group*				
Intermediate	107	(27%)	104	(26%)
High	290	(73%)	303	(74%)
Seminal vesicle dose group				
1	79	(20%)	79	(19%)
2	193	(49%)	199	(49%)
3	125	(31%)	129	(32%)
Androgen deprivation therapy				
No	130	(33%)	137	(34%)
Yes	267	(67%)	270	(66%)
Duration androgen deprivation therapy (months)	32.6	(11.2-45.6)	32.2	(9.7-41.5)

Table Legend: Data are n (%) or median (interquartile range). *According to Chism et al (11)

pulmonary disease (two hypofractionation); and one who died before treatment (assigned hypofractionation; Figure 1).

5-year relapse-free survival was 80.5% (95% CI 75.7–84.4) for patients assigned hypofractionation and 77.1% (71.9–81.5) for those allocated conventional fractionation (adjusted HR 0.86, 95% CI 0.63–1.16; log-rank p=0.36; Figure 2A). Treatment failure was reported in 169 (21%) of 804 patients, 80 (20%) of 407 allocated hypofractionation and 89 (22%) of 397 assigned conventional fractionation. The first reported type of failure was biochemical recurrence in 70 (88%) of 80 patients assigned hypofractionation and 82 (92%) of 89 who were allocated conventional fractionation. All other first reported failures were clinical relapses.

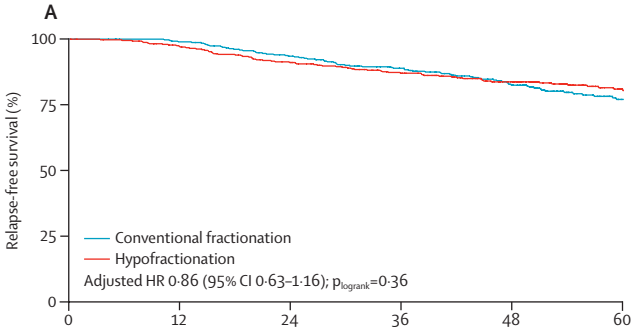
Post-hoc assessment of 5-year overall survival was 86.2% (95% CI 82.3–89.4) in patients assigned hypofractionation and 85.9% (81.8–89.2) in those allocated conventional fractionation group (HR 1.02, 95% CI 0.71–1.46; p=0.92; Figure 2B). 61 (15%) of 407 patients assigned hypofractionation died compared with 59 (15%) of 397 allocated conventional fractionation. 16 (26%) of 61 deaths in the hypofractionation group and 15 (25%) of 59 in the conventional fractionation group were related to prostate cancer; the relation between death and prostate cancer was uncertain in 11 (18%) patients assigned hypofractionation and in 8 (14%) allocated conventional fractionation. Other causes of death in patients assigned hypofractionation were cardiovascular disease in 6 (10%), infection in 3 (5%), and other or unknown reasons in 36 (59%); for those allocated conventional fractionation, other causes of death were cardiovascular disease in 9 (15%), infection in 3 (5%), and other or unknown reasons in 32 (54%). No direct treatment-related deaths were reported.

In post-hoc multivariate analyses, a Gleason score of 7 or lower and androgen deprivation therapy for longer than 12 months versus none were associated with a decreased risk of relapse (Table 2). Patients in seminal vesicle dose group 3 (>25% risk of vesicle involvement) had an increased risk of relapse compared with those in group 1 (risk <10%; Table 2). Age, PSA concentration, T stage, prostate volume, and treatment were not associated with relapse-free survival outcome. Post-hoc analyses of relapse-free survival showed no interaction between treatment group and any subgroup; comparable survival was recorded within almost all subgroups (Figure 3).

DISCUSSION

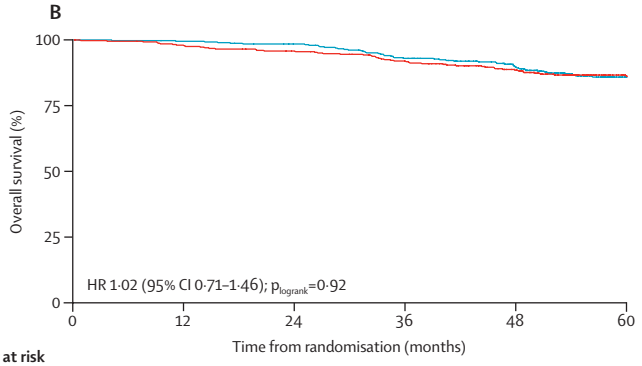
The findings of our phase 3 trial provide no evidence for the postulated superiority of hypofractionated radiotherapy over conventional fractionation in terms of relapse-free survival in

Figure 2. Kaplan-Meier estimates of (A) relapse-free survival and (B) overall survival



Number at risk						
Conventional fractionation	397	386	356	314	247	127
Hypofractionation	407	384	350	309	254	142

Number censored						
Conventional fractionation	0	7	9	25	46	108
Hypofractionation	0	11	11	26	44	105



Number at risk						
Conventional fractionation	397	391	382	354	306	177
Hypofractionation	407	396	384	360	311	185

Number censored						
Conventional fractionation	0	4	5	7	36	118
Hypofractionation	0	2	4	9	36	119

Figure legend: Hazard ratios (HRs) adjusted for the stratification factors of risk group and treatment center

Figure 3. Forrest plot of relapse-free survival in prognostic subgroups

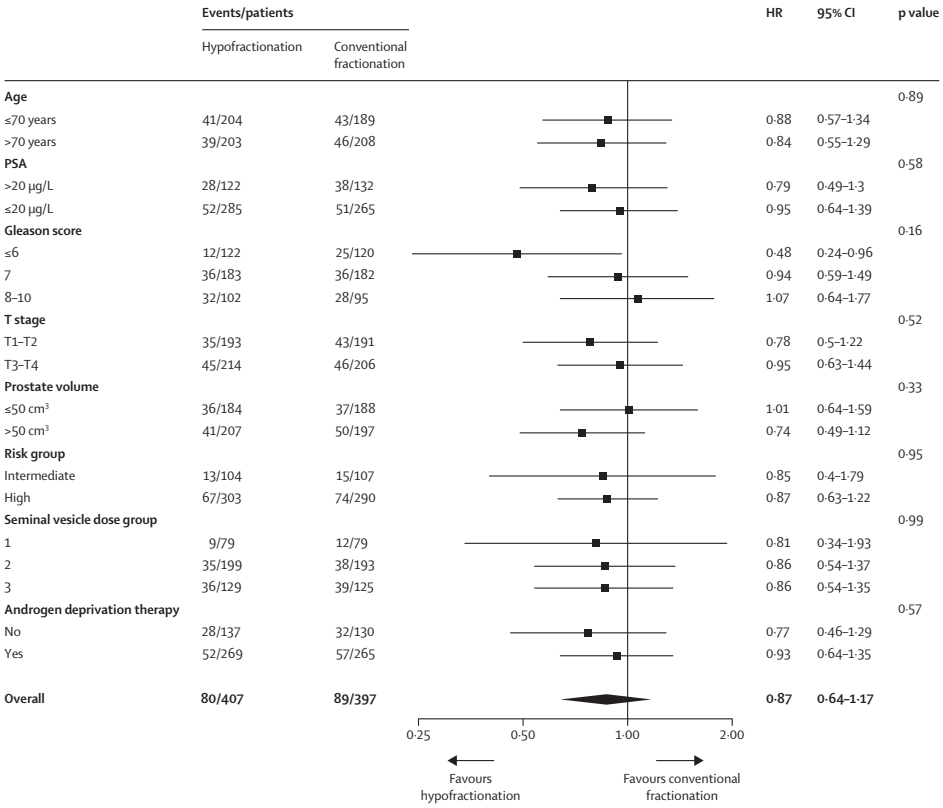


Figure Legend: Seminal vesicle dose groups: 1, risk of seminal vesicle involvement <10%; 2, risk 10-25%; 3, risk >25%

Figure Abbreviations: HR= Hazard ratio, PSA= Prostate-specific antigen

patients with intermediate-risk and high-risk localized prostate cancer. Assuming an α/ß ratio for prostate cancer of 1.5 Gy (7,8) we calculated that hypofractionated radiotherapy would result in a dose escalation to the equivalent of 12.4 Gy in 2.0 Gy fractions. We postulated that this dose escalation would result in a 10% absolute increase in 5-year relapse-free survival. When designing the HYPRO trial, relapse-free survival of 70% was expected with conventional fractionation, based on data from a Dutch dose-escalation trial (4). 5-year relapse-free survival was 77% in the conventional fractionation group, which is somewhat higher than originally estimated. The median duration of androgen deprivation therapy was 32 months, and prolonged low testosterone levels can be expected after androgen deprivation therapy is discontinued. Effects of androgen suppression might have had substantial effects on 5-year relapse-free survival within both treatment groups. Prolonged follow-up is, therefore, essential

Table 2. Results of univariate and multivariate Cox proportional hazards analysis for disease relapse

	Univariate		Multivariate	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age				
(>70 years vs. ≤70 years)	1.04 (0.77-1.41)	0.79	0.89 (0.64-1.22)	0.46
PSA concentration				
(≤20 µg/L vs. >20 µg/L)	0.65 (0.48-0.88)	0.0071	0.96 (0.62-1.48)	0.84
Gleason score				
(≤7 vs. 8-10)	0.50 (0.37-0.69)	<0.0001	0.46 (0.32-0.66)	<0.0001
T-stage				
(T3-T4 vs. T1-T2)	1.09 (0.80-1.47)	0.58	1.12 (0.74-1.69)	0.60
Seminal vesicle dose group		<0.0001		0.0029
(Group 2 vs. group 1)	1.51 (0.93-2.45)	0.099	1.33 (0.79-2.22)	0.28
(Group 3 vs. group 1)	2.75 (1.69-4.48)	<0.0001	2.59 (1.36-4.93)	0.0037
Prostate volume				
(>50 cm3 vs. ≤50 cm3)	1.17 (0.86-1.59)	0.32	1.15 (0.82-1.61)	0.42
Duration of androgen deprivation therapy		0.27		0.0048
(≤12months vs. none)	0.69 (0.43-1.12)	0.13	0.61 (0.35-1.05)	0.072
(>12 months vs. none)	0.95 (0.68-1.33)	0.78	0.50 (0.31-0.80)	0.0037
Treatment arm				
(hypofractionated vs. conventional)	0.87 (0.64-1.17)	0.36	0.81 (0.59-1.11)	0.20

and will be continued until 10 years after treatment. The first update on relapse-free survival is scheduled when follow-up of 7 years is achieved. These results might establish whether androgen suppression obscured potential benefits of hypofractionation at 5-year follow-up.

To date, treatment outcomes after hypofractionation have only been reported from small randomized trials (15–17). Arcangeli et al. (15, 16) did a small single-center study of 168 patients with prostate cancer treated with three-dimensional conformal radiotherapy to 80.0 Gy in 40 fractions or 62.0 Gy in 20 fractions of 3.1 Gy. They postulated that hypofractionation would achieve iso-effectiveness with respect to biochemical control, whereas the hypofractionated regimen should result in a considerably lower dose to healthy tissue. Although they could confirm iso-effectiveness of these treatments, late side-effects were not reduced significantly

(15,16) Pollack et al. (17, 18) did a single-institution study of 303 patients with mainly intermediate-risk and high-risk prostate cancer, who were randomized to either 70.2 Gy in 26 fractions of 2.7 Gy or 76.0 Gy in 38 fractions of 2.0 Gy. They assumed an α/ß ratio of 1.5 Gy and postulated that hypofractionation would result in a 15% reduction in biochemical and clinical failure (17). In line with our results, superiority of hypofractionation was not shown, with 5-year relapse of 21.4% after conventional treatment and 23.3% after hypofractionation. Two randomized controlled trials in patients with prostate cancer were undertaken before the dose-escalation era and an insufficient treatment dose was used, by present standards (19–21).

For prostate cancer, enhanced biological efficacy of delivered radiation dose with reduced overall treatment time has been reported (22). By comparison with schedules with a longer overall treatment time, this finding translates into an enhanced effective dose. Vogelius and Bentzen (22) reported that each day of reducing overall treatment time effectively resulted in an enhanced dose of 0.31 Gy. At the time the HYPRO study was designed, this effect was not known. However, to avoid excessive acute toxic effects with hypofractionation, we delivered only three fractions per week in the hypofractionation regimen, resulting in an overall treatment time of 6.5 weeks, compared with 8 weeks for conventional fractionation (9). As a result, with an additional 0.31 Gy per day that overall treatment time is reduced, the additional increase in effective dose with our hypofractionation schedule should be fairly small – i.e., around 3.0 Gy. The enhancement of effective dose with hypofractionation might be obscured by prolonged use of androgen deprivation therapy in the HYPRO trial. On the other hand, with an overall treatment time effect, the observed similar relapse-free survival in both treatment groups could point at an even further enhanced α/ß ratio for prostate cancer compared with the postulated 1.5 Gy. Results of other trials also raise questions about the fraction-dose sensitivity of prostate cancer (17,19). Data from other large, randomized, hypofractionation trials and subsequent meta-analyses are needed to reach consensus on the α/ß ratio and optimum fraction dose for prostate cancer.

The randomized, non-inferiority CHHiP trial treated 3216 patients with low-risk to high-risk prostate cancer with either 74.0 Gy in 37 fractions or one of two hypofractionated schedules: 57.0 Gy in 19 fractions or 60.0 Gy in 20 fractions (23, 24). In view of the substantial advantages of hypofractionation in terms of patients' convenience and hospital logistics, a non-inferiority design is also an effective method of showing the clinical benefit of hypofractionated treatment. Dearnaley et al. (24) did a preplanned analysis of side-effects in the CHHiP trial up to 2 years after treatment of the first 457 patients; they have also published patient-reported outcomes of 2100 patients in a quality-of-life sub study (23). The incidence of side effects was low and no significant differences between treatment groups were noted. 5-year outcomes of the CHHiP trial have now been presented (25); treatment with 20 fractions of 3.0 Gy was non-inferior to

conventional treatment with 37 fractions of 2.0 Gy in terms of tumor progression, and late toxic effects did not differ between groups.

Radiation-induced toxic effects should be considered when interpreting relapse-free survival in our study. Dose escalation to the apex of the prostate is limited by increased risks of rectal toxicity (1). The possibility of toxic effects in the rectum usually results in reductions of safety margins towards the rectum during the boost, which might interfere with tumor control. Growing evidence for a low α/ß ratio for prostate cancer, which is lower than that of surrounding rectal tissue, indicates that hypofractionation in particular should be applicable to enhance the biological tumor dose without increasing toxic effects. However, in the HYPRO trial, non-inferiority could not be shown between treatment groups for acute or late toxic effects (9,10). Acute grade 2 or worse genitourinary toxic effects were comparable between treatment groups, whereas the cumulative incidence of acute grade 2 or worse gastrointestinal toxic effects was significantly higher after hypofractionation than conventional fractionation (9). Differences in acute toxic effects between treatment groups had dissipated by 3 months after radiotherapy (9). 3-year cumulative incidence of late gastrointestinal and genitourinary grade 2 or worse toxic effects was comparable between treatment groups (10). The incidence of grade 3 or worse nocturia (at least six times per night) was significantly higher for hypo fractionation than for conventional fractionation, contributing to a significantly increased cumulative incidence of overall grade 3 or worse late genitourinary toxic effects (19%, 95% CI 15.2–23.2 for hypofractionation vs 13%, 9.7–16.7 for conventional fractionation; p=0.021) (10). Future planned analyses should establish whether the temporary differences in reported acute toxic effects between treatment groups, and increased grade 3 or higher toxic effects, had an effect on health-related quality of life. Some late toxic effects might occur at an even later stage, and prolonged follow-up is needed.

An independent strong predictor of disease relapse was high risk (>25%) of seminal vesicle involvement (dose group 3). When designing the HYPRO trial in 2006, seminal vesicle dose groups were defined based on the risk of vesicle infiltration according to Partin's tables (12,13). Unfortunately, these tables do not reflect contemporary pre-radiotherapy staging with multiparametric MRI. We recorded lower failure rates after hypofractionation compared with conventional treatment in patients with a Gleason score of 6 or lower. Our trial was not powered for subgroup analyses, and therefore we cannot conclude that patients with a Gleason score of 6 or lower benefit significantly from hypofractionation.

A limitation of the HYPRO trial was that central review of patients' eligibility was not done before randomization.

This drawback resulted in an unbalanced dropout of patients; however, we do not believe these differences in dropout were related to the allocated treatment. 13 of 16 patients deemed ineligible were initially allocated conventionally fractionated radiotherapy, which is the standard of care for radiotherapy in the Netherlands. Hypofractionated radiotherapy was only offered to trial participants; therefore, ineligible patients opting for radiotherapy would have received conventionally fractionated radiotherapy (39 fractions of 2.0 Gy).

The findings of the HYPRO trial show that hypofractionated radiotherapy with 19 fractions of 3.4 Gy cannot be regarded as the new standard of care for patients with intermediate-risk and high-risk prostate cancer. However, comparable relapse-free survival was noted with these treatments, differences in grade 2 or higher acute toxic effects between treatment groups had dissipated by 3 months after treatment, and no significant differences in grade 2 or higher late toxic effects were recorded (9,10). Baseline symptoms equal to grade 2 or higher RTOG-EORTC toxicity scores were the strongest baseline predictor of acute and late toxic effects (9,10). To avoid additional toxic effects, we believe that hypofractionation with 19 fractions of 3.4 Gy could be offered to patients with intermediate-risk and high-risk prostate cancer and few genitourinary and gastrointestinal baseline symptoms. Prospective validation is needed to support this statement. Updated results of the HYPRO trial with 7-year follow-up, and findings from other randomized trials (23,24), will further help define the role of hypofractionation in clinical practice.

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SUPPLEMENTARY FILES

Appendix Table 1. List of participating centers including local investigator and recruited number of patients

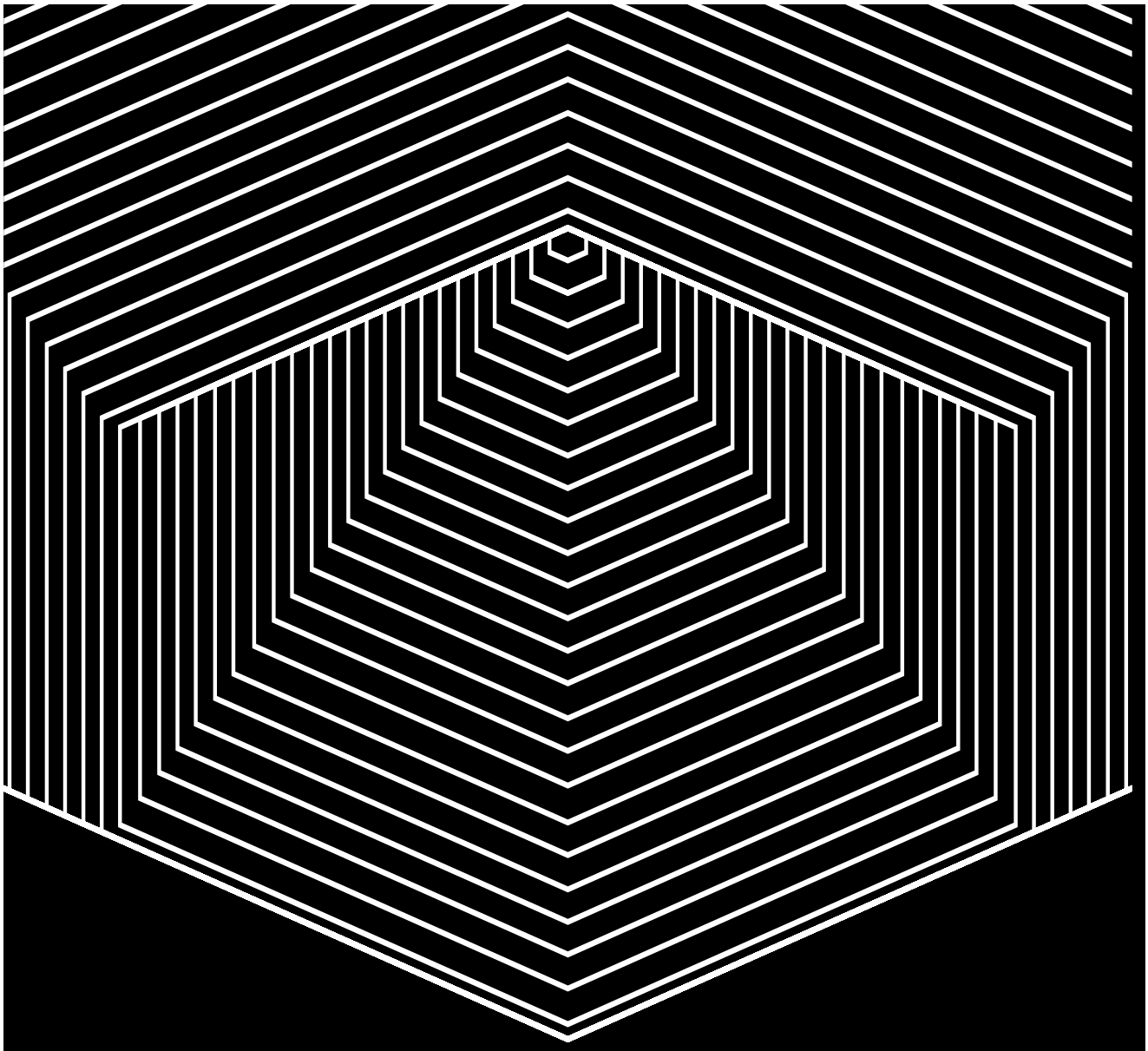
Site	Local Investigator	Recruited patients
Erasmus MC Cancer Institute, Rotterdam	Luca Incrocci	256
Netherlands Cancer Institute, Amsterdam	Floris Pos	199
Institute for Radiation Oncology, Arnhem	Erik Schimmel	101
Nijmegen University Medical Centre, Nijmegen	Emile van Lin	90
Leiden University Medical Centre, Leiden	Stijn Krol	81
Catharina Hospital, Eindhoven	Peter-Paul van der Toorn	50
Radiotherapy Centre West, The Hague	Hanja de Jager	43
		820 Total

Appendix Table 2. Test of proportional-hazards assumption

Time: Kaplan-Meier				
	Rho	Chi 2	Df	Prob >chi2
Arm	-0.12202	2.50	1	0.1142
Global test		2.50	1	0.1142

Appendix Table 3. Duration of androgen deprivation therapy per treatment arm

Duration (months)	Conventional Fractionation	Hypofractionation	Total
0	130	137	267
≤6	29	42	71
7-12	40	26	66
13-24	28	30	58
25-36	66	76	142
>36	94	84	178
Duration unknown	10	12	22
Total	397	407	804



“SOMETIMES, LESS IS MORE.”

William Shakespeare

CHAPTER

07

Hypofractionated radiotherapy in genitourinary cancer: Better with less

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ABSTRACT

Over the years most innovations in hypofractionated radiotherapy for malignancies of the genitourinary tract have involved treatment of prostate cancer, which will therefore be the focus of this chapter. The rationale for hypofractionated radiotherapy, contemporary treatment techniques, and results of clinical trials of hypofractionated external beam radiation therapy (EBRT) or stereotactic body radiation therapy (SBRT) will be discussed. Finally, the implications of clinical data on general practice and future directions of research will be discussed.

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, and the fifth leading cause of cancer-related death (1). Since the introduction of prostate specific antigen (PSA) testing in the 1980s, the incidence of prostate cancer has doubled. More than 1 million men were estimated to have been diagnosed with prostate cancer in 2012 (2). Most patients are diagnosed with localized disease and are therefore candidates for curative treatment (2). Patients with localized disease can be offered several treatment options including active surveillance and brachytherapy for selected patients, radical prostatectomy, and external beam radiation therapy (EBRT).

For several decades EBRT has been delivered in conventional fractions of 1.8-2.2 Gy at five consecutive days per week. Clinical trials have demonstrated that dose-escalated EBRT for prostate cancer up to overall treatment doses of 74-78 Gy significantly improves local control as compared to previous schedules of 64-70 Gy (3-5). These dose-escalated treatments are often associated with increased genitourinary and gastrointestinal toxicities (3-5), which limit the options for further dose-escalation using conventional 2-Gy fractions. Hypofractionated radiotherapy, in which fewer high-dose fractions are delivered, has the potential to increase the radiobiological dose to tumor.

In this chapter we will discuss the rationale for hypofractionated radiotherapy in prostate cancer treatment and the technological improvements over the past two decades which have enabled delivery of high dose conformal treatment plans with reduced dose to adjacent normal tissues. We will also provide an overview of the clinical data on hypofractionated radiotherapy. For this purpose, we have reviewed randomized phase III trials of moderately hypofractionated (fraction doses of 2.4-3.5 Gy) EBRT and prospective clinical data from studies of stereotactic body radiation therapy (SBRT) to deliver extreme hypofractionation treatments (fraction doses of 5-10 Gy). Based on these results, we will discuss the implications of hypofractionation in the general practice and future directions for clinical research.

Rationale for hypofractionated radiotherapy for the treatment of prostate cancer

The α/ß ratio is a radiobiological model used to express the sensitivity of tumor and normal tissues to changes in fractionation. After Brenner and Hall first (6) suggested a uniquely low α/ß ratio for prostate cancer of approximately 1.5, the interest in its radiobiology has considerably increased. Others have analyzed large clinical data sets and corroborated these earlier results (7,8).

Tumors with low α/ß ratios are generally resistant to low fraction doses, and therefore require larger radiation doses per fraction to improve tumor control. Normal tissues surrounding the

prostate are less sensitive to larger fraction doses due to suggested α/ß ratios between 4-6 Gy (9-11). The proposed low α/ß ratio of prostate cancer in relation to surrounding normal tissue demonstrates the potential benefit of hypofractionated radiotherapy as a means to improve clinical outcomes.

In general, two hypofractionation designs can be considered to exploit the hypothesized radiobiological advantages: 1) to achieve de-escalation of the normal tissue total dose while maintaining similar predicted tumor control, and 2) to achieve escalation of the radiobiological tumor dose while maintaining similar predicted late normal tissue effects (12). Hypofractionation schedules can be compared using the α/ß ratio and the Linear Quadratic (LQ) model, in which the dose to tumor and normal tissue applied in each scheme are calculated in conventional 2-Gy fractions (13). The LQ model, however, is subject to uncertainties, particularly with respect to the upper limit of fraction sizes for which it remains valid (12,14).

TREATMENT TECHNIQUES

External beam radiation therapy (EBRT)

The ability to deliver high-dose treatment fractions used for hypofractionated EBRT has been greatly improved after the introduction of intensity modulated radiotherapy (IMRT). This technique enables dose-escalation to tumors with irregular shapes using beams of non-uniform radiation intensity with improved sparing of normal tissue (15,16).

More recently, image-guided radiotherapy (IGRT) techniques that include implanted intraprostatic fiducial markers have been developed. Daily imaging using 2-dimensional portal images, 3-dimensional cone-beam computed tomography (CBCT), or 3-dimensional ultrasound localization allow for accurate prostate alignment before each fraction. IGRT techniques replaced previous protocols which were based on bony anatomy localization or skin marks matched to in-room lasers. As a result, the precision of radiotherapy has been further increased. Safety margins which are used to correct for variations in patient positioning, intra-fractional prostate motion, and inaccurate dose delivery can be safely reduced from approximately 1cm to a 5-mm margin using fiducials (17). EBRT using IMRT and image-guidance enables treatment planning with high conformity and steep dose gradients without compromising tumor coverage (18,19). Application of both techniques also significantly reduces the dose to adjacent organs at risk (OAR) and toxicity levels as compared to previous 3D-conformal radiotherapy (3D-CRT) techniques (15,16).

Stereotactic body radiation therapy (SBRT)

According to the American Society for Radiation Oncology (ASTRO), SBRT is precise EBRT which is designed to deliver very high radiation doses, using a single dose or typically up to five fractions (20). Cross-firing beams of ionizing radiation and image guidance are used to achieve high levels of treatment conformality and rapid dose fall-off.

In contrast to conventional EBRT, which is generally delivered via standard gantry-based linear accelerators (linacs), SBRT can be delivered by several platforms (Table 1). Gantry-based linacs can also deliver SBRT if daily image-guidance is available. For example, the Calypso® system (Varian Medical Systems, Palo Alto, USA) is used for SBRT to enable real-time prostate monitoring via implanted transponders (21). In case of prostate motion beyond user-defined thresholds, typically between 3-5mm, treatment is interrupted to enable patient repositioning.

Table 1. Treatment platforms

Platform	Treatment	Description	Image-guidance	Correction
Gantry-based Linac	SBRT, EBRT (3D-CRT, IMRT, VMAT)	Linac on gantry with multileaf collimator	Intra-prostatic fiducials, orthogonal X-rays, on-board CT	Prior to fraction
Calypso®	SBRT	Image-guidance for gantry-based Linac	Intra-prostatic transponders	Real-time, manual correction
CyberKnife®	SBRT	Non-coplanar beams delivered via Linac on robotic arm	Intra-prostatic fiducials, orthogonal X-rays	Real-time, automated correction
Tomotherapy ®	SBRT, EBRT	Linac with multileaf collimator in helical ring of CT scanner	On board CT	Prior to fraction

Table Abbrevations: CT= computed tomography, EBRT= external beam radiation therapy, IMRT= intensity modulated radiation therapy, Linac= linear accelerator, SBRT= stereotactic body radiation therapy, VMAT= volumetric arc therapy

Most prospective clinical data on SBRT are collected in studies using the Cyberknife® robotic radiosurgery system (Accuray, Sunnyvale, Ca. USA). Cyberknife treatment is delivered via a linear accelerator which is mounted on a robotic arm (22). Highly conformal dose distributions are delivered using multiple non-coplanar beams. Image-guidance is based on implanted fiducial markers and orthogonal kV imaging with user-defined intervals during dose delivery (23). Subsequent correction for intra-fraction prostate motion occurs by adjusting the position and orientation of the robotic manipulator or treatment couch (23).

HYPOFRACTIONATED EXTERNAL BEAM RADIOTHERAPY (EBRT)

Clinical studies

The first hypofractionated EBRT treatments were mainly carried out to improve efficiency and patient convenience, and were generally well tolerated (24-26). However, as these were non-randomized studies mainly conducted before prostate specific antigen (PSA) testing became routinely available, treatment efficacy was difficult to assess. The hypothesized high fraction sensitivity of prostate cancer has greatly increased clinical interest and ultimately led to the development of several randomized phase III clinical trials of moderate hypofractionation (2.4-3.4 Gy per fractions) (Table 2). In the following sections, clinical data, outcomes and implications of the eight phase III trials using moderately hypofractionated EBRT that have been published will be discussed.

Treatment planning

Most of the recent studies applied IMRT and image-guidance, whereas the earlier studies used 2D or 3D-conformal techniques (Table 2). CT images were used for tumor delineation and normal tissue contouring in six of eight studies (27-32), whereas magnetic resonance imaging (MRI)-based planning was introduced by Pollack and colleagues and Incrocci and colleagues (33,34). Two studies reported that all patients received treatment of the prostate only (28,32), whereas others also included the seminal vesicles in the target volumes. Expansion of the clinical target volume to yield the planning target volume was 10-15mm in studies using 2D or 3D-CRT techniques (27-29,31), and 5-10mm in most studies using IMRT and image-guidance (30,32-34). In some studies, safety margins were reduced with 4-7mm posteriorly to reduce the rectal dose (28,29,31,34).

Conventional treatment fractions were always delivered on five consecutive days (e.g. Monday-Friday). Most studies also applied hypofractionation schedules with five fractions weekly (Table 2). In the HYPRO trial (33) and the Arcangeli et al. (35) study, however, hypofractionated treatment was delivered at 3 and 4 days per week, respectively. For acute toxicity, overall treatment time is an important factor and excessive acute effects can be avoided by prolonging the duration of treatment.

Treatment efficacy

The first two trials published by Lukka et al. and Yeoh et al. were conducted before the era of dose-escalation (27,28) (Table 2). The prescribed treatment doses in both trials are well below current clinical doses, which might account for the low relapse-free survival (RFS) rates in both treatment arms. Two recently published randomized trials aimed to demonstrate superiority of a hypofractionated regimen compared to conventional with regard to RFS (33,34). The Dutch HYPRO trial randomized 820 intermediate to high risk patients to 39 fractions of 2 Gy (5

weekly fractions) or 19 fractions of 3.4 Gy (3 weekly fractions). This study was designed to test whether an increased dose of 12.4 Gy in 2-Gy fractions using hypofractionated EBRT would achieve a significant increase in RFS of 10% as compared to conventional treatment (33). At a median follow-up of 60 months no significant differences in RFS survival were achieved with RFS rates of 80% and 77% after hypofractionation and conventional fractionation (HR=0.86, 95% CI 0·63–1·16); p=0.36), respectively. In line with these results, Pollack and colleagues of the Fox Chase Cancer Center also could not demonstrate superiority of hypofractionation in 303 prostate cancer patients treated to 76 Gy in 2-Gy fractions or 26 fractions of 2.7 Gy (34). It was hypothesized that the overall increase in treatment dose of 8.4 Gy in 2-Gy fractions using hypofractionation would result in 15% reduction of biochemical failure. At a median follow-up of 68 months, 5-year RFS was 77% for hypofractionation and 79% for conventional fractionation (p=0.75). Both trials included a substantial proportion of patients receiving long-term androgen deprivation therapy (ADT) for at least 24 months, which might have had a substantial effect on RFS rates at follow-up. Additional follow-up could demonstrate whether the effects of androgen suppression on tumor recurrence has obscured the potential benefits of hypofractionated treatment.

The enormous advantages in terms of patient convenience and hospital logistics associated with hypofractionation justify non-inferiority study designs, which in this case are a more prudent method to demonstrate clinical benefits of hypofractionated treatment. The CHHiP trial randomized 3216 patients with intermediate or high risk prostate cancer to conventional fractionation of 74 Gy in 37 fractions or two hypofractionation schedules: 57 Gy in 19 fractions or 60 Gy in 20 fractions (30). Hypofractionated treatment using 60 Gy in 20 fractions was found non-inferior to conventional treatment with 5-year RFS rates of 88% and 91% after conventional and hypofractionated treatment, respectively. The RTOG 0415 trial by Lee et al. (32) also demonstrated non-inferiority of hypofractionated EBRT of 70 Gy in 28 fractions versus 73.8 Gy in 41 fractions. This study included 1115 patients with low-risk prostate cancer only and as such, complemented data from the CHHiP trial.

Whether low-risk patients are in fact the most clinically relevant study population with which to apply hypofractionation remains open to debate. Firstly, patients allocated hypofractionated EBRT in the RTOG 0415 trial received an increased radiobiological dose of 6.2 Gy in 2-Gy fractions (based on an α/β ratio of 1.5) as compared to those allocated conventional treatment (32). However, a previous Dutch dose-escalation trial (68 Gy vs. 78 Gy) demonstrated no effect of dose-escalation on disease control in patients with low-risk features (3). In addition, Arcangeli et al. (29, 35, 36) randomized 168 patients to 80 Gy in 40 fractions or hypofractionated treatment of 62 Gy in 20 fractions over a period of five weeks. Although no significant differences in RFS between both treatment arms were found, a benefit for hypofractionation (HR=0.09, 95% CI 0.03-0.31) was suggested only in patients with aggressive tumors (e.g. Gleason ≥ 4+3). Second

Table 2. Phase III studies of moderate hypofractionation for localized prostate cancer

Author	n	Patient population	Device & Technique	Regimen	BED Tumor (α/β= 1.5)	BED OAR (α/β=4-6)	ADT (months)
Incrocci et al (33,38,39)	820	Intermediate-high risk cT1b-T4 PSA ≤60	Linac IMRT xFiducials	39x 2Gy (Daily)	78 Gy	78Gy	66% (6-36m)
HYPRO Trial The Netherlands				19x 3.4Gy (3 Fr/ Wk)	90.4 Gy	75.9-79.6 Gy	
Dearnaley et al (30)	3216	Intermediate-high risk cT1b-T3a PSA ≤30	Linac IMRT 30% IGRT	37x 2Gy (Daily)	74Gy	74Gy	97% (3-6m)
CHHiP Trial United Kingdom				20x3Gy (Daily)	77.1 Gy	67.5-70 Gy	
				19x 3Gy (Daily)	73.1 Gy	64.1-66.5 Gy	
Lee et al (32)	1115	Low risk cT1b-T2c Gleason 2-6 PSA<10	Linac 3D-CRT/ IMRT Fiducials	41x 1.8 Gy (Daily)	73.8 Gy	73.8 Gy	0%
RTOG 0415 Trial USA				28x 2.5 Gy (Daily)	80 Gy	74.4-75.8 Gy	
Pollack et al (34, 37)	303	Intermediate-high risk cT1-T3 PSA ≤80	Linac IMRT	38x2Gy (Daily)	76 Gy	76 Gy	47% (≤4-24m)
Fox Chase USA				26x2.7Gy (Daily)	84.2 Gy	76.3-78.4 Gy	45% (≤4-24m)
Hoffman et al (31)	203	Low-intermediate risk cT1b-T3b PSA≤20	Linac IMRT Fiducials	42x 1.8Gy (Daily)	72.2 Gy	72.2 Gy	21% (4m)
MD Anderson USA				30x2.4Gy (Daily)	80.2 Gy	75.6-76.8 Gy	
Arcangeli et al (29,35,36)	168	High risk T1-T4 PSA ≤100	Linac 3D-CRT No IGRT	40x2Gy (Daily)	80 Gy	80 Gy	100% (9m)
Italy				20x3.1Gy (4 Fr/ Wk)	81.5 Gy	70.5-73.4 Gy	
Yeoh et al (27)	217	cT1-T2	Linac 2D/3D-CRT No IGRT	32x 2Gy (Daily)	64 Gy	64 Gy	0%
Australia				20x 2.75 Gy (Daily)	66.8 Gy	60.2-61.9 Gy	
Lukka et al (28)	936	cT1-T2 PSA≤40	Linac 3D-CRT No IGRT	33x 2Gy (Daily)	66 Gy	66 Gy	0%
Canada				20x 2.625 Gy (Daily)	61.8 Gy	56.6-58.0 Gy	

Table Abbreviations: α/β = alpha/beta ratio, ADT= androgen deprivation therapy, BED= biologically equivalent dose (in 2-Gy fractions), CTCAE= Common Terminology Criteria for Adverse Events, EORTC= European Organization for Research and Treatment of Cancer, Fr=fractions, FU= Follow-up, G2+ grade 2 or worse, G3+= grade 3 or worse, G4= grade 4, IGRT= Image-guided radiotherapy, IMRT=Intensity

FU (months)	RFS	Acute Toxicity Bladder	Acute Toxicity Bowel	Late Toxicity Bladder	Late Toxicity Bowel
60	5-y bcRFS: 77%	RTOG-EORTC G2+ 58% 1x (<1%) G4	RTOG-EORTC G2+ 31%	RTOG-EORTC 3-y G2+ 39% 3x (<1%) G4	RTOG-EORTC 3-y G2+ 18%
	80% (NS)	61% (NS) 1x (<1%) G4	42% (p=0.002)	41% (NS) 2x (<1%) G4	22% (NS)
62	5-y bcRFS 88%	RTOG G2+ 46%	RTOG G2+ 25%	RTOG 5-y G2+ 9%	RTOG 5-y G2+ 14%
	91% (NS)	49% (NS)	38% (p<0.001)	12% (NS)	12% (NS)
	86% (NS)	46% (NS)	38% (p<0.001)	7% (NS)	11% (NS)
70	5-y bcRFS 85%	CTCAE G2+ 27%	CTCAE G2+ 10%	CTCAE G2+ 23% 1x G4 (<1%)	CTCAE G2+ 14% 1x G4 (<1%)
	86% (NS)	27% (NS)	11% (NS)	30% (G2 p=.009)	22% (G2: p=0.005)
68	5-y bcRFS 79%	LENT/RTOG G2+ 56%*	LENT/RTOG G2+ 8%*	LENT/RTOG 5-y G2+ 13%	LENT/RTOG 5-y G2+ #9%
	77% (NS)	48% (NS)	18% (NS)	22% (NS)	# 9% (NS)
75	5-y bRFS 92%	Not reported	Not reported	RTOG 5-y G2+ 17%	RTOG 5-y G2+ 5%
	96% (NS)			16% (NS)	10% (NS)
70	5-y bRFS 79%	G2+ 40%	G2+ 21%	3-y G2+ 11%	3-y G2+ 14%
	85% (NS)	47% (NS)	35% (NS)	16% (NS) 1x (1%) G4	17% (NS)
90	7.5-y bRFS 34%	Not reported	Not reported	LENT-SOMA (NS)	LENT-SOMA (NS)
	53% (p<0.05)				
68	5-y bcRFS 47%	NCIC G3+ 5%	NCIC G3+ 3%	NCIC G3+ 2%	NCIC G3+ 1%
	40%	9%	4%	2% (NS)	1% (NS)

Modulated Radiotherapy, NCIC= National Cancer Institute of Canada, NS= not significant, OAR= organs at risk, PSA= prostate specific antigen, RFS= relapse-free survival, SV= seminal vesicle, 3D-CRT= 3D conformal radiotherapy.

Table Legend: *Based on preliminary acute toxicity data (37), # estimated

and most important, many patients with low-risk features are candidates for active surveillance and may not need any curative treatment at all. Nonetheless, for those patients with low-risk prostate cancer patients who do prefer curative treatment hypofractionation is a good option.

Radiation-induced toxicity

Toxicity was scored using the Radiation Therapy Oncology Group (RTOG) criteria, European Organization for Research and Treatment of Cancer (EORTC) criteria, the Common Terminology Criteria for Adverse Events (CTCAE), National Cancer Institute of Canada (NCIC) scoring criteria, or Late Effects of Normal Tissues/ Subjective, Objective, Management, Analytic (LENT/SOMA) criteria (Table 2).

Normal tissues were estimated to receive a similar or lower biologically equivalent dose (BED) in 2-Gy fractions with hypofractionated treatments as compared to the conventional treatments. In practice, however, reported grade 2 or worse acute bowel toxicities in several studies were substantially higher using hypofractionated regimens (30,34,36-38). There was significantly more grade 2 or worse bowel toxicity in the CHHiP trial and the HYPRO trial (30,38). In both trials, however, the observed differences in bowel toxicity between arms had dissipated by 3-4 months after completion of treatment (30,38). Interestingly, the CHHiP trial reported that acute toxicity peaked sooner in the hypofractionated schedules than in the control, at 4-5 weeks compared with 7-8 weeks (30). In contrast to bowel toxicity, all trials reported comparable acute bladder toxicities between treatments schemes.

In terms of late toxicity, results of the RTOG 0415 trial demonstrated significantly increased grade 2 bowel (HR= 1.59, 95% CI 1.22-2.06) and bladder toxicity (HR=1.31, 95% CI 1.07-1.61) in 1115 patients treated with hypofractionated EBRT (28 fractions of 2.5 Gy) as compared to conventional treatment (41 fractions of 1.8 Gy) (32). Results of the HYPRO trial could not demonstrate the postulated non-inferiority of hypofractionation (39). In fact, a significantly increased cumulative incidence of grade 3 or worse bladder toxicity was found after hypofractionation (19% vs. 13% respectively; p=0.021). The risk of grade 3 nocturia (≥6 /night) was significantly higher in patients allocated to hypofractionation (HR=4.94, 95% CI 1.87-13.09) (39). Both the HYPRO trial (39) as well as the Pollack et al. (34) study concluded that men with compromised urinary function at baseline were at risk of late bladder toxicity. Specifically, Pollack et al. (34) reported that patients with a baseline International Prostate Symptom Score (IPSS) >12 who receive hypofractionation were significantly associated with increased risk of late grade 2 or worse toxicity.

Sexual function

In contrast to radiation-induced bowel and bladder toxicity, sexual function has remained largely unaddressed in these trials. A sub-study of the CHHiP trial of 2100 men addressed

sexual function and quality-of-life domains assessed with the UCLA-Prostate Cancer Index (UCLA-PCI) and the Expanded Prostate cancer Index Composite (EPIC) questionnaires (40). Most patients used short-term ADT for 3-6 months. At 24 months no significant differences were found between treatment arms. Dearnaley et al. (30) also found no significant differences in sexual bother at a 5-year follow-up, and the proportion of LENT-SOM grade 2 or worse sexual toxicity was similar across treatment groups. Results from the Dutch HYPRO trial showed no significant differences in erectile functioning between both treatment arms in patients who received no or short-term ADT (41).

Clinical implications

We have sufficient evidence in the current literature supporting non-inferiority of moderately hypofractionated EBRT as compared to conventional treatments. However, the HYPRO trial as well as the Pollack and colleagues trial, that were both designed to demonstrate superiority of hypofractionation in terms of RFS have failed to do so (33,34). Based on these trials one might question the validity of the LQ model and the commonly suggested α/β ratio.

Figure 1 shows the calculated BED in 2-Gy fractions with corresponding control rates per treatment arm as reported by phase III studies applying overall treatment doses larger than 70 Gy. Treatment arms within each study are connected, demonstrating that the BED 2-Gy is higher in the hypofractionation arm of all studies. In four studies the BED 2-Gy was substantially increased with 6-12 Gy using hypofractionated treatment, with no substantial benefits in terms of RFS (31-34,42). Meta-analyses including all recently published data could establish whether the currently applied α/β ratio for prostate cancer of 1.5 might, in fact, be higher.

As most of the recent trials reported increased acute (30,38) or late toxicities (32,39) with hypofractionation, it remains questionable whether hypofractionated regimens will become common clinical practice given the absence of improved treatment efficacy. Dearnaley et al. (30) of the CHHiP trial however, concluded that their hypofractionated regimen of 60 Gy in 3-Gy fractions should be considered as new standard of care for EBRT of localized prostate cancer. Incrocci et al. (33) reported that the HYPRO treatment schedule of 19 fractions of 3.4 Gy can be offered to intermediate-high risk patients with few bowel and bladder symptoms at baseline, whereas Lee et al. (32) believe the RTOG 0415 hypofractionation schedule of 70 Gy in 28 fractions can be prescribed in men with low-risk disease who opt for curative treatment, although an increase in late adverse events might be expected. In this setting, patient selection is paramount to safely deliver hypofractionated EBRT. The integration of hypofractionated treatment schemes in clinical practice together with prolonged follow-up of these phase III trials will help in clarifying the role of hypofractionation for prostate cancer in the near future.

Figure 1. Relapse-free survival rates per treatment arm in relation to biologically equivalent doses in 2-Gy fractions of phase III hypofractionation trials applying treatment doses >70 Gy.

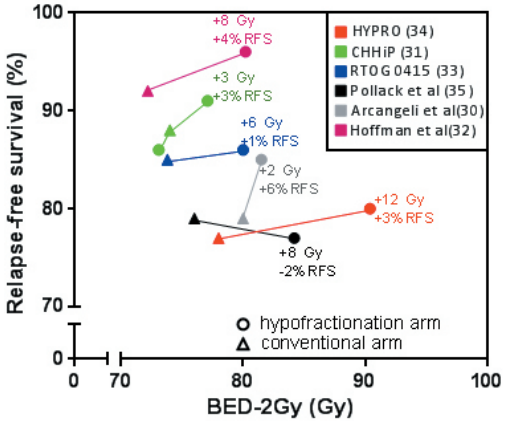

Figure Legend: Conventional treatment arm (triangular shape) is connected with hypofractionation arm (round shape) within each study to demonstrate differences in biologically equivalent dose in 2-Gy fractions (BED-2Gy) and relapse-free survival rates (RFS). The differences in BED-2Gy and RFS between treatment arms are summarized for each study.

STEREOTACTIC BODY RADIATION THERAPY (SBRT)

Clinical studies

SBRT treatment schedules applying extreme fraction doses of 5-10 Gy have not been randomized and compared with other standard of care treatment modalities. At this point, prospectively collected data are only available from case series and single arm phase I/II studies (Table 3).

Treatment planning

In five studies the Cyberknife® system was used to administer 35-51 Gy in 4-7 fractions, either delivered daily or on alternate days (43-47) (Table 3). Aluwini et al. (43) treated 50 patients with the Cyberknife® up to 38 Gy in 4 daily fractions and applied an integrated boost to 11 Gy per fraction to the dominant lesion if visible on MRI.

Others used standard Linacs with daily image-guidance for 5 weekly fractions of 7 Gy (48) or 9 weekly fractions of 5 Gy (49). Mantz (21) used Varian Trilogy/Truebeam® (Varian, Sunnyvale, Ca. USA) Linacs with the Calypso® System for real-time tumor localization, whereas the Tomotherapy® (Sunnyvale, Ca. USA) ring gantry accelerator was used by Kim et al. (50).

Most of the studies (5 out of 9, 56%) used CT images fused with prostate MRI for accurate delineation (43-46,50), whereas others used CT imaging only. In two studies the clinical target volume consisted of the prostate with or without the seminal vesicles (44,45), the remaining studies treated the prostate only. Safety margins of 2-5mm were added to the clinical target volume to yield the planning target volume. In the phase II study of Zimmerman and colleagues however, 3D-CRT was used and larger safety margins of 1-1.5cm were applied in all directions except posteriorly (0.5-1.0cm) (49).

Treatment efficacy

The BED in 2-Gy fractions of all treatment schedules exceeded 80 Gy, hypothetically offering a therapeutic benefit over most currently applied conventional treatment schemes. With follow-up ranging between 23-83 months, relapse-free survival rates exceeded 90% in low to intermediate risk patients. It should be noted that only two studies included a small proportion of high-risk patients, ranging from 7% (46) to 17% (44) of their respective patient populations. Benign PSA bounces with subsequent normalization occurred in 12-70% and after a median follow-up of 12-24 months (21,43-45,48,49). The currently available efficacy data are difficult to use comparatively; however, the control rates are comparable to those reported in patients treated with high-dose conventional EBRT (51).

Radiation-induced toxicity

The assessment of radiation-induced toxicities is a key factor in current reports on SBRT, as most patients had low or intermediate risk disease and can expect disease control regardless of treatment modality. Late grade 2 or worse bladder toxicity ranged between 4-31%, and bowel toxicity was reported in 1-30% of patients (Table 3). RTOG, CTCAE and EORTC scoring criteria were used to report toxicity.

Of the studies using gantry-based Linacs for delivery, Kim et al. (50) treated 91 patients up to 45-60 Gy in 5 fractions. With fraction sizes up to 10 Gy, they applied the most extreme hypo-fractionation schedule. Some patients were treated without intra-fraction image-guidance as they had implanted fiducial markers, whereas others had Calypso based real-time monitoring. Five patients out of 91; all five treated to 50 Gy (5%), required a diverting colostomy due to severe rectal toxicity or fistulation (50). A strong correlation between high-grade rectal toxicity and dose to rectal wall volume was found. Loblaw and colleagues (48) treated 84 patients to 35 Gy in 5 weekly fractions with IMRT and fiducial based image-guidance. After a median follow-up of 55 months, grade 2 or worse toxicity scores of 5% and 8% were found for bladder and bowel complaints, respectively. One patient developed a grade 4 fistula-in-ano requiring surgery. Somewhat higher toxicity scores were reported by Zimmermann and colleagues, who treated 80 patients with image-guided 3D-CRT (49). Grade 2 or worse bowel and bladder toxicity ranged between 30-31%, and one patient developed hemorrhagic cystitis requiring cystectomy.

Table 3. Prospective studies of extreme hypofractionation with at least 50 localized prostate cancer patients

Author	n	Patient population	Device & Technique	Regimen	BED Tumor (α/β= 1.5)	BED OAR (α/β=4-6)	ADT (months)
Aluwini et al (43)	50	Low-intermediate risk T1-T3a, PSA<20 Gleason 6-7	Cyberknife Fiducials	4x 9.5 Gy (daily)	119 Gy	74- 86 Gy	0%
Bolzicco et al (44)	100	Low-high risk T1-T2c Gleason 4-10	Cyberknife Fiducials	5x 7 Gy	85 Gy	57- 64 Gy	7% (3-36)
Fuller et al (45)	79	Low-intemediate risk T1-T2 Gleason 5-7	Cyberknife Fiducials	4x 9.5 Gy (daily)	119 Gy	74-86 Gy	0%
Katz et al (46)	515	Low-high risk T1a-T2a, PSA<20 Gleason 6-9	Cyberknife Fiducials	5x 7/7.25 Gy (daily)	85-91 Gy	57-68 Gy	14%
Kim et al (50)	91	Low-intermediate risk T1-T2b Gleason 2-7, PSA<20	IMRT/ Tomo Fiducials/ Calypso	5x 9/9.5/10 Gy (alternate days)	135-164 Gy	84-117 Gy	18%
King et al (47)	67	Low risk T1c-T2b, PSA<10 Gleason 6-7	Cyberknife Fiducials	7x 7.25 Gy (daily or alternate)	91 Gy	60-68 Gy	0%
Loblaw et al (48)	84	Low risk T1-T2b	IMRT Fiducials	5x 7 Gy (weekly)	85-91 Gy	57-68 Gy	0%
Mantz (21)	102	Low risk T1c-T2a, PSA <10, Gleason 6-7	Trilogy/ TrueBeam Calypso	5x 8 Gy (alternate days)	109 Gy	70-80 Gy	0%
Zimmermann et al (49)	80	Low risk T1a-T2a PSA≤10, Gleason ≤6	3D-CRT Fiducials/ ultra-sound	9x 5 Gy (weekly)	84 Gy	62-68 Gy	0%

Table Abbreviations: α/β = alpha/beta ratio, ADT= androgen deprivation therapy, BED= biologically equivalent dose (in 2-Gy fractions), EORTC= European Organization for Research and Treatment of Cancer, Fr=fractions, FU= Follow-up, G2+ grade 2 or higher, G3+= grade 3 or higher, IGRT= Image-

	FU (months)	RFS	Acute Toxicity Bladder	Acute Toxicity Bowel	Late Toxicity Bladder	Late Toxicity Bowel
	23	2-y bcRFS 100%	RTOG-EORTC G2+ 23%	RTOG-EORTC G2+ 14%	RTOG-EORTC 2-y G2+ 16%	RTOG-EORTC 2-y G2+ 3%
	36	3-y bcRFS 94%	RTOG G2+ 12%	RTOG G2+ 18%	RTOG G2+ 4%	RTOG G2+ 1%
	NR	5-y bRFS 98% low risk 92% intermediate	CTCAE G2+ 10%	CTCAE G2+ 0%	CTCAE G2+ 15%	CTCAE G2+ 1%
	72	7-y bRFS 96% Low risk 90% Intermediate 69% High	RTOG G2+ 4%	RTOG G2+ 4%	RTOG G2+ 9% (overall) 6% (5x 7 Gy) 12% (5x 7.25 Gy)	RTOG 2+ 4% (overall) 3% (5x 7 Gy) 5% (5x 7.25 Gy)
	25	NR	CTCAE G2+ 22%	CTCAE G2+ 21%	CTCAE G2+ 13%	CTCAE 2+ 29% 5x (5%) colostomy (G4)
	32	4-y bRFS 94%	NR	NR	RTOG G2+ 8%	RTOG G2+ 2%
	55	5y bRFS 98%	CTCAE G2+ 20%	CTCAE G2+ 10%	RTOG G2+ 5%	RTOG G2+ 8% 1x (1%) fistula (G4)
	>60	5-y bRFS 100%	NR	NR	NR	NR
	83	5-y bRFS 96%	RTOG G2+ 36%	RTOG G2+ 14%	RTOG G2+ 31% 1x (1%) cystectomy (G4)	RTOG G2+ 30%

guided radiotherapy, IMRT=Intensity Modulated Radiotherapy, NS= not significant, OAR= organs at risk, PSA= prostate specific antigen, RFS= relapse-free survival, SV= seminal vesicle, 3D-CRT= 3D conformal radiotherapy

In studies applying Cyberknife® RRS, both acute and late toxicity were predominated by bladder complaints. Late grade 2 or worse toxicities ranged between 4-16% for bladder and between 2-5% for bowel (43-47). The largest series reported on by Katz and colleagues consisted of 515 patients treated to 35 Gy in 5 fractions. After a median follow-up of 72 months, grade 2 or worse bladder and bowel toxicity was 9% and 4%, respectively (46). These toxicity scores are encouraging; however, one should keep in mind that these data come from non-randomized studies.

Sexual function

Most studies reporting on sexual function used the EPIC questionnaire (21,46,49), whereas others used the EORTC Quality-of-Life PR25 questionnaire (43) or the International Index of Erectile Function (IIEF) questionnaire (45). Studies reporting on sexual function found a decrease in sexual function during the first 12 months post-treatment, with subsequent stabilization (21,43,45,46,49). Fuller et al. (45) and Katz et al. (46) reported that 65-67% of the initially potent patients remained potent at last follow-up.

Clinical implications

Current clinical data provide excellent short-term control rates for SBRT; toxicity induced by extreme hypofractionation schedules does not appear to be substantially higher as compared to conventional treatments (51-54). Severe toxicity (grade 4) might occur somewhat more frequently compared to conventional treatments, especially after dose delivery using gantry-based Linacs (48,50). We are eagerly awaiting long-term follow-up from current studies of extreme hypofractionation.

The ongoing phase III PACE trial (NCT01584258) addresses the need for randomized comparison with other treatment modalities and aims to randomly allocate more than 1700 hormone-naïve men with low or intermediate risk cancer between SBRT of 36.25 Gy in 5 fractions and laparoscopic prostatectomy (55). If patients are unsuitable for or do not wish to undergo surgery, they are randomized between SBRT and conventional IMRT of 78 Gy in 39 fractions. Until comparative phase III studies have been completed, extremely hypofractionated SBRT can best be offered in the setting of prospective clinical studies.

FUTURE DIRECTIONS

Treatment schedule

The concept of hypofractionated radiotherapy has such clear-cut advantages in terms of cost- and timesaving that future research activities will continue to focus on novel and even more

extreme SBRT treatment schemes. The optimal schedule has yet to be determined, since SBRT treatment fractions are now either delivered daily, on alternate days, or weekly (Table 3). The phase II PATRIOT trial (NCT01423474) aims to investigate the effects on bowel Quality-of-Life after SBRT to 40 Gy in 5 fractions delivered in 11 vs. 29 days. A similar phase II study from Switzerland (NCT01764646) randomizes patients between SBRT to 36.25 Gy in 5 fractions delivered either on alternate days or during weekly fractions. The primary endpoints are acute and late toxicity. These studies will help determine the safety of hypofractionation.

Hypofractionated boost

The introduction of magnetic resonance imaging (MRI) for contouring has also provided new options for focal treatment of macroscopic tumor. The Dutch phase III FLAME trial (NCT01168479) which has completed accrual of 567 intermediate or high risk patients, randomized between conventional EBRT of 77 Gy in 35 fractions with or without a high-dose boost to 95 Gy in fractions of 2.7 Gy to the MRI-defined macroscopic tumor (56). The phase II hypo-FLAME study (NCT02853110) investigates whether SBRT of 35 Gy in 5 weekly fractions and an additional integrated focal boost of 50 Gy to the MRI-defined tumor volume is feasible and associated with acceptable toxicity (57). Weekly MRIs will be performed as a preparation for MRI-guided treatments using novel MRI-Linacs. This technique can potentially better define soft tissue changes as result of rectum and bladder filling than currently available image-guidance techniques, and could therefore play an important role in future hypofractionated treatments.

Treatment technique

The reliance on imaging, position verification and treatment technology will continue to increase if fraction doses are increased, and more patients with high risk disease will be treated. The first experiences with fraction doses up to 10 Gy delivered by gantry-based Linacs demonstrated that severe grade 4 toxicities might occur in up to 5% (50). Novel dose-escalation studies might require Cyberknife® treatment, which has been shown to deliver treatment doses with sub-millimeter precision (58), and enables safety margins as low as 2mm.

Cyberknife® dose-escalation studies will continue to occur in order to explore which treatment doses can safely be prescribed; however, gantry-based Linacs are widely more available. Developing evidence using such techniques should be continued and might even impact clinical practice to a larger extent. The Swedish phase III HYPO-RT-PC trial (ISRCTN45905321) accrued 592 intermediate risk prostate cancer patients between conventional treatment of 78 Gy in 39 fractions or 7 fractions of 6.1 Gy up to 42.7 Gy (55,59). Both treatments are delivered using 3D-CRT or IMRT with daily fiducial-based image guidance. The primary endpoint is 5-year RFS.

Androgen deprivation therapy (ADT)

Randomized trials have demonstrated that addition of ADT significantly improves RFS or overall survival in intermediate or high risk prostate cancer patients treated by EBRT (60-62). ADT is therefore generally added to EBRT in these patients. However, radiation treatment doses on which these results are based vary between 66-78 Gy (60-62), and are therefore well below radiobiological doses as applied in some hypofractionated treatments. Further dose-escalation using SBRT might obviate ADT in selected patient populations, reducing ADT-related severe side effects including metabolic complications (63), erectile dysfunction (64), and increased risk of cardiovascular events (65). To date, only Katz et al. (46) analyzed the impact of addition of ADT to SBRT on biochemical RFS among a subgroup of 97 high-risk patients included in their prospective trial. No significant benefit of ADT was found (66), however novel studies designed to specifically address these questions are warranted.

CONCLUSIONS

Sufficient evidence is available supporting the non-inferiority of moderately hypofractionated EBRT for localized prostate cancer patients. However, these hypofractionated treatments are often associated with increased toxicities, but do offer logistic convenience and increase hospital capacity. Novel SBRT schedules, which should offer more therapeutic gain based on radiobiological models, yield excellent early control rates in low to intermediate risk groups. Long-term follow-up and results of comparative trials are needed before SBRT can be generally recommended in clinical practice. Future research will focus on identifying optimal treatment doses and schedules to improve disease control and reduce radiation-induced toxicity. Novel treatment techniques and imaging modalities will enable us to continue improving treatment delivery and conformality. Future research and improvements might also obviate the need for ADT in selected patients.

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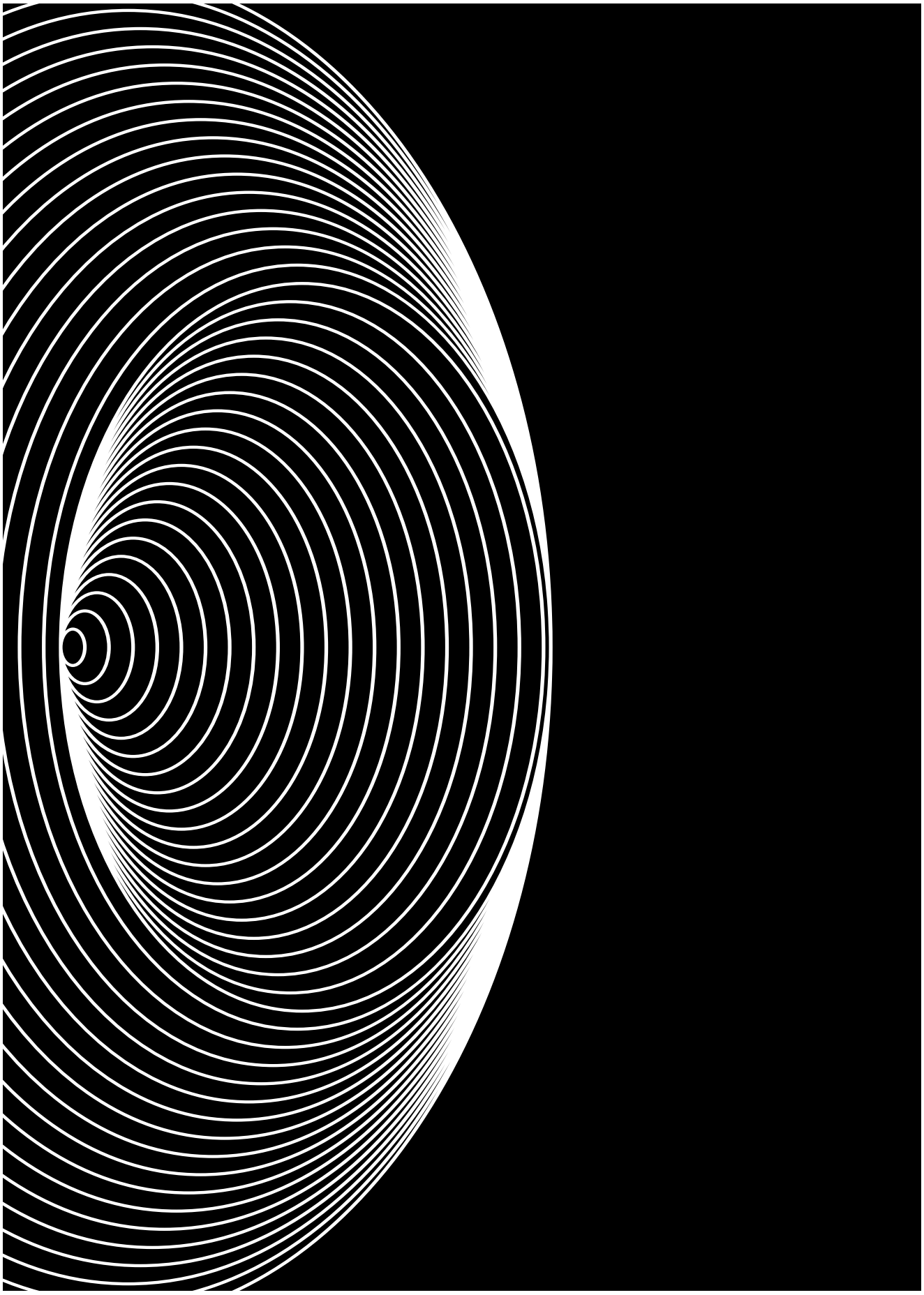
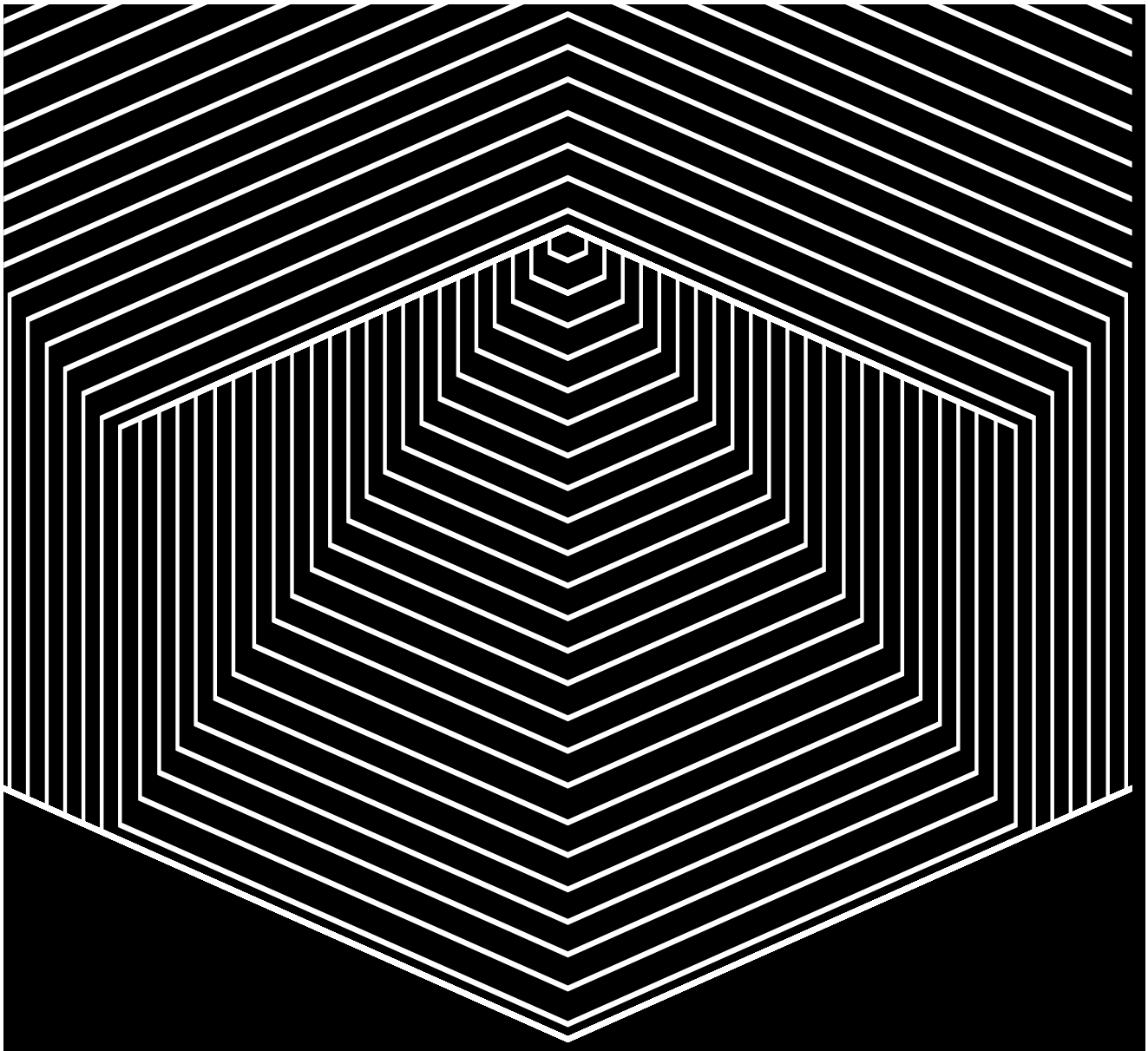


PART III

Quality of life and sexual function



“THE GREAT CHALLENGE OF ADULTHOOD IS HOLDING ON TO YOUR IDEALISM AFTER YOU LOSE YOUR INNOCENCE.”

Bruce Springsteen

CHAPTER 09

Sexual function after hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: results from the randomized phase 3 HYPRO trial

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ABSTRACT

Introduction

Hypofractionated radiotherapy could increase the radiobiological tumor dose for localized prostate cancer. The effects of hypofractionation on sexual function are not well-known.

Aim

To compare sexual function in prostate cancer patients treated to 78 Gy in 39 fractions vs 64.6 Gy in 19 fractions of 3.4 Gy.

Methods

820 men with intermediate-high risk T1b-T4NX-0MX-0 prostate cancer were enrolled in the phase III HYPRO trial (2007-2010) and randomized between conventional fractionation (39x 2 Gy) or hypofractionation (19x 3.4 Gy). Sexual function was assessed at baseline, at six, 12, 24 and 36 months after treatment using the International Index of Erectile Function (IIEF). For this analysis, we included patients (n=322) with a baseline assessment, ≥1 follow-up assessment, and no or short-term (6 months) androgen-deprivation therapy (ADT).

Main outcome measures

Mean IIEF domain scores were compared between treatments among the total population and hormone-naïve population (n=197) using the independent t-test. Incidences of severe erectile dysfunction (ED) (domain score <11) at last follow-up were calculated in patients with partial or full baseline function. Binary logistic regression analyses were applied to calculate the odds ratio (OR) of hypofractionation vs conventional fractionation and to adjust for clinical factors.

Results

Median age was 71 (interquartile range 67-71) and median follow-up was 37 months (interquartile range 25-38). ADT was prescribed in 125 (39%). IIEF domain scores decreased after treatment but were comparable between treatment arms at baseline and during follow-up. Orgasmic function scores in hormone-naïve patients were significantly higher at three years after hypofractionation (4.08 vs. 2.65, p=0.031). Among patients (n=120) with partial or full baseline erectile function, incidences of ED at last follow-up were 34.4% for hypofractionation vs 39.3% for conventional treatment (adjusted OR=0.84, 95% CI 0.37-1.90, p=0.67).

Conclusion

No significant differences in erectile functioning between conventional and hypofractionated radiotherapy were found. Hormone-naïve patients reported significantly higher orgasmic function scores at three years after hypofractionation.

INTRODUCTION

Dose-escalated external beam radiotherapy (EBRT) significantly improved relapse-free survival in patients with localized prostate cancer (1-3). Further dose-escalation using conventional fractionation is restricted due to associated increase in gastrointestinal and genitourinary toxicity rates (2-4).

Other methods to increase the radiobiological tumor dose include application of hypofractionated radiotherapy, in which fewer high-dose fractions are delivered. The rationale for hypofractionation is based on reports suggesting a lower α/ß ratio for prostate cancer as compared to surrounding normal tissues (5,6). In radiotherapy, the α/ß ratio can be used to measure the sensitivity to changes in fractionation. A low α/ß ratio for prostate cancer implies that a larger dose of radiation per fraction can improve tumor control, while the surrounding normal tissues with higher α/ß ratios are less sensitive to the increased fraction dose and similar toxicity levels can thus be maintained. The radiobiological tumor dose of hypofractionated treatment schedules can be calculated and compared to conventional treatment schedules of 2-Gy fractions using the Linear Quadratic model (7). Using hypofractionated treatment with fewer fractions not only offers possibilities to increase the tumor dose, patient convenience and hospital resources can also be improved, whereas health care costs can possibly be reduced.

Between 2007 and 2010, we conducted the randomized multicenter phase III HYPRO trial in The Netherlands to investigate whether hypofractionated EBRT (19x 3.4 Gy) improves relapse-free survival without increasing toxicity compared to conventionally fractionated (39x 2 Gy) treatment. We recently reported the final efficacy results from the HYPRO trial, demonstrating comparable 5-year relapse-free survival rates of 80.5% for patients assigned hypofractionation versus 77.1% for patients assigned conventionally fractionated radiotherapy (8). The hypothesized non-inferiority with respect to acute and late toxicity could not be demonstrated (9,10). The phase III CHHiP trial recently demonstrated non-inferiority of hypofractionated treatment of 60 Gy in 20 fractions as compared to conventional treatment using 74 Gy in 37 fractions (11). Based on these results Dearnaley and colleagues recommended hypofractionated treatment of 20x 3Gy as a new standard of care for EBRT of localized prostate cancer (11).

According to Sanda and colleagues (12), the quality of life related to sexual function in prostate cancer patients is significantly associated with treatment satisfaction and should therefore not be neglected. Despite several hypofractionation trials that have been conducted, the impact of dose-escalated hypofractionated EBRT on sexual function is not yet clearly defined (13-17). Dose-escalation using conventional fractionation increased the likelihood of erectile dysfunction (ED) according to Zelefsky and colleagues (18). In contrast, van der Wielen et al.

found comparable sexual function outcomes between patients treated to 68 Gy or 78 Gy in a dose-escalation trial (19).

In the HYPRO trial sexual function was assessed using the International Index of Erectile Function (IIEF) (20). Here, we report the results on sexual function.

MATERIALS AND METHODS

Study design and participants

We conducted the open-label, phase III HYPRO trial in 2x 410 patients to demonstrate a 10% increase in relapse-free survival after hypofractionated radiotherapy (19 fractions of 3.4 Gy) as compared to conventional fractionated treatment (39 fractions of 2 Gy) (9,10). The study was designed to also demonstrate non-inferiority of hypofractionation with respect to the cumulative incidence of grade ≥2 acute and late gastrointestinal and genitourinary toxicity according to Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria (9). We recruited patients with intermediate- or high-risk stage T1b-T4 NX-0MX-0 prostate cancer, an initial prostate specific antigen (PSA) concentration ≤ 60 μg/L and a WHO performance status of 0-2 (9). Criteria for exclusion were previous radical prostatectomy or pelvic radiotherapy, evidence of pelvic nodal disease (assessed with pelvic computed tomography scan) or distant metastases (assessed by bone scintigraphy), and low-risk disease (stage T1b-T2a and Gleason score ≤6, and PSA concentration <10 μg/L) (9,21). Every center applied its own protocol for prescription of androgen-deprivation therapy (ADT), which was equal for both treatment arms.

For the current analysis we only included patients who returned a baseline assessment of sexual function including at least the completed erectile function domain, and a minimum of one follow-up assessment. To minimize the effects of androgen suppression on long-term sexual function, for the current analysis we only included patients with no or with short-term ADT (6 months) (22,23). We therefore excluded all patients with long-term ADT (>6 months). No patients specifically reported the use of phosphodiesterase type 5-inhibitors (PDE-5is) at baseline, but prescription of a PDE-5i during follow-up was allowed.

This trial was coordinated and managed by the Department of Radiation Oncology and Clinical Trials Center at Erasmus MC, the Netherlands. The trial was approved by the medical ethics committee of Erasmus MC, and registered at www.controlled-trials.com (ISRCTN85138529). All patients provided written informed consent.

Randomization and masking

This phase III trial was done at seven radiotherapy centers in The Netherlands. We randomly assigned patients (in a 1:1 ratio) to conventional fractionation of 78.0 Gy or hypofractionation of 64.6 Gy, applying a minimization procedure (9,10). Independent randomization using a web-based application was done by the Clinical Trials Center (Erasmus MC Rotterdam). We used biased coin randomization to ensure overall balance and balance within each stratum of the applied stratification factors (i.e. risk group and treatment center) (9,10,21). Notification of the assigned treatment group was sent to local investigators via e-mail or fax immediately after randomization.

Radiotherapy

For patients assigned conventional fractionation, we administered 78.0 Gy in 39 fractions of 2.0 Gy over eight weeks (five fractions per week) (9). For patients allocated hypofractionated treatment, we administered 64.6 Gy in 19 fractions of 3.4 Gy over 6.5 weeks (9). To avoid excessive acute toxic effects, we delivered hypofractionated radiotherapy in three fractions weekly. Considering an α/ß ratio for prostate cancer of 1.5 Gy (6,24), the equivalent total dose in 2 Gy fractions was 78.0 Gy for conventional fractionation and 90.4 Gy for hypofractionation. The clinical target volume consisted of the prostate with or without seminal vesicles (SVs) (9). Based on the risk of SV involvement (25), we defined three SV dose groups. In group 1 (risk <10%) no dose was prescribed to the SVs. Patients in dose group 2 (risk 10-25%) received a reduced SV dose. As for the conventional arm, this was realized either by using a simultaneously integrated boost (SIB) technique delivering 39 fractions of 1.85 Gy to the SVs and 39x 2 Gy to the prostate, or by prescription of 34 fractions of 2 Gy to the prostate-plus-SVs and a boost of 5x2 Gy to the prostate only (sequential boost). In the hypofractionation arm, the SVs were treated with 19 fractions of 3.04 Gy (SIB) or 16 fractions of 3.4 Gy (sequential boost). In group 3 (risk >25%) the SVs were treated up to the prescribed dose of 78 Gy for conventional fractionation or 64.6 Gy for hypofractionation, respectively. In the Netherlands, elective irradiation of the pelvic lymph nodes is generally not applied due to inconclusive evidence of efficacy (26). In this study, elective lymph node irradiation was neither allowed nor performed. Safety margins of 3-10 mm were added to the clinical target volume to yield the planning target volume (9). During the boost, these margins were reduced to 3-5 mm, except towards the rectum (0 mm). Anorectal and anal dose constraints were applied, whereas no constraints were used for penile structures (9).

Sexual function assessment

We measured sexual function with the International Index of Erectile Function (IIEF) (20), which was sent to patients via regular mail at baseline and at 6, 12, 24 and 36 months after radiotherapy. Patients independently completed the questionnaire without the presence or help of a third party affiliated to the hospital. The IIEF is a 15-item self-report questionnaire designed to measure five domains of male sexual function: erectile function (six questions),

orgasmic function (two questions), sexual desire (two questions), intercourse satisfaction (three questions) and overall satisfaction (two questions). To our knowledge, the IIEF questionnaire has not been formally validated in patients receiving prostate cancer treatments such as EBRT or prostatectomy, but remains the most frequently used questionnaire for assessment of male sexual function also in cancer trials.

Statistical analysis

We reported mean IIEF domain scores among the total population and hormone-naïve population, which received no neo-adjuvant or concomitant ADT, at baseline and at each of the follow-up assessments. Statistical differences between both treatments at each time point were assessed using the independent-samples t-test. We excluded patients from further analyses in case of disease relapse. We calculated the incidences of ED at last follow-up among patients with partial or full baseline erectile function (IIEF domain score ≥ 11). ED was defined as severe ED (IIEF domain score <11) according to the classification of Cappelleri et al (27). We used the binary logistics regression model to calculate the odds ratio (OR) of hypofractionation versus conventional fractionation and to adjust for the clinical factors age, baseline erectile dysfunction, diabetes mellitus, cardiovascular medication, prostate volume, ADT, SV dose group, and previous transurethral resection of prostate (TURP). First, we calculated the crude OR of each clinical factor in a baseline model including treatment arm. Second, treatment arm and each clinical factor with a p-value <0.1 in the baseline model were included in the final multivariate model. An alpha of 0.05 (two-sided) was considered the limit of significance. Statistical analyses were performed using SPSS 21.0 software (SPSS, Chicago, IL).

RESULTS

Baseline characteristics

Between March 19, 2007, and December 3, 2010, 820 patients were randomized to hypofractionation (n=410) or conventional fractionation (n=410). Among the registered patients, 14 patients were ineligible, nine received no treatment, one patient died prior to treatment and one double entry was recorded; all 25 patients were excluded from further analyses (Figure 1). After excluding patients without an assessment at baseline (n=109) or during follow-up (n=82), and after excluding men receiving long-term ADT (n=282), a total of 322 patients (166 in hypofractionation arm vs. 156 in conventional arm) were available for sexual function analysis. The median length of follow-up from start of treatment was 37 months (interquartile range 25-38). All baseline characteristics were evenly distributed between treatment arms (Table 1).

Figure 1. Study Flowchart

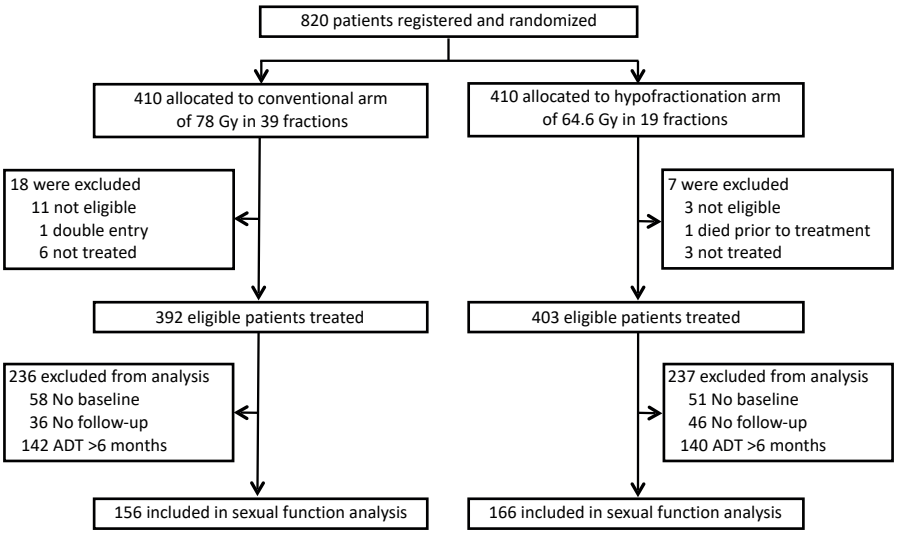

Figure Abbreviations: ADT= Androgen deprivation therapy

Short-term ADT of six months was prescribed in 64 (38.6%) of 166 patient sin the hypofractionation arm and 61 (39.1%) of 156 patients in the conventional arm, respectively. ADT was initiated at a median of 78 days (IQR 42-180) before the first fraction in the hypofractionation arm vs. 70 days (interquartile range (IQR) 37-179) for conventional fractionation. Twenty-five patients (15 in hypofractionation arm vs 10 in conventional arm) had progressive disease and were excluded from further analyses, whereas 19 (11 hypofractionation arm vs. eight conventional arm) died during the follow-up period of three years. There were no treatment-related deaths.

PDE-5is were prescribed to 33 patients (14 patients in hypofractionation arm vs. 19 in conventional arm) at some point during follow-up. No other erectile function aids were specifically reported during follow-up.

Sexual function domains

All domain scores assessed within the IIEF were comparable between treatment arms at baseline (p's >0.05) (Figure 2a-e). Mean erectile function scores (Figure 2a) gradually decreased over time, whereas sexual desire scores (Figure 2b) remained relatively stable throughout follow-up. Orgasmic function-, intercourse satisfaction- and overall satisfaction scores (Figure 2c-e) mainly decreased during the first 12 months following treatment. No significant differences between treatment arms were found at any point during follow-up (p-values >0.05).

Table 1. Baseline patient and treatment characteristics

	Conventional Fractionation (n=156)	Hypofractionation (n=166)
Age (years)	71 (67-75)	71 (66-74)
Follow-up (months)	36.8 (25.7-37.8)	36.7 (25.1-37.4)
PSA concentration (ng/ml)	13.3 (8.7-18.3)	12.4 (8.8-12.0)
T stage		
1	34 (21.8)	33 (19.9)
2	71 (45.6)	77 (46.4)
3	51 (32.6)	56 (34.7)
Gleason score		
4-6	65 (41.7)	68 (41.0)
7	74 (47.4)	76 (45.8)
8-10	17 (10.9)	22 (13.2)
Risk Category		
Intermediate risk	77 (49.4)	75 (45.2)
High risk	79 (50.6)	91 (54.8)
Treatment group		
1	54 (34.6)	44 (26.5)
2	77 (49.4)	92 (55.4)
3	25 (16.0)	30 (18.1)
Androgen deprivation therapy	61 (39.1)	64 (38.6)
Prostate volume	51.0 (38.0-67.5)	55.2 (38.6-70.3)
Diabetes mellitus	21 (13.5)	26 (15.7)
Cardiovascular medication	23 (14.7)	27 (16.3)
Smoking		
Yes	20 (12.8)	16 (9.6)
Unknown	29 (18.6)	33 (19.9)
Transurethral resection of prostate	18 (11.5)	10 (6.0)
Intensity-modulated radiotherapy	151 (96.9)	165 (99.4)
Image-guidance (fiducial markers)	145 (92.9)	156 (94.0)
Safety margins (mm)		
5-6	73 (46.8)	80 (48.2)
7-10	82 (52.9)	85 (51.2)
Unknown	1 (0.6)	1 (0.6)

Table Legend: Data are n (%) or median (IQR). **Table Abbreviations:** PSA= prostate specific antigen

As for the hormone-naïve population, a difference in terms of orgasmic function between both treatment arms arising two years after irradiation resulted in significantly higher scores at three years in the hypofractionation arm (4.08 vs. 2.65, p= 0.031) (Figure 2c). No significant differences (p-values >0.05) between treatment arms were found in any of the other domains.

Figure 2. Mean Internal Index of Erectile Function domains scores (+/- standard error) per treatment arm

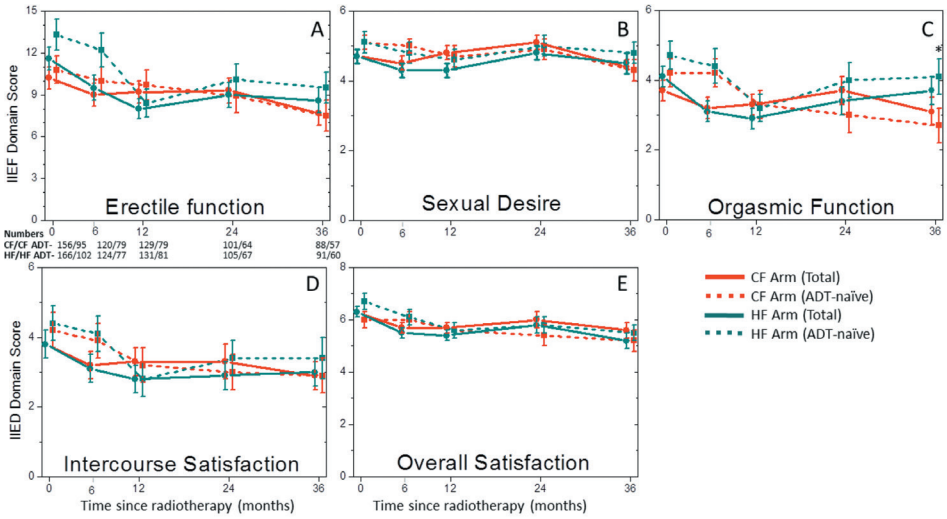

Figure Legend: *P value <0.05 for ADT-naïve population (independent t-test)

Figure Abbreviations: CF= Conventional Fractionation, HF= Hypofractionation, ADT-=Androgen deprivation therapy-naïve (patients).

9

Erectile dysfunction

202 (62.7%) of 322 patients reported to have ED at baseline or developed clinical relapse during follow-up. 120 patients (64 in hypofractionation arm vs. 56 in conventional arm) had partial or full erectile function (IIEF-EF domain score ≥11) at baseline. Median length of follow-up in these patients was 37 months (IQR 25-38). In 23 patients the date of last follow-up was between one and two years after treatment, 26 had a follow-up of 24-35 months, whereas the remaining 71 patients had a follow-up of at least 36 months. Severe ED was reported at last follow-up by 22 (34.4%) out of 64 after hypofractionation and 22 (39.3%) out of 56 after conventional fractionation. The adjusted OR was 0.84 (95% CI 0.37-1.90, p=0.67) (Table 2). Significant predictors of ED at last follow-up were cardiovascular disease (OR=3.13, 95% CI 1.04-9.45, p=0.043) and baseline function (OR=0.26, 95% CI 0.11-0.62, p=0.002). The clinical relevance of baseline function as a predictor of ED is best reflected by the fact that 91-96% of patients with severe ED at baseline also had severe ED at last follow-up (Figure 3, left pair of

columns). In patients with mild-moderate ED at baseline, these incidences were 53% and 50% for conventional fractionation and hypofractionation, respectively (Figure 3, middle columns). Patients with full erectile function before treatment developed severe ED in 20% and 23%, respectively (Figure 3, right columns). Around one third of patients with full baseline erectile function (score ≥26) retained function at last follow-up.

Figure 3. Erectile dysfunction at last follow-up according to baseline erectile dysfunction

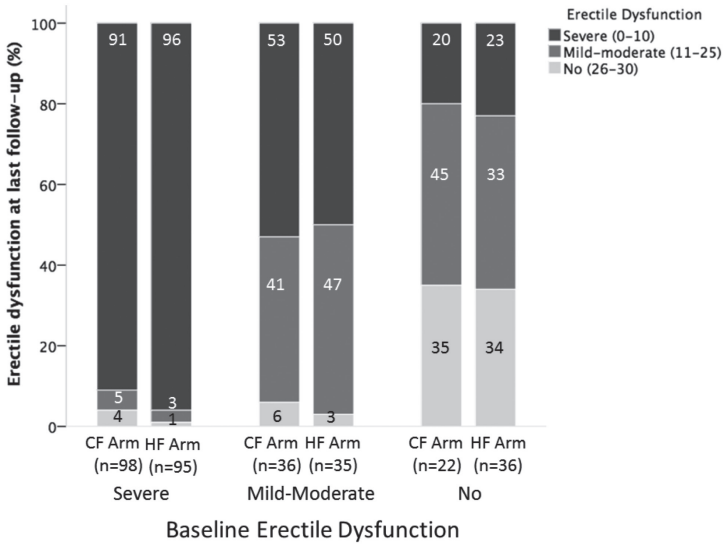

Figure Legend: Erectile function according to Cappelleri et al.
Figure Abbreviations: CF= conventional fractionation, HF= hypofractionation

DISCUSSION

The HYPRO trial has shown no clinically meaningful differences in sexual function between conventionally fractionated and hypofractionated radiotherapy. Orgasmic function scores in hormone-naïve patients though were statistically significantly higher at 3-year follow-up in the hypofractionation arm. The incidence of patients with a previous TURP within the hormone-naïve population was slightly higher in the conventional fractionated arm (n=12, 12.6%) compared to the hypofractionated arm (n=4, 4.9%). This might have impacted orgasmic function scores since transurethral procedures are associated with orgasmic disorders such as retrograde ejaculation (28).

Table 2. Results of binary logistics regression analysis for the incidence of erectile dysfunction at last follow-up

	Erectile dysfunction (IIEF-EF domain score <11)			
	Baseline model		Final model	
Factor	**OR**	**p**	**OR (95% CI)**	**p**
Age (≥71yr vs. <71yr)	2.02	0.07	1.59 (0.71-3.59)	0.26
Baseline erectile dysfunction (no vs. mild-moderate)	0.26	0.001	0.26 (0.11-0.62)	0.002
Diabetes mellitus (yes vs. no)	1.49	0.42		
Cardiovascular medication (yes vs. no)	2.63	0.065	3.13 (1.04-9.45)	0.043
Prostate volume (>50cm3 vs. ≤50cm3)	1.17	0.69		
Androgen deprivation therapy (yes vs. no)	0.92	0.96		
Seminal vesicle dose group (1 vs. 2 vs. 3)	1.44	0.22		
Transurethral resection of prostate (yes vs. no)	0.33	0.32		
Treatment arm (hypofractionation vs. conventional)	0.80	0.71	0.84 (0.37-1.90)	0.67

Table Abbreviations: IIEF-EF= International Index of Erectile Function-Erectile Function domain, OR= odds ratio, CI= confidence interval

In patients with partial or full erectile function at baseline the incidences of severe ED at last follow-up were 34.4% for hypofractionation and 39.3% for conventional fractionation. These incidences might have been influenced by the fact that the majority of patients (66 of 120, 55%) had mild to moderate baseline ED (IIEF domain score between 11-25) and are more prone to develop severe ED during follow-up as demonstrated at multivariate analysis.

The etiology of post-radiation ED is multi-factorial and related to neural-, vascular-, endothelial- and smooth muscle damage (29,30). Several authors reported conflicting results on possible relationships between the dose to the corpora cavernosa, the neurovascular bundles, the penile bulb and the incidence of radiation-induced ED (31,32). Roach et al. (31) advocate limiting the mean dose to 95% of the penile bulb volume to <50 Gy. They acknowledged that the penile

bulb is not the critical component of the erectile apparatus, but a surrogate for yet to be determined critical structures (31). Van der Wielen et al. (32) concluded that penile bulb sparing for preservation of erectile function was not sufficiently supported by current literature. They even suggested that penile bulb sparing might interfere with radiation dose coverage for the apex of the prostate, while it is uncertain whether this would improve erectile preservation (32). The penile bulb and other penile structures were not routinely contoured and no dose constraints were applied in the HYPRO trial. The α/ß ratio of anatomic structures responsible for erectile function is unknown. As a result, the expected impact of hypofractionated treatment on the radiobiological dose to critical structures could not be known.

Clinical outcomes from other hypofractionation trials are required to gain a better understanding of the impact of hypofractionated radiotherapy on sexual function. The CHHiP trial randomized 3216 patients between 74 Gy in 37 fractions and one of two hypofractionated schedules: 57 Gy in 19 fractions of 3 Gy or 60 Gy in 20 fractions (16,17). Most patients received ADT for 3-6 months before and during radiotherapy. A quality of life sub study of the CHHiP trial among 2100 patients based on patient-reported outcomes up to 24 months derived from the UCLA Prostate Cancer Index (UCLA-PCI) and Expanded Prostate Cancer Index Composite (EPIC) questionnaires demonstrated no significant differences between treatments (16). Dearnaley et al. (11) also found no significant differences in grade ≥ 2 LENT-SOM sexual dysfunction scores between treatment arms at 5-years. To our knowledge, no other randomized hypofractionation trials have reported results on sexual function (13-15).

This study has several limitations. First, given the fact that only intermediate- to high-risk patients were included in this trial, a large proportion of patients received ADT of various durations. ADT is intended to cause severe hypogonadism, and low testosterone has been associated with severe ED (33). The side effects of ADT on sexual function can be substantial, and a large variety of sexual problems might result in decreased sexual activity, reduced quality of life and low self-esteem (34). ADT was usually prescribed well before the first fraction and an assessment of sexual function before its initiation was in general not performed. Therefore, we do not know what impact ADT had on baseline IIEF domain scores. We only included patients on short-term ADT of 6 months in order to minimize the effects of androgen suppression on the endpoint of erectile dysfunction at last follow-up. Several authors reported that recovery of serum testosterone levels should occur within approximately 18 months in >90% of patients after withdrawal of short-term ADT (22,23). Time to normalization of testosterone levels after cessation of long-term ADT is substantially longer, and long-term erectile function is therefore more likely to be affected (22,23). It should be noted that these studies used pre-defined cut-off values of normal serum testosterone and did not take into account the large interpersonal variation in testosterone levels before initiation of ADT. Sexual function could be impaired if testosterone levels fail to return to baseline after cessation, despite being classified as normal.

Our multivariate analysis did not demonstrate ADT for 6 months as a significant predictor for the incidence of ED at last follow-up. This might indicate that the serum testosterone levels were normalized after cessation of ADT. However, recovery of testosterone levels may vary between patients (35), and routine assessments of hormone levels were not performed.

Second, PDE-5is are widely used as treatment for ED and might attenuate the effects of radiotherapy on sexual function. PDE-5is were prescribed to 33 patients at some point during follow-up. We only recorded whether PDE-5is were prescribed and had no data on actual use of PDE-5is. The impact of PDE-5i prescription on sexual function is therefore not well-known.

Finally, IIEF-15 questionnaire addresses sexual function and activity, and might score sexually inactive patients with good erections as having ED. The use of questionnaires can also introduce recall bias, since some patients cannot remember what their past sexual performance and activity was like. This concept, however, is more relevant to the IIEF-5 or Sexual Health Inventory for Men (SHIM), which addresses erectile function over the last six months, as compared to 4 weeks for the IIEF-15.

In conclusion, our results demonstrated no significant or clinically relevant differences in erectile functioning between conventional (39x2 Gy) and hypofractionated (19x3.4 Gy) radiotherapy up to three years after treatment. In hormone-naïve patients significantly higher orgasmic function scores were found at three years in the hypofractionation arm.

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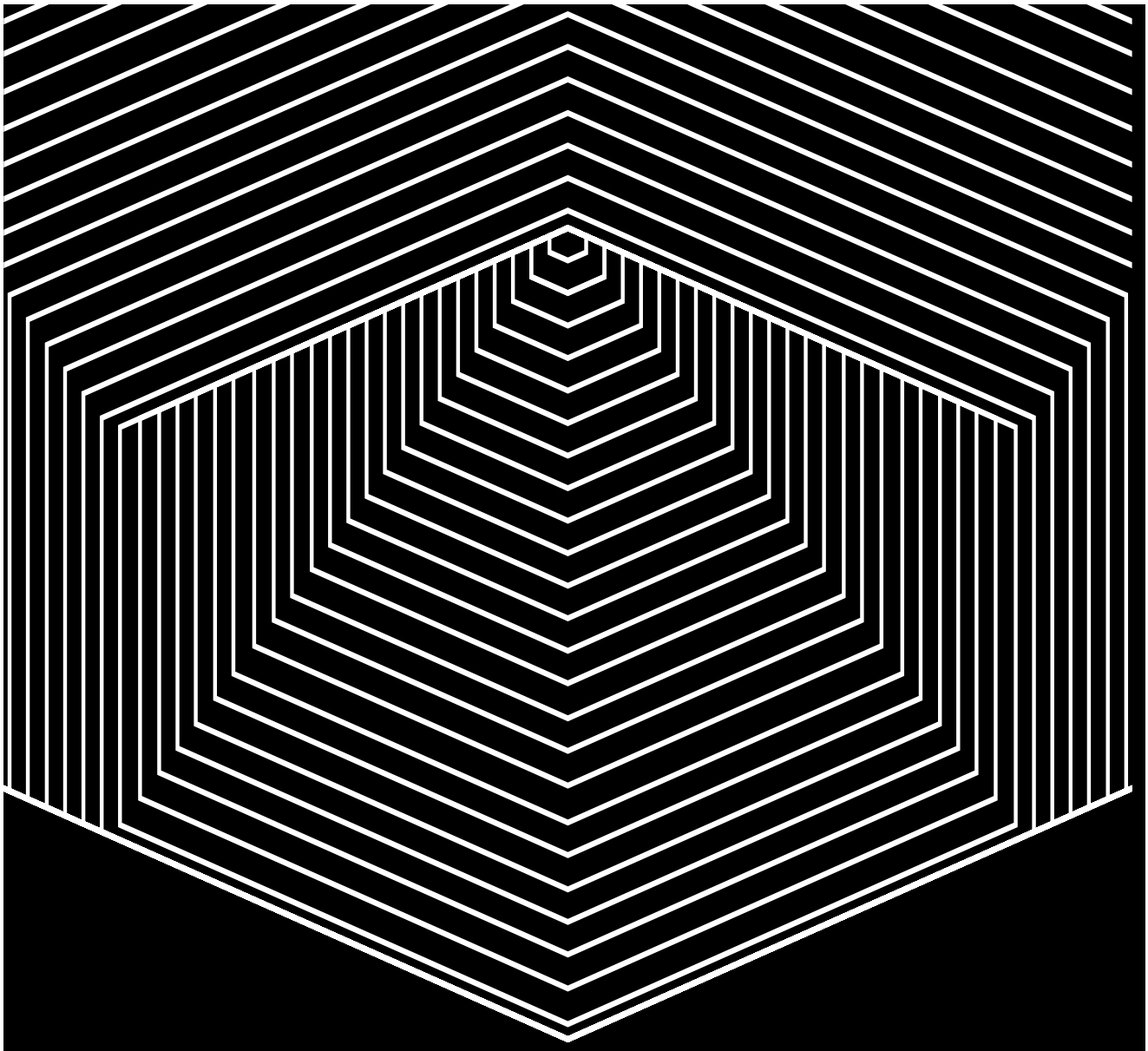

IF YOU CAN'T DO THE LITTLE THINGS RIGHT,
YOU'LL NEVER BE ABLE TO DO THE BIG THINGS RIGHT.

William H. McRaven

CHAPTER 10

Reporting erectile function outcomes after radiation therapy for prostate cancer: Challenges in data interpretation

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ABSTRACT

Background

Choice of prostate cancer treatment is frequently influenced by the expected chance of treatment-induced side effects such as erectile dysfunction (ED). However, great discrepancy in cited ED rates exists in the contemporary radiation therapy literature

Aim

To analyse the reported ED rates and cause of discrepancies, and explore the strengths and limitations in literature on radiation-induced ED.

Methods

We performed a PubMed literature search and reviewed literature on ED rates associated with external beam radiotherapy (EBRT) and brachytherapy (BT) from the past 10 years. A total of 18 studies were eligible for inclusion and subsequently reviewed.

Outcomes

Variables which are required for interpretation of erectile function outcomes including patient demographics, treatment characteristics and sexual function outcomes.

Results

A large variety in the reported incidence of ED was found between studies. In part, these differences resulted from large variations in 1) study populations, 2) patient characteristics, 3) treatment characteristics, 4) prescription of androgen deprivation therapy, 5) means of data acquisition, 6) definitions of ED, 7) temporal considerations, and 8) erectile aid use. Relevant data required for adequate appraisal of sexual function outcomes were not always reported.

Clinical implications

Based on the findings of the current research, we present general recommendations for reporting of erectile function outcomes after radiotherapy for prostate cancer. These should improve future reports.

Strengths and limitations

This is the first report that presents general requirements on reporting erectile function outcomes in the setting of radiotherapy for prostate cancer. We have not conducted a formal meta-analysis as we focused on concepts of research design; this might be considered a limitation.

Conclusion

In this review we have highlighted the strengths and deficiencies of current literature on ED after EBRT and BT for prostate cancer. We have made general recommendations in order to achieve some degree of standardization between reports and improve clinical interpretability.

INTRODUCTION

Patients with early-stage localized prostate cancer have favorable relapse-free survival outcomes regardless of treatment (1). The choice of treatment is therefore frequently based on the expected treatment-induced side effects including sexual side effects. Over the years, large prospective studies focused on analyzing side effects of various treatments. The study by Sanda et al. (2) analyzed quality-of-life outcomes after radical prostatectomy (RP) (n=602), external beam radiotherapy (EBRT) (n=292) and brachytherapy (BT) (n=306). They reported that at 2-year follow-up erections not firm enough for intercourse were present in 64%, 66% and 56% after RT, EBRT and BT, respectively. Precautious interpretations of these results are warranted due to the lack of randomization and differences between patient populations (2). Resnick et al. (3) also analyzed outcomes after radical prostatectomy (n=1164) vs EBRT (n=491) and found that patients undergoing radical prostatectomy were more likely to have erectile dysfunction (ED) at 2-year and 5-year follow-up. The radiotherapy populations in both studies were on average substantially older than prostatectomy patients, ranging between 5-10 years (2,3). Such differences impede comparisons between prostate cancer treatments and adequate patient counseling prior to treatment selection.

However, large discrepancies also exist when comparing sexual function outcomes of treatments separately. In a review by Incrocci et al. (4) the reported incidences of ED varied between 6-84% after conventionally fractionated EBRT and ranged from 0-51% following BT. While differences in applied techniques, treatment planning and expertise between treatment centers can contribute to apparent discrepancies in ED rates, we believe that the differences in populations studied, means of data collection and data presentation are more important as contributors to the rate discrepancies.

The main objective of this review was to explore the cause of such discrepancies in reported ED rates. In order to do so we have conducted a review of contemporary literature on radiation-induced ED after conventionally fractionated EBRT and BT. This is not an effort to conduct a meta-analysis, rather we attempted to address the strengths and limitations of the literature and provide general recommendations for the reporting of erectile function outcomes after radiotherapy for prostate cancer. This might lead to some degree of standardization between future reports and could thus improve clinical data interpretability. By including literature on EBRT and BT we have aimed to demonstrate that our findings are applicable to all aspects of modern pelvic radiotherapy.

MATERIALS AND METHODS

On February 25th, 2017, we have conducted a literature search using title search terms (radiotherapy OR brachytherapy OR radiation therapy) AND (erectile OR potency OR sexual OR patient-reported outcomes) AND prostate. Eligible for inclusion were studies written in English which reported on original clinical data with a study population of at least 100 men. In addition, we have only included reports from the past 10 years, as older studies generally report on previous 2-dimensional radiation techniques which cannot be compared to modern and generally applied techniques such as 3D-conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). We excluded all studies which presented data on other techniques or treatments than BT or conventionally fractionated EBRT, and all studies which focussed mainly on erectile devices or medication.

RESULTS

We retrieved a total of 81 studies which were screened for both title and abstract. After careful review, a total of 63 studies did not meet the inclusion criteria. Eighteen studies met all inclusion criteria and were therefore included in this review (Table 1). The complete flowchart is presented in Figure 1. Investigated radiation techniques included EBRT (3D-CRT, IMRT, VMAT), low-dose rate (LDR) and high-dose rate (HDR) BT, or combination of techniques (Table 2).

Erectile function after radiotherapy for prostate cancer

The National Institutes of Health (NIH) define ED "the consistent inability to obtain and/or maintain an erection sufficient for satisfactory sexual performance" (5). A modified variation of this definition was frequently used (Table 3). The reported preservation rates of erectile function after treatment varied between 22-70% for reports on EBRT, and ranged from 20-81% for studies concerning BT either with or without additional EBRT (Table 3). Large variation in study populations, data acquisition, data reporting, and definitions of erectile function and dysfunction contributed to reported differences in sexual function outcomes.

In the following paragraphs we will discuss the key elements which in our opinion should beconsidered when reporting on erectile function outcomes after radiotherapy for prostate cancer. These include: 1) study population, 2) patient characteristics, 3) treatment characteristics, 4) prescription of androgen deprivation therapy, 5) means of data acquisition, 6) definitions of ED, 7) temporal considerations, and 8) erectile aid use.

Study population

All of the reviewed studies included more than 100 patients, and two major centers reported on at least 1.000 patients (6,7). The validity of studies, however, should not only be defined by the included study sample but also by the proportion of patients that actually completed follow-up. As shown in Table 1, substantial differences can be found in the reported number of patients that were included for analysis at baseline and those that actually completed follow-up. In addition, some authors only included patients with functional erections at baseline (7-9), whereas others only reported erectile function outcomes of a proportion of the patient population and not the entire study cohort (10,11). This patient selection bias, choosing youngest, healthiest patients with best baseline erectile function can lead to erectile function outcomes, which are unrealistic for the general population. In our series, the highest erectile preservation rates have been reported by single center series for both EBRT (12) and BT (7,13) (Table 3). While these centers might offer higher-quality treatment, patient selection is likely also a relevant factor contributing to such high erectile preservation rates. In general, when reviewing data on erectile function outcomes it should be clear whether the study population was treated in a multicenter setting or as part of a single center series. In general, when reviewing data on erectile function outcomes it should be clear how many centers were involved in the study, what inclusion criteria were applied and how many patients completed follow-up

Patient characteristics

A detailed description of baseline characteristics offers valuable information with regards to erectile function outcomes. Several of the reviewed studies demonstrated that good erectile function at baseline is a significant predictor (odds ratios ranging between 1.8-6.6) of erectile preservation after treatment (7,8,12,14). Baseline ED rates are therefore an important instrument to appraise sexual function outcomes after radiotherapy, but ED rates at baseline were not provided by five of the reviewed studies (15-19). Ideally, baseline data should be collected before hormone suppressing agents are initiated. An important methodological question related to baseline sexual function is whether patients with ED prior to treatment should be included in analyses. Five of the reviewed studies mainly focused on erectile function outcomes of patients without baseline ED (7-11). This is naturally the best method to assess the true effects of radiotherapy on erectile function, even though such patient populations cannot be regarded as an accurate representation of clinical practice.

Patient age has also been identified as an important predictor of erectile function outcomes (6-9,11,14,19-22). The mean or median age of patients treated with BT was generally lower as compared to those receiving EBRT (Table 1). In studies on EBRT as monotherapy the median or mean age varied between 62-72 years (10-12,15-17,20,23), as compared to 62—69 years for studies including BT (6-9,14,21,24) (Table 1). Also in both studies that directly compared outcomes after both techniques, patients treated with EBRT were older, with differences

Table 1. Patient Demographics

First Author	Treatment Modality	Patient number (total included #)	Mean Age (median)
Pinkawa (20)	EBRT	123	(71)
Donovan (23)	EBRT	545	62
Bruner (15)	EBRT	505	(71)
Siglin (12)	EBRT	143	(69)
Van der Wielen (28)	EBRT	139 (194)	(68)
Daly (11)	EBRT	141 (230)	(65)
Kushnir (16)	EBRT	213	71
Haugnes (17)	EBRT	73	(66)
	EBRT	85	(68)
Taira (8)	BT ± EBRT	124	(63)
Nishimura (14)	BT ± EBRT	665	66
Snyder (7)	BT ± EBRT	1063	(60-70)
Wang (24)	BT ± EBRT	732	65
Keyes (6)	BT	2929	65
Ong (9)	BT	366	62
Matsushima (21)	BT	119	NR
Olssen (22)	EBRT	165	(72)
	EBRT + BT	229	(69)
Marina (13)	EBRT	192	(64)
	BT	192	(63)
Putora (19)	EBRT	91	(72)
	BT	135	(63)

Table Legend: *= at 1 year, **= at 2 years, ***= at 3 years, §= at 5 years, #= Included patients who were not further analyzed because of baseline erectile dysfunction.
Table Abbreviations: FU = follow-up, BT= brachytherapy, CV= cardiovascular, DM= diabetes mellitus EBRT= external beam radiotherapy, HT= hypertension, NR=Not reported

	≥1 Baseline Comorbidities (%)	Minimum FU (months)	Mean (median) FU in months	Completing Study (N/%)	Baseline Erectogenic Medication (%)
	56	12	(16)	123/100*	2
	NR	NR	(72)	NR/86	NR
	NR	6	(24)	310/61**	NR
	8 (CV), 12 (DM)	6	(48)	114/80**	27
	3 (DM), 25 (CV)	12	27	79/57***	<1
	30 (CAD, 4 (DM)	4	(86)	120/85***	NR
	28 (DM)	3	11	213/213	22
	6 (CV), 11 (DM)	17	(38)	73/73	NR
	12 (DV), 12 (DM)	17	(30)	85/85	NR
	44 (HT), 8 (DM)	NR	(77)	124/100§*	0
	10 (DM)	NR	(>60)	550/83§	NR
	NR	24	(67)	NR	NR
	84	12	(34)	NR	NR
	33 (HT), 10 (DM)	10	(42)	1142/39§	NR
	32	3	(41)	NR	5
	24 (HT), 13 (DM), 11 (CV)	12	(34)	29/24***	0
	NR	12	(72)	NR	NR
	NR	12	(60)	NR	NR
	NR	6	24	NR	NR
	NR	6	24	NR	NR
	NR	12	(24)	NR/58***	NR
	NR	12	(24)	NR/58***	NR

Table 2. Treatment characteristics

First Author	Treatment technique	Treatment dose	Dose to penile bodies reported	ADT (%)	Mean (median) months ADT
Pinkawa (20)	3D-CRT	70-72 Gy	NR	0	NA
Donovan (23)	3D-CRT	74 Gy	NR	100	3-6
Bruner (15)	3D-CRT vs. IMRT	79 Gy	Yes $	0	NA
Siglin (12)	NR	67-79 Gy	NR	0	NA
Van der Wielen (28)	3D-CRT	68 Gy vs 78 Gy	NR	0	NA
Daly (11)	3D-CRT	70 Gy	NR	100	4 vs. 8
Kushnir (16)	3D-CRT/IMRT/ VMAT	77 Gy	NR	67	(11)
Haugnes (17)	3D-CRT/ IGRT	70 Gy	NR	67	(12)
	3D-CRT/ IGRT	76 Gy	NR	87	(12)
Taira (8)	LDR +/- EBRT	BT: 90-144 Gy, +/- EBRT: 20-44 Gy	Yes #	25	(4)
Nishimura (14)	LDR & 3D-CRT	BT: 145 Gy BT: 100Gy + EBRT: 45 Gy	NR	81	(8)
Snyder (7)	LDR & 3D-CRT/IMRT	BT: 200 Gy[1] BT: 106 Gy[2] + EBRT: 45 Gy	NR	49	(4-6)
Wang (24)	3D-CRT/IMRT LDR	EBRT: 67-81 Gy BT: 125-145 Gy BT: 100-109 Gy + EBRT: 45 Gy	NR	50	NR
Keyes (6)	LDR	144 Gy	NR	44	6
Ong (9)	LDR	145 Gy	NR	0	NA
Matsushima (21)	LDR	145-160 Gy	NR	0	NA
Olssen (22)	3D-CRT	70 Gy	NR	14	12
	3D-CRT + HDR	50 Gy+ 20Gy/2 Fr	NR	19	12
Marina (13)	IG-IMRT	74-82 Gy	NR	0	NA
	HDR	27-38 Gy / 2-4 Fr	NR	0	NA
Putora (19)	3D-CRT	70-78 Gy	NR	<5	NR
	LDR	145 Gy	NR	<4	NR

Table Legend: 1= Median biologically equivalent dose, 2=Median dose to 90% of prostate, $= dose to penile bulb was reported, #= dose to penile bulb, proximal- and distal crura were reported

Table Abbreviations: 3D-CRT= 3D-conformal radiotherapy, ADT= androgen deprivation therapy, BED= Biologically Equivalent Dose, BT= brachytherapy, EBRT= external beam radiotherapy, Fr= fractions, HDR= high dose-rate brachytherapy, IG= image-guided, IMRT= intensity modulated radiotherapy, VMAT= Volumetric Modulated Arc Therapy, LDR= low dose-rate brachytherapy, NA= Not applicable, NR=Not reported

ranging between 1-9 years (13,19). Such differences in age (i.e. 9 years) might have impacted erectile function outcomes in the Putora et al. (19) study which compared EBRT of 70-78 Gy vs. low-dose rate (LDR)-BT up to 145 Gy and reported that in patients with baseline IIEF-5 scores >17 BT was associated with on average 3.1 point higher IIEF scores as compared to EBRT at 36 months. The Marina et al. study (13) also compared both techniques and showed favorable 3-year erectile preservation rates of 81% in patients treated with high-dose rate (HDR)-BT (median age 63 year) as compared to 69% for EBRT (median 64 years) (Table 3).

Also associated with ED, both in the general population and in prostate cancer patients after radiotherapy, is the presence of comorbidities such as diabetes, hypertension, and cardiac disease (6,8,9,20,24). In an interesting retrospective study, Wang et al. (24) studied the influence of vascular comorbidities (hypertension, diabetes, hyperlipidemia) on post-radiation ED incidence in 732 patients. In general, the 4-year incidence of post-radiation ED significantly increased with the number of vascular comorbidities (24). For example, the ED incidence in patients without comorbidities ranged between 40-46% as compared to 71-76% for those with three vascular comorbidities. These data require prospective validation but underline the importance of conducting an assessment of comorbidity status prior to treatment. Few efforts have been made so far to explore the relation between severity of comorbidity and ED post-treatment. Attempts to integrate nuances in relevant comorbidities could improve the ability to generate more accurate prediction models.

In the Taira et al. study (8) on 226 BT patients, prostate size was identified as a significant predictor for potency preservation. In radiotherapy treatment planning, as the prostate size increases, a larger volume of adjacent organs at risk is at risk of high irradiation doses. This might explain increased risk of erectile dysfunction. Kushnir and colleagues demonstrated that patients with higher education had better sexual function than those with school education only (16). Increased knowledge and access to sexual counseling and therapy were suggested explanations for this disparity.

Treatment characteristics

Over the last decades, substantial experience has been gained in the use of different BT approaches (retropubic, suprapubic, transperineal), implantable permanent LDR isotopes (Iodine-125, Iridium-192, Palladium-103), imaging techniques, and treatment planning systems (4,25). More recently, high-dose rate (HDR) BT has been implemented in clinical practice (13,25). HDR-BT involves a radiation source that is delivered from a chamber through catheters that are temporarily placed transperineally within the prostate (25).

As for EBRT, the introduction of intensity modulated radiotherapy (IMRT) and image-guidance has enabled significant reductions in dose to normal tissues surrounding the prostate as

Table 3. Sexual function assessment and outcome

First Author	Assessment	Evaluation	Definition of ED
Pinkawa (20)	EPIC	Prospective	Insufficient for sexual intercourse
Donovan (23)	EPIC	Prospective	Not firm enough for intercourse
Bruner (15)	IIEF-15 & Physician-reported	Prospective	NR
Siglin (12)	BSFI	Prospective	Not firm enough for intercourse
Van der Wielen (28)	Dutch Questionnaire	Prospective	Unable to achieve or maintain erection, or sexually inactive due to erectile problems
Daly (11)	Physician-reported	Prospective	Partial or no erection
Kushnir (16)	EPIC	Retrospective	NR
Haugnes (17)	EPIC	Retrospective	Not firm enough for intercourse
	EPIC	Retrospective	Not firm enough for intercourse
Taira (8)	IIEF-15	Prospective	IIEF≤12
Nishimura (14)	MSEFS or Interview	Prospective	MSEFS < 2 (Insufficient for sexual intercourse)
Snyder (7)	MSEFS	Prospective	MSEFS <2 (Insufficient for sexual intercourse)
Wang (24)	Physician-reported	Retrospective	≥Moderate problems obtaining adequate erections/ use of erectile aids
Keyes (6)	Physician-reported & SHIM	Prospective	Insufficient for sexual intercourse
Ong (9)	SHIM	Prospective	SHIM <17
Matsushima (21)	IIEF-15	Prospective	IIEF<11
Olssen (22)	Swedish questionnaire	Retrospective	Inability to get an erection
	Swedish questionnaire	Retrospective	Inability to get an erection
Marina (13)	CTCAE 4.0	Retrospective	CTCAE grade ≥2
	CTCAE 4.0	Retrospective	CTCAE grade ≥2
Putora (19)	SHIM	Prospective	IIEF<17
	SHIM	Prospective	IIEF<17

Table Legend: **= at 2 years, ***= at 3 years, ****= at 4 years, §= at 5 years, §*= at 6 years, §**= at 7 years, ¶= of patients with functional erections at baseline, ~= estimated

	ED Baseline (%)	ED Last Follow-up (%)	Functional Erection Baseline (%)	Erectile Function Preservation (%)	Erectogenic Medication During Follow-up (%)
	56	73*	39	53*¶	9
	32	63§*	68	27§*	NR
	NR	NR	51	NR	NR
	26	30**¶	74	70**¶	NR
	28	38***¶	72	62***¶	5
	39	63 (ADT:4m)¶ 75 (ADT:8m)¶	61	28 (ADT 4m)§ ¶ 24 (ADT 8m)§ ¶	24¶
	NR	NR	NR	NR	NR
	NR	69***	NR	31***	17
	NR	78***	NR	22***	15
	0	44§**	100	56§**¶	0
	42	48§¶	58	52§¶	16
	0	32§	100	68§¶	70
	22	58****	78	42****	NR
	21	NR	79	58 (60-64y)§¶ 41 (65-69y)§¶	30
	0	53§	100	59§¶	40
	60	~80***	40	~20***	0
	NR	27§*	NR	73§*	NR
	NR	23§	NR	77§*	NR
	13	32***	88	69***¶	NR
	13	29***	88	81***¶	NR
	NR	NR	NR	NR	0
	NR	NR	NR	NR	4

Table Abbreviations: ADT= Androgen deprivation therapy, BSFI= Brief male Sexual Function Index, CTCAE Common Toxicity Criteria for Adverse Events, ED= Erectile dysfunction, EPIC= Expanded Prostate Cancer Index Composite, IIEF= International Index of Erectile Function, MSEFS= Mt. Sinai Erectile Function Score, PCSI= Prostate Cancer peer Support Index, SHIM= Sexual Health Inventory for Men.

compared to 3D-conformal radiotherapy (3D-CRT) techniques (26,27). Kushnir and colleagues (16) reported no impact of treatment technique (3D-CRT vs. IMRT/ Volumetric Modulated Arc Therapy) on sexual outcomes. In addition, Bruner and colleagues (15) analyzed erectile function outcomes of the Radiation Therapy Oncology Group (RTOG) 0126 Prostate Cancer Trial among men who received 79.2 Gy with either 3D-CRT or IMRT. IMRT significantly reduced the penile radiation dose, but no significant differences in international index of erectile function (IIEF) scores were found between both treatments.

Total treatment dose also affects dose to critical structures and can thus influences erectile function. In the study by Ong and colleagues BT patients with a biologically equivalent dose of at least 150 Gy had a 1.8 times increased risk of developing moderate to severe ED as compared to those with doses up to 150 Gy (9). In contrast, Haugnes and colleagues compared sexual function after EBRT to 70 Gy or 76 Gy and reported erectile preservation in 31% after 22% respectively (17). Van der Wielen et al. (10) could also not demonstrate an association between dose-escalated EBRT and ED. Currently, there is no consensus on dose constraints to penile bodies (28,29), as there is still a lack of evidence-based knowledge on the anatomical regions involved in ED after radiotherapy, which lead to difficulties delineating the appropriate organ at risk (29). None of the reviewed studies reported on penile dose constraints, and only Bruner and colleagues (15) and Taira and colleagues (8) mentioned the radiation dose to penile structures such as penile bulb (8,15), and crura (8). In the study by Taira et al. (8), BT patients receiving 25 Gy or less to the penile bulb had a 7-year potency rate of 71% compared with 45% for those with penile bulb dose of at least 25 Gy.

Given the rapid technical innovations in modern radiotherapy, and wide variety of treatment doses and dose constraints we believe it to be critical that some delineation of treatment characteristics are included

Prescription of androgen deprivation therapy

Patients receiving ADT might not be ideal candidates to analyze the effects of radiotherapy on erectile function outcomes. Prescription of ADT was related to worse sexual outcomes in several studies (6,7,16). The use of ADT increased markedly through the 1990s but has subsequently stabilized (30). ADT is administered to initiate castrate levels of serum testosterone and has been associated with severe ED (31). Decreased levels of sexual activity and absence of nocturnal erections combined with collagenization of corporal smooth muscle all lead to significant permanent erectile problems. Patients receiving ADT were excluded in seven studies (9,12,13,15,21,32,33) (Table 2). The duration of ADT was not mentioned in two studies (19,24). Daly et al. (11) specifically addressed the effects of differences in duration of ADT by reporting erectile function outcomes of a clinical trial randomizing patients to EBRT of 70 Gy with ADT for 4 months vs. EBRT with ADT for 8 months. Erectile function was assessed by physician directed

questions, using a 4-point Likert scale. No significant differences were observed between both regimens during 8-year follow-up after EBRT. Unfortunately, serum testosterone levels were not routinely tested to identify whether the differences in duration of ADT had an impact on testosterone recovery (11).

Means of data acquisition

Erectile function data is generally collected using patient interviews, physician-reported scores, validated self-report questionnaires, or a combination of the above. In case data collected by patient interviews or physician-reported scores are presented, the reader should keep in mind that the data is potentially biased if the treating radiation oncologist was involved in data acquisition. This might introduce social desirability, which implies that patients tell their physician what they believe the physician would want to hear. It has been previously shown that physician-reported data represent an underestimation of health-related quality of life problems in patients after prostate cancer treatment (34). Addition of self-report patient questionnaires results in more accurate identification of true radiation-induced complaints (35).

Except for five retrospective studies (13,16,17,22,24), all others reported prospectively collected data using various self-report instruments for sexual function assessment (Table 3). The most well-known instrument is the International Index of Erectile Function (IIEF), which is a 15-item self-report questionnaire addressing five sexual function domains. The IIEF addresses five domains of male sexual function over the prior 4 weeks (36). The IIEF-5, better known as Sexual Health Inventory for Men (SHIM), is the shorter version which only addresses erectile function but does so over a period of six months, which introduces the issue of recall bias (37). The IIEF-15 and SHIM have validated cutoffs for no, mild, moderate and severe ED (37).

Other validated questionnaires that were used (Table 3) do not have such clear cut-off values to define severity of ED, and frequently only use one question to report on ED outcomes. We therefore believe that prospective assessment using the IIEF is the most appropriate instrument to analyze erectile function. In non-English speaking countries, validated translations of questionnaires were used (16,17,19-21), whereas van der Wielen and colleagues and Olssen and colleagues used a Dutch and Swedish questionnaire, respectively (10,22).

Definition of erectile dysfunction

ED outcomes were frequently derived from one question (Table 3), which might not detect slight changes in erectile function. For instance, patients with perfect function at baseline could experience decreased erectile rigidity or erectile consistency post-radiotherapy, but still remain able to perform successful intercourse. Even though these men might have functional erections according to the applied definition of ED as derived from a single-question, quality of life might decrease as a result of erectile dissatisfaction and reduced confidence. The multi-question

SHIM or IIEF erectile function domain was used in four studies (8,9,19,21). These questionnaires do capture slight changes in erectile function to a better extent, and might therefore be the preferred assessment tool (38,39). Regardless of applied questionnaire, adequately defining erectile function and/or ED is essential to improve clinical relevance. Readability might be improved if proportion of men preserving erectile function during follow-up are reported.

Temporal considerations

Some studies suggest that the nadir in erectile function after EBRT and BT is found during the first 24-36 months after treatment with relative stabilization subsequently (9,10,12,24). Siglin and colleagues and Van der Wielen and colleagues reported significant deterioration of erectile function in their EBRT populations during the first 12 and 24 months, respectively (10,12). Thereafter no significant changes were noted. In the retrospective EBRT/BT study by Wang et al. (24), the ED incidence increased from 22% at baseline to 52% after one year. At two- and four-year follow-up only a modest increase to 56% and 58% was found, respectively. Ong and colleagues (9) reported a notable proportion of patients developing ED within the first 3 months after LDR-BT, which might have been a reflection of decreased sexual activity. The proportion of men in each IIEF-category subsequently stabilized, and 59% had preserved erectile function at 5 years.

Others reported progressively increasing ED rates during longer-term follow-up (6,11). A dramatic decrease in adequate erectile function has been reported immediately post-treatment for both EBRT and BT patients (6,9,11,12,14,24). However, as the onset of changes in corporal smooth muscle, vascular (endothelial) tissue and neural tissue are delayed, these immediate changes in erectile function scores are likely, at least for the patient with good baseline erectile function, to be related to patient stress, anxiety, and reduced sexual self-confidence. The chronic and progressive nature of radiation-induced sexual problems requires sufficient follow-up in order to identify the true incidence of ED. Substantial variation was seen among the reviewed studies in the minimum follow-up length (Table 1), with six studies applying a minimum follow-up of only 3-6 months (9,11-13,15,16). Despite substantial differences in minimum follow-up duration, 16 of the reviewed studies reported mean or median follow-up of at least 24 months (Table 1), which should be considered a minimum to adequately interpret erectile function outcomes following radiation therapy.

Erectile aid use

A key issue in defining erectile function outcomes relates to the use of erectogenic medication such as phosphodiesterase type-5 inhibitors (PDE-5i) or other erectile aids. The NIH definition does not mention any form of medical assistance, where Common Terminology Criteria for Adverse Events (CTCAE) defines ED according to the need for erectile aids. Authors should clearly document and report whether patients reported natural erections or used any form of

erectile aids. The use of erectogenic medication was not reported in 7 of the reviewed studies (12,13,15,16,22-24) (Table 3). As for other studies, the wide variety in documented use of PDE-5i should be taken into account when reviewing erectile function outcomes. Only 5% of patients were prescribed PDE-5is in the study by Van der Wielen et al. (10), whereas up to 70% of all men had used PDE-5i at some point during follow-up in the study by Snyder et al. (7). In their cohort however, only 39% still used a PDE-5i at last follow-up after a median follow-up of 5.7 years. These discrepancies among the reviewed studies highlight some of the challenges in the reporting of erectile aid use, namely that the use of PDE-5i is frequently not well documented and many patients use PDE-5i intermittently or inconsistently. In general, authors should clearly document and report whether patients used any form of erectile aids

DISCUSSION

Despite evident links between prostate cancer treatment and its effects on in sexual function, this is infrequently discussed in the clinical setting (40). Due to the high workload, consultations might be more focused on treatment and disease response, instead of psychosexual issues (40). Discussing such matters is appreciated as time-consuming because sexual side effects after radiotherapy show great variability among patients. We have found substantial differences in the current literature on radiation-induced ED, which might prevent giving adequate patient guidance prior to treatment and during follow-up. Differences resulted from large variations in 1) study populations, 2) patient characteristics, 3) treatment characteristics, 4) prescription of androgen deprivation therapy, 5) means of data acquisition, 6) definitions of ED, 7) temporal considerations, and 8) erectile aid use. We have highlighted the strengths and deficiencies of the current literature on ED after EBRT and BT for prostate cancer. In addition to that, in Table 4 we have suggested what we considered to be the basic requirements for reporting erectile function outcomes after radiotherapy.

The fact that we included data from studies on various techniques and treatment regimens demonstrates that the suggestions are suitable to a broad range of radiotherapeutic prostate cancer treatments. However, by doing so, we decided not to conduct a formal systematic review, which focusses more on presenting and analyzing the actual data instead of discussing concepts and requirements of research design; this might be considered a limitation of this study.

Our recommended requirements might increase the level of homogeneity and comparability in future reports. Such parameters are desirable and should be included whenever possible, even though we do acknowledge that this might not always be feasible. Increased homogeneity is, however, desirable due the scarce availability of randomized trials comparing sexual outcomes

Table 4. Requirements for Reporting of Erectile Function Outcomes after Radiotherapy for Prostate Cancer

Methods of patient selection
Patient characteristics including comorbidity profile
Treatment characteristics including applied technique, dose constraints and treatment dose
Use and duration of androgen deprivation therapy
Baseline sexual function data
Methods of data collection
Use of validated questionnaire
Follow-up of at least 24-36 months
Definition of erectile function and erectile dysfunction
Proportion of men preserving erectile function
Use of erectile function aids

after different treatment modalities. For that matter the ProtecT trial by Donovan et al. should be applauded (23), as they randomized screening-based prostate cancer patients to RP (n=553) vs. EBRT (n=545) vs. active surveillance (n=545), using the EPIC questionnaires completed up to 6-years post-treatment. Erectile function was worse in the RP group at all time points as compared to both other treatments (23). Such studies are also required within the radiotherapy community to gain better insight in the actual differences between radiotherapy treatments in terms of health-related quality of life.

In conclusion, decision making between available options for treatment of localized prostate cancer is frequently influenced by the expected risk of treatment-induced side effects, such as ED. Substantial differences in erectile function outcomes after radiotherapy are present in the current literature. Key elements which contribute to this large variability in outcomes may include factors related to study population, patient and treatment characteristics, androgen deprivation therapy, means of data acquisition, follow-up duration, and the definition of erectile function. These factors should be taken into account when reviewing data on erectile function outcomes after radiation therapy for prostate cancer.

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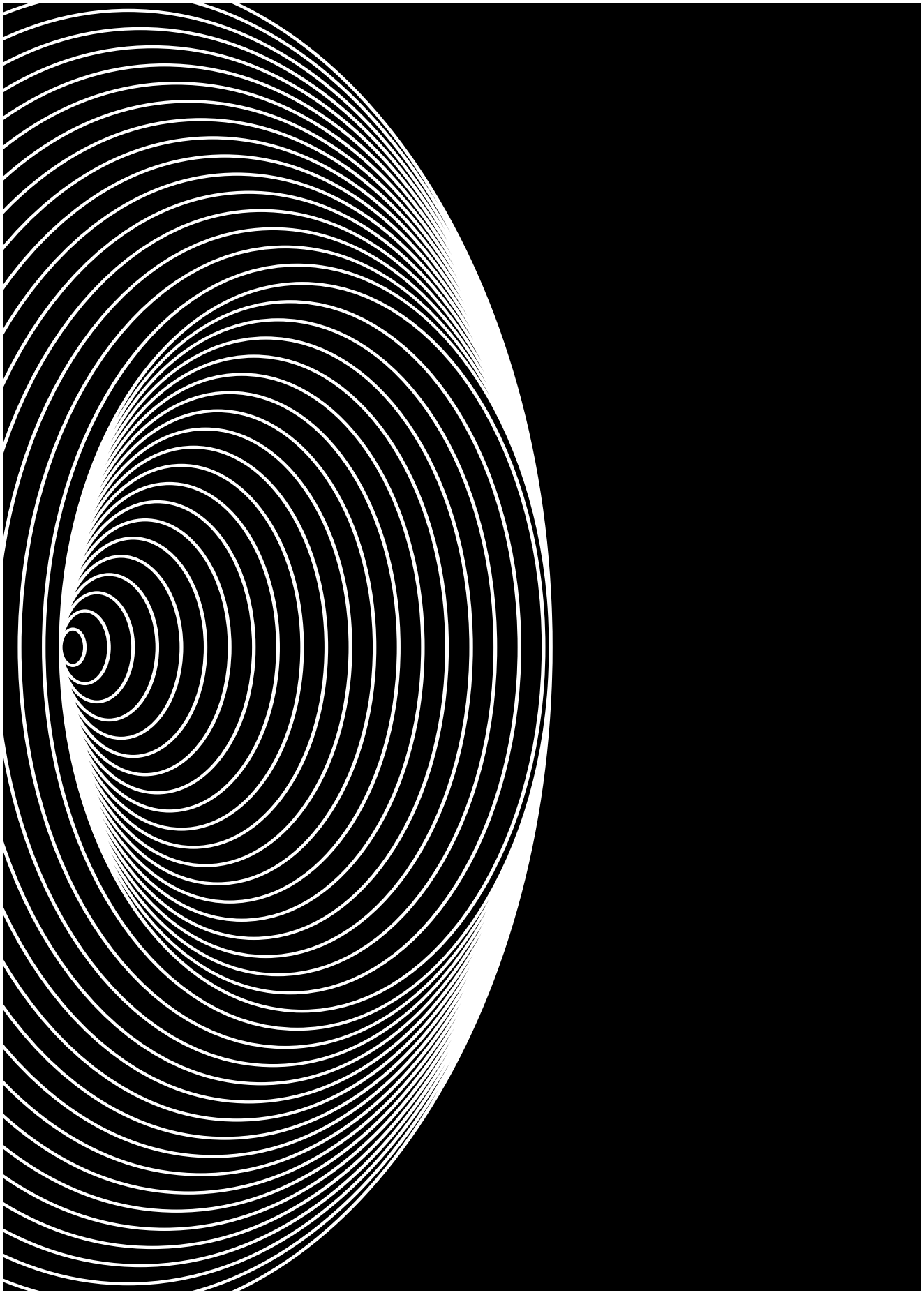

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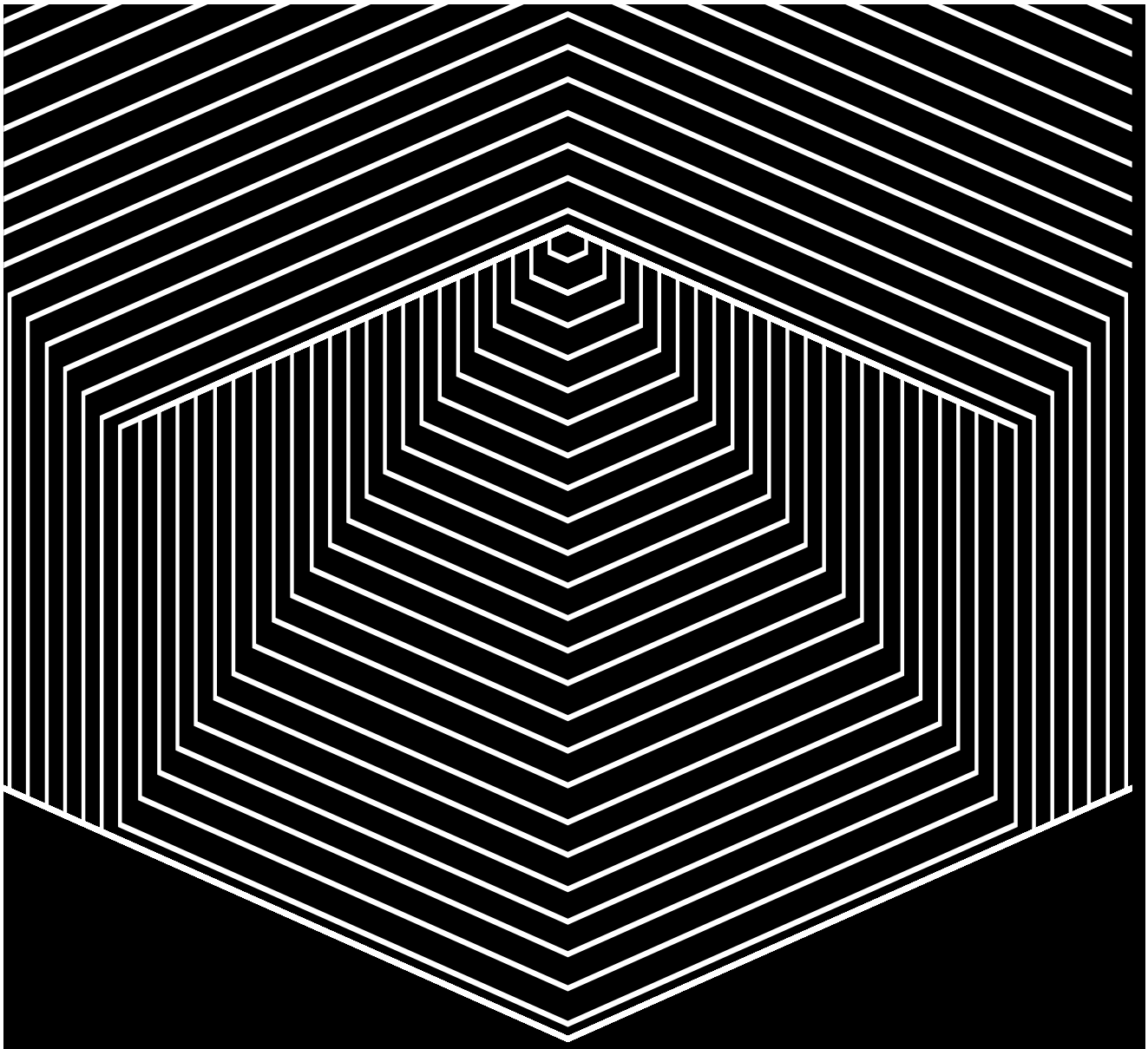

“THERE’S A LOT OF GOOD WAITING FOR YOU ON THE OTHER SIDE OF TIRED. GET YOURSELF TIRED.”

Andre Agassi, Open

CHAPTER 12

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In this thesis, we studied the impact of modern external beam radiotherapy and hypofractionation on treatment outcomes for patients with localized prostate cancer. In the first part (**Chapter 2-5**) we studied several technological evolutions in prostate cancer treatment, such as image-guided radiotherapy, intensity modulated radiotherapy (IMRT), use of magnetic resonance imaging (MRI) in treatment planning and their impact on radiation-induced side effects. In addition, we also studied the impact of local protocol variations on toxicity levels. The second (**Chapter 6-7**) and third (**Chapter 8-10**) part of this thesis primarily concerns results on treatment efficacy, and patient-reported outcomes on quality of life and sexual function from the Dutch phase 3 hypofractionation HYPRO trial (HYPRO). The concept of hypofractionation is generally attractive because such treatments consist of less fractions than conventionally fractionated treatments, resulting in reduced treatment costs, increased hospital capacity and improved patient convenience. The Dutch HYPRO trial has been designed to further improve relapse-free survival rates, while keeping toxicity risks at the same level, compared to currently achieved results with conventionally fractionated dose-escalated treatment regimens (1-3). In the current chapter we will discuss the studies performed including their impact on clinical practice. In addition, we will discuss future perspectives of clinical research on external beam radiotherapy for localized prostate cancer.

PART I: RADIATION-INDUCED TOXICITY

In **Chapter 2, 3 and 4** we have demonstrated that modern image-guided IMRT (IG-IMRT) reduced the risks and severity of radiation-induced toxicity compared to 3-dimensional conformal radiotherapy (3D-CRT) techniques, as we hypothesized. Our research confirmed the findings of previous planning studies showing that novel techniques such as IG-IMRT and volumetric modulated arc therapy (VMAT) reduce the dose to organs at risk without compromising the planning target volume (4-7). We demonstrated that reductions in the dose to organs at risk that were achieved with IG-IMRT resulted in the expected lower incidences of long-term gastrointestinal toxicities (37.6% grade ≥2 toxicities following 3D-CRT vs 24.9% following IG-IMRT; adjusted hazard ratio 0.59, p=0.005), whereas long-term genitourinary toxicity remained similar (36.4% grade ≥2 toxicities after 3D-CRT vs 46.2% after IG-IMRT; adjusted hazard ratio 1.19, p=0.33). This might be related to the fact that the bladder neck and prostatic urethra are inevitably included in the planning target volume with both techniques. To date, however, dose constraints for the bladder have not been well-defined and therefore hardly used in clinical practice. It has been demonstrated that dose to sub-regions of the bladder is associated with toxicity risks in a 3D-CRT population (8). In future analyses of the HYPRO trial we plan to

investigate whether we can identify anatomic regions within the bladder which are associated with its toxicity in an IG-IMRT population treated with either conventional- or hypofractionation. Such data might lead to the development of clinically relevant dose constraints, and subsequent reductions in genitourinary toxicities for future patients.

In **Chapter 5** we have established that local protocol variations between participating hospitals of the HYPRO trial were associated with differences in anorectal dose distributions and gastrointestinal toxicity in patients treated with IG-IMRT. The incorporation of magnetic resonance imaging (MRI) in treatment planning and use of an endorectal balloon were associated with reduced gastrointestinal toxicity, whereas a 2-3 mm difference in safety margins did not translate into differences in toxicity. Especially the use of MRI, which offers superior soft tissue contrast, might be attractive in treatment planning as a means to decrease dose to organs at risk (9). The results of this study should be interpreted with caution as we might have overlooked differences in treatment planning procedures between hospitals that could have influenced toxicity rates as well. Planning studies have demonstrated that prostate volumes delineated using MRI are smaller compared to CT-based delineation, which generally leads to reduced dose exposure to organs at risk (10-12). In future analyses of the HYPRO trial we should compare the oncological outcomes of the MRI-delineated patients versus CT-delineated patients in order to determine whether MRI delineation did not negatively affect tumor control.

PART II: TREATMENT EFFICACY

In **Chapter 6** we presented the results on treatment efficacy from the phase 3 randomized HYPRO trial, which compared 19 fractions of 3.4 Gy versus 39 fractions of 2 Gy in patients with intermediate- or high-risk localized prostate cancer. In the HYPRO trial, we could not demonstrate the hypothesized superiority of the hypofractionated treatment regimen over the conventional treatment. Comparable 5-year relapse-free survival rates of 80.5% after hypofractionation versus 77.1% after conventional fractionation were achieved (p=.0.36). Based on these results and the fact that non-inferiority of hypofractionation in terms of acute and late toxicity was previously not demonstrated, we could not recommend the HYPRO treatment schedule as new standard of care (13,14). In line with the results from the HYPRO trial, Pollack et al. (15) from Fox Chase Cancer Center could also not demonstrate the proposed superiority of hypofractionation in 303 patients treated with 38 fractions of 2 Gy or 26 fractions of 2.7 Gy. Instead of the hypothesized reductions in treatment failure of 15% with the hypofractionated treatment schedule, similar 5-year relapse free survival rates of 77% for hypofractionation and 79% for conventional fractionation were achieved. Based on the phase 3 HYPRO and Fox Chase Cancer Center trials, superiority of hypofractionation in terms of treatment efficacy has

to date not been demonstrated. In contrast, several non-inferiority trials have been able to demonstrate that moderately hypofractionated radiotherapy was non-inferior to conventional fractionation, and should therefore be considered as a clinically attractive alternative in prostate cancer treatment. An overview of relevant clinical trials has been presented in **Chapter 7.** The randomized phase 3 CHHiP trial demonstrated in 3216 patients with mainly intermediate risk prostate cancer that 60 Gy in 20 fractions was non-inferior to 74 Gy in 37 fractions (16). In addition, the RTOG 0415 trial demonstrated in 1115 patients with low-risk features that 70 Gy in 28 fractions was non-inferior to 73.8 Gy in 41 fractions (17). Finally, the PROFIT trial recently demonstrated non-inferiority of 60 Gy in 20 fractions versus 78 Gy in 39 fractions in patients with intermediate risk prostate cancer (18).

In general, a growing body of evidence is available at present to conclude that moderately hypofractionated treatment regimens are non-inferior to conventionally fractionated treatments (19). Based on the non-inferiority trials (16-18), Royce et al. (20) recently conducted a systematic review and meta-analysis. The applied hypofractionated schedules compared with the conventional schedules, pooled over the studies were associated with significantly improved relapse-free survival in men with intermediate-risk prostate cancer (HR=0.87, p=0.047). At the same time, late grade 2 or higher genitourinary toxicity were more frequently observed after hypofractionation (20). They concluded that hypofractionation might be the preferred treatment in men with intermediate-risk prostate cancer, provided that those with risk factors for late genitourinary complications are excluded.

As such moderately hypofractionated treatments will be further integrated into clinical practice, future studies will continue to identify the optimal treatment regimen. Recently, clinical phase 1-2 studies with extremely hypofractionated radiotherapy delivered using stereotactic body radiation therapy techniques have been conducted (21-25). These studies show excellent results as presented in **Chapter 7.** Phase 3 randomized trials comparing moderately hypofractionated treatments with extremely hypofractionated treatments in larger patient groups, delivered via stereotactic body radiation techniques either using the Cyberknife® system or state-of-the-art gantry-based linear accelerators, should be conducted to verify these positive results in small patient series.

PART III: QUALITY OF LIFE AND SEXUAL FUNCTION

Successful treatment for prostate cancer includes besides cure, also retaining good quality of life. The patient-reported outcomes on health-related quality of life from the HYPRO trial **(Chapter 8)** demonstrated that the majority of patients in both arms experienced no deterioration in

gastrointestinal and genitourinary quality of life at 36 months after treatment, whereas sexual function was severely impaired. Non-inferiority of hypofractionation was demonstrated for sexual function, sexual activity and androgen-deprivation therapy related complaints, whereas we could not demonstrate non-inferiority for the genitourinary and gastrointestinal quality of life domains of the EORTC-PR25 prostate cancer specific quality of life questionnaire. In the CHHiP trial comparable patient-reported symptoms were found between the treatment groups; a non-inferiority test was however not performed (26). The hypofractionation trial from Fox Chase Cancer Center also presented patient-reported outcomes and found no significant differences between both treatments over time (27).

As we shift towards patient-reported quality of life as a means to evaluate outcome of treatment a deeper understanding of the cause of decreases in quality of life is required. Future HYPRO analyses will be done to identify to what extent grade 2 or worse toxicity according to the Radiation Therapy Oncology Group- European Organization for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria correlate to changes in health-related quality of life. These analyses should establish which specific RTOG-EORTC toxicities provoked negative changes in the specific quality of life domains.

The quality of life data analysis of the HYPRO trial demonstrated substantial impairments in the sexual function quality of life subscale within both arms of the HYPRO trial. Impaired sexual functioning might in part be the result of long-term androgen-deprivation therapy that was frequently prescribed. In **Chapter 9** we have separately studied sexual function in patients who were not on long-term androgen deprivation therapy. With follow-up up to 3 years, no differences in erectile function were found between both study arms with erectile dysfunction rates of 34.4% and 39.3% after hypofractionation and conventional fractionation, respectively (p=0.67). These data indicate that patients in both treatment arms experienced severe adverse effects on sexual function.

Sanda et al. (28) have previously demonstrated that sexual function was closely related to treatment outcome satisfaction. Expectations on preservation of sexual function could therefore play a decisive role in the process of treatment choice. In the overview of available modern literature on radiation-induced erectile dysfunction **(Chapter 10)**, we found large discrepancies in the reported erectile function preservation rates, ranging between 22% and 70% after external beam radiotherapy. In part, these discrepancies are the result of differences in patient populations, prescribed treatments, definitions of erectile dysfunction, means of data collection and presentation. We made recommendations for reporting of erectile function outcomes after radiotherapy to improve homogeneity of future reports. This should be the first step to increase transparency and improve clinical interpretability.

Attempts to improve post-radiation sexual outcomes should also be initiated. In line with the surgical strategy of the nerve-sparing radical prostatectomy as a means to preserve sexual function, radiotherapy regimens focused on erectile preservation could also be designed. Such attempts to improve sexual function outcomes might, however, compromise the chance of curation. Implementation of MRI in the clinical workflow is crucial; not only will MRI treatment planning improve prostate delineation, it will also enable to define the critical structures such as the neurovascular bundles and the internal pudendal arteries (29). These structures show a high extent of variation from the classical anatomy, and the improved accuracy of MRI over CT would allow personalized treatment plans aimed at sexual preservation (29). Medical treatments to protect male sexual function during radiotherapy might some day also be introduced. Prospective clinical data from Memorial Sloan Kettering Cancer Center suggested that Sildenafil during and after radiotherapy was associated with better sexual function outcomes compared to placebo (30). In order to unravel the mechanisms by which such protective effects of sildenafil on erectile function are mediated, we conducted *in vitro* radiotherapy studies on endothelial cells and demonstrated that Sildenafil had protective effects against radiation induced oxidative stress, endothelial dysfunction and apoptosis **(Chapter 11).** These studies require further *in vivo* studies.

In summary, we proposed the following clinical research perspectives:

- Identify anatomic regions within the bladder that are associated with bladder toxicities, in order to construct bladder dose constraints and subsequently attempt to further reduce toxicity levels.

- Further study the relation between radiation-induced toxicities and patient-reported quality of life.

- Facilitate implementation of MRI in treatment planning, in order to further study the impact of its improved soft tissue contrast on tumor control, dose reductions to organs at risk, and vessel-sparing radiotherapy for erectile function preservation.

- Initiate new randomized trials, comparing moderately hypofractionated treatments with more extremely hypofractionated treatments. For this purpose, either novel gantry-based linear accelerators or the Cyberknife® system could be used to deliver stereotactic body radiation.

CONCLUSION

The work in this thesis has provided important insights in the relationship between treatment techniques and risks of radiation-induced side effects. The results of the HYPRO trial presented in this thesis contributed to the exciting debate about hypofractionation and the developing evidence supporting the use of moderately hypofractionated treatment regimens. The hypofractionated treatment schedule as applied in the HYPRO trial has, however, demonstrated to be non-superior to the conventional treatment, and can therefore not be recommended as new standard of care. Future studies should be done to further improve treatment efficacy while minimizing treatment-related side effects.

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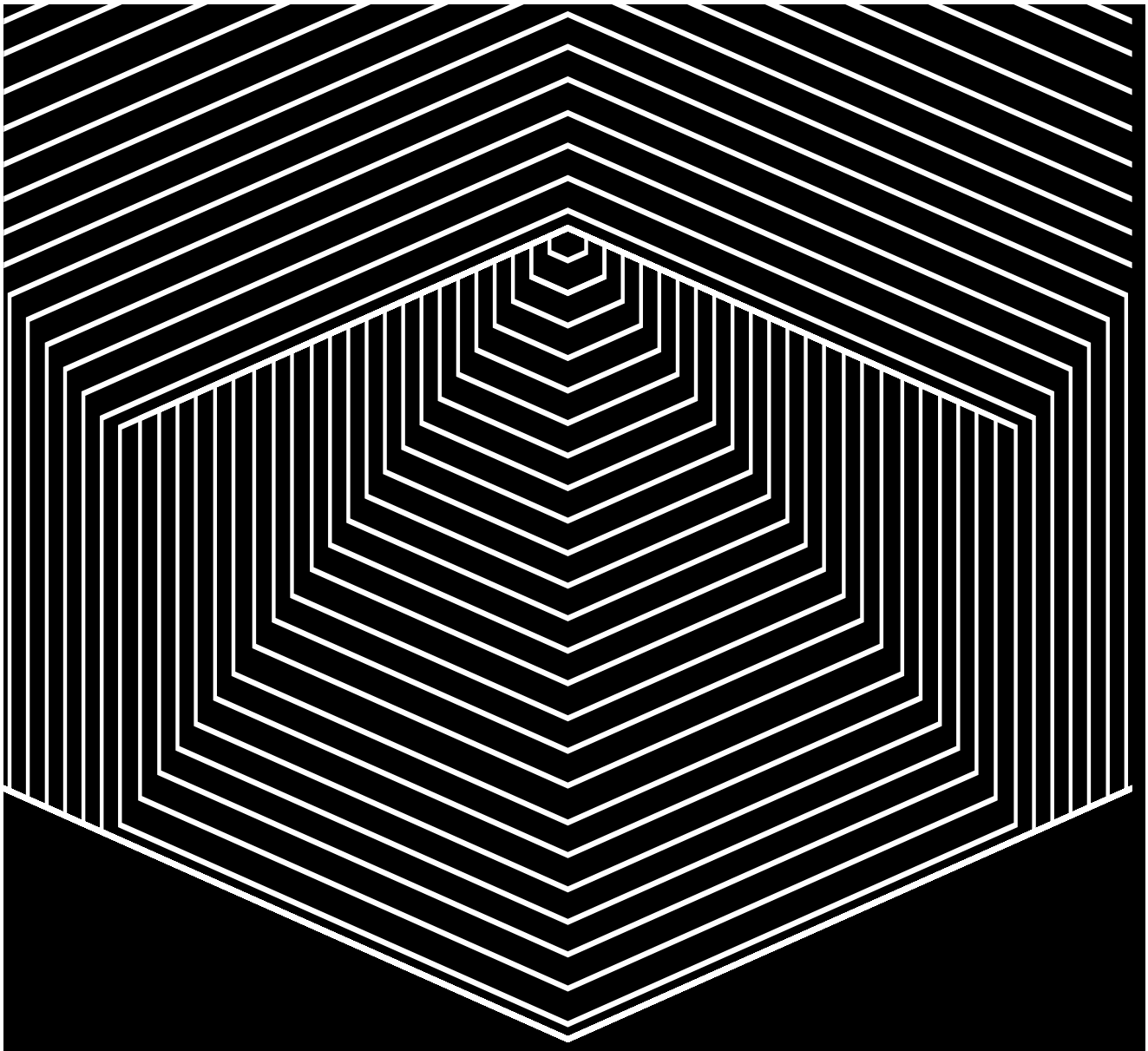


“BEGIN ALTIJD MET HET EINDE IN GEDACHTE.”

Eberhard van der Laan

CHAPTER 13

Summary

Summary in Dutch | Nederlandse samenvatting

SUMMARY

This thesis describes the results of studies on the effects and side effects of novel techniques and treatment schedules in radiotherapy for prostate cancer. In **Chapter 1** we provided a general introduction and outline of the thesis. This thesis is subsequently divided in three parts. Part I focusses on radiation-induced gastrointestinal and genitourinary side effects associated with novel treatments. Part II focusses on treatment efficacy of hypofractionated radiotherapy. In Part III, quality of life and sexual function after modern EBRT are studied.

PART I: RADIATION-INDUCED TOXICITY

In **Chapter 2** we compared the acute side effects in patients treated to 78 Gy in 39 fractions using either 3-dimensional conformal radiotherapy (3D-CRT) or image-guided intensity modulated radiotherapy (IG-IMRT). Patients treated with 3D-CRT (n=215) were selected from a previous dose-escalation trial (CKTO-9610), whereas IG-IMRT patients were selected from a more recent hypofractionation trial (HYPRO trial) (n=260). The incidence of patient-reported Radiation Therapy Oncology Group (RTOG) grade ≥2 gastrointestinal toxicity was significantly lower after IG-IMRT compared to 3D-CRT, with cumulative incidences of 29% vs. 49%. With incidences of 38% after IG-IMRT vs 48% following 3D-CRT, the differences in grade ≥2 genitourinary toxicity were less distinct but still statistically significant. In this study we also demonstrated significant reductions in mean dose to the bladder, anorectum and anal canal, using IG-IMRT compared to 3D-CRT. We conclude that clinically relevant dose reductions and acute toxicity reductions have been achieved with the introduction of IG-IMRT, implying tighter safety margins, improved technique, and improved dose constraints.

In **Chapter 3** we studied anorectal dose distributions and its relation to acute gastrointestinal toxicities in the same 3D-CRT and IG-IMRT patient populations. For this purpose, two-dimensional dose-surface maps were generated for the complete anorectum, anal canal and high-dose region of the rectum next to the prostate for each individual patient. In a second step, average dose maps were created for each specific toxicity: an average map for patients with and without the toxicity. Subsequently, dose difference maps were constructed, which showed significant relationships between acute rectal toxicity and local dose distributions. These relationships may serve as a basis for dose-effect modeling and subsequent improved dose constraints.

In **Chapter 4** we compared the late side effects in the IG-IMRT and 3D-CRT population. Treatment with IG-IMRT resulted in significantly lower incidences of RTOG-EORTC late grade ≥2

gastrointestinal toxicity with 5-year cumulative incidences of 24.9% vs 37.6%, whereas genitourinary toxicities were comparable. A remarkable finding was that rectal incontinence rates where however not reduced. Based on the data provided in **Chapters 2, 3, and 4** we concluded that IG-IMRT is associated with clinically relevant reductions in dose to organs at risk and toxicity rates compared to 3D-CRT techniques.

In **Chapter 5** we investigated the effect of local protocol variations on toxicity risks, in patients treated with IG-IMRT in participating centers of the HYPRO trial. Reference center A (n=242 patients) used the smallest safety margins of 5-6 mm, as compared to 7 mm in center B (n=170) and center C (n=85), whereas the larges safety margins of 8 mm were used in center D (n=75). Treatment center B used magnetic resonance image (MRI) scans for treatment planning, whereas all other centers used CT scans only. In center C, an endorectal balloon was inserted rectally prior to each fraction. By inserting this endorectal balloon, the posterior side of the rectum is pushed outside of the high-dose region surrounding the prostate. The results demonstrated favorable dose distributions in center B (MRI delineation) and center C (endorectal balloon) as compared with centers A and D. These favorable dose distributions were associated with significantly lower incidences of patient-reported complaints of rectal incontinence, use of incontinence pads, and rectal discomfort in both centers. In addition, lower incidences of increased frequency of stools (≥4 per day) and mucous loss were observed for center C. We concluded that the use of MRI delineation and endorectal balloon application were associated with favorable rectal dose distribution and toxicity profiles, whereas the use of 2-3 mm smaller safety margins as applied in center A as compared to center D did not translate into observed toxicity reductions. This might indicate a suboptimal treatment plan optimization process in this center.

PART II: TREATMENT EFFICACY

In **Chapter 6** we presented the final efficacy results of the HYPRO trial. The primary objective of this trial was to demonstrate superiority of the hypofractionated regimen of 19 fractions of 3.4 Gy over conventional fractionated treatment of 29 fractions of 2.0 Gy in terms of relapse-free survival. The 5-year relapse-free survival rates were 80.5% for patients assigned hypofractionation and 77.1% for those allocated to conventional fractionation. These differences were not statistically significant, and hypofractionation was therefore not superior to conventional fractionated treatment. Based on these results and fact that previous reports demonstrated that hypofractionation resulted in higher toxicity levels than conventional fractionation, we concluded that hypofractionation cannot be regarded as the new standard of care for patients with intermediate-risk and high-risk prostate cancer. Sub-analysis

demonstrated that hypofractionation might be offered to patients with few genitourinary and gastrointestinal baseline symptoms. In **Chapter 7** we provided a critical overview of the currently available results of hypofractionation trials. In this chapter we concluded that substantial evidence is available suggesting that moderate hypofractionation is non-inferior to conventionally fractionated treatments. Hypofractionated treatments will therefore be integrated into clinical practice more frequently and future research will continue to investigate new and more extremely hypofractionated treatments.

PART III: QUALITY OF LIFE AND SEXUAL FUNCTION

In **Chapter 8** we presented the 5-year patient-reported outcomes on quality of life from the HYPRO trial. The validated European Organization of Research and Treatment of Cancer (EORTC) quality of life questionnaire prostate cancer module (PR25) was used to assess quality of life related to gastrointestinal symptoms, genitourinary symptoms, sexual functioning, sexual activity, and complaints related to androgen-deprivation therapy. We could not demonstrate non-inferiority of hypofractionation for gastrointestinal- and genitourinary quality of life, whereas non-inferiority was demonstrated for sexual functioning, sexual activity, and complaints related to androgen deprivation therapy.

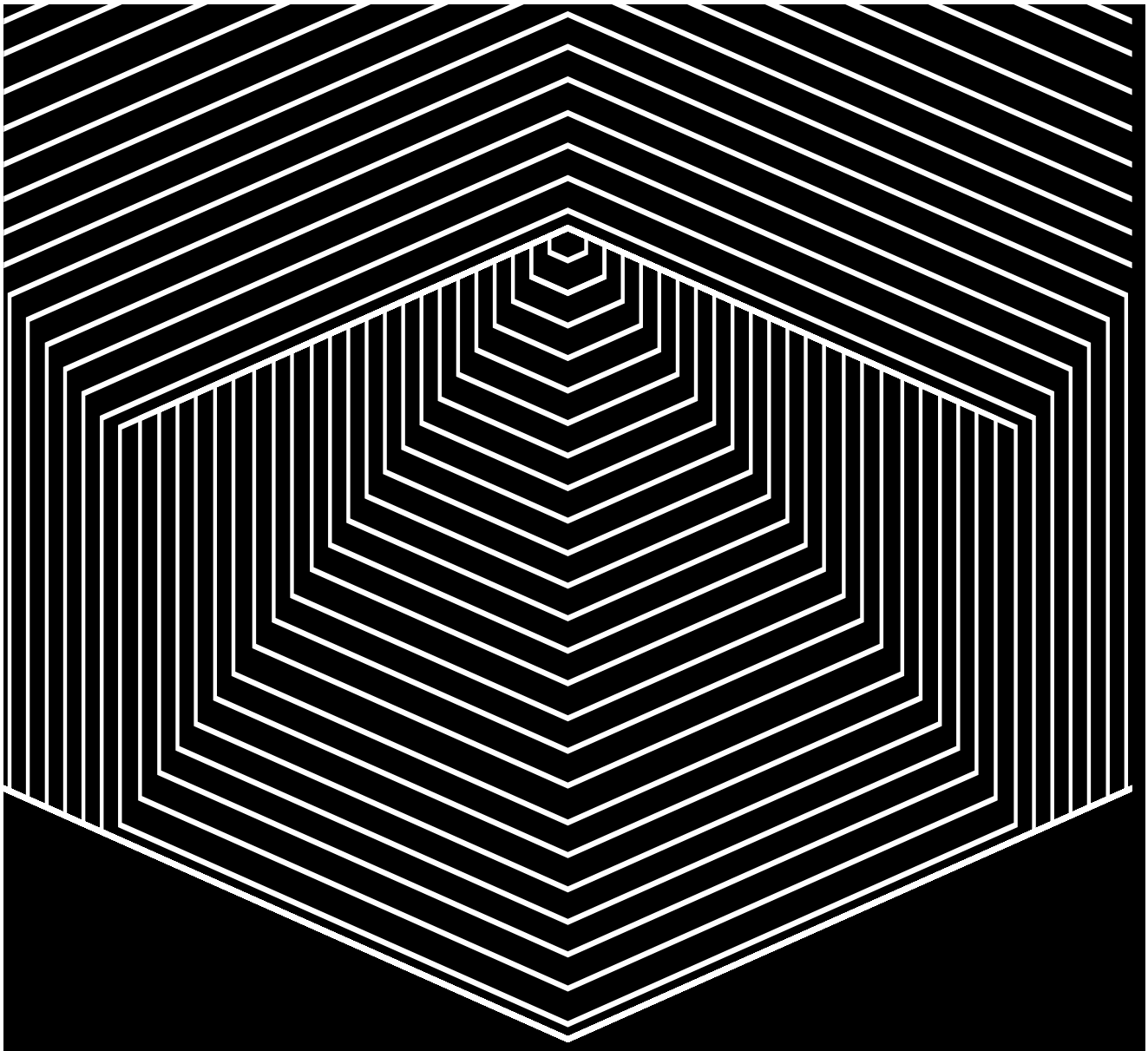
In **Chapter 9** we discussed the results of the sexual function outcomes of the HYPRO trial. Sexual function was measured using the International Index of Erectile Function (IIEF) questionnaire, which comprises 15 questions on five domains of male sexual function. To minimize the effects of androgen-deprivation therapy on long-term sexual function, all patients with androgen-deprivation therapy for more than six months were excluded. At 3-years, no significant differences in erectile functioning were found between hypofractionation and conventional fractionation. In patients with partial of full erections at baseline, the incidence of erectile dysfunction at last follow-up was 34.4% for hypofractionation vs 39.3% for conventional fractionation. These data demonstrate that both radiotherapy protocols have substantial adverse effects on sexual function.

In **Chapter 10** we have reviewed contemporary literature on erectile function after radiotherapy in order to analyze the cause of discrepancies in reported erectile dysfunction rates that are present in literature on radiation-induced erectile dysfunction. Based on our findings, we presented general recommendations for reporting of erectile function outcomes after radiotherapy for prostate cancer. These should improve the quality and homogeneity of future reports, which also benefits clinical interpretability.

In **Chapter 11** we present the results of *in vitro* studies that were performed in collaboration with Memorial Sloan Kettering Cancer Center in New York. A prospective clinical study from that hospital demonstrated that the use of Sildenafil (Viagra©) during and after radiotherapy was associated with improved sexual function compared with placebo. They hypothesized that Sildenafil might have a protective effect on endothelial cells, which are essential for adequate penile erections. We demonstrated in bovine endothelial cells that Sildenafil significantly inhibited radiation-induced overproduction of the *reactive oxygen species* superoxide, which is a potent inducer of oxidative stress and endothelial dysfunction. In addition, Sildenafil also inhibited the pro-apoptotic ASMase/ceramide pathway, which resulted in decreased levels of endothelial apoptosis. Future *in vivo* studies should further unravel the mechanisms by which the protective effects of sildenafil are mediated.

In **Chapter 12** we reflected on the findings presented in this thesis about relationships between different radiation treatments for prostate cancer and tumor control, toxicity, and quality of life. We discussed its relevance for clinical practice and presented future research options to further optimize radiotherapy for prostate cancer.

In conclusion, the work in this thesis has demonstrated important insights in the relationship between radiation techniques and risks of radiation-induced side effects. In addition, the results of the Dutch HYPRO trial have revealed that the hypofractionated treatment of 19 fractions of 3.4 Gy results in similar relapse-free survival rates as compared to the conventionally fractionated treatment of 39 fractions of 2.0 Gy in men with localized prostate cancer. The hypofractionated treatment cannot be regarded as new standard of care because of the increased risks of radiation-induced side effects that were associated with the treatment.



**“ALS IK ZOU WILLEN DAT JE HET BEGREEP,
HAD IK HET WEL BETER UITGELEGD.”**

Johan Cruijff

CHAPTER 13

Summary

Summary in Dutch | Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift richt zich op de radiotherapeutische behandeling van prostaatkanker. De prostaat is een klier gelegen vlak onder de blaasuitgang en rondom de plasbuis. Deze maakt deel uit van het mannelijk voortplantingssysteem en produceert prostaatvocht waarmee zaadcellen tijdens de ejaculatie vervoerd worden. In Nederland wordt jaarlijks bij ruim 11.000 mannen prostaatkanker geconstateerd (1). De diagnose wordt bij klinische verdenking in de regel gesteld door echogeleide biopsie van de prostaat. Ongeveer de helft van alle patiënten is 70 jaar of ouder op het moment van diagnose (1).

De meerderheid van de patiënten heeft bij diagnose geen uitzaaiingen buiten de prostaat, waardoor ze in aanmerking komen voor een behandeling die zich richt op volledige genezing. Een van deze behandelingen betreft uitwendige radiotherapie (bestraling) van de prostaat, waarbij gebruik wordt gemaakt van straling met een hoge energie. Het doel van radiotherapie is het vernietigen van het erfelijk materiaal in de kankercellen, waardoor geen celdeling meer kan optreden en de kankercellen afsterven. Wetenschappelijk onderzoek en technische ontwikkelingen binnen de radiotherapie hebben zich gedurende de laatste decennia voornamelijk gericht op het verhogen van de bestralingsdosis op de prostaat, het verlagen van de ongewenste dosis op omliggende organen zoals de blaas en de endeldarm, en het vaststellen van het optimale bestralingsschema.

Hoofdstuk 1 biedt een algemene inleiding over prostaatkanker en de radiotherapeutische behandeling hiervan. De ontwikkeling van moderne bestralingstoestellen heeft in de jaren '80 geleid tot de introductie van 3-dimensionale (3D) conformele radiotherapie. Met behulp van CT-scans en planningssystemen, programma's waarmee radiotherapie-behandelplannen geconstrueerd worden, kan het 3-dimensionale bestralingsveld precies bepaald worden. Belangrijk onderdeel hierbij zijn de zogeheten intekeningen, waarbij handmatig de contouren van de prostaat en andere relevante structuren geïdentificeerd worden op elke doorsnede van de CT-scan. Aan de hand van deze intekeningen wordt een 3-dimensionale weergave van de relevante structuren gegenereerd en kan uiteindelijk een behandelplan worden gemaakt. Doel van het behandelplan is om de geplande bestralingsdosis af te leveren op de prostaat, terwijl de ongewenste dosis op de omliggende weefsels zo laag mogelijk wordt gehouden. De totale behandeldosis wordt afgegeven in meerdere doses (fracties). Ten tijde van de introductie van 3D-conformele radiotherapie bedroeg de reguliere bestralingsdosis voor prostaatkanker 64-70 Gray (Gy), verdeeld over dagelijkse fracties van 1,8-2,2 Gy.

In de jaren daarna hebben verschillende grote patiënt-gerelateerde klinische onderzoeken aangetoond dat het verhogen van de totale bestralingsdosis tot 74-78 Gy een positief effect heeft op de tumorcontrole. Zo vergeleek de Nederlandse CKTO 96-10 trial in een onderzoekspopulatie

van 669 patiënten de standaardbehandeling van 68 Gy in 34 fracties met een experimentele behandeling van 78 Gy in 39 fracties. Na een follow-up van 5 jaar bleek de tumorcontrole in de groep die bestraald werd tot 78 Gy significant beter dan in de controlegroep. Ondanks het feit dat bijwerkingen van de blaas en endeldarm frequenter voorkwamen na behandeling tot 78 Gy, werd dit nieuwe schema landelijk ingevoerd (2).

De invoering van intensiteit-gemoduleerde radiotherapie (IMRT) zorgde voor een verdere toename van de precisie van radiotherapie. IMRT heeft het vermogen straling af te geven met verschillende intensiteit. Dit komt goed van pas bij het bestralen van de prostaat, aangezien gezond weefsel zeer nabij gelegen is. Door middel van beeld-geleide IMRT, waarbij voorafgaand aan het bestralingstraject 3 tot 4 kleine goudmarkers in de prostaat worden ingebracht, werd de precisie van bestraling verder geoptimaliseerd. Deze goudmarkers worden dagelijks voorafgaand aan de bestralingsfractie radiologisch in beeld gebracht, waardoor de precieze anatomische locatie van de prostaat in het bekken beter gevisualiseerd kan worden. Voordat goudmarkers in de praktijk werden gebruikt werd de anatomische locatie van de prostaat, en daarmee het bestralingsveld, bepaald door middel van de onderlinge relatie van de prostaat en de botten van het bekken, hetgeen een grotere foutmarge kent. Door deze toename in nauwkeurigheid werd het mogelijk om de dosis op omliggend gezond weefsel te verlagen door veiligheidsmarges van het bestralingsveld te verkleinen. Omdat het belangrijk is dat de gehele prostaat bestraald wordt, zijn deze veiligheidsmarges vereist om te corrigeren voor bijvoorbeeld onzekerheden tijdens het instellen en afleveren van de bestralingsdosis, of bewegingen van de prostaat tijdens het afleveren van de fractie. Marges variëren in de regel van 3 tot 10 mm en worden rondom de prostaat toegevoegd aan het gebied dat bestraald wordt. Indien ruimere veiligheidsmarges worden toegepast, zal de bestralingsdosis dus onvermijdelijk voor een deel afgegeven worden op omliggend gezond weefsel, waarmee de kans op bijwerkingen vergroot wordt.

Ondanks de technologische ontwikkelingen werden mogelijkheden om bestralingsdoses boven 80 Gy in reguliere fracties van circa 2 Gy toe te dienen beperkt geacht, gezien de kans op ernstige bijwerkingen van de omliggende blaas en endeldarm. Daarnaast zou een verhoging van de dosis leiden tot een verdere toename van de behandelduur, waardoor de kwaliteit van leven van patiënten negatief beïnvloed zou worden. Verschillende onderzoeken hebben aangetoond dat gehypofractioneerde radiotherapie de totale behandeldosis mogelijk wel kan verhogen zonder dat het aantal fracties, en daarmee de behandelduur, verhoogd wordt. Bij gehypofractioneerde radiotherapie is er sprake van een vermindering van het aantal fracties, maar wordt een hogere dosis per fractie toegediend. Deze vorm van radiotherapie wordt als potentieel zeer effectief beschouwd bij prostaatkanker, aangezien verschillende radiobiologische modellen hebben aangetoond dat prostaatkankercellen zeer gevoelig zijn voor grotere fractie-doses (3-5). Door de voor prostaatkanker kenmerkende langzame celdeling vindt er bij reguliere (conventionele)

bestraling herstel van de aangebrachte schade plaats tussen de fracties door. De hogere fractiedosis bij gehypofractioneerde bestraling zorgt direct voor onherstelbare schade aan het DNA en daarmee voor een betere uitkomst. Daarnaast is hypofractioneren ook goedkoper en patiëntvriendelijker gezien het lagere aantal fracties en dus een kortere behandelduur.

In de periode 2007- 2010 werd in Nederland de HYPRO trial uitgevoerd, waarin 820 prostaatkanker patiënten werden behandeld middels conventionele bestraling van 78 Gy in 39 fracties van 2,0 Gy of gehypofractioneerde bestraling bestaande uit 19 fracties van 3,4 Gy. Radiobiologische calculaties hebben aangetoond dat de omgerekende biologische dosis op de prostaat in de gehypofractioneerde groep hoger is dan in de conventionele groep, hetgeen volgens de hypothese zou leiden tot een verbetering van de tumorcontrole na 5 jaar follow-up. Doordat het omliggende weefsel minder gevoelig is voor hogere fractiedoses, zou het aantal bijwerkingen van de blaas en endeldarm niet verschillend zijn tussen beide groepen. De mate van ernst van bijwerkingen wordt binnen de radiotherapie geclassificeerd aan de hand van Europese criteria en ingedeeld van graad 1 (mild) t/m graad 4 (zeer ernstig). Bijwerkingen van de blaas betreffen bijvoorbeeld urineverlies waarvoor meer dan 2x per week luiergebruik (graad 2), of hematurie (bloed in de urine) waarvoor behandeling nodig is (graad 2), of nycturie (plasfrequentie ≥6 per nacht, graad 3), terwijl darmklachten zich kunnen presenteren als stoelgang ≥6x per dag (graad 2), of diarree waarvoor meer dan twee keer per dag medicatie nodig is (graad 3).

Dit proefschrift richt zich op bijwerkingen, oncologische resultaten, kwaliteit van leven en seksueel functioneren na radiotherapie. Het behandelt de resultaten van klinische onderzoeken naar de effecten en bijwerkingen van eerdergenoemde nieuwe technieken en bestralingsschema's.

DEEL I: BIJWERKINGEN VAN RADIOTHERAPIE

In **Hoofdstuk 2, 3 en 4** onderzochten wij bij prostaatkankerpatiënten in hoeverre het gebruik van beeld-gestuurde IMRT-technieken het risico op vroege en lange-termijn bijwerkingen heeft verlaagd ten opzichte van 3D-conformele technieken. Beide technieken worden wereldwijd veelvuldig gebruikt. Voor onze onderzoeken werden twee patiëntengroepen vergeleken die dezelfde dosisvoorschriften van 78 Gy (39 fracties van 2 Gy) hadden gekregen, waarbij de ene groep behandeld werd met een 3D-conformele techniek, en de andere met een beeldgeleide IMRT-techniek. Identieke bijwerkings-scores en vragenlijsten waren beschikbaar, omdat alle patiënten waren behandeld in studieverband. Patiënten die waren bestraald middels 3D-conformele radiotherapie waren geïncludeerd in de bovengenoemde CKTO 96-10 trial

(1997-2003), terwijl patiënten in de beeld-geleide IMRT-groep waren geselecteerd uit de meer recente HYPRO trial (2007-2010).

In **Hoofdstuk 2** tonen wij aan dat beeld-geleide IMRT ten opzichte van 3D-conformele radiotherapie leidt tot een significant lager optreden van vroege bijwerkingen. Gedurende de behandeling tot aan de eerste 90 dagen na afronding werden matig tot ernstige (graad ≥2) darmbijwerkingen ondervonden door 29% van de geselecteerde 260 patiënten behandeld met beeld-geleide IMRT en 49% van de 215 patiënten die 3D-conformele radiotherapie hadden ondergaan. Voor blaasbijwerkingen waren de verschillen minder uitgesproken, maar desalniettemin significant: 38% ondervond graad ≥2 bijwerkingen na beeld-geleide IMRT versus 48% na 3D-conformele radiotherapie. Een verklaring voor deze verschillen lijkt de vermindering in bestralingsdosis op de blaas, endeldarm en anus, hetgeen mogelijk is doordat beeld-geleide IMRT met grotere precisie geleverd wordt waardoor kleinere veiligheidsmarges toegepast worden.

In **Hoofdstuk 3** hebben we in dezelfde patiëntenpopulatie onderzocht of er aantoonbare relaties aanwezig waren tussen de dosisverdeling van de endeldarm en het optreden van acute darmbijwerkingen. Hiervoor werd gebruik gemaakt van de 3-dimensionale planning CT-scans, waarmee zogenaamde dose surface maps werden gegenereerd. Deze maps geven een 2-dimensionale weergave van de dosisverdeling van de anus, het deel van de endeldarm rondom de prostaat, en de gehele endeldarm. Door middel van deze dose surface maps hebben we vast kunnen stellen dat de dosisverdeling bij patiënten met specifieke bijwerkingen verschillend was ten opzichte van patiënten die een dergelijke bijwerking niet ontwikkelden. Voor proctitis bijvoorbeeld, een ontsteking van de endeldarm die frequent voorkomt na bestraling, werden in de achterwand van de endeldarm en het gebied van de darm boven de prostaat dosisverschillen tot wel 10 Gy waargenomen tussen patiënten met en zonder deze bijwerking. Deze informatie is relevant en kan dienen als leidraad voor vervolgstudies waarbij zogenaamde dose constraints (dosisbeperkingen) voor bepaalde gebieden worden vastgesteld waaraan een behandelplan in de toekomst zou moeten voldoen.

In **Hoofdstuk 4** hebben we laten zien dat beeld-geleide IMRT ook leidt tot lagere lange-termijn graad ≥2 darmbijwerkingen ten opzichte van 3D-conformele radiotherapie, met een cumulatieve 5-jaars incidentie van 25% vs. 38%. Ondanks het feit dat er geen significante verschillen werden aangetoond ten aanzien van bijwerkingen gerelateerd aan de blaas, concluderen wij op basis van de data omtrent vroege en lange-termijn bijwerkingen dat het gebruik van beeld-geleide IMRT de te prefereren behandeling is.

In **Hoofdstuk 5** wordt onderzoek beschreven dat we binnen de HYPRO trial verricht hebben naar de effecten van verschillende behandelprotocollen en technieken op darmbijwerkingen. Ondanks het feit dat alle voor dit onderzoek geselecteerde patiënten (n=572) waren behandeld met beeld-geleide IMRT en de behandeldoses in het onderzoeksprotocol van de HYPRO trial waren vastgelegd, bestonden er substantiële verschillen in de behandeling binnen de vier grootste deelnemende centra binnen de HYPRO trial. In centrum A (n=242 patiënten), dat voor dit specifieke onderzoek werd gebruikt als referentiecentrum, werden de krapste veiligheidsmarges van 5 tot 6 mm toegepast, ten opzichte van 7 mm bij centrum B (n=170) en centrum C (n=85), en 8 mm in centrum D (n=75). In centrum B werd bij het intekenen gebruik gemaakt van magnetic resonance image (MRI) scans naast de CT-scans die in andere centra enkel werden gebruikt. MRI-beeldvorming kan leiden tot grotere precisie bij het intekenen van de prostaat, omdat de prostaat beter onderscheiden kan worden van omliggend weefsel dan het geval is bij CT-beeldvorming. In centrum C werd dagelijks voor elke fractie een endo-rectale ballon opgevoerd in de endeldarm tot voorbij de prostaat. Door deze op te blazen met lucht wordt het achterste deel van de darmwand weggeduwd uit het hoge-dosis gebied rondom de prostaat, die aan de voorzijde van de darmwand gelegen is. In centrum B (MRI-planning) en centrum C (endo-rectale ballon) zagen we gunstigere dosisverdelingen ten opzichte van de andere centra. De gemiddelde dosis op de endeldarm was significant lager in centra B en C, hetgeen uiteindelijk heeft geleid tot een lagere incidentie van bijwerkingen. In centrum B werd dit waarschijnlijk behaald doordat met behulp van de MRI scans een kleiner bestralingsveld werd bepaald, hetgeen vervolgens leidt tot minder neven-bestraling op de endeldarm. In centrum C werd het effect naar verwachting behaald door het verplaatsen van de achterwand van de endeldarm uit het hoge-dosis gebied door middel van de ballon. Er werden in dit onderzoek geen substantiële verschillen in dosisverdeling en bijwerkingsprofielen waargenomen door het gebruik van verschillende veiligheidsmarges.

DEEL II: ONCOLOGISCHE RESULTATEN

In **Hoofdstuk 6** worden de resultaten besproken van de landelijke HYPRO trial waarbij in 820 patiënten met tot de prostaat beperkte (niet-uitgezaaide) prostaatkanker werd onderzocht of een behandeling met een gehypofractioneerd schema van 19 fracties van 3,4 Gy zou leiden tot een betere tumorcontrole dan met de geldende standaardbehandeling van 39 fracties van 2,0 Gy. Na een mediane follow-up van vijf jaar werd vastgesteld dat het tumorvrije overlevingspercentage na hypofractioneren 80,5% betrof in vergelijking met 77,1% na standaardbehandeling. Dit verschil was niet significant waardoor wij, mede gezien het feit dat uit eerdere publicaties is gebleken dat hypofractioneren leidt tot een hogere incidentie van bijwerkingen, moeten concluderen dat hypofractioneren niet beschouwd kan worden

als de nieuwe standaardbehandeling. Op basis van sub-analyses lijkt het echter wel veilig om hypofractioneren aan te bieden aan patiënten met weinig darm- en blaasklachten voorafgaand aan radiotherapie. In **Hoofdstuk 7** presenteren wij een kritisch overzicht van de huidige klinische literatuur over studies betreffende gehypofractioneerde radiotherapie van prostaatkanker. Hierin komt duidelijk naar voren dat hypofractioneren gezien kan worden als gelijkwaardige behandeling ten opzichte van de oude standaardbehandelingen. Door de evidente voordelen die hypofractioneren biedt op het gebied van kostenbesparing en belasting voor de patiënt, zal hypofractioneren in de toekomst steeds vaker worden toegepast. Toekomstig onderzoek zal zich richten op het identificeren van nieuwe en extremer gehypofractioneerde bestralingsschema's.

DEEL III: KWALITEIT VAN LEVEN EN SEKSUEEL FUNCTIONEREN

In **Hoofdstuk 8** presenteren wij de resultaten van een analyse naar de kwaliteit van leven in de HYPRO trial (39x 2 Gy vs 19x 3,4 Gy). Een gevalideerde vragenlijst, specifiek gericht op de kwaliteit van leven na behandeling van prostaatkanker, werd gebruikt om de volgende domeinen van kwaliteit van leven te analyseren: darmklachten, blaasklachten, seksueel functioneren, seksuele activiteit en klachten gerelateerd aan hormonale behandeling die frequent wordt toegepast naast de bestraling. We hebben vast kunnen stellen dat gedurende de eerste maanden na bestraling een daling van de kwaliteit van leven optrad. Na deze eerste 6-12 maanden stabiliseerde de kwaliteit van leven in de regel, waarna in sommige gevallen herstel optrad. Op basis van de analyses hebben we niet geheel uit kunnen sluiten dat hypofractioneren inferieur is aan de standaardbehandeling wat betreft kwaliteit van leven gerelateerd aan blaas- en darmklachten. Gelijkwaardigheid van beide behandelingen werd wel vastgesteld voor seksueel functioneren, seksuele activiteit en klachten gerelateerd aan hormonale behandeling.

In **Hoofdstuk 9** hebben wij een analyse verricht specifiek gericht op het seksueel functioneren binnen de HYPRO trial (39x 2,0 Gy vs. 19x 3,4 Gy). Seksuele disfunctie is een frequent voorkomende bijwerking van bestraling, welke zeer negatieve invloed kan hebben op de kwaliteit van leven. Seksuele functie werd onderzocht door middel van een internationale vragenlijst waarin verscheidene aspecten van het seksueel functioneren aan bod komen. Een substantieel deel van de patiënten uit de HYPRO trial werd naast radiotherapie behandeld met hormoontherapie, hetgeen chemische castratie bewerkstelligt en zeer nadelige gevolgen heeft voor de seksuele functie. Om puur de effecten van beide bestralingsschema's te kunnen onderzoeken werden patiënten die langdurig (>6 maanden) behandeld werden met hormoontherapie niet meegenomen in deze analyse. Na een follow-up van drie jaar waren er geen verschillen in de erectiele functie tussen beide behandelingen. Van de patiënten met redelijk goede tot volledige erecties bij aanvang van radiotherapie rapporteerden bij de laatste controleafspraak maar

liefst 34,4% en 39,3% van de patiënten dat er sprake was van ernstige erectiestoornissen, na respectievelijk hypofractioneren en conventionele behandeling. Deze data tonen aan dat er op het gebied van seksueel functioneren vooralsnog geen verschil lijkt te zijn tussen beide behandelingen, echter dat radiotherapie nog altijd een grote negatieve invloed heeft op het seksueel functioneren.

Gezien het scala aan behandelopties voor prostaatkanker, wordt de keuze van patiënten voor een specifieke prostaatkankerbehandeling tegenwoordig in steeds hogere mate beïnvloed door de kans op bijwerkingen, zoals de zojuist beschreven erectiestoornissen. In de huidige literatuur wordt echter grote discrepantie weergegeven betreffende de gerapporteerde incidentie van erectiestoornissen na radiotherapie. In **Hoofdstuk 10** hebben we de literatuur geanalyseerd en op basis van de sterke punten en beperkingen van de gepresenteerde onderzoeken aanbevelingen gedaan waarmee de kwaliteit van toekomstige studies verbeterd kan worden. Deze aanbevelingen kunnen de homogeniteit van onderzoek verhogen en daarmee leiden tot meer inzichtelijke resultaten en adequatere voorlichting van patiënten.

In **Hoofdstuk 11** presenteren wij de resultaten van onderzoek dat we hebben verricht in het Memorial Sloan Kettering Cancer Center te New York. Eerder gepubliceerd onderzoek uit dit ziekenhuis heeft aangetoond dat het gebruik van sildenafil (Viagra ©) tijdens en na de bestraling een beschermend effect heeft op de erectiele functie bij mannen met prostaatkanker. Gedacht werd dat Sildenafil mogelijk een beschermend effect zou uitoefenen op endotheelcellen, welke de binnenkant van de peniele bloedvaten bekleden en belangrijk zijn voor het verkrijgen van goede erecties. Door middel van *in vitro* experimenten op endotheelcellen, hebben wij vast kunnen stellen dat sildenafil de productie van bepaalde reactive oxygen species vermindert, waardoor minder endotheel-disfunctie optreedt. Verder hebben we vastgesteld dat sildenafil een beschermend effect uitoefent tegen het optreden van celdood van de endotheelcellen als gevolg van de bestraling. Deze proeven zullen voortgezet worden in diermodellen om de werking en toepasbaarheid van Sildenafil verder te ontrafelen.

Na deze drie delen wordt in **Hoofdstuk 12** een algemene discussie van dit proefschrift gepresenteerd en bespreken wij de toekomst van het onderzoek zoals we die nodig achten om de optimale radiotherapeutische behandeling van prostaatkanker te ontwikkelen.

In conclusie, het werk in dit proefschrift heeft geleid tot belangrijke inzichten ten aanzien van de relatie tussen verschillende bestralingstechnieken en risico's op bijwerkingen. Daarnaast hebben de resultaten van de Nederlandse HYPRO trial aangetoond dat het gehypofractioneerde schema van 19 fracties van 3,4 Gy bij mannen met prostaatkanker leidt tot een tumorcontrole vergelijkbaar met die van de geldende standaardbehandeling. Echter, dit gehypofractioneerde

schema kan door de hogere kans op bestralings-gerelateerde bijwerkingen bij bepaalde patiëntengroepen vooralsnog niet gezien worden als nieuwe gouden standaard.

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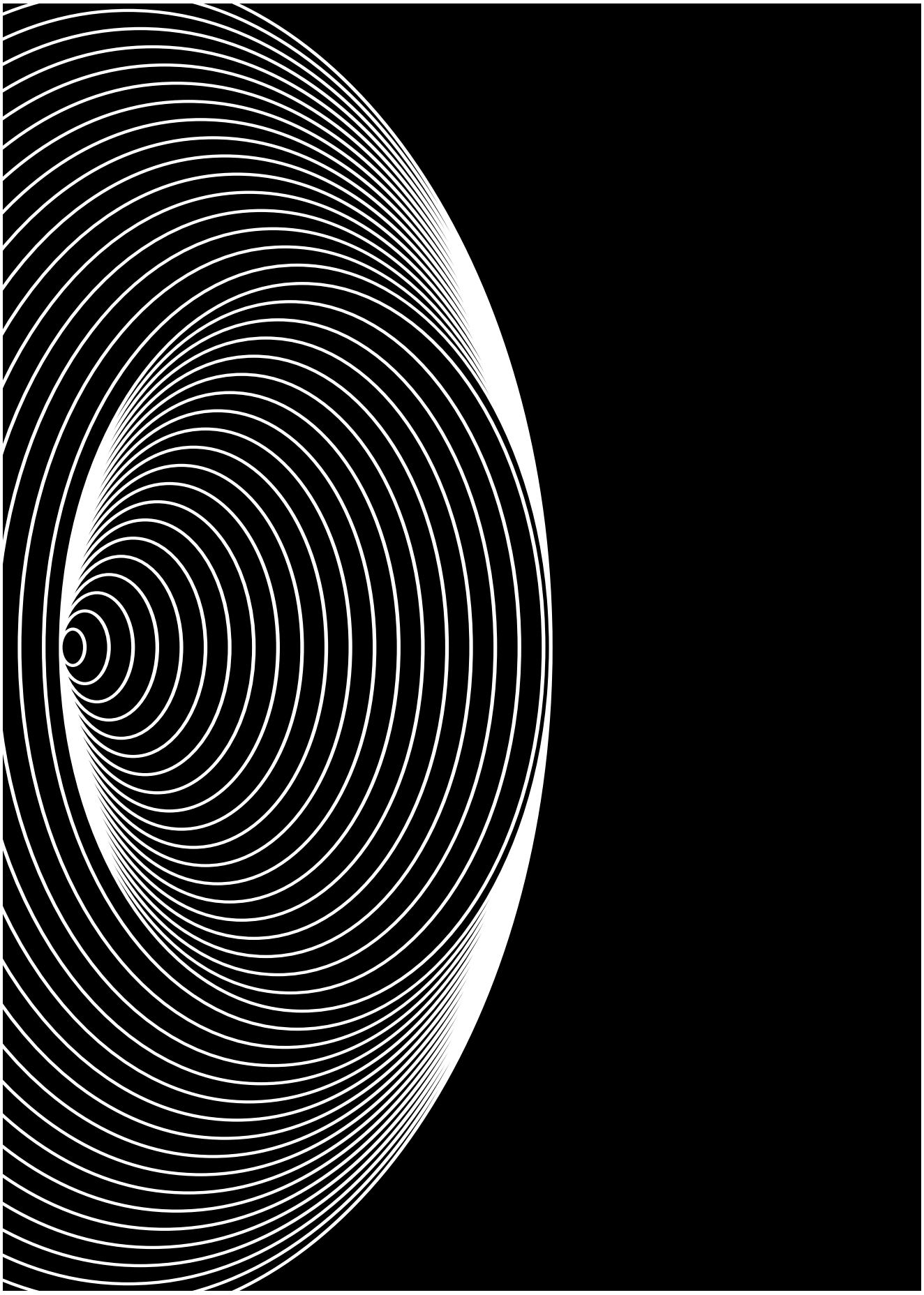
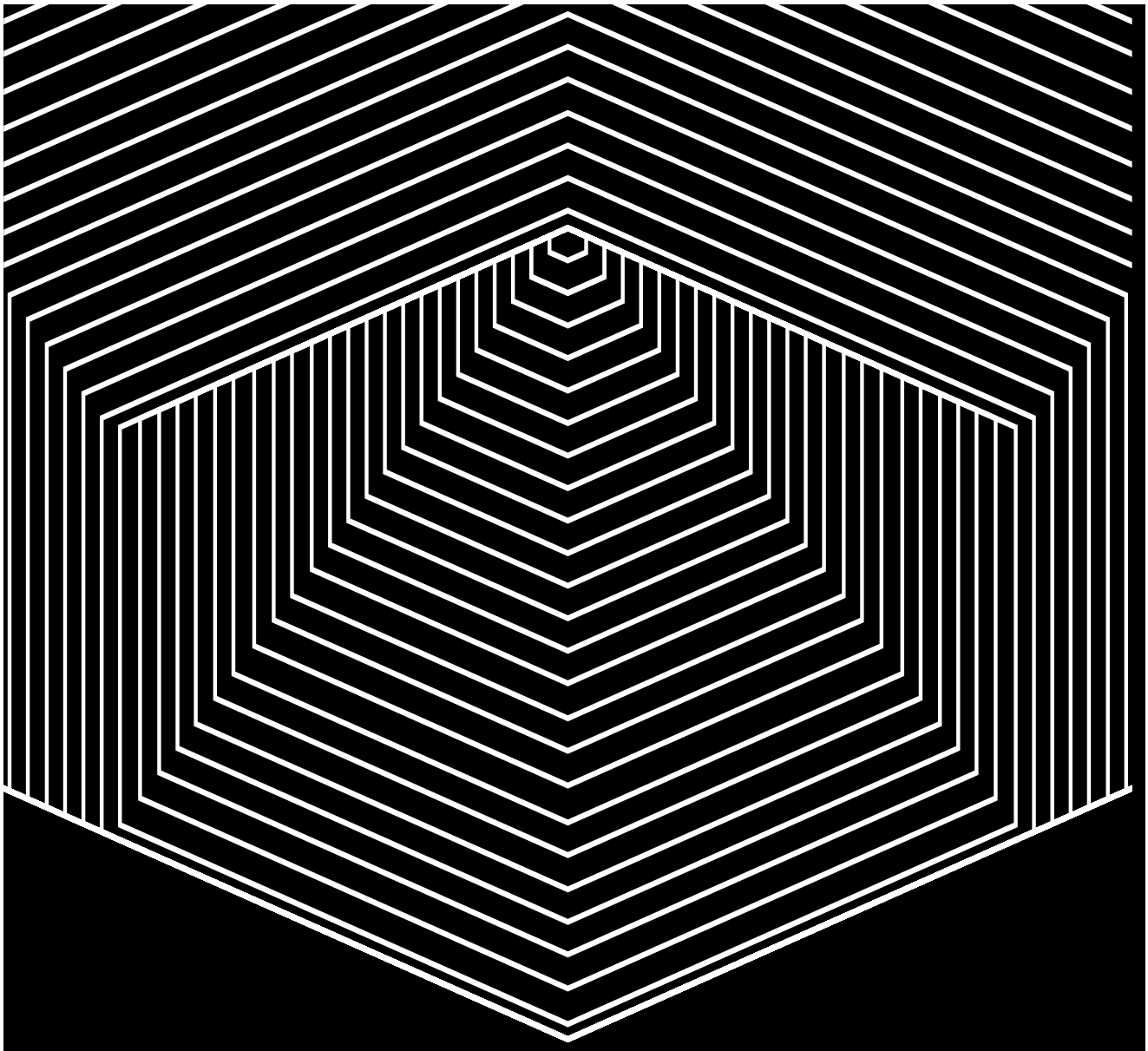


Appendices



GROTE DADEN VERRICHTEN DE ZWAKSTEN, MITS ZIJ VEREEND ZIJN.

Homerus, Ilias

CHAPTER 14

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List of publications

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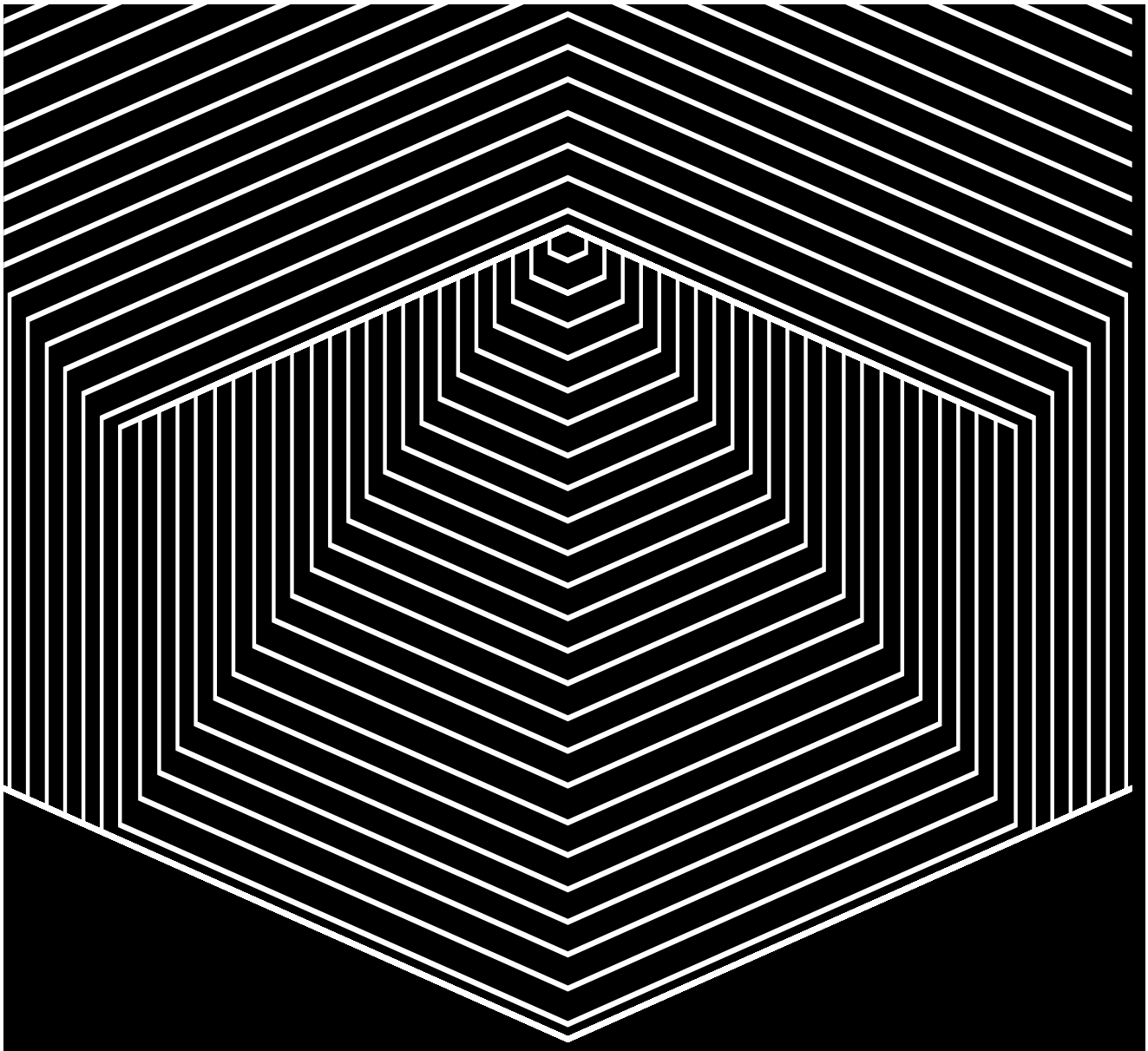


“SCHRIJVEN IS ZITTEN BLIJVEN TOT DAT HET ER STAAT.”

Kees van Kooten

CHAPTER 14

LIST OF PUBLICATIONS

Heemsbergen WD, **Wortel RC**, Incrocci L, Smeenk RJ, Witte MG, Pos FJ, Krol S. In Reply to Güngör et al. *Int J Radiat Oncol Biol Phys 2018; 100: 1091-1094.*

Wortel RC, Incrocci L, Mulhall JP. Reporting Erectile Function Outcomes After Radiation Therapy For Prostate Cancer: Challenges in Data Interpretation. *J Sex Med 2017; 14: 1260-1269.*

Wortel RC, Heemsbergen WD, Smeenk RJ, Witte MG, Krol ADG, Pos FJ, Incrocci L. Local protocol variations for Image-Guided Radiotherapy in the multicenter HYPRO trial: impact of rectal balloon and MRI delineation on anorectal dose and gastrointestinal toxicity levels *Int J Radiat Oncol Biol Phys 2017; 99: 1243-1252.*

Wortel RC,* Incrocci L,* Ghidey W, Aluwini S, Schimmel E, Krol ADG, van der Toorn PP, de Jager H, Heemsbergen WD, Heijmen BJM, Pos FJ. (*equal contributions). Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomized, multicenter, open-label, phase 3 trial. *The Lancet Oncol. 2016; 17: 1061-9.*

Wortel RC, Pos FJ, Heemsbergen WD, Incrocci L. Sexual function after hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: results from the randomized phase 3 HYPRO trial. *J Sex Med 2016; 13: 1695-1703.*

Wortel RC, Incrocci L, Pos FJ, van der Heide UA, Lebesque JV, Aluwini S, Witte MG, Heemsbergen WD. Late side effects after image-guided intensity modulated radiotherapy compared to 3D-conformal radiotherapy for prostate cancer: results from two prospective cohorts. *Int J Radiat Oncol Biol Phys 2016;* 95: 680-689.

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: 515-520.*

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 radiotherapy (IG-IMRT) compared to 3D-conformal radiotherapy (3D-CRT) in prostate cancer patients. *Int J Radiat Oncol Biol Phys 2015; 91: 737-744.*

Ten Donkelaar CS, **Wortel RC,** Lock MT. Rare case of urinary tract infections and the "forgotten" solution. *Scand J Urol 2015; Jul 6: 1-2.*

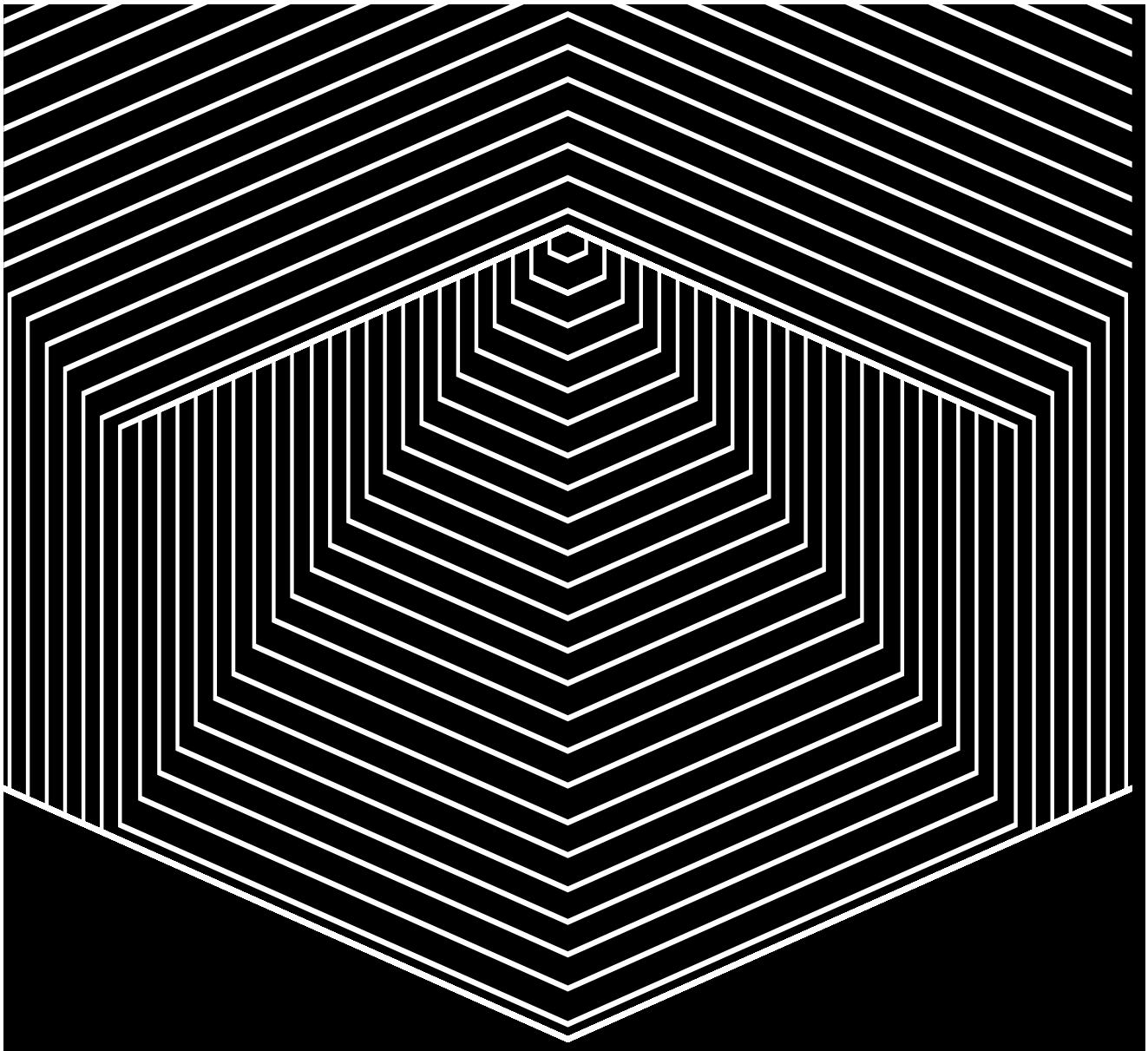
Wortel RC, Ghidey Alemayehu W, Incrocci L. Orchiectomy and radiotherapy for stage I-II testicular seminoma: a prospective evaluation of short-term effects on body image and sexual function. *J Sex Med 2015; 12: 210-218.*

Wortel RC, Mizrachi A, Enyedi B, Li H, Mulhall JP, Haimovitz-Friedman A. Sildenafil protects endothelial cells from radiation-induced oxidative stress. *(submitted).*

Wortel RC, Oomen-de Hoop E, Heemsbergen WD, Pos FJ, Incrocci L. Moderate hypofractionation in intermediate and high risk, localized prostate cancer: Health-related quality of life from the randomized, phase 3 HYPRO trial. *(submitted).*

BOOK CHAPTERS

Wortel RC, Incrocci L. Hypofractionated radiotherapy in genitourinary cancer: Better with less. *Alternate Fractionation in Radiotherapy 2018. [Editor M. Trombetta et al]*



“MEDICINE IS A SCIENCE OF UNCERTAINTY AND AN ART OF PROBABILITY.”

William Osler

CHAPTER 14

List of contributing authors

List of publications

PhD portfolio

Dankwoord

Curriculum vitae

PHD PORTFOLIO

Name PhD Student	: R.C. Wortel
Erasmus MC department	: Radiation Oncology
Title Thesis	: Prostate cancer radiotherapy: a field in motion
Promotor	: Prof. dr. L. Incrocci
Copromotor	: Dr. W.D. Heemsbergen
Date defense thesis	: 31st October 2018

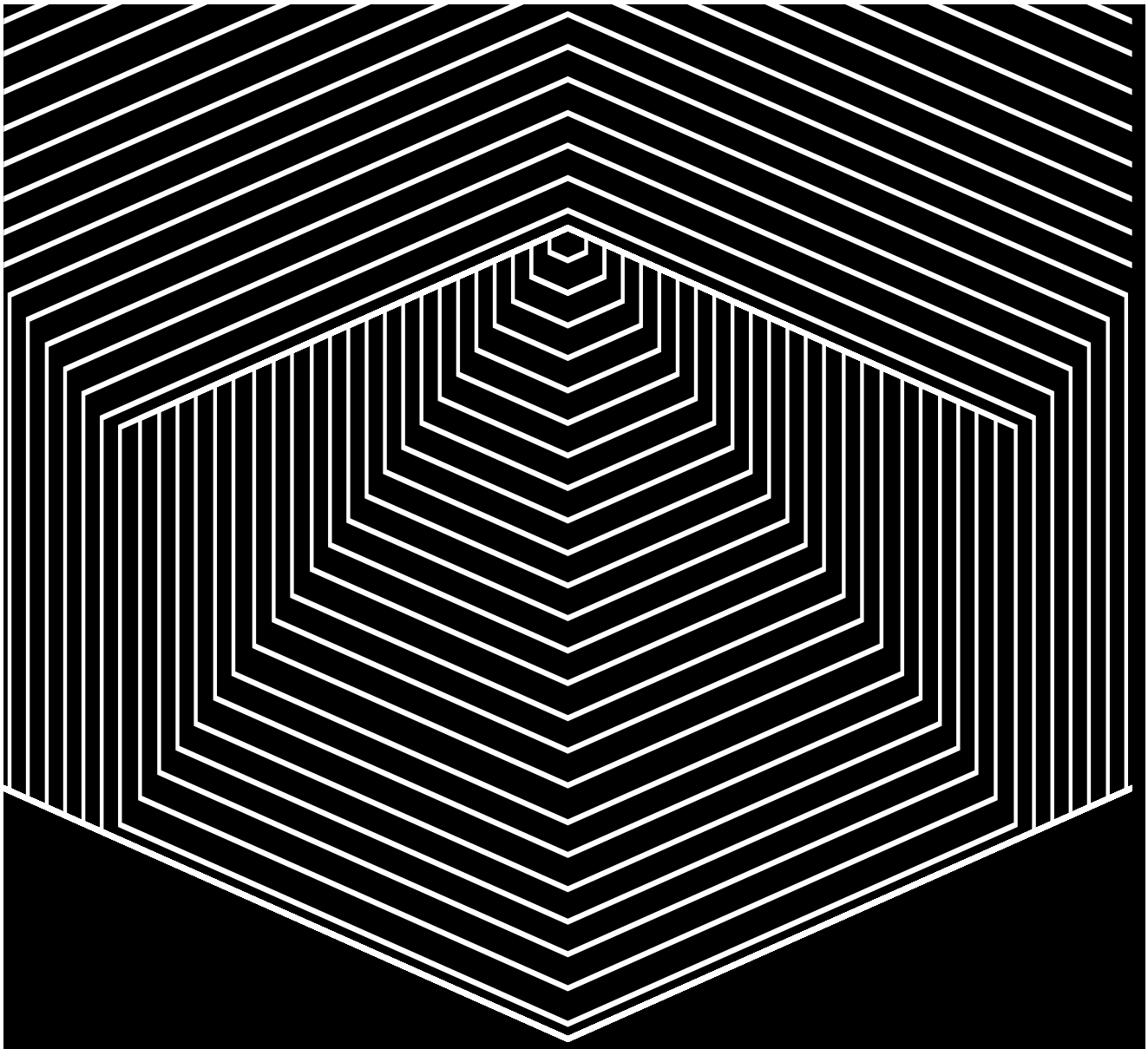
PHD TRAINING

IN-DEPT COURSE	YEAR	ECTS
Biomedical English Writing Course, Erasmus MC, Rotterdam	2015	2.0
"How to write high impact papers and what to do when they are rejected," VU Medisch Centrum, Amsterdam	2015	1.0
Survival Analysis Course, Erasmus MC, Rotterdam	2014	1.0
Basic course oncology- Biological, Physical and Clinical Aspects. Nederlands Kanker Instituut, Amsterdam	2014	1.0
Basiscursus Regulatie en Organisatie in Klinisch Onderzoek (BROK), Erasmus MC Rotterdam	2014	1.5
Scientific Integrity Course, Erasmus MC, Rotterdam	2014	0.3
Basic introduction Course on SPSS, Erasmus MC, Rotterdam	2013	1.0

PRESENTATIONS (POSTER 0.5 POINTS, ORAL 1 POINT)	YEAR	ECTS
Hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year treatment outcome of the Dutch randomized phase III HYPRO trial. AUA Annual Meeting, San Diego	2016	1.0
Sexual function after hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: results of the phase 3 HYPRO trial. AUA Annual Meeting, San Diego	2016	1.0

Hypofractionated radiotherapy for prostate cancer; results from therandomized phase III HYPRO trial. IKNL Symposium Urologische Tumoren, Capelle aan de IJssel	2016	1.0
State-of-the-art radiotherapy for prostate cancer: what have we gained? Stafavond Antoni van Leeuwenhoek Ziekenhuis, Amsterdam	2015	1.0
Hypofractionated versus conventionally fractionated radiotherapy for prostate cancer:5-year oncologic outcomes of the Dutch randomized phase 3 HYPRO trial. Onderzoeksschool Oncologie Amsterdam Retreat, Renesse	2015	1.0
Acute toxicity after image-guided intensity-modulated radiotherapy (IG-IMRT) compared to 3D-conformal radiotherapy (3D-CRT) in prostate cancer patients. ESTRO Forum, Barcelona	2015	1.0
Sexual function in cancer patients. Wetenschappelijk Congres Nederlandse Vereniging Voor Seksuologie, Amsterdam	2014	1.0
Acute toxicity after image-guided intensity-modulated radiotherapy (IG-IMRT) compared to 3D-conformal radiotherapy (3D-CRT) in prostate cancer patients. Onderzoeksschool Oncologie Amsterdam Retreat, Renesse	2014	0.5
Journal Clubs department of radiation oncology, Erasmus MC, Rotterdam	2013-2016	2.0

CONFERENCES AND SCIENTIFIC MEETINGS	YEAR	ECTS
Annual American Urological Association (AUA) Meeting, San Diego	2016	1.0
European Society for Radiotherapy & Oncology Forum, Barcelona	2015	1.0
Annual Retreat Onderzoeksschool Oncologie Amsterdam, Renesse	2014-2015	2.0



VRIENDSCHAP IS LIEFDE OP HET EERSTE WOORD.

Harry Mulisch

CHAPTER 14

DANKWOORD

De afgelopen jaren van onderzoek hebben mij gebracht in Rotterdam, Amsterdam en New York. Verschillende mensen hebben elk op eigen wijze een bijdrage geleverd aan mijn werkplezier en daarmee de totstandkoming van dit proefschrift. Ik ben deze mensen veel dank verschuldigd en graag neem ik hierbij de gelegenheid om een aantal mensen in het bijzonder te bedanken.

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Geachte prof. dr. M. Verheij, beste Marcel, dank voor de gastvrijheid op jouw afdeling gedurende de afgelopen jaren. Ik heb me vanaf het begin thuis gevoeld in het AvL.

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Alle collega's en onderzoekers van de afdeling Radiotherapie in het Antoni van Leeuwenhoek ziekenhuis, dank voor het warme welkom en alle gezelligheid. In het bijzonder Natasja Janssen en Tom Konert, de ochtendkoffietjes waren goud waard.

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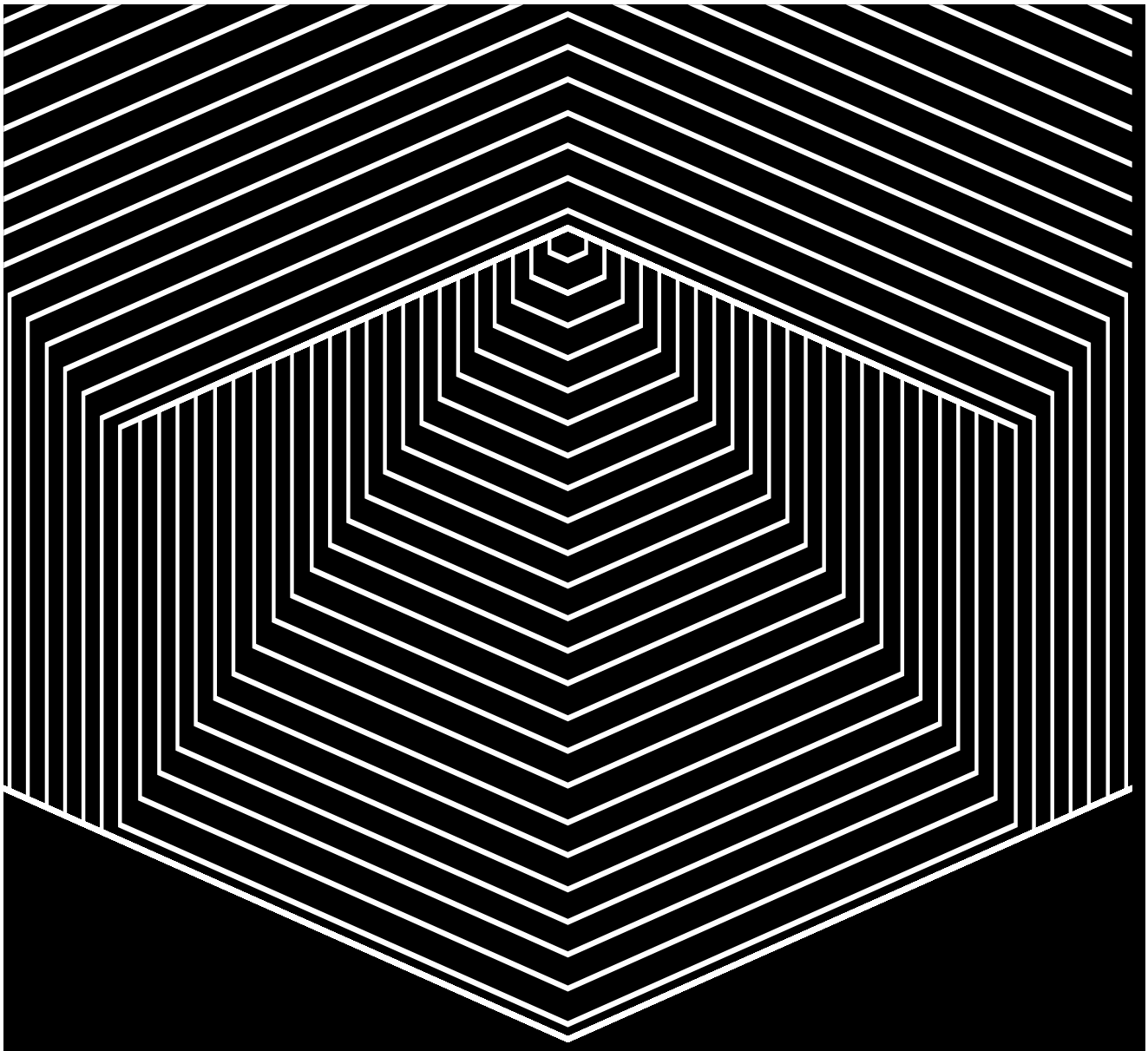
Liefste Emily, ik ben getrouwd met het meisje van mijn dromen. Jouw glimlach betekent alles voor mij.



“IF YOU WANT TO GO FAST, GO ALONE.
IF YOU WANT TO GO FAR, GO TOGETHER.”

African proverb

CHAPTER 14

CURRICULUM VITAE

Ruud Christiaan Wortel was born on November 1st, 1984. He lived in Utrecht his entire childhood, and after graduating from Christelijk Gymnasium Utrecht in 2003, he continued with medical school at the University of Groningen. In 2011, he obtained his medical degree and started working as urology resident (not in training), first at University Medical Center Utrecht, followed by a position at Central Military Hospital.

In 2013, he began his PhD training under the auspices of prof. dr. L. Incrocci at the department of radiation oncology of Erasmus MC Cancer Institute. In 2014, he started collaborating with the department of radiation oncology of the Netherlands Cancer Institute under supervision of dr. W.D. Heemsbergen. His research focused on the efficacy and side effects of radiotherapy techniques and treatment schedules for patients with localized prostate cancer.

In 2016, Ruud was granted a Koningin Wilhelmina Kankerfonds (KWF) grant to continue his research at the department of urology at Memorial Sloan Kettering Cancer Center, New York. Under supervision of dr. J.P. Mulhall and dr. Haimovitz-Friedman he studied the protective effects of phosphodiesterase type 5-inhibitors on endothelial cells, which are important in male sexual function, after irradiation.

Ruud is currently appointed as surgical resident in training at the Flevoziekenhuis in Almere as part of his urology training at the University Medical Center Utrecht. He is happily married to Emily Postma, and lives in Amsterdam.