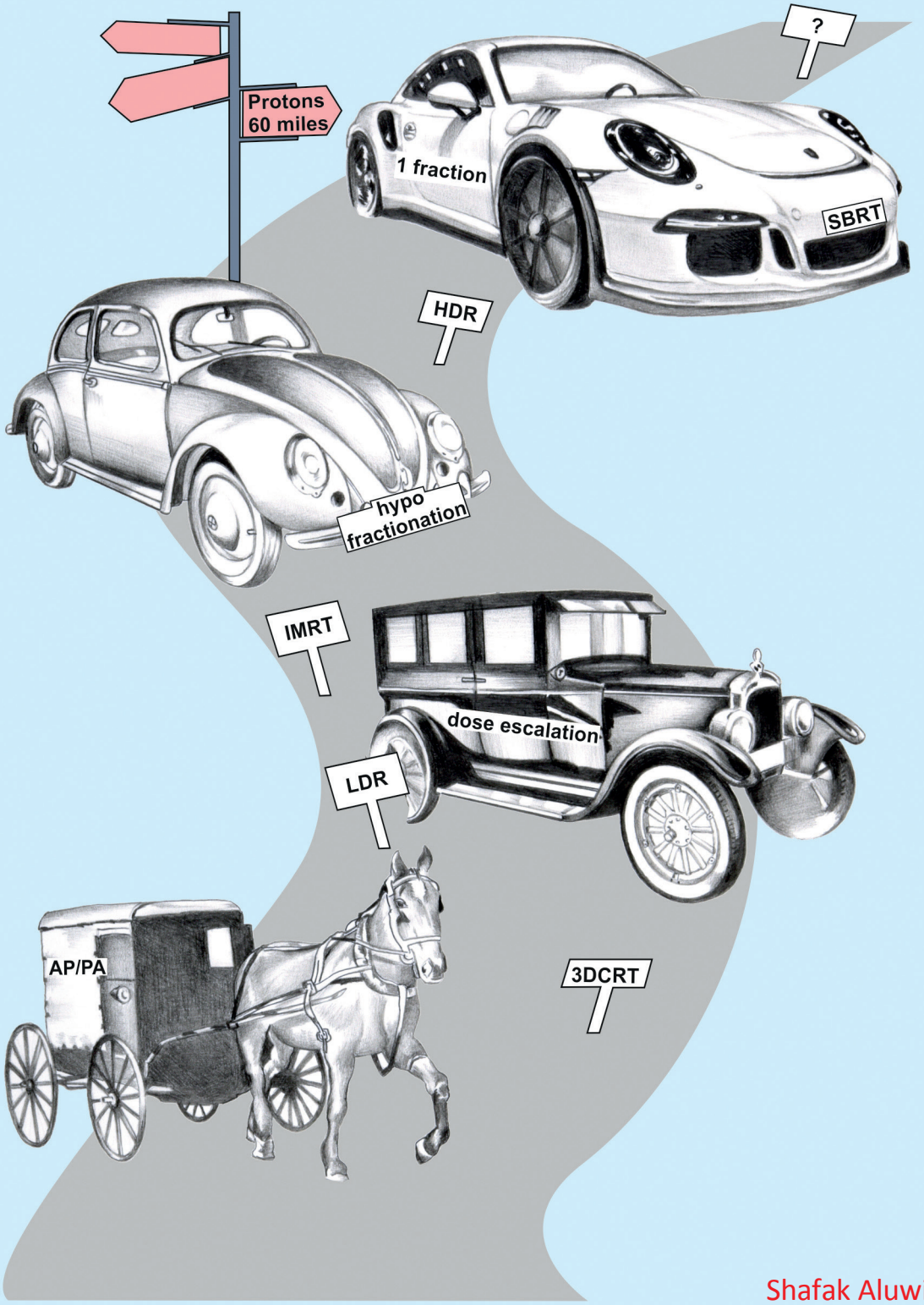
Hypofractionated radiotherapy for prostate cancer: How far can we go?



Shafak Aluwini

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The investigations presented in this thesis were performed at the Department of Radiation Oncology of the Erasmus University Medical Center, Rotterdam, The Netherlands.

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Hypogefractioneerde radiotherapie voor prostaatkanker:
Hoe ver kunnen we gaan?

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Voor Hala, Mike en Saba

PROPOSITIONS ACCOMPANYING THE THESIS

Hypofractionated radiotherapy for prostate cancer: How far can we go?

1. Applying moderately hypofractionated radiotherapy for prostate cancer enhances the incidence of acute gastrointestinal toxicity, even when only three fractions per week are delivered. (Chapter 2)
2. Using only physician scoring toxicity reports after prostate cancer radiotherapy can substantially underestimate acute and late toxicity. (Chapters 2 and 3)
3. Inter-fraction correction of catheter displacements in HDR-BT monotherapy for prostate cancer is feasible and may contribute to avoidance of excessive toxicity. (Chapters 5 and 6)
4. The use of a HDR-BT boost to escalate the prostate dose without increasing rectum toxicity is desirable. (Chapter 4)
5. Prostate cancer patients treated with hypofractionated radiotherapy may possibly be selected based on baseline symptoms. (Chapters 2, 3, 7 and 9)
6. Future radiotherapy trials on prostate cancer should pay more attention to quality of life endpoints as these are more important than local control.
7. The availability of proton therapy centers will increase the expense of our health care system with only a limited benefit for a limited group of patients.
8. Androgen deprivation therapy has a severe impact on relatively young patients and needs to be better investigated.
9. Women cannot suffer from prostate cancer but from a partner with prostate cancer.
10. Sex performance enhancers can only increase life expectancy in men and therefore create more equality in the life expectations of men and women.
11. The sound of your own Porsche 911 GT3 RS is more beautiful and joyful than that of Adele in her best performance.

STELLINGEN BEHORENDE BIJ HET PROEFSCHRIFT

Hypogefractioneerde radiotherapie voor prostaatkanker: Hoe ver kunnen we gaan?

1. Het toepassen van gematigd hypogefractioneerde radiotherapie voor prostaatkanker verhoogt de incidentie van acute gastro-intestinale toxiciteit, zelfs wanneer slechts drie fracties per week worden gegeven. (Hoofdstuk 2)

2. Het gebruik van alleen de scores van de behandelende artsen voor het bepalen van de toxiciteit na radiotherapie voor prostaatkanker kan resulteren in aanzienlijke onderschattingen van de incidenties van de acute en late schade. (Hoofdstukken 2 en 3)

3. Correctie van katheterverschuivingen tussen opeenvolgende fracties bij HDR brachytherapie als monotherapie voor prostaatkanker is haalbaar en draagt mogelijk bij aan het vermijden van overmatige toxiciteit. (Hoofdstukken 5 en 6)

4. Het gebruik van een HDR brachytherapie boost voor het verhogen van de totale dosis in de prostaat zonder verhoging van rectum toxiciteit is wenselijk. (Hoofdstuk 4)

5. Prostaatkanker patiënten die worden behandeld met hypogefractioneerde radiotherapie kunnen mogelijk geselecteerd worden op basis van baseline symptomen. (Hoofdstukken 2, 3, 7 en 9)

6. Toekomstige radiotherapie studies over prostaatkanker zouden meer aandacht moeten besteden aan kwaliteit van leven als eindpunt, aangezien dit belangrijker is dan lokale controle.

7. De beschikbaarheid van protonentherapiecentra zal de kosten in ons gezondheidszorgstelsel laten toenemen met een beperkt voordeel voor slechts een beperkte groep patiënten.

8. Androgeen deprivatie therapie heeft een ernstige impact op de kwaliteit van leven van relatief jonge patiënten en moet verder worden onderzocht.

9. Vrouwen kunnen geen last hebben van prostaatkanker, maar wel van een partner met prostaatkanker.

10. De lustpil kan de levensverwachting alleen bij mannen vergroten en brengt meer gelijkheid in de levensverwachting van mannen en vrouwen.

11. Het geluid van je eigen Porsche 911 GT3 RS is mooier en plezieriger dan dat van Adele in haar beste optreden.

CONTENTS

Chapter 1

Introduction

GENERAL INTRODUCTION

Prostate cancer (PCa) is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide with an estimated 899.000 new cases, and 258.000 new deaths in 2008[1]. According to the Dutch Cancer registry, PCa is the first most diagnosed cancer in men, with around 11.000 new cases, and 2535 deaths in 2013[2], which is a substantial burden for the Dutch healthcare system. The number of patients with PCa is expected to increase due to the growth and aging of the global population and screening. Since the introduction of serum prostate specific antigen (PSA) based screening, the majority of PCa cases is diagnosed with organ-confined disease, which is often asymptomatic. Almost 60% of new PCa cases involves men over the age of 70 years[1-3].

There are several treatment options for organ-confined PCa. Next to surgery, external-beam radiotherapy (EBRT), High-Dose-Rate (HDR) and Low-Dose-Rate (LDR) brachytherapy (BT), and for selected patients, active surveillance are all considered effective treatment methods. Choice of treatment is mainly based on risk profile[4], age, symptoms, co-morbidity and available treatment facilities.

Several large randomized studies have shown the importance of EBRT dose escalation to improve relapse free survival (RFS)[5-7]. An improvement of RFS was often achieved with increased toxicity. In addition, conventional, high dose, fractionated EBRT treatments are protracted over 7-9 weeks, which impacts the patient's quality of life and utilization of hospital resources.

According to the linear-quadratic model for cell-killing, the surviving fraction of cells has a component linear in delivered dose, αD, and another component quadratic with delivered dose, βD^2. For most cancers, the α/β ratio is high (~10 Gy), indicating that these tissues are more sensitive to the total radiation dose, rather than the dose per fraction. For the late-reacting normal tissues surrounding the prostate such as rectum and bladder, the α/β is low (around 4-6 Gy)[8,9], indicating a higher sensitivity to fraction size. There is now growing evidence that the α/β for PCa cells[8,10-16] may be lower than that of surrounding normal tissues, perhaps as low as 1.5 Gy[11,13,17-21]. This means that increasing fraction dose and reducing total dose could enhance the therapeutic ratio, as demonstrated in modeling studies[19]. In a recent systematic analysis[18], the clinical outcome of various hypofractionated schedules, involving over 2.800 patients, was compared to conventional fractionated regimens, delivered to 11.000 patients. This study (with other smaller studies) confirmed that PCa has a very high sensitivity to the dose per fraction, with an α/β of 1.0 to 1.7 Gy[18,22], indicating a potential clinical advantage of hypofractionation for the treatment of PCa. Apart from the potential therapeutic gain, hypofractionated schedules also have economic and logistic advantages due to the reduction in the number of treatment fractions and the related hospital visits.

In the last decade, many efforts have been made to improve the dose delivery accuracy in EBRT, such as the introduction of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), the use of implanted (gold) fiducials, and in-room imaging with Cone Beam Computed Tomography (CBCT). These sophisticated techniques have in general resulted

in decreased toxicity[17,23-25]. The availability of these techniques to prevent excessive toxicity favored the development of studies on hypofractionated EBRT regimens.

For hypofractionation in PCa, several strategies are being explored. Moderate hypofractionation, using fraction doses < 4 Gy, is generally delivered with EBRT using conventional linear accelerators. For extreme hypofractionation (fraction dose ≥ 6 Gy), both HDR-BT and Stereotactic Body Radiation Therapy (SBRT) delivered with a conventional linear accelerator or a robotic Cyberknife are applied.

SCOPE OF THE THESIS

The general purpose of this thesis was to investigate the feasibility of moderate and extreme hypofractionated radiotherapy for prostate cancer, with emphasis on treatment induced side effects. In this context, in all clinical studies toxicity was scored by both physicians and patients, using patient self-assessment questionnaires (PSAQ).

OUTLINE OF THIS THESIS

Part 1: Moderate hypofractionation with EBRT

In 2006 only few, small randomized trials had been published for moderate hypofractionation[10-12], which were mostly performed with low treatment doses (66-72 Gy). In 2007 we started with the multicenter, randomized phase III HYPRO trial, comparing a conventional schedule of 39x2 Gy with a schedule of 19x3.4 Gy, with 410 patients in each arm. The primary aim of the HYPRO trial was to detect an absolute 10% increase in the 5-year RFS with hypofractionation, with non-inferiority in cumulative grade ≥ 2 acute and late genitourinary (GU) and gastrointestinal (GI) toxicities[26]. This thesis contains the final reports on acute and late toxicity (**Chapters 2 and 3**).

Part 2: Extreme hypofractionation with HDR brachytherapy

The use of HDR-BT as a boost combined with EBRT has been advocated for organ-confined PCa in several publications [27,28,29]. In these studies toxicity was only scored by treating physicians. In **Chapter 4** we report on our long-term outcome and toxicity of EBRT (25 fractions of 1.8 Gy) with an HDR-BT boost consisting of 3 fractions of 6 Gy for hormone-naive patients with low- or intermediate-risk PCa[30]. Long term toxicity results were derived from physicians' reports and PSAQ.

The excellent results of this combined regimen gave a motivation to investigate the feasibility and effectiveness of HDR-BT as monotherapy (4 fractions of 9.5 Gy) for organ-confined PCa. The aim was a treatment time reduction from 6 weeks to 2 days, without compromising oncological outcome and keeping toxicity rates acceptable. As HDR-BT as monotherapy was delivered in 4 fractions in a short period of time (36 hours)[31,35], the overall dosimetric accuracy and reproducibility depended on the stability of catheter positions in the prostate. Displacement of catheters in between fractions can occur, which, if not corrected, can influence the dose distribution drastically[39,40]. Only few papers have addressed catheter displacement[35,41]. In **Chapter 5**, the effect of catheter displacement is analyzed in a systematic simulation study, both for target coverage and organs at risk (OAR) exposure. In **Chapter 6**, the clinical impact of catheter displacements and corrections of displacements on acute and late

toxicity in HDR-BT monotherapy is investigated. **Chapter 7** presents oncological outcome in terms of biochemical RFS, disease specific survival (DSS), and overall survival (OS), and acute and late toxicity for HDR-BT as monotherapy. Furthermore the quality of life using the PR-25[42] questionnaires was evaluated.

Part 3: Extreme hypofractionation with SBRT using the Cyberknife

Although HDR-BT as monotherapy is an excellent treatment option for organ-confined PCa, the limited surgery capacity and the increased number of (older) patients with co-morbidities or contra-indications for anesthesia raise the need to offer those patients also a short treatment course with results comparable to HDR-BT monotherapy. For this purpose, a treatment protocol for the robotic Cyberknife, mimicking HDR-BT, was developed to accurately deliver 4 fractions of 9.5 Gy in a single week. **Chapter 8** reports on the clinical feasibility for low and intermediate-risk PCa patients.

Studies on patterns of failure following conventionally fractionated EBRT show that the dominant intra-prostatic nodule is responsible for local recurrence in 89% [43] – 100% [44,45] of cases. Possibly, higher doses to the dominant lesion could enhance the biochemical control rate while avoiding the increase in side effects seen with whole gland dose escalation[46,47]. A protocol for Cyberknife SBRT was developed for low- and intermediate-risk PCa to deliver 4 fractions of 9.5 Gy to the whole gland, with a 2.5-3 Gy boost to the MRI-visible tumor. In **Chapter 9**, toxicity, biochemical control rate, and quality of life results are reported for the first 50 patients treated with this protocol.

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PART 1

Moderate hypofractionation with external beam radiotherapy

Chapter 2

Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial

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SUMMARY

Background

In 2007, we began the randomised phase 3 multicentre HYPRO trial to investigate the effect of hypofractionated radiotherapy compared with conventionally fractionated radiotherapy on relapse-free survival in patients with prostate cancer. Here, we examine whether patients experience differences in acute gastrointestinal and genitourinary adverse effects.

Methods

In this randomised non-inferiority phase 3 trial, done in seven radiotherapy centres in the Netherlands, we enrolled intermediate-risk or high-risk patients aged between 44 and 85 years with histologically confirmed stage T1b–T4 NX-0 MX-0 prostate cancer, a PSA concentration of 60 ng/mL or lower, and WHO performance status of 0–2. A web-based application was used to randomly assign (1:1) patients to receive either standard fractionation with 39 fractions of 2 Gy in 8 weeks (five fractions per week) or hypofractionation with 19 fractions of 3·4 Gy in 6·5 weeks (three fractions per week). Randomisation was done with minimisation procedure, stratified by treatment centre and risk group. The primary endpoint is 5-year relapse-free survival. Here we report data for the acute toxicity outcomes: the cumulative incidence of grade 2 or worse acute and late genitourinary and gastrointestinal toxicity. Non-inferiority of hypofractionation was tested separately for genitourinary and gastrointestinal acute toxic effects, with a null hypothesis that cumulative incidences of each type of adverse event were not more than 8% higher in the hypofractionation group than in the standard fractionation group. We scored acute genitourinary and gastrointestinal toxic effects according to RTOG-EORTC criteria from both case report forms and patients' self-assessment questionnaires, at baseline, twice during radiotherapy, and 3 months after completion of radiotherapy. Analyses were done in the intention-to-treat population. Patient recruitment has been completed. This study is registered with www.controlled-trials.com, number ISRCTN85138529.

Findings

Between March 19, 2007, and Dec 3, 2010, 820 patients were randomly assigned to treatment with standard fractionation (n=410) or hypofractionation (n=410). 3 months after radiotherapy, 73 (22%) patients in the standard fractionation group and 75 (23%) patients in the hypofractionation group reported grade 2 or worse genitourinary toxicity; grade 2 or worse gastrointestinal toxicity was noted in 43 (13%) patients in the standard fractionation group and in 42 (13%) in the hypofractionation group. Grade 4 acute genitourinary toxicity was reported for two patients, one (<1%) in each group. No grade 4 acute gastrointestinal toxicities were observed.

We noted no significant difference in cumulative incidence by 120 days after radiotherapy of grade 2 or worse acute genitourinary toxicity (57·8% [95% CI 52·9–62·7] in the standard fractionation group vs 60·5% (55·8–65·3) in the hypofractionation group; difference 2·7%, 90% CI –2·99 to 8·48; odds ratio [OR] 1·12, 95% CI 0·84–1·49; p=0·43). The cumulative incidence of grade 2 or worse acute gastrointestinal toxicity by 120 days after radiotherapy was higher in patients given hypofractionation (31·2% [95% CI 26·6–35·8] in the standard fractionation group vs 42·0%

[37·2–46·9] in the hypofractionation group; difference 10·8%, 90% CI 5·25–16·43; OR 1·6; p=0·0015; non-inferiority not confirmed).

Interpretation

Hypofractionated radiotherapy was not non-inferior to standard fractionated radiotherapy in terms of acute genitourinary and gastrointestinal toxicity for men with intermediate-risk and high-risk prostate cancer. In fact, the cumulative incidence of grade 2 or worse acute gastrointestinal toxicity was significantly higher in patients given hypofractionation than in those given standard fractionated radiotherapy. Patients remain in follow-up for efficacy endpoints.

Funding

The Dutch Cancer Society.

INTRODUCTION

Prostate cancer is the second most common cancer and the sixth leading cause of cancer death in men worldwide.[1] External beam radiotherapy is the treatment of choice for a large proportion of patients. Findings of several trials have shown significant improvements in relapse-free survival after external beam radiotherapy for patients with prostate cancer because of dose escalation.[2–4] However, this improvement in relapse-free survival was associated with a significant increase in toxic effects,[2,4,5] which makes further dose escalation not preferable. Several investigators have reported a low α/β ratio for prostate cancer,[6–8] suggesting that hypofractionation could be used to enhance the biological tumour dose without increasing toxic effects.[8] Additionally, the reduction in the number of treatment fractions has economic and logistical advantages. Small studies reported encouraging results for hypofractionation.[8–12] In 2007, the randomized phase 3 multi centre HYPRO trial was initiated in the Netherlands to investigate the effect of hypofractionation on relapse-free survival in patients with prostate cancer. Here we report data for acute toxic effects.

METHODS

Study design and participants

In this open-label, randomised, phase 3 study, we recruited intermediate-risk and high-risk patients[13] aged between 44 and 85 years with histologically confirmed stage T1b–T4 NX-0 MX-0 prostate cancer, a prostate-specific antigen concentration of 60 ng/mL or lower, and a WHO performance status of 0–2. We excluded patients with previous pelvis irradiation, radical prostatectomy, evidence of pelvic nodal disease (by CT of the pelvis), presence of distant metastases (by bone scintigraphy), and low-risk patients (stage T1b–T2a, Gleason score of ≤6, PSA concentration of 10 ng/mL).[3] This trial was approved by the medical ethics committee of the Erasmus MC Cancer Institute, Rotterdam, the Netherlands (06-045). All patients provided written informed consent. The trial was coordinated and managed by the departments of Radiation Oncology and the Clinical Trials Center of the Erasmus MC

Cancer Institute. Each participating centre used its own protocol for adjuvant hormonal therapy in both groups. The rate of use of adjuvant hormonal therapy in the seven institutions ranged between 51% and 87% and the duration of hormonal therapy varied from 6 months to 3 years.

Randomisation and masking

We randomly assigned (1:1) patients to receive standard fractionation or hypofractionation, applying a minimization procedure, ensuring balance overall and within each stratum of the stratification factors (treatment centre and risk group). Patients were assigned via a web-based application (done by the Clinical Trials Center, Erasmus MC Cancer Institute, Rotterdam) and the assigned treatment group was sent immediately via fax or email to local investigators. The local investigators were treating physicians, so they were not masked to treatment. Randomization took place at least 4 weeks before the start of treatment.

Procedures

Patients randomly assigned to receive standard fractionation were treated with 39 fractions of 2 Gy, while those randomly assigned to receive hypofractionation were treated with 19 fractions of 3·4 Gy. Assuming the α/β ratio was 1·5 Gy for prostate cancer,[8] the tumour equivalent dose in 2 Gy fractions (EQD_{2Gy}) for hypofractionation was 90·4 Gy compared with 78 Gy with standard fractionation. Considering an α/β ratio in the range of 4–6 Gy for late toxic effects,[7] the rectum and bladder EQD_{2Gy} for the prescribed hypofractionation dose would be 77·5–79·7 Gy (ie, close to standard fractionation of 78 Gy). To avoid potential excessive acute toxic effects in the hypofractionation group, only three fractions per week were given to this group, resulting in an overall treatment time of about 6·5 weeks. In the standard fractionation group, patients received five daily fractions of 2 Gy a week (overall treatment time about 8 weeks). Assuming an α/β ratio of 10 Gy for acute toxicity, this would result in weekly and total acute toxicity EQD_{2Gy} values of 11·4 Gy for the hypofractionation regimen and 72·1 Gy for standard fractionation compared with 10 Gy for the hypofractionation regimen and 78 Gy for standard fractionation.

Three treatment groups were defined on the basis of the risk of seminal vesicle involvement: [14] group 1 had a risk of 10% or less; group 2 had a risk of 10–25%; group 3 had a risk of higher than 25%. For group 1, the clinical target volume consisted of the prostate only, to be treated to the prescribed dose. For group 2, the prostate was treated to the prescribed dose, whereas the seminal vesicle was treated to a dose of 35 fractions of 2 Gy or 39 fractions of 1·85 Gy (standard fractionation), or a dose of 16 fractions of 3·4 or 19 fractions of 3·04 Gy (hypofractionation group). For group 3, both the prostate and the seminal vesicle were treated up to the prescribed dose. In the Netherlands, elective lymph node irradiation is not applied because of inconclusive evidence.[15] Depending on the set-up verification and correction strategy used in each participating institute, margins of 3–10 mm were added to the clinical target volume equal in both groups, yielding the planning target volume. For the boost, these margins could be reduced to 0 mm towards the rectum, and 3–5 mm in other directions. This boost could either be delivered sequentially or simultaneously integrated depending on the institute's preference. The planning CT or MRI was done 2 weeks before start of radiotherapy.

After the end of the radiation treatment, patients were seen every 3 months for the first 2 years, every 6 months in years 2–5, and once a year up to 10 years. Acute toxicity was scored before treatment to give baseline values, twice during the radiotherapy course and at 3 months after the radiation therapy. Late toxicity was scored at 6 months, and at 1, 2, 3, 4, and 5 years after completion of radiation therapy. Quality of life was assessed at 6 months, and 1,2, 3, 4, and 5 years after treatment.[16,17] Assessment of tumour response was done by PSA testing every 3 months the first 2 years after treatment, every 6 months the third, fourth, and fifth year, and from then once a year till 5–10 years. Transrectal ultrasound of the prostate, a CT scan of the pelvis, and a bone scintigraphy were done in case of suspicion of tumour recurrence or metastases.

We scored acute genitourinary and gastrointestinal toxicities by case report form with the Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria,[18] and patients' self-assessment questionnaires at baseline, as previously used in the CKVO 96-10 trial.[5] Acute toxicity scores from both sources were determined at four points—ie, pre radiotherapy (before start of radiotherapy until 6 days after start of radiotherapy); 4 weeks (between 7 and 34 days after start of radiotherapy); 6 weeks (between 35 days after start of radiotherapy to 59 days after completion of radiotherapy); and 3 months after radiotherapy (between 60 days till 120 days after completion of radiotherapy). We also recorded incidences

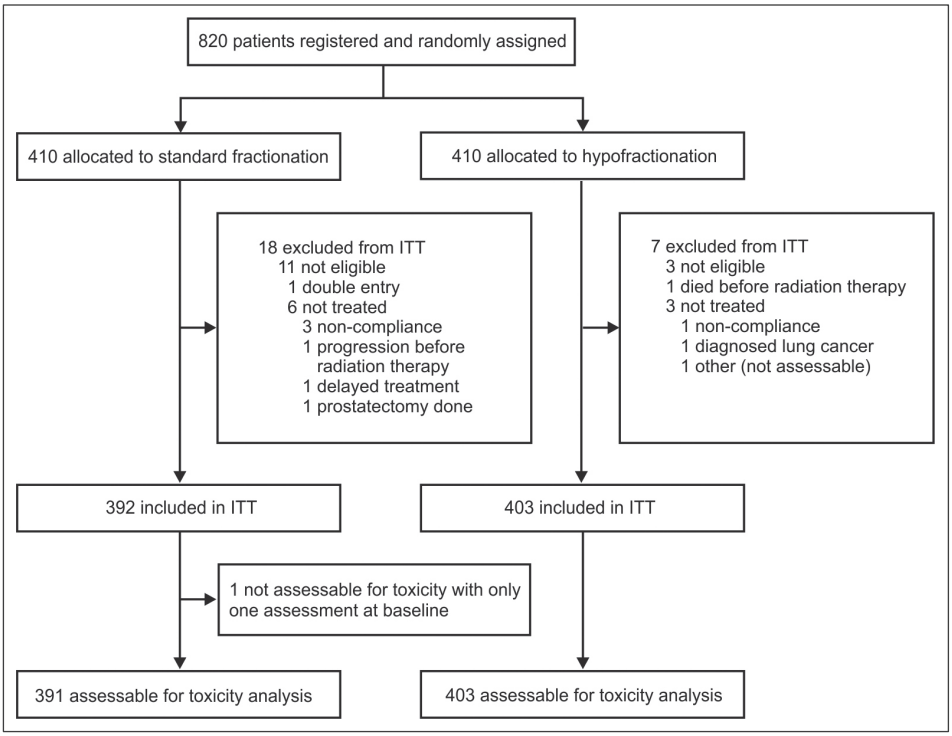

Figure 2.1 | Trial profile

ITT=intention-to-treat

Table 2.1 | Patient characteristics at baseline

	standard fractionation group (n=391)	hypofractionation group (n=403)
Age (years)	71 (67-75)	70 (66-74)
Transurethral prostate resection	42 (11%)	35 (9%)
Abdominal surgery	106 (27%)	93 (23%)
Gastrointestinal comorbidity	41 (10%)	36 (9%)
Adjuvant hormonal therapy	261 (67%)	265 (66%)
T-stage		
T1a	1 (0%)	0
T1b	3 (1%)	3 (1%)
T1c	55 (14%)	55 (14%)
T2a	45 (12%)	50 (12%)
T2b	38 (10%)	35 (9%)
T2c	48 (12%)	49 (12%)
T3a	160 (41%)	157 (39%)
T3b	38 (10%)	47 (12%)
T4	3 (1%)	7 (2%)
PSA concentration (ng/ml)*		
< 10	103 (26%)	124 (31%)
10 – 20	157 (40%)	159 (39%)
>20	131 (34%)	120 (30%)
Gleason score		
≤6	119 (31%)	122 (30%)
7	178 (46%)	181 (45%)
8	57 (15%)	60 (15%)
9	33 (8%)	37 (9%)
10	4 (1%)	3 (1%)
Treatment group		
1	78 (20%)	79 (20%)
2	190 (49%)	198 (49%)
3	123 (31%)	126 (31%)
Risk group		
Intermediate	106 (27%)	104 (26%)
High	285 (73%)	299 (74%)
Prostate volume (cm^3)		
≤50	186 (48%)	182 (45%)
>50	196 (50%)	207 (51%)
Unknown	9 (2%)	14 (3%)
Duration of HT use before RT		
≤2 months	120 (31%)	117 (29%)
>2 months	136 (35%)	145 (36%)
Unknown	6 (2%)	4 (1%)

Data are n (%) or median (IQR). *PSA concentration median in the standard Fractionation group 14.8 (IQR 9.8–24.0) and 13.9 (9.2–21.3) in the hypofractionation group.

of a number of symptoms, including nocturia, frequency, pain, haematuria and incontinence for genitourinary effects, and pain with urge and discomfort, frequencies, use of pads, bleeding, and diarrhoea for gastrointestinal effects (part of toxicity scores derived from both the case report form and the RTOG questionnaires).[19]

Outcomes

The primary endpoint is 5-year relapse-free survival. Relapse was defined as biochemical relapse, clinical relapse, locoregional or distant relapse, or start with hormonal therapy, whichever happened first. Biochemical relapse was defined as PSA concentration greater than the present nadir plus 2 ng/ml, without backdating. Patients who died without evidence of previous relapse and not because of toxic effects of treatment were censored at date of death. Additional key endpoints were acute and late gastrointestinal and genitourinary toxicity, defined as the cumulative incidence of grade 2 or worse acute and late genitourinary toxic effects. Secondary endpoints were quality of life and erectile functioning.

Statistical analysis

The primary hypothesis of the HYPRO trial was to detect a 10% improvement in relapse-free survival improvement with the hypofractionation regimen compared with standard fractionation, with non-inferiority of hypofractionation with respect to the cumulative incidence of grade 2 or worse acute and late genitourinary and gastrointestinal toxic effects. The power for the relapse-free survival endpoint was 92%, for late genitourinary effects 84%, for late gastrointestinal effects 86%, and for acute toxic effects 71%, and so we calculated that we would need to enroll 820 patients, including allowance for a dropout of 20 patients. Analyses were intention-to-treat.

The analyses presented here are for the comparison of the cumulative incidences of grade 2 or worse acute toxic effects; for each patient, we included the highest grade recorded until 120 days after completion of radiotherapy. Non-inferiority of hypofractionation was tested separately for genitourinary and gastrointestinal acute toxic effects, with a null hypothesis that cumulative incidences in the hypofractionation group were not more than 8% higher than in the standard fractionation group. Non-inferiority of the hypofractionation group was tested at a significance level of 5% with a two-sided 90% CI that correspondingly gives the upper limit of the one-sided 95% CI. An upper limit of the CI for the recorded difference in cumulative incidence less than 8% suggested non-inferiority of the hypofractionation group. The sample size of the HYPRO trial was based mainly on power considerations for the relapse-free survival endpoint. With 400 patients per group and proportions of grade 2 or worse acute toxicity of about 50% in both groups,[5] the standard error of the difference between the two proportions would be 3·5% and the 90% two-sided CI would be between –5·8 and 5·8 from the recorded difference between the proportions. Thus, an upper limit of 8% as pre specified in the study protocol would imply a difference between the two proportions of 2·2%, which was deemed small and not suggestive of a clear increase in acute toxicity.

We applied logistic regression analysis to compare the incidences of acute toxicity in the two groups with calculation of odds ratios and 95% CI. We did univariate and multivariate logistic regression

Table 2.2 | Cumulative incidences of acute genitourinary and gastrointestinal toxicity by grade

	Genitourinary			Gastrointestinal		
	standard fractionation group	hypo-fractionation group	P value*	standard fractionation group	Hypo-fractionation group	P value*
Before radiotherapy						
n	391	403		391	402	
1	115 (29%)	124 (31%)	0·45	30 (8%)	43 (11%)	0·044
≥2	85 (22%)	93 (23%)	0·65	9 (2%)	16 (4%)	0·18
2	73 (19%)	70 (17%)	-	7 (2%)	14 (3%)	-
3	12 (3%)	23 (6%)	0·068	2 (1%)	2 (<1%)	0·98
4	-	-	-	-	-	-
4 weeks						
n	385	401		385	400	
1	118 (31%)	120 (30%)	0·41	117 (30%)	104 (26%)	0·22
≥2	171 (44%)	191 (48%)	0·37	70 (18%)	108 (27%)	0·0031
2	131 (34%)	144 (36%)	-	62 (16%)	97 (24%)	-
3	40 (10%)	45 (11%)	0·55	8 (2%)	11 (3%)	0·54
4	-	2 (<1%)	-	-	-	-
6 weeks						
n	376	376		378	376	
1	100 (27%)	98 (26%)	0·46	98 (26%)	81 (22%)	0·27
≥2	178 (47%)	171 (45%)	0·61	86 (23%)	117 (31%)	0·01
2	144 (38%)	125 (33%)	-	72 (19%)	104 (28%)	-
3	33 (9%)	45 (12%)	0·16	14 (4%)	13 (3%)	0·86
4	1 (<1%)	1 (<1%)	-	-	-	-
3 month after radiotherapy						
n	325	327		326	327	
1	56 (17%)	91 (28%)	0·0045	47 (14%)	56 (17%)	0·51
≥2	73 (22%)	75 (23%)	0·89	43 (13%)	42 (13%)	0·90
2	47 (14%)	51 (16%)	-	39 (12%)	32 (10%)	-
3	25 (8%)	23 (7)	0·75	4 (1%)	10 (3%)	0·11
4	1 (<1%)	1 (<1%)	-	-	-	-
Maximum toxicity score after radiotherapy						
n	391	403		391	402	
1	114 (29%)	120 (30%)	0·14	140 (36%)	129 (32%)	0·028
≥2	226 (58%)	244 (61%)	0·43	122 (31%)	169 (42%)	0·0015
2	155 (40%)	160 (40%)		104 (27%)	146 (36%)	
3	69 (18%)	82 (20%)	0·34	18 (5%)	23 (6%)	0·48
4	2 (1%)	2 (<1%)	-	-	-	-

*Reported p values are for significance test of the difference in toxicity of the respective grade or higher.

analyses to assess the effect of symptoms of baseline grade 2 or worse, age, PSA concentration, Gleason score, T stage, previous transurethral prostate resection, use of hormonal therapy, previous abdominal morbidity and surgery, prostate volume, treatment group according to risk of seminal vesicle involvement, and treatment group[5,17] on incidence of acute toxic effects. Differences in percentages were tested applying Pearson's $\chi 2$ or Fisher's exact tests. Comparison of the correlated proportions of patients with toxicities according to the case report form and patients' self-assessment questionnaires was done with McNemar's test.

According to the protocol, Cox regression modelling was used for late toxic effects but not for acute toxic effects. No corrections for multiple testing were applied and all reported p values were based on two-sided tests. We deemed a p value of less than 0·05 as significant. Analyses were done with STATA (version 13.1). This study is registered with www.controlled-trials.com, number ISRCTN85138529.

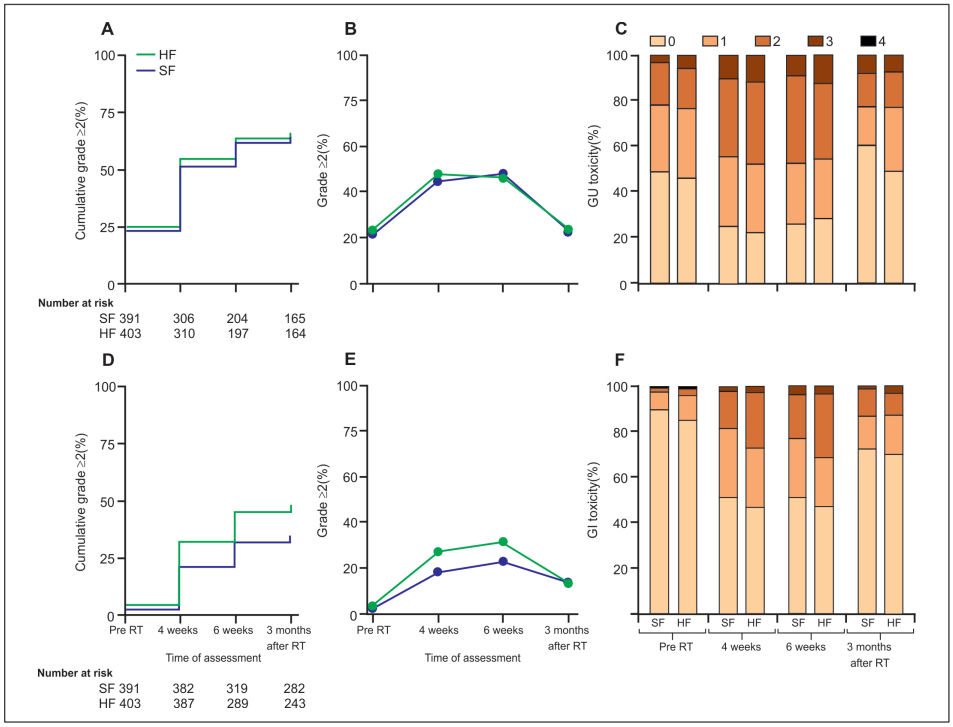

Figure 2.2 | Acute toxicity as a function of time

Cumulative incidence of grade 2 or worse genitourinary toxic events (A), prevalence of grade 2 or worse genitourinary toxic events (B), and distribution of genitourinary toxicity scores (C). Cumulative incidence of grade 2 or worse gastrointestinal toxic events (D), prevalence of grade 2 or worse gastrointestinal events (E), and distribution of gastrointestinal toxicity scores (F). HF=hypofractionation. SF=standard fractionation. RT=radiotherapy. GU=genitourinary. GI=gastrointestinal.

Table 2.3 | Specific symptoms according to treatment group

	Standard fractionation group (n=390)	Hypofractionation group (n=402)	p value
Genitourinary			
Pain needing drugs (grade 2)	14 (4%)	21 (5%)	0·26
Macroscopic haematuria (grade 3)	9 (2%)	15 (4%)	0·24
Increased frequency at day (grade 2)	96 (25%)	100/401 (25%)*	0·92
Increased frequency at night five to seven times (grade 2)	107 (27%)	125/401 (31%)*	0·25
Increased frequency at night >seven times (grade 3)	26 (7%)	46/401 (12%)*	0·019
Incontinence (grade 3)	39/364 (11%)*	49/372 (13%)*	0·30
Gastrointestinal			
Pain needing drugs (grade 2)	18 (5%)	35 (9%)	0·021
Diarrhoea with drugs (grade 2)	19 (5%)	21 (5%)	0·82
Increased frequency ≥ six (grade 2)	31 (8%)	58 (15%)	0·0035
Use of pads (grade 3)	22 (6%)	32 (8%)	0·19
Blood or mucous loss (grade 3)	15 (4%)	22 (6%)	0·28

* The number of assessable patients per specific symptom can vary and the denominator is indicated when that happens.

Role of the funding source

The funder provided peer-reviewed approval for the trial, but had no other role in study design, collection, analysis or interpretation of data. The corresponding author and the principal investigators of the study (LI and FP) had full access to all data and had final responsibility for the decision to submit for publication.

RESULTS

Between March 19, 2007, and Dec 3, 2010, 820 patients from seven Dutch radiotherapy centres (appendix) were randomly assigned to treatment with standard fractionation or hypofractionation (410 patients in each group). 25 patients (18 in the standard fractionation group and seven in the hypofractionation group) were excluded because of non-eligibility (n=14), double entry (n=1), not being treated or they died before start of treatment (n=10), or non-evaluability for acute toxicity (n=1), resulting in 794 assessable patients (391 in the standard fractionation group and 403 in the hypofractionation group; figure 1). Table 1 shows baseline characteristics. There were treatment delivery deviations in 14 patients (six in the standard fractionation group, eight in the

hypofractionation group) that included temporary interruption for three patients (two in the standard fractionation group, one in the hypofractionation group), discontinuation of irradiation in three patients because of toxic effects (one in the standard fractionation group, two in the hypofractionation group), technical failure (two in the standard fractionation group), on patients' requests (two in the hypofractionation group), and other (three in the standard fractionation group, one in the hypofractionation group).

Hormonal therapy was given to around two-thirds of patients in each group (table 1). Intensity-modulated radiation therapy and set-up verification and correction based on implanted fiducials were used in 370 (95%) of 391 patients in the standard fractionation group and in 380 (94%) of 403 patients in the hyprofractionation group. Median time from onset of hormonal therapy to the date of planning CT or MRI was 1·7 months (IQR 0·8–2·8) in the standard fractionation group and 1·8 months (0·9–3·3) in the hyprofractionation group. At closure of the database (Sept 12, 2014), 716 patients (354 in standard fractionation group and 362 in hyprofractionation group) were still alive with a median follow up of 49·2 months (IQR 9·2–58·2). We noted no significant difference in cumulative incidence up to 120 days after radiotherapy of grade 2 or worse acute genitourinary toxicity (57·8% [95% CI 52·9–62·7] in the standard fractionation group *vs* 60·5% [55·8–65·3] in the hypofractionation group; difference 2·7%, 90% CI –2·99 to 8·48; OR 1·12, 95% CI 0·84–1·49; p=0·43; table 2). Thus hypofractionation was not non-inferior to standard fractionation in terms of acute genitourinary toxicity.[20] Figure 2 and table 2 show differences between standard fractionation and hypofractionation in incidence of grade 2 or worse acute genitourinary toxicity as a function of time.

The cumulative incidence of grade 3 genitourinary toxicity was 17·6% (95% CI 13·9–21·4) for standard fractionation and 20·3% (16·4–24·3) for hypofractionation (p=0·34). In each group, two patients had grade 4 acute genitourinary toxicity. Table 3 shows the comparison between standard fractionation and hypofractionation for specific symptoms. Nocturia seven times or more per night was reported more in the hypofractionation group than in the standard fractionation group (OR 1·81, 95% CI 1·10–3·00; p=0·019; table 3). The cumulative incidence of grade 2 or worse acute gastrointestinal toxicity up to 120 days after radiotherapy was higher in patients given hypofractionation than those treated with standard fractionation (31·2% [95% CI 26·6–35·8] in the standard fractionation group *vs* 42·0% [37·2–46·9] in the hypofractionation group; difference 10·8%, 90% CI 5·25–16·43; OR 1·6; 95% CI 1·19–2·14; p=0·0015; table 4). Thus hypofractionation was not non-inferior to standard fractionation in terms of acute gastrointestinal toxicity. Figure 2 and table 2 show differences between standard fractionation and hypofractionation groups in incidence of grade 2 or worse acute gastrointestinal toxicity at the various time points. The difference in toxicity between standard fractionation and hypofractionation had dissipated by 3 months after radiotherapy (p=0·90; figure 2 and table 2). In the standard fractionation group, the cumulative incidence of grade 3 gastrointestinal toxicity was 4·6% (95% CI 2·5–6·7) versus 5·7% (3·4–8·0) in the hypofractionation group (p=0·48). We did not record any grade 4 gastrointestinal toxicity (table 2). Pain with urge and discomfort was frequently noted in the hypofractionation group (OR 1·98, 95% CI 1·10–3·55; p=0·021; table 3). Stool frequency greater than six per day was also significantly increased with hypofractionation compared with standard fractionation (OR 1·96, 95% CI 1·24–3·10; p=0·0035; table 3).

Table 2.4 | Univariate and multivariate logistic regression analyses exploring the association of baseline factors with the observed cumulative incidence of grade 2 or worse acute gastrointestinal and genitourinary toxic effects

	Univariate		Multivariate	
	p value	OR (95% CI)	p value	OR (95% CI)
Genitourinary				
Genitourinary complications (equal to grade 2 or worse RTOG toxicity score) at baseline	15·7(8·4-29·5)	<0·001	14·5(7·7-27·3)	<0·001
Age (>70 years)	1·45(1·09-1·92)	0·011	1·38(1·00-1·90)	0·051
PSA (≤20)	0·90(0·66-1·22)	0·49	-	
Gleason(≤7)	0·68(0·49-0·96)	0·026	-	
T-stage(T3-T4 vs T1-T2)	1·24(0·93-1·64)	0·14	-	
Transurethral prostate resection	0·86(0·53-1·38)	0·53	0·88(0·52-1·49)	0·63
Adjuvant hormonal therapy	1·11(0·82-1·50)	0·49	-	
Months hormonal therapy before RT		0·53*		0·61*
≤2 vs none	1·07(0·75-1·52)	0·72	0·99(0·65-1·51)	0·96
>2 vs none	1·11(0·79-1·57)	0·53	1·10(0·73-1·65)	0·65
Abdominal surgery	1·19(0·86-1·65)	0·30		
Gastrointestinal comorbidity	1·03(0·64-1·66)	0·92	0·97(0·57-1·65)	0·90
Prostate volume (>50 vs <50 cm3)	1·28(0·96-1·71)	0·088	1·36(0·98-1·89)	0·064
Treatment group		0·11*		0·75*
2 vs 1	1·07(0·74-1·56)	0·72	1·01(0·67-1·53)	0·97
3 vs 1	1·36(0·91-2·05)	0·14	1·29(0·80-2·07)	0·29
Treatment group (hypofractionation vs standard fractionation)	1·12(0·84-1·49)	0·43	1·07(0·78-1·46)	0·68 †
Gastrointestinal				
Gastrointestinal complications (equal to grade 2 or worse RTOG toxicity score) at baseline	5·8(2·3-14·6)	<0·0001	5·5(2·1-14·3)	0·0010
Age (>70 years)	1·23(0·92-1·64)	0·17	1·23(0·91-1·68)	0·18
PSA (≤20)	0·86(0·63-1·18)	0·35	-	
Gleason (≤7)	0·84(0·60-1·17)	0·29	-	
T stage (T3-T4 vs T1-T2)	0·98(0·74-1·31)	0·90	-	
Transurethral prostate resection	0·81(0·49-1·34)	0·41	0·75(0·45-1·27)	0·29
Adjuvant hormonal therapy	0·74(0·55-1·00)	0·052	-	
Months of hormonal therapy		0·009*		0·007*
before radiotherapy	0·91(0·63-1·30)	0·59	0·88(0·59-1·31)	0·52
≤2 vs none	0·63(0·44-0·89)	0·009	0·58(0·39-0·87)	0·008
>2 vs none				

Abdominal surgery	0·93(0·66-1·29)	0·65		1·0
GI comorbidity	1·25(0·78-2·02)	0·36	1·24(0·74-2·06)	0·41
prostate volume (>50 vs <50 cm3)	1·49(1·11-2·00)	0·008	1·33(0·97-1·82)	0·079
Treatment group		0·11*		0·009*
2 vs 1	1·24(0·84-1·84)	0·28	1·37(0·90-2·08)	0·14
3 vs 1	1·41(0·93-2·15)	0·11	1·79(1·12-2·86)	0·015
Treatment group (hypofractionation vs standard fractionation)	1·60(1·19-2·14)	0·0015†	1·57(1·16-2·13)	0·0034†

RTOG=Radiation Therapy Oncology Group. PSA=prostate-specific antigen. *p values for linear trend tests across the categories. †p value based on likelihood ratio test.

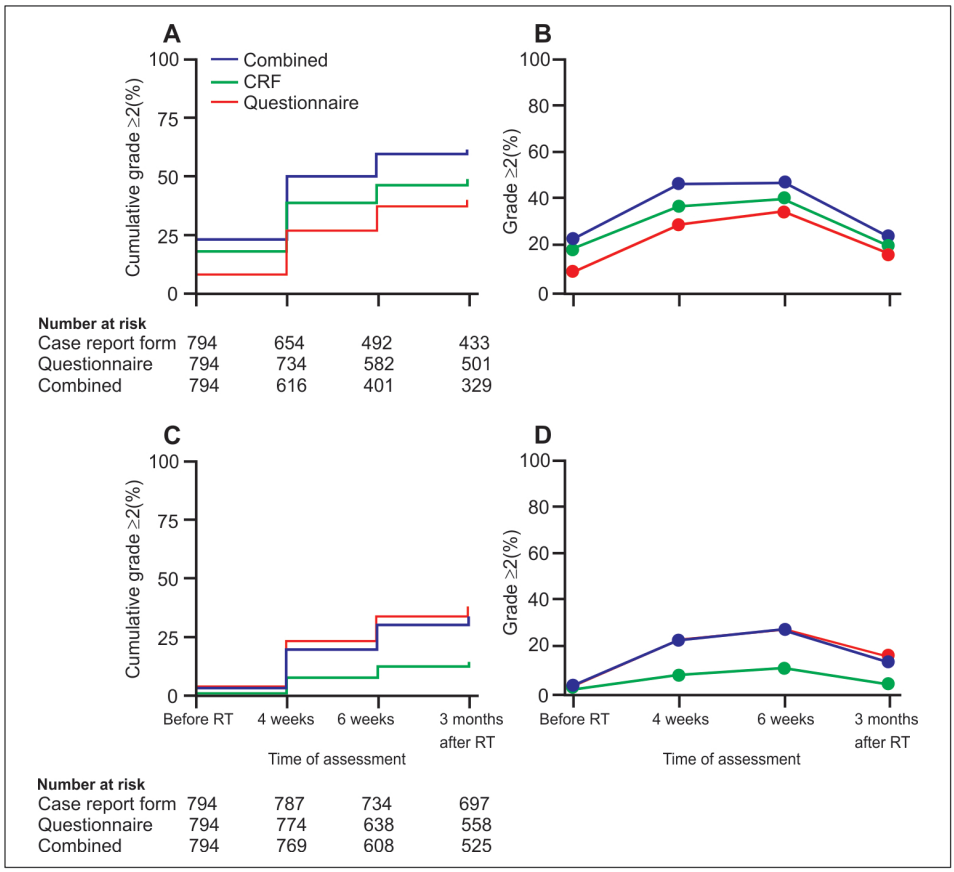

Figure 2.3 | Acute toxicity reported by case report forms, patient self-assessment, and combined**.** Cumulative incidence of grade 2 or worse genitourinary toxic events, (A) prevalence of grade 2 or worse genitourinary toxicity, (B) cumulative incidence of grade 2 or worse gastrointestinal toxicity, (C) prevalence of grade 2 or worse gastrointestinal toxicity (D).

The presence of baseline grade 2 or worse genitourinary symptoms was the only significant prognostic factor for increased cumulative incidence of grade 2 or worse acute genitourinary toxicity in multivariate analyses (OR 14·5, 95% CI 7·7–27·3; p<0·0001; table 4). Baseline grade 2 or worse gastrointestinal symptoms were associated with an increased incidence of gastrointestinal toxicity (OR 5·5, 95% CI 2·1–14·3; p=0·0010). Hormonal therapy use for 2 months or longer before start of radiotherapy compared with no hormonal therapy was associated with a reduction in incidence of gastrointestinal toxicity (OR 0·58, 95% CI 0·39–0·87; p=0·0085). Additionally, we noted a significant trend in increasing gastrointestinal toxicity when going from treatment group 1 to 2 to 3 (trend test p=0·0089). For group 1, the clinical target volume consisted of the prostate only, to be treated to prescribed dose. For group 2, the prostate received the prescribed dose, while the seminal vesicle were treated to a dose of 35 fractions of 2 Gy or 39 fractions of 1·85 Gy (standard fractionation), or a dose of 16 fractions of 3·4 Gy or 19 fractions of 3·04 Gy in the hypofractionation group. For group 3,

RESEARCH IN CONTEXT

Systematic review

We searched Medline without language restriction between February, 2005, and May, 2006, with the search terms "prostate cancer", "radiotherapy", "hypofractionation", "alpha beta ratio", "toxicity".[6–8,10–12,21] The scientific literature shows evidence for a low α/β ratio for prostate cancer[6–8] with a potential for an enhanced therapeutic ratio for hypofractionated radiotherapy. In the development phase of the HYPRO trial, only a few, small randomised hypofractionation trials had been published,[10–12] which were mostly done with lower treatment doses (66–72 Gy). The use of intensity-modulated radiation therapy and image-guided radiotherapy are associated with low toxicity rates.[22–25] The availability of these techniques to prevent excessive toxicity favoured launching of a hypofractionation trial. The aim of the HYPRO trial is to show superior relapse-free survival for hypofractionation compared with standard fractionation, with non-inferiority for toxicity, prescribing an enhanced tumour EQD_{2Gy}.

To our knowledge, only one other trial aimed at relapse-free survival enhancement with hypofractionation with a small patient sample,[26] whereas other trials[11,27] addressed toxicity or non-inferiority by use of a low tumour EQD_{2Gy}.

Interpretation

Hypofractionation was not non-inferior to standard fractionation for acute genitourinary and gastrointestinal toxicity; indeed, the cumulative incidence of grade 2 or worse acute gastrointestinal toxicity was significantly higher for hypofractionation. However, by 3 months after completion of radiotherapy, differences in genitourinary and gastrointestinal toxicities were not significant. Presence of baseline symptoms was the most important predictive factor for acute toxicity. The use of patients' self-assessment questionnaires complementary to case report forms can prevent serious under-reporting of toxic effects and is recommended. These finding are useful for patients and physicians when considering treatment with a hypofractionated regimen with a fraction dose higher than 3 Gy.

both the prostate and the seminal vesicle were treated up to prescribed dose, group 3 patients had a higher risk of gastrointestinal toxicity than patients in group 1 (table 4). In the multivariate analysis, when adjusting for all those factors, hypofractionation remained associated with a significantly higher cumulative incidence of grade 2 or worse acute gastrointestinal toxicity than with standard fractionation (OR 1·57, CI 1·16–2·13; p=0·0034).

For both genitourinary and gastrointestinal adverse events, the total reported incidences derived from the combined use of case report form and patients' self-assessment questionnaires were substantially higher than for case report form only (figure 3).

DISCUSSION

On the basis of our findings, hypofractionation is not non-inferior to standard fractionation in terms of acute grade 2 or worse genitourinary and gastrointestinal toxicity (panel). There was no significant difference in the cumulative incidence of grade 2 or worse acute genitourinary toxicity between the groups; however, grade 2 or worse acute gastrointestinal toxicity was significantly more common in the hypofractionation group than in the standard fractionation group. Although 3 months after completion of radiotherapy this difference had dissipated, it is possible that late gastrointestinal toxicity will be worse, due to the known association between acute and late toxicity;[5] patients remain in follow-up and we will investigate this association in the future.

It is possible that our trial was underpowered to conclude non-inferiority for acute toxic effects. The trial's sample size was mainly based on power considerations for relapse-free survival. When designing the trial, a power of 71% for the acute toxicity comparisons was accepted to avoid a substantial increase in the number of patients, resulting in an unfavourable time for completion of the trial. Further, the per-protocol defined margin for non-inferiority of 8% might have been stringent with only 800 patients included.

Several investigators have reported increased acute toxicity with hypofractionation. In these studies, the overall treatment time was shorter for the hypofractionation group than the standard fractionation group (5·0–5·5 weeks *vs* 7–8 weeks).[9,11,28] In our trial, the overall treatment times of hypofractionation and standard fractionation differed only by 1·5 weeks. We chose a longer schedule for our hypofractionation regimen to eliminate overall treatment time as a study variable and to avoid excessive acute toxicity. Because of this protracted dose delivery, the time saving of hypofractionation was reduced compared with the other studies, but still the reduction from 39 to 19 fractions benefited patients in terms of convenience.

The α/β ratio for acute side-effects with radiotherapy is often assumed to be about 10 Gy. For an α/β ratio of 10 Gy, the EQD_{2Gy} for hypofractionation would be almost 6 Gy lower than for standard fractionation. The recorded increase in acute gastrointestinal toxicity with hypofractionation in this trial could indicate that the α/β ratio is actually around 4 Gy. However, notwithstanding the similarity of overall treatment time in the standard fractionation and hypofractionation groups in our trial, the

predicted weekly EQD_{2Gy} for acute toxicity was 1·4 Gy higher in the hypofractionation group than in the standard fractionation group, which could possibly have contributed to the higher rate of acute gastrointestinal toxicity. More research is needed to better understand the radiobiology of acute toxicity in hypofractionated radiotherapy in relation to the α/β ratio and overall treatment time.

Findings of the CHHiP trial[27] showed a peak in acute toxicity at 7–8 weeks from the start of standard fractionated radiotherapy; for hypofractionation there was a peak at 4–5 weeks (the duration of the hypofractionation course was 4 weeks). Investigators of the CKVO 96-10 trial[29] reported a steady increase in acute toxic effects during the first 7 weeks for standard fractionation. We recorded toxicity during treatment at only two time points. Thus we may have missed the peak toxicity in the standard fractionation group. More measurements during the acute phase would have provided us with a better resolution of data. However, from earlier experiences, more than three assessments during radiotherapy is a heavy burden for patients.

We stratified patients according to treatment centre, and in each centre the same treatment technique was used in both groups. This method ensured balance between the groups within each stratum and thus avoided bias in the overall results, despite inter-institutional technique variations.

The cumulative incidence of grade 2 or worse acute genitourinary toxicity in this trial was similar to that recorded in the high-dose group (39 fractions of 2 Gy) in the CKVO 96-10 trial.[5] However, the cumulative incidence of grade 2 or worse acute gastrointestinal toxicity in the high-dose group of the CKVO 96-10 trial was much higher than we noted. In the CKVO 96-10 study, most patients were given three-dimensional conformal radiotherapy. Almost all patients in our trial were given intensity-modulated radiation therapy with daily online set-up verification and correction on the basis of implanted fiducials. These differences in treatment technique might have contributed to the lower gastrointestinal toxicity in our trial.

Our reported acute toxicity is higher than in other published studies of hypofractionation.[9,11,12,21,27,28] Often, acute toxicity scoring is based on case report forms only. In our trial, scoring was based on both case report forms and patients' self-assessment questionnaires. The addition of patients' self-assessment questionnaires to the analyses resulted in significant increases in the reported incidence of acute toxicity (figure 3). Underestimation of toxicity by use of case report forms has been reported previously.[30] Addition of patients' self-assessment questionnaires results in more robust toxicity scores and might seriously affect conclusions drawn from studies. The means of toxicity scoring should be accurately described to allow comparison with other studies. Preferentially, both case report form and patients' self-assessment questionnaires should be used.

Compared with some other studies,[12,27] the HYPRO trial included more high-risk patients (584 [74%] of 794), and for 249 (31%) of 794 of these patients the whole seminal vesicle was given the prescribed dose. The inclusion of the seminal vesicle in the target volume might have contributed to an enhanced incidence of acute toxicity in our study. Furthermore, the mean age of the patients in our trial was higher than in other series.[5,26,27] In our trial, being older than 70 years was a negative prognostic factor for genitourinary toxicity (in both groups) only in the univariate analysis, but

Pollack and colleagues[26] reported age 67 years or older as a poor prognostic factor for genitourinary toxicity in their hypofractionation group.

In our multivariate analyses, we noted a decrease in risk of acute gastrointestinal toxicity with the use of neoadjuvant hormonal therapy; this has also been reported before.[5,31] Hormonal therapy could have resulted in a decrease in prostate volume, and consequently reduced organs at risk dose delivery. However, hormonal therapy remained significant in the multivariate analyses including the prostate volume.

The incidence of grade 2 or worse genitourinary toxicity 3 months after completion of radiotherapy was about 23% in both groups, which is the same as the baseline level. This finding suggests that most acute genitourinary symptoms were reversible in both groups within 3 months after radiotherapy. Presence of baseline grade 2 or worse gastrointestinal or genitourinary symptoms was strongly associated with enhanced incidence of acute gastrointestinal and genitourinary toxicity in both groups, which was also reported in the CKVO 96-10 trial.[5] The high baseline rate of grade 2 or worse genitourinary symptoms (about 23% of patients), compared with 10% in the CKVO 96-10 trial,[5,32] might partly explain the high acute genitourinary toxicity in the our trial, although most patients were given intensity-modulated radiation therapy and daily online set-up correction.

In conclusion, hypofractionated radiotherapy for men with prostate cancer is not non-inferior in terms of acute grade 2 or worse genitourinary and gastrointestinal side effects. Indeed, the cumulative incidence of grade 2 or worse acute gastrointestinal toxicity was significantly higher for hypofractionation. Patients in this trial remain in follow-up for the main efficacy endpoint of recurrence free survival.

Contributors

SA contributed to the recruitment of patients, data collection, data interpretation, and writing of this report; LI and FP were the principal investigators and contributed to study design, patients' recruitment, data interpretation, and writing this report; ES, EvL, SK, PPvdT, and HdJ were involved in protocol development, patient recruitment, and reviewing this report; MD contributed to data interpretation, and reviewing this report; WGA was responsible for statistical analysis, data interpretation, and writing of this report; and BH was involved in protocol development, data interpretation, and writing this report.

Declaration of interests

We declare no competing interests.

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Chapter 3

Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial

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SUMMARY

Background

Several studies have reported a low α to ß ratio for prostate cancer, suggesting that hypofractionation could enhance the biological tumour dose without increasing genitourinary and gastrointestinal toxicity. We tested this theory in the phase 3 HYPRO trial for patients with intermediate-risk and high-risk prostate cancer. We have previously reported acute incidence of genitourinary and gastrointestinal toxicity; here we report data for late genitourinary and gastrointestinal toxicity.

Methods

In this randomised non-inferiority phase 3 trial, done in seven radiotherapy centres in the Netherlands, we enrolled intermediate-risk or high-risk patients aged between 44 and 85 years with histologically confirmed stage T1b–T4 Nx–0 Mx–0 prostate cancer, a prostate-specific antigen concentration of 60 ng/mL or lower, and WHO performance status of 0–2. A web-based application was used to randomly assign (1:1) patients to receive either standard fractionation with 39 fractions of 2 Gy in 8 weeks (five fractions per week) or hypofractionation with 19 fractions of 3·4 Gy in 6·5 weeks (three fractions per week). Randomisation was done with the minimisation procedure, stratified by treatment centre and risk group. The primary endpoint was to detect a 10% enhancement in 5-year relapse-free survival with hypofractionation. A key additional endpoint was non-inferiority of hypofractionation in cumulative incidence of grade 2 or worse acute and late genitourinary and gastrointestinal toxicity. We planned to reject inferiority of hypofractionation for late genitourinary toxicity if the estimated hazard ratio (HR) was less than 1·11 and for gastrointestinal toxicity was less than 1·13. We scored toxicity with the Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (RTOG/EORTC) criteria from both physicians' records (clinical record form) and patients' self-assessment questionnaires. Analyses were done in the intention-to-treat population. Patient recruitment for the HYPRO trial was completed in 2010. The trial was registered with www.controlled-trials.com, number ISRCTN85138529.

Findings

Between March 19, 2007, and Dec 3, 2010, 820 patients (410 in both groups) were randomly assigned. Analyses for late toxicity included 387 assessable patients in the standard fractionation group and 395 in the hypofractionation group. The median follow-up was 60 months (IQR 51·2–67·3). The database for all analyses (both groups and both genitourinary and gastrointestinal toxicities) was locked on March 26, 2015. The incidence of grade 2 or worse genitourinary toxicity at 3 years was 39·0% (95% CI 34·2–44·1) in the standard fractionation group and 41·3% (36·6–46·4) in the hypofractionation group. The estimated HR for the cumulative incidence of grade 2 or worse late genitourinary toxicity was 1·16 (90% CI 0·98–1·38), suggesting that non-inferiority could not be shown. The incidence of grade 2 or worse gastrointestinal toxicity at 3 years was 17·7% (14·1–21·9) in standard fractionation and 21·9% (18·1–26·4) hypofractionation.

RESEARCH IN CONTEXT

Evidence before this study

When the HYPRO trial was being planned and developed, only a few, small randomised hypofractionation trials had been published, which were done mostly with lower treatment doses (66–72 Gy). Scientific literature showed initial evidence for a low α to ß ratio for prostate cancer. There was a clear need for large randomised trials to test the predicted enhanced therapeutic ratio with hypofractionation. The use of intensity-modulated radiotherapy and image-guided radiation therapy with lower published toxicity had become common. Availability of these techniques to prevent excessive toxicity favoured launching of a hypofractionation trial. The HYPRO trial aimed to show superior relapse-free survival with hypofractionation, by prescribing an enhanced tumour equivalent dose in 2 Gy fractions (EQD_{2Gy}) compared with standard fractionation, without increasing toxicity. To our knowledge, only one other trial aimed at relapse-free survival enhancement with hypofractionation with a small patient sample, whereas other trials addressed toxicity or non-inferiority, using a lower tumour EQD_{2Gy}.

Added value of this study

Our findings could not confirm the per-protocol hypothesized non-inferiority of hypofractionation for late genitourinary and gastrointestinal toxicity. Moreover, the cumulative incidence of grade 3 or worse late genitourinary toxicity was significantly higher in the hypofractionation group. Because the hypothesized non-inferiority of hypofractionation for late toxicity was based on calculations with the linear-quadratic model with the generally applied α to β ratio of 4–6 Gy for late toxicity, this approach might be questionable. The use of patient self-assessment questionnaires on top of clinical record forms did significantly enhance reported late toxicity.

Implication of all available evidence

Together with previous findings that were unable to show non-inferiority of hypofractionation for both acute gastrointestinal and genitourinary toxicity, and the recorded significant increase in incidence of acute gastrointestinal toxicity, the findings of late toxicity question the added value of hypofractionation with a fraction dose higher than 3 Gy for all patients, and the need for patient selection—eg, based on baseline symptoms, which can reduce both genitourinary and gastrointestinal toxicity. Before conclusions can be made about the value of hypofractionation, treatment outcomes need to be reported. The addition of patient self-assessment questionnaires to toxicity reporting with clinical record forms could avoid serious toxicity under-reporting. The findings of reported genitourinary and gastrointestinal toxicity on the application of the linear-quadratic model should be considered in the design of new hypofractionation trials. Whether hypofractionation can be incorporated in to routine clinical practice will depend on the toxicity and outcome results of continuing studies with long follow-up.

With an estimated HR of 1·19 (90% CI 0·93–1·52) for the cumulative incidence of grade 2 or worse late gastrointestinal toxicity, we could not confirm non-inferiority of hypofractionation for cumulative late gastrointestinal toxicity. Cumulative grade 3 or worse late genitourinary toxicity was significantly higher in the hypofractionation group than in the standard fractionation group (19·0% [95% CI 15·2–23·2] vs 12·9% [9·7–16·7], respectively; p=0·021), but there was no significant difference between cumulative grade 3 or worse late gastrointestinal toxicity (2·6% [95% CI 1·2–4·7]) in the standard fractionation group and 3·3% [1·7–5·6] in the hypofractionation group; p=0·55).

Interpretation

Our data could not confirm that hypofractionation was non-inferior for cumulative late genitourinary and gastrointestinal toxicity compared with standard fractionation. Before final conclusions can be made about the utility of hypofractionation, efficacy outcomes need to be reported.

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INTRODUCTION

Published data for the unique radiobiology of prostate cancer reported a low α to ß ratio, suggesting a therapeutic advantage of hypofractionation for the treatment of intermediate-risk and high-risk prostate cancer.[1,2] Findings of trials [3,4,5] in which fractions of 3 Gy or less were used showed acceptable rectum and bladder toxicity after hypofractionation (these trials had small numbers of patients or short follow-up). In 2007, the randomised phase 3 multicentre HYPRO trial[6] was initiated in the Netherlands to test hypofractionated treatment with a fraction dose of 3·4 Gy, delivered during 19 fractions, three fractions per week, to investigate the potential benefit for relapse-free survival with non-inferiority for acute and late toxicity. As previously reported,[6] assuming an α to ß ratio of 1·5 Gy for prostate cancer, the tumour equivalent dose in 2 Gy fractions (EQD_{2Gy}) for 19 × 3·4 Gy would be 90·4 Gy (compared with 78 Gy for standard fractionation) with an expected increase in relapse-free survival of 10% compared with standard fractionation. Considering an α to ß ratio of 4–6 Gy for late genitourinary and gastrointestinal toxicity,[7,8] the EQD_{2Gy} for 19 × 3·4 Gy would be 77·5–79·7 Gy, close to the 78 Gy for standard fractionation. Therefore, we expected incidences of late genitourinary and gastrointestinal toxicities to be similar to late genitourinary and gastrointestinal toxicity in standard group. We chose three fractions per week for hypofractionation to make the overall treatment time as similar as possible in both groups, avoiding excessive acute toxicity for hypofractionation. After our report of acute toxicity,[6] here we report data for late genitourinary and gastrointestinal toxicity, as primary endpoints of the HYPRO trial.

METHODS

Study design and participants

In this open-label, phase 3 study, we recruited intermediate-risk and high-risk patients with prostate cancer[9] aged between 44 and 85 years who had histologically confirmed stage T1b–T4 Nx–0 Mx–0, prostate-specific antigen of 60 ng/mL or less and a WHO performance status of 0–2. In cases in which patients had prostate-specific antigen less than 20 ng/mL or a Gleason score lower than 8, patients could be included without a work-up for metastases. We excluded patients with previous pelvis irradiation, radical prostatectomy, evidence of pelvic nodal disease (determined by CT of pelvis), presence of distant metastases (determined by bone scintigraphy), and low-risk patients (stage T1b–T2a, Gleason score ≤6, prostate-specific antigen ≤10 ng/mL).[9,10] Each participating centre followed its own protocol for adjuvant hormonal therapy, which had to be applied equally for both study groups. This trial was approved by the medical ethics committee of the Erasmus Medical Centre in Rotterdam, the Netherlands (06-045). All patients provided written informed consent. The trial was coordinated and managed by the Department of Radiation Oncology and the Clinical Trials Center of the Erasmus MC Cancer Institute.

Randomisation and masking

Patients were randomly assigned (1:1) to open-label treatment groups with standard fractionation or hypofractionation, applying a minimisation procedure. There was a random element in the randomisation and it ensured overall balance and within each stratum of the stratification factors (i.e., treatment centre and risk group). Patients were assigned via a web-based application (done by the Clinical Trials Center, Erasmus MC Cancer Institute, Rotterdam) and the assigned treatment group was sent immediately via fax, telephone, or email to the local investigator.[6] The local investigators were treating physicians, so they were not masked to treatment. Randomisation took place at least 4 weeks before the start of treatment.

Procedures

Patients were randomly assigned to receive either standard fractionation (39 fractions of 2 Gy, five fractions per week) or hypofractionation (19 fractions of 3·4 Gy, three fractions per week). Three treatment groups were defined based on the risk of seminal vesicle involvement:[11] group 1 with risk of 10% or less, group 2 with risk between 10% and 25%, and group 3 with a risk of more than 25% (current pre-radiotherapy MRI staging might change the role of the applied Partin's table[11] for assessment of the risk of seminal vesicle invasion). For group 1, the clinical target volume consisted of the prostate only, to be treated to the prescribed dose i.e., 39 × 2 Gy for standard fractionation and 19 × 3·4 Gy for hypofractionation. For group 2, the prostate received the prescribed dose, whereas the seminal vesicle was treated to a dose of 35 fractions of 2 Gy up to 70 Gy or 39 fractions of 1·85 Gy (standard fractionation group), or a dose of 16 fractions of 3·4 Gy or 19 fractions of 3·04 Gy (hypofractionation group). For group 3, both the prostate and the seminal vesicle were treated up to the prescribed dose.[6]

Depending on the set-up verification and correction strategy used in each participating institute, margins of 3–10 mm were added to the clinical target volume (equal in both groups), yielding the planning target volume.[6] For the boost, these margins could be reduced to 0 mm towards the rectum, and 3–5 mm in other directions. This boost could either be delivered sequentially or simultaneously integrated depending on the institute's preference. The planning CT or MRI was done 2 weeks before start of radiotherapy.

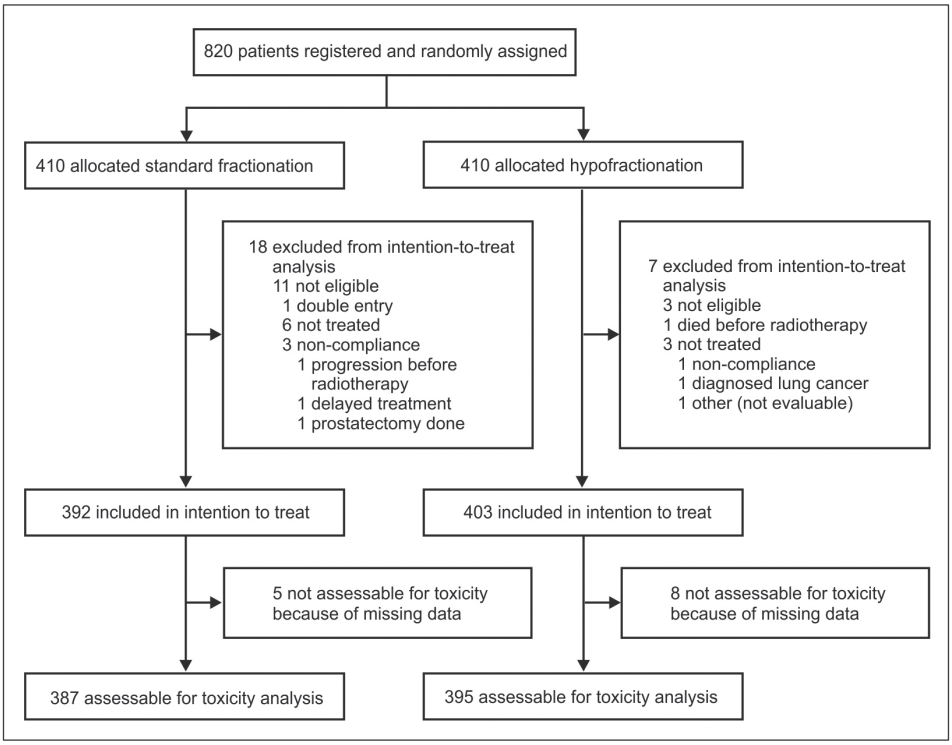

Figure 3.1 | Trial profile

As prescribed by the study protocol, patients were assessable for late toxicity as long there was no evidence of relapse. Genitourinary and gastrointestinal toxicity were scored by clinical record form, as reported by the treating physician, following the Radiation Therapy Oncology Group-European Organisation for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria,[6] and by patient self-assessment questionnaires.[10,12] Both for late genitourinary and gastrointestinal toxicity overall (cumulative) toxicity scores were taken as the highest of the two scores. The earliest date from either source on which a toxicity score of grade 2 or worse was reported was defined as the date of incidence of grade 2 or worse late toxicity.[6,12] We assessed late toxicity from 90 days after treatment (at 6, 12, 24, 36, 48, and 60 months). We recorded incidences of clinically relevant symptoms, including nocturia, frequency, dysuria needing medication, haematuria and incontinency for genitourinary toxicity, and pain with urge and discomfort, frequency, use of pads,

bleeding, and diarrhoea needing medication for gastrointestinal toxicity.[6,12,13] Information about smoking was collected after randomisation and before treatment.

Outcomes

The primary endpoint of this trial is 5-year relapse-free survival. Key endpoints are 3-year cumulative grade 2 or worse acute and late gastrointestinal and genitourinary toxicity, with hypothesised non-inferiority of hypofractionation. Secondary endpoints are quality of life and erectile function. The protocol defined 3-year late toxicity for the non-inferiority endpoint. This was based on the results of our dose escalation study[12] in which most toxicities were reported in the first 3 years after treatment. We waited for the 5 years late toxic effect results to report on in this paper.

Statistical analysis

The HYPRO trial was powered to show a reduction from 30%[10] (based on the results of the Dutch dose escalation study[10]) to 20% in relapse-free survival (the primary endpoint) with a power of 92% for 800 patients. Non-inferiority for late toxicity was tested separately for late genitourinary and gastrointestinal toxicities, with the null hypothesis that the cumulative incidence in the hypofractionation group was 8% or higher than in the other group against the alternative hypothesis that the cumulative incidence in the hypofractionation group was less than or equal to that of standard fractionation. For the non-inferiority hypotheses, one-sided tests with an α of 0·05 were used for each of the endpoints without adjustment for multiple testing. For standard fractionation, the expected cumulative incidence of grade 2 or worse genitourinary toxicity at 3 years was 31%.[10] A difference of 8% corresponds with a hazard ratio (HR) of 1·33. The null hypothesis of inferiority was to be rejected only if the estimated hazard ratio of the incidence of late genitourinary toxicity in the hypofractionation group compared with the control group was less than 1·11, which corresponds with a maximum absolute increase of 2·8%. The expected cumulative incidence of grade 2 or worse late gastrointestinal toxicity at 3 years for standard fractionation was 26%.[10] A difference of 8% corresponds with an HR of 1·38. The null hypothesis of inferiority was to be rejected only if the estimated HR of the incidence of late gastrointestinal toxicity in the hypofractionation group compared with the control group was less than 1·13, which corresponds with a maximum absolute increase of 2·8%. For late genitourinary and gastrointestinal toxicity, the power for showing non-inferiority for 2 × 400 patients was 84% and 86%, respectively. This power was decided acceptable to avoid a substantial increase in the number of patients, resulting in an unfavourable time for completion of the trial. For example, if we had powered the test with 90%, then the sample size would have been 2 × 688 patients. Incidence probabilities of grade 2 or worse late toxicity were estimated by the Kaplan-Meier method and compared between the standard fractionation and hypofractionation groups using the Cox likelihood ratio (LR) test. Univariate and multivariate Cox-regression analyses were done to assess the effect of: baseline symptoms equivalent to grade 2 or worse toxicity, acute toxicity, age, prostate-specific antigen, Gleason score, T stage, previous transurethral resection of the prostate (TURP), use of hormonal therapy, previous abdominal morbidity and surgery, prostate volume, treatment group according to risk of seminal vesicle involvement, and treatment group on late toxicity incidence. Hazard ratios (HRs) with 95% CIs were determined. The treatment effects in subgroups were explored in post-hoc analyses by

comparing the subgroup incidences of grade 2 or worse late toxicity by estimating the HRs with 95% CIs and testing for interaction effect of the risk factors with treatment group.

We tested differences in percentages by applying Pearson's $\chi 2$ test (Fisher's exact test was applied if the percentage in one of the groups was very small). There was no data imputation of the missing data and all available data were analysed. We compared the correlated proportions of patients with toxicity according to the clinical record form and patients' self-assessment questionnaires by applying the McNemar's test. No corrections for multiple testing were applied and all reported p values were based on two-sided tests. We regarded a p value of less than 0·05 as significant. Analyses were intention to treat. We used Stata (version 13.1) for the analyses.

This trial was approved by the medical ethics committee of the Erasmus Medical Center in Rotterdam, the Netherlands (06-045), and registered with www.controlledtrials.com, number ISRCTN85138529.

Role of the funding source
The funder provided peer-reviewed approval for the trial, but had no other role in study design, collection, analyses or interpretation of data. The corresponding author and the principal investigators of the study (LI and FP) had full access to all data and had final responsibility for the decision to submit for publication.

Table 3.1 | Baseline characteristics

	Standard fractionation group (n=387)	Hypofractionation group (n=395)
Age (years)	71 (67-75)	70 (66-74)
T-stage		
T1a	1 (0%)	0
T1b	3 (1%)	3 (1%)
T1c	54 (14%)	52 (14%)
T2a	44 (12%)	49 (12%)
T2b	38 (10%)	35 (9%)
T2c	48 (12%)	49 (12%)
T3a	159 (41%)	155 (39%)
T3b	37 (10%)	46 (12%)
T4	3 (1%)	6 (2%)
PSA concentration (ng/ml)		
< 10	102 (26%)	122 (31%)
10 – 20	155 (40%)	157 (40%)
>20	130 (34%)	116 (29%)

Median PSA (range)	14·8 (1·1-59·6)	13·8 (1-59)
Q1	9·8	9·2
Q3	24	21·1
Gleason score		
≤6	118 (30%)	120 (30%)
7	176 (45%)	179 (45%)
8	56 (14%)	59 (15%)
9	33 (9%)	34 (9%)
10	4 (1%)	3 (1%)
Treatment group		
1	78 (20%)	78 (20%)
2	188 (49%)	196 (50%)
3	121 (31%)	121 (31%)
Risk group		
Intermediate	105 (27%)	103 (26%)
High	282 (73%)	292 (74%)
Prostate volume (cm3)		
≤50	183 (47%)	177 (45%)
>50	195 (50%)	205 (52%)
Unknown	9 (2%)	13 (3%)
Adjuvant hormonal therapy	260 (67%)	259(66%)
≤ 6 months	38 (10%)	45 (11%)
6-12 months	37 (10%)	34 (9%)
> 12 months	112 (29)	114 (29%)
Unknown duration	73 (19%)	67 (17%)
Duration of hormonal therapy use before radiotherapy		
≤2 months	119 (31%)	114 (29%)
>2 months	136 (35%)	142 (36%)
Unknown	6 (2%)	4 (1%)
Transurethral resection of prostate	42 (11%)	33 (8%)
Abdominal surgery	106 (27%)	89 (23%)
Gastrointestinal comorbidity	41(11%)	35(9%)

Data are median (IQR) or n (%). PSA=prostate-specific antigen. Q1 and Q3 are the lower and upper bounds of IQR, respectively. Number of assessable patients differs from the report of acute toxicity because some were not assessable.

RESULTS

Between March 19, 2007, and Dec 3, 2010, 820 patients from seven Dutch centres were randomly assigned to treatment with standard fractionation (n=410) or hypofractionation (n=410). Patient recruitment for the HYPRO trial was completed on Dec 3, 2010. 25 patients (18 in the standard fractionation group, and seven in the hypofractionation group) were excluded from the intention-to-treat analysis (figure 1). Of the remaining 795 patients, 13 were not included in the late toxicity analyses because of missing data, resulting in 782 evaluable patients (387 in the standard fractionation group, and 395 in the hypofractionation group). The median follow-up was 60 months (IQR 51·2–67·3). The median follow-up for standard fractionation was 59·7 months (IQR 51·3–69·0) and 60·4 months (50·8–66·9) for hypofractionation. The baseline characteristics were equally distributed (table 1). 756 (97%) of 782 patients were given intensity modulated radiotherapy (370 [96%] of 387 patients in the standard fractionation group vs 376 [95%] of 395 patients in the hypofractionation group), and 739 (95%) of 782 patients had implanted gold fiducials for image guidance (366 [95%] in the standard fractionation group and 373 [94%] in the hypofractionation group).

Of the 782 patients, the response rates from either source (clinical record form and patients' self-assessment questionnaires) was 96% at 2 years, 93% at 3 years, 86% at 4 years, and 69% at 5 years (95%, 93%, 86%, and 68%, respectively in standard fractionation, and 97%, 93%, 86%, and 70%, in hypofractionation). The database for both groups and both gastrointestinal and genitourinary toxicities was locked on March 26, 2015.

At 3 years after radiotherapy, the cumulative incidence of grade 2 or worse toxicity was 39·0% (95% CI 34·2–44·1) for patients in the standard fractionation group compared with 41·3% (36·6–46·4) for those in the hypofractionation group (HR 1·16, 95% CI 0·94–1·43; Cox LR test p=0·16). The estimated HR for cumulative incidence of grade 2 or worse late genitourinary toxicity was 1·16 (90% CI 0·98–1·38), suggesting that non-inferiority could not be shown. Figure 2A shows a comparison of the Kaplan-Meier estimates of cumulative late genitourinary toxicity incidence for standard fractionation and hypofractionation. The cumulative incidence of grade 3 or worse late genitourinary toxicity was significantly higher in the hypofractionation group (19·0% [95% CI 15·2–23·2] vs 12·9% [9·7–16·7] for standard fractionation; p=0·021). In the standard fractionation group, three patients had grade 4 late genitourinary toxicity compared with two in the hypofractionation group.

3-year cumulative incidences of grade 2 or worse late gastrointestinal toxicity were 17·7% (95% CI 14·1–21·9) in the standard fractionation group versus 21·9% (18·1–26·4) for the hypofractionation group (HR 1·19, 95% CI 0·88–1·59; Cox LR test p=0·26). With an estimated HR of 1·19 (90% CI 0·93–1·52) for the cumulative incidence of grade 2 or worse late gastrointestinal toxicity, we could not confirm non-inferiority of hypofractionation for cumulative late gastrointestinal toxicity. Figure 2B shows Kaplan-Meier estimates of cumulative incidence. Cumulative grade 3 or worse late gastrointestinal toxicity was 2·6% (95% CI 1·2–4·7) in the standard fractionation group and 3·3% (1·7–5·6) in the hypofractionation group (p=0·55).

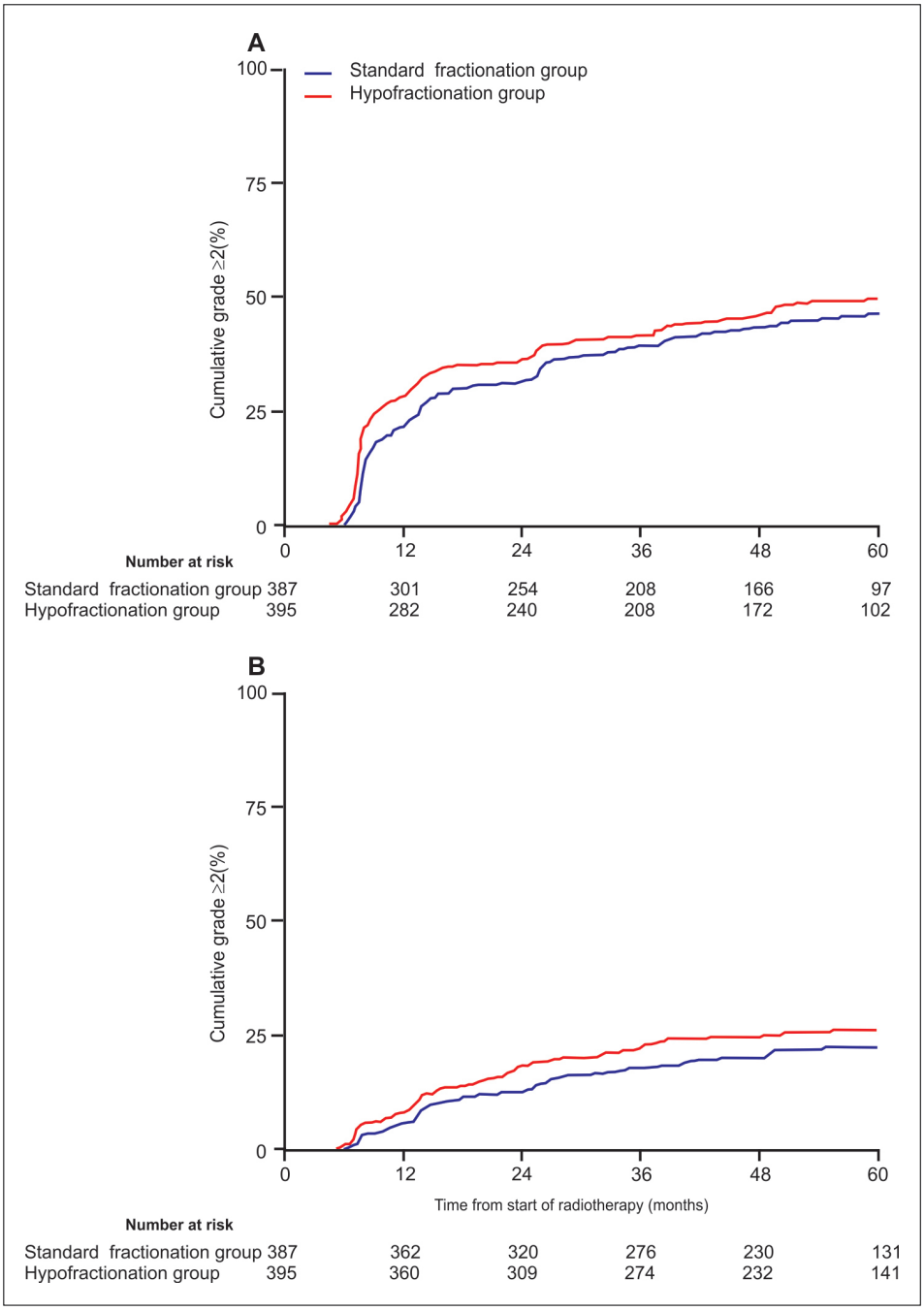

Figure 3.2 | (A) Cumulative grade ≥2 late genitourinary toxicity, (B) cumulative grade ≥2 late gastrointestinal toxicity

Table 2 presents specific symptoms of late genitourinary and gastrointestinal toxicity in the hypofractionation and standard fractionation groups. Incidences of nocturia (≥6 times per night; OR 4·94, 95% CI 1·87–13·09; p=0·0005) and incontinence (1·52; 1·03–2·24; p=0·04) were significantly higher in the hypofractionation group than in the standard fractionation group. Stool frequency of more than six per day was significantly increased with hypofractionation (7%) compared with standard fractionation (3%; OR 2·11, 95% CI 1·07–4·15; p=0·034; table 2).

Table 3 presents the results of the univariate and multivariate Cox proportional hazards regression analyses. Data for smoking was missing for 20% of patients and there was no information about the duration of smoking, hence smoking was not included in the univariate analyses. In a multivariate analysis including prognostic factors and treatment group, cumulative grade 2 or worse acute genitourinary toxicity (HR 2·51, 95% CI 1·98–3·17; p<0·0001), age older than 70 years (1·56, 1·26–1·93; p<0·0001), and the use of adjuvant hormonal therapy (1·36, 1·07–1·74; p=0·012) were independently significantly associated with increased cumulative incidence of grade 2 or worse late genitourinary toxicity. In a multivariate analysis for late gastrointestinal toxicity, cumulative grade 2 or worse acute gastrointestinal toxicity (HR 2·75, 95% CI 2·02–3·73; p<0·0001) and treatment group 3 (seminal vesicles treated to the prescribed dose) versus 1 (=10% risk of seminal vesicle involvement; 1·65, 1·02–2·67; p=0·042) were significantly associated with increased cumulative incidence of grade 2 or worse late gastrointestinal toxicity. Table 4 shows all symptoms that are significantly associated with prognostic factors identified in the multivariate analyses for both late genitourinary and gastrointestinal toxicity.

Figure 3 shows the results of post-hoc analyses to assess the heterogeneity of the effect of hypofractionation across subgroups of the risk factors (figure 3A for genitourinary toxicity and figure 3B for gastrointestinal toxicity). We noted a significant interaction effect of the treatment group and prostate volume on late genitourinary toxicity; the risk was significantly higher for prostate volume greater than 50 cm^3 but not for prostate volume 50 cm^3 or less group. For late gastrointestinal toxicity there were significant interactions of treatment group with age and treatment group.

For 362 (46%) of 782 assessable patients, 172 (44%) of 387 patient in the standard fractionation group versus 190 (48%) of 395 patients in the hypofractionation group, a cumulative incidence of grade 2 or worse late genitourinary toxicity was registered in clinical record form, patients' self-assessment questionnaires, or both. For 240 (31%) of these patients (118 [31%] in standard fractionation vs 122 [31%] in hypofractionation), this toxic effect was reported in the clinical record form. Consequently, the addition of toxic effect scoring with patients' self-assessment questionnaires to clinical record form scoring resulted in an overall increased reporting of toxicity by 16% (14% in the standard fractionation group and 17% in the hypofractionation group). For 250 (32%) of patients (109 [38%] given standard fractionation vs 141 [36%] given hypofractionation), cumulative incidence of grade 2 or worse late genitourinary toxicity was reported in the patients' self-assessment questionnaires. The difference in reported cumulative grade 2 or worse late genitourinary toxicity incidence between scoring with clinical record form only and patients' self-assessment questionnaires only was not significant (McNemar's p value 0·21). For 178 (23%) of 782

Table 3.2 | Specific symptoms according to treatment group

	Standard fractionation group (n=387)	Hypofractionation group (n=395)	OR (95% CI)	p-value*
Late genitourinary toxicity				
Drugs for pain	56 (15%)	68 (17%)	1·23 (0·84–1·81)	0·33
Interventional treatment with proctoscopy/ colonoscopy needed by mean of local anticoagulant treatment	9 (2%)	12 (3%)	1·32 (0·55–3·16)	0·66
Frequency at day ≥16 urination/voiding	30 (8%)	40 (10%)	1·34 (0·82–2·20)	0·26
Frequency at day ≥ 32 urination/voiding	5 (1%)	8 (2%)	1·58 (0·51–4·87)	0·58
Frequency at night 4-6 urination/voiding	75 (19%)	92 (23%)	1·26 (0·90–1·78)	0·19
Frequency at night ≥6 urination/voiding	5 9 (1%)	24 (6%)	4·94 (1·87–13·09)	<0·0005
Incontinency	52 (14%)	75 (20%)	1·52 (1·03–2·23)	0·04
Late gastrointestinal toxicity				
Drugs for pain	31 (8%)	32 (8%)	1·01 (0·60–1·69)	1·00
Drugs for diarrhoea	9 (2%)	6 (2%)	0·65 (0·23–1·84)	0·44
Frequency ≥ 6	13 (3%)	27 (7%)	2·11 (1·07–4·15)	0·034
Use of pads	45 (12%)	63 (16%)	1·44 (0·96–2·18)	0·097
Incontinence	46 (12%)	58 (15%)	1·28 (0·84–1·93)	0·29
Bleeding needing Argon Plasma Coagulation	9 (2%)	18 (5%)	2·01 (0·89–4·52)	0·11

*p values are based on Fisher's exact test.

assessable patients (82 [21%] given standard fractionation vs 96 [24%] given hypofractionation), a cumulative incidence of grade 2 or worse late gastrointestinal toxicity was registered in clinical record form, patients' self-assessment questionnaires, or both. For 141 (18%) of these patients (64 [17%] standard fractionation vs 77 [20%] hypofractionation), these toxicities were reported in the clinical record form. Therefore, the addition of patients' self-assessment questionnaires

Table 3.3 | Univariate and multivariate Cox proportional hazards regression analyses exploring the association of baseline and treatment-related factors with the recorded cumulative incidence of grade 2 or worse late gastrointestinal and genitourinary toxicity

	Univariate*		Multivariate	
	HR(95% CI)	P value	HR(95% CI)	P value
Genitourinary toxicity				
Genitourinary toxicity at baseline,† equivalent to grade ≥ 2	2·27(1·81-2·83)	<0·001		
Acute genitourinary toxicity, grade ≥ 2	2·57(2·03-3·25)	<0·001	2·51(1·98-3·17)	<0·0001
Age (>70 years)	1·54(1·25-190)	<0·001	1·56(2·26-1·93)	<0·0001
PSA (≤20)	1·11(0·88-1·39)	0·369		
Gleason (≤7)	0·69(0·55-0·87)	0·002		
Tumour stage (T3-T4 vs T1-T2)	1·13(0·92-1·39)	0·246		
TURP	1·3(0·93-1·81)	0·145		
Adjuvant hormonal therapy	1·24(0·99-1·55)	0·054	1·36(1·07-1·74)	0·012
Months hormonal therapy use before radiotherapy		0·260		
≤2 vs 0	1·34(1·04-1·74)	0·026		
>2 vs 0	1·16(0·90-1·50)	0·248		
Abdominal surgery	1·15(0·91-1·45)	0·258		
Gastrointestinal comorbidity	1·29(0·93-1·77)	0·138		
Prostate volume (>50 vs ≤50 cm^3)	1·02(0·83-1·26)	0·842		
Treatment group		0·424		0·868
2 vs 1	1·27(0·96-1·69)	0·091	1·27(0·96-1·69)	0·099
3 vs 1	1·17(0·86-1·59)	0·313	1·02(0·74-1·41)	0·897
Treatment group (hypofractionation vs standard fractionation)	1·16(0·94-1·43)	0·158	1·21(0·98-1·49)	0·073
Gastrointestinal toxicity				
Gastrointestinal toxicity at baseline, † equivalent to grade ≥ 2	3·43(1·98-6·04)	<0·001		
Acute Gastrointestinal toxicity, grade ≥ 2	2·77(1·06-3·74)	<0·001	2·75(2·02-3· 73)	<0·0001
Age (>70 years)	1·20(089-1·61)	0·224	1·16(0·86-1·56)	0·338
PSA (≤20)	0·83(0·61-1·13)	0·233		
Gleason (<7)	0·80(0·57-1·11)	0·184		
Tumour stage (T3-T4 vs T1-T2)	1·14(0·85-1·53)	0·387		
TURP	1·03(0·62-1·69)	0·921		

Adjuvant hormonal therapy	1·07(078-1·46)	0·683	1·04(0·74-1·47)	0·809
Months hormonal therapy use before radiotherapy		0·794		
≤2 vs 0	1·06(0·73-1·54)	0·754		
>2 vs 0	1·05(0·73-1·50)	0·791		
Abdominal surgery	1·16(0·84-1·62)	0·377		
Gastrointestinal comorbidity	1·03(0·62-1·70)	0·913		
Prostate volume (>50 vs ≤50 cm^3)	0·76(0·57-1·03)	0·077		
Treatment group		0·008		0.036
2 vs 1	1·38(0·89-2·13)	0·155	1·31(0·84-2·04)	0·239
3 vs 1	1·79(1·14-2·82)	0·012	1·65(1·02-2·67)	0·042
Treatment group (hypofractionation vs standard fractionation)	1·19(0·88-1·59)	0·256	1·03(0·76-1·39)	0·860

HR=hazard ratio. PSA=prostate-specific antigen. TURP=transurethral prostate resection. *Only significant factors from the univariate analyses were included in the multivariate analyses. †Because of the high correlation between baseline toxicity and acute toxicity, both for genitourinary and gastrointestinal, we did not consider baseline toxicity in the multivariate analyses.

for toxic effect scoring resulted in an increase of toxicity reporting by 4·7 percentage points (5% in both groups) compared with scoring with only clinical record form (overall relative increase in reporting 26%). For 73 (9%) of 782 patients (31 [8%] given standard fractionation and 42 [11%] given hypofractionation), the cumulative incidence of grade 2 or worse late gastrointestinal toxicity was reported by patients' self-assessment questionnaires. For gastrointestinal toxicity, the difference between scoring with clinical record form only and patients' self-assessment questionnaires only was significant (McNemar's p value <0·0001).

DISCUSSION

The results of our randomised, phase 3 trial comparing hypofractionation with standard fractionation for patients with intermediate-risk and high-risk prostate cancer showed that non-inferiority of hypofractionation for late genitourinary and gastrointestinal toxicity could not be confirmed. According to the study protocol, the included 820 patients were supposed to prove non-inferiority of hypofractionation for late toxicity with a power of 84% for genitourinary and 86% for gastrointestinal, considering the results of the CKTO dose escalation trial.[10,12] Such power percentages are generally accepted in randomised trials. The pre-defined margin for non-inferiority in HR for late genitourinary and gastrointestinal toxicity of 8% was desirable because of the importance of late toxicity for patients.

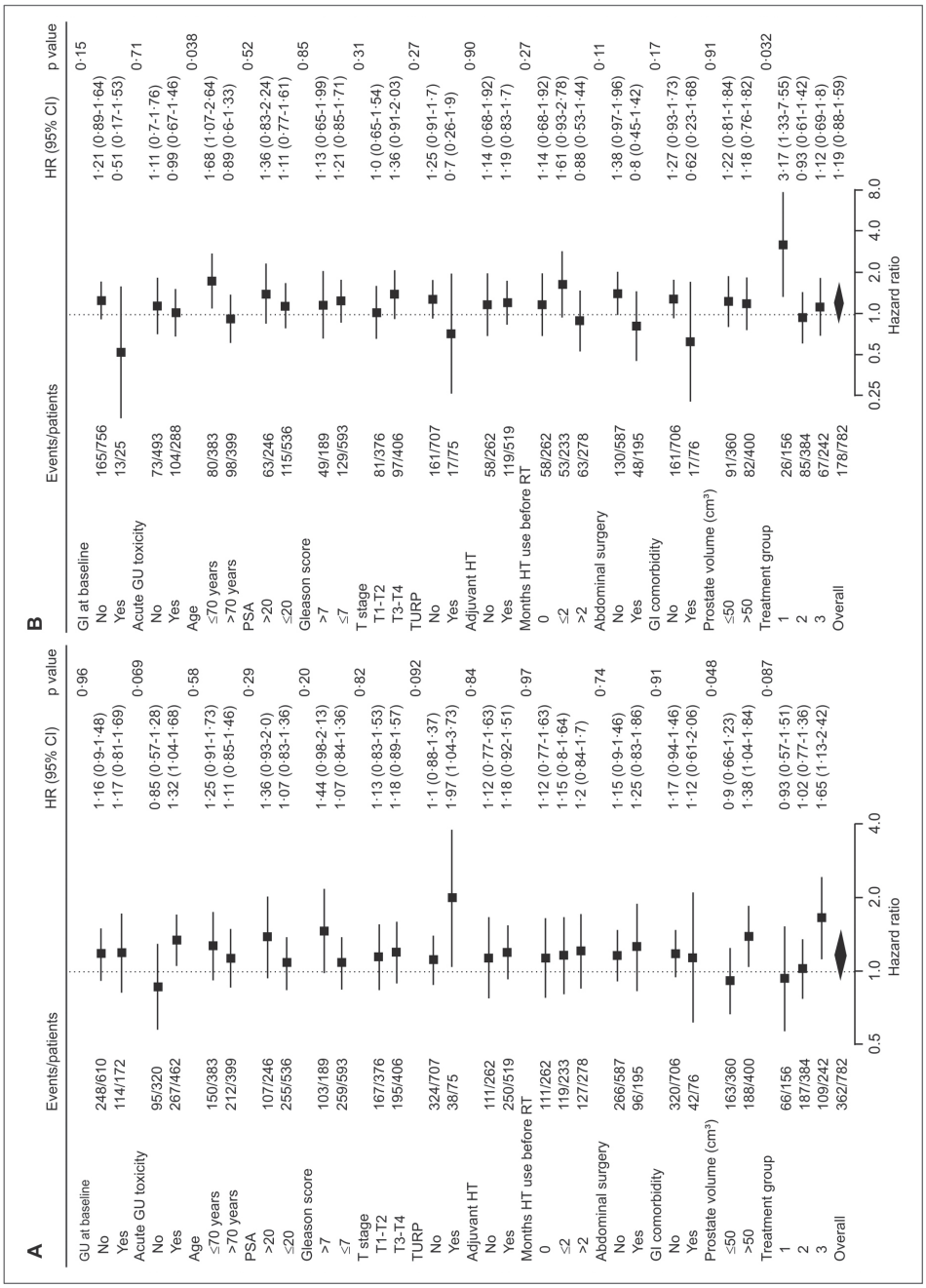

Figure 3.3 | Forest plots of hypofractionation compared to standard fractionation for grade 2 or worse late toxicities for (A) genitourinary and (B) gastrointestinal in prognostic subgroups

HR=hazard ratio. GU=genitourinary. PSA=prostate-specific antigen. TURP=transurethral resection of prostate. HT=hormonal therapy. RT=radiotherapy. GI=gastrointestinal. p value is for the test of the interaction between the treatment and a subgroup variable.

Table 3.4 | Symptoms for late gastrointestinal and genitourinary toxicity that are significantly associated with the significant prognostic factors identified in the multivariate analysis

	*OR (95% CI)	p value
Late genitourinary toxicity		
Acute genitourinary toxicity		
Nocturia ≥6 per night	9·87 (2·33–41·80)	<0·0001
Day frequency ≥12 per day	6·04 (2·85–12·81)	<0·0001
Drugs for pain	3·41 (2·13–5·46)	<0·0001
Incontinence	2·39 (1·55–3·67)	<0·0001
Age >70 years		
Nocturia ≥4 per night	1·58 (1·11–2·23)	0·010
Incontinence	2·16 (1·45–3·23)	<0·001
Late gastrointestinal toxicity		
Acute gastrointestinal toxicity		
Stool frequency ≥6 per day	3·82 (1·94–7·53)	<0·0001
Drugs for pain	4·76 (2·69–8·41)	<0·0001
Incontinence	2·55 (1·69–3·85)	<0·0001
Treatment group (3 vs 2, 2 vs 1)		
Drugs for diarrhoea	2·23 (0·99–5·04)	0·042

*OR=odds ratio.

In the HYPRO trial, the recorded 5-year cumulative incidence of grade 2 or worse late genitourinary toxicity was 46%, which is higher than the 5-year to 7-year late genitourinary toxicity reported in other studies using a conventional three-dimensional treatment technique.[12] The effect of intensity modulated radiotherapy and image guidance (as applied for most patients in the HYPRO study) on sparing of the urethra and the bladder base is probably low because a large part of these structures will unavoidably get high doses, resulting in a low effect on the incidence of genitourinary toxicity. This is especially true for the HYPRO study because there were no planning objectives or constraints for the bladder in the study protocol.[6]

Hormonal therapy was reported as significantly associated with higher incidences of late genitourinary toxicity,[12] which was confirmed here. 66% of our patients had hormonal therapy, which could partly explain the higher late genitourinary toxicity incidence for standard fractionation in the HYPRO study. In the HYPRO trial, hormonal therapy was not stratified before randomisation, which is a possible limitation. The decision to use hormonal therapy for the patients in the study was dependent on the institutions' policies, but the same hormonal therapy protocol had to be used for standard fractionation and hypofractionation. The median age of 71 years of patients in our trial (399 patients >70 years, 204 in the standard fractionation group and 195 in the hypofractionation group) could also have contributed to the increased incidence of

cumulative grade 2 or worse late genitourinary toxicity, because being aged 70 years or older was found to be significantly associated with enhanced incidence of late genitourinary toxicity (table 3).

Another contribution to the high incidence of late genitourinary toxicity in the HYPRO trial is the high percentage of patients with baseline genitourinary symptoms equivalent to 2 or worse toxicity, which we found was significantly associated with incidence of both acute[6] and late genitourinary toxicity. Possibly, patients with predisposing factors such as baseline toxicity are less tolerant to the applied hypofractionation treatment regimen and need to be excluded, in line with selection criteria for high dose rate brachytherapy.[14]
Finally, the use of patients' self-assessment questionnaires, added to the clinical record form scoring, led to a large increase in registered toxicity. The quite low reported incidences of toxicity in previously published series using only clinical record form could be an underestimation of the real toxicity.[6,12,15]

In multivariate analyses, there was no significant difference in grade 2 or worse late genitourinary toxicity for hypofractionation (p=0·073), but the recorded cumulative incidence of grade 3 late genitourinary toxicity was significantly higher in the hypofractionation group (p=0·021). Incidence of grade 3 night frequency of voiding or urination (≥six per night) was significantly higher in the hypofractionation group than the standard fractionation group (6% vs 1%, respectively). This is considered a grade 3 toxicity and interferes negatively with quality of life in patients given radiotherapy by affecting night rest and daily activities. Incidence of daily urine incontinence with use of pads was significantly higher in the hypofractionation group than in the standard fractionation group, which has been shown previously.[16–19] However, in these previous studies, lower fractionation doses were used.

The cumulative incidence of grade 2 or worse late gastrointestinal toxicity for standard fractionation in this report (22%) is lower than the reported 30% for the 39 × 2 Gy group of the previous CKTO 96-10 dose escalation trial[12] which applied the same scoring criteria. The majority use of intensity modulated radiotherapy (95%) in the HYPRO trial, compared with 12% in the CKTO study, the frequent use of implanted fiducials and daily set-up verification and correction, and the more restrictive constraints for rectum dose delivery could all have contributed to the lower rate of gastrointestinal toxicity in the HYPRO trial, despite the higher percentage (31% in the HYPRO trial vs 15% in CKTO) of patients treated in group 3 (treatment of seminal vesicle up to prescribed dose).

In the HYPRO trial, the decision to treat the seminal vesicle to the prescribed dose was dependent on the risk of seminal vesicle invasion according to Partin's table,[11] which was widely used in general practice at the time of designing the HYPRO trial (2006). In current practice with the increasing use of MRI to detect invasion of the seminal vesicle, the use of Partin's table can be avoided. In the HYPRO trial, stool frequency of more than six per day was significantly higher in the hypofractionation group than in the standard fractionation group; however, it was lower than the 10% for the 39 × 2 Gy group of the CKTO 96-10 study.[12] On the other hand, the use of faecal incontinence pads more than twice per week for patients in the hypofractionation group is 16% higher than published

data[20] for standard fractionation (12% for standard group vs 16% for the hypofractionation group). The reported incidences of grade 2 or worse late genitourinary and gastrointestinal toxicity for hypofractionated regimens show a wide range of variability.[16–19,21,22] Although cross-trial compairsons must be made with caution, the findings of the phase 3 CHHiP hypofractionation trial[17] showed much lower late toxicity after a follow-up of 2 years than reported here. However, both the total dose and fraction dose were lower (57–60 Gy in 3 Gy fractions) than in the HYPRO trial, and the toxicity was derived only from clinical record form (physician-reported toxicity). Recently, the 2-year patient-reported outcomes for 2100 patients included in the CHHiP trial were published,[23] reporting no differences in quality of life between the applied standard and hypofractionated regimens. The questionnaires applied in the CHHiP trial were quality-of-life measurement instruments, in contrast to the patients' self-assessment questionnaires used in the HYPRO trial to report genitourinary and gastrointestinal toxicity.[6] However, these quality-of-life data support the evidence from the first CHHiP report[17] on toxicity that the applied fraction dose and total dose, in combination with a delivery of five fractions per week, did not lead to increased toxicity in the hypofractionation group compared with standard fractionation. Long-term toxicity reports for the almost 3000 patients included in the CHHiP trial are needed to fully assess toxicity for the applied hypofractionation schedule and the efficacy outcome results need to be available before final conclusions can be drawn. The latter is especially important because for the CHHiP trial, non-inferiority in outcome was planned as the primary endpoint, whereas Pollack and colleagues[19] hypothesised a higher local control for their hypofractionated group because of a presumed higher biological tumour dose, which could not be shown.[19] For a fraction dose of 2·7 Gy and 26 treatment fractions, Pollack and colleagues reported a late genitourinary toxicity incidence of 45% similar to HYPRO for 19 fractions of 3·4 Gy, and a slightly lower incidence for late gastrointestinal late toxicity.[19] Investigators reported that baseline International Prostate Symptom Score (IPSS) as correlated with higher incidence of late genitourinary toxicity (HR 2·54). The IPSS was not used in the HYPRO trial, but we found a clear correlation between late genitourinary toxicity and the presence of baseline symptoms equivalent to grade 2 or worse genitourinary late toxicity (HR 2·27 [1·81–2·83]). Pollack and colleagues[19] reported a higher rate of late genitourinary toxicity for patients older than 67 years over 5 years (HR 1·91), in agreement with the increased incidence in the HYPRO study in patients older than 70 years (HR 1·56 [95% CI 1·26–1·93]). Additionally, in the high-risk group (treatment of seminal vesicles to prescribed dose, pelvic nodes to 50 Gy, and long-term hormonal therapy) was correlated with higher rate of late genitourinary toxicity.[19] This high-risk group corresponds with our treatment group 3, which was significantly associated with higher late gastrointestinal toxicity (HR 1·65, 95% CI 1·02–2·67), but not genitourinary toxicity. Pollack and colleagues used smaller planning target volume margins for the hypofractionation group and dose constraints for the bladder during planning, by contrast with the HYPRO trial. In the HYPRO study we used the same margins for both groups and did not consider dose limiting constraints for the bladder.

Previously published hypofractionation series used different fraction and total doses, different toxicity scores, generally included fewer patients than HYPRO, and reported different length of

follow-ups.[16–19] All these factors should be taken into consideration when comparing results of different series.[16,18,19] Moreover, until now, patients' self-assessment questionnaires had not been used for reporting toxicity in most published trials. In this report, adding patients' self-assessment questionnaires scoring to clinical record form resulted in increases in reported late toxicity of 51% and 26% for genitourinary and gastrointestinal, respectively. However, the use of only clinical record form scoring did not change the conclusions regarding non-inferiority for both late genitourinary and gastrointestinal toxicity.

In the HYPRO trial, the number of patients filling out questionnaires was high, contributing to an accurate registration of (high) toxicity rates, especially because there was no imputation of missing data used and all available data was analysed. For the CHHiP trial, the response rate at 2 years was 91%[17] compared with 96% at 2 years in the HYPRO trial. As per protocol, we will continue to follow up patients for 10 years.

In this study, data for smoking were missing for 20% of the included patients, and information about the duration and continuation (pack-years) of smoking was not collected. In the univariate analyses for acute toxicity of the HYPRO trial,[6] no significant effect was found between smoking and acute toxicity. Hence, smoking was not included in the univariate analyses for late toxicity.

In our previous study[6] of observed acute toxicity, we discussed evidence that the α to ß ratio for acute toxicity might be lower than the generally considered value of 10 Gy.[6] The late toxicity findings in the HYPRO trial might also raise questions about the validity of the applied α to ß ratio of 4–6 Gy for late toxicity[7] (which might in reality be lower) for comparing conventional with hypofractionated treatment because the suggested 4–6 Gy ratio gave the impression that the delivered dose to rectum and bladder should be the same around the 78 Gy in both groups; the results of higher toxicity in the hypofraction group could suggest an α to ß ratio lower than 4 Gy. Therefore, researchers should consider the possibilty of lower α to ß ratio for organ at risk.

For both acute[6] and late genitourinary and gastrointestinal toxicity, non-inferiority of hypofractionation could not be confirmed. Moreover, the cumulative incidence of grade 3 or worse late genitourinary toxicity was significantly higher in the hypofractionation group than for standard fractionation. Furthermore, we noted a significant increase in cumulative incidence of grade 2 or worse acute gastrointestinal toxicity in the hypofractionation group.[6] These toxicity findings need to be considered alongside future outcome data for the HYPRO trial, and toxicity and outcome data for trials in progress with lower fraction doses. In view of the strong associations recorded between late toxicity and baseline symptoms, age, hormonal therapy, and treatment of the seminal vesicles, the hypofractionation regimen investigated in the HYPRO trial might be best for a selected population of patients.

Toxicity data are not sufficient to influence routine clinical implementation of the tested hypofractionation schedule; the efficacy data are also needed before such adjustments can be made. However, toxicity is of increasing importance when considering the choice of treatment modality for patients with prostate cancer because of the large variety of treatment options, which was why

both acute and late toxicity were considered as key endpoints in the HYPRO trial. Moreover, because of the importance of toxicity for patients and clinicians, we think that toxicity results should be published as soon as available and publication should not wait for efficacy results that have not yet been completed. The toxicity results could also affect the design of new studies on hypofractionated radiotherapy for prostate cancer. Both for acute[6] and late toxicity we have found results that might question the validity of the linear-quadratic model and the (generally) applied α to ß ratios. These findings could also be taken into consideration in the design of new trials.

Contributors

SA recruited patients, collected, analysed, and interpreted data, and wrote the report; LI and FP were the primary investigators involved in study design, recruited patients, interpreted data, and reviewed the report; ES, SK, PPvT, and HdJ contributed to protocol development, recruited patients, and reviewed the report; WH interpreted data and reviewed the report; WGA did statistical analyses, interpreted data, and reviewed the report; and BH developed the protocol, interpreted data and wrote the report.

Declaration of interests

We declare no competing interests.

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PART 2

Extreme hypofractionation with High-Dose-Rate brachytherapy

Chapter 4

High-Dose-Rate (HDR) Brachytherapy and External Beam Radiotherapy (EBRT) for hormone-naïve low and intermediate risk prostate cancer: A 7-year experience.

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ABSTRACT

Purpose:
To report clinical outcome, early and late complications in 264 hormone-naïve patients with low and intermediate risk prostate cancer (PC) treated with high-dose-rate brachytherapy (HDR-BT) and external beam radiotherapy (EBRT).

Methods and materials:
Between February 2000 and July 2007, 264 patients underwent HDR-BT in combination with EBRT as a treatment for their low to intermediate risk PC. HDR-BT was performed using ultrasound based implantation. The total HDR-BT dose was 18 Gy in 3 fractions within 24 hours with a 6 hours minimum interval. EBRT started 2 weeks after HDR-BT and was delivered in 25 fractions of 1.8 Gy to 45 Gy within 5 weeks.

Results:
After a mean follow-up of 74.5 months, four patients showed a PSA progression according to the ASTRO definition (1.5%) and eight patients according to the Phoenix definition (3%). A biopsy proven local recurrence was registered in one patient (0.4%), clinical progression (bone metastases) was documented in two patients (0.7%). Seven years actuarial freedom from biochemical failure (FFBF) was 97%, seven years disease specific survival (DSS) and overall survival (OS) were 100% and 91%, respectively. Toxicities were comparable to other series.

Conclusions:
Treatment with interstitial HDR-BT plus EBRT treatment shows a low incidence of late complications and a favourable oncological outcome after 7 years follow-up.

Key Words:
Prostate cancer, Radiotherapy, Brachytherapy, Toxicity.

SUMMARY

To report 7 years clinical outcome and toxicity in 264 prostate cancer patients treated with external-beam radiotherapy and HDR-brachytherapy boost. Brachytherapy dose was 18 Gy in 3 fractions followed with EBRT in 25 fractions to 45 Gy. Eight patients had a biochemical recurrence according to Phoenix definition. Local recurrence in 1 patient and clinical progression in 2 patients. Freedom from biochemical failure was 97%. Toxicity was low and comparable to other series.

INTRODUCTION

External beam radiotherapy (EBRT) is one of the most used options for the treatment of localized prostate cancer (PC). High doses >70 Gy have to be used to achieve a good local control, but may increase complications[1,2]. High dose conformal radiotherapy can also be achieved with brachytherapy. The use of HDR brachytherapy in one or multiple implants as a boost combined with EBRT is advocated. Martinez *et al.*[2] reported good results using two to three implants with fractions of 5.5-11.5 Gy. With a median follow-up of 8.2 years, the overall survival at 8 years in the series of Galalae et al.[3] was 70% after 40 Gy EBRT and 2x 15 Gy HDR-BT with local recurrence rate of 6% for intermediate and high risk group PC patients. This combined radiotherapy approach may enhance the local control and decrease complications because HDR-BT creates a highly conformal dose of radiation within the prostate with a rapid dose fall-off outside. The HDR boost also has a radiobiological advantage gained by hypofractionation[4]. Starting in 2000 we treated hormone-naïve patients with a low and intermediate risk PC with HDR-BT as a boost in combination with EBRT to shorten the overall treatment time and to reduce toxicity. We report here our long term results and toxicity.

METHODS AND MATERIALS

Patients:

Between February 2000 and July 2007, 264 patients with low and intermediate risk PC were treated with EBRT in combination with a HDR-BT boost. These patients had a stage T1a-T2c histologically proven PC, an initial Prostate Specific Antigen (iPSA) <15 ng/ml, and a Gleason-score (GS) ≤7. Pre-treatment evaluations included a clinical history, physical examination, and blood laboratory findings. A bone scan, and pelvic computed tomography were recommended on demand. TNM scoring was according to the AJCC 2003 guidelines. Patients with T1b-T2a, GS 6 and PSA ≤10 ng/ml were defined to have a low risk PC, other patients with one of more of the following: PSA >10 ng/ml, GS 7, T2b, were defined to have an intermediate risk PC. Patients with a previous transurethral resection of the prostate (TURP), lymph nodes metastases or hormonal treatment were excluded. All patients were seen every 3 months in the first year, and yearly afterwards in a joined out clinic evaluation of the urologist and radiation-oncologist. A routine physical examination and PSA analysis were performed (patient characteristics are listed in table 1).

Toxicity:

All patients were followed prospectively; they were asked to participate in the collection of self-administered European Organization for Research and Treatment of Cancer-Radiation Therapy Oncology Group prostate toxicity questionnaires. Questionnaires were send to the patients at time points; baseline, weekly after treatment until 10 weeks, at 3-6-12 months, and yearly afterwards.

Table 4.1 | Patient characteristics

Characteristics	Value*
Patients(n)	264
Patient factors	
Age (y)	
Mean	66.0
Pre-BT prostate volume(cm^3)	
Mean	30
Range	11-93
Pre-BT IPSS	
Mean	8.6
Range	0-32
T-stage	
T1a	4 (1.5)
T1b	1(0.4)
T1c	159(60.2)
T2a	85(32.2)
T2b	9 (3.4)
T2c	3 (1.1)
Unknown	3 (1.1)
GS	
2+2	6 (3.2)
2+3	9 (3.4)
3+3	162 (83.5)
3+4	17 (6.4)
iPSA	
Median	6.8
range	3-15

Abbreviations: BT = brachytherapy; IPSS = international Prostate Symptom Score; GS = Gleason core; iPSA = initial prostate-specific antigen value.

* Data in parentheses are percentages.

Radiation Therapy:

Treatment consisted of HDR-BT followed after 2 weeks by EBRT. The EBRT technique consisted of Computed Tomography (CT) based conformal planning, admitted in a 5-field technique in 47 patients (17.8%) and in a 3-field technique in 217 (82.2%). Total EBRT dose was 45 Gy in 25 fractions of 1.8 Gy delivered in 5 weeks. The planning target volume (PTV) was the prostate expanded with

7-10 mm margins to all directions. HDR-BT was performed using ultrasound guided implantation and CT based planning using the PLATO planning system and a ^{192}Ir-MicroSelectron (Nucletron, The Netherlands). The total dose was 18 Gy in 3 fractions within 24 hours with a minimum interval of 6 hours between 2 fractions. The same plan was used to deliver the consecutive fractions. Therefore a lateral X-ray was made before each fraction to check the position of the catheters relative to the implanted markers. Deviations of >3 mm were corrected [5]. The PTV was the prostate without expanded margins.

Oncological outcome:
The biochemical failure (BF) was analysed according to the Phoenix definition (every rise of PSA ≥2 above Nadir). A second analysis according to the ASTRO definition has been done: 3 consecutive PSA rises after Nadir without backdating. Freedom from biochemical failure (FFBF) was defined as the percentage of patients still alive without evidence of BF. Cause Specific Survival (CSS) registered mortality due to PC.

STATISTICAL ANALYSIS

The gastrointestinal (GI) and genitourinary (GU) toxicities were evaluated according to the RTOG morbidity scales, using a combination of the patient EORTC-RTOG questionnaire information, and the RTOG scores from the physicians notes and patient charts. Toxicities within 90 days after radiation therapy were considered acute toxicities, and considered late toxicities after 90 days. Patients with a BF were excluded from QoL results after the date of failure. A failure-free survival (FFS) is defined as survival from biochemical or clinical failures. Disease specific survival (DSS) and overall survival (OS) were also measured. The non-parametric variables were analysed with the Wilcoxon-Mann-Whitney test, and the binairy variables using a logistic regression. The Kaplan-Meier (KM) estimate was used to calculate survival. Two-tailed tests were used with a p value ≤0.05 considered significant.

RESULTS

The median age of patients was 66.0 years (range, 45-79). Median follow-up was 74.5 months (range, 2.0-133.0 months). Patients contributed with a median of 13 (range, 1-21) EORTC-RTOG assessments to QoL results. All but 13 patients (95.1%) contributed with minimal 1 QoL assessment to these results, and all but 2 patients (99.3%) contributed with a minimum of 1 PSA analysis. The T-stages of the patients were: T1a (1.5%), T1b (0.4%), T1c (60.2%), T2a (32.2%), T2c (1.1%), T2b (3.4%), T2c (1.1%) and unknown T (1.1%). The GS was 7 in 6% of the patients and 94% had a GS of 6 or less. Median iPSA was 6.8 (range, 3-15 ng/ml). The median number of needles implanted was 19 (range, 12-29), the median prostate volume was 30 cm^3 (range, 11-93 cm^3), the mean PTV V100 (volume PTV receiving 100% of prescribed dose) was 93.4% (range, 63.0-99.7%), the mean urethra V120 (volume urethra receiving 120% of prescribed dose) was 0.0 cc (range, 0.0-0.2 cc), the mean

rectum V80 (volume rectum receiving 80% of prescribed dose) was 0.1cc (range, 0.0-1.2 cc). In 4 patients the dose of the EBRT was 50 Gy in 2 Gy fractions instead of the protocol dose of 45Gy/1.8 Gy, 2 patients received 39.6 Gy EBRT because of urinary retention.

Survival

During the follow-up 30 (11.4%) patients died. Cause of death in these patients was in 13 patients (43.3%) a 2nd primary tumor, in 10 patients (33.3%) a cardiovascular, and in 7 patients (23.4%) an intercurrent reason or natural cause. The 7 years OS and FFS were 91% (C.I. 89-93%) and 96% (92-97%), respectively (Fig 1).

Treatment sequelae:

Acute toxicity:

Peroperative bladder perforation was recorded in 25 patients (9%), seven patients (2.5%) needed a Foley catheter during the first 4 weeks after treatment for at least 4 weeks (range, 4-27 weeks). The incidence of grade 2 and grade 3 acute GU toxicity after 4 weeks was 24% and 13%, and decreased to 17% and 3% after 3 months, respectively. For the acute GI toxicity the percentage of grade 2 was 16%, and 4% after 4 and 12 weeks, respectively. The percentage of grade 3 GI acute toxicity was 3% at 3 months.

Late toxicity:

Two patients underwent a TURP after HDR-BT at 14 and 37 months respectively due to progressive obstructive complaints (0.75%). Four patients needed a single coagulation therapy because of a rectal bleeding (1.5%); all 4 were treated after the first year following HDR-BT. For the GU late toxicity registered with the RTOG-score, the percentage of patients with grade 2 toxicities was 6.3% at 6 months, and remained at an average of 10% afterwards. Late grade 3 GU toxicities were registered at an average incidence of 3%. Urinary retention was reported in 2.5% and urinary stricture in 2.5% with a cumulative overall incidence of grade 3 GU toxicities of 4.2% (fig. 2). The grade 2 GI toxicity was registered at an average of 3% during FU; the percentage of grade 3 toxicity was 1.0% (fig 3).

PSA Nadir and Bounce:

The PSA Nadir of the BF-free patients was reached after a mean of 43.5 months (range, 5.5-122.1 months) with a mean value of 0.32 ng/ml (range, 0.0-4.3 ng/ml). A Nadir ≤ 1 was reached after a mean of 44.9 months (range, 5.5-122.0 months) in 95.0% whilst in 4.9% of the patients the Nadir > 1 was reached in 17.9 months (range, 5.7-40.2 months). Three patients had a Nadir above 2 without progression with a minimum of 4 years FU after treatment.

We defined a PSA bounce as an increase of at least 0.4 ng/ml followed by any decrease. One PSA bounce was recorded in 87 patients (33%), 20 (7.6%) had 2 bounce episodes, and 6 (2.3%) 3 episodes. The mean interval to the first PSA bounce was 21.9 months (range, 6.7-110.0 months), while the mean time to the second PSA bounce episode was 28.3 months (range, 19.3-54.9 months), and the mean time to the third bounce was 45.0 months (range, 32.1-64.9 months). Of the patients with a BF 6 out of 8 showed a PSA bounce at a median of 23.1 months (range, 10.8-57.4 months). The

patients with a bounce reached their Nadir in a shorter period of 21.0 months than the non-bounce patients (p=0.024).

Recurrence:
Eight patients met the condition of a BF according to the Phoenix definition, out of them 4 met the ASTRO definition as well. Mean time to the BF was 48 months (range, 21-83 months). One patient had a biopsy proven local recurrence, and underwent a radical prostatectomy 8 years after the treatment with EBRT+HDR-BT. Bone metastases were detected in 2 patients with a BF; they were treated with hormonal therapy (HT). For the other 5 patients with BF a watchful waiting policy was followed; in 3 of them the prostate biopsies are still negative without signs of distant metastases. In our group there was no significant difference in incidence of BF or FFS between the low- and intermediate-risk groups.

DISCUSSION

High-dose-rate brachytherapy in combination with EBRT was given for localized low- and intermediate-risk PC. This group of patients can be treated with radical prostatectomy with a freedom from biochemical failure (FFBF) ranging from 70-80% [6]; long-term results of the laparoscopic prostatectomy report the same results [7]. EBRT in this risk group has a good oncological outcome but toxicity is a major concern [1,8]. The majority of our patients were low-risk patients with a relatively good prognosis, in which long-term toxicity is a very important concern. This is especially true with the new perspectives of active surveillance policy widely followed for a part of patients in this risk group showing only 23-42% of patients with disease progression within 3-5 years after diagnosis [9]. Debate is not yet settled about the necessity of treatment (with its risk of developing treatment-related toxicity) for this group. HDR-BT could provide better sparing of organs at risk, while delivering a higher dose to the prostate comparable to a seven-field conformal EBRT. With the use of high dose per fraction no fraction dose limiting toxicity was reported using HDR-BT [10,11]. Because of the need for dose escalation ≥70 Gy for good FFBF which increases the rectal toxicities, the use of HDR-BT as a boost could keep the high rate of local control reached with EBRT dose escalation, but decrease rectal toxicities. HDR-BT also reduced the overall treatment time and is the most ultimate conformal therapy without setup uncertainties and organ motion control as in 3D-conformal EBRT. Furthermore the use of HDR-BT reduced the irradiated volume because the CTV volume equals the PTV volume without extra margins. The currently accepted idea about the low α/β ratio of PC, lower than 5 for tumor control probability, makes the hypofractionated HDR-BT more powerful [12].

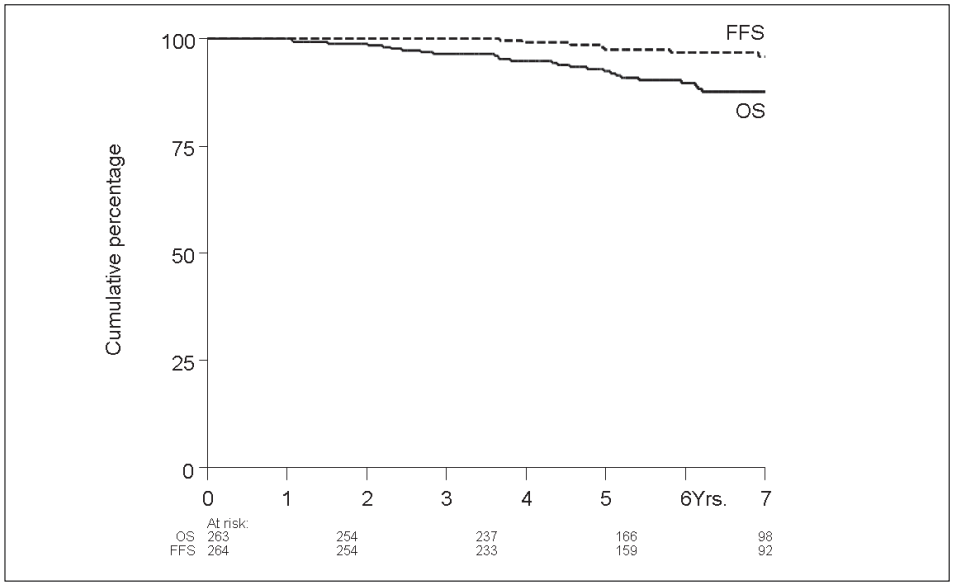

Figure 4.1. | Overall survival (OS) and failure-free survival (FFS).

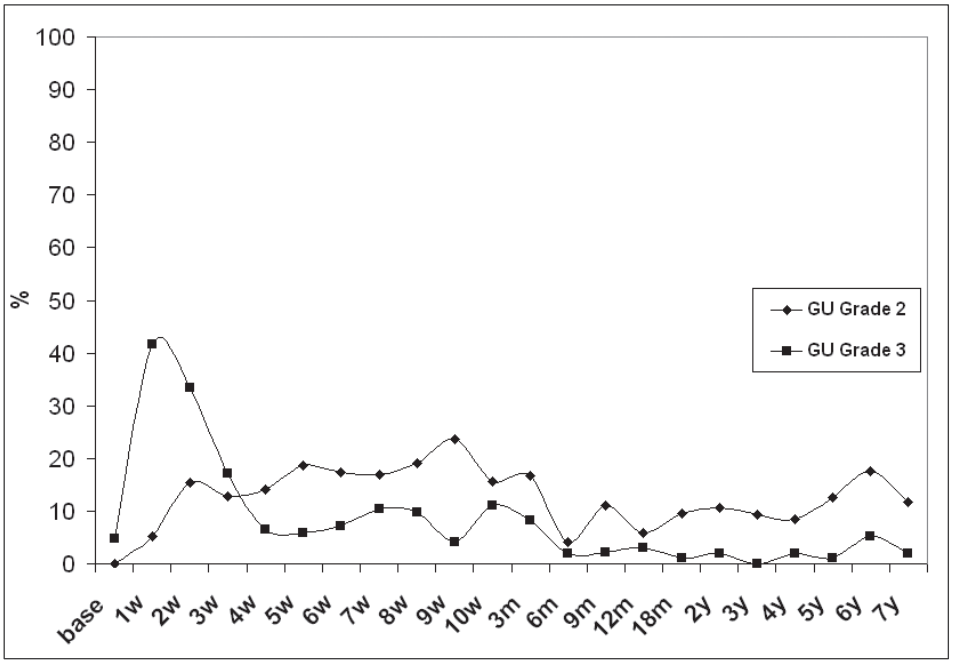

Figure 4.2. | Radiation Therapy Oncology Group gastrourinary (GU) ≥ grade 2 toxicity (%).

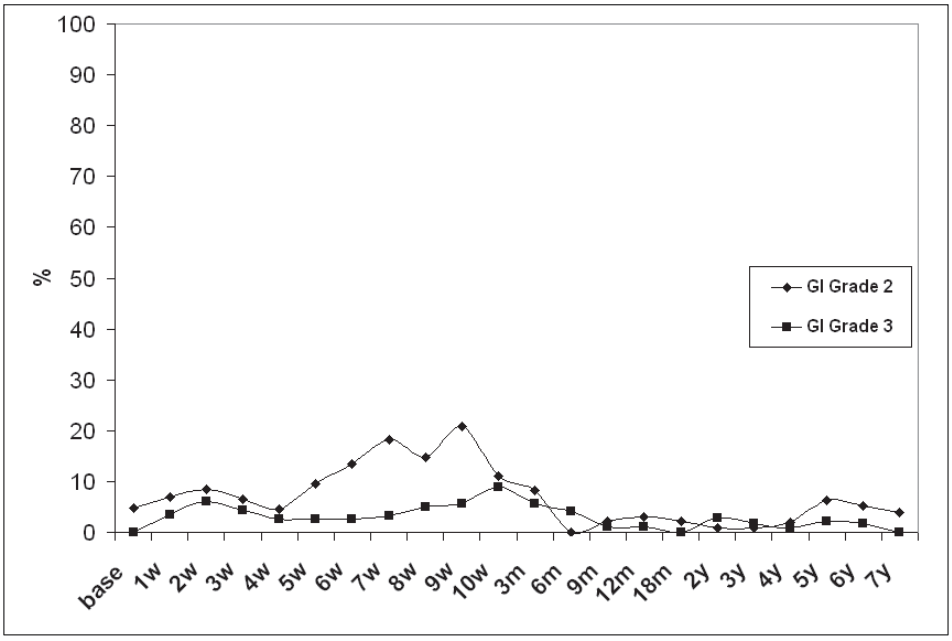

Figure 4.3. | Radiation Therapy Oncology Group gastrointestinal (GI) grade 2 toxicity (%).

Oncological outcome:

Our results are similar to previous outcomes of HDR–BT with EBRT in HT-naïve patients, showing excellent FFBF and DSS with a very low rate of urinary and bowel toxicities in HT naïve patients. Almost all other series used HT in part of their patient's population. Sato et al.[4] reported a small series of 53 hormone naïve patients treated with EBRT and HDR-BT with a five year OS and DSS of 88% and 100%, respectively. Galalae et al.[3] reported 5 year biochemical control for low and intermediate risk patients of 96% and 88%, respectively. The cause specific survival (CSS) at 5 years was 99% and 100%, respectively for these 2 risk groups. About 30% of these patients received a short course of neoadjuvant/ concurrent androgen deprivation therapy [3]. Demanes et al.[13] reported a 10 year OS and CSS of 79% and 97%, respectively. Martinez et al.[2] used a dose escalation regimen in intermediate and high risk patients with a 5 years biochemical control of 87% and 52% for low and high risk group respectively.

Biochemical Failure:

In patients with a BF, we were careful not to initiate HT before a proven clinical recurrence. The patient with a proven local recurrence in the prostate was successfully treated with laparoscopic radical prostatectomy with an undetectable PSA afterwards. Two patients with proven bone metastases started HT and the other 5 patients with BF are conservatively followed with a yearly biopsy and bone scintigram. In our group no differences were found in oncological outcomes between the low and intermediate risk group. This may be because of the low incidence of BF and the excellent DSS, besides the inclusion of low-intermediate risk patients only where the doses have been given may be high enough for these risk groups. However we used the clinical staging to

distinguish low from intermediate risk group, we are aware about the difficulties and uncertainties of this staging to give a valuable prognostic system.

PSA bounce:

We defined a PSA bounce as an increase of at least 0.4 ng/ml followed by any decrease as used by Horwitz *et al.* [14] in his multi-institutional pooled analysis. From the 4,839 patients analysed, 978 patients (20%) experienced a bounce according to his definition. The result of PSA bounce in our group corresponds with the data published. Toledano *et al.* [15] reported a rate of 32% of patients with a bounce of at least 0.4 ng/ml, in patients treated with permanent implant brachytherapy. In patients treated with EBRT and HDR-BT boost the bounce is not well defined. Bachand *et al.* [16] was the first to report a rate of 10%, of these patients with a bounce using a high PSA threshold of 2 ng/ml. The majority was also treated with HT. We are the first reporting the bounce in this treatment modality according to the currently accepted definition in hormonal naïve patients. We did not find a relation between bounce and age, G-score, T-stage, and PSA level. This relation was also not reported in the published literature. Hinnen *et al.* [17] reported bounce changes in patients treated with ^{125}I implantation monotherapy, 32% of the 975 analyzed experienced a bounce with a median time to bounce of 18 months. He observed a better FFBF, DSS and OS for patients experiencing a bounce. In our group there was no relation between bounce and BF, DSS or OS found. It is very important to be aware of this phenomenon before initiating any HT, especially in the first 2 years after radiotherapy.

Acute and late toxicities:

Compared with the results from literature, we report a very acceptable and low rate of grade ≥ 2 GU and GI toxicities. Martinez et al. [2] reported a 5-year actuarial rate for grade 3 and 4 toxicities of 8% and 0% for GU toxicities and 0.5% and 0.5% for GI toxicities, respectively. Galalae *et al.* [3] reported 2% in terms of cystitis and 4.1% proctitis and 6% incontinence. Sato *et al.* [4] reported a very low grade 2 GU and GI toxicities of 0% and 3.8%, respectively.

Demanes et al.[18] report results with long FU of 6.7% and 1% for grade 3 and 4 for late GU toxicities respectively. Grade 2 rectal toxicity has been reported in 2%, no grade 3 or 4 rectal toxicities developed[18]. We found urinary retention in 2.5% and urinary stricture in 2.5% after 7 years with overall grade 3 GU toxicity of 4.2%. Late rectal grade 2 and 3 toxicity after 7 years was registered in 3% and 1% respectively.

These results if compared to the results of EBRT alone and low-dose-rate could indicate a benefit of HDR-BT boost plus EBRT in lowering the toxicity depending on the regimen, dose, and fractionation used. In low-dose-rate series urinary retention is reported for 2-22% of the patients.

In general late GU grade 3 toxicity has been reported in 3-9% for patients treated with permanent-seed monotherapy [18,19]. Rectal toxicity has been reported at 2-9.5% for grade 2, 0.5-2% for grade 3, and 0.4% for grade 4 at 5 year follow-up. Late morbidity for conformal EBRT after dose escalation to 78 Gy has been reported by 2 trials; Peeters *et al.*[1] reported the toxicity of the Dutch dose

escalation trial with a cumulative incidence of grade 2 or higher GI toxicity of 26% at 3 years while the incidence of grade 2 or higher GU toxicity was 29% with 6% rate of grade 3 GU toxicities. Pollack *et al.* [11] reported the results of a randomised dose escalation trial comparing 70 Gy versus 78 Gy with an incidence of grade 2 or higher GI toxicity at 6 years of 26% for the 78 Gy arm. However our good results for low and intermediate risk patients give no guarantee that the HDR monotherapy for this group will give the same results, the increasing evidence that the HDR monotherapy is safe and reasonable [19] gave us the argument to stop this regimen of EBRT plus HDR-BT in 2007 and to start a monotherapy HDR-BT regimen to treat low- and intermediate-risk patients giving 4 fractions of 9.5 Gy within 36 hours. We have previously reported our early experience[20].

Future

We will initiate the same treatment regimen (EBRT plus HDR-BT) for a (high) intermediate-risk group.

CONCLUSION:

We reported our long-term follow-up results of EBRT plus HDR-BT for low- and intermediate-risk prostate cancer patients, in terms of oncological outcome and toxicity, and we compared our results with available literature. We confirm the excellent results for low- and intermediate-risk PC patients using EBRT plus HDR-BT. We suggest the use of less intensive treatment for this group, using monotherapy HDR-BT. We also suggest the treatment of a higher (intermediate)-risk patient with this regimen (EBRT plus HDR-BT) to decrease the percentage of late toxicities.

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Chapter 5

HDR monotherapy for prostate cancer: A simulation study of catheter displacement on target coverage and normal tissue irradiation

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ABSTRACT

Purpose:

The aim of this study was to systematically analyse the effect of catheter displacements both on target coverage and normal tissue irradiation in fractionated high dose rate (HDR) prostate brachytherapy, using a simulation study, and to define tolerances for catheter displacement ensuring that both target coverage and normal tissue doses remain clinically acceptable. Besides the effect of total implant displacement, also displacements of catheters belonging to selected template rows only were evaluated in terms of target coverage and normal tissue dose, in order to analyse the change in dose distribution as a function of catheter dwell weight and catheter location.

Material and methods:

Five representative implant geometries, with 17 catheters each, were selected. The clinical treatment plan was compared to treatment plans in which an entire implant displacement in caudal direction over 3, 5, 7 and 10 mm was simulated. Besides, treatment plans were simulated considering a displacement of either the central, most ventral or most dorsal catheter rows only, over 5 mm caudally.

Results:

Due to displacement of the entire implant the target coverage drops below the tolerance of 93% for all displacements studied. The effect of displacement of the entire implant on organs at risk strongly depended on the patient anatomy; e.g. for 80% of the implant geometries the V80 of the rectum exceeded its tolerance for all displacements. The effect of displacement of catheters belonging to selected template rows depended strongly on the relative weight of each catheter row when considering the target coverage and on its location when considering the dose in the organs at risk.

Conclusion:

This study supports the need for a check of the catheter locations before each fraction and correction of deviations of the catheter position exceeding 3 mm.

INTRODUCTION

The use of high dose rate (HDR) brachytherapy, either as a boost after external beam irradiation or as monotherapy for early stage prostate cancer patients is increasing worldwide [1-6]. General recommendations on how to perform HDR temporary brachytherapy for prostate cancer can be found in Kovács et al.[7]. HDR temporary brachytherapy offers several advantages over the use of permanent low dose rate seeds from a practical, physical and biological point of view[1], e.g. the reduced radiation hazard because of the use of remotely controlled afterloading, the ability of dose optimization by dwell time optimization and the increased effectiveness of a high dose per fraction due to a low α/β ratio. HDR brachytherapy usually is a fractionated treatment, with the number of fractions varying between two and five. Therefore needle displacement between fractions can occur, which, if not corrected, can influence the dose distribution drastically [3,8-13]. By checking (using ultrasound (US), computed tomography (CT) or fluoroscopy) and subsequently adjusting the needle positions before each fraction, these deviations can be corrected.

After several years of applying HDR brachytherapy as a boost in combination with external beam irradiation [14], we embarked on HDR monotherapy recently. In our institute HDR brachytherapy as monotherapy is performed using US guided implantation and CT guided treatment planning, which is similar to the procedure used for the boost treatment, as described earlier [15]. The total dose is 38 Gy delivered in 4 fractions within 36 hours, according to the protocol proposed by Martinez et al.[3].

Over this period of 36 hours a displacement of the implant in caudal direction is sometimes observed. Therefore, a lateral X-ray is made before each fraction to check the position of the tip of the catheters relative to implanted markers using a set-up protocol. The position of the catheters is adjusted if needed by pushing the catheters to the planned depth as indicated by their position relative to the markers. Analysis of the first 45 patients treated, revealed that in 11 out of these 45 patients, a catheter displacement before one or more fractions was detected and corrected. However, this procedure is time consuming and we decided to define the limits for implant displacement to ensure that target coverage and normal tissue irradiation would remain within clinical tolerances.

In the literature, clinically encountered displacements [8,13] and corresponding effects on dose distribution are discussed [3,9-12,16]. The majority of these papers discuss the dose degradation, focusing on the decrease in target coverage, in relation to the clinically encountered implant displacements. Simnor et al. also analysed the changes in dose in organs at risk, i.e. rectum and urethra[12]. However, this study only discussed the clinically observed implant displacements and did not analyse the effect as a function of increasing implant displacement. Tiong et al.[11] is the only one who systematically studied the effect of implant displacement on the dose distribution by simulating the decrease in target coverage and tumor control probability (TCP) as a function of implant displacement. However, the effect on the dose in organs at risk was not evaluated.

The aim of this study is to systematically analyse the effect of catheter displacements both on target coverage and normal tissue irradiation using a simulation study, in order to establish tolerances for catheter displacement ensuring that both target coverage and normal tissue doses

remain clinically acceptable. Besides the effect of total implant displacement, also displacements of catheters belonging to selected template rows are evaluated in terms of target coverage and normal tissue dose.

MATERIALS AND METHODS

Five representative implant geometries, with 17 catheters each, were selected because presently most of our patients are treated with an implant consisting of 17 catheters, resembling the geometry proposed by Mate et al. [17]. The clinical target volume (CTV) was defined as the prostate without margin; no planning target volume (PTV) to CTV margin has been used. The mean CTV, as measured on postimplant CT, covered by the implants used for this study was 59.1 cc (range 48.5 – 69.9 cc). The mean delineated rectum (delineated from the lower border of the SI joint to the anal ring) and urethra (as delineated from the outer contour of the inserted Foley catheter from the urethro-bladder point to 3 cm under the prostate) volumes were 102.9 cc (range 76.3 – 134.0 cc) and 2.7 cc (range 2.3 – 3.2 cc), respectively. A clinical treatment plan was calculated, taking into account the following constraints for target and organs at risk: prostate D90 > 9.5 Gy, V100 > 93%, rectum V80 < 1 cc, bladder V80 < 1 cc, urethra V120 < 1%.

The clinical treatment plan (Figure 1A) was compared to treatment plans in which an entire implant displacement in caudal direction over 3, 5, 7 and 10 mm was simulated (Figure 1B). In this case all dwell positions were translated over 3, 5, 7 and 10 mm in caudal direction along the catheters relative to the delineated target and organs at risk. The dwell times were kept according to the clinical treatment plan and the dose distribution was evaluated in terms of target coverage and dose to organs at risk.

Besides, treatment plans were simulated in which a displacement of catheters belonging to selected template rows was present, in order to evaluate the degradation of the dose distribution as a function of catheter dwell weight and catheter location. In this simulation two neighbouring rows were displaced concurrently in order to predict critical factors. In the case of the most ventral or dorsal catheters this situation could be representative for a tilt of the template. For this simulation a displacement of 5 mm was chosen, as most of our clinically encountered displacements are on the order of 5 mm. In this case only dwell positions of selected catheters were translated in caudal direction along the catheters relative to the delineated target and organs at risk. Again, the dwell times of all dwell positions were kept according to the clinical treatment plan and the dose distribution was evaluated in terms of target coverage and dose to organs at risk, taking into account the dwell weight and the locations of the selected catheters. This situation is illustrated in figure 1C with a displacement of the two most dorsal catheter rows.

All clinical treatment plans as well as simulated treatment plans were calculated on Plato BPS version 14.2.6 (Nucletron, The Netherlands) and assumed a situation present during all fractions.

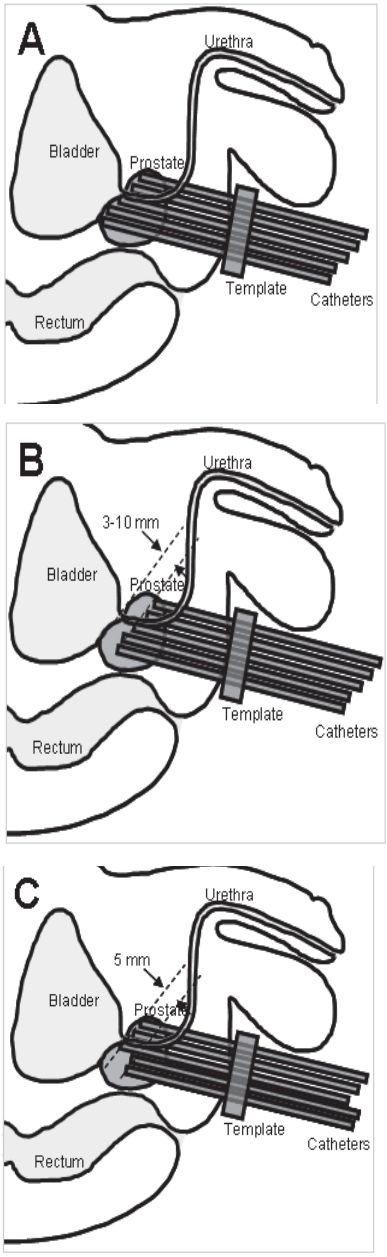

Figure 5.1 | Sagital impression of the implant situation during simulations

A: the clinical treatment plan with all catheters inserted until the base of the prostate;

B: virtual displacement of the entire implant over 3, 5, 7 and 10 mm;

C: virtual displacement of selected catheter rows over 5 mm.

RESULTS

The tolerances for target and organs at risk were well met in the clinical treatment plans (table 1). Only for one patient the bladder tolerance was not met (V80 = 1.35 cc). The change in target coverage, rectum V80 and urethra V120 is summarized in table 1 and shown in more detail for each patient in figure 2. The effect of implant displacement on the rectum V80 and urethra V120 strongly depended on the patient anatomy (Figure 2B and 2C): the individual rectum V80 increased by a factor ranging between 1.6 and 5.8, the individual urethra V120 by a factor ranging from negligible to 26. As expected the dose in the bladder decreased rapidly as a function of a caudal implant displacement. For all patients the V80 bladder became negligible for an implant displacement of 3 mm or more. Therefore, the effects of catheter displacements on the bladder dose were not analysed in more detail.

The effect of displacement of selected catheter rows is evaluated for the case in which two neighbouring rows are displaced concurrently in order to predict critical factors. In figures 3 and 4, the location of the two displaced rows is depicted on the X-axis. On the left, the clinical treatment plan is shown, i.e. the case without displacement of any catheter rows. From left to right more dorsal towards more ventral neighbouring rows of catheter rows are selected. In figure 3 the dashed lines present the target coverage (on the left Y-axis), while the solid lines present the corresponding total dwell weight of the two selected catheter rows (on the right Y-axis). It is clear that a displacement of the combination of rows with the highest weight, i.e. rows 1.5 and 2 according to the denomination on the template (see sketch in figure 3), results in the lowest target coverage. However, regarding the effect on the organs at risk, it is clear that the location of the two selected catheter rows dictates the effect of a displacement more than the weight, i.e. the dorsal rows for the rectum (fig. 4A), and the more ventral rows for the urethra (fig. 4B).

DISCUSSION

The effect of catheter displacements both on target coverage and normal tissue irradiation in HDR prostate brachytherapy was systematically analysed using a simulation study. Our results show that displacement of the entire implant has a large effect on the dose distribution. The target coverage drops below the tolerance of 93% for all displacements studied, i.e. 3 to 10 mm. Therefore, our results confirm the conclusions of Tiong et al. [11] that the tolerance of implant displacement is smaller than 3 mm, in order to achieve adequate target coverage. On top of this conclusion, our results also show that, besides target coverage, due to normal tissue tolerances the same tolerance of 3 mm for implant displacement should be employed as for 4 of the 5 implant geometries studied the V80 of the rectum exceeds the tolerance of 1 cc. From this latter point of view it is not acceptable to employ the solution of extension of the target volume in cranial direction by adding a 1 cm margin, as suggested by Damore et al. [8], because their solution does not solve the dose increase in normal tissues. A solution which overcomes Damore's shortcoming is suggested by Hoskin et al.[9], who implant catheters 1 cm beyond the base of the prostate. Both, the drop in target coverage and the overdosage in organs at risk can be corrected simultaneously, as this elegant solution enables to shift active dwell positions cranially

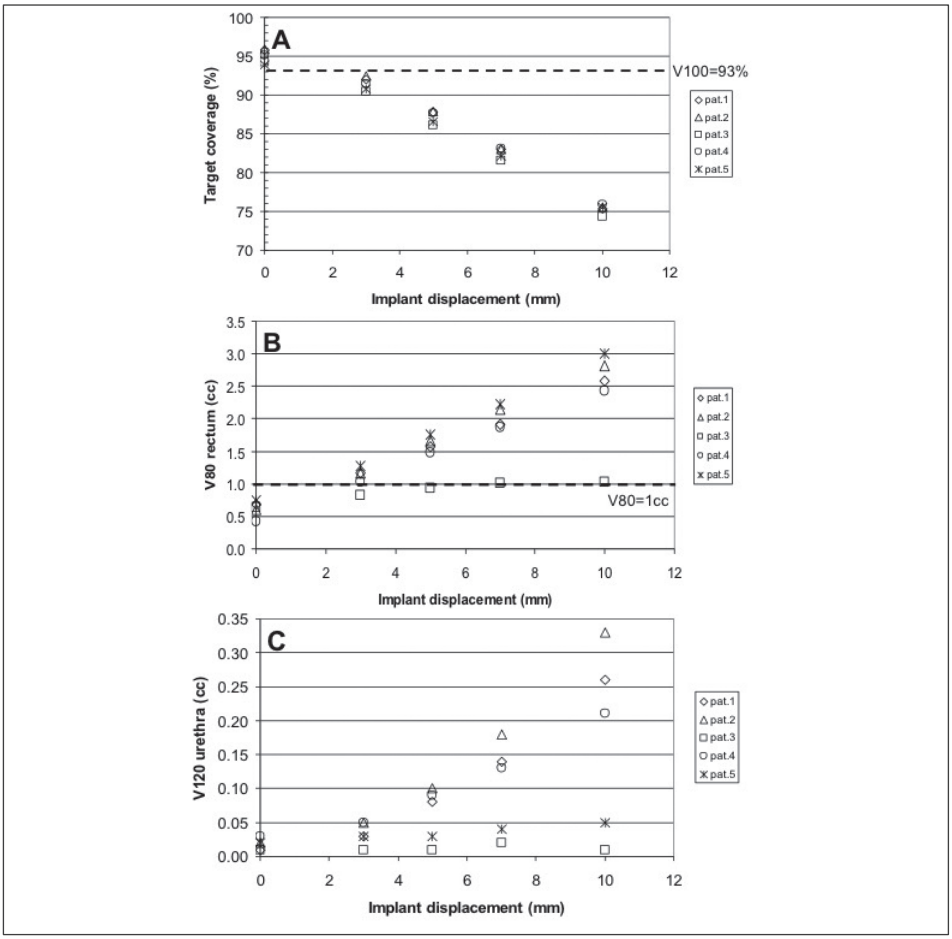

Figure 5.2 | Effect of total implant displacement on: (A) target coverage, (B) V80 rectum and (C) V120 urethra.

Table 5.1 | The change in target coverage, bladder V80, rectum V80 and urethra V120 as a function of implant displacement.

Implant displacement (mm)	Target coverage (%)		V80 bladder (cc)		V80 rectum (cc)		V120 urethra (cc)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
0*	95.0	93.9 – 95.9	0.66	0.24 – 1.35	0.6	0.4 – 0.7	0.02	0.01 – 0.03
3	91.4	90.5 – 92.4	0.02	0.00 – 0.04	1.1	0.8 – 1.3	0.03	0.01 – 0.05
5	87.2	86.1 – 87.9	0.00	0.00 – 0.00	1.5	0.9 – 1.8	0.06	0.01 – 0.10
7	82.6	81.5 – 83.1	0.00	0.00 – 0.00	1.8	1.0 – 2.2	0.10	0.02 – 0.18
10	75.3	74.4 – 75.9	0.00	0.00 – 0.00	2.4	1.0 – 3.0	0.17	0.01 – 0.33

*: 0 mm implant displacement represents the clinical treatment plan.

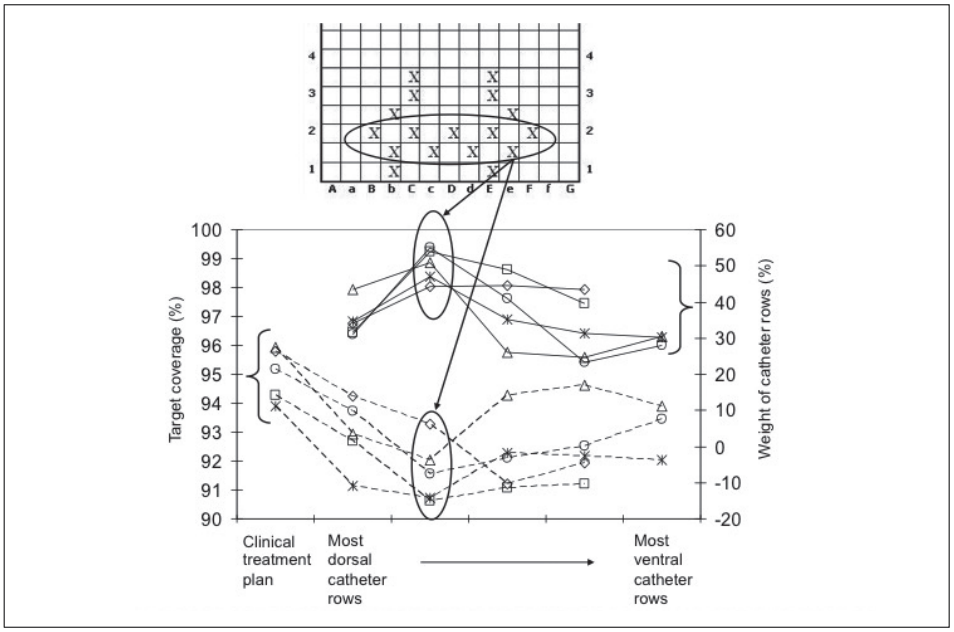

Figure 5.3 | The target coverage (dashed lines relative to the left Y-axis) as a function of a 5 mm displacement of two selected catheter rows. At the left side of the X-axis the clinical treatment plan, i.e. no catheter displacements; from left to right displacement of the two most dorsal towards the two most ventral catheter rows. The solid lines depict the corresponding dwell weights of the two selected catheter rows (on the right Y-axis). The marked displacements and weights correspond to the marked rows in the template diagram.

to compensate implant displacement without the necessity to manipulate catheters. A drawback of this method in our view is that catheters are implanted deeper than necessary, although the authors state that this can be done without additional bladder morbidity.

Several authors [8,11,12] use a margin, e.g. 3 mm, between clinical target volume (CTV) and planning target volume (PTV). A CTV to PTV margin is an appropriate method to ensure adequate target coverage in presence of implant displacement. However, it is not a solution for the dose increase in surrounding normal tissues due to implant displacements. In case implant displacements are well controlled, a CTV to PTV margin is not necessary to achieve adequate target coverage, which is a clear advantage over external beam radiotherapy and even stereotactic radiotherapy [18-20].

The range of displacements studied are well representative for the ones clinically encountered. In the literature mean implant displacements up to 10 mm are frequently mentioned [3,8-13] depending on implantation technique but also varying along the treatment course. In general the largest displacements occur in the beginning of the treatment course. Occasionally a single patient with an implant displacement up to 30 mm is detected, necessitating corrective action. In general, displacements encountered in our institute are in the order of 5 mm.

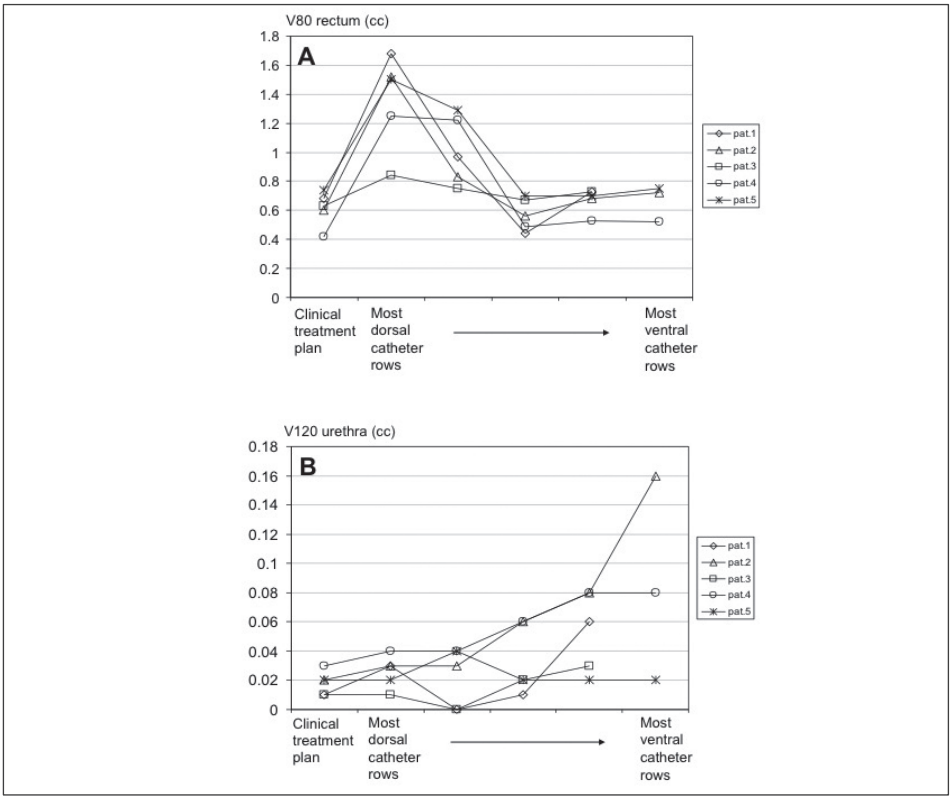

Figure 5.4 | The V80 rectum (A) and V120 urethra (B) as a function of a 5 mm displacement of selected catheter rows. At the left side of the X-axis the clinical treatment plan, i.e. no catheter displacements; from left to right displacement of the two most dorsal towards the two most ventral catheter rows.

Although most papers concentrate on the decrease of target coverage due to implant displacement, Simnor et al. also included a discussion on the dose increase in surrounding normal tissues as rectum and urethra due to clinically observed implant displacements [12]. They conclude that the rectum and urethra volume receiving the tolerance dose increases on average with an amount of 0.4 to 0.7 cc with a large interpatient and interfraction variability. In their study a CT scan was made before each fraction. A limitation was that target and organs at risk were delineated retrospectively on each of these CT scans. This introduced an unknown variation in organ definition leading to inaccuracies in their results. A similar interpatient variability is also seen in our simulation study. However, our current study concerns a more systematic analysis of the dose increase in organs at risk using a simulation, including a varying implant displacement and a single delineation of target and organs at risk. On top of the interpatient variability we also demonstrated the increasing dose degradation due to an increasing implant displacement.

The discussion on the dosimetric effects due to implant displacement should be viewed in relation to other uncertainties in HDR brachytherapy, leading either to systematic or random errors in dose delivery, as discussed by Elfrink et al.[21]. A typical systematic uncertainty in HDR prostate brachytherapy is discussed by Kim et al.[22], i.e. the dose inaccuracy due to the uncertainty in needle tip localisation as a function of the CT slice thickness. This simulation study including both random as well as systematic deviations in needle tip localisation revealed that a slice thickness of 3 mm is a good compromise, minimizing the needle tip localisation error without increasing the number of slices. This recommended 3 mm slice thickness is very similar to the proposed 3 mm tolerance for implant displacement as both introduce a discrepancy or inaccuracy in the needle position relative to target and normal tissues. Prostate volume changes, frequently discussed in permanent seed implants because of its effects on the dosimetry, are much smaller in temporary HDR prostate brachytherapy due to the short time course [3,23]. Another source of inaccuracy in dosimetry is due to the inaccuracy in prostate delineation. CT based treatment planning for prostate brachytherapy is known to have a larger contouring variability as compared to magnetic resonance imaging (MRI)- or transrectal ultrasound (TRUS)-based planning[24]. When using TRUS- in combination with CT-based treatment planning dosimetric effects because of implant deformation due to posture changes were observed by Seppenwoolde et al.[25]. It was shown that the dose distribution changed dramatically when shifting from a TRUS patient set-up to a CT patient set-up influencing both target as well as dose in organs at risk.

In general, most displacements concern a total implant displacement. Displacement of selected catheters due to sliding in the template is not likely to occur. However, due to tilting of the template caused by tilting of the pelvis, it is possible that selected pairs of catheter rows exhibit a displacement relative to the target and organs at risk. This effect of displacement of selected catheters has not been evaluated before. We have analysed the effects of displacements of selected catheter rows in order to predict critical factors. As expected, displacement of catheter rows with a higher total dwell weight has the largest effect on target coverage. Usually, these are the 2nd and 3rd row dorsally. With the most dorsal row having a relatively low catheter weight one can expect that a tilt with a caudal displacement of dorsal rows is expected to have a large effect. Usually ventral rows have a low catheter weight, thus a relatively small effect on target coverage due to displacements, and a negligible effect on rectum dose. Therefore, one could decide not to correct displacement of these ventrally located catheters if the urethra dose is not too critical. However, due to target coverage degradation and overdosage of the rectum one should always be reluctant not to correct more dorsally located catheters. The implant method that has demonstrated the least displacement in fractionated therapy, enabling to speed-up the procedure by avoiding the necessity of a check of the implant position before each fraction, is the use of self-anchoring catheters[16]. Pieters et al. show that the mean implant displacement during a 3 day treatment was limited to 1.2 mm, resulting in minor alterations in the dose distribution which were of no clinical importance. We have the intention to introduce this type of catheters in our procedure to be able to skip the imaging before each fraction and keep doses within clinical tolerances.

CONCLUSION

This study supports the need for a check of catheter locations before each HDR prostate brachytherapy fraction and correction of deviations of the catheter position exceeding 3 mm, not only because of target coverage degradation, but also to avoid an overdosis in organs at risk. The results support the development and use of self-anchoring catheters.

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Chapter 6

Fractionated HDR brachytherapy as monotherapy in prostate cancer: does implant displacement and its correction influence acute and late toxicity?

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Article in press, Brachytherapy.

ABSTRACT

Background and purpose:
In fractionated high-dose-rate brachytherapy (HDR-BT) for prostate cancer (PCa) with one implant for several fractions, dose delivery relies on reproducibility of catheter positions. However, caudal displacement of implanted catheters does occur between fractions and needs to be corrected. Our protocol prescribes correction of displacements >3mm. We investigated whether displacement and its corrections influence acute and late toxicity incidences.

Methods and Materials:
We analyzed 162 PCa patients treated with HDR-BT monotherapy between 2007 and 2013. The implant remained in situ between the four fractions. Catheter displacement was assessed before each fraction using lateral X-ray images and corrected if needed. Genitourinary (GU) and gastrointestinal (GI) acute and late toxicities were assessed using clinical record forms and patient self-assessment questionnaires.

Results:
Implant displacement corrections (DC) were needed in 71 patients (43.8%) whereas no displacement corrections (NDC) were needed in 91 patients (56.2%). No statistically significant differences were seen in acute and late grade ≥2 GU and GI toxicity incidences between DC and NDC groups. The maximum displacement nor the number of corrections had any influence on toxicity.

Conclusions:
The occurrence and subsequent correction of implant displacements exceeding 3mm during fractionated HDR-BT monotherapy for PCa did not lead to increased incidences of acute or late GU and GI toxicity. This indicates that our clinical protocol to correct displacements >3mm results in safe treatment regarding organ at risk toxicity.

SUMMARY

Catheter displacements in high-dose-rate brachytherapy (HDR-BT) for prostate cancer need to be corrected if exceeding 3mm to ensure accurate dose delivery. The clinical effect of displacement correction on genitourinary and gastrointestinal toxicity incidences was evaluated in 162 patients treated with HDR-BT. No significant differences were seen in acute and late toxicity incidences between patients with and without the need for displacement correction. The maximum displacement or the number of corrections did not influence toxicity either.

INTRODUCTION

High-dose-rate brachytherapy (HDR-BT) is a safe and effective treatment option for low- and intermediate-risk prostate cancer (PCa) and has been increasingly used as monotherapy [1-3]. From a dosimetric point of view, HDR-BT is an ideal technique enabling intensity modulation and individual adaptation of the dose, resulting in a highly conformal treatment with an excellent dose distribution in the target and rapid dose fall-off outside [4]. In case HDR-BT monotherapy is delivered in several fractions (mainly 2-6 fractions) in a short period of time using one implant [1,5], all dosimetric advantages rely on accuracy and reproducibility of the position of the catheters before each fraction. Even though catheters are fixated to the template and the template is sutured to the patients skin, the implant can displace between fractions. Since the same treatment plan is used for all fractions, displacements can result in changes in the delivered dose to the target and organs at risk (OAR). Several papers have addressed catheter displacement[6-12]. All these series showed that displacement of catheters (usually occurring in caudal direction) needs to be corrected to ensure good target coverage and avoid overdosing OAR. The clinical consequence of catheter displacement and its correction, however, is lacking in literature.

Our earlier simulation study showed that catheter displacements of more than 3mm resulted in target coverage degradation and overdosing OAR [10]. Based on these findings, we implemented a protocol in our clinical practice to check catheter positions and correct displacements exceeding 3mm before delivering each fraction. The purpose of this study was to assess our hypothesis that optimal correction of catheter displacement will keep the dosimetric parameters at the planned levels and that no effect of the corrected displacements on toxicity incidences is expected. We analysed whether catheter displacement and its correction before each fraction in HDR-BT monotherapy for low- and intermediate-risk PCa influence acute and late toxicity incidences.

METHODS AND MATERIALS

Patients

The patient population of the present study is a subset of 162 patients from the population in our previous study[3] for which data on implant displacement and correction before each fraction was available. Patients with histologically confirmed PCa, clinical stage T1b-T2b, Nx-0, Mx-0, Gleason score ≤7, PSA ≤16 ng/ml and WHO performance status of 0-2 were eligible for HDR-BT monotherapy and were treated between September 2007 and December 2013. From 2011 on, patients with IPSS score >18 were no longer eligible. Other exclusion criteria were prior transurethral resection of the prostate, prostate volume >50ml on transrectal ultrasound, prior radiotherapy or surgery in the pelvic area and the concomitant use of androgen deprivation therapy. TNM scoring was according to the AJCC 2003 guidelines[13]. Patient characteristics of all patients included in the analysis are shown in Table 1.

Radiotherapy

HDR-BT monotherapy with a total dose of 38 Gy was administered in four fractions of 9.5 Gy with a minimum interval of six hours between fractions. All fractions were delivered within 36 hours according to one treatment plan and using one implant. The first two fractions were delivered on the day of the implant, the last two the next day. The procedures for implantation and planning have been described previously in more detail [3,10,14]. In short, 6F plastic needles (ProGuide; Elekta, Sweden) were implanted template-based using transrectal ultrasound imaging with the patient under spinal anaesthesia and in lithotomy position. Treatment planning was performed with PLATO up to 2009 and Oncentra Brachy (Elekta, Sweden) afterwards based on CT imaging. A microSelectron HDR or Flexitron HDR afterloader (Elekta, Sweden) was used to deliver treatment.

Before catheter implantation, four markers were inserted: two at the base and two at the apex of the prostate. Immediately after catheter implantation and the planning CT scan, a reference lateral X-ray was acquired with six metal dummy sources inserted in the most lateral placed catheters in three rows, including the top and bottom rows. The X-ray tube was positioned such that the catheter tips were in the centre of the image. Before each fraction a new lateral X-ray was acquired using the same localiser configuration and patient position as for the reference image.

Both the reference image and prefraction image were imported in the treatment planning system. Both images were aligned by placing a coordinate system in the image with a cranial marker as centre point and the y-axis through a caudal marker. By marking the catheter tips (with dummies inserted) in both images, the displacement was calculated. Figure 1 shows an example of the lateral X-ray images as used for assessing catheter displacement. Catheter displacements >3mm were corrected by manually adjusting the catheter positions. The displaced distance was marked on the catheters, which were then moved until the marking reached the template. Subsequently, a second X-ray image was acquired to confirm the correction in the planning system (Figure 1C). In case of a residual displacement, the above mentioned procedure was repeated until the remaining displacement was within 1mm to ensure a conformal dose distribution[10]. In this method of checking for displacement, it is assumed that all catheters displace the same distance and that the implanted markers do not migrate through the prostate. All patients remained in bed during X-ray imaging and dose delivery. The transfer tubes were connected just before the first fraction and disconnected only after the fourth fraction. This way displacement resulting from patient transfer and connecting the transfer tubes was minimized.

Data analysis

All patients were prospectively followed every three months during the first year, and twice yearly thereafter. Genitourinary (GU) and gastrointestinal (GI) toxicities grade ≥2 were assessed using a European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) toxicity score based questionnaire [15,16]. This self-assessment questionnaire was sent to all patients at baseline (before treatment), at 1, 2, 3, 6, 12, 18, and 24 months after treatment and yearly thereafter. Both GU and GI toxicity were evaluated using a combination of questionnaires and physicians charts, according to EORTC-RTOG toxicity scores [16,17]. The highest score of toxicity between the two sources was registered.

The date of the implantation and first two fractions of HDR-BT was considered day 0. Toxicity within 100 days after the start of radiation-therapy (implantation day) was considered acute toxicity, and toxicity after 100 days as late toxicity.

For each patient and each fraction was recorded whether there was implant displacement that needed correction and, if applicable, the extend of the displacement correction. To determine the effect of displacement correction on toxicity, several groups were statistically compared. First, the group with no displacement corrections (NDC) was compared to the group with displacement corrections (DC). The NDC group consisted of patients who had no displacements exceeding 3mm during all four fractions. The DC group comprised patients in whom a displacement >3mm occurred that needed to be corrected before one or more fractions. Within the DC group, the total number of displacement corrections during all four fractions was taken into account and a comparison was made between only one correction before one fraction and corrections before more than one fraction.

The DC group was also stratified according to the maximum corrected displacement over all fractions to analyse differences in toxicity. Patients with maximum displacement corrections up to

Table 6.1. | Patient and tumour characteristics

		n (%)	Median (IQR)
Patients		162	
Age (yr)			68.9 (62.7-72.7)
Clinical T-stage	T1c	110 (67.9%)	
	T2a	50 (30.9%)	
	T2b	2 (1.2%)	
Gleason score	2+2	1 (0.6%)	
	2+3	1 (0.6%)	
	3+3	140 (86.4%)	
	3+4	19 (11.7%)	
	4+3	1 (0.6%)	
PSA (ng/ml)			7.9 (5.6-9.8)
IPSS baseline score			5 (3-10)
Urinary flow baseline (Qmax; ml/s)			14.5 (10.3-20.5)
Number of needles			17 (15-18)
PTV volume (cm^3)			59.5 (48.8-68.2)

Note: IQR = interquartile range

5mm were compared to those with corrections >5mm. An overview of all analysed groups and the number of patients per group is presented in Table 2.

Statistical significance of differences in acute toxicity between groups was tested using Pearson's Chi-squared test. To compare the incidence rates of late toxicity the log-rank test was applied. To analyse the effect of multiple factors on late toxicity a Cox regression analysis was performed. Two-tailed tests were used and p-values ≤0.05 were considered significant. Statistical analyses were performed using IBM SPSS Statistics v21.0 (IBM Corp).

Table 6.2 | Number of patients per group

		Number of patients (%)
Displacement correction		
	No correction	91 (56.2%)
	Correction	71 (43.8%)
Maximum displacement correction		
	>3-5 mm	45 (63.4%)
	>5 mm	26 (36.6%)
Number of displacement corrections		
	1	56 (78.9%)
	>1	15 (21.1%)

RESULTS

In 91 patients (56.2%) no catheter displacement corrections (NDC) were needed, whereas in 71 patients (43.8%) one or more catheter displacement corrections (DC) were performed. In 56 (78.9%) of the DC patients a displacement correction before one of the four fractions was done, whereas 15 patients (21.1%) needed corrections before more than one fraction. Within the DC group a maximum displacement correction of >3-5mm was observed in 45 patients (63.4%) and >5mm in 26 patients (36.6%). The largest displacement correction performed was 18mm, whereas the median correction was 5mm.

Of all displacement corrections, 3 (3.4%) were performed before fraction 1, 42 (47.2%) before fraction 2, 28 (31.4%) before fraction 3 and 16 (18.0%) before fraction 4.

Acute toxicity

Median follow-up was 25 months, with a mean of 35 months and ranging from 2 to 78 months. Acute GU grade ≥2 toxicity was reported in 33.0% and 31.0% of the NDC and DC groups, respectively. This difference between the groups was not statistically significant (p=0.866). Within the DC group, the

maximum displacement correction and the number of corrections did not show any statistically significant effect on acute toxicity incidences. Acute GU toxicity incidences were 37.8% and 19.2% for >3-5mm and >5mm corrections, respectively (p=0.119). In patients with one displacement correction GU toxicity was reported in 28.6% compared to 40.0% in the group with more than one displacement correction (p=0.530). Acute GI grade ≥2 toxicity was reported in 26.4% of the NDC group and in 28.2% of the DC group (p=0.859). In the DC group, acute GI grade ≥2 toxicity incidences were 26.7% and 30.8% for >3-5mm and >5mm corrections, respectively (p=0.787). GI toxicity was reported by 25.0% in the one displacement correction group compared to 40.0% in the group with more than one displacement correction (p=0.333). None of these differences were statistically significant. An overview of acute toxicity per group is presented in Table 3.

Late toxicity

Late GU grade ≥2 toxicity was reported by 47.7% of patients in the NDC group, whereas this was 31.9% in the DC group. The difference between the groups appeared to be statistically significant with a p-value of 0.043. However, in a multivariable Cox regression analysis including risk factors (age, presence of acute grade ≥2 toxicity, baseline IPSS score, baseline urinary flow, comorbidity, number of needles and prostate volume), the effect of displacement correction on the incidence of late GU toxicity was not statistically significant (p=0.121) with a relative hazard ratio of 0.43 (95% confidence interval 0.15-1.25). None of the other factors in the regression analysis showed significant association with late GU toxicity.

Regarding the maximum displacement correction and the number of displacement corrections, there were no statistically significant differences observed in GU grade ≥2 toxicity between the groups. Cumulative late GU toxicity incidences during the follow-up were 34.1% and 28.0% for the groups with >3-5mm and >5mm correction, respectively (p=0.834). In the group with only one correction, late GU grade ≥2 toxicity was reported in 35.2%, versus 20.0% in the >1 displacement corrections group (p=0.214).

Late GI grade ≥2 toxicity was observed in 10.2% of NDC and 8.7% of DC patients, which difference was not statistically significant (p=0.888). The maximum corrected displacement did not have statistically significant influence on GI grade ≥2 toxicity with 11.4% and 4.0% for the groups with >3-5mm and >5mm correction, respectively (p=0.520). In the group with only one displacement correction, late GI toxicity was reported in 9.3%, versus 6.7% in the group with more than one correction (p=0.742).

All late toxicity incidences are presented in Table 3. Late GU toxicity incidences over time are depicted in Figure 2 for the NDC and DC group separately.

Table 6.3 | Acute and late toxicity incidence in relation to displacement correction

	Displacement correction			Maximum displacement correction			Number of displacement corrections		
	No correction (n=91)	Correction (n=71)	p-value	>3-5 mm (n=45)	>5 mm (n=26)	p-value	1 (n=56)	>1 (n=15)	p-value
Acute GU grade ≥2 (n)	33.0% (30)	31.0% (22)	0.866	37.8% (17)	19.2% (5)	0.119	28.6% (16)	40.0% (6)	0.530
Acute GI grade ≥2 (n)	26.4% (24)	28.2% (12)	0.859	26.7% (12)	30.8% (8)	0.787	25.0% (14)	40.0% (6)	0.333
Late GU grade ≥2 (n)	47.7% (42)	31.9% (22)	0.043 *	34.1% (15)	28.0% (7)	0.834	35.2% (19)	20.0% (3)	0.214
Late GI grade ≥2 (n)	10.2% (9)	8.7% (6)	0.888	11.4% (5)	4.0% (1)	0.520	9.3% (5)	6.7% (1)	0.742

* p-value of log-rank test; in multivariable Cox regression p=0.121

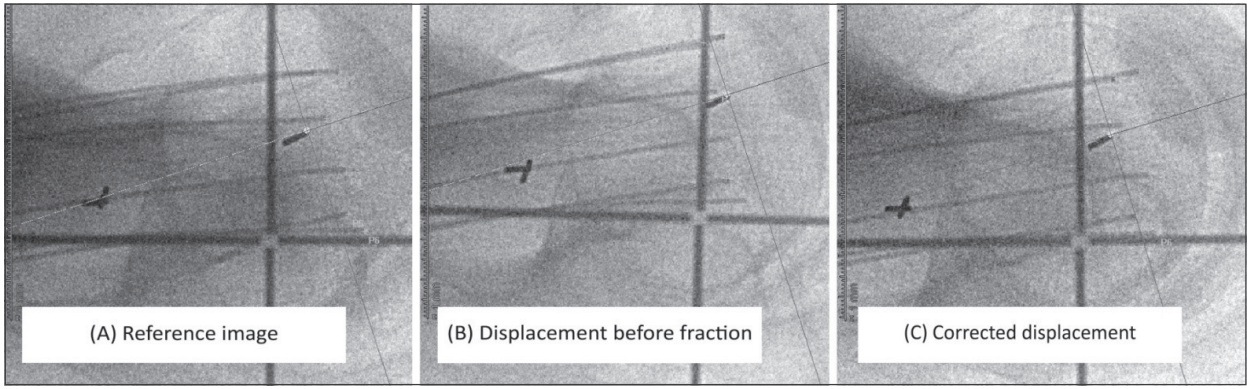

Figure 6.1 | Lateral X-ray images for assessing catheter displacement. (A) Reference image after implantation, (B) before fraction 3 with catheter displacement of 5 mm, and (C) before fraction 3 after correction of catheter displacement with residual shift <1 mm.

DISCUSSION

Correction of implant displacements exceeding 3mm did not significantly influence GU or GI toxicity incidences in both the acute and late phase compared to the treatments where no corrections were needed. There were no significant differences in toxicity associated with the number of corrected displacements nor with the maximum amount of displacement correction.

HDR-BT allows for a conformal high dose to the prostate by optimizing the source dwell times and positions in the implanted catheters[4]. However, the accuracy of dose delivery relies on dwell positions being accurately reproduced for all fractions during treatment. In clinical practice, caudal migration is often observed between fractions [6-9]. Hoskin et al. identified potential sources of catheter displacement: external migration of the catheters through the skin, internal movement of the prostate gland and edema build-up between the prostate apex and perineum[8]. Since the catheters were locked in the template that was sutured to the skin, caudal displacement of the catheters through the template and thus the skin was unlikely. Edema after catheter implantation has been described by several authors. Prostate volume change in the two days after implantation has been shown to be largest in craniocaudal direction[6,7,9,18-20]. Analogue to these authors, we expect edema to be the main cause of catheter displacement between fractions. We found that most displacements occurred before fractions 2 (47.2%) and 3 (31.4%), suggesting that edema build-up is limited in the time between implantation and the first fraction.

In our patients, one or more displacement corrections were needed in 43.8% of the patients. This shows the importance of a check and subsequent correction of catheter displacement in HDR-BT.

To our knowledge, this is the first report on the clinical effect of catheter displacement and its correction during HDR-BT as monotherapy for PCa. As stated by Nuyen and Ciezki, the main technical concern on HDR-BT monotherapy is catheter displacement and the resulting undercoverage of the prostate base and overdosage to the OAR [21]. Other authors have previously reported on catheter displacement between fractions and the corrections that were needed. Based on simulations of catheter displacements and the effects on target coverage and OAR dose, both Kolkman-Deurloo et al. and Tiong et al. suggested to correct displacements exceeding 3mm[10,22]. Other authors have shown with simulation studies that correcting catheter displacements resulted in restoring the target coverage to the planned level[8,9,23]. As the same is true for OAR dose, one could expect that toxicity incidences would be similar for the DC group compared to the NDC group. We have implemented the 3mm limit for correction in our clinical protocol and our results indicate that correction of catheter displacements above this limit resulted in similar toxicity incidences in clinical practice. Therefore, catheter displacement is no longer a concern once checked and corrected.

We used markers implanted in the prostate and lateral X-rays to assess catheter displacements and corrected the catheter positions by manual adjustments. Instead of lateral X-rays, AP X-rays could also be used. However, Damore et al. have described that AP images tend to overestimate the amount of catheter displacement with an average of 13% compared to lateral images[6]. This is described to be due to variations in the amount of pelvic flexion between the different images, despite the use of skin markers.

There are some uncertainties in the used method for determining and correcting catheter displacement. First, we assume that the markers do not migrate through the prostate after implantation and that there is only limited effect of prostate volume changes due to prostatic edema. These assumptions are supported by literature. Changes in prostate volume during the time interval between implantation and the last fraction are minimal, as mean volume changes of 2.7 to 6.2% or absolute changes of 1.2 to 3.9cm^3 were described for this period [7,12,19]. Marker distance changes that were reported are, therefore, also small. Mean absolute changes of 0.6 to 3mm were reported for the 36 hour period of our HDR-BT scheme [12,19,24]. As both marker migration and prostate volume changes are small, the uncertainties related to these factors in displacement measurement are expected to be limited.

Another assumption is that all catheters displace the same amount and that the six checked catheters are representative of the overall displacement. This is based on the fact that all catheters are locked in the template and are therefore unlikely to move through the skin. Damore et al. have shown before that all catheters displaced the same amount in almost all of their 96 patients [6].
In the described method there might also be an inaccuracy in displacement measurement, caused by the manual identification of both marker points and catheter tips in each lateral X-ray separately. However, this inaccuracy is difficult to assess and quantify.

Even though there are several assumptions and limitations to the described method of displacement measurement and correction, we can conclude that our method of displacement correction is accurate enough to avoid dose violations in organs at risk based on the toxicity incidences reported here.

Other authors suggested different methods to assess and correct displacements, such as CT imaging before each fraction and/or adjusting dwell positions in case of displacements [7-9,23]. However, using CT imaging is time consuming and more expensive than X-ray, and patient transfer to the CT table and back to the bed may induce catheter displacement by itself. In our method, patients remained in bed from the first lateral X-ray until the last fraction, to avoid implant displacements as much as possible. Pieters et al. described self-anchoring catheters that reduced the mean displacement to 1.2mm[25], which is less than the 3mm limit for corrections in our protocol. However, these catheters have a larger diameter and were used to deliver pulsed-dose-rate BT. An option to compensate for interfraction catheter displacement and ensure PTV coverage could be to add margins to the PTV in cranio-caudal direction. However, this would significantly increase OAR dose, possibly resulting in increased toxicity incidences. Therefore, this option is not preferred.

Recent developments towards HDR-BT monotherapy in a single dose-escalated fraction, as suggested by Hoskin et al. and Mavroidis et al.[26,27], might avoid the need for checking and correcting implant displacements as we have found only 3 displacements before the first fraction in our 162 patients. However, other authors have shown displacements to occur in almost all patients in HDR-BT boost regimens of one fraction[28,29]. This confirms the necessity to check for displacement and correct if needed before each fraction, irrespective of the used regimen.

Toxicity incidences of HDR-BT have been reported by several other authors. Depending on the inclusion criteria and the fractionation schemes, incidences of late grade ≥2 toxicity up to 40% for GU and 10% for GI were reported[5,30-32]. Our late GU toxicity incidences were slightly higher than those reported in literature. However, most reported results were based on physicians charts only, without the use of questionnaires, whereas we have collected toxicity scores prospectively in all included patients using a combination of both questionnaires and physicians charts. Adding questionnaires to data retrieved from physicians charts is reported to increase toxicity incidences [17,33]. This could explain the differences in incidences between our results and the incidences in literature.

Regarding late GU toxicity, we found a borderline significant difference between NDC and DC. The incidence of late GU grade ≥2 toxicity in the DC group was almost half of that in the NDC group. However, if other factors were also taken into account in the multivariable regression, the difference was clearly non-significant with a p-value of 0.121. This indicates that the differences between the two groups with regard to other factors have a larger effect on the toxicity incidences than the displacement correction.

There are some limitations of this study. Firstly, the two groups (NDC vs. DC) were prospectively followed but not randomized. However, as other studies have shown previously that displacements >3mm result in underdosage of the tumor, it could not be ethically justified to study this in a randomized setting. Secondly, in the DC group only 15 patients (20%) needed displacement correction before more than 1 fraction. Even though the differences in toxicity between the groups with one and more than one displacement corrections (GU 35.2% vs 20.1%; GI 25.0% vs 40.0%) seemed rather large and might be clinically relevant, the relatively limited number of patients in the second group was not enough to detect a statistically significant difference. However, the statistical analysis outcome (i.e. the high p-values) implies that there is no different outcome to be expected with larger groups.

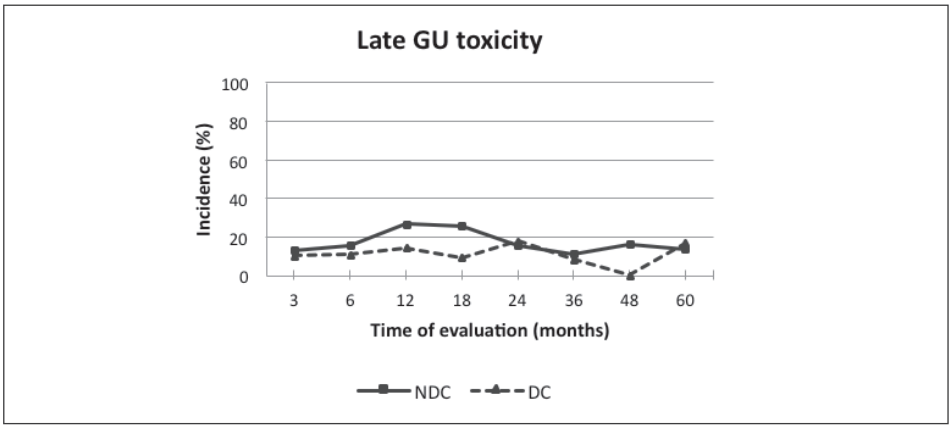

Figure 6.2 | Incidences of late GU grade ≥2 toxicity over time. NDC = no displacement correction, DC = displacement correction

CONCLUSION

The occurrence and subsequent correction of catheter displacements exceeding 3mm before each fraction in HDR-BT as monotherapy for PCa did not lead to increased acute or late GU and GI toxicity incidences. The maximum displacement and the number of displacement corrections had no influence on toxicity incidences. This indicates that our clinical protocol to correct only displacements over 3mm results in safe treatment.

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Chapter 7

Toxicity and quality of life after high-dose-rate brachytherapy as monotherapy for low- and intermediate-risk prostate cancer

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ABSTRACT

Background and purpose

The use of HDR brachytherapy (HDR-BT) as monotherapy for prostate cancer (PC) is increasing worldwide with good tumour control rates and acceptable toxicity. We report our results on toxicity and quality of life (QoL) after HDR-BT monotherapy for PC patients.

Materials and methods

166 low- and intermediate-risk localized PC patients were treated with HDR-BT to a total dose of 38 Gy in four fractions. Genitourinary (GU) and gastrointestinal (GI) toxicities were prospectively assessed using EORTC-RTOG questionnaires and physicians charts. QoL was evaluated using EORTC QLQ-PR25 questionnaires.

Results

Three months after treatment, acute GU and GI toxicities were reported in 10.8% and 7.2%. Acute toxicity resolved within two months in the majority of patients (61%). Late grade ≥2 GU and GI toxicity were reported in 19.7% and 3.3% of patients 12 months after HDR-BT. Mean QLQ-PR25 scores showed clinically relevant changes from baseline for urinary symptoms and sexual functioning. With a mean follow-up of 35 months, biochemical failure was observed in 2.4%. Overall survival at 60 months was 93.6% and cancer-specific survival was 100%.

Conclusions

HDR-BT monotherapy for localized PC showed excellent clinical outcome and acceptable acute and late toxicity. Urinary symptoms and sexual function QoL decreased after treatment.

INTRODUCTION

High-dose-rate brachytherapy (HDR-BT) is a safe and effective treatment option for prostate cancer (PC) [1-3]. There is accumulating evidence that PC cells have a higher sensitivity to fraction dose, which suggests a significant therapeutic benefit of hypofractionation[4,5]. HDR-BT is the ideal technique for extreme hypofractionation because of its highly conformal dose distribution within the prostate with a rapid dose fall-off outside, sparing the organs at risk[6]. The biochemical control rate in favourable risk PC patients has been shown to be good for different radiotherapy treatment options[1-3,7-9]. Therefore, toxicity rates and health-related quality of life (QoL) are important and relevant factors for patients to choose between the different treatment options. The literature on toxicity and clinical outcome in HDR-BT using a scheme of four fractions of 9.5 Gy is scarce [10-13]. Prospective validated questionnaires to monitor long-term toxicity of HDR-BT are hardly used and data on QoL for this treatment option is lacking in literature. In this paper, we report long-term toxicity and QoL of HDR-BT as monotherapy for patients with low- and intermediate-risk PC.

METHODS AND MATERIALS

Patients

This study was approved by our institution's medical ethics committee (MEC-2012-364). Between September 2007 and December 2013, 166 patients with histologically confirmed PC clinical stage T1b-T2b, Nx-0, Mx-0, Gleason score (GS) ≤7, PSA ≤ 16 ng/ml and WHO performance status of 0-2 were treated with HDR-BT monotherapy. TNM scoring was according to the AJCC 2003 guidelines[14]. Patients with clinical stage T1c-T2a, GS 6 and PSA ≤ 10 ng/ml were defined as low-risk PC (67%), whereas patients with PSA >10 ng/ml, T2b and/or GS 7, were defined as intermediate-risk PC (33%)[15]. The concomitant use of androgen deprivation therapy (ADT) was not allowed. Patient characteristics are shown in Table 1.

Radiotherapy

HDR-BT was performed in one transperineal implant during a two-day admission[1,16]. Before implantation, four fiducials were inserted: two at the base and two at the apex of the prostate. Plastic needles were inserted using transrectal ultrasound guidance and a template. Needle depth was controlled by cystoscopy to ensure that the needle tips were placed just beyond the prostate base for a good coverage of the base. After implantation a planning CT scan was acquired, in which the prostate, rectum, bladder and urethra were delineated. The Planning Target Volume (PTV) was the prostate without margins. Anatomy-based inverse planning was used such that the prescribed dose (PD) covered ≥95% of PTV. The doses to 1cm^3 of the rectum and the bladder were limited to 80% of PD. The dose to 1% of the urethra volume was limited to 120% of PD. The total dose administered was 38 Gy in four fractions within 36 h with a minimum interval between fractions of six hours. All fractions were delivered according to one treatment plan. Before each fraction a lateral X-ray was acquired to check needle positions relative to the implanted markers. Needle displacements >3 mm were corrected to ensure good conformity of the dose distribution[16].

Table 7.1 | Patient and tumour characteristics

		n (%)	Mean (min-max)
Patients		166	
Age (year)			68 (47-79)
Follow-up (months)			35 (2-78)
Clinical stage	T1c	112 (67%)	
	T2a	52 (31%)	
	T2b	2 (1%)	
Gleason score	2+2	1 (1%)	
	2+3	1 (1%)	
	3+3	142 (86%)	
	3+4	21 (13%)	
	4+3	1 (1%)	
PSA (ng/ml)			8 (1-16)
Risk group	Low	112 (67%)	
	Intermediate	54 (33%)	
Prostate volume (cm^3)			34 (15-55)
IPSS baseline score			6 (0-24)
Urinary flow baseline (Qmax; ml/s)			16 (2-41)

Follow-up and questionnaires

All patients were followed up prospectively and were seen every three months in the first year, and twice yearly thereafter. Toxicity questionnaires were sent to all patients at baseline (before treatment), at 1, 2, 3, 6, 12, 18, 24 months after treatment and yearly thereafter. QoL questionnaires were sent following the same scheme, except at 1 and 2 months.

The European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) toxicity score based questionnaires were used to assess genitourinary (GU) and gastrointestinal (GI) toxicities[17,18]. The International Prostate Symptom Score (IPSS) was used to evaluate the urinary function after treatment. QoL was assessed by the prostate-specific EORTC QLQ-PR25 questionnaire[19]. The QLQ-PR25 is a validated QoL instrument and consists of four domains: urinary symptoms, bowel symptoms, hormonal treatment related symptoms and sexual activity and functioning. The hormonal domain is not analysed as all treated patients were hormone-naïve.

Oncologic outcome and PSA

Biochemical failure (BF) was determined according to the Phoenix definition (every rise of PSA ≥2ng/ml above nadir)[20]. A PSA bounce was defined as a ≥0.4ng/ml rise in PSA level with subsequent normalization of PSA values [21]. Freedom from BF (FFBF) was defined as the percentage of patients still alive without evidence of BF. Cancer-specific survival (CSS), defined as mortality due to PC, and overall survival (OS) were also analysed. Patients who died from other causes than PC or who were lost to follow-up were censored at the date of last PSA test or contact for the survival analysis.

Data analysis

The date of the implantation was considered day 0. GI and GU toxicities were evaluated according to EORTC-RTOG toxicity scores, using a combination of patient questionnaires and physician charts (as was also used in other multicentre trials before[17,22]). The highest toxicity score of the two was taken. Toxicity within 100 days after HDR-BT was considered acute toxicity, and toxicity after 100 days as late toxicity. IPSS scores were assessed and compared to baseline to evaluate the effect of treatment on urinary function and symptoms. In the IPSS analysis, the question on QoL was left out, resulting in scores ranging from 0 to 35. QLQ-PR25 scores were analysed to obtain the net effect on QoL compared to baseline. Raw QLQ-PR25 scores were linearly transformed to values between 0 and 100, where higher scores reflect more symptoms in the urinary and bowel symptoms domain or higher levels of sexual functioning[19]. For all domains changes of ≥10 points were considered clinically relevant[23]. Statistical significance was tested with the Wilcoxon signed-rank test for differences between 12, 24 and 36 months versus baseline.

Logistic (univariate) regression was applied to determine the effect of prognostic factors presented in table 2 on acute toxicity, while Cox regression was applied for the effect on late toxicity. The cut-off points of these factors were based on mean values of our patient population in general. The Kaplan-Meier method was applied to estimate survival probabilities. Two-tailed tests were used and p-values <0.05 were considered significant. Statistical analyses were performed using Stata® 13.1 (StataCorp).

RESULTS

Mean follow-up (FU) was 35 months (2-78), with a median of 25 months. The overall response rate on all sent questionnaires was 90.3%. For the toxicity questionnaires the mean response rate per patient was 89.8%, with a median of 100% (range 33.3-100). The QoL questionnaires had a mean response rate of 90.9% (median 100%, range 14.3-100). From 3 months after treatment on, all questionnaires were sent together to the patients. Therefore, return rates are similar.

Table 7.2 | Variables tested in univariate logistic regression for the effect on acute and late GU and GI toxicity

	Lower limit	Upper limit
Age (year)	≤70	>70
IPSS score before treatment	≤12	>12
Number of needles used	≤17	>17
PTV volume (cm^3)	≤40	>40
Urinary flow before treatment (Qmax; ml/s)	≤15	>15
Urinary residue before treatment (ml)	≤30	>30
Prostate volume before treatment (cm^3)	≤40	>40

Acute toxicity

The chronological incidences of grade ≥2 GU and GI toxicities are depicted in Fig. 1A and B, respectively. The incidence of grade 2 and 3 acute GU toxicity was 19.3% and 12.7%, respectively. The incidence of grade 2 and 3 acute GI toxicity was 21.7% and 4.8%, respectively. Highest incidences of grade 2 and 3 acute toxicity were reported within 4 weeks after treatment. Most patients (61%) had relief from their toxicity within two months after treatment. Eight patients (4.8%) needed an indwelling bladder catheter during the first 7 weeks after HDR-BT for at least 3 weeks (0.75-14 months).

Most reported acute GU complaints were increased night voiding frequency (20.9%; 5-7x/night in 17.3% and >7x/day in 3.6%), urinary incontinence with use of pads (17.9%; daily use of pads in 9.8% and >2x/week use in 8.1%) and increased day voiding frequency (14.9%; 12-16x/day in 10.7% and >16x/day in 4.2%). Increased stool frequency of ≥ 6x/day was the main GI complaint (10.8%).

Late toxicity

The chronological incidences of late grade 2 and grade 3 late toxicities is shown in Fig. 1C and D. During the 60 months FU grade 2 and 3 GU toxicity was registered in 20.3% and 3.1% of patients, respectively. The highest levels of GU toxicities were reported at 12 months, with 19.7% ≥ grade 2. Grade 2 GI toxicity was reported in 8.6% of patients and no grade 3 GI toxicity was reported.

The main causes of late GU toxicity were increased day voiding frequency (16.6%; 12-16x/day in 13.5% and >16x/day in 3.1%), incontinence with daily use of pads (14.8%) and increased night voiding frequency (9.2%; 5-7x/night in 7.7% and >7x/night in 1.2%).

Regarding GI toxicity, increased stool frequency of ≥6x/day was reported by 8.0% and incontinence with daily use of pads 7.4% of patients.

The course of the IPSS score over time is shown in Fig. 2. The mean IPSS score before treatment was

6/35. After treatment the mean score increased to 11/35 at 3 months to a maximum of 12/35 at 36 months. After that the mean score decreased to 10/35 at 48 and 60 months.

Prognostic factors for toxicity

Baseline urinary flow (Qmax) >15ml/s was significantly correlated with lower incidence of acute GU toxicity (p=0.047) with an odds ratio of 0.46 (95% confidence interval (CI) 0.21-1.00) compared to Qmax ≤15ml/s. Baseline IPSS score >12 showed a tendency to correlate with higher incidence of late GU toxicity (p=0.074) with a relative hazard ratio of 2.70 (95% CI 1.01-7.22). Other evaluated factors were statistically not significant for GU nor GI toxicity.

Quality of life assessment

Urinary symptoms score of the QLQ-PR25 increased >10 points compared to baseline (clinically relevant) during the first three years after treatment (p<0.0001), but improved thereafter. Mean bowel symptoms score showed a slight increase compared to baseline. Although statistically significant (p≤0.02), the mean bowel symptoms QoL score increase of three points in three years was not clinically relevant. Mean sexual functioning score decreased to a lowest score at 18 months FU and improved subsequently. Compared to baseline, the differences were both statistically significant (p<0.0001) and clinically relevant. All QLQ-PR25 scores are graphically represented in Fig. 3.

Oncologic outcome and PSA

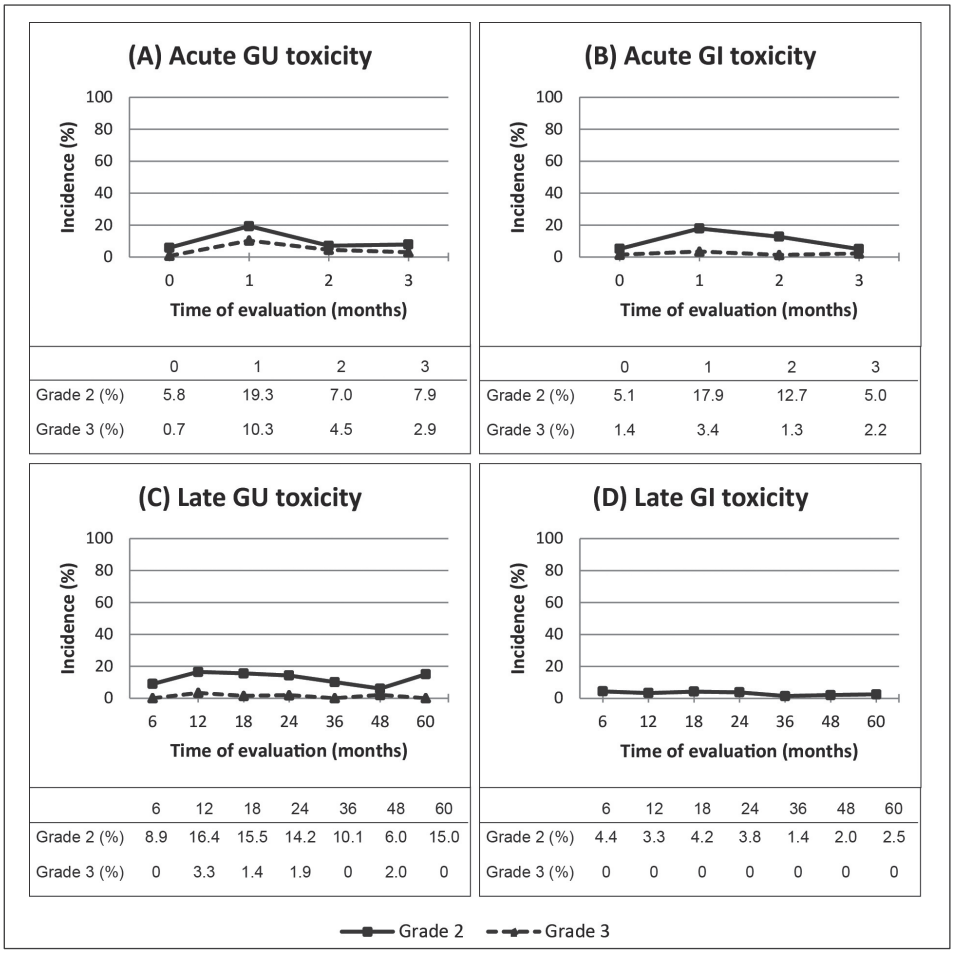
Five patients (3.0%) died after a mean of 30.8 months after HDR-BT (range 17.4-56.2 months). None of the deaths had biochemical progression. The 3- and 5-year OS were 95.8% (95% CI: 89.1-98.4) and 93.6% (95% CI: 84.3-97.5), respectively, and the 5-year CSS was 100%. Four patients developed BF (2.4%). Two of them had low-risk PC and two intermediate-risk PC. FFBF was 99% at 36 months FU and 96% at 60 months.

The mean PSA nadir was 0.74 ng/l (0.01-6.90), which was reached after a mean of 29 months (1-72). A nadir < 1.0 ng/ml was registered in 74.8% of our patients.

One or more PSA bounces were recorded in 48 patients (28.9%). Of these, six patients had two bounces and three patients had three bounces. The mean interval from treatment to the first bounce was 10.8 months (3-29 months). None of the patients with BF showed a PSA bounce.

Discussion

We report on the toxicity and the QoL of HDR-BT as monotherapy in low- and intermediate-risk PC patients. In the acute phase (up to 100 days after treatment), grade ≥2 GU and/or GI toxicity were seen in >25% of our patients. However, at three months after treatment toxicity scores had almost returned to baseline and most acute toxicities resolved within the first 4-8 weeks, a time period that is comparable to a regular EBRT course. In the late phase, the highest incidence of GU toxicity was seen at 12 months after HDR-BT which decreased thereafter. Late GI toxicity was very low without



	0	1	2	3
Grade 2 (%)	5.8	19.3	7.0	7.9
Grade 3 (%)	0.7	10.3	4.5	2.9

	0	1	2	3
Grade 2 (%)	5.1	17.9	12.7	5.0
Grade 3 (%)	1.4	3.4	1.3	2.2

	6	12	18	24	36	48	60
Grade 2 (%)	8.9	16.4	15.5	14.2	10.1	6.0	15.0
Grade 3 (%)	0	3.3	1.4	1.9	0	2.0	0

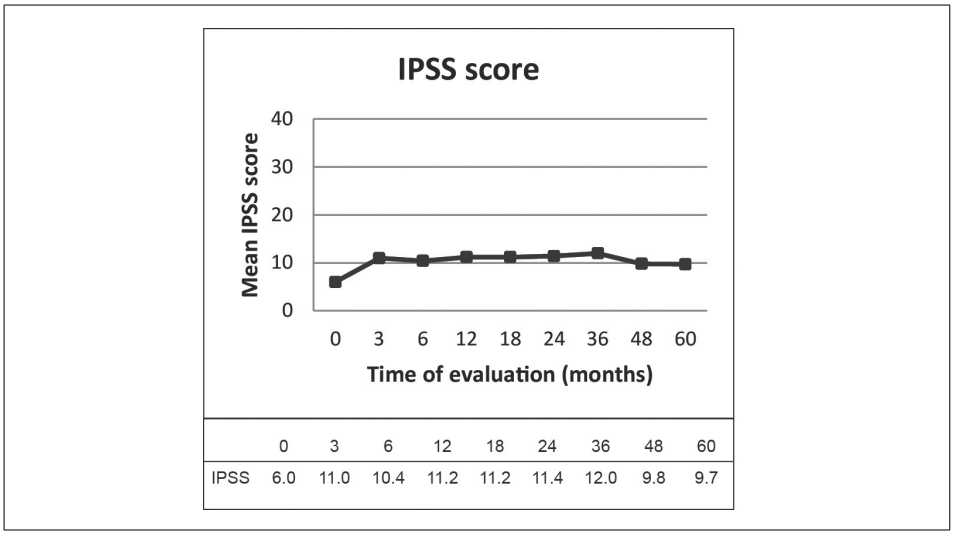
	6	12	18	24	36	48	60
Grade 2 (%)	4.4	3.3	4.2	3.8	1.4	2.0	2.5
Grade 3 (%)	0	0	0	0	0	0	0

Figure 7.1. | Acute GU (A), acute GI (B), late GU (C) and late GI toxicity (D).
During the acute phase (A and B), highest incidences of grade 2 and 3 toxicity are seen in the first 4 weeks, after which the incidence decreases towards baseline. Highest incidences of late toxicities (C and D) are seen up to 18 months.

any grade 3 toxicity. Mean IPSS score after treatment was relatively stable with a very acceptable post treatment mean of 11/35, which reflects a fairly satisfying voiding function. QoL score for urinary symptoms showed a clinically relevant increase in the first three years. Sexual functioning reached a minimum at 18 months after treatment and improved thereafter.

Toxicity

Acute urinary retention for which an indwelling bladder catheter was needed, was registered in eight patients (4.8%). This percentage was high compared with literature and made us change our inclusion policy to exclude patients with IPSS >18/35 during the remainder of the study. After this



	0	3	6	12	18	24	36	48	60
IPSS	6.0	11.0	10.4	11.2	11.2	11.4	12.0	9.8	9.7

Figure 7.2. | Mean IPSS score showing an increase after treatment to a maximum at 36 months after treatment and a decrease thereafter.

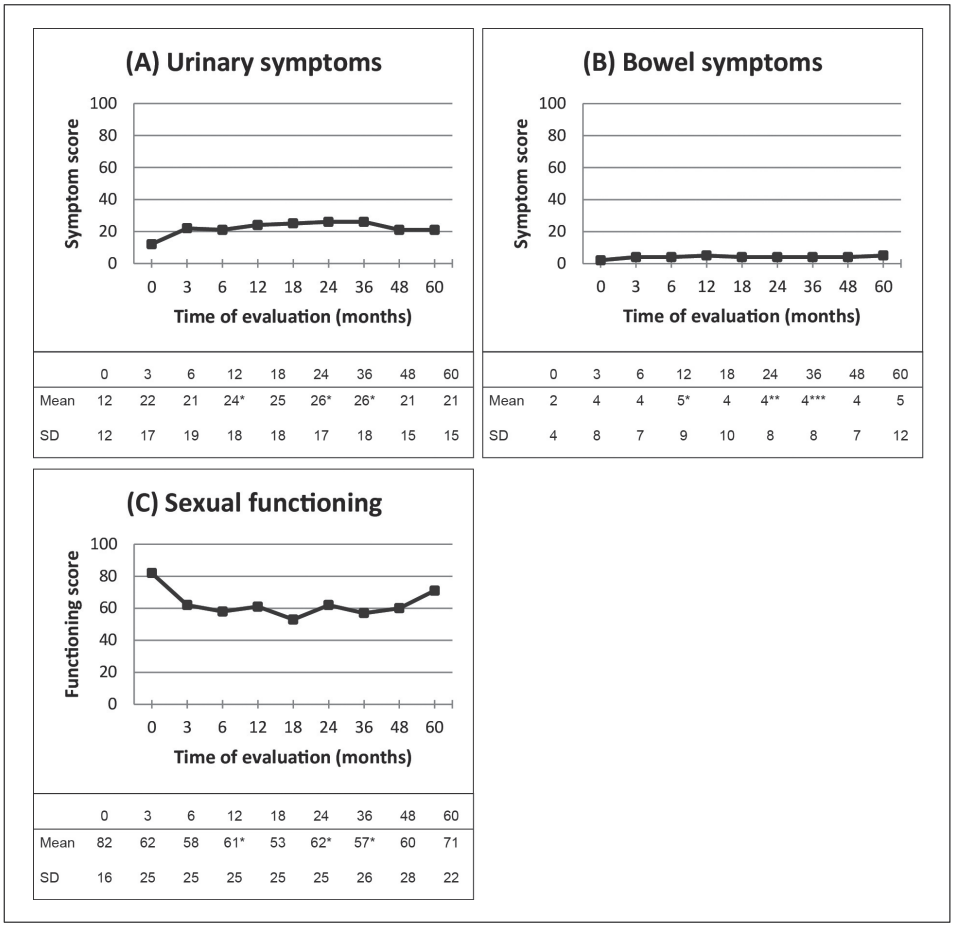
change in 2011, only one patient needed an indwelling bladder catheter due to urinary retention. The mean IPSS score showed minimal changes after treatment, which may be explained by the good tolerance and adaptation of patients to the registered GU toxicity.

Baseline IPSS score >12 showed a tendency to correlate with late GU toxicity with a nearly three times higher risk. This finding is in concordance with the series of Pollack et al. in the hypofractionated EBRT arm of their randomized trial [24]. This confirms the necessity for sharp selection criteria for patients to be treated with hypofractionated regimens. Also, the found relation between good Qmax of >15 ml/s with the lower risk of acute toxicity is important for patient selection to limit acute toxicity. Incorporating both these risk factors in the inclusion criteria, could substantially reduce toxicity rates. We would therefore recommend to include baseline IPSS score ≤12 and Qmax >15 ml/s in the selection criteria for hypofractionated brachytherapy regimens.

GI toxicity was very low, which is consistent with the sharp constraint to limit rectal wall dose to 80% of PD to only 1 cm^3 of the rectum. The monitoring and correction of implant position changes during treatment probably contributed to the low GI toxicity too.

Several reports have shown comparable results with GU grade ≥2 toxicities of 13-18%, and <4% for GI toxicity[2,25,26].

In most of these series toxicity was registered only by the physician and no questionnaires were used. Our results, however, were based on both. As the use of questionnaires has been reported to increase the incidence of reported toxicity compared to physician charts only[22,27], this could explain the slightly higher toxicity percentages in this report compared to literature.



	0	3	6	12	18	24	36	48	60
Mean	12	22	21	24*	25	26*	26*	21	21
SD	12	17	19	18	18	17	18	15	15

	0	3	6	12	18	24	36	48	60
Mean	2	4	4	5*	4	4**	4***	4	5
SD	4	8	7	9	10	8	8	7	12

	0	3	6	12	18	24	36	48	60
Mean	82	62	58	61*	53	62*	57*	60	71
SD	16	25	25	25	25	25	26	28	22

Figure 7.3. | EORTC QLQ-PR25 scores on urinary symptoms (A), bowel symptoms (B) and sexual functioning (C), with all scores on a scale from 0 to 100. For urinary symptoms (A) and bowel symptoms (B), higher scores reflect more symptoms. For sexual functioning (C), higher scores indicate better functioning. In all domains changes ≥10 points are considered clinically relevant. Statistically significant changes from baseline (0 months) are indicated with an * (* = p<0.0001; ** = p=0.0014; *** = p=0.02). SD = standard deviation.

Quality of life assessment

We reported a clinically relevant increase in urinary symptoms scores and clinically relevant decrease in sexual functioning. This is consistent with literature on other PC treatment options. For EBRT with BT boost QLQ-PR25 scores have been described by Conaglen et al. who showed significant changes which did not resolve after two years, especially not the sexual domain[28]. Also after both IMRT and LDR-BT clinically relevant decrease of sexual functioning was described [29,30]. However, in most published series on QoL there was no consistent prospective yearly use of the questionnaires, which results in lack of information on the intervening time points. As we did use

the questionnaires yearly, the course of QoL scores over time could be evaluated and the results showed an improvement in QoL after three years FU.
For both urinary symptoms and sexual functioning, age has been described to be associated with changes in QoL score after treatment. Hampson et al. showed that older men have lower baseline sexual functioning scores, but also show less recovery after treatment[31]. In our study, 85% of our patients were over 60 years of age at the time of HDR-BT and 40% was even older than 70 years. This could have biased the sexual functioning scores towards less favourable results.
Sexual functioning can also be assessed with the International Index of Erectile Function (IIEF) questionnaire[32], which will provide more details and could confirm the results of the QLQ-PR25.

Oncologic outcome and PSA

Our results with only four BF's are comparable to those reported in literature[2,25,33,34]. However most series allowed the concomitant use of ADT, whereas in our series none of the patients used ADT because it could confuse PSA response evaluation.
Besides the absence of ADT, we used one fractionation schedule for all patients, while in most publications on HDR-BT monotherapy different fractionation schedules were used. Demanes et al. described HDR-BT monotherapy in 298 patients with localized PC, in which almost 50% of the patients received a fractionation schedule identical to ours. The 8-year biochemical control rate was 97% [2]. Other series reported a 5-year biochemical control rate of 88-97% using different fractionation schemes [25,35,36].
PSA bounce is a known phenomenon in PC patients treated with radiotherapy and observed in 20-40% of patients[1,21,37,38]. The results of this study are in line with those in literature. We used the definition of Horwitz where an increase of ≥0.4 ng/ml followed by any decrease was considered a bounce[21]. In his multi-institutional pooled data of 4839 patients, 20% experienced a bounce according to this definition. Most reports on bounce are from series in which ADT was used. Reports on PSA bounce after HDR-BT monotherapy in hormone-naïve patients are scarce. In a cohort that used HDR-BT monotherapy in five fractions of 7-7.25 Gy, PSA bounce was reported in 43% of patients using a lower threshold of 0.2 ng/ml and the mean time to bounce was 1.3 years[37]. In a previous series in hormone-naïve patients treated with a combination of EBRT and HDR-BT boost, we observed bounce in 33% of patients and the mean interval to bounce was 22 months[1]. Information on PSA bounce and time to bounce is important to explain PSA results after radiotherapy and to guide subsequent management.

CONCLUSIONS

This hypofractionated regimen using HDR-BT as monotherapy for low- and intermediate-risk PC is feasible and well tolerated, providing high precision in delivery of radiation dose to the prostate. The clinical outcome in this patient population is excellent and toxicity is acceptable with very low and mild GI toxicity. Overall, the toxicity incidence decreased within two months after treatment. QoL decreased in the first three years after treatment for urinary symptoms and sexual functioning.

Sharper selection of patients to these extreme hypofractionated regimen could limit toxicity and improve QoL. The rates of acute and late toxicity could be limited by sharpening the inclusion criteria regarding IPSS score and Qmax at baseline.

Conflicts of interest statement:
None of the authors have any financial disclosures or conflicts of interest pertaining to this research.

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PART 3

Extreme hypofractionation with Stereotactic Body Radiation Therapy using the Cyberknife

Chapter 8

Cyberknife stereotactic radiotherapy as monotherapy for low to intermediate stage prostate cancer: Early experience, feasibility and tolerance.

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ABSTRACT

Purpose

The Cyberknife, a linear accelerator mounted on a robotic device, enables excellent dose conformation to the target and minimizes dose to surrounding normal tissue. It is a very suitable device for performing hypofractionated stereotactic body radiotherapy (SBRT) as monotherapy for low- to intermediate-risk prostate cancer patients. We report our early experience using this technique.

Material & Methods

Between June 2008 and June 2009 ten patients underwent Cyberknife monotherapy as treatment for their prostate cancer (stage ≤ T2b, Gleason score (GS) ≤ 7, initial PSA (iPSA) ≤ 15 ng/ml). The prescribed dose (PD) was 38 Gy in 4 daily fractions of 9.5 Gy. The International Prostate Symptom Score (IPSS), and Radiation Therapy Oncology Group (RTOG) symptom scale were prospectively administered before and at 0.5, 1, 2, 3, 6 and 12 months.

Results

Median age of the patients was 71 years (range 66-76). Three patients had stage T2a and 7 a T1c disease, one patient had GS of 7, and all others had GS of 6. Median follow-up was 5.1 months. Median iPSA was 8.3 ng/ml (range 1.3-13.6 ng/ml). Median PTV volume delineated on CT after matching with the MRI scan was 107 cc (range 42-158cc). The median V100 of the prostate was 95.8% (range 94.8-97.2). The D95 of the prostate was 38.3 Gy (range 38.1-38.8 Gy). The constraints for the bladder, rectum and urethra were well met. The IPSS-scores after 3 months were stable compared to the pre-treatment scores. Urinary and bowel RTOG symptoms were mild and within the expected levels.

Conclusions

This regimen of stereotactic Cyberknife monotherapy for low- to intermediate-risk prostate cancer with excellent dose coverage of the prostate was well tolerated. Ongoing data collection is being performed for further assessment of toxicity and PSA response.

INTRODUCTION

Prostate cancer is the most common cancer in men. About 60%-70% of men presenting with prostate cancer have an organ-confined disease[1]. Treatment options for this group include surgery, external beam radiation therapy, interstitial brachytherapy (Low-Dose-Rate with Iodine seeds or High-Dose-Rate), hormonal therapy, watchful waiting and active surveillance[2]. Drawbacks of external beam radiation are the normal tissue toxicity and the long treatment course (8 weeks). Several publications suggested a radiobiological rationale for hypofractionated radiotherapy course in prostate cancer, due to a low α/β ratio (a linear-quadratic model showing the dose response curve of tumor cells). This α/β ratio is potentially as low as 1.5[3-5]. This suggests that prostate cancer cells are more sensitive to a fraction dose > 3 Gy than the conventional daily fraction of 2 Gy. This was the base for a wide use of hypofractionated radiation regimens with a high fraction dose for early stage prostate cancer[6-7]. These radiation regimens used stereotactic body radiation therapy (SBRT) or High dose rate (HDR) brachytherapy. SBRT dose level treatments (fraction dose higher than 4 Gy), were able to significantly decrease tumor volume and PSA level in mice[8]. The efficacy of the High Dose Rate (HDR) brachytherapy as monotherapy was established, encouraging the wide usage of this accurate hypofractionated radiation delivery mechanism [9-11]. Several clinical series that used hypofractionated external beam regimens have also shown advantage of hypofractionation, with doses per fraction ranging from 2.5 to 3.1 Gy [12-13]. Another clinical series used a linac-based SBRT technique delivering 5 fractions of 6.7 Gy in 5 consecutive days with promising results[14].

Cyberknife is an excellent treatment device for performing hypofractionated accelerated SBRT[15] [figure 1]. Due to its submillimeter accuracy and image guided tracking technology, an optimal dose distribution to the target is possible, creating very steep dose gradients in surrounding normal tissue.

Fuller et al. reported the opportunity to construct Cyberknife SBRT plans that closely resemble HDR brachytherapy dosimetry[16]. In our preparing phase we reached the same conclusions of Fuller after comparing our HDR plans with virtual CK plans.

In this report, we present our preliminary results in a prospectively, well documented ongoing clinical series using a Cyberknife SBRT for localized low to intermediate-risk prostate cancer patients, delivering 38 Gy in 4 daily fractions of 9.5 Gy.

METHODS AND MATERIALS

Patients

From our experience with HDR brachytherapy delivering 38 Gy in 4 fractions within 36 hours, we started a planning study to evaluate the possibility to give an optimal HDR-like dose distribution with the Cyberknife technique. The promising results of this study have lead to a clinical protocol for a pilot study to treat low- to intermediate-risk prostate cancer patients with the Cyberknife

using a hypofractionated regimen. Inclusion and exclusion criteria were equal to the ones we have used for years for our HDR-brachytherapy regimen (table 1), because of our wide experience in this group regarding the tolerance to the dose given, and the excellent PSA response. Our choice was to initiate an alternative treatment for this group of patients eligible for our HDR-brachytherapy protocol who do not want an invasive treatment or were not eligible for surgery. The 10 patients treated were well informed about this new treatment. All other options for the treatment of their prostate cancer were widely discussed with them. Our aim was to reach the same PSA-response but with less toxicity (by avoiding the mechanical damage due to needle insertion in HDR-brachytherapy). From June 2008 through June 2009 10 patients underwent HDR-like Cyberknife monotherapy as primary treatment for their biopsy proven early to moderate-risk prostate cancer, receiving 38 Gy in 4 daily fractions of 9.5 Gy. All patients followed a low-fiber diet and were given laxatives before and during the radiation course in order to minimize the daily variations in intestine filling and its effect on the prostate movement. Bladder catheters were used to keep a constant bladder filling of 100 cc during the computed tomography (CT) and magnetic resonance imaging (MRI) scans (which could also be used as an extra reference for matching these 2 scans), and during the radiation course for the first 8 patients. Ultrasound measurements of bladder filling were registered before, during and after the radiation session, to check the changes in bladder filling during the fraction and to be able to correct it if necessary. The last 2 patients were irradiated without catheter (a catheter was only used during the CT- and MRI-scans). The bladder catheters were not used in these 2 patients after the evaluation of the data of the first 8 patients showing that ultrasound measurement of the bladder filling before and during the radiation was sufficient to keep a constant filling during the radiation fraction making insertion of a catheter not necessary. Four golden fiducials were implanted into the prostate before the treatment for target tracking during irradiation. All patients received a questionnaire at the end of the treatment to evaluate their satisfaction about all steps of this regimen.

Table 8.1. | Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
T1c-T2b	Hormonal therapy
GS ≤ 7	Prostatectomy
PSA ≤ 15	Previous pelvic irradiation
Tumor load > 50% of the biopsy	Prostate volume > 90 cc
International Prostate Symptom Score > 15	Other malignancy (except well treated basal-cell carcinoma of the skin)
WHO-score ≤ 2	Clips previous operations in prostate region

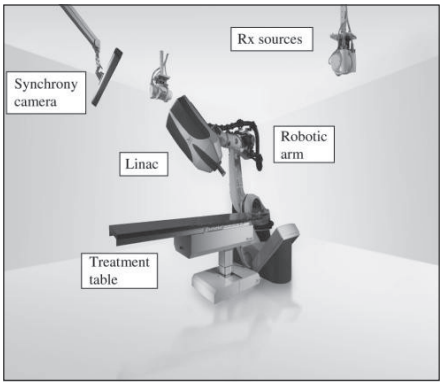

Figure 8.1. | CyberKnife accelerator.

Table 8.2. | Dosimetric Constrains and Objectives

Targets or OAR	Doses(Gy)	Reference dose (%)
Planning target volume: Reference dose	38	100
Anterior rectal wall: Dmax	38	100
Rectal mucosa: Dmax	28.5	75
Rectum: Dose to 1 cc	32.3	85
Bladder: Dose to 1 cc	38	100
Bladder: Dmax	41.8	110
Urethra: Dose to 5% of the volume	45.5	119.7
Urethra: Dose to 10% of the volume	42	110.5
Urethra: Dose to 50% of the volume	40	105.3
Sigmoid / intestine	28.5	75.0
Femur head	24	63.2

Treatment planning

For each patient a CT and MRI-scan of the prostate region was made. Prostate delineation occurs on the prostate MRI, three- dimensionally co-registered with the prostate MRI imaging, plus a 3 mm volume expansion in all directions for the planning target volume (PTV). Both MRI and CT-scans were made on the same day in the same position; a second CT-scan was made several days afterwards to evaluate the variations in rectum filling. The urethra was identified by insertion of a Foley catheter, which was also used as an extra reference point to match MRI- and CT images.

Our set of constraints and objectives for each CK SBRT include the following (table 2): minimal dose coverage of the planning's target volume (PTV) of 95% (at least 95% of the PTV volume has to receive 100% of the PD) with a maximum dose of <150% of the prescribed dose (PD) (57 Gy) allowed. The maximum rectal wall dose (Dmax rectal wall) should be less than 100% of the prescribed dose (38 Gy) and the Dmax rectal mucosa (a solid structure obtained by 3 mm contraction of the rectal wall) has to be less than 75% of the prescribed dose (28.5 Gy). The highest dose to 1 cc of the rectum must be limited to 85% of the prescribed dose (32.5 Gy). A maximum bladder dose of 110% of the prescribed dose (41.8 Gy) is allowed, and the highest dose to 1 cc of the bladder has to be limited to 100% of the prescribed dose. The urethral dose is limited to 120% of the prescribed dose (45.6 Gy). These constraints are the same as used in our HDR brachytherapy protocol[11].

Patient reported Quality of life assessments

The primary outcome of this report is the early and intermediate toxicity score and the early PSA response. Validated quality of life (QoL) questionnaires were prospectively administered before, at baseline, and at 0.5, 1, 2, 3 and 6 months post radiation. PSA analyses were made before treatment, at baseline, and every 3 months post radiation. Functions and complaints were measured using the questionnaires of the International Prostate Symptom Score (IPSS), and Radiation Therapy Oncology Group (RTOG), and European Organization for Research and Treatment of Cancer Prostate Module (EORTC QLQ-PR25): the EORTC QLQ-PR25 data are not reported here. The IPSS [17, 18] for benign prostate hypertrophy calculates the amount of voiding symptom severity: (urinary QoL scale), and urinary bother scale (UB). The urinary QoL is calculated by a summation of 7 items scores (range 0-35), and the UB is a single item scale (range 0-6). Gastrointestinal (GI) and genitourinary (GU) toxicity were graded using the RTOG scales[19-20]; both scales are summarized multi-item scales. Computation of the QoL scales of the questionnaires is made according to the instructions; for missing data the rule of half is used: imputation of the missing items with the mean scale score is accepted if less than half of the items of a scale are missing.

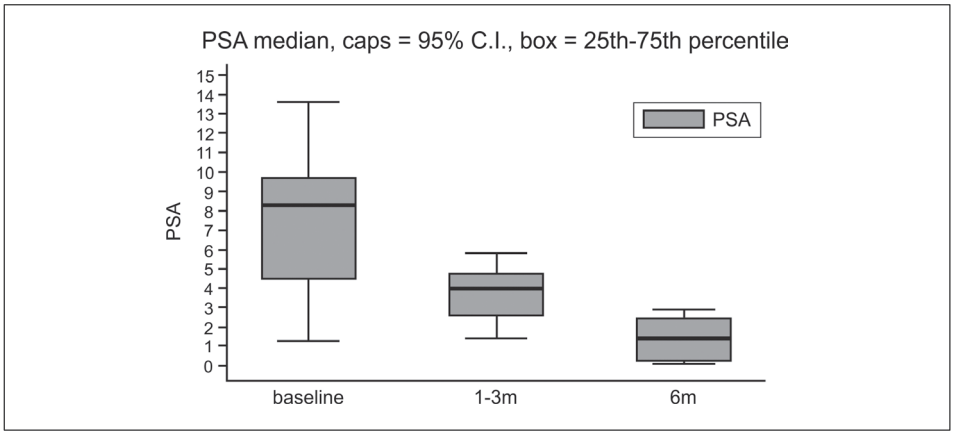

Figure 8.2. | Prostate-specific antigen response.

RESULTS

Median age of patients was 71 years (range 66-76), 3 patients had stage T2a and 7 T1c diseases, one patient had GS of 7, and all others had GS of 6. Median iPSA was 8.3 ng/ml (range 1.3-13.6 ng/ml). Median PTV volume delineated on CT after matching with the MRI scan was 107 cc (range 42-158cc). The median follow up was 5.1 months (range 2-13 months). Figure 2 shows the patterns of PSA response. There is a decline of the mean PSA to 3.8 (SD 2), and 1.6 (SD 2), at three and 6 months follow up respectively. This means a decline of 53% after 3 months and 81% after 6 months.

Table 8.3. | Radiation Therapy Oncology Group Toxicity

	No. of patients (%)				
Radiation Therapy Oncology Group defecation symptoms					
	2 weeks	1 months	2 months	3 months	6 months
Mild	2/10 (20)	1/10 (10)	1/10 (10)	1/9 (11)	0/8 (0)
Moderate	1/10 (10)	0/10 (0)	0/10 (0)	0/9 (0)	0/8 (0)
Severe	0/10 (0)	0/10 (0)	0/10 (0)	0/9 (0)	0/8 (0)
Radiation Therapy Oncology Group urinary symptoms					
Mild	5/10 (50)	4/10 (40)	2/10 (20)	3/9 (33)	2/8 (25)
Moderate	2/10 (20)	2/10 (20)	2/10 (20)	1/9 (11)	1/8 (12)
Severe	0/10 (0)	0/10 (0)	0/10 (0)	0/9 (0)	0/8 (0)

0= no toxicity reported at that moment.

Acute toxicity

The median IPSS-score increased from a baseline of 7 to 10 and 11 after 3 and 6 months respectively. The satisfaction-scores did not change due to this increase and remained stable after 3 and 6 months. Three out of 10 patients treated, are still using alpha–blockers after 2 months follow up, which were usually prescribed during the first 4 weeks after the radiation course. One patient started the treatment with a baseline IPSS of 24/35 and needed a bladder catheter 2 weeks after completion of the radiation course (4 months till now). (This was the second patient that we treated; due to this experience we changed the protocol: IPSS should be < 15). The RTOG rectal toxicity shows a mild toxicity (grade 1-2) in 2/10 patients after 2 weeks, returning to normal after 4 weeks except for one patient where the symptoms were relieved after 3 months. Rectal bleeding was registered in one patient, which was transient, started after 2 weeks and relieving 4 weeks after radiation. The RTOG urinary toxicity shows mild symptoms in 5/10 patients after 2 weeks, and in 2/10 after 2 months, with another peak after 3 months (3/9). Table 3 shows the RTOG toxicity-scores.

Patients Satisfaction

After the treatment each patient received a questionnaire about all steps of preparation and treatment. The response rate was 100%: 80% was very satisfied about the procedures of this treatment regimen, 20% was neutral. The only point that patients were not satisfied about, was the Foley catheter during the irradiation (4/8 50%). The use of catheter was replaced by ultrasound measurements in the protocol.

DISCUSSION

Acute toxicity

In this pilot study, our data using the Cyberknife for early to intermediate stage prostate cancer demonstrate that this course is well tolerated with an acceptable expected percentage of acute urinary, bowel and rectum symptoms. The percentages of urinary and rectal acute toxicities were similar to those reported by patients treated with conventionally fractionated courses[26]. Also from our experience with the same hypofractionated course (4 x 9.5 Gy) in the HDR-brachytherapy setting, we noticed that the Cyberknife hypofractioanted stereotactic radiotherapy course caused even less acute urinary toxicity [21-23]. The mechanical trauma due to needle insertion during the HDR-brachythyerapy may well explain the difference between these 2 modalities (our data will be reported in the future). Until now we have not observed any severe acute urinary or rectal toxicity and the only patient that needed a catheter 2 weeks after his Cyberknife treatment was the one with the worst IPSS-score (24/35) before treatment. He described his urinary QOL as "mostly dissatisfied". This patient also had a prostate volume of 97 cc. Such a huge prostate volume can be a predisposing factor for acute toxicities.[24, 25] These observations led to a modification of our protocol: the prostate volume should be smaller than 90 cc and patients with an IPSS-score >15 were excluded. Fuller et al. reported an acceptable acute urinary and rectal toxicity for his first 10 patients treated with the Cyberknife following the same regimen we used (4 fractions of 9.5 Gy)[16]. King et al. reported that patients treated with a hypofractionated stereotactic course of radiotherapy for localized prostate cancer using 5 fractions of 7.25 Gy had the same urinary and rectal toxicities as experienced with conventionally fractionated courses with an excellent PSA response[26]. In their data, no biochemical failure was reported after a median FU of 33 months. We are aware that 10 patients is a too small population and that our follow-up is too short to draw conclusions. That's why we have to be cautious about any interpretation; however it is very encouraging to reproduce similar results to the few data published about the use of hypofractionated stereotactic radiotherapy for early- to intermediate-stage prostate cancer using the Cyberknife. The results of our treatment evaluating questionnaire suggest that this new method of hypofractionated radiosurgery giving a non-invasive treatment for low to intermediate risk prostate cancer was appreciated by our entire patients because of the short treatment course and the limited acute toxicity. This has yet to be confirmed by long-term results.

PSA response

Our patients show a good and more rapid PSA decline compared to literature regarding conventional external beam radiotherapy[27, 28]. The same response after hypofractionated regimen using the Cyberknife for SBRT has been reported before[16, 26]. A PSA bounce effect and other recurrence phenomena were not experienced in this study, possibly because of the short follow-up period. This encouraging PSA response may support the radiobiologic assumption of a low α/β ratio of prostate cancer. A longer follow-up is needed to confirm this.

CONCLUSIONS

This regimen was well tolerated in our pilot group, with a very acceptable acute toxicity. Expanding our data with more patients and longer follow-up is needed to further evaluate this new method.

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest in connection with this article and they disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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Chapter 9

Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: early results.

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ABSTRACT

Background

There is growing evidence that prostate cancer (PC) cells are more sensitive to high fraction dose in hypofractionation schemes. High-dose-rate (HDR) brachytherapy as monotherapy is established to be a good treatment option for PC using extremely hypofractionated schemes. This hypofractionation can also be achieved with stereotactic body radiotherapy (SBRT). We report results on toxicity, PSA response and quality of life (QoL) in patients treated with SBRT for favorable-risk PC.

Methods

Over the last 4 years, 50 hormone-naïve patients with low- and intermediate-risk PC were treated with SBRT to a total dose of 38 Gy delivered in four daily fractions of 9.5 Gy. An integrated boost to 11 Gy per fraction was applied to the dominant lesion if visible on MRI. Toxicity and QoL were assessed prospectively using validated questionnaires.

Results

Median follow-up was 23 months. The 2-year actuarial biochemical control rate was 100%. Median PSA nadir was 0.6 ng/ml. Median International Prostate Symptoms Score (IPSS) was 9/35 before treatment, with a median increase of 4 at 3 months and remaining stable at 13/35 thereafter. The EORTC/RTOG toxicity scales showed grade 2 and 3 gastrointestinal (GI) acute toxicity in 12% and 2%, respectively. The late grade 2 GI toxicity was 3% during 24 months FU. Genitourinary (GU) grade 2, 3 toxicity was seen in 15%, 8% in the acute phase and 10%, 6% at 24 months, respectively. The urinary, bowel and sexual domains of the EORTC-PR25 scales recovered over time, showing no significant changes at 24 months post-treatment.

Conclusions

SBRT to 38 Gy in 4 daily fractions for low- and intermediate-risk PC patients is feasible with low acute and late genitourinary and gastrointestinal toxicity. Longer follow-up preferably within randomized studies, is required to compare these results with standard fractionation schemes.

Keywords

Clinical outcome; Low- and intermediate-risk; Radiotherapy; Prostate cancer; Stereotactic Body radiation.

BACKGROUND

Although external beam radiotherapy (EBRT) is a highly effective treatment for prostate cancer (PC), the long course of 7-9 weeks can have a negative impact on the patients' quality of life (QoL) and hospital resources. Hypofractionated radiotherapy is used increasingly because of its radiobiological benefits, acceptable toxicity, economic and social advantages.

Several publications suggest a radiobiological rationale for hypofractionated radiotherapy in PC[1,2]. This indicates a high sensitivity of PC to fraction dose but not to the total dose, suggesting the possibility of significant therapeutic benefit from hypofractionation in terms of local control and reduction of normal tissue complication probability for bladder and rectum[1-3].

Brachytherapy is commonly used as treatment for PC because of the possibility to deliver a high dose to the prostate while sparing the surrounding organs at risk (OARs). The use of high-dose-rate brachytherapy (HDR-BT) is proven to be safe and effective and this technique is increasingly used either as a boost after EBRT or as monotherapy.[4, 5] Fuller et al.[6] demonstrated that it is possible to achieve the same dose distributions with SBRT as with HDR-BT. Based on these findings and our HDR-BT experience, we initiated an SBRT protocol to treat low- and intermediate-risk PC patients. This protocol was used for patients who were not eligible for HDR brachytherapy.

METHODS

Patients and planning

Between June 2008 and November 2011, 50 hormone-naïve patients with biopsy-proven low- to intermediate-risk PC underwent SBRT treatment of PC, using the Cyberknife®, in four daily fractions of 9.5 Gy to a total dose of 38 Gy. The first 10 patients were treated in a pilot study with the results reported in 2010[7]. The inclusion criteria can be found in this report as well. These patients were not eligible for HDR brachytherapy because of a large volume of the prostate (> 50 cc), or a combination of limited urine flow/second (Q-max < 10 ml/sec.) and a significant residual volume in the bladder (>100 cc) (37/50, 74%). Other reasons were: transurethral resection of the prostate in the medical history in six patients (12%), pelvic surgery in two (4%) and hip joint prostheses in five (10%). Patients with clinical stages T1c-T2a, Gleason-score 6 and PSA ≤10 ng/ml were defined as low-risk PC. Patients with PSA 10-20 ng/ml and/or T2b-T3a and/or Gleason-score 7, were defined as intermediate-risk PC [8]. In all patients, four gold fiducial seeds were implanted in the prostate through ultrasound-guided trans-perineal pre-loaded needles. One week after fiducial implantation, computed tomography (CT) and magnetic resonance image-scan (MRI) were acquired. T1- and T2-weighted sequences were performed (1.5 Tessla without endorectal coil) to elaborate the treatment plan after placement of a Foley catheter. The Foley catheter was delineated as the urethra. The CT and MRI images were matched on the markers and the Foley catheter. All patients followed a low fiber dietary protocol to minimize intestinal activity. The MultiPlan (version 2.1.5, Accuray) treatment planning system was employed. If the dominant tumor was visible on

the MRI, an integrated boost to the visible tumor was planned up to 11 Gy/fraction which is 120% of the prescribed dose (PD). The planning target volume (PTV) included the prostate expanded by 3 mm in all directions and had to receive ≥ 95% of the PD. Minor violation of the constraints up to 110% of the constraint dose were accepted. Details on treatment planning and applied constraints can be found in an earlier report[7].

PSA measurement, toxicity, and QoL

All patients were followed prospectively. Biochemical failure (BF) was determined according to the Phoenix definition (nadir PSA + 2 ng/ml)[9]. A PSA bounce is defined as a transient rise in the PSA level with a subsequent normalization of the PSA values[10]. GI and GU toxicity was defined and reported using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG-EORTC) scoring criteria[11]. RTOG-EORTC toxicity and the IPSS questionnaires were sent to the patients at the following time points: baseline, at 1, 2, 3, 6, 12 months after treatment, and twice yearly thereafter. International Index of Erectile Function (IIEF) and the EORTC QLQ-PR25 questionnaires were sent at baseline, 6 and 12 months after treatment, and yearly afterward. All patients were seen every 3 months in the first year and subsequently twice yearly.

Statistical analysis

The GI and GU toxicity were evaluated according to the EORTC-RTOG toxicity scores, using a combination of the patients' questionnaires and physicians' charts. The highest-score of toxicity was recorded. Toxicity within 90 days after radiotherapy was considered acute toxicity, and toxicity after 90 days was considered late toxicity. The IPSS, the PR-25 and the IIEF questionnaires were used to asses the GU, GI functional QoL and erectile function. These questionnaires were analyzed to obtain the net effect on function compared to baseline.

RESULTS

Table 1 shows patient characteristics. The MRI staging was: T1c (9, 18%), T2a (22, 44%), T2b (4, 8%), T2c (2, 4%), T3a (13, 26%). The mean dosimetric constraints were mostly met but in 30% a minor violation was accepted.

In 14 patients (28%), a visible dominant tumor was detected on the contrast-enhanced MRI with a mean tumor volume of 1.2 cc (range, 0.46-4.1 cc). In three patients more than one lesion was detected. The mean dose to this visible dominant tumor area defined as gross target volume (GTV) was 47.8 Gy (40.3- 53.8 Gy) which is 120-150% higher than the PD. Capsule invasion on T2-weighted MRI was registered in 13 (26%) patients. The area of invasion was included in the high dose area (> 100 PD) without changing the margin used.

The treatment time was between 60-130 minutes per fraction. There was no difference between patients with or without boost.

Table 9.1. | Patient, tumor and treatment characteristics.

		n	n%	Mean (min.-max.)
Age				68 (48-80)
Fup (months)				23 (9-47)
TNM	T1cN0	30	60%	
	T2aN0	17	34%	
	T2bN0	1	4%	
	T2cN0	1	2%	
Gleason	3+3	41	82%	
	3+4	9	18%	
IPSA				8.2 (1.3-16)
Prostate volume				48 (22-110)
Q-max				13 (4-33)
Residual				87 (0-300)
Risk Group	Low risk	30	60%	
	Intermediate risk	20	40%	
Position positive biopsy	Single sided	31	62%	
	Double sided	19	38%	
Count positive biopsy	1	12	24%	
	2	14	28%	
	3	9	18%	
	4	8	16%	
	5	5	10%	
	7	2	4%	

All patients were alive without biochemical failure at the end of follow-up.

Acute Toxicity

The mean IPSS before treatment was 9/35 and did not increase in the acute phase. The percentages of grade 2 and 3 acute GI toxicity were 12% and 2%, respectively. The incidence of grade 2 and 3 acute GU toxicity was 15% and 8%, respectively.

The most common GU complaints during this phase were urinary urge and increased night voiding frequency. Increased stool frequency was the main GI complaint. One out of the first 10 patients needed an indwelling bladder catheter because of urinary retention 1 week after completion of the radiation course. This patient had a baseline prostate volume of 110 cc; the maximum prostate volume allowed was lowered to 90 cc in our protocol following this incident.

Late toxicity

The chronologic incidence of grade ≥ 2 GI and GU toxicity is shown in Figure 1. The mean IPSS increased to 13/35 at 12 months after treatment, resolved to 10/35 at 24 months (figure 2). The main cause of grade 2 GU toxicity was increased night voiding frequency (> 4x/night). This reached a peak at 12 months in 20% of patients resolving to 10% at 24 months. Other complaints were urge and radiation prostatitis in two patients which were treated by NSAID. The GI toxicity was limited to increased stool frequency and necessity of using adult diapers which resolved in all (2) patients within 6 months.

There were no differences in toxicity between the group patients with MRI-visible tumor receiving a boost in comparison to the others without MRI-visible tumor.

PSA nadir and bounce

The median PSA nadir for patients with a follow-up ≥ 24 months was 0.6 ng/ml (range, 0.1-2 ng/ml) and 1.1 ng/ml for patients with a FU ≥ 12 months (Figure 3). Nadir PSA < 1 was reported in 27 patients (59%). PSA bounce was recorded in seven patients (14%), and the mean interval to the bounce episode was 12 months (range, 4.0-22 months).

QoL

The mean changes in the EORTC-QLQ PR25 score for each domain are shown in Figure 4. The median PR-25 GU score was increased from 13 before the treatment to 25 at 12 months returning to 21 after 2 years (p=0.264). The median bowel symptoms did not change after the treatment. The sexual function was decreased from 75 at the baseline to 66.76 after 2 years (p=*0.145*). The incontinence and bother score was slightly and insignificantly increased in the first 12 months post-treatment, returning to normal afterward. The IIEF results with only 24 months FU are not yet mature for publication[12].

DISCUSSION

SBRT is increasingly used because of the possibility of this image-guided technique to minimize the margins needed for treatment, reducing normal tissue dose and resulting in a lower percentage of toxicity. This, in combination with the possibility of SBRT to deliver a high radiobiological dose in few fractions makes this technique ideal for the treatment of PC. Our fractionation scheme was used in HDR-brachytherapy series with excellent 10-year results[5]. Despite such good results, the invasive character and the need of hospitalization and anesthesia makes brachytherapy less convenient and a labor intensive method.

PSA response

In our patients, an excellent early PSA nadir was achieved. This is comparable to HDR and EBRT series with longer FU[5, 13]. This is important because the PSA nadir could predict long-term BF and distant metastases-free survival[5, 13, 14]. Because of our short FU, the final nadir may not yet have been reached. Other SBRT series have reported lower PSA nadirs after longer follow-up[15, 16]. The

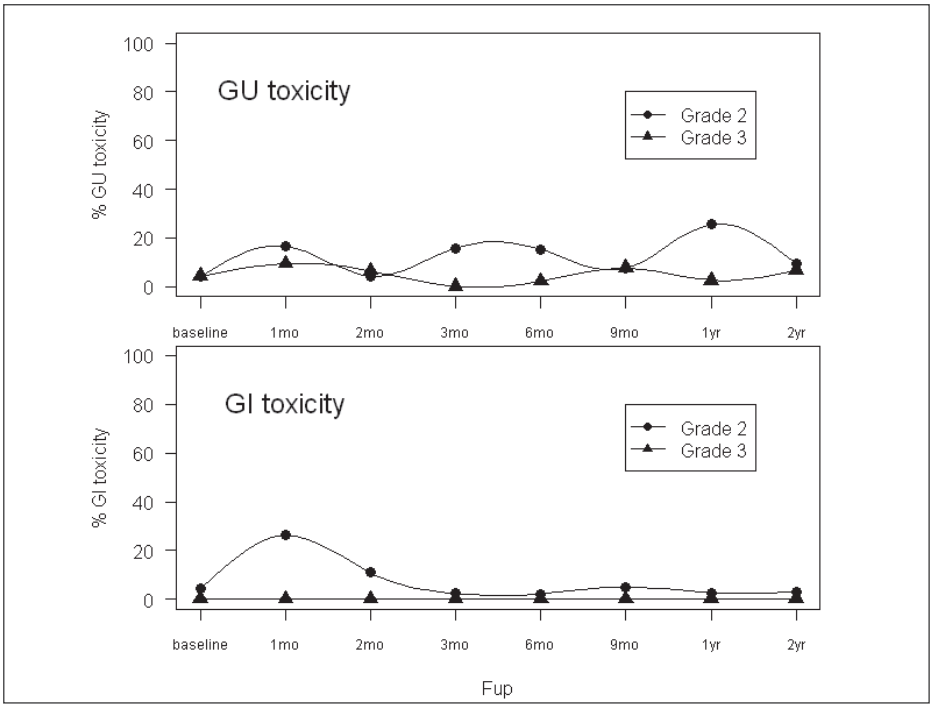

Figure 9.1. | GU and GI
Genitourinary and Gastrointestinal toxicity (%)

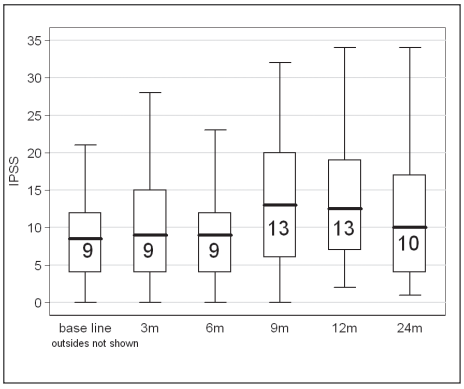

Figure 9.2. | IPSS
International Prostate Symptoms Score (IPSS) changes (mean)

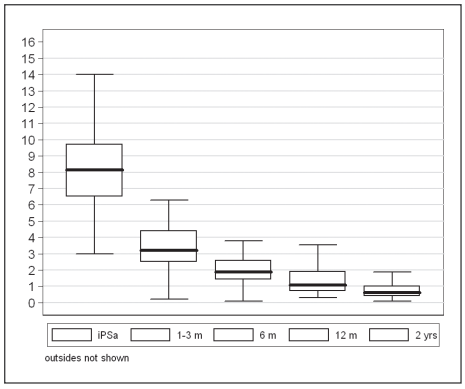

Figure 9.3. | PSA
PSA response (outsides not shown)

Table 9.2. | Toxicity SBRT published series

	N patients	fractionation	FU months	Acute GU Grade 2 %	Acute GU Grade 3 %	Late GU Grade 2 %	Late GU Grade 3 %	Acute GI Grade 2 %	Acute GI Grade 3 %	Late GI Grade 2 %	Late GI Grade 3 %
Townsend 2011 [19]	48	5x7-7,25		10	8			13	0		
King 2012 [16]	67	5x7.25	31			5	3			2	0
Freeman 2011 [15]	41	5x7-7,25	55			7	2.5			0	0
Katz 2010 [17]	304	5x7-7,25	30	4.7	0	2.9	0	3.6	0	2.9	0
Madsen 2010[22]	40	5x6.7	60	20.5	2.5	12.5	2.5	13	0	7.5	0
Jabbari 2012 [20]	38	4x9.5	18	45	0	8	5	5	0	3	0
This report	50	4x9.5	24	15	8	10	6	12	2	3	0

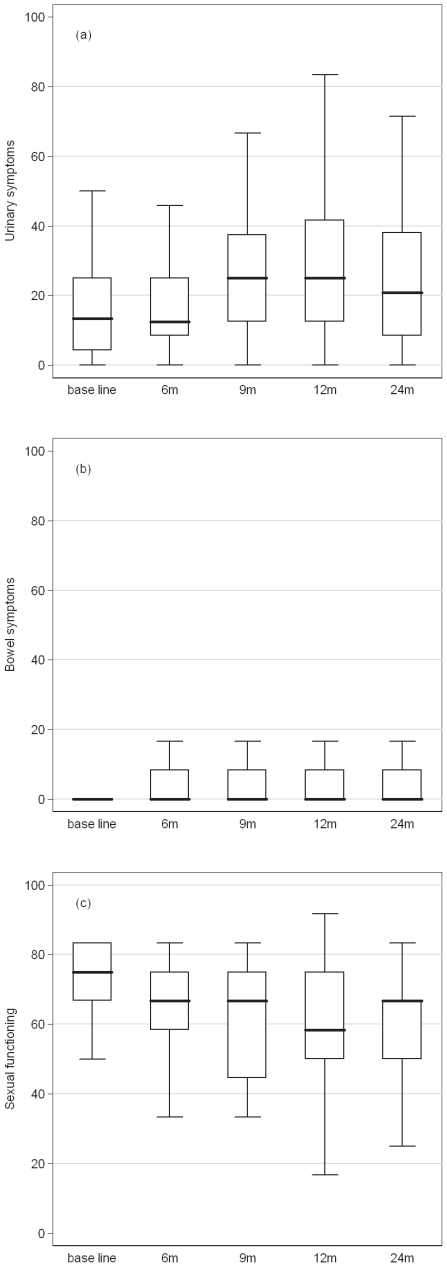

Figure 9.4. | PR-25
EORTC QLQ-PR-25 changes (mean) a: urinary symptoms, b: bowel symptoms, c: sexual function

percentage of patients with bounce phenomena was lower than the percentage in brachytherapy and EBRT series[4, 10]; the short FU may explain this.

Toxicity

The toxicity percentage was conform literature. Although this group had more GU complaints because of their predisposing factors (large volume, bad flow, high IPSS, TURP or abdominal surgery) before the treatment, they did not show more toxicity in the acute neither in the late phase. This suggests that our treatment could reach lower toxicity percentages in patients without these predisposing factors as confirmed in other SBRT series; e.g. Freeman et al[15] reported 7% and 2.5% grade 2 and 3 GU toxicity, respectively with 2.5%, 0% grade 2, 3 GI toxicity, respectively. King et al used the same fractionation scheme (5 fractions) as Freeman[16] and reported 5% and 3.5% for grade 2 and 3 GU late toxicity, respectively. The grade 2 GI toxicity was reported in only 2% of the patients. Several series reported toxicities between 3% and 20%[17-19]. The treatment time was relatively high comparing with conventional series (> 60 minutes). Fowler et al.[20] mentioned the influence of treatment time for high fraction dose on the log cell kill (BED) suggested a decrease in the BED for fraction duration of more than 30 minutes. Although this subject requires more discussion it may play a role in decreasing late toxicity for this regimen. Using our fractionation scheme Jabbari et al.[21] reported a higher grade 2 late toxicity, but a lower grade 3 late toxicity. The number of patients treated with monotherapy was only 20 patients with a shorter follow-up. To date Jabbari published the only series using our HDR like 4x9.5 Gy scheme. The relative higher grade 3 GU toxicity in our series compared to other SBRT series could be explained by patient selection; we treated patients with more complaints and predisposing factors. We also used the combination of questionnaires and physician's charts reporting the highest score from both, which could result in higher scores. The difference in measurement instrument using the EORTC/RTOG criteria[7, 15-17] in our group where some other series used the Common terminology Criteria for adverse events (CTCAE)[18, 19, 21, 22], makes a comparison between series difficult. The different dose levels and fractionation schemes between series could also be a reason for differences in toxicity records. Table 2 shows toxicity of published SBRT series.

QoL

The EORTC-QLQ PR-25 questionnaire is a validated 25-item instrument with four domains (urinary, bowel, sexual, and hormonal), as well as two urinary subscales of incontinence and irritative/bother[23]. Responses are transformed to a scale of 0-100. For functional scales, higher scores represent better QoL. For symptom scales, higher scores indicate more symptoms or more problems. In our cohort, there was a significant increase in the urinary symptoms in the first year which was reversed at 24 months. The bowel symptoms did not increase and remained stable during the 24 months after treatment, which indicates limited bowel toxicity. The sexual function changes were more obvious at 12 months but not significant after 24 months. This has to be confirmed with the results of the IIEF-questionnaires. There is very limited data published regarding sexual function after SBRT for PC. The group of King et al.[12] reported the sexual function during 3 years FU of 32 PC patients having undergone SBRT with 5 fractions of 7.25 Gy. They used the

Expanded Prostate Cancer Index Composite (EPIC)[12], unfortunately with the same limitations as the PR-25 questionnaires to give a detailed analysis about the effect of treatment on the sexual function.

SBRT

Published results of SBRT as monotherapy reported a short FU and many variations in fraction size, total dose, and technique used. Also, the toxicity was measured with different tools making comparison difficult. The group of Freeman and King used five fractions of 7-7.25 Gy first in daily fractions but later in every-other-day fractions[15, 16]. They planned a more homogeneous dose distribution and used less strict constraints. This is in contrast to our technique, which was also used by Jabbari [21] administering four daily fractions of 9.5 Gy, where the dose distribution inside the prostate is heterogeneous up to 40% above the PD. This heterogeneity contributes to a higher dose in the entire prostate which, in the light of the low alpha/beta of the prostate, may contribute to the excellent HDR brachytherapy results. Furthermore, this gives us the opportunity to shape the dose distribution in the critical area of the prostate to give higher dose in the entire peripheral zone of the prostate where almost 65% of prostate tumors were found in prostatectomy specimens[24]. Our constraints for bladder and rectum were the same as that of our HDR brachytherapy, restricting the volumes receiving 80% of the PD to <1.5 cc. Minor violations for the rectum and bladder constraints were accepted (80% PD to 1.5-2 cc) in 30% of the patients, according to the position of the tumor and the patient's anatomical variation, as more than 50% of this group had a prostate volume >50 cc with a prominent transient zone.

King et al. reported more rectal toxicity in the daily treated group versus the every-other-day treated group[16]. In our current cohort, 10 patients were treated with a weekend rest of 2 days between the four fractions due to logistic reasons. These 10 patients did not show a lower rectal or bladder toxicity. We are aware that the limited number of patients and the relatively short FU make it hard to reach a conclusion about this point. The number of patients with a visible tumor on the MRI was low (28%), this could be explained because of the inclusion of more low-risk patients with a Gleason-score of 6 which is not always visible on the MRI. SBRT is an emerging treatment approach for PC and so far has been safe and effective as monotherapy. However trials are warranted addressing many of the raising questions about the optimal fraction dose, total dose, safety constraints and the optimal technique to be used. Recently, the results of a phase 1 study concerning dose escalation and toxicity has been published[25]. Next year we will start a phase III trial to compare this SBRT schemes with the standard EBRT of 39x2 Gy to address outcomes, toxicity and QoL.

CONCLUSIONS

In this cohort where many patients were not suitable for HDR brachytherapy, an SBRT regimen of four daily fractions of 9.5 Gy shows low toxicity in line with the published literature. The PSA response to date is good without any BF. More patients and longer FU is needed to confirm this conclusion.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

SA, PvR, MH, IK, CB have made substantial contributions to conception and design; SA, PvR, WK made substantial contributions to acquisition of data; PvR to the analysis of data; SA, PvR were involved in drafting the document; IK, WK, CB, MH revised the document critically. All authors approved this version to be published.

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Chapter 10

General discussion

INTRODUCTION

Prostate cancer is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide. Details on epidemiology are provided in Chapter 1 of this thesis. There are various treatment options for men with organ-confined prostate cancer. Surgery, fractionated EBRT, brachytherapy (HDR or LDR) and, for selected patients, active surveillance are all considered to be effective methods for treating prostate cancer[5,27,31,48-60]. So far, none of these options has been proven to be superior. In clinical practice all suitable options are discussed with the patient to enable treatment to be tailored to his stage, circumstances and preferences. Physicians wish to give patients the best advice. This is not possible without the support of scientific evidence on efficacy, toxicity and quality of life, preferably obtained from randomized trials. In recent radiotherapy literature, there are radiobiological, technological, economical and practical arguments in favor of hypofractionated treatment. In this thesis, studies are reported that investigate the clinical impact of both moderate and extreme hypofractionation schedules.

MODERATE HYPOFRACTIONATION: WHAT TO DO IN DAILY PRACTICE?

Summary of published randomized phase III trials

Studies on the α/β ratio for prostate cancer, based on different radiotherapy treatment options, have suggested that it may be as low as 1.5 Gy[8,10-13,15,18-20,22]. If correct, this would predict an enhanced therapeutic ratio for hypofractionated schedules compared to the currently applied standard schedules using 1.8-2.0 Gy daily fractions. To date, reports are available of six phase III randomized studies that have investigated moderate hypofractionation[59,61-64]. Two trials were executed prior to the era of dose escalated radiotherapy[29,30]. Lukka et al.[64] reported results of 936 patients with low- and intermediate-risk prostate cancer in a non-inferiority phase III hypofractionation trial, comparing delivery of 33x2 Gy in 45 days with 20x2.625 Gy in 28 days. The use of hormonal therapy (HT) was an exclusion criterion. The study failed to confirm the non-inferiority endpoint for hypofractionation, with a 5-year biochemical relapse free survival (bRFS) of 52.95% for standard fractionation versus 59.95% for the hypofractionation arm. Grade 3 and 4 acute toxicity was higher in the hypofractionation arm (11.4% versus 7% for standard fractionation), while late toxicity was 3.2% in both arms. Yeoh et al.[63] reported on 217 low- and intermediate-risk prostate cancer patients, randomized in a phase III trial. Standard fractionation with 32x2 Gy (6.5 weeks) was compared with hypofractionation, delivering 55 Gy in 20 fractions in 4 weeks. The trial was designed to show a decrease in rectum toxicity for hypofractionation, based on an assumed rectum α/β ratio of 4 Gy. Low- and intermediate-risk patients were included. The use of HT was an exclusion criterion. At 90 months, a significantly higher level of bRFS was observed for hypofractionation: 53% vs 34% for standard fractionation ($p<0.05$). The study failed to demonstrate the hypothesized reduction in rectum toxicity.

Arcangeli et al.[61] published results of a phase III study (180 high risk patients), comparing 40x2 Gy (5 fractions/week) with 20x3.1 Gy (4 fractions/week) with the use of (neo)adjuvant HT for 9

months. The hypotheses of this study were a reduction of late rectal toxicity from 29% for standard fractionation to 12% for hypofractionation, and iso-effectivity with regard to bRFS. However, at 3 years, differences in GI and GU toxicity were statistically not significant; GI and GU toxicity rates were 17% and 14% for hypofractionation vs. 16% and 14% for standard fractionation, respectively. The observed 3-year bRFS for hypofractionation was superior to standard fractionation (87% compared to 79%, p=0.035). This is to date the only randomized study with a high dose standard fractionation arm that shows statistically superior bRFS for the hypofractionation arm. However, the study was not powered for this endpoint and failed to show a reduction in rectum toxicity as a planned endpoint.

Pollack et al.[59] reported on a phase III trial (303 intermediate and high risk patients), comparing delivery of 26 fractions of 2.7 Gy in 5.2 weeks (EQD_{2Gy}= 84.4 Gy for an assumed α/β ratio of 1.5 Gy) with the conventional treatment (38x2 Gy delivered in 8 weeks). The study aimed to demonstrate a reduction in 4-year biochemical relapse with hypofractionation from 30% to 15%. The use of short (4 months) and long term HT (24 months) was allowed according to risk group and the institution's policy. The hypothesized increase in bRFS was not observed: 76.7% vs. 78.6% for standard fractionation (p=0.74). There were no differences in late toxicity.

The CHHiP trial[62] is the largest randomized controlled trial to date, comparing hypofractionated schedules of 60 Gy in 20 fractions (4 weeks) and 57 Gy in 19 fractions (3.8 weeks) with standard fractionation delivering 74 Gy in 37 fractions (7.5 weeks). Based on assumed α/β ratios of 2.5 Gy and 1.5 Gy for the tumor, non-inferiority in 5-year bRFS was hypothesized for the hypofractionated 60 Gy and 57 Gy arms, respectively, without increase in toxicity rates. The trial recruited 3216 patients (in all risk groups excluding patients with T3b or those with PSA > 30 ng/l), and closed in June 2011. All patients received short course HT for 3-6 months. Early data from the trial suggested that moderate hypofractionation is safe and well tolerated[62]. The 2-year patient-reported quality of life outcome was similar in all arms[65]. Recently, the 5-year efficacy and toxicity results were presented, showing non-inferiority of 60 Gy regimens, with comparable late toxicity rates[66].

In the Dutch HYPRO trial, 820 intermediate and high risk patients were randomized to a hypofractionated treatment with 19 fractions of 3.4 Gy delivered in 6.5 weeks (EQD_{2Gy}=90.4 Gy for an assumed α/β ratio of 1.5 Gy) or a standard fractionation with 39 x 2Gy in 8 weeks[26]. Both short term and long term HT was allowed. Primary endpoints were superiority of hypofractionation in outcome (10% increase in 5-year bRFS) and non-inferiority of the hypofractionation arm in acute and late cumulative grade ≥2 GU and GI toxicity[67]. Superiority in 5-year bRFS for hypofractionation was not observed (80% vs. 77% for standard fractionation, p=0.36)[68]. For both acute[67] and late[69] GU and GI toxicity, non-inferiority of hypofractionation could also not be confirmed. Instead, we observed a significant increase in the cumulative incidence of grade ≥ 2 acute GI toxicity in the HF arm (42% vs. 31% for SF, p=0.0015). Moreover, the cumulative incidence of grade ≥3 late GU toxicity was significantly higher in the hypofractionation arm (19%) compared to standard fractionation (13%) (p=0.021). For both acute and late toxicity, several rates of specific toxicity symptoms were significantly increased for the hypofractionation arm.

Given the summary above, it can be concluded that the only randomized study to date that met its endpoint(s) is the CHHiP trial. In the other trials, the hypotheses were not confirmed.

Published hypofractionation series used different fraction doses, different total doses, different overall treatment times, and different toxicity scores. It also included different numbers of patients and reported different follow-up (FU) periods. The policy on the use of HT was always different. All these factors should be carefully taken into consideration when comparing results from various series[59,67,70,71].

Evidence for increased treatment efficacy with hypofractionation

So far, only the randomized trials by Yeoh et al.[63] and Arcangeli et al.[61] have shown an increase in bRFS using hypofractionation. However, none of the two was powered to demonstrate an efficacy increase. Both studies aimed at a decrease in rectum toxicity with hypofractionation and included a low number of patients. Even when assuming an α/β ratio as low as 1.5 Gy, the prostate EQD_{2Gy} values for the hypofractionation arms in the studies by Yeoh et al.[72] and Arcangeli et al.[70] were only 2.8 Gy and 1.5 Gy higher than for the corresponding standard fractionation schedules. In the trials by Lukka et al.[64] and Yeoh et al.[63], low total dose EBRT in the standard arm was used and treatment was delivered with 2D and 3D techniques. Therefore, the results are not representative for the current practice. The increase in bRFS in the trial by Yeoh et al. was only observed after 90 months and was not seen five years after treatment[72]. Apart from the low number of patients in the study by Arcangeli et al.[61], the reported enhanced bRFS for hypofractionation was based on a FU of only three years, despite the fact that all patients were included with a high-risk profile and they received 9 months of (neo)adjuvant HT.

Only the randomized trial by Pollack et al.[59] and the HYPRO trial[26] hypothesized superiority of hypofractionation in treatment outcome, and they both failed to meet this endpoint. In the study by Pollack et al., the assumed enhancement in EQD_{2Gy} of 8.4 Gy resulted in a non-significant reduction in bRFS by 0.9%, instead of the hypothesized 15% improvement.[59] In the HYPRO trial, the assumed increase in EQD_{2Gy} by 12.4 Gy only resulted in a non-significant increase in 5-year bRFS of 3% instead of the hypothesized 10%.[26]

The reported limited gain in the 5-year bRFS for hypofractionation in the HYPRO trial could point at an α/β ratio that is higher than the assumed 1.5 Gy. However, there was a substantial number of patients with long-term use of HT in the trial, which could delay the biochemical recurrences. Therefore, with longer FU, a bRFS advantage for hypofractionation might still be observed.[68]

In the CHHiP trial[62], hypofractionation was non-inferior in bRFS, as hypothesized. For an α/β ratio of 1.5 Gy, the differences in EQD_{2Gy} compared to standard fractionation were -0.8 Gy and +3.1 Gy for the 19x3 Gy and 20x3 Gy schedules, respectively. However, clinical T3b patients (seminal vesicle invasion) and patients with PSA levels > 30 ng/l were excluded and 3-6 months (neo)adjuvant HT was used for all patients. In case the α/β ratio for prostate cancer is 2.5 Gy or higher, the delivered EQD_{2Gy} for the two hypofractionation arms in the CHHiP trial have total doses that are lower than 73 Gy. Given these conditions, it is questionable whether the CHHiP hypofractionation protocols are suited for high-risk patients as included in the HYPRO trial and in the study by Pollack et al. [59]

Recently, an enhanced biological efficacy of delivered radiation dose with reduced overall treatment time (OTT) of 0.3 Gy/day of treatment time reduction was reported for prostate cancer[73]. In the randomized trials by Arcangeli et al.[70], Pollack et al.[59], and Dearnaley et al.[62], OTT was 2.8-4 weeks shorter in the hypofractionation arm, which would suggest an enhanced advantage for hypofractionation by decreasing the OTT. In the study by Arcangeli et al.[61] this could have contributed to the observed gain in bRFS in the hypofractionation arm. However, Pollack et al. did not observe the expected superiority of hypofractionation. Also in the HYPRO trial, OTT for hypofractionation was shorter than for standard fractionation (6.5 vs. 8 weeks). However, superiority of hypofractionation was not observed.[68] In the CHHiP trial, OTT for hypofractionation was 3.5 weeks shorter than for the standard arm. Nevertheless, bRFS was similar, in line with the presumed α/β ratio of 2.5 Gy for both arms.

To date, the above mentioned trials did not show enhanced efficacy with hypofractionation. This indicates the need for caution when applying these schedules to avoid enhanced complication rates for patients.

Late toxicity and the α/β ratio: is 5 Gy low enough?

When the HYPRO trial was designed, the assumed α/β ratio for late toxicity was 5-6 Gy[26,69], based on published papers at that time[8,9]. Here we will discuss this choice in the context of data from recently published clinical trials, including the HYPRO trial.

When assuming an α/β ratio of 5 Gy for late toxicity, the rectum EQD_{2Gy} for hypofractionation in the study by Lukka et al.[64] would be 57.2 Gy compared to 66 Gy for the standard arm, i.e. a reduction of almost 9 Gy for hypofractionation. However, no reduction in late toxicity in the hypofractionation arm was observed. In the study by Yeoh et al.[63,72] an assumed α/β ratio for late rectal toxicity of 5 Gy results in a rectum EQD_{2Gy} of 60.9 Gy for the hypofractionation schedule vs. 64 Gy for standard fractionation. The hypothesized reduced late rectal toxicity was not observed. In the study by Arcangeli et al.[70] the rectal EQD_{2Gy} for hypofractionation was 8.3 Gy lower than the 80 Gy in the standard arm, when assuming an α/β ratio of 5 Gy. Nevertheless, also in this study, no reduction in late rectal toxicity in the hypofractionation arm was observed. For an assumed α/β ratio of 5 Gy, the rectum EQD_{2Gy} for hypofractionation in the study by Pollack et al.[59] was 0.8 Gy lower than for standard fractionation. As expected, no difference in late rectal toxicity was observed. For an α/β ratio of 5 Gy, the rectal EQD_{2Gy} for the 20 and 19 fraction regimens in the CHiPP trial are 68.6 and 65.1 Gy, respectively, compared to 74 Gy for the standard arm. Notwithstanding the calculated reduced rectal dose for hypofractionation, observed toxicity was not different from standard fractionation. In the HYPRO trial, the assumed α/β ratio of 4-6 Gy resulted in highly similar EQD_{2Gy} values in the two treatment arms. However, the hypothesized non-inferiority of hypofractionated treatment regarding cumulative grade ≥ 2 late GI and GU toxicity could not be confirmed. Moreover, cumulative grade ≥3 late GU toxicity was significantly enhanced in the hypofractionation arm. The above analyses seem to point at an α/β ratio for late toxicity substantially lower than 5 Gy, assuming that occurrence of late toxicity is indeed mostly correlated with delivery of high doses, more specifically the maximum tumor dose. Inter-observer variability in rectum delineation is well described[74-76]. There is however

no indication that the variability would be different for hypofractionation compared to standard deviation. Therefore, it is to be expected that delineation uncertainty will not impact the conclusion that the rectum α/β ratio is probably considerably lower than 5 Gy.

Toxicity scoring by physicians and patients

The way of scoring acute and late toxicity and the system used for toxicity registration are important to interpret the toxicity results and to compare results of various trials. In the HYPRO trial, scoring was based on both clinical record forms (CRFs) filled in by physicians and patient's self-assessment questionnaires (PSAQ). It was demonstrated that adding the PSAQ to the analyses resulted in significant increases in reported incidences of toxicity. Underestimation of toxicity by use of CRFs only has been reported previously[77]. Adding PSAQ to the CRFs in reporting toxicity results in more robust toxicity scores and may seriously impact conclusions drawn from studies. In most published hypofractionation trials the source of the toxicity report (only CRFs or both CRFs and PSAQ) is not clearly mentioned. The reported relatively low 2-year late toxicity rates in the CHHiP trial of 4.3% (74 Gy arm), 3.6% (60 Gy arm), 1.4% (57 Gy arm) for GI, and for GU 2.2% in both the 74 Gy and 60 Gy arms and no patients with reported late GU toxicity in the 57 Gy arm, compared to results observed in the HYPRO trial, are most certainly (partially) related to the use of physician scoring only in the former trial.

EXTREME HYPOFRACTIONATION WITH HDR BRACHYTHERAPY

HDR-BT is widely used as boost after EBRT with excellent bRFS and acceptable late toxicity[27,32,78]. Our long term results[79] for an HDR-BT boost of 3 fractions of 6 Gy followed by EBRT (25x1.8 Gy) confirmed the efficacy of this concept (Chapter 4). The prospective character of collecting data and the use of patients' self assessment questionaires, besides the long FU period, make these results robust. The reported 7-years bRFS of 97% is excellent even for low- and intermediate-risk patients, especially in the light of low rates of late GI and GU toxicity. Martinez et al.[27] published their data on HDR-BT boost dose escalation after EBRT, delivering 3 fractions of 6.5 Gy and 2 fractions of 11.5 Gy for intermediate- and high-risk patients[80]. The higher total HDR-BT boost dose, delivered in 2 fractions significantly increased bRFS without increasing toxicity, which in itself supports the theory that the α/β ratio for prostate cancer is lower than that of the surrounding normal structures. These data motivated us making a switch from our regimen of HDR-BT boost dose of 3x6 Gy on top of 25x1.8 Gy EBRT[38] to a boost of 1x13 Gy, combined with 20x2.2 Gy EBRT for intermediate- and high-risk patients in 2007. This regimen is being compared with EBRT, delivering 35x2.2 Gy in a National phase III randomized study.

Increasing belief in a low α/β ratio for prostate cancer encouraged the use of HDR-BT as monotherapy. The rapid fall-off of the dose towards the rectum and bladder may explain the low toxicity reported after HDR-BT. Compared to EBRT series, our 5 year report on HDR-BT monotherapy showed relatively low toxicity, despite toxicity registration using both physician reports and PSAQ[77,81]. The investigated QoL using the EORTC-QLQ PR25 questionaires[42] gave important additional information besides the toxicity and outcome results. The QoL studies

showed the advantage of HDR-BT monotherapy in keeping QoL in the bowel domain stable without deterioration after treatment, and showing the possibility of improvement in sexual function after a decrease in the first year of FU, even in this group of patients with a median age of 70 years. In our report, several factors were associated with acute and late GU toxicity, as the baseline International Prostate Symptoms scores (IPSS) (with acute GU) and the maximum urininary flow (Qmax) (with late toxicity). Other factors have been reported to be associated with toxicity too; Hoskin et al.[82] reported in 2014 on the correlation of the mean PTV with stricture formation after HDR-BT monotherapy and the important correlation of IPSS ≥ 20 with higher incidence of acute GU toxicity. In our study we observed a correlation of acute GU toxicity with an IPSS of ≥ 13. Ghilezan et al.[83] reported the importance of limiting the rectum volume receiving 100% of the prescribed dose because of its correlation with increased incidence of acute and late GI toxicity.

Because HDR-BT monotherapy is mostly given in several fractions using the same plan, the safety of the treatment and the long term biochemical control probabilty is dependent on the accuracy of the dwell positions in all fractions. In our study on the influence of catheter corrections (Chapter 6), we observed no difference in toxicity between patients with displaced catheters that were corrected and the patients where no displacements were registered. This could reflect the safety of our correction protocol. On the other hand, the need for corrections points to the importance of decreasing the number of fractions (preferably 1) and the overall treatment time to limit the hazard of displacement. Other advantages of an HDR-BT regimen of 1-2 fractions delivered in one day are improvements in logistics, patient comfort, shorter/fewer hospital visits and saving resources.

Few authors reported their clinical experiences with 1-2 fraction regimens. Hoskin et al.[84] reported that “Reduction in number of fractions (3 to 2) has not been associated with any reduction in efficacy or increase in toxicity”. Ghilezan et al.[83] reported on a dose escalation study with 2 fractions HDR-BT monotherapy in one day. They used 2x12 Gy for 50 patients and 2x13.5 Gy for another 44 patients with low and intermediate risk prostate cancer. No differences between the two schemes were observed in reported toxicity, but the FU was short (17 months for 2x12 Gy and 9 months for 2x13.5 Gy). Prada et al.[85] reported results of a one fraction HDR-BT regimen of 19 Gy in 40 patients with low- and intermediate-risk prostate cancer and reported after a relatively short FU (range 8-32 months) no acute and late GU ≥ 2 toxicity. In 5 patients grade 1 anal mucositis was reported. Hoskin et al.[84] published in 2014 the results of 3 regimens (2x13 Gy/115 patients, 1x19 Gy/24 patients, 1x20 Gy/26 patients) HDR-BT monotherapy for intermediate- and high-risk prostate cancer patients. Except for the higher percentage urinary retention with the need for a temporarily Foley catheter in the one fraction regimens (7% with 2 fractions vs. 20-33% with a single fraction), he reported no differences between the groups.

At this moment, several trials are open in different institutions investigating HDR-BT monotherapy in 1 or 2 fractions[86]. In general, reported results of HDR-BT monotherapy are excellent compared to EBRT results. However, as reported in the review paper by Demanes et al.[87]: “There is no consensus on the optimal dose and fractionation for HDR-BT as monotherapy”. There is still a need to determine the optimal dose and number of fractions in randomized trials.

EXTREME HYPOFRACTIONATION WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT).

In this section, the literature on prostate SBRT is discussed, including our contribution (Chapters 8 and 9).

Reported toxicity for prostate SBRT

Freeman et al. reported their 5-year experience of treating 41 low-risk prostate cancer patients with 35-36.25 Gy in 5 fractions[88]. None received hormonal therapy. One patient experienced acute grade 3 GU toxicity, but there was no acute grade 3 or higher GI toxicity. No grade 2 or higher GI toxicity was reported, while late grade 2 and 3 GU toxicity was observed in 7% and 2.5% of cases, respectively. Katz et al. reported the results of 304 men with low-risk prostate cancer treated in 5 fractions of 7-7.25 Gy with the Cyberknife[89]. Acute grade 2 GU and GI toxicity rates were 4.7% and 3.6%, respectively. Late GU and GI toxicity was experienced by 3% of patients. Neither acute nor late grade 3 GI toxicity was reported. In patients with more than 12 months FU, there was 1 patient with grade 3 GU toxicity. Friedland et al. treated 112 prostate cancer patients with the CyberKnife in 5 fractions of 7 Gy[90]. Patients' GI and GU symptom scores had returned to baseline at 4 months after treatment, only 1 patient developed a rectal bleeding (grade 3). King et al.[91] treated 67 low-risk prostate cancer patients in 5 fractions of 7.25 Gy using CyberKnife. Late grade 2 and 3 GU toxicity was reported in 5% and 3.5% of patients, respectively. Late GI toxicity occurred in 2% of cases with no grade 3 GI toxicity. Importantly, King et al. [92]reported lower toxicity rates for those patients receiving alternate day treatment compared with an uninterrupted daily regimen, but the number of patients was too small to draw definitive conclusions.

Several papers have reported on profound hypofractionation treatment with a conventional linac. Madsen et al. used 5 fractions of 6.7 Gy to treat 40 patients[93]. With a median FU of 42 months, the incidences of acute grade ≥ 2 GU and GI toxicity were 23% and 13%, respectively. Late grade 2 GU toxicity was observed in 20% of patients and late grade 2 GI toxicity in 7.5%. No late grade 3 toxicity was reported. Tang et al. reported on 30 low-risk prostate cancer patients treated on a conventional linac, receiving 5 fractions of 7 Gy over 29 days[94]. With a FU of only 6 months, the acute toxicity was not higher than for standard fractionation.

All the above mentioned studies were performed with conventional SBRT dose distributions, i.e. no attempt to mimic HDR-BT. Jabbari et al. [9] reported results of only 20 patients treated with a HDR-like regimen using a fractionation schedule of 4x9.5 Gy. They observed grade 2 acute GU and GI toxicity rates of 45% and 5%, respectively. With a FU of only 18 months, the incidences of late GU and GI toxicity were 5% and 3%, respectively. The very limited number of patients and short FU make it difficult to compare these results with other data.

We published our 2-year toxicity results for 50 low- and intermediate-risk prostate cancer patients, treated with HDR-like dose distributions delivering 38 Gy in 4 fractions using the CyberKnife. (Chapter 9)[96]. Observed acute grade 2-3 GU and GI toxicity rates were 23% and 14%, respectively. The late grade 2 and 3 GU toxicity rates were 10% and 6%, respectively, while only 3% of our patients experienced

a grade 2 late GI toxicity (no grade 3 late GI toxicity was reported). Despite the use in our study of PSAQ for toxicity reporting on top of physician scoring and the delivery of HDR-like dose distributions, toxicity rates were very acceptable and comparable with other series. However, the number of patients in all above mentioned single institutional series was small with relatively short FU.

Reported outcome for prostate SBRT

Published series for prostate SBRT report excellent bRFS, but with relatively short FU periods[88,89,92]. Data on bRFS of patients treated with SBRT in 8 institutions were published in 2013[97]. For the 1100 patients (58% low-risk, 30% intermediate-risk and 11% high-risk), the 5-year bRFS was 93%, but only 135 had a follow-up of 5 years or more. Katz et al.[89] reported outcome for 304 patients (70% low-risk, 26% intermediate-risk and 4% high-risk) with a failure rate of 1.3%. The follow up was short (range 17-30 months). Other series used the same fractionation schedule as Katz et al. and reported 93-94% 4-year bRFS for low-risk patients[88,97]. Madson et al.[93] reported a 90% 4-year bRFS for low-risk patients for a relatively low total dose of 33.5 Gy in 5 fractions. For our series (60% low-risk, and 40% intermediate-risk patients), we have reported an encouraging 100% bRFS. However, the median FU was only 2 years (Chapter 9), and longer FU is needed for definitive conclusions.

Quality of Life studies

As the majority of patients treated with SBRT is low-risk with an excellent bRFS and long survival, it is particularly important to also investigate quality of life (QoL). Unfortunately QoL data for prostate SBRT are scarce. A pooled QoL analysis[98] was performed for treatments with 4-5 fractions and a median total dose of 36.25 Gy, including data of 864 prostate cancer patients (14% received hormonal therapy). The mean FU was 3 years. Modest declines in the urinary and bowel domains of the used Expanded Prostate Cancer Index Composite (EPIC) were reported that were followed by a recovery after around 6 months. The sexual function declined in the first 9 months after treatment. In our QoL report (Chapter 9) the QLQ-PR25 questionnaires were used, which were comparable to the above mentioned EPIC scores. The patterns of recovery were comparable to the results of the pooled analysis, with a significant decline in the GU domain at 9-12 months and recovery at 24 months. Changes in the bowel domain were minimal and showed no deterioration in bowel symptoms during the first 2 years after treatment. The sexual function part of our QoL analyses shows the same pattern as the pooled data results.

Although thousands of prostate cancer patients have been treated with profound SBRT hypofractionation, there are as yet no randomized studies that have compared this approach with standard fractionation. In the UK, an on-going randomized trial is investigating this approach[99].

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

Interpretation of study results and comparison of studies on moderate hypofractionation with EBRT need great caution because of differences in inclusion criteria, delivered total and fraction dose, overall treatment time, FU period, system for toxicity registration, and the use of HT. Nonetheless,

the current literature appears inconclusive on the added value of moderate hypofractionation with EBRT. In the study by Pollack et al.[59] and the HYPRO trial[26,68,69], hypothesized large increases in bRFS were not observed, posing questions on the widely assumed low α/β-ratio for prostate cancer. In the CHHiP trial[66], the expected non-inferiority of hypofractionation was indeed demonstrated, however, applied tumor doses were possibly on the low side, especially for high-risk patients. Compared to the study by Pollack et al.[59] and the CHHiP trial, the fraction dose in the HYPRO trial was 0.7-0.4 Gy higher. This may have contributed to the failure to prove the hypothesized non-inferiority regarding acute and late GU and GI toxicity in the latter trial. On the other hand, multivariate analyses hinted at a possibility of selecting patients for the hypofractionated regimen. Clearly, there is a need for future studies on the optimal fractionation regimen for prostate cancer treatment with moderate hypofractionation.

The use of HDR-BT as boost in combination with EBRT is proven to be effective, but the impact of this regimen on toxicity warrants further investigation in randomized trials.

HDR-BT (monotherapy) and SBRT are promising, both regarding reported outcome and toxicity. However, the series are often small, FU is short, and evaluation in randomized studies has not yet been performed. There is a clear need for more data to fully appreciate the value of extreme fractionated regimens. In the clinical studies described in this thesis, toxicity reporting was based both on scoring by physicians and by the use of PSAQ. It was demonstrated that the addition of PSAQ can have a dramatic impact on reported toxicity. For future trials the use of PSAQ is highly recommended, as it gives a more complete picture of experienced toxicity. Addition of QoL studies can further enrich our knowledge on treatment related morbidity as experienced by patients.

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SUMMARY

With an incidence of 11.000 new patients, prostate cancer is responsible for more than 2500 deaths each year in the Netherlands. External-beam radiotherapy (EBRT), High-Dose-Rate (HDR) and Low-Dose-Rate (LDR) brachytherapy (BT) are common treatment options for organ confined prostate cancer. In recent years there has been a lot of attention for hypofractionated (daily dose > 2 Gy) radiotherapy in prostate cancer, mainly due to the assumed low α/β ratio that determines the sensitivity of prostate cancer cells for hypofractionated radiotherapy.

The purpose of this thesis was to investigate the feasibility of moderate and extreme hypofractionated radiotherapy for prostate cancer with emphasis on treatment induced morbidity, scored by both treating physicians and patients using patient self-assessment questionnaires (PSAQ). Moderately hypofractionated treatments were delivered with a conventional linac (results reported in Chapters 2 and 3), while extreme hypofractionation was delivered with HDR brachytherapy (results reported in Chapters 4-7) or a robotic Cyberknife unit (results reported in Chapters 8 and 9).

In Chapters 2 and 3, results on acute and late toxicity are reported as observed in the national HYPRO randomized phase III trial in which patients with intermediate- or high-risk prostate cancer were randomly assigned to standard fractionation (SF) given 39 fractions of 2 Gy in eight weeks or hypofractionation (HF) given in 19 fractions of 3.4 Gy in 6.5 weeks. Patients were stratified to center and risk group. Per protocol, non-inferiority of HF for cumulative grade ≥ 2 acute and late GU and GI toxicity were primary endpoints of the trial.

In Chapter 2, we report on the acute toxicity in the HYPRO trial with 391 and 403 evaluable patients in the SF and HF arm, respectively. The analyses were based on 4 measurements per patient; at baseline, twice during EBRT, and 3 months after completion of EBRT. The hypothesized non-inferiority for acute GU and acute GI toxicity could not be demonstrated. The cumulative incidence of grade ≥2 acute GI toxicity was higher for HF (42% vs. 31.2%, p=0·0015). Three months after completion of treatment, there was no difference between the arms in grade ≥ 2 acute GI toxicity. The use of the PSAQ on top of physician scoring largely increased reported toxicity incidences.

In Chapter 3, we report on the late toxicity in the HYPRO trial, including 387 SF and 395 HF evaluable patients with a median follow up of 60 months. Five years after treatment, non-inferiority of HF for late GU and GI toxicity was not demonstrated. Grade ≥3 late GU toxicity was significantly higher for HF (19% vs. 13% SF, p=0·021). The presence of acute GU toxicity, age > 70 years and use of hormonal therapy were associated with an increased rate of late GU toxicity, while acute GI toxicity and treatment of seminal vesicles resulted in increased late GI toxicity. Again, addition of PSAQ resulted in substantial increases in reported toxicity.

Chapter 4 reports on the toxicity and long-term outcome of 264 low- and intermediate- risk prostate cancer patients treated with a hypofractionated HDR-BT boost of 3x6 Gy + EBRT in 25

fractions of 1.8 Gy. Even with toxicity scoring by both physicians and patients, the late toxicity rates were lower than published for EBRT only; especially the late grade ≥2 GI with an average of 3% was very low. With a 7-year bRFS of 97% this regimen demonstrated an excellent outcome.

Chapter 5 reports on the influence of in-between-fraction catheter displacement in HDR brachytherapy monotherapy, delivering 4 fractions of 9.5 Gy, on target coverage and organ at risk doses. This study confirmed the need to check the catheter positioning at the start of each fraction. Corrections were found necessary when displacements exceeded 3 mm.

In Chapter 6, we reported on the consequences of performing corrections in case of catheter displacements for reported acute and late toxicity in the HDR-BT monotherapy regimen of 4 fractions of 9.5 Gy. No differences in toxicity were found between the group of patients that needed corrections for proper treatment and the group of patients that did not need corrections. Neither the extent of displacements, or the number of displacements had an influence on acute and late toxicity. The applied protocol for corrections may have prevented occurrence of excessive toxicity.

Chapter 7 reports the long-term outcome, toxicity and QoL for an HDR-BT monotherapy regimen of 4x9.5 Gy in 166 patients. Acute toxicity was comparable with other series and most toxicity was resolved within 2 months. Late toxicity rates (GU grade ≥2 of 20%, GI grade ≥2 of 3%) were low and comparable to other radiotherapy treatment options. QoL scores, using the EORTC-QLQ PR25 questionnaires, showed no changes for GI symptoms, and no relevant clinical changes (>10 points) for urinary symptoms and sexual function. With a value of 97%, the 5-year bRFS was excellent.

In Chapter 8 we describe the clinical feasibility of an HDR-like SBRT regimen, consisting of 4 daily fractions of 9.5 Gy delivered with the robotic Cyberknife treatment unit. Low- and intermediate-risk patients were included in the study. The imposed constraints for PTV and OARs were all feasible in the first 10 patients investigated. The acute toxicity was acceptable (3/10 presented with grade 2 GU acute toxicity and 2/10 grade 1-2 acute GI toxicity) and comparable to other radiotherapy options.

Chapter 9 reports on the toxicity and QoL in 50 low- and intermediate-risk prostate cancer patients treated with the Cyberknife using 4 daily fractions of 9.5 Gy. With a median follow-up of 2 years, the bRFS was 100%. The IPSS score for GU toxicity showed a temporary light increase from 9/35 to 13/35 in the 2 years follow-up period. Acute grade ≥ 2 toxicity rates (14% GI acute toxicity and 23% acute GU toxicity) were comparable to those of HDR-BT monotherapy, and grade 2 late GI toxicity was low (3%) with no grade 3 registered in the 2 years after treatment. Late grade ≥ 2 GU toxicity (16%) was acceptable and comparable to other series.

NEDERLANDSE SAMENVATTING

Met een incidentie van 11.000 nieuwe patiënten in Nederland is prostaatkanker verantwoordelijk voor meer dan 2500 doden per jaar. Als de kanker nog tot de prostaat beperkt is, is radiotherapie een belangrijke behandeloptie. De mogelijkheden zijn: uitwendige bestraling ('external beam radiotherapy', EBRT) en inwendige bestraling (brachytherapie), waarbij zowel een laag dosistempo ('low dose rate', LDR) als een hoog dosistempo ('high dose rate', HDR) gebruikt kan worden. In de afgelopen jaren is er veel aandacht geweest voor het hypofractioneren van de bestraling van prostaatkanker, wat voornamelijk samenhangt met de veronderstelde lage α/β ratio.

Het doel van dit proefschrift was het onderzoeken van de haalbaarheid van matig en extreem hypogefractioneerde radiotherapie voor prostaatkanker. Hierbij werd vooral gekeken naar de bijwerkingen (toxiciteit) van de behandeling, zoals die werden gescoord door de behandelend artsen en door de patiënten zelf, middels gevalideerde vragenlijsten ('patient self-assessment quesionnaires', PSAQ). Matig hypogefractioneerde bestralingen werden uitgevoerd met een conventionele versneller (Hoofdstukken 2 en 3), terwijl extreem hypogefractioneerde bestralingen werden uitgevoerd met HDR brachytherapie (Hoofdstukken 4-7), of een robotversneller, de Cyberknife (Hoofdstukken 8 en 9).

In de hoofdstukken 2 en 3 worden de acute en late urogenitale en gastro-intestinale toxiciteit van de bestraling gerapporteerd, zoals waargenomen in de nationale HYPRO studie. In deze gerandomiseerde fase III studie werden patiënten met matig- of hoog-risico prostaatkanker willekeurig ingedeeld voor behandeling met de standaard fractionering (SF) van 39 fracties van 2 Gy in 8 weken of de hypogefractioneerde (HF) behandeling van 19 fracties van 3.4 Gy in 6½ week. Patiënten werden gestratificeerd naar deelnemend centrum en risicogroep. Ten aanzien van toxiciteit waren de primaire eindpunten van deze studie de non-inferioriteit van HF voor de cumulatieve incidentie van graad ≥ 2 acute en late urogenitale en gastro-intestinale bijwerkingen.

In hoofdstuk 2 wordt gerapporteerd over de acute toxiciteit in de HYPRO studie voor 391 en 403 patiënten die respectievelijk behandeld zijn met SF en HF. De analyses zijn gebaseerd op 4 meetmomenten per patiënt: voorafgaand aan de behandeling, twee keer tijdens de behandeling en 3 maanden na afronding van de bestraling. De hypothese van non-inferioriteit voor acute urogenitale en gastro-intestinale toxiciteit kon niet worden bevestigd. De cumulatieve incidentie van graad ≥ 2 acute gastro-intestinale toxiciteit was hoger voor HF (42% vs. 31.2%, p=0.0015). Drie maanden na afronding van de behandeling was er geen verschil in graad ≥ 2 acute gastro-intestinale toxiciteit. Het gebruik van PSAQ in aanvulling op de scores van de behandelend artsen zorgde voor een sterke verhoging van de gerapporteerde toxiciteit incidentie.

In hoofdstuk 3 wordt de late toxiciteit in de HYPRO studie gerapporteerd voor 387 patiënten in de SF arm en 395 patiënten in de HF arm. De mediane 'follow-up' was 60 maanden. Vijf jaar na de behandeling kon de non-inferioriteit van HF voor late urogenitale en gastro-intestinale toxiciteit niet worden aangetoond. Incidentie van graad ≥ 3 urogenitale toxiciteit was significant hoger in de HF arm (19% vs. 13%, p=0.021). De aanwezigheid van acute urogenitale toxiciteit, leeftijd > 70

jaar en het gebruik van hormonale therapie waren gerelateerd aan een verhoogde kans op late urogenitale toxiciteit. De kans op late gastro-intestinale toxiciteit was verhoogd bij het optreden van acute gastro-intestinale toxiciteit en bij behandeling van de zaadblaasjes. Ook voor late schade resulteerde het toevoegen van de PSAQ in substantiële verhogingen van de gerapporteerde toxiciteit incidenties.

In hoofdstuk 4 worden de toxiciteit en lange-termijn uitkomsten beschreven voor 264 laag- en matig-risico prostaatkankerpatiënten die behandeld zijn met een HDR boost van 3x6 Gy, gecombineerd met 25 fracties EBRT van 1.8 Gy. Zelfs met de gecombineerde toxiciteitsscore van zowel arts als patiënt was de incidentie van late toxiciteit lager dan voor gepubliceerde studies met EBRT alleen. Vooral de graad ≥ 2 late gastro-intestinale toxiciteit was met een gemiddelde incidentie van 3% erg laag. Met een 7-jaar recidiefvrije overleving van 97% is aangetoond dat dit behandelschema een uitstekende tumorcontrole geeft.

In hoofdstuk 5 wordt de invloed onderzocht van katheterverschuivingen tussen de fracties op de dosisverdeling in de prostaat en de dosis in de risico-organen in HDR brachytherapie. Dit onderzoek bevestigde dat het noodzakelijk is om de katheterpositionering te controleren vóór de start van elke fractie. Correctie van verschuivingen > 3mm wordt noodzakelijk geacht.

Het effect van het corrigeren van katheterverschuivingen > 3mm op acute en late toxiciteit in HDR brachytherapie als monotherapie met 4 fracties van 9.5 Gy wordt beschreven in Hoofdstuk 6. Er werden geen verschillen gevonden tussen de groep patiënten bij wie correcties nodig waren en de groep waarbij dit niet nodig was. Noch de grootte van de verschuivingscorrectie noch het aantal correcties hadden invloed op de acute en late toxiciteit. Het toegepaste protocol voor het corrigeren van katheterverschuivingen heeft waarschijnlijk bijgedragen aan het voorkomen van ernstige toxiciteit.

In hoofdstuk 7 wordt gerapporteerd over de lange-termijn uitkomsten, toxiciteit en kwaliteit van leven (QoL) van 166 patiënten die behandeld zijn met HDR brachytherapie als monotherapie met 4x9.5 Gy. De acute toxiciteit was vergelijkbaar met andere studies en het merendeel van de toxiciteit verdween weer binnen 2 maanden. Late toxiciteit incidenties (20% graad ≥ 2 urogenitaal, 3% graad ≥2 gastro-intestinaal) waren laag en vergelijkbaar met andere bestralingsopties. QoL scores, verkregen met de EORTC-QLQ PR25 vragenlijst, toonden voor gastro-intestinale symptomen geen veranderingen ten opzichte van vóór de behandeling en voor urogenitale symptomen en seksueel functioneren geen klinisch relevante veranderingen (> 10 punten). De 5-jaar recidiefvrije overleving was met 96% uitstekend.

In hoofdstuk 8 wordt een onderzoek beschreven naar de klinische uitvoerbaarheid van extreem hypogefractioneerde bestralingen met de Cyberknife robotversneller. Uitgangspunt was een bestraling met 4 dagelijkse fracties van 9.5 Gy, afgegeven met een dosisverdeling die HDR brachtherapie behandeling nabootst. Laag- en matig-risico patiënten werden in deze studie geïncludeerd. De opgelegde dosisbeperkingen (‘constraints’) voor de tumor en de risico-organen werden allemaal gehaald in de eerste 10 onderzochte patiënten. De acute toxiciteit was acceptabel

(3 patiënten hadden graad 2 urogenitale toxiciteit en 2 hadden graad 1-2 gastro-intestinale toxiciteit) en vergelijkbaar met andere bestralingsopties.

In hoofdstuk 9 worden de toxiciteit en QoL beschreven voor 50 laag- en matig-risico prostaatkankerpatiënten die behandeld werden met de Cyberknife met 4 dagelijkse fracties van 9.5 Gy. Met een mediane follow-up van 2 jaar was de recidiefvrije overleving 100%. De IPSS score voor urogenitale toxiciteit liet een tijdelijke, lichte stijging zien van 9/35 naar 13/35 in de 2 jaar 'follow-up' periode. Acute graad ≥ 2 toxiciteit incidenties (14% gastro-intestinaal en 23% urogenitaal) waren vergelijkbaar met die van HDR brachytherapie. In de eerste 2 jaar na behandeling was de incidentie van graad 2 late gastro-intestinale toxiciteit laag (3%), terwijl er geen graad 3 toxiciteit werd geregistreerd. Late graad ≥ 2 urogenitale toxiciteit (16%) was acceptabel en vergelijkbaar met andere studies.

CURRICULUM VITAE

Shafak Aluwini was born on August 2nd 1963 in Baghdad, Iraq. In 2000 he graduated from the faculty of medicine, University of Groningen, The Netherlands. In 2007 he completed his training in radiation oncology at the University Medical Center in Utrecht. In 2007 he started working at the department of Radiation Oncology at the Erasmus Medical Center - Daniel Den Hoed Cancer Center. His main area of interest is uro-oncology, with HDR-brachytherapy and SBRT for prostate cancer as main research activities.

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PhD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Shafak Aluwini Erasmus MC Department: Radiotherapy Research School: Molecular Medicine	PhD period: 2009-2016 Promotor(s): Prof. dr. L. Incrocci Prof. dr. B.J.M. Heijmen

1. PhD training

	Year	Workload (Hours/ECTS)
-BROK course (basis cursus regelgeving klinisch onderzoek)	2013	40/1.5 ECTS
-Good clinical practice	2013	16/0.5 ECTS
-Course survival analysis	2015	30/1.0 ECTS
-Course writing a successful grant proposal	2015	30/1.0 ECTS
-Course research integrity	2016	16/0.5 ECTS
-Course research management for PhD students	2016	16/0.5 ECTS
Specific courses (e.g. Research school, Medical Training)		
-ESTRO course; rectum carcinoma, Roma, Italy	2011	10/0.5 ECTS
-Delineation course, Barcelona, Spain	2015	30/1.0 ECTS
Seminars and workshops		
-Refereeravond department of Radiation Oncology	2010-2016	2.0 ECTS
-Research rounds department of Radiation Oncology	2015-2016	1.0 ECTS
Presentations		
-ESTRO 31, Barcelona Spain	2012	40/2.0 ECTS
-2nd ESTRO forum April 2013, Geneva, Switzerland	2013	40/2.0 ECTS
-ASTRO's 55th annual meeting, Atlanta, USA	2013	40/2.0 ECTS
-ESTRO 33, Vienna, Austria	2014	40/2.0 ECTS
-3rd ESTRO forum, Barcelona, Spain	2015	40/2.0 ECTS
-ESTRO 35, Turin, Italy	2016	40/2.0 ECTS
-Presentations Nederlandse Vereniging voor Radiotherapie en Oncologie	2013	16/1.0 ECTS
-Presentations Nederlandse Vereniging voor Urologie	2013-2015	2.0 ECTS
-Presentations Integraal kankercentrum Nederland	2013-2016	2.0 ECTS
(Inter)national conferences		
-European Multidisciplinary Cancer Conference (ECCO, ESMO, ESTRO), Stockholm, Sweden	2011	30/1.0 ECTS
-4th European Multidisciplinary meeting on Urological Cancers (EMUC), Barcelona, Spain	2012	30/1.0 ECTS
-ASTRO's 57th Annual meeting, San Antonio, USA	2015	30/1.0 ECTS
-American Brachytherapy Congress (ABS)/GEC/ESTRO, San Francisco, USA	2016	30/1.0 ECTS

	Year	Workload (Hours/ECTS)
Other		
-Supervising research activities AIOS radiation oncology and urology	2011-2016	2.0 ECTS
-PI phase 3 multicenter phase 3 randomized trial (PROBACH Trial)	2013-2016	2.0 ECTS
-PI phase I/II trial on single fraction HDR brachytherapy		
2. Teaching		
	Year	**Workload (Hours/ECTS)**
Lecturing		
-Postgraduate lectures	2010-2016	1.0 ECTS
-Education AIOS radiation oncology, Erasmus MC	2010-2016	3.0 ECTS
-OMBO workshops Erasmus MC	2010-2016	4.0 ECTS
Supervising practicals and excursions, Tutoring		
-Supervising post doc MRI guided brachytherapy	2014-2016	2.0 ECTS
Supervising Master's theses		
-Prostate brachytherapy master theses	2015-2016	1.0 ECTS
Other		
14 peer reviewed papers in 4 journals	2012-2016	