The Dynamics of Dose Escalation of Radiotherapy for Localized Prostate Cancer

Abrahim Al-Mamgani

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The Dynamics of Dose Escalation of Radiotherapy for Localized Prostate Cancer

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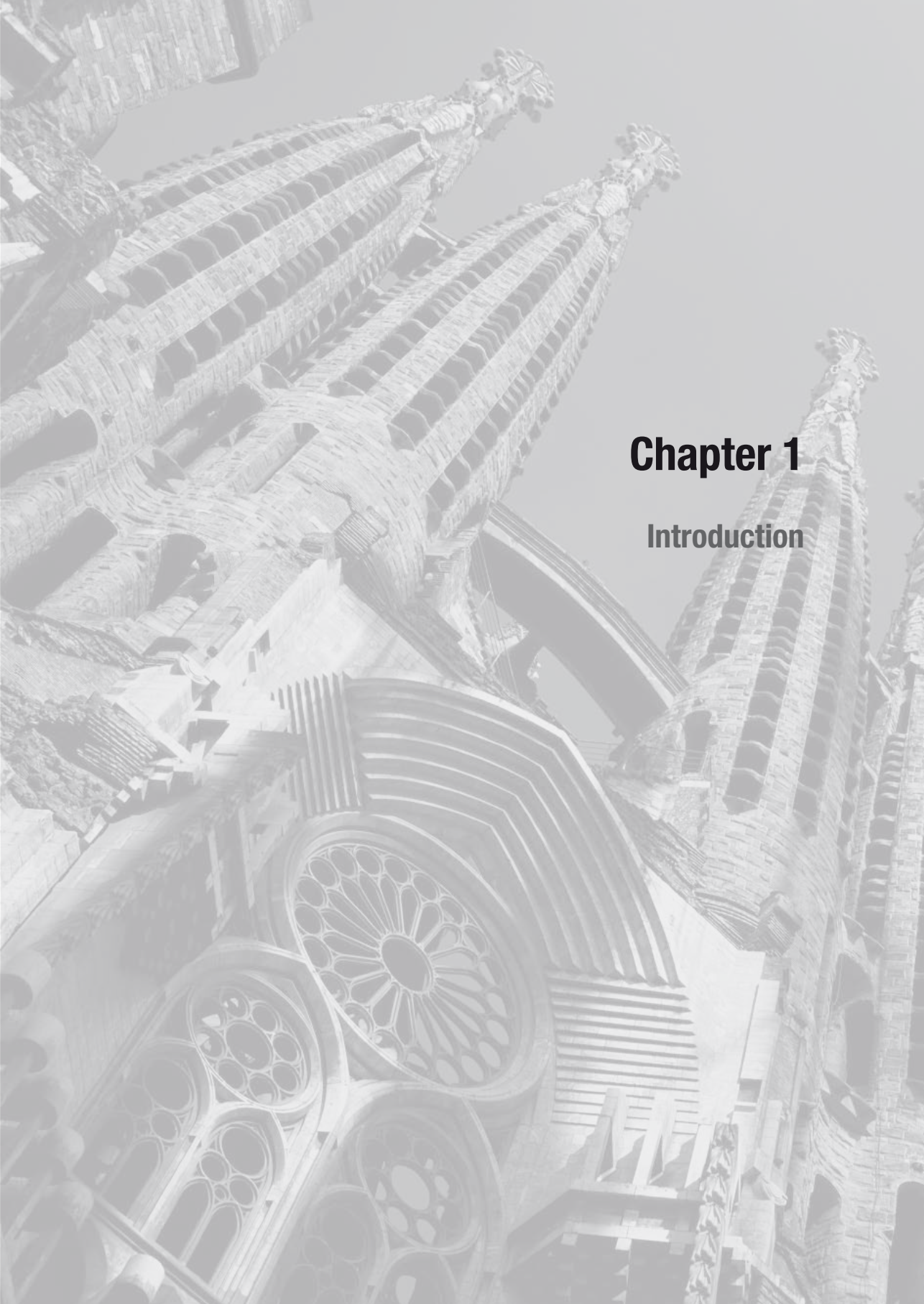
Promotor:	Prof.dr. P. C. Levendag
Overige leden:	Prof.dr. B. Heijmen
	Prof.dr. J. Battermann
	Prof.dr. C. H. Bangma
Copromotoren:	Dr. J. V. Lebesque
	Dr. L. Incrocci

To my patients, who taught me with their dedication, courage and perseverance
To my teachers, who inspired me with their knowledge, endeavors, and insight
To my parents

CONTENTS



Chapter 1

Introduction

INTRODUCTION

Prostate cancer remains a significant health problem; one out of ten men is affected by prostate cancer during their life span. It is the second leading cause of cancer death in men in western countries (1). Most patients have no complaints and the diagnosis is made only because of the elevated level of prostate-specific antigen (PSA), being a specific tumor marker for prostate cancer. Symptomatic patients complain of urinary problems such as hesitancy, frequency during the day and at night, dysuria, weak stream, and rarely haematuria and urinary retention.

After a wide clinical examination, patients with elevated PSA will undergo a biopsy of the prostate to establish the diagnosis histologically and to assess the stage and aggressiveness of their disease. Prostate cancer, as other cancers, would be staged according to the American Joint Committee on Cancer guidelines (TNM stage: Tumor-Node-Metastases). Tumor stage (T stage) can be determined by digital and ultrasonic rectal examination with or without additional CT or MRI scan. In short: T1 tumor not palpable by rectal examination and not visible by any radiological technique, T2 tumor palpable or visible but still confined to the prostate gland, T3 tumor extends beyond the prostatic capsule or invades the seminal vesicles, and T4 tumor invades the adjacent structures (rectum, bladder or pelvic wall) (2). Lymph node involvement (N stage) can be detected by CT or MRI scan; for patients with high risk of lymph nodal spread, currently laparoscopic lymph node sampling is frequently the preferred diagnostic approach. In the nearby future more accurate assessment of the lymph nodal status can be done using advanced generation of MRI scanning with ultra-small iron oxide particles in order to contrast the involved nodes only. Bone scans are the standard method to detect skeletal metastases in patients with high risk criteria's.

RISK STRATIFICATION

Prostate cancer patients are stratified into different risk groups based on clinical tumor stage, PSA-level at the time of diagnosis and Gleason score (a histological grading system which reflect the aggressiveness of prostate cancer including risk of extracapsular spread, lymph node involvement and distant metastases). The Gleason score is determined from the diagnostic biopsy of the prostate and is graded between 2-10; the higher the score, the more aggressive is the cancer.

In the Dutch randomized dose escalation trial, patients were divided into three risk groups (low-, intermediate- and high-risk), based on the single-factor model of Chism (3). Patients with T1-2 and Gleason 2-6 and PSA $\leq$ 10 μg/L, were considered to be at low risk, whereas patients with T3-4 or Gleason 8-10 or PSA > 20 μg/L were at high risk. All the other patients were considered as intermediate risk.

TREATMENT MODALITIES

At present, when diagnosed with localized prostate cancer, several therapeutic options are available. These include open or laparoscopic prostatectomy (PR) (surgical removal of the prostate), or external beam radiotherapy (EBRT) with or without brachytherapy (BT). In case of BT, currently radioactive seeds e.g. I-125 for low-dose rate BT or plastic after-loading catheters for high-dose rate Ir-192 sources are implanted into the prostate. Impotence and urinary incontinence are well-known long-term complications after radical PR (4). Some believe that the incidence of these complications can to be reduced with the currently used nerve-sparing laparoscopic surgical techniques (5). Erectile dysfunction after EBRT is less common than after RP. According to recent data reported in the literature, however, no definitive dose-effect relationship has been demonstrated for erectile dysfunction (6-8). Van der Wielen et al. (6) from our group found no correlation between the radiation dose to different anatomical structures (neurovascular bundle, corpora cavernosa, penile bulb) and sexual problems. Patients treated with EBRT have a higher risk of bowel complications (9), while patients treated with BT have more genitourinary problems (10).

With regard to the different treatment options available, no consensus was found regarding the optimal treatment strategies. Apart from these options, watchful waiting can also be adopted in patients with early-stage disease with slowly rising PSA level and limited tumor load, specifically in patients with short life expectancy (below 10 years) from the date of diagnosis (11).

Generally speaking, low-risk patients have a high probability of having organ-confined disease and therefore a higher chance of cure. On the other hand, high-risk patients have a high probability of having non-organ-confined disease and are at high risk of lymph node spread and micrometastases. These tumors are usually treated with adjuvant long-term hormonal therapy (HT) and 3-dimentional conformal radiotherapy (3DCRT). HT for 2-3 years appeared to improve survival by 20-30% in high-risk patients, because of the synergistic role of RT and HT in destroying micrometastases (12-14). Intermediate-risk patients are suitable candidates for radical PR or 3DCRT (with or without HT) (15). Besides the abovementioned prognostic criteria, selection of the appropriate treatment for patients with localized prostate cancer is frequently based on others factors, for instance general condition of the patient, comorbidity, age, possibility of treatment complications, patients' preference, the treating doctor, and the available facilities at that particular cancer center.

RADIOTHERAPY OF PROSTATE CANCER

After diagnosis and decision making as to what type of treatment modalities are to be used, in case of radiation therapy as the treatment modality of preference, simulation will be the

next step. This procedure consist of a number of steps including patient preparation, patient positioning, planning CT scanning, target definition, RT planning, dose prescription and plan verification. Before the start of each fraction the patient is instructed to drink sufficiently to finally achieve a full bladder to a comfortable level, in order to reduce the volume of small bowel irradiated; also mild laxative are prescribed in order to have an empty rectum and consequently limit the high dose area of the anorectal wall (16). To ensure reproducibility of setup of daily radiation treatment delivery, patients treated with 3DCRT for prostatic cancer should be fitted in an easily reproducible supine position, usually without immobilization device. To allow the radiation oncologist to draw the prostate gland on the CT simulation image and to verify the radiation fields during the treatment using portal imaging technology, a number of institutions place fiducials markers in the prostate. Because of the multifocal nature of prostate cancer, the entire prostate gland is delineated as clinical target volume (CTV). A margin is then added to the CTV (nowadays ranging from 5 to 10 mm) (17) to allow for prostate movement, delineation uncertainties and patient setup variability on the treatment machine. This way new target volume called planning target volume (PTV) is defined. The radiation oncologist may also decide to include the seminal vesicles and/or the pelvic lymph nodes in the PTV in patients at significant risk for spread to these tissues. Multiple RT-fields (typically 3-6) are used in order to minimize the volume of normal tissue receiving a high dose. A 3D dose calculation is performed; the radiation oncologist reviews the overall treatment plan including field arrangement, doses at the surrounding critical organs and subsequently prescribed the dose. In general, the PTV should receive full prescription dose ± 5% to ensure adequate homogeneity of the dose throughout the intended target volume (18). Typical doses per fraction for 3DCRT are 1.8-2.0 Gy/day. The treatment is delivered on a daily basis 5 days per week over 6-8 weeks, somewhat depending on the dose per fraction and total dose. During the treatment, portal images are used to verify accurate alignment of the fields. Adjustment can be made on a daily basis if the prostate is not being accurately targeted. By the mid-1990's, further development of treatment planning software coupled with the integration of multi-leaf collimators (MLC), a type of mechanized radiation beam shaping device, allowed for the introduction of a more conformal treatment mode, that is intensity modulated radiation therapy (IMRT). With this technique, the radiation beam is divided into individual beamlets, so that differences in position of tumor vs. normal tissue can be exploited with varying the dose. Planning is facilitated by assigning maximal dose to the target and minimal dose to normal tissue volumes at risk. IMRT has permitted not only further prostate dose escalation beyond 81 Gy but also a better understanding of the relationship between doses to specific volumes of organs at risk and morbidity (19-21).

DOSE-RESPONSE RELATIONSHIP

It is a well-known fact that there is a dose-response relationship for clinical control of localized prostate cancer. The need for increased dose of above conventional levels (66-70 Gy) was suggested by dose-response studies (22-25). However, increasing the dose of RT above those levels using conventional RT techniques was limited by the dose of the surrounding normal critical structures. After the introduction of 3DCRT and IMRT, several phase II trials have shown that, with 3DCRT, higher than conventional doses are feasible (26-29). This advanced technology allows for the initiation of different phase III dose escalation trials in North America, the UK, The Netherlands, and France (30-34).

SCOPE OF THE THESIS

As already mentioned, EBRT is an important treatment modality for prostate cancer patients. Level I evidence is nowadays available from different randomized controlled clinical trials (30-33) supporting the benefit of high-dose RT in the management of most of these patients. Although the toxicity of irradiated patients remains considerable, little is known from these studies about the impact of such treatment on the quality of life (QoL). Further improvement in clinical outcome of prostate cancer patients while maintaining the toxicity at acceptable levels could be achieved by careful selection of the patients for dose escalation of RT and the use of high accuracy radiation techniques. These topics are thoroughly studied in the next chapters of this book. This thesis is covering some of the related questions in the following chapters:

Chapter 2

Question: Is dose escalation of radiotherapy in patients with localized prostate cancer really necessary?
Paper: Update of the Dutch multicenter dose escalation trial of radiotherapy for localized prostate cancer.
Source: International Journal Radiation Oncology Biology Physics 2008;72:980-988.

Chapter 3

Question: Does the use of intensity-modulated radiotherapy reduce the radiation-related toxicity in patients treated with high-dose radiotherapy?
Paper: The role of intensity modulated radiation therapy in reducing toxicity in dose escalation for localized prostate cancer.
Source: International Journal Radiation Oncology Biology Physics 2009;73:685-691.

Chapter 4

Question: What are the clinical and dosemetric predictors of late urinary obstruction after dose escalation of radiotherapy in prostate cancer?
Paper: Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): specific relationships between local dose, acute effects and baseline characteristics.
Source: International Journal Radiation Oncology Biology Physics 2010 (Epub ahead of print).

Chapter 5

Question: What is the impact of dose escalation of RT dose on QoL?
Paper: Dose-escalation and quality-of-life in patients with localized prostate cancer treated with radiotherapy: long-term results of the Dutch randomized dose-escalation trial (CKTO 96-10 trial).
Source: International Journal Radiation Oncology Biology Physics 2010 (Epub ahead of print).

Chapter 6

Question: Which subgroup of patients benefits most from dose escalation?
Paper: Subgroup analysis of patients with localized prostate cancer treated within the Dutch randomized dose-escalation trial.
Source: Radiotherapy and Oncology 2010;96:13-18.

Chapter 7

Question: What is the optimal management of high-risk prostate cancer?
Paper: Controversies in the treatment of high-risk prostate cancer: what is the optimal combination of hormonal therapy and radiotherapy: a review of literature.
Source: The Prostate 2010,70:701-709.

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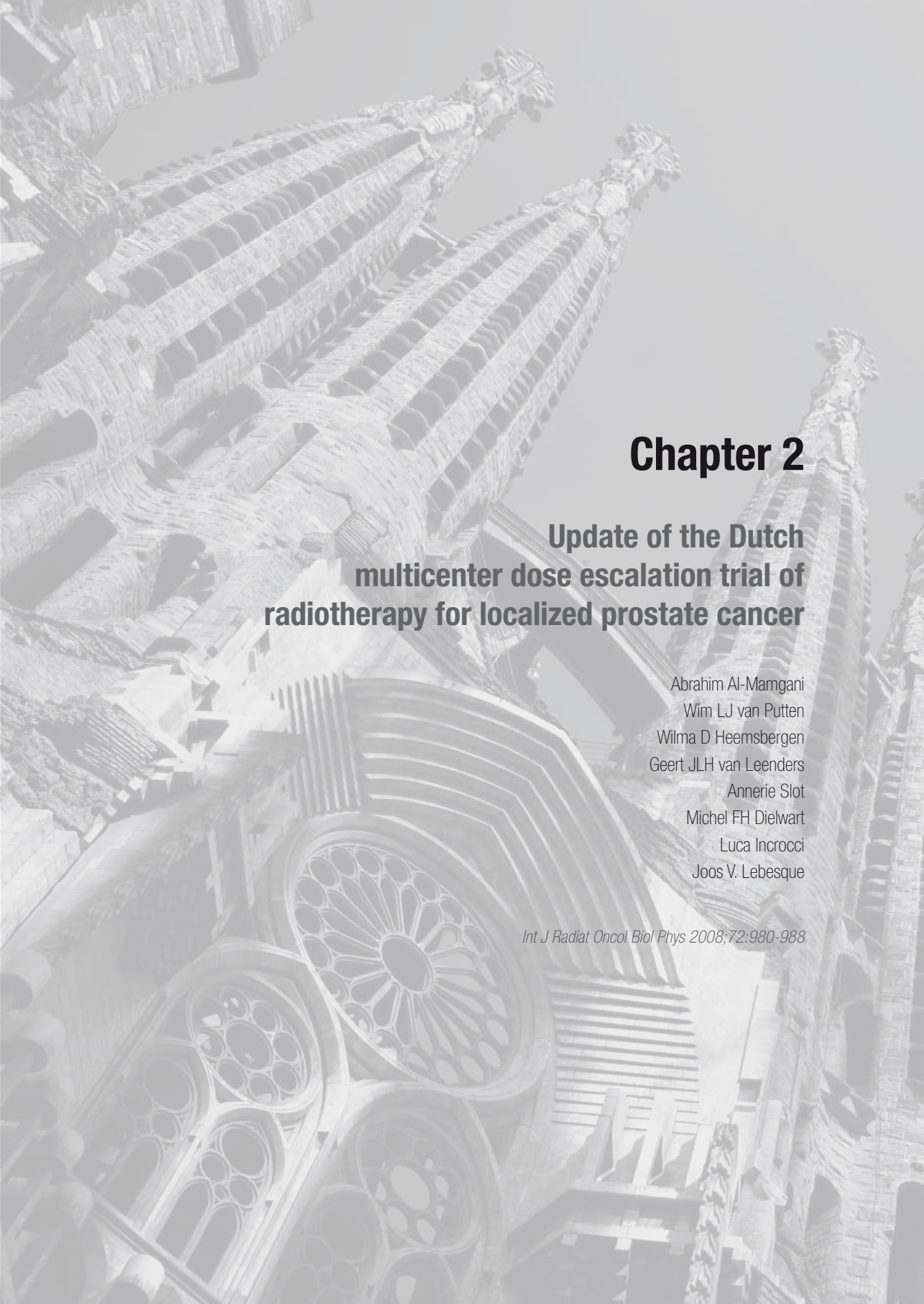

Chapter 2

Update of the Dutch multicenter dose escalation trial of radiotherapy for localized prostate cancer

Abrahim Al-Mamgani
Wim LJ van Putten
Wilma D Heemsbergen
Geert JLH van Leenders
Annerie Slot
Michel FH Dielwart
Luca Incrocci
Joos V. Lebesque

Int J Radiat Oncol Biol Phys 2008;72:980-988

ABSTRACT

Purpose

To update the analysis of the Dutch dose escalation trial of radiotherapy for prostate cancer.

Patients and Methods

A total of 669 patients with localized prostate cancer were randomly assigned to receive 68 or 78 Gy. Patients were stratified by age, institution, use of (neo)adjuvant hormonal therapy, and treatment groups. The primary end point was freedom from failure (FFF), which was defined as clinical or biochemical failure (BF). Two definitions of BF were used; the ASTRO-definition (3 consecutive rises of PSA level) and the Phoenix definition (the nadir plus 2). Secondary end points were freedom from clinical failure (FFCF), overall survival (OS), genitourinary (GU) and gastrointestinal (GI) toxicity.

Results

After a median follow-up of 70 months, FFF (ASTRO) was significantly better in the 78-Gy arm compared with the 68-Gy arm (7-year FFF rate is 54% vs 47%; p= 0.04). FFF (Phoenix) was also significantly better in the 78-Gy arm with 7-year FFF rate of 56% vs 45%, respectively (p = 0.03). However, no differences in FFCF and OS were observed. The incidence of late GU toxicity grade ≥ 2 was similar in both arms (40% vs 41% at 7 years; p= 0.6), while the cumulative incidence of late GI toxicity grade ≥ 2 was increased in the 78-Gy arm (35% vs 25% at 7 years; p= 0.04).

Conclusion

The results of our study have shown a statistically significant improvement in FFF in prostate cancer patients treated with 78 Gy but with a greater rate of late gastrointestinal toxicity.

INTRODUCTION

The incidence of prostate cancer is rapidly increasing in all industrialized countries. External beam radiotherapy is one of the options used to treat about 8,000 men diagnosed with prostate cancer annually in The Netherlands. The need for increased dose of radiotherapy (RT) above conventional levels was suggested by dose response observations by Perez et al. (1) and Hanks et al. (2). The past few decades witnessed the development of new radiation techniques such as 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT). These advanced techniques will achieve improved conformality of high dose levels of RT to the target volume while sparing the normal tissues, reducing complications and may permit safe dose escalation and therefore improving local control. Studies of dose escalation with 3D-CRT have been initiated by investigators in North America, the UK, France and in The Netherlands (3-8). These studies consistently showed an improvement in freedom from failure (FFF), but without improvement in overall survival (OS), probably because of the competing risk of death from intercurrent illnesses, the short follow-up period or because of lack of statistical power in these studies.

Because of the increasing need for a good definition for biochemical failure (BF) and the recent publications that the Phoenix definition (PSA nadir plus 2 μg/L after RT) is a better approximation of eventual clinical failure (CF) (9, 10, 11, 12, 13) than the ASTRO definition, we will make a comparison between the rate and pattern of failures according to both definitions.

In our first reported outcome results, this trial has shown, after a median follow-up of 51 months, that high dose of RT (78 Gy) is beneficial in terms of FFF, without significant differences in freedom from clinical failure (FFCF) and OS (4). In this report we present the results on outcome and toxicity of this, meanwhile more mature, trial with a median follow-up of 70 months.

PATIENTS AND METHODS

Study design

This phase III multicenter randomized trial was designed to compare two different radiation doses delivered by conformal techniques for patients with localized prostate cancer and was carried out in four Dutch institutions.

Participants

Patients with histologically proven T1a-4 adenocarcinoma of the prostate with initial prostate-specific antigen (iPSA) less than 60 μg/L were eligible, provided there were no distant metastases and no cytologically or histologically proven positive regional lymph nodes. However, patients with T1a and well-differentiated (or Gleason score < 5) T1b-c with iPSA ≤ 4 μg/L were not included. Patients using anticoagulants, with previous radical prostatectomy or pelvic irradiation, previous

malignant disease (other than basal cell carcinoma), and patients having Karnofsky performance scores of ≤ 70, were excluded. TNM classification was done according to the AJCC 1997 guidelines. All participants provided written informed consent. This study entered 669 patients with between June 1997 and February 2003. Patients were randomly assigned to receive either 68 or 78 Gy. Stratification was performed at randomization to ensure balanced groups. Patients were stratified by age (≤ 70 v > 70 years), institution (A, B, C, or D), use of (neo)adjuvant hormonal therapy (HT) (yes or no), and treatment groups (groups I, II, III or IV). Patients were stratified into 4 treatment groups, defined according to the estimated risk of the seminal vesicles (SV) involvement, according to Partin (14) (Table 1). Patients who belong to treatment group I have an estimated risk of SV involvement of < 10%, while patients in group II have an estimated risk of 10-25%. Patients in group III and IV have an estimated risk of SV involvement of > 25%.

Table 1. Treatment groups, according to the risk of involvement of SV, Partin et al, 2004

		T1b, T1c, T2a*				T2b, T3a*	T3b, T4*
Gleason score	Differentiation grade	PSA 0-4	PSA 4-10	PSA 10-20	PSA 20-60	PSA 0-60	PSA 0-60
2-4	Good	I	I	I	II	III	IV
5-7	Moderate	I	II	II	III	III	IV
8-10	Poor	II	III	III	III	III	IV

* According to the American Joint Committee on Cancer 1997 guidelines

Retrospectively, patients were also divided into three prognostic risk groups (low-, intermediate- and high-risk), according to the single factor model of Chism et al. (15). Patients with T1-2 and Gleason 2-6 and PSA ≤ 10 μg/L, were at low risk, whereas patients with T3-4 or Gleason 8-10 or PSA > 20 μg/L were at high risk. All the other patients were at intermediate risk.

(Neo)adjuvant hormonal therapy (HT) was allowed and prescribed in two institutions (n= 143), mostly to high-risk patients (n= 125) and rarely to intermediate- or low-risk patients (n= 18). The use of HT was well balanced between both treatment arms (Table 2). Institution A gave long-term HT (3 years), while institution B used short-term HT (6 months). Androgen deprivation was achieved using 3-monthly depot injection of a luteinising hormone-releasing hormone analogue preceded by a short course of cyproterone acetate to prevent testosterone flare.

Radiation treatment

Simulation and treatment were carried out in supine position with a comfortably full bladder and without specific immobilization. All patients underwent CT scanning of the pelvis in treatment position. For both arms, the fraction size was 2 Gy prescribed to the isocenter (the ICRU reference point). The mean dose to the planning target volume (PTV) was between –5% and +7% of the prescribed dose, and 99% of the PTV received ≥ 95% of the prescribed dose. The rectum was defined from the anal verge until inferior border of the sacro-iliacal joints or to the point where the rectum was no longer close to the sacrum. The percentage of the rectum

Table 2. Patients, tumor and treatment characteristics

Characteristics	68-Gy arm (N = 331)	78-Gy arm (N = 333)
Mean age (year)	68.6	68.8
Median follow-up (months)	70.3	71
Radiation dose (%)		
68 Gy	100	
68-76 Gy		11
78 Gy		89
Hormonal therapy (total) (%)	22	21
Short-term	11	9
Long-term	11	12
Institution (%)		
A	61	61
B	26	26
C	10	10
D	3	3
Treatment groups (%)		
I	17	16
II	20	20
III	46	49
IV	17	15
Risk groups (%)		
Low	17	19
Intermediate	27	27
High	56	54
Gleason score (%)*		
Gleason 2-6	49	51
Gleason 7	34	35
Gleason 8-10	17	14
Tumor stage (%)		
T1	18	21
T2	45	41
T3	35	37
T4	2	1
PSA (%)		
0-10	36	41
10-20	38	38
20-60	26	21

* For 46 patients the Gleason score was not available and a score was assigned based on differentiation grade

receiving ≥ 74 Gy was limited to 40%, while the small bowel dose should not be > 68 Gy. The PTV included the prostate with or without the SV as clinical target volume (CTV), with a margin of 10 mm during the first 68 Gy and 5 mm (except towards the rectum 0 mm) for the last 10 Gy in the high-dose arm. CTV for treatment group I was defined as the prostate only, and for group IV, it was the prostate and the SV. For treatment group II and III the CTV also included the prostate and SV, but the SV was excluded from the CTV after 50 and 68 Gy, respectively.

Institutions A, B and D used a three-field technique (n= 594), and institution C a four-field technique (n =70). For 41 patients in the high-dose arm, an IMRT-technique was used for the simultaneous integrated boost in institution B. For these patients the boost was irradiated to 78 Gy with a fraction size of 2 Gy. The PTV minus boost region was defined by the 5-10 mm shell formed by the PTV from which the boost region was subtracted. This shell was irradiated to at least 95% of 68 Gy (64.6 Gy) in 39 fractions, resulting in dose per fraction in this shell, varying between 1.9 Gy (95% of 2 Gy) and 1.66 Gy (16)

Follow-up

All patients were scheduled to be seen every 3 months for the first year, every 4 months for the second year, every 6 months for the next 3 years, and annually thereafter. Assessment of disease status was made using history, clinical examination and PSA measurement.

Toxicity

Late radiation side effects were assessed at each follow-up visit, using patient's questionnaires and slightly modified Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (RTOG/EORTC) scoring criteria (17). We scored also more detailed gastrointestinal (GI) and genitourinary (GU) symptoms (17), called indicators for RTOG/EORTC grade ≥ 2 (Table 3).

Table 3. Cumulative incidence at 7 years (Kaplan-Meier estimates) for all late GI and GU endpoints, including grade ≥ 2 toxicity indicators. Statistically significant (Log rank test) differences ($P < 0.05$) are indicated in bold.

	Cumulative incidence at 7 years (%)		
Endpoints	68 Gy	78 Gy	p value
GI			
RTOG/EORTC ≥ 2	25	35	**0.04**
RTOG/EORTC ≥ 3	4	6	0.3
Rectal bleeding (laser / transfusion)	3	8	**0.01**
Fecal incontinence (pads > 2 days a week)	7	13	**0.02**
High stool frequency (≥ 6 a day)	7	10	0.2
Steroids for proctitis	5	6	0.5
Pain/cramps/tenesmus requiring medication	9	13	0.3
GU			
RTOG/EORTC ≥ 2	41	40	0.6
RTOG/EORTC ≥ 3	12	13	0.6
Haematuria (laser / transfusion)	0.7	0.4	0.5
Urinary incontinence (pads > 2 days a week)	7	7	0.9
High urinary frequency during the day (≥ 16)	6	5	0.9
Nocturia (≥ 4)	26	30	0.2
Dysuria requiring medication	12	16	0.3
Urinary obstruction requiring treatment	8	11	0.2

End points

The primary end point was FFF, which was defined as BF or CF, whichever was first. BF was defined according to the ASTRO-definition (three consecutive rises in PSA with backdating to midway between the nadir and the first rise) (18). Because of concerns that backdating may influence the timing and the degree of BF (19), a second analysis was performed without backdating. In addition to the ASTRO definition, we also applied the Phoenix definition (rise of ≥ 2 μg/L greater than the PSA nadir after RT) (12). CF was defined as local relapse (palpable and/or biopsy-proven), regional relapse, distant metastases (DM), or initiation of salvage HT because of a rising PSA level. Other end points were OS, GI and GU toxicity. Cancer-related death was defined as death resulting from loco-regional failure or DM. All other causes of death were considered as disease unrelated.

Statistical analysis

FFF, FCFF, and OS were calculated using the Kaplan-Meier method, and the differences were assessed with the log-rank test. To detect a clinically relevant difference of 10% in the primary end point (FFF), 600 patients were required with sufficiently long follow-up, based on a two-sided test with $\alpha = 0.05$ and power of 80%. Analysis was done according to the intention-to-treat principle. Multivariate analysis of prognostic factors was performed, using Cox proportional hazards regression model, to analyze differences between both arms. All p-values are based on two-side tests, with p-value < 0.05 considered statistically significant. Retrospectively, we performed subgroup analyses according to the risk groups (15) and a test of interaction by risk groups using odds ratios.

RESULTS

Between June 1997 and February 2003, 669 patients were enrolled in the study. Five patients were excluded because they were ineligible. From the remaining 664 patients, 331 patients were randomly assigned to receive 68 Gy and 333 patients entered into the high-dose arm of 78 Gy. The median follow-up was 70 months (range 10-115 months). All the patients in the 68-Gy arm received the prescribed dose. In the high-dose arm, however, 11% received a dose lower than 78 Gy: 6% received 68 Gy because of the dose constraints for rectum and small bowel, 3% between 74 and 76 Gy and 1.8% between 70 and 72 Gy because of acute toxicity, technical problems or because of patient's request. One patient (0.3%) died during the treatment from a disease-unrelated cause and had received only 16 Gy. HT was prescribed in 143 patients; 73 in the low-dose arm and 70 in the high-dose arm. Patient, tumor and treatment characteristics are provided in Table 2.

Outcome

The FFF was significantly better in the 78-Gy arm compared with the 68-Gy arm according to the ASTRO definition and Phoenix definition (7-year FFF rate ASTRO-definition is 54% and 47%, respectively, p = 0.04 and for Phoenix definition is 56% and 45%, respectively, p = 0.03). Because we know that ASTRO definition with backdating might influence the timing and the rate of BF, we repeated the analysis without backdating. The FFF remained significantly different, in favour of the high-dose arm (49% and 37%, p = 0.04) (Figures 1A-C). There was no difference between high-dose and low-dose arms in FFCF rates (70% vs 68% at 7 years; p = 0.68) and in OS rates (75% both arms at 7 years; p = 0.45).

Salvage HT was started in 22 patients because a CF has occurred or because of a rising PSA level but before the point of a formal BF (ASTRO): 12 patients in the low-dose arm and 10 patients in the high-dose arm. Eighty-three patients have developed clinical progression, 40 patients in the low-dose arm and 43 in the high-dose arm. In total there were 23 local failures, 12 regional failures and 56 DM. No significant differences were seen between both arms regarding the type of CF. There were 68 deaths in the high-dose arm, with 45 of those deaths prostate cancer-related, while 42 of the 75 deaths in the low-dose arm were prostate cancer-related. The remaining patients died because of intercurrent diseases (mostly cardiovascular or pulmonary disease) or other malignancies. The type and number of failures as well as the deaths by treatment arm are shown in Table 4.

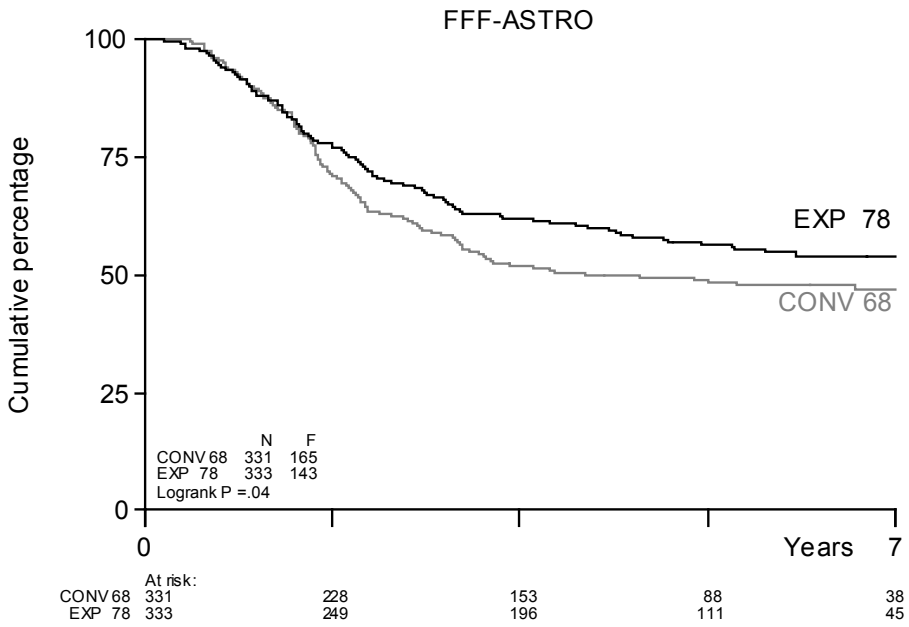

Figure 1A Kaplan-Meier curve of 7-year rates of freedom from failure (FFF) by dose randomization (68 vs. 78 Gy), defined according to the ASTRO definition (3 consecutive rises of PSA level, backdated to midway between the nadir and first rise)

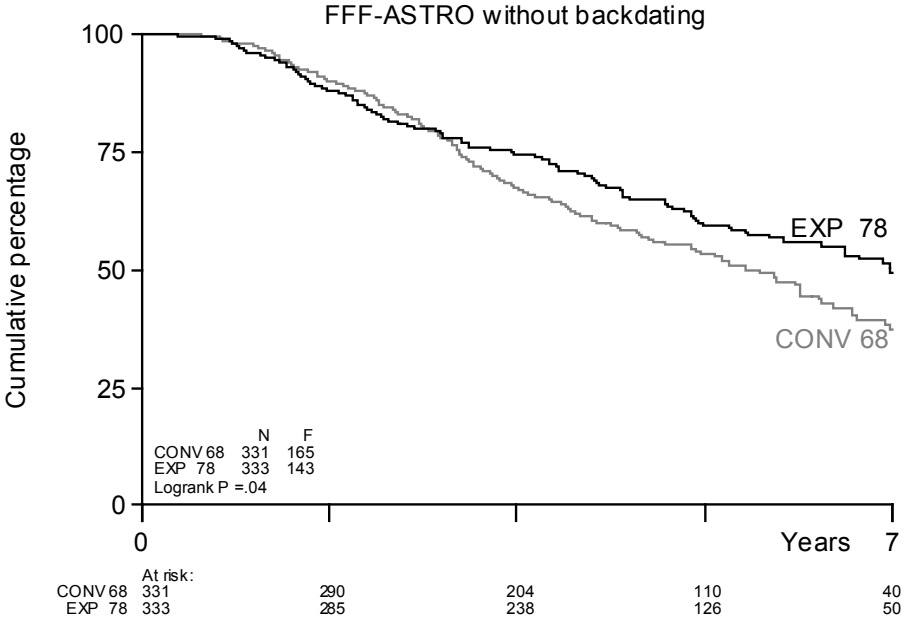

Figure 1B Kaplan-Meier curve of 7-year rates of freedom from failure (FFF) by dose randomization (68 vs. 78 Gy), defined according to the ASTRO definition without backdating.

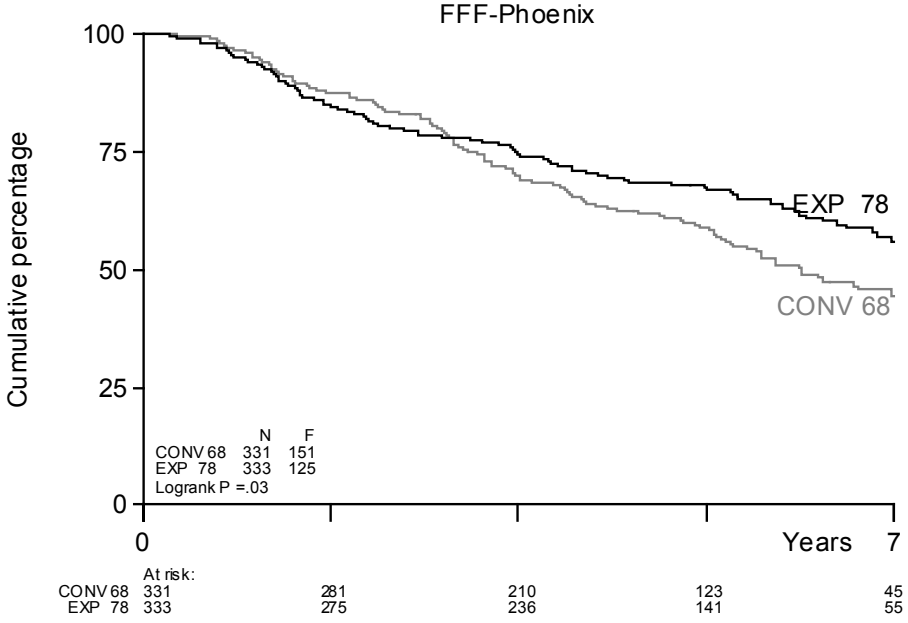

Figure 1C Kaplan-Meier curve of 7-year rates of freedom from failure (FFF) by dose randomization defined according to the Phoenix definition (the nadir plus 2 μg/L after RT)

Table 4. BF, CF and death by treatment arm

	Total	68-Gy arm	78-Gy arm
Failure	(n = 664)	(n = 331)	(n = 333)
BF (ASTRO) (1)	244	135	109
BF (Phoenix) (1)	238	131	107
CF (total)	83	40	43
Local	21	15	6
Regional	5	1	4
Distant metastases (DM)	49	21	28
Local and DM	1	0	1
Local and regional	1	1	0
Regional and DM	6	2	4
Salvage HT (2)	22	12	10
Death (total)	143	75	68
Cancer-related	87	42	45
Non-cancer related	56	33	23

Abbreviation: BF: biochemical failure; CF: clinical failure; DM: distant metastases; Salvage HT: salvage hormonal therapy; (1) as first failure before CF; (2) only salvage HT without previously a formal ASTRO BF or a CF on the basis of rising PSA are counted here

Retrospectively, we did a subgroup analysis based on the three risk groups (15) and a test of interaction between these risk groups. The odds ratio of the total group was equal to 0.75 (p = 0.04) in favor of the high-dose arm. The benefit of high dose RT was most apparent in the intermediate-risk group with an odds ratio of 0.6 (95% CI = 0.33-0.87; p = 0.01). There was a clear trend in the high-risk group, but not in the low-risk group. Furthermore, when this analysis was done with actually given dose instead of dose at randomization, the difference in FFF in the high-risk group was statistically significant (p = 0.03).

Toxicity

The cumulative incidence of late GU toxicity grade ≥ 2 was 40% in high-dose arm and 41% in low-dose arm at 7 years (p = 0.6), while the cumulative incidence of late GI toxicity grade ≥ 2 was increased in the 78-Gy arm (35% and 25%, respectively at 7 years, p = 0.04) (Figures 2A and 2B, and Table 3). No differences were found between high- and low-dose arm regarding late GU toxicity grade ≥ 3 (13% and 12%, respectively, p = 0.6) and late GI toxicity grade ≥ 3 (6% and 4%, respectively, p = 0.3). One percent (n = 3) in both treatment arms developed late GU toxicity grade 4. Late GI toxicity grade 4 has been observed in 3 patients of high-dose arm (1%) but not in the low-dose arm. All 5 GI indicators were higher for the high dose arm. Rectal bleeding requiring laser or transfusion was significantly increased in the high-dose arm (8% vs 3 %, Table 3 and Figure 3A). The incidence of rectal bleeding stabilized after 5 years, since no new cases were observed after 5 year. For fecal incontinence, the incidence was higher by a factor of two in the high-dose arm (13% vs 7 %, Table 3 and Figure 3B), but this incidence did not stabilize.

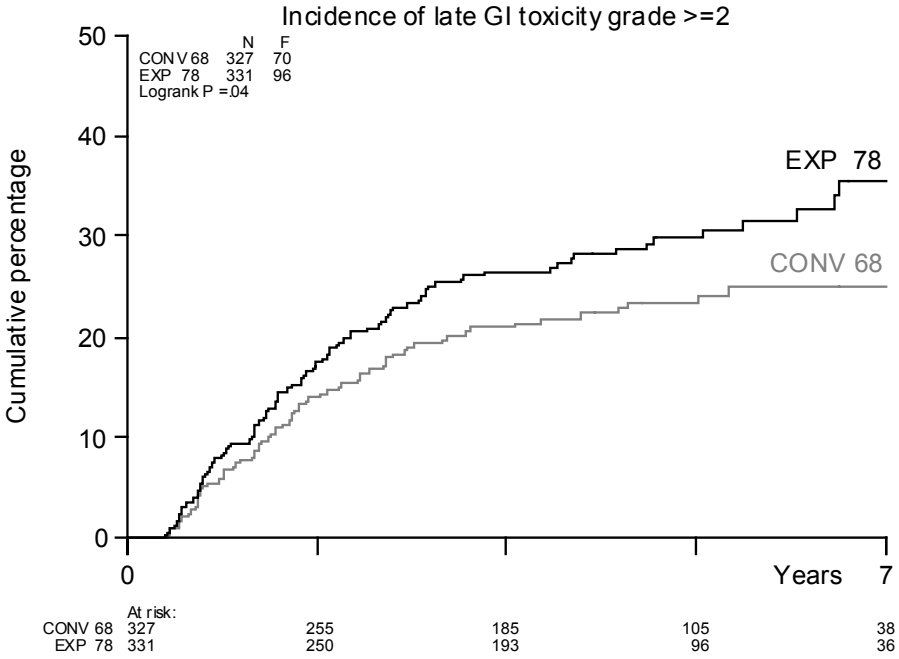

Figure 2A Kaplan-Meier curve of 7-year cumulative incidence of late GI toxicity grade ≥ 2 by randomization arm

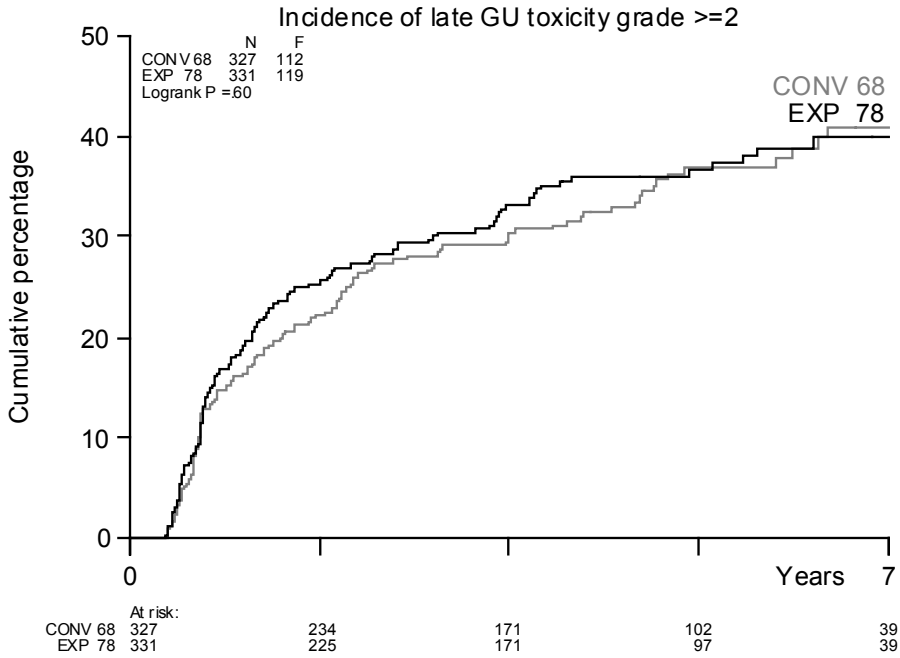

Figure 2B Kaplan-Meier curve of 7-year cumulative incidence of late GU toxicity grade ≥ 2 by randomization arm

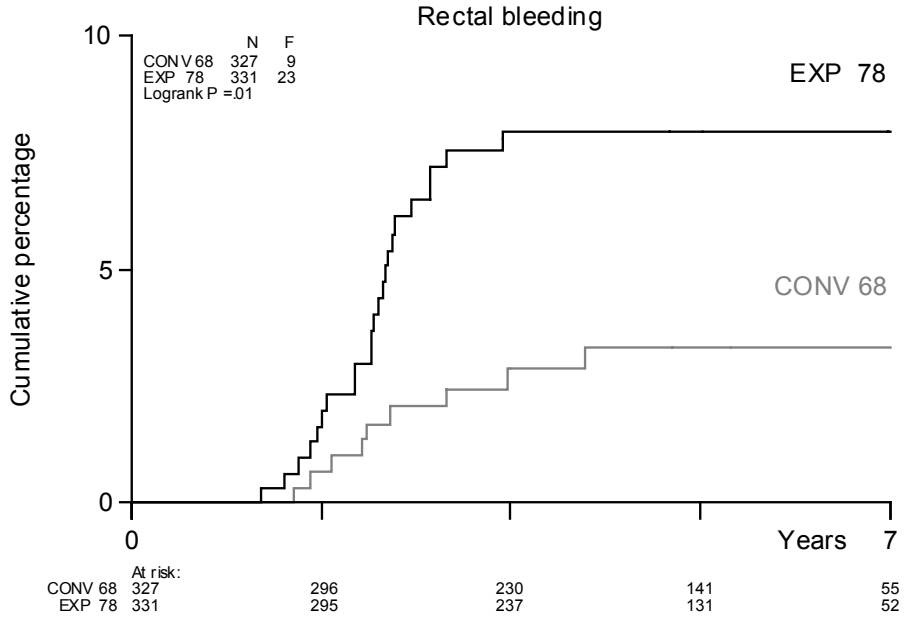

Figure 3A Kaplan-Meier curve of 7-year cumulative incidence of rectal bleeding requiring laser or transfusion by treatment arm.

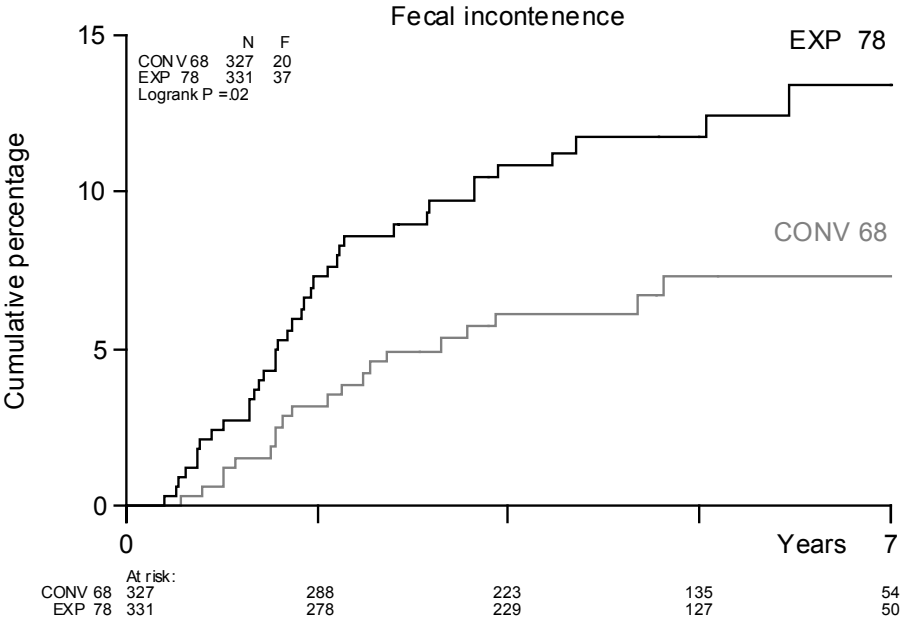

Figure 3B Kaplan-Meier curve of 7-year cumulative incidence of fecal incontinence by treatment arm.

DISCUSSION

Outcome

The development of more accurate radiation techniques has considerably altered the practice of radiation oncology, allowing for a higher dose to the prostate while limiting the dose to the bladder and rectum. Pollack et al. (5) published the first randomized trial, carried out at the MD Anderson Cancer Center. Long-term results of this trial showed a significant improvement in FFF with high dose RT (8-year FFF rate is 59% for the 70-Gy arm and 78% for the 78-Gy arm, p = 0.004) (20) and also an improvement in FFCF. Dearnaley et al. (21) reported a significant improvement of biochemical progression-free survival (bPFS) in the escalated group (74 Gy) in comparison with the standard group (64 Gy). The 5-year bPFS rates in the escalated and standard groups were 71% vs 60%, respectively (p = 0.007). The HR for clinical PFS was 0.69 (p = 0.064). To date, at least five randomized trials, investigated the effect of dose escalation (3, 4, 6, 7, 8). All these trials, with the exception of that of Shipley et al. (7), have decisively demonstrated improved biochemical control by increasing the dose to the primary tumor of the prostate.

Biochemical failure

Our trial showed a statistically significant improvement in FFF in prostate cancer patients treated with 78 Gy in comparison with 68 Gy, using the ASTRO definition (with and without backdating) and the Phoenix definition. In our earlier analysis (median follow-up: 51 months), the 5-year FFF-rate (Phoenix) was better in the high- than in the low-dose arm (67% vs. 61%), but this difference was statistically not significant (p = 0.2) (4). At that time, we had already realized that there is a backdating censoring artifact by using the ASTRO definition. Repeating the analysis without backdating also yielded a significant difference (p=0.02) between the treatment arms (4). Therefore it might be possible that in a randomized trial, the ASTRO definition (with and without backdating) might demonstrate a significant difference between the randomization arms earlier in time compared to the Phoenix definition

Definitions for biochemical failure

Despite the known shortcomings of the ASTRO definition, it is still used widely as indication of BF. Because of the recent recommendations (9, 10, 11, 12, 13, 22), one should use the Phoenix definition beside the ASTRO definition after RT for prostate cancer. Lack of specificity of the ASTRO-definition is one of those weaknesses when HT is used. These patients may show a transient rise of PSA level when the HT stopped. There is a potential for false positives secondarily to such a benign PSA bounce, but these false positives would have been present in both treatment arms. The second problem of the ASTRO-definition is the backdating, which is reasonably solved by performing the analysis without backdating. Another reason for using both definitions (ASTRO with and without backdating and Phoenix) is the fact that the ASTRO

definition (with backdating) systematically underestimates late BF. While using the Phoenix definition and the ASTRO definition (without backdating) the occurrence of BFs spread more evenly among years 0-10 (12, 23). We also have observed the same pattern of failures according to these three definitions. Early control rates look better using Phoenix definition, while later results favour the ASTRO definition with backdating (Figures 1A-C). The definition of BF according to Phoenix, has been found to be strongly related to clinical failure than the ASTRO-definition and less frequently influenced by the use of HT or the length of follow-up. Vicini et al (10) have studied 19 different definitions for BF and their correlation with CF and cause specific survival and found that nadir plus 2 is highly specific and very accurate for identifying BF and also better correlate with CF than other definitions using a specific number of consecutive rises in PSA level, as the ASTRO definition.

Clinical failures

Biochemical control has been shown to correlate not only with local failure but also with DM, cause-specific survival and disease-free survival (9, 10). Morgan et al. (23) have shown that the 5-year actuarial DM rates decreased from 8% to 2% with increasing radiation dose ($p = 0.01$). However, our trial did not show a significant difference between both treatment arms in terms of FFCF ($p = 0.68$). In our opinion, this is because most of the patients with CF developed a rising PSA value long before their CF became clinically manifest and some of them ($n = 22$) were started with salvage HT before the point of their CF has occurring. The use of HT is a potential confounding factor in the analysis of the effect of high dose RT on the rate of DM and local failure since HT could destroy micro-metastases and subsequently postpone or even definitively eliminate the appearance of DM or local recurrence. Our study did not find a lower DM rate in patients treated with higher dose RT, the likely explanations are either our study was underpowered for this purpose and/or because of the used HT. Morgan et al. (23) reported a reduction in the rate of DM in two waves. In patients receiving a dose $\geq$ 74 Gy, especially the late wave of DM appeared to be reduced to a greater degree. The reduction of DM rate in the high dose arm of our trial might, therefore, become manifested much later than the BF. Another factor which makes the assessment of CF rate difficult is the fact that we did not systematically performed prostate re-biopsy for men with post-radiation increase in the level of PSA, because it was difficult to encourage elderly men to undergo re-biopsy as a surrogate end point for local control.

Overall survival

Another critical, but much more complicated issue is whether improved biochemical control will eventually lead to a significantly better overall survival. The impact of high-dose RT on OS has been reviewed. Mathematical studies by Kuban and Yorke (24, 25) predict an increase in survival of 16-30% if 100% local control could be reached. A retrospective analysis from the RTOG suggest an improved survival in patients who received high dose RT. In comparison with

patients who received < 66 Gy, high grade cancer patients who received radiation doses ≥ 66 Gy had a 20% lower risk of death from prostate cancer and a 27% reduction in overall mortality (26). A clear OS benefit of dose escalation was also demonstrated in the systemic review of van Tol-Geerdink et al. (27). An estimated increase in 5 year survival ranging from 10 to 11% was reported when the equivalent dose was increased from 70 to 80 Gy. No single randomized trial, including our own, so far has demonstrated a significant survival benefit from dose escalation. In our trial the 7-year OS rates were 75% for both treatment arms (p = 0.45), probably because our trial was underpowered for this end point. Also no differences were observed in cause-specific mortality between both arms. However, using this metric might overestimate percentage of men who actually died of prostate cancer because competing mortality is substantial. This bias is more pronounced in older men, in patients with low-risk disease and increasing with each year of follow-up (28).

The already reported and the ongoing dose escalation trials are going to recruit, in total, over 4500 patients. When the data of all these trials are completely available, a meta analysis of all these randomized trials should give the answer on this critical issue. The ongoing RTOG 0126 trial, in which OS is the primary end point, will probably help us to further resolve this problem.

In the subgroup analysis, the odds ratios in these subgroups were not significantly different from the odds ratio of the total group, because of the overlapping confidence intervals. Therefore we cannot exclude the possibility that also low-risk patients, or perhaps a subgroup of them, might also benefit from dose escalation in terms of outcome. Our study was not designed to detect differences between treatment arms.

Toxicity

In this study, late morbidities following high dose RT for localized prostate cancer were in line with experiences from other dose escalation trials (3, 5, 7, 8). The cumulative incidence of late grade ≥ 2 GU toxicity was the same in both arms, while the cumulative incidence of late grade ≥ 2 GI toxicity was increased in the high-dose arm. No differences were found in the rate of late GI and GU grade ≥ 3 toxicities between both arms. As already reported analysis on toxicity from our group, Peeters et al. (17) have shown an increased incidence of grade ≥ 2 late GI toxicity by high-dose arm, especially in patients with history of abdominal surgery and in patients with pre-treatment GI-symptoms. However, even excluding these patients from our analysis, we still found a significant increase in the grade ≥ 2 late GI toxicity in the high-dose arm (results not shown).

Rectal bleeding and fecal incontinence occurred in the high-dose arm about twice as often compared to the low-dose arm. Fortunately, the incidence of rectal bleeding stabilized at 5 year because there were no new patients diagnosed with bleeding. The incidence of fecal incontinence did not stabilize and therefore the overall GI toxicity did not stabilize. In the most available dose escalation studies, however late GI toxicity seems to stabilize after a follow-up of 5 years. A possible explanation for this difference is that in our study the scoring of fecal

incontinence was done by the patients themselves, using questionnaires. It is quite possible that in the other studies, this complication was underscored. As reported by other investigators, the incidence of late GI toxicity can be significantly lowered by using IMRT. In a study by Zelefsky et al. (29), the 3-year actuarial incidence of late GI grade ≥ 2 in patients managed by 81 Gy with IMRT was 2% compared with 14% in those treated with 3D-CRT by the same dose (p=0.005).

Although the incidences of late GU toxicity are higher than those of late GI toxicity, no dose escalation trial has shown a significant differences in late GU toxicity with higher dose RT. However, it is well known that GU symptoms tend to accumulate and continue to emerge during the next 15 years after treatment. Gardner et al. (30) showed that short follow-up period might underestimate urinary problems. In their long-term analysis of toxicity of 77.4 Gy in patients with prostate cancer, they reported a 15-year incidence of grade ≥ 2 GU toxicity of 59%. Despite improved conformality of high dose levels of radiotherapy, all of the prostatic urethra receives a full dose. Therefore, we share the concerns of the investigators of the Massachusetts General Hospital about the possibility of increasing late GU toxicity with increasing follow-up period. We have, therefore, scheduled the next analysis after a median follow-up of about 12 years. However, we also recognize the possible shortcomings of a longer follow-up time, such as the high death rate of this already old population of patients from other cancers and intercurrent diseases and the usual increase in urinary symptoms with advancing age. These factors make it impossible to distinguish between GU symptoms due to aging process and those due to late radiation effects.

Future research

Even with the substantial gains realized in the external beam radiotherapy for prostate cancer there is still room for further improvement. Beside dose escalations, another approach that has received attention is the hypofractionated technique (31). The disparity between α/β of about 3-4 Gy for late complications and $\alpha/\beta \leq 2$ for prostate tumors raises the prospect that one might improve outcomes after conformal RT for prostate cancer with hypofractionation. These schedules might lead to improvement of the therapeutic ratio and could achieve economic and logistic advantages. Therefore, a randomized multicenter phase III study has been started in The Netherlands to compare the relapse-free survival and toxicity of 78 Gy in daily fractions of 2 Gy with a hypofractionated schedule of 19 fractions of 3.4 Gy, 3 times/week, to a total dose of 64.6 Gy.

CONCLUSIONS

The data presented here confirmed our earlier findings that dose escalation of RT in patients with localized prostate cancer is feasible and associated with a statistically significant improvement of FFF but without differences in FFCF and OS. These findings further substantiate conclusions

of other investigators that dose escalation is strongly recommended in the treatment of patients with prostate cancer, especially for intermediate- and high-risk groups, but we cannot exclude that patients with low-risk, or at least a subgroup of those patients, might also benefit from high-dose RT. Dose escalation is also associated with a statistically significant increase in late GI toxicity without increase in late GU toxicity. In our opinion, the higher rate of late GI toxicity can dramatically be lowered with the use of innovative radiotherapy techniques as IMRT and IGRT (image-guided radiotherapy).

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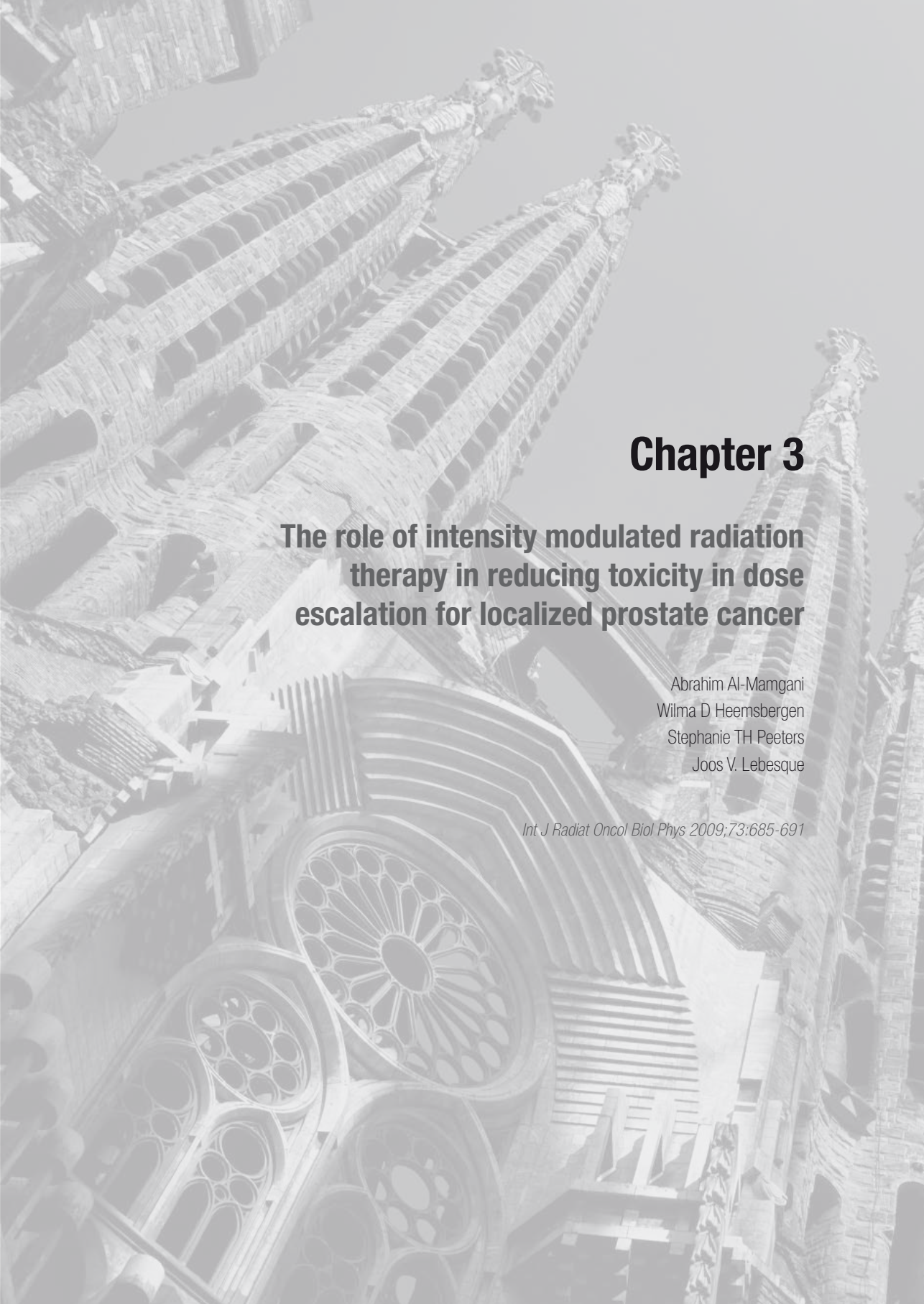

Chapter 3

The role of intensity modulated radiation therapy in reducing toxicity in dose escalation for localized prostate cancer

Abrahim Al-Mamgani
Wilma D Heemsbergen
Stephanie TH Peeters
Joos V. Lebesque

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ABSTRACT

Purpose

To compare acute and late gastrointestinal (GI) and genitourinary (GU) toxicities in prostate cancer patients treated to a total dose of 78 Gy with either a 3D-conformal radiotherapy technique with a sequential boost (SEQ) or a simultaneous integrated boost using IMRT (SIB-IMRT).

Patients and methods

A total of 78 prostate cancer patients participating in the randomized Dutch trial comparing 68 Gy to 78 Gy are the subject of this analysis. They were all treated in the same institution to a total dose of 78 Gy. The median follow-up was 76 months and 56 months for SEQ and SIB-IMRT respectively. The primary end points were acute and late GI and GU toxicity.

Results

A significantly lower incidence of acute grade ≥ 2 GI toxicity occurred in patients treated with SIB-IMRT compared to SEQ (20% vs 61%, p = 0.001). For acute GU toxicity and late GI and GU toxicity, the incidences were lower with SIB-IMRT, but these differences were not statistically significant. There was no statistically significant difference in 5-year freedom from biochemical failure (Phoenix) between the two groups (70% for the SIB-IMRT vs 61% for the SEQ, p = 0.3). The same was true for the 5-year freedom from clinical failure (90% vs 72%, p = 0.07).

Conclusion

The results of our study have shown that SIB-IMRT reduced the toxicity without compromising the outcome in patients with localized prostate cancer treated to 78 Gy radiation.

INTRODUCTION

Confirmation that high dose radiotherapy (RT) improves biochemical no evidence of disease (bNED) comes from different randomized dose escalation trials (1-4). Our Dutch phase III trial, comparing 68 Gy to 78 Gy, has shown 11% improvement of 7-year FFF (Phoenix) from 45% in the low-dose arm to 56% in the high-dose arm (p = 0.03) (4). However, the improved biochemical control in these dose escalation studies was also associated with an increased rate of late complications, mainly late GI toxicity. In our Dutch phase III trial the 7-year rate of late grade ≥ 2 GI toxicity was 35% in high-dose arm vs 25% in the low-dose arm (p = 0.04) (4). As already known, GI complications were already reduced using 3D conformal RT (3D-CRT) rather than conventional RT techniques (5). Despite these tremendous gains, the radiation oncology community continues to struggle with the question how to further reduce the late complications of RT, because decreasing these complications has an important impact on the quality of life of prostate cancer patients treated with high dose RT. IMRT is a new conformal RT technique that produces highly conformal dose distributions, facilitating selective dose escalation to the target volume with acceptable normal tissue dose, therefore producing better local tumor control without a concomitant increase in normal tissue toxicity. In a prostate cancer study by Zelefsky *et al.* (6), the 3-year actuarial incidence of late grade ≥ 2 GI toxicity in patients managed by 81 Gy with IMRT was 2% compared with 14% in those treated with 3D-CRT by the same dose (p=0.005). These data serve as proof-of-principle that IMRT can effectively reduce the volume of normal tissue irradiated to higher doses.

To further validate this approach, an unplanned subset analysis was performed to compare the toxicity of 41 prostate cancer patients treated with IMRT to 78 Gy with that of 37 patients treated with the 3D-CRT approach at the same dose level within the Dutch dose escalation trial.

PATIENTS AND METHODS

Participants

Seventy-eight prostate cancer patients participating in a Dutch randomized trial comparing 68 Gy to 78 Gy (4, 5) are the subject of this analysis. They were all treated in the same institution to a total dose of 78 Gy. Details on pre-treatment imaging, planning, patient preparation and delivery of treatment to patients participated in that trial are described thoroughly elsewhere (4, 5). In brief, four dose-volume groups were defined according to the risk of involvement of the seminal vesicles (SV), as described by Partin *et al.* (7). Patients with a T1b, T1c and T2a prostate cancer with a risk of involvement of < 10%, 10-25% and > 25% were included in dose-volume groups I, II and III respectively. All patients with a T2b and T3a were treated in group III. Group IV comprised all patients with a T3b or T4. For each dose-volume group, specific planning target volumes (PTV) were defined. The clinical target volume (CTV) for treatment group

I was defined as the prostate only, and for group IV, it was the prostate and the SV. For treatment group II and III the CTV also included the prostate and SV, but the SV was excluded from the CTV after 50 and 68 Gy, respectively. The mean dose to the PTV was between –5% and +7% of the prescribed dose, and 99% of the PTV received ≥ 95% of the prescribed dose. The PTV included the prostate with or without the SV as CTV, with a margin of 10 mm during the first 68 Gy and 5 mm (except towards the rectum 0 mm) for the last 10 Gy in both groups.

Radiation treatment

Two different techniques were used; a 3D-conformal technique using a sequential boost (SEQ) and an IMRT technique using a simultaneous integrated boost (SIB-IMRT). The SEQ was used at the beginning of the trial, while the SIB-IMRT was introduced later. The first thirty-seven patients were treated with a SEQ technique using one anterior and 2 lateral wedged fields. The following 41 patients were treated with a SIB-IMRT technique as described by Bos *et al.* (8). For these patients the boost region was irradiated to 78 Gy with a fraction size of 2 Gy. The PTV minus the boost region was defined by the 5-10 mm shell formed by the PTV from which the boost region was subtracted. For the large-field and boost irradiation, we employed five fields consisting of intensity-modulated beams, applied in a "step-and-shoot" mode, using several segments per beam orientation. The SIB-IMRT technique combines the large-field and the boost irradiation plan. Hence, the SIB-IMRT consists of five beam orientations consisting of 11 segments that were defined for the PTV and 11 segments defined for the boost region. Beam-weight optimization of the plans was performed using an optimization module of the treatment planning system (8). A verification procedure, using orthogonal portal imaging, with decision rules for setup corrections was specified according to the guidelines published by a collaborative study in The Netherlands. Using this protocol, systemic errors should not exceed 5 mm (9).

Toxicity

Patients completed a self-assessment questionnaire at the start of therapy, during therapy and at each follow-up visit. Side effects occurring within 120 days from start of RT were considered to be acute toxicity. Late toxicity was scored from 120 days after start of the treatment. For acute morbidity we used a slightly modified RTOG scoring system. For late toxicity the patient's questionnaire, together with the physicians notes, were used to classify late GI and GU symptoms according to the GI and GU RTOG/EORTC scoring systems (10). Because we know that a general toxicity scale such as the RTOG/EORTC should not be used alone to investigate dose-volume effects because of the possible loss of information (11), we used for the evaluation of late toxicity more detailed GI and GU symptoms, called 'indicators', in order to be able to analyze the origin of high scores and differences between the various scoring systems. Scoring for an indicator results in a grade ≥ 2 in one or both scoring systems. Six indicators were defined for the GU symptoms and 5 for GI symptoms.

As shown in Table 1, we have generated different dose-volume histogram (DVH) parameters which were strongly correlated with acute and late GI and GU toxicities in different studies (2, 11, 12, 13). The rectal parameters derived were maximal dose, mean dose, and the relative rectal wall volumes receiving 35, 60, 65 and 70 Gy (rV35, rV60, rV65 and rV70). For the bladder, the absolute dose-surface histograms (DSHs) of the bladder surface were generated for each patient. Hoogeman *et al.* (14) from our group, found that the absolute histograms were more invariant under changes in the bladder filling during treatment than the relative histograms. The bladder parameters derived were maximal dose, mean dose, and the absolute bladder surface receiving 30, 45, 65 and 80 Gy (aS30, aS45, aS65, and aS80).

Many authors reported on the predictive value of acute proctitis for the development of late grade ≥ 2 GI toxicity (15-17). We looked, therefore, specifically to the incidence of that endpoint in our patients.

Table 1. Dosimetric parameters for rectum and bladder

	SEQ	SIB-IMRT	p-value
Rectum			
Dmean (Gy)	47.6	46.3	0.3
Dmax (Gy)	78.8	76.8	**< 0.001**
rV35 (%)	68	72	0.08
rV60 (%)	39	30	**< 0.001**
rV65 (%)	33	22	**< 0.001**
rV70 (%)	26	15	**< 0.001**
Bladder			
Dmean (Gy)	44.5	45.5	0.6
Dmax (Gy)	79.7	79.8	0.6
aS30 (cm2)	143	126	0.08
aS45 (cm2)	122	90	**< 0.001**
aS65 (cm2)	68	51	**< 0.001**
aS80 (cm2)	2.1	1.3	0.3

Abbreviations: SEQ: sequential boost 3D-CRT; SIB-IMRT: simultaneous integrated boost with IMRT; rV35: relative volume of rectum received 35 Gy; aS30: absolute bladder surface received 30 Gy. Statistically significant (Log rank test) differences ($p < 0.05$) are indicated in bold.

Outcome

FFF was defined as biochemical (BF) or clinical failure (CF), whichever was first. BF was defined according to the Phoenix definition (rise of ≥ 2 μg/L greater than the PSA nadir after RT) because in the recent publications this definition seems to be a better approximation of eventual CF than the ASTRO-definition (18). CF included local relapse, regional relapse, distant metastases or initiation of salvage HT.

Follow-up

Follow-up visits were scheduled once every three months in the first year, every four months in the second year, biannually in the following three years and yearly thereafter. When patients were diagnosed with a loco-regional recurrence or distant metastasis, further assessment of complications was omitted from that moment on, as distinction between treatment- or recurrence-related symptoms can be difficult.

Statistical analysis

The occurrence of acute and late GI and GU toxicities was the primary end point in our analysis. Cumulative incidences of toxicity at 5 years were calculated using Life Table estimates. For comparing the toxicities between the two techniques, the total curves were evaluated by calculating Log Rank statistics.

Table 2. Distribution of patients by pretreatment characteristics and treatment technique

	SEQ	SIB-IMRT
	n=37	n=41
Mean age (years) (SD)	69.1 (6.3)	68.3 (6.1)
Median follow-up (months)	76	56
Dose-volume groups		
Group I	2 (6%)	3 (7%)
Group II	7 (19%)	11 (27%)
Group III	19 (51%)	22 (54%)
Group IV	9 (24%)	5 (12%)
T-stage		
T1	3 (8%)	13 (32%)
T2	17 (46%)	15 (38%)
T3	17 (46%)	13 (32%)
Gleason score		
2-4	3 (8%)	4 (10%)
5-7	28 (76%)	29 (70%)
8-10	6 (16%)	8 (20%)
Abdominal surgery	12 (32%)	6 (15%)
Mean initial PSA (µg/L) (SD)	17.3 (10.1)	15.5 (12.3)
Hormonal therapy	10 (27%)	17 (41%)
TURP	3 (8%)	3 (7%)
Diabetes mellitus	3 (8%)	4 (10%)
Cardiovascular history	14 (38%)	18 (44%)
Smoking	9 (24%)	13 (32%)
Use of acetyl salicylic acid	7 (19%)	6 (15%)

Abbreviations: SEQ: sequential boost 3D-CRT; SIB-IMRT: simultaneous integrated boost with IMRT; SD: standard deviation; TURP: transurethral resection of the prostate

RESULTS

Pre-treatment characteristics for both treatment techniques are shown in Table 2. More patients with a past history of abdominal surgery were treated with SEQ than with SIB-IMRT (12 vs 6, p = 0.06). The lower abdominal surgery which is expected to cause higher complication rate was equally distributed between both groups (5 vs 4). More patients treated with SEQ had upper abdominal or laparoscopic surgery (7 vs 2). More patients with dose-volume group IV were treated with SEQ than with SIB-IMRT (24% vs 12%), but this difference was statistically not significant (p = 0.3). The median age of both groups of patients was 69 year. The median follow-up was 76 months (range 12-110) and 56 months (range 30-77) for the SEQ and SIB-IMRT, respectively. The SEQ was used at the beginning of the trial, while the SIB-IMRT was introduced later. This is the main reason why the follow-up of patients treated with SEQ is longer than those treated with SIB-IMRT.

Toxicity

As shown in Figure 1, there was a significantly higher incidence of acute grade ≥ 2 GI toxicity in patients treated with SEQ compared to SIB-IMRT (61% vs 20%, p = 0.001). No patient treated with SIB-IMRT developed acute grade ≥ 3 GI toxicity, while 5 patients (13%) in the SEQ-group developed acute grade ≥ 3 GI toxicity (p = 0.001). The incidence of acute proctitis was significantly reduced by using SIB-IMRT compared to the SEQ (15% vs 38%, p = 0.03). The incidence of acute grade ≥ 2 GU toxicity was higher with the SEQ, but this difference was statistically not significant (69% vs 53%, p = 0.3). Regarding the incidences of acute grade ≥ 3 GU toxicity, no differences were found between both groups.

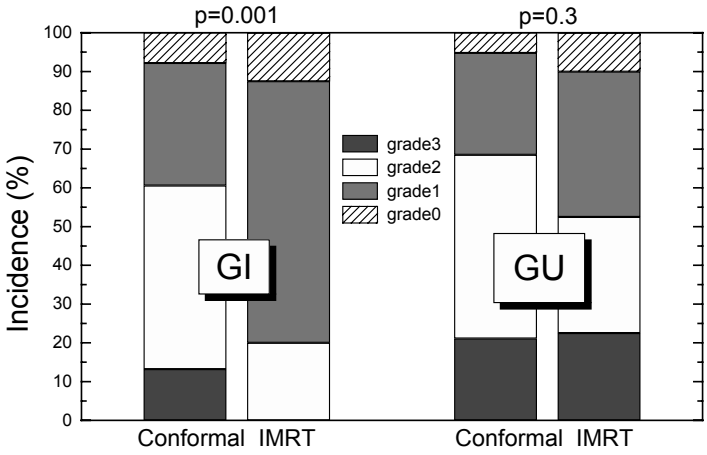

Figure 1. Incidences of acute GI and GU toxicity for SEQ (conformal) and SIB-IMRT.

As shown in Tables 3, Figure 2A and 2B, both incidences of late GI and GU toxicities were lower in patients treated with SIB-IMRT than with SEQ, but the differences were statistically not significant. The cumulative incidence of late grade ≥ 2 GI toxicity at 5 year was 21% for SIB-IMRT group and 37% for SEQ group and (p = 0.16), while the incidence of late grade ≥ 3 GI toxicity at 5 year was 0% and 7%, respectively (p = 0.1). The cumulative incidence of late grade ≥ 2 GU toxicity at 5 year was 43% for SIB-IMRT group and 45% for SEQ group (p = 1.0), while the cumulative incidence of late grade ≥ 3 GU toxicity at 5 year was 15% and 22%, respectively (p = 0.5). Also for all other endpoints (indicators), except for 'pain/cramps/tenesmus requiring medication', dysuria, and 'frequency during day' the cumulative incidences of toxicity were lower using SIB-IMRT, but these differences were statistically not significant.

Figure 3A and Table 1 show that from all the analyzed relative rectal DVH parameters, V60, V65 and V70 were significantly reduced by using SIB-IMRT compared to SEQ (p = < 0.001). Regarding absolute DSH parameters of the bladder, aS45 and aS65 were significantly reduced by using SIB-IMRT compared to SEQ (p = < 0.001). Both aS30 and aS80 were also lowered, although statistically not significant (p = 0.08 and p = 0.3, respectively) (Figure 3B and Table 1).

Table 3. Cumulative incidence at 5 years (Life Table estimates) for all late GI and GU endpoints, including grade ≥ 2 toxicity indicators comparing SEQ and SIB-IMRT.

	Cumulative incidence at 5 years (%)		
Endpoints	SEQ	SIB-IMRT	p-value
GI			
RTOG/EORTC ≥ 2	37	21	0.16
RTOG/EORTC ≥ 3	7	0	0.1
Rectal bleeding (laser / transfusion)	10	3	0.2
Fecal incontinence (pads > 2 days a week)	9	8	0.7
High stool frequency (≥ 6 a day)	21	5	0.06
Steroids for proctitis	7	0	0.1
Pain/cramps/tenesmus requiring medication	11	13	0.5
GU			
RTOG/EORTC ≥ 2	45	43	1
RTOG/EORTC ≥ 3	22	15	0.5
Haematuria (laser / transfusion)	4	0	0.3
Urinary incontinence (pads > 2 days a week)	20	6	0.1
High urinary frequency during the day (≥ 16)	0	7	0.09
Nocturia (≥ 4)	33	30	0.9
Dysuria requiring medication	18	20	0.5
Urinary obstruction requiring treatment	18	10	0.4

Abbreviations: GI: gastrointestinal; GU: genitourinary; SEQ: sequential boost 3D-CRT; SIB-IMRT: simultaneous integrated boost.
p-value: Log rank test.

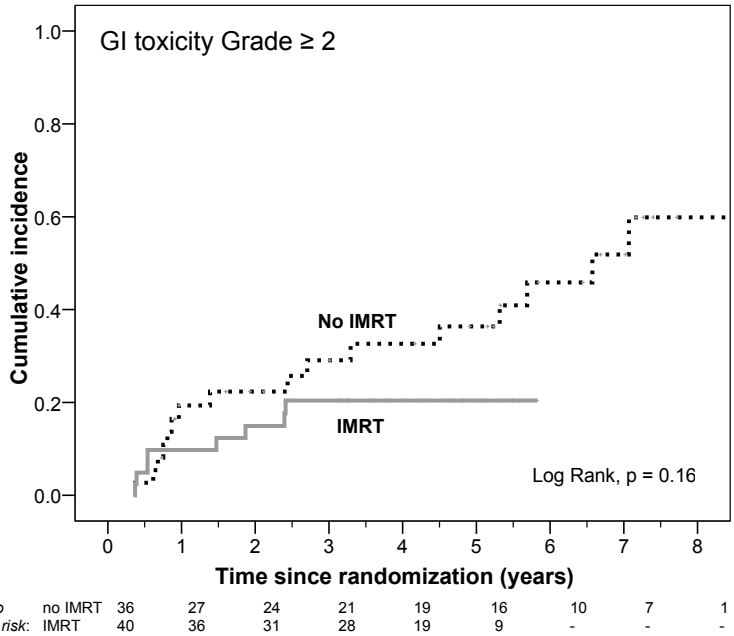

Figure 2A. Kaplan-Meier curve of the cumulative incidences of late GI RTOG/EORTC grade ≥ 2 toxicity for both treatment techniques.

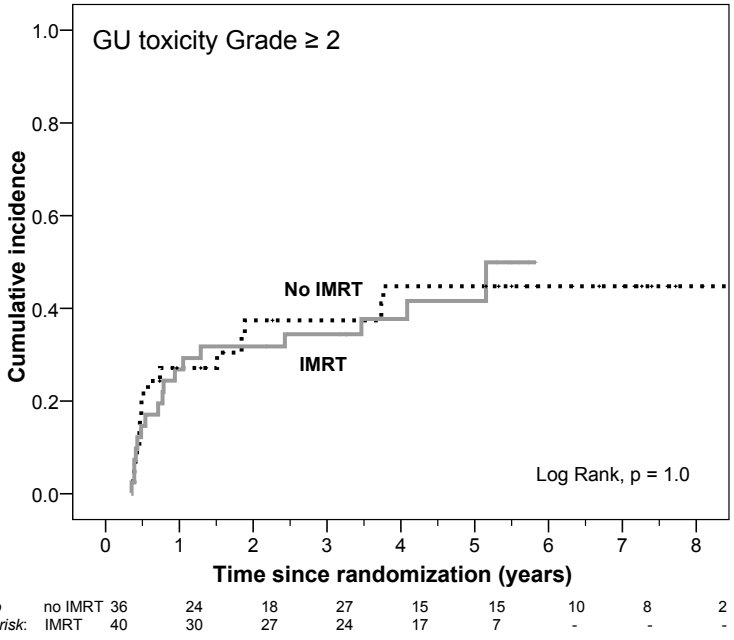

Figure 2B. Kaplan-Meier curve of the cumulative incidences of late GU RTOG/EORTC grade ≥ 2 toxicity for both treatment techniques.

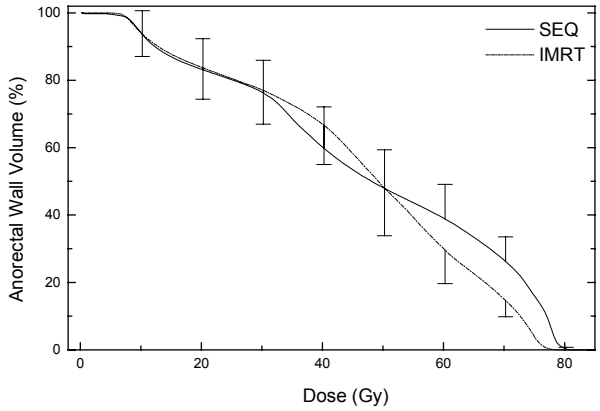

Figure 3A. Cumulative dose-volume histogram of anorectal wall (relative) for SEQ and SIB-IMRT shows that the rectal wall volume irradiated to any dose is lowered by using IMRT, except for the intermediate-dose region (35-45 Gy). Error bars indicate 1 standard deviation.

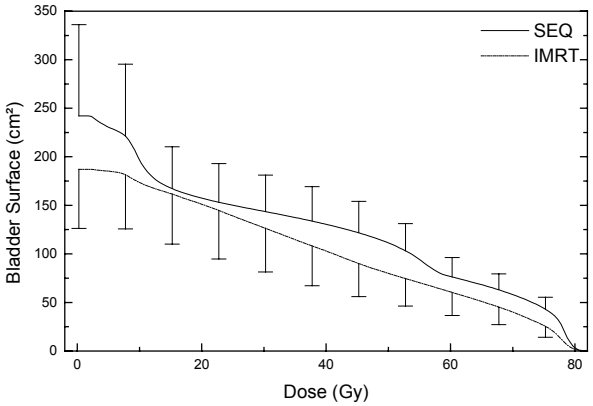

Figure 3B. Cumulative dose-surface histogram of bladder wall (absolute) for SEQ and SIB-IMRT shows that the bladder surface irradiated to any dose is lowered by using IMRT. Error bars indicate 1 standard deviation.

Outcome

There was no statistically significant differences in 5-year FFF rate (Phoenix) and 5-year freedom from clinical failure (FFCF) between both groups (FFF 70% for the SIB-IMRT vs 61% for the SEQ ; p = 0.3, FFCF 90% vs 72%, p = 0.07). However, these results should be interpreted with caution because of the non-randomized nature of the cohorts.

DISCUSSION

The significant improvement in bNED in different randomized dose escalation trials (1-4) for prostate cancer patients was associated with increased side effects. Late grade ≥ 2 rectal

toxicity was increased from 25% to 35% at 7-years (0.04) in our Dutch trial (4), from 12% to 26% at 6-years (p = 0.001) in the trial of the M.D. Anderson Cancer Center (2) and from 9% to 18% at 5-years (p = 0.005) in the MGH/Loma Linda University Medical Center trial (1). In an attempt to reduce these toxicities without compromising the outcome, we have used the advantage of IMRT in enhancing conformality and allowing greater sparing of the surrounding normal tissues. In this study we found a significant decrease in acute GI toxicity by using IMRT. The late GI, early and late GU toxicities were also decreased, albeit statistically not significant. Regarding outcome, patients treated with IMRT technique had comparable FFF and FFCF.

Different studies have also shown that despite the enhanced conformality achieved with implementing an IMRT-technique, the bNED is apparently not compromised. In a study by Zelefsky *et al.* (6), the 3-year actuarial incidence of late grade ≥ 2 GI toxicity in patients managed by 81 Gy with IMRT was 2% compared with 14% in those treated with 3D-CRT by the same dose (p=0.005), while the 3-year bNED was similar in patients treated with both techniques and varied from 92% for favorable and 81% for unfavorable risk groups. The therapeutic gain achieved in our study and in that of others is likely owing to the dosimetric advantages of IMRT. In most reports, no correlation between rectal DVHs and acute rectal toxicity could be found (2, 19), whereas this correlation was clearly demonstrated in the study of Peeters *et al*. (12) from our group. They showed that rectal wall volumes treated to intermediate (V35) and high doses (V65) were significant variables in predicting acute GI toxicity in the multivariate analysis. Even with a low V65 (10%), the probability of acute GI toxicity was still around 40% (12). The significant decrease in acute grade ≥ 2 GI toxicity observed in our patients treated with SIB-IMRT compared to those treated with SEQ (p = 0.001) may be explained by the significant reduction of V65 (p = < 0.001) by using IMRT.

Several authors have pointed out the importance of different DVH parameters for the development of late GI toxicity. V60, V65, and V70 were the most significant parameters associated with late grade ≥ 2 GI toxicity (2, 11, 12). In many ways, it should not be surprising that we have also shown a decrease in late GI toxicity by using IMRT in comparison with 3D-CRT, albeit statistically not significant. Pollack *et al* (2) concluded in the M.D. Anderson study that dose escalation techniques limiting the V70 to < 25% will dramatically reduce late GI toxicity. According to that study, when the V70 was limited to ≤ 25%, the overall late grade ≥ 2 GI toxicity at 6 year was 16%, compared with 46% by a V70 > 25% (p = 0.001). In our patients, we found a V70 of 14% and 26% for SIB-IMRT and SEQ, respectively (p < 0.001), with a corresponding decrease in late grade ≥ 2 GI toxicity. V65 is the most significant parameter associated with rectal bleeding according to Peeters and colleagues (12). The incidence of this complication at 4 years was only 1% when V65 was below 23%, whereas it was about 10% when V65 was ≥ 28%. In this analysis, we found a V65 of 22% in patients treated with SIB-IMRT vs 33% in patients treated with SEQ (p < 0.001), with the corresponding incidences of rectal bleeding at 5 years of 3% vs 10%, respectively (p = 0.2).

The significant reduction of acute GI toxicity achieved with IMRT might also be partially responsible for the subsequent reduction of the late GI toxicity. A number of investigators have shown a strong correlation between the incidence and severity of acute and chronic GI toxicity in prostate cancers treated with RT (15). Heemsbergen *et al.* (15) concluded that acute GI toxicity and more specifically acute proctitis were both significant predictors of late GI toxicity, suggesting a significant consequential component in the development of late grade ≥ 2 GI toxicity. Patients with acute proctitis had a higher risk for developing late grade ≥ 2 GI toxicity with 40% cumulative incidence at 5-year vs 16% in patients without acute proctitis. The significant decrease in the incidence of acute proctitis achieved with use of IMRT in our patients (from 38% to 15%, $p = 0.03$) might lead to further decrease in late grade ≥ 2 GI toxicity with longer follow-up. Acute proctitis as a predictor of late GI toxicity was also reported by Denham *et al.* (16) and Zelefsky *et al.* (17).

Regarding GU toxicity, Peeters *et al.* (12) found a significant correlation between acute GU toxicity and aS45 and aS65 at the multivariate regression analysis. In our analysis, both aS45 and aS65 were significantly decreased by using IMRT technique ($p < 0.001$). In order to reduce late grade ≥ 3 GU toxicity and grade ≥ 2 urinary retention, Harsolia *et al.* (13) recommended to limit the V30 to < 30 cm^3 and the V82 to < 7 cm^3, when possible. In our group, both parameters were reduced by using IMRT. Cheung *et al.* (20) found a significant higher rate of late GU toxicity when the dose to 2.9% of the bladder was ≥ 78 Gy. Once again, this parameter was also reduced in our patients treated with SIB-IMRT and was < 2.9 % (results not shown). However bladder doses were lowered with IMRT in our patients (Table 1 and Figure 3B), but this still did not translate to reduction of acute and late GU toxicity. The lack of differences in observed rate of late GU toxicity between both techniques may related to similarities in urethral dose, which was not specifically constrained, because we know that all of the prostatic urethra receives a full dose as well by using 3D-CRT as by IMRT technique. Whether IMRT can restrict the dose to the urethra without creating unacceptable cold spots in the PTV is unknown.

Peeters *et al.* (10) from our group performed a Cox proportional hazard analysis testing all potential prognostic clinical factors for the end points late grade ≥ 2 GI and GU toxicity and found that a history of abdominal surgery and pre-treatment GI symptoms were associated with a higher incidence of late grade ≥ 2 GI toxicity, whereas hormonal therapy, pre-treatment GU symptoms, and prior transurethral resection of the prostate were all highly significant ($p \leq 0.006$) prognostic factors for late grade ≥ 2 GU toxicity. These prognostic clinical factors were equally distributed among both groups and have, therefore, not influenced the incidence of late toxicity in our analysis. However, more patients in the SIB-IMRT had upper abdominal or laparoscopic surgery than in the SEQ group, the incidence of GI toxicity is unlikely to be influenced by this type of surgery.

Our analysis contains a number of limitations. First, the follow-up is relatively short, especially for late GU toxicity, and the number of patients treated is limited. Although the SEQ and SIB-IMRT groups were well-balanced in terms of patient's characteristics, the major difference

between both groups was the significantly longer follow-up in the SEQ patients. This was due to the relatively recent implementation of IMRT in our patients at that time. The difference in number of patients of group IV (24% vs 12%, p = 0.3) could possibly have biased the results of the reduced GI toxicity for the SIB-IMRT group. In order to study the impact of this difference, we did an additional analysis of GI toxicity after stratifying patients in 4 dose-volume groups. The acute and late GI toxicity was still better in patients treated with SIB-IMRT (p= 0.001 and p = 0.1, respectively). Moreover, the rectum dose in group II-IV was similar, but higher than in group I. The distribution of our patients among group I and group II-IV was identical. Therefore the distribution of patients among the dose-volume groups might not have biased our results regarding GI toxicity. The difference between both groups regarding FFF might have been influenced by the slightly more patients in group IV treated with SEQ than with SIB-IMRT.

Our results raise also the question whether the improvement seen here is also clinically significant. Although low grade symptoms were common, these are not trivial and may results in considerable distress with subsequent decrease in the quality of life of these patients. Denham *et al*. reported that fecal urgency and bleeding have the highest impact on quality of life (16), while the analysis of Koper *et al.* revealed that mucus discharge, soiling and fecal loss were the most bothering complaints (21). It is our belief that the favorable impact of IMRT on chronic GI sequelae is clinically significant and justifies the increased cost and time of IMRT planning and treatment in these patients.

Another potential concern that has been raised with the use of IMRT-treatment delivery technique is the greater chance of geometrical uncertainties. As a result of enhanced conformality, one might be afraid of increasing treatment uncertainties and target motion with IMRT. Bos *et al.* (22) have applied different IMRT-techniques for 5 patients in order to determine the effect of geometrical uncertainties on IMRT dose distributions for the prostate. They found that the IMRT-technique used in our patients to be insensitive to geometrical uncertainties (organ motion and patient set-up) and guarantees adequate coverage of the CTV. Therefore, we can reasonably conclude that concerns about geographic miss of the target are unfounded, also because our results showed comparable biochemical and clinical control rates for patients treated with IMRT compared to those treated with 3D-CRT.

Finally, we believe that the recent implementation of image-guided RT will further enhance the safety and accuracy of IMRT by better correction of both inter-fraction positional variation and intra-fraction prostate motion and achieve, therefore, further decrease in the late toxicity.

CONCLUSION

Our results provide the first assessment of toxicity in prostate cancer patients treated with IMRT within the Dutch dose escalation trial. The acute toxicity is significantly lowered by using IMRT. Overall, the risk and severity of chronic GI toxicity in these patients were low and compared

favorably to that seen in patients treated with SEQ. Moreover, the improved toxicity profile achieved with IMRT was not achieved at the cost of tumor control. However, these results should be interpreted with caution, given the relatively short follow-up and limited number of patients. Nonetheless, our results are promising and suggest that the dosimetric benefits achieved with IMRT planning in prostate cancer patients may translate into long-term benefits in patients' outcome and toxicity.

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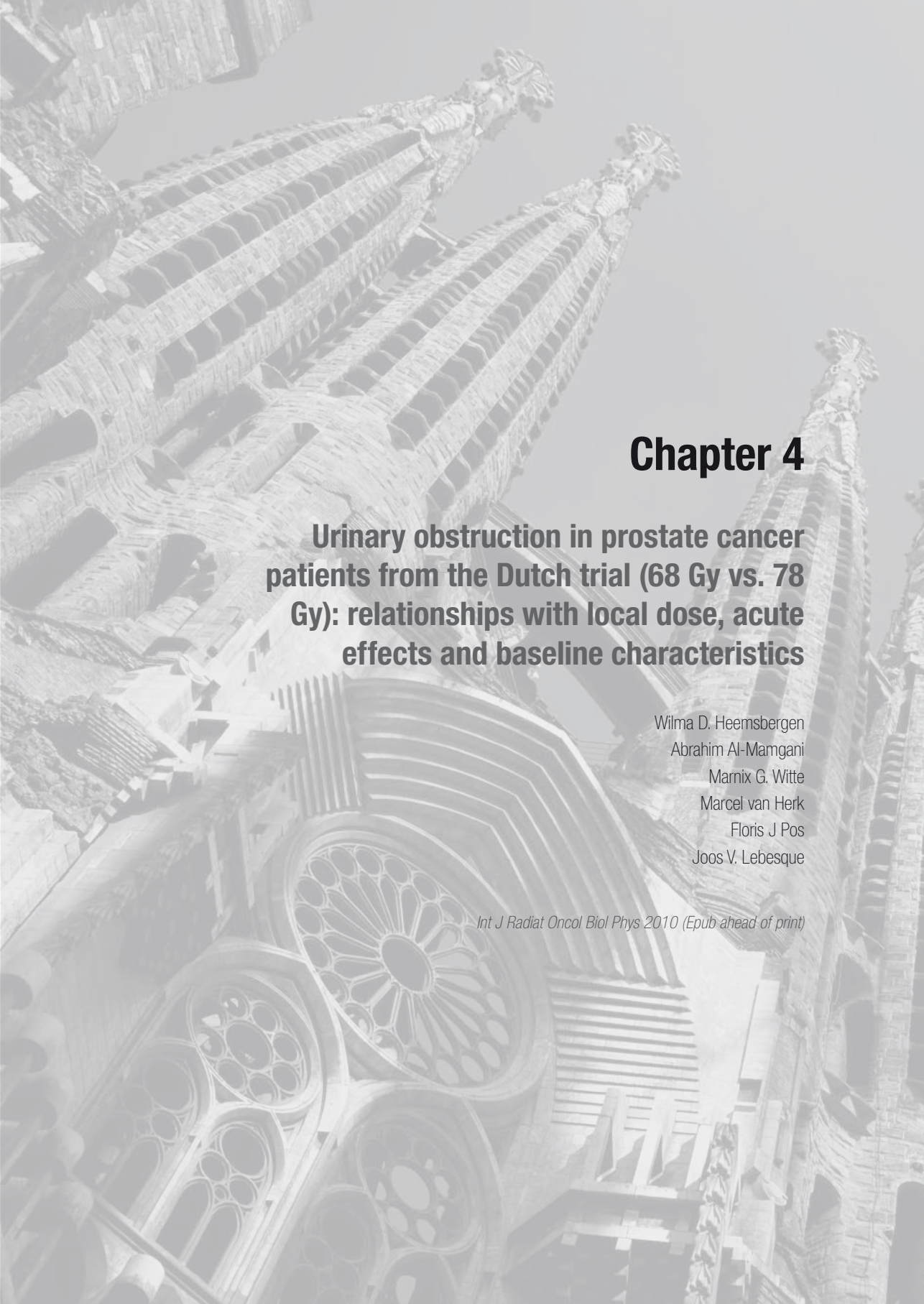

Chapter 4

Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects and baseline characteristics

Wilma D. Heemsbergen
Abrahim Al-Mamgani
Marnix G. Witte
Marcel van Herk
Floris J Pos
Joos V. Lebesque

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ABSTRACT

Purpose

To investigate the relationship between late urinary obstruction and details of the dose distribution of irradiated prostate cancer patients, taking into account baseline symptoms and acute complaints.

Methods

We selected patients of the Dutch multicenter trial randomizing between 68 Gy and 78 Gy, for whom toxicity data and dose data were available (n = 557). Absolute dose surface parameters of the delineated bladder were calculated. Next we constructed 3D dose maps of the area around the prostate, providing an approximate identification of corresponding anatomical locations. Dose difference maps were constructed by subtracting the mean dose maps of patients with and without late urinary obstruction. Selected local dose points were analyzed in a Cox regression analysis.

Results

For 40 patients late urinary obstruction was scored: 19/296 patients receiving 68-72 Gy, 21/261 76-78 Gy. There were 19 events within 2 years after irradiation and 21 later on. The bladder surface receiving ≥ 80 Gy predicted ($p < 0.01$) for obstruction within 2 years. The dose difference map indicated highly significant differences in the bladder neck situated in the trigonal region ($p < 0.001$), which where especially predictive for obstructions after 2 years and for diagnosed bladder neck obstruction. Baseline complaints as well as TURP and acute complaints were mainly predictive for obstruction within 2 years.

Conclusions

Relatively early events of urinary obstruction are associated with urinary problems existing before RT, acute toxicity, previous TURP and hotspots in the bladder. Events after a lag period of 2 years were associated with the local dose in the trigonal area.

INTRODUCTION

External radiotherapy for prostate cancer is the main treatment option when there is considerable risk for tumor invasion of the prostatic capsule and/or seminal vesicles. Nowadays conformal radiotherapy with dose levels of 74-80 Gy has become clinical practice since several studies reported improved freedom from failure compared to levels of 64-70 Gy. (1) Side-effects of radiotherapy mainly concern the rectum and bladder. A severe complication can be urinary retention. This symptom is in most cases the result of a severe outflow obstruction (stricture) in the bladder neck or urethra, which can be divided in the proximal part close to the bladder neck, the prostatic urethra, and the distal urethra near the external sphincter. Possible other causes of obstruction are ureter obstruction, and an enlarged prostate.

In a recent study (2) of prostate cancer patients (n = 6597), the estimated cumulative incidence of treated urethral strictures at 4 years was 5 % for external radiotherapy, 11 % for brachytherapy and 11 % for radical prostatectomy. In their study they noticed that prostatectomy and brachytherapy leads to relatively early obstructions (within 24 months) whereas onset of obstruction was delayed after radiotherapy. Harsolia et al. (3) studied a trial population of 332 patients with a median follow up of 1.6 years who received high doses (median 79 Gy). The cumulative incidence of treated urinary retention at 3 years was 5 % in their population. In our Dutch trial, the cumulative incidence at 3 years was similar: 6 % in the 78 Gy arm and 4 % in the 68 Gy arm. (4) At 7 years this incidence was increased to 11 % and 8 %. (1)

Data on hypothesized radiation dose-effect relationships concerning urinary toxicity are not conclusive. The elderly patient population is also subject to development of complaints due to aging, which obscures toxicity scoring. Another aspect is that a number of these patients were visiting an urologist because of pre-existing urinary problems, when their prostate cancer was diagnosed. Apart from determining the most relevant toxicity, also the measurement of relevant dose parameters is not trivial. Studied dose parameters are usually derived from the total delineated bladder without evaluating local structures (like the bladder neck) separately. Due to variable filling and stretching of the bladder during treatment, the position of the bladder on the planning CT scan is probably of limited value which can obscure dose-effect relationships.

A number of reported baseline parameters associated with GU toxicity are: prostate volume, hormonal therapy, diabetes and TURP (3-5). A consequential relationship between acute and late GU toxicity has also been reported (3, 6, 7).

In the present study, we investigated the relationship between dose parameters and late urinary obstruction, taking into account baseline problems and specific acute complaints. We analyzed absolute dose surface data as well as dose maps representing the dose in the total “bladder region” around the prostate. We hypothesized that such dose maps could be useful to identify more local dose-effect relationships for late GU toxicity.

PATIENTS AND METHODS

Patient group

In the Dutch trial, 664 patients were randomized to 68 Gy or 78 Gy. Its patient population and treatment has been described extensively elsewhere (1, 4). We selected patients for whom acute and late toxicity was scored using checklists, which was the case for most of the patients treated at two hospitals (n=566). For five patients, no late toxicity data were available due to limited follow-up and for four patients, not all dose data were available, leaving 557 patients for our current analysis.

Treatment

Treatment plans were constructed using CT scan data. The Clinical Target Volume (CTV) was defined as the prostate or prostate plus seminal vesicles (SV), depending on the estimated risk of SV invasion. Delineations were done in the transversal CT slides and at that time the software did not allow to check delineations in sagittal view, which caused typical deformations like the CTV shape in Fig. 1. There was no MRI available to establish the border between prostate and bladder neck; therefore part of the bladder neck was included in the CTV for a number of patients. A 1 cm margin was applied to the CTV for construction of the Planning Target Volume (PTV) for the first 68 Gy (2 Gy per fraction). A margin of 5 mm (0 mm towards the rectum) was applied for the 10 Gy boost. Bladder and rectum were delineated. For the bladder there were no dose constraints in the trial protocol.

Toxicity scoring

Acute (28-120 days after start of RT) and late toxicity (> 120 days) was scored by the trial data managers, using the RTOG/EORTC and LENT/SOMA toxicity scales. (4) Patients reported complaints on a checklist, before during and after radiotherapy. This checklist included: (high) frequency during day and/or night, pain/cramps when passing urine, urinary incontinence (leakage) and a weak urinary stream. We labeled patients as having urinary obstruction when they were treated for symptoms of (complete) urinary retention: scoring on Grade ≥2 items of catheterization, TUR and / or dilatation. We also analyzed the events by defining relatively early events and events after a lag period. As a cutoff we took 2 years of follow-up. Because of the delay in reporting events (follow up was scheduled every 3-6 months) we included events reported up to 26 months after start of radiotherapy as events < 2 years.

Dose Surface Histogram parameters

We used a volumetric database that had direct access to the CT images, dose distributions and delineations. For each patient the outer bladder wall was delineated on the planning CT scan and the 2D contours were triangulated to a 3D surface. We calculated the absolute surface receiving ≥ 5 Gy – ≥ 80 Gy, with dose steps of 5 Gy. As described by Hoogeman et al. (8),

absolute dose-surface data are the best choice because they are less variant under bladder filling changes than relative data or dose-volume data.

Construction of dose maps

Dose maps offer a method to compare or combine the treatment planning dose distributions of different patients in 3D. We visualized the dose in the bladder region using dose maps, without considering the delineated bladder contours. Within 6 cm outside the prostate surface of each patient, the dose was calculated for the same set of dose points, defined by their radius from the surface and their direction relative to the center of mass (given by two angles). We started with the coordinates of dose grid voxels of a first patient (the template patient). For all other patients, dose values for the same sets of radius - angle values were calculated, by trilinear interpolation of the nearest dose points of the individual dose grid. In this way, the obtained dose maps of all patients were comparable and could be averaged by averaging the dose in the dose points with identical radius and angle. Mean dose maps of patients without and with obstruction were created and subtracted to form a dose difference map. This map visualizes the local areas where patients with obstruction received more dose than patients without obstruction. For each point in the dose difference maps, we also calculated the p value for the local dose difference (based on t-distributions) in order to determine roughly the regions of interest. Mapped dose distributions were visualized using the anatomy of the template patient. This patient had a prostate volume of 52 cm^3, a rectal volume of 41 cm^3, and a bladder volume of 389 cm^3.

Selection of dose points

From our dose difference maps, we selected 2 dose points for further evaluation. First, we selected a dose point (referred to as trigone point) in the trigonal area of our template patient. The trigonal area is defined as the triangle-shaped area where the bladder neck is situated, the urethra starts, and where the ureters end in the bladder. For this purpose, we looked up the coronal CT slice where the prostatic urethra was visible (Fig. 1A) and we followed visually the urethra to the prostate edge where the urethra starts. Then we marked a point in the trigone area 2 cm above the starting point of the prostatic urethra. It is not expected to find dose-effect relationships for dose points closer to the prostate contour and bladder neck because this part will be mainly situated in the PTV, receiving about the same dose as the targeted prostate. We also picked a second dose point in the dose difference map where the dose differences were most significant (referred to as max point).

Validation of dose maps

We picked the trigone point in our template patient, assuming that this point was situated in the trigone area for all other patients as well. In order to validate this assumption, we manually checked this for 69 patients. For this purpose, we determined individually the correspond-

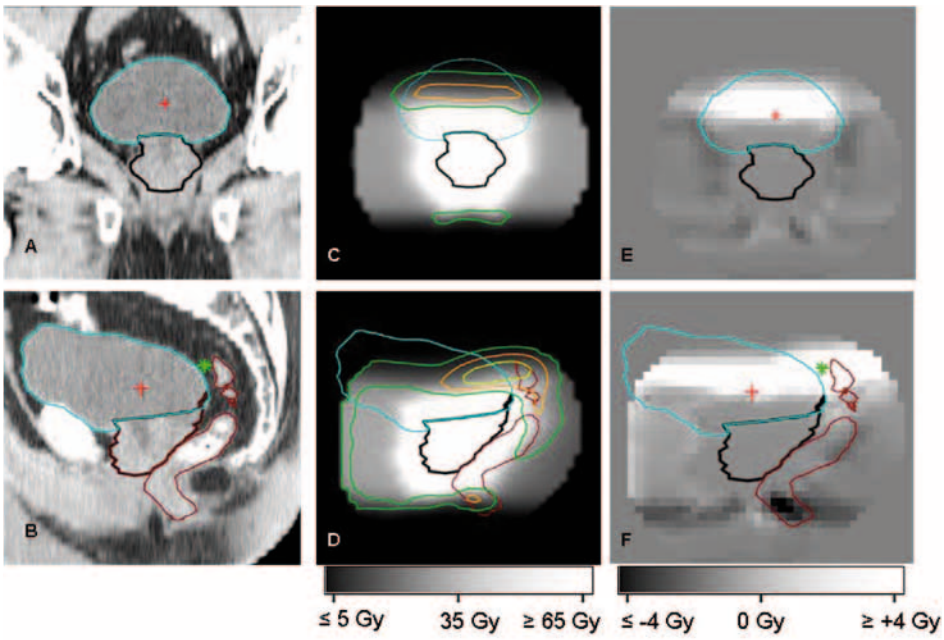

Figure 1. Figures. 1A and 1B. Coronal and sagittal view of a CT scan in the prostate/bladder region for the template patient (blue: bladder, black: prostate, dark red: rectum). The cross indicates the trigone point 2 cm above the starting point of the prostatic urethra, in a coronal slice where the urethra is visible. The asterisk in Fig. 1B indicates the region where the largest dose differences are found (Fig. 1EF).

Figures 1C and 1D. The average planned dose for all patients, in corresponding coronal and sagittal view. Apart from the delineated organs, contours of standard deviations are included to indicate roughly where the largest dose variations are present (green 10 Gy contour, orange 15 Gy, yellow 20 Gy).

Figures 1E and 1F. Dose difference maps (coronal and sagittal view): mean dose map of patients without urinary obstruction subtracted from mean dose map of patients with obstruction. White region indicates significant dose differences ($p<0.02$), range 4 - 12 Gy.

ing point in the same way as we did for the template patient (as described in the previous paragraph).

The local dose and the anatomical position (dose map coordinates) of this manual trigone point were then compared with those of the trigone point from the mapping procedure. For this procedure we selected 23 patients with a determined bladder neck obstruction and/or obstruction later than 2 years and we randomly picked another 46 patients by selecting the study number above and below the patients with obstruction. Patients with hotspots were excluded.

The dose in the trigone point according the manual procedure correlated highly with the dose in the trigone point according the automated dose mapping procedure (Pearson correlation coefficient was 0.92). The mean dose in the selected obstruction group (n = 23) was 57.3 Gy according the dose mapping and 58.0 Gy according to the manual procedure. For the group without obstruction (n = 46) these numbers were 47.2 Gy and 47.5 Gy, respectively. The mean

distance between the two points was 0.07 cm (0.2 cm 1SD), 0.08 cm (0.2 cm 1SD) and 0.05 cm (0.5 cm 1SD) for the left-right, cranio-caudal and anterior-posterior direction, respectively.

Statistical analysis

We determined in a univariate analysis which parameters were significantly associated with late urinary obstruction and we evaluated which factors remained significant in a multivariate (MV) model (Cox regression). We also determined the prognostic value of relevant parameters separately for events < 2 years and > 2 years and for diagnosed bladder neck obstruction. Time-to-event was calculated from the start of RT. ©SPSS for Windows software was used for the analyses (release 15.0, SPSS Inc., Chicago, Illinois).

RESULTS

General statistics

Median follow-up time was 71 months for patients alive. Table 1 shows the distribution of the patients with regard to T stage, dose and pretreatment characteristics. The group of 296 patients receiving 68-72 Gy consisted of 278 patients randomized to 68 Gy and 18 patients randomized to 78 Gy but receiving a lower dose mainly due to dose limiting constraints. Table 2 summarizes the calculated dose parameters and characteristics of the bladder. The cumulative

Table 1. Characteristics of the study population.

Variable	Total group (N = 557)	
	N	%
Tumor stage:		
T1 / T2A	239	43 %
T2B / T3A	236	42 %
T3B / T4	82	15 %
RT dose VS:		
0 Gy	99	18 %
48-50 Gy	102	18 %
66-78 Gy	356	64 %
RT dose prostate:		
68 Gy	293	53 %
70-72 Gy	3	1 %
76-78 Gy	261	47 %
Hormonal therapy	134	24 %
TURP	65	12 %
Diabetes	33	6 %
Age (mean, SD)	68 years	6.4 years

Table 2. Bladder and dose characteristics.

Variable	Total group (N = 557) Mean (SD)
Bladder surface	241 (92) cm^2
Bladder volume	292 (181) cm^3
Dose surface histogram	
Surface ≥ 20 Gy	161 (39) cm^2
Surface ≥ 40 Gy	127 (34) cm^2
Surface ≥ 60 Gy	75 (23) cm^2
Surface ≥ 80 Gy (n, %)	
0 cm^2	515 (92 %)
0 - 0.49 cm^2	8 (1 %)
0.5 – 14.7 cm^2	34 (6 %)
Dose map	
Dose trigone point	47 (14) Gy
Dose max point	31 (23) Gy

incidence of urinary obstruction was 9.7 % at 7 years of follow-up for all patients, 8.4 % for patients receiving 68-72 Gy and 11.2 % for patients receiving 76-78 Gy (p=0.4).

Urinary obstruction

Urinary obstruction was observed in 40 patients, mainly scored as Grade 3 toxicity. The earliest event was scored at 7 months after RT and the latest at 8.5 years. Nineteen events were within 2 years and 21 later than 2 years. We studied patient files to determine the location of the obstruction. It was located in or close to the bladder neck for 16 patients (of whom one patient was known with an obstruction of both ureters). For 14 patients the location was indicated as “urethra” or “prostatic urethra”: it can not be excluded that it was close to the bladder neck as well. For 3 patients the obstruction was located in the distal urethra, and for 2 patients obstruction was probably caused by an enlarged prostate. The location remained unknown for 5 patients.

Baseline and acute variables

A previous TURP was strongly associated with obstruction (Table 3, Fig. 2). Fig. 2 shows that the effect of a TURP is present during the first 2 years and also in the following years where the Kaplan Meier curves are still separating. Estimated Hazard Ratio’s (HR) were 3.6 and 2.8, respectively (Table 3). No relationships were found for diabetes, prostate volume, hormonal therapy, smoking and age. Predictive GU baseline complaints were (Table 3): urinary leakage (incidence of 12 %) and nocturia ≥ 3 (27 %). Furthermore, these factors were stronger predictors for events < 2 years compared to > 2 years.

Table 3. Results of Cox regression for the endpoints urinary obstruction (all events, univariate and multivariate) and for established bladder neck obstructions, events within 2 years and events later than 2 years (all univariate analysis).

	Univariate								Multivariate	
Parameter / Endpoint	Urinary obstruction (40 events)		Bladder neck obstruction (16 events)		<2 years obstruction (19 events)		>2 years obstruction (21 events)		Urinary obstruction (40 events)	
	HR	p	HR	p	HR	p	HR	p	HR	p
Baseline										
TURP (yes/no)	3.2	**0.001**	2.8	0.07	3.6	**0.009**	2.8	**0.04**	3.6	**0.001**
Urinary leakage (yes/no)	2.9	**0.003**	1.7	0.4	3.3	**0.02**	2.5	0.07	2.7	**0.007**
Nocturia ≥ 3	2.7	**0.004**	2.4	0.1	5.6	**0.002**	1.5	0.4	-	
Acute toxicity										
Pain passing urine	3.1	<**0.001**	3.2	**0.02**	4.3	**0.003**	2.4	0.05	3.4	<**0.001**
Urinary leakage (yes/no)	2.5	**0.006**	2.9	**0.04**	5.9	**0.001**	1.2	0.6	-	
Dose parameter										
Surf > 80 Gy <0.5 cm^2>	3.2	**0.01**	6.0	**0.002**	5.9	**0.001**	1.0	1.0	3.5	**0.006**
Trigone point <47 Gy>	2.7	**0.01**	5.4	**0.03**	1.7	0.3	4.5	**0.02**	2.6	**0.02**
Max point <31 Gy>“	2.6	**0.005**	5.4	**0.009**	1.8	0.2	3.9	**0.008**	-	
Prostate dose (per 10 Gy)	1.3	0.4	1.9	0.2	1.6	0.3	1.0	**0.9**	-	
Sem Ves dose (per 10 Gy)	1.2	**0.03**	1.4	0.09	1.2	0.2	1.2	0.2	-	

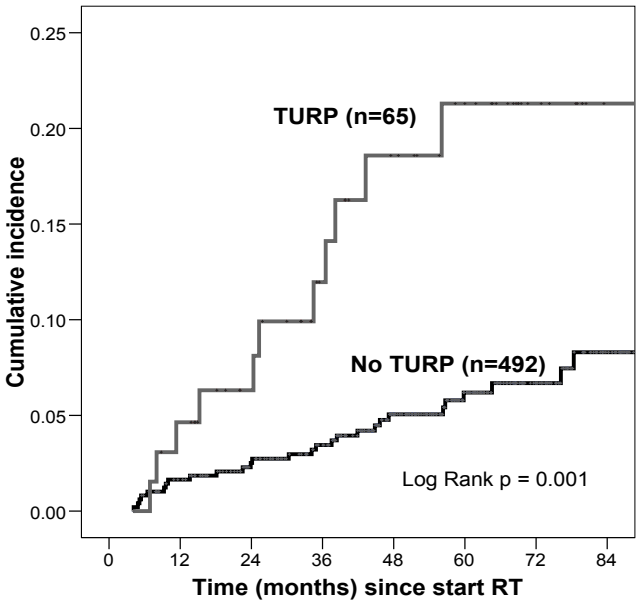

Figure 2. Kaplan-Meier curve showing the higher incidence (p=0.001) of late urinary obstruction for patients with a previous TURP compared to the patient group without a previous TURP.

Predictive acute complaints (maximum score) were: pain when passing urine (incidence of 64 %) and urinary leakage (28 %). The correlation of obstruction with acute toxicity seems only to be present for events < 2 years where the HRs are very significant ($p \leq 0.001$).

Dose Surface Histogram (DSH)

In Fig. 3 DSH's are plotted for patients with and without urinary obstruction. DSH's are close to each other with large standard deviations. The total bladder surface (and volume) was on average slightly larger for the patients with obstruction ($p = 0.2$). Hotspots, which were defined as areas > 0.5 cm^2, were significantly associated with obstruction: HR was 3.2 for area > 0.5 cm^2 vs. smaller areas (Table 3 and Fig. 4A). The HR was 6.0 for diagnosed bladder neck obstructions. Hotspots were mainly associated with events < 2 years (HR = 5.9) and not with events > 2 years (HR = 1.0). The subgroup of patients with hotspots was however small; only 39 patients with a surface of ≥ 0.5 cm^2 receiving ≥ 80 Gy.

Dose map

In Fig. 1, results of the mapping procedure are shown for an coronal (A, C, E) and sagittal (B, D, F) slice. In Fig. 1A and 1B the anatomy of the CT scan of our template patient is illustrated, including the delineated prostate, rectum and bladder. Figure 1C and 1D show mean dose maps of the total group with contours of standard deviations (SD). The dose difference map

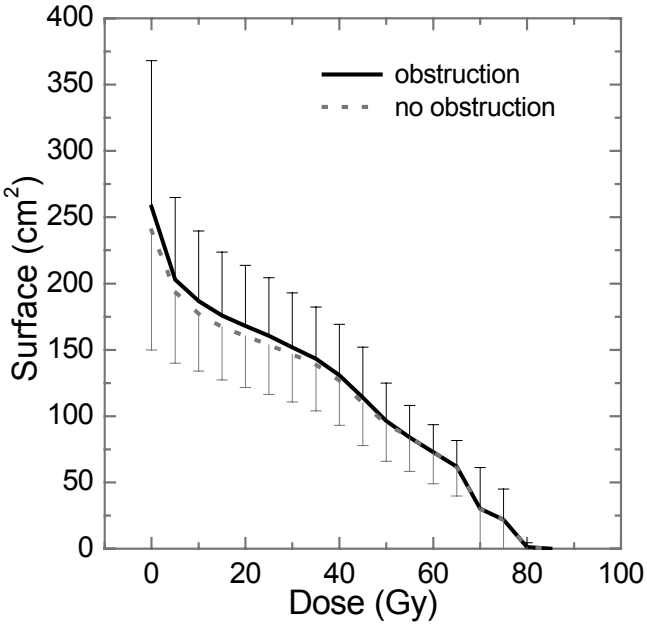

Figure 3. Absolute dose-surface histograms for patients with and without urinary obstruction.

indicated large significant dose differences up to 12 Gy ($p< 0.01$) superior of the PTV i.e. in the bladder area (Fig. 1E-1F). The trigone point is indicated with a cross. The max point, indicating the area with the most significant dose difference, was situated about 4 cm dorsally and 2 cm cranial from the trigone point (asterisk in panel B and F). The mean dose in these points was 47 Gy and 31 Gy, respectively (Table 2). For 515 patients with no obstruction the mean dose in the

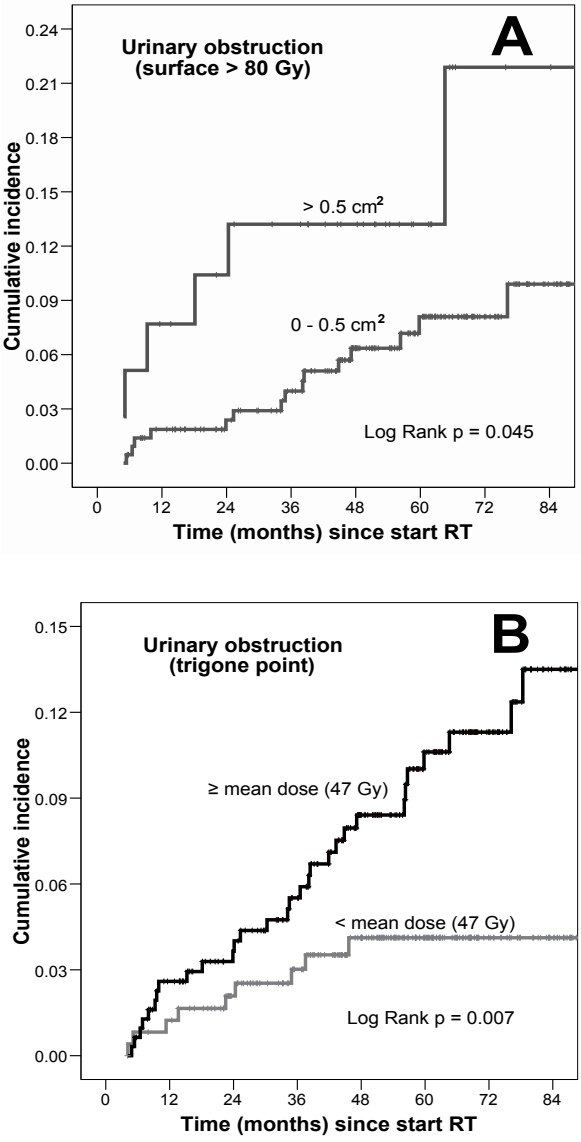

Figure 4 A and B. Kaplan Meier estimates for obstruction: A) cumulative incidence for patients with and without hotspots (surface receiving > 80 Gy below or above 0.5 cm^2), and B) cumulative incidence for subgroups receiving a dose above and below the mean dose in the trigone point.

trigone point was 46.7 Gy (14 Gy 1SD), and 52.1 Gy (12 Gy 1SD) for patients with obstruction. For established bladder neck obstruction the mean dose was 52.3 Gy (10 Gy 1SD). Patients with a previous TURP had on average a significantly higher dose in the trigone dose point (52.1 Gy vs. 46.4 Gy, p= 0.002). The dose in the trigone point and the max point were highly correlated and both significant predictors for obstruction and predicted especially for bladder neck obstruction and events > 2 years (Table 3). Fig. 4B shows the Kaplan Meier curves above and below the mean dose in the trigone point.

Dose to the prostate and seminal vesicles (SV)

As indicated in Table 3, dose to the prostate was no significant predictor for any endpoint whereas dose to the seminal vesicles was a significant predictor for urinary obstruction. Further explorative analyses revealed that the cranio-caudal extent of the delineated SV (calculated as extent of prostate + SV minus extent of the prostate) was significantly associated with urinary obstruction as well (p=0.03) and that the bladder volume on the planning CT scan was significantly associated with the cranio-caudal extent of the SV (p= 0.001). The bladder volume on the CT scan itself (volumes > 500 cm^3 vs. smaller volumes) was associated with obstruction (HR = 2.0, p= 0.07) for patients irradiated to the SV. These correlations strongly suggested that when the bladder fills, the SV are moving along. As a result, a patient with a full bladder on the CT scan will therefore have a larger cranio-caudal extent of the RT field to cover the stretched SV. For this reason, more dose will be planned to the bladder neck area, increasing the risk for bladder toxicity.

Multivariate analysis (MV)

When we tested the factors in an MV analysis with urinary obstruction as endpoint (Table 3), the urinary leakage in the acute phase, which is correlated to leakage at baseline, is no more significant. There seems to be only a consequential effect (acute complaints predicting for late) for 'pain passing urine'. Dose to the max point and dose to the seminal vesicles were not entered in this model because they were highly correlated with dose to the trigone point; replacing the trigone point with the max point or VS dose gave similar results.

DISCUSSION

We found baseline and acute factors to be significantly associated with urinary obstruction, which is in agreement with the findings of other studies. (3, 5-7) In the DSH analyses, we found that high dose regions (≥ 80 Gy) contributed to the development of urinary obstruction, which was also recently reported by others. (3, 9) The incidence of hotspots was however only 13 % for our high-dose group. In our study, the effect of hotspots was most apparent for diagnosed bladder neck obstructions, which can be expected since bladder hotspots are usually found

in the bladder neck area close to the CTV. Furthermore, hotspots were mainly associated with urinary retention < 2 years.

By constructing dose maps, we found strong indications for a local dose-effect relationship in the trigonal area, which was the most outspoken for patients with diagnosed bladder neck obstruction and for events > 2 years. Mean local dose in the trigone point was 47 Gy. Validation of the dose map procedure showed good correspondence of the dose and anatomical location of the trigone point from the automated mapping procedure compared to the trigone point of the manual procedure. The results from the dose mapping should be interpreted with care; local areas of clinical interest are indicated rather than local points. It is likely that bladder DSH analyses can find the local dose effect for late obstruction in case the relevant area is delineated, providing more conclusive evidence of a dose-effect relationship.

In our study, we had 40/557 patients with urinary obstruction at a median follow-up of 71 months, which seems rather high. In general, we have higher Grade ≥ 2/3 incidences of GU toxicity in our trial compared to other similar dose escalation trials (10-12), which we attribute to our detailed and frequent follow-up procedures. Most other dose escalation trials have not reported detailed information on urinary obstruction. In the MRC RT01 study, it was reported that 20/422 patients receiving 74 Gy, had urethral structures (median follow-up of 63 months).

Transurethral Resection of the Prostate (TURP)

We found that a previous TURP is associated with a higher post-RT risk of GU complications, in this case urinary retention. As hypothesized by others, this can be explained by local damage caused by the TURP, relative devascularization and a decreased repair capacity of the mucosa. (5) A TURP was on average associated with a higher dose in the trigone area, which probably also contributed to the observed increased toxicity rate. This phenomenon can be explained by the anatomy of a prostate with a previous TURP: the base is usually broadened and therefore the CTV is broadened at the bladder site, leading to inclusion of a larger part of the bladder neck into the PTV.

Bladder neck obstruction

For 16 patients an obstruction in the bladder neck region was confirmed, which was significantly associated with the dose in the trigone point. We see however in the dose difference map that the largest dose differences occur cranial from the bladder neck, which seems counterintuitive. An explanation for this phenomenon could be that the dose in this area is correlated from one point to another; the largest (and most significant) dose differences usually appear in the penumbra. Therefore a higher or lower dose in the bladder neck area will be associated with an even more pronounced dose difference in the penumbra at a certain distance of the point of interest. Second, the dose next to the bladder neck area could also be relevant, since the bladder neck will probably move in and out of this area during treatment. Furthermore, the dose just cranial from the prostate is probably predictive for bladder neck obstruction, however, there

is only limited dose variation in this area since it is included in the PTV and will mainly receive 68 Gy or 78 Gy. The cumulative incidence of confirmed bladder neck obstructions at 7 years was 2.6 % and 6.1 % for the 68-72 Gy and 76-78 Gy dose groups, respectively (p= 0.2).

The presented data highly suggest that bladder neck obstruction is a result of delivered dose in the trigonal area. Limiting dose to this area is often not an aim in dose planning. Omitting hotspots in the bladder neck and restrict the dose to the lower part of the bladder (wall) would lower the risk for this severe adverse event and could therefore be a very relevant aim in treatment optimization.

Obstruction within and after 2 years

By defining events before and after 2 years of follow-up, we were able to discriminate between factors predicting for early events, late events after a lag period, or for both in this explorative analysis. Persisting and aggravating baseline complaints as well as TURP, acute complaints and high hotspots were mainly predictive for events within 2 years. The local dose in the trigone point was especially predictive for obstructions after 2 years. It is plausible that factors causing mechanical damage, like TURP and hotspots, induce tissue damage and consequential clinical problems after a shorter period than (is to be expected from) radiation damage. On the contrary, radiation effects are to be expected after a lag period. It is likely that radiation induced obstruction can be found after longer periods of follow-up then we have now. For this purpose it would be interesting to update the trial toxicity data up to 10-15 years of follow-up.

Other GU endpoints

In our explorative analysis, we produced also dose maps for other endpoints: presence/absence of haematuria, incontinence, nocturia ≥ 4 and day frequency ≥ 16. For some endpoints, dose differences were noticed further away from the prostate where the dose maps are less reliable with respect to correspondence between patients in anatomical locations, which made it hard to interpret the results unambiguously. For the endpoint haematuria we found clear dose differences in the bladder wall of the lower bladder, which were most pronounced at the posterior side. We will further study these dose map results in future analyses.

CONCLUSIONS

Urinary obstruction within 2 years after RT is associated with urinary problems existing before RT, acute toxicity, previous TURP and hotspots in the bladder. Events after a period of 2-7 years are associated with the local dose in the trigonal area as well as with other correlated dose points in this bladder area. Limiting dose to the bladder neck area is often not an aim in treatment optimization. Because of the serious nature of urinary obstruction, sparing of the bladder neck area is however advised in order to prevent the patient from unnecessary risks.

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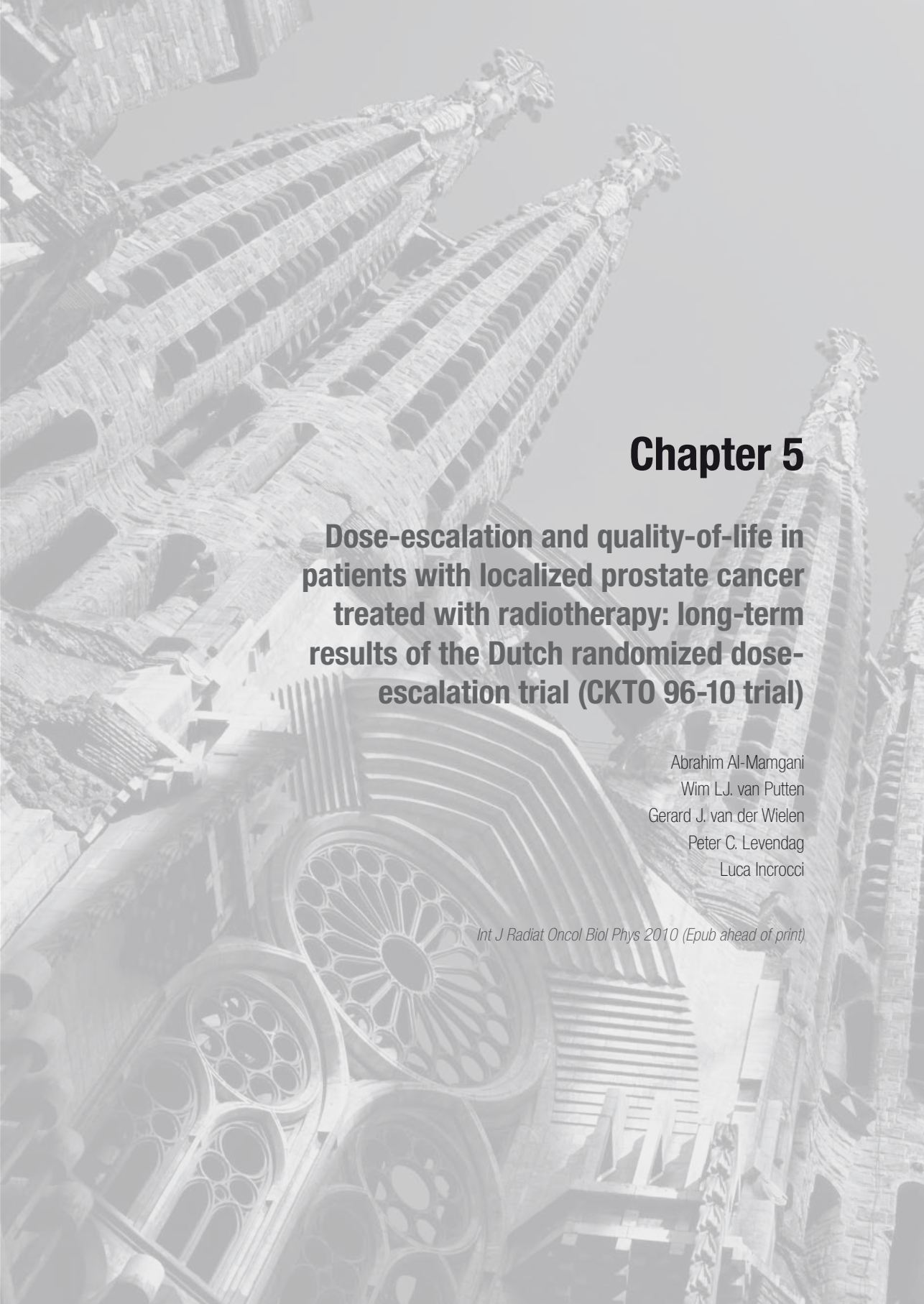

Chapter 5

Dose-escalation and quality-of-life in patients with localized prostate cancer treated with radiotherapy: long-term results of the Dutch randomized dose-escalation trial (CKTO 96-10 trial)

Abrahim Al-Mamgani
Wim L.J. van Putten
Gerard J. van der Wielen
Peter C. Levendag
Luca Incrocci

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ABSTRACT

Purpose

To assess the impact of dose-escalation of radiotherapy on quality-of-life (QoL) in prostate cancer (PC) patients.

Patients and methods

Three-hundred prostate cancer patients participating in the Dutch randomized trial (CKTO 96-10) comparing 68 to 78 Gy are the subject of this analysis. These patients filled out the SF-36 QoL-questionnaires before radiotherapy (baseline) and 6, 12, 24 and 36 months thereafter. Changes in QoL over time of ≥ 10 points were considered clinically relevant. Repeated-measures regression analyses was applied to estimate and test the QoL-changes over time, the differences between the two arms and for association with a number of covariates.

Results

At 3-year follow-up, the summary-score physical-health was 73.2 for the 68-Gy arm vs. 71.6 for the 78-Gy arm (p= 0.81) and the summary-score mental-health was 76.7 for the 68-Gy arm vs. 76.1 for the 78-Gy arm (p= 0.97). Statistically significant (p< 0.01) deterioration in QoL-scores over time was registered in both arms in 6 scales. The deterioration over time was more pronounced in the high-dose arm in most scales. However clinically relevant deterioration (> 10 points) was seen only in two scales. None of the tested covariates were significantly correlated with QoL-scores.

Conclusion

Dose-escalation did not result in significant deterioration of QoL in PC-patients. In both randomisation arms, statistically significant decreases in QoL-scores over time were seen in six scales. The deterioration of QoL was more pronounced in the physical- than in the mental-health domain and in some scales more in the high- than in the low-dose arm, but the differences between the arms were not statistically significant.

INTRODUCTION

Prostate cancer (PC) has become the most frequent malignancy in men in Western countries. Beside definitive radiotherapy (RT), prostatectomy, and hormonal therapy (HT), observation might be applied in early-stage low-risk disease. Our group and others (1-3) have demonstrated that escalating the dose of RT not only improves tumor control but also increases late toxicity. The Dutch randomized trial (CKTO 96-10) has shown that freedom from failure at 7-years was significantly better in the 78 Gy arm compared with the 68 Gy arm (54% vs. 47%; p= 0.04). While there was no difference in overall survival, late GI toxicity was increased in the 78 Gy arm (p= 0.04) (3). Beside the achievement of cure as primary goal of radical treatment of PC, toxicity and assessment of quality-of-life (QoL) have become very important secondary considerations, especially in view of the arguments in favour of watchful waiting.

To date, none of the randomized dose-escalation studies have thoroughly reported on the impact of dose-escalation of RT on QoL by using validated QoL-questionnaires.

The current analysis was undertaken within the framework of the Dutch randomized trial (CKTO 96-10) to assess the impact of dose-escalation on QoL of PC patients treated with either 68 or 78 Gy using 3-dimensional conformal RT techniques (3-DCRT). The analysis was done by intention-to-treat. We used a validated QoL-questionnaire (SF-36) (4) to investigate the impact of increasing the dose of RT on QoL and the changes over time in different scales of SF-36 in these patients. Correlation of different independent covariates with QoL was also investigated.

PATIENTS AND METHODS

Between June 1997 and February 2003, 669 patients with localized PC were enrolled in the Dutch trial (CKTO 96-10) and randomly assigned to receive either 68 or 78 Gy of 3-DCRT. The trial was carried out at four Dutch cancer institutions (3). Briefly, patients with localized PC with initial prostate-specific antigen (i-PSA) $\leq$ 60 μg/L were eligible. Patients with low-risk disease, with lymphatic or distant metastases and those having Karnofsky scores $\leq$70 were excluded. (Neo)adjuvant HT was allowed and was prescribed for a period of three years. For both arms, the fraction size was 2 Gy prescribed to the isocenter (the ICRU reference point). The mean dose to the planning target volume (PTV) was between –5% and +7% of the prescribed dose, and 99% of the PTV received $\geq$ 95% of the prescribed dose. The percentage of the rectum receiving $\geq$ 74 Gy was limited to 40%, while the small bowel dose should not be > 68 Gy. The PTV included the prostate with or without the SV as clinical target volume (CTV), with a margin of 10 mm during the first 68 Gy and 5 mm (except towards the rectum 0 mm) for the last 10 Gy in the high-dose arm. A verification procedure, using orthogonal portal imaging, with decision

rules for set-up corrections was used according to the guidelines published by a collaborative study in the Netherlands. By using this protocol, systematic errors should not exceed 5 mm (3).

The cohort contains only patients who were treated at the Erasmus MC-Daniel den Hoed Cancer Center in Rotterdam (n= 404). Patients from other participating institutions did not participate in the side trial on QoL.

We elected to use the self-administered SF-36 QoL-questionnaire. The structure of SF-36 questionnaire is shown on Table 1. In brief, it consists of 36 questions compressed into eight scales within physical and mental domains. These scales are assessed quantitatively, each on the basis of answers to multiple choice questions. The scoring of the SF-36 is a two-step process. First, All items are scored between 0 and 100 with a higher score indicating a better QoL (5). Scores represent the percentage of total possible score achieved. In step-2, items in the same scale are averaged together to create the 8 scales scores. Items that are left blank (missing data) are not taken into account when calculating the scale scores. The scales of SF-36 are divided into two dimensions. The first five scales make up the "physical health" dimension and the last five form the "mental health" dimension. The scales vitality and general-health are two overlapping scales. The summary scores of the two dimensions and the total SF-36 score are based on mathematical averaging of the scale components.

QoL assessment was done before starting RT (baseline) and at 6, 12, 24, and 36 months. The questionnaires were handed over to the patients by the nurse of our department. Patients were instructed to answer the questions at the specific points in time (baseline, 6, 12, 24, and 36 months) and return the questionnaires at their next visit to the department. QoL assessment stopped when the patient showed disease progression (clinical failure or the initiation of salvage hormonal therapy).

QoL changes over time of ≥ 10 points were considered clinically relevant. Osaba et al. (6) have determined the significance of the numerical changes in time and suggested that "moderate changes" (mean change between 10-20) to be clinically relevant. The mean change in patients who indicated a "small change" (better or worse) in scores was about 5-10, and for "very much changes" greater than 20.

Statistical analysis

All patients with at least one QoL assessment are considered as responders and included in the analysis. As shown in Table 2, responders and non-responders were compared with respect to patient and tumor characteristics using a chi-square test for categorical variables and the Kruskal-Wallis test for ordinal variables.

For all scales, missing values for the items contributing to that scale were substituted by a predicted value if the patient had responded to at least 50% of the items of a scale. Otherwise

the scale of this patient was excluded from further analysis. The predicted value was calculated with linear regression on the non-missing items of the scale.

QoL assessments were divided in 5 periods: baseline (before day 10 after starting RT), 6 months (between 3 months and 9 months after starting RT), 1 year (between 9 and 18 months), 2 years (between 18 and 30 months), and 3 years (between 30 and 42 months after starting RT). QoL assessments between day 10 and day 91 after starting RT and after 42 months after RT were excluded.

For each of the SF-36 scales, repeated measurements regression analyses were applied to obtain estimates of and test for treatment effects and to test for differences over time and for association with covariates. The following variables were used in these models:

[1] an indicator variable with value 1 for the 78 Gy treatment arm at baseline and value 0 otherwise: used to test for a possible difference at baseline between the arms; [2] an indicator variable with value 1 for the 78 Gy treatment arm after treatment and value 0 otherwise: used to test for a difference between the arms after treatment; [3] an indicator variable post with value 1 for all scores after treatment and 0 otherwise: used to test for a difference between scores after treatment compared to baseline; [4] a time variable measuring the time of QoL scoring in months since end of RT with value 0 for baseline scores: used to test for a trend over time in scores after RT, and in combination with the variable post to test for overall differences over time. Interaction terms were added to these models to test for interactions between time after RT and treatment arm.

Descriptive median scores are presented in Table 3. The P-value in the baseline column is for the test of no difference between the two arms at baseline. The P-value in the Time column is for the test of no difference between baseline and post RT scores and no trend over time in scores post RT. The P-value in the R (randomization arm) column is for the test of no difference in scores between both arms post RT. The P-value in the Time by arm column is for the test of no interaction between arm and time post RT.

Associations between QoL-scores and covariates were tested by adding to these models the following covariates: age at baseline, comorbidity at baseline (0= no, 1= yes), adjuvant hormonal treatment (0= no, 1= yes), and the concurrent RTOG/EORTC GI and GU toxicity scores measured at or before the QoL assessment. The results of these analyses are presented in Table 4 with P-values for all tests and the beta regression coefficients for these variables in the models. The sign (- or +) of these coefficients indicates the direction of the association of the covariable and the QoL scale.

To guard against false positive results due to multiple testing, a two sided p-value of 0.01 was considered statistically significant. All statistical analyses were performed using Stata, version 10.0 (Stata Corporation, College Station, TX, USA).

Table 1. The SF-36 quality-of-life scoring system and its scales and dimensions

Item's no	Items	Scales	Dimensions	
3a	Vigorous activities	Scale 1: Physical-functioning	Physical dimension	
3b	Moderate activities			
3c	Lifting or carrying groceries			
3d	Climb several flights of stairs			
3e	Climb one flight of stairs			
3f	Bending, kneeing or stooping			
3g	Walking more than a mile			
3h	Walking several blocks			
3i	Walking one block			
3j	Bathing or dressing yourself			
4a	Cut down time	Scale 2: Role-functioning		
4b	Accomplished less than you would like			
4c	Limited in kind of work or activity			
4d	Had difficulty in performing work or activity			
7	Pain magnitude past 4 weeks	Scale 3: Bodily-pain		
8	Pain interference with your work past 4 weeks			
1	General health rating	Scale 4: General- health		
11a	Get sick easier than other people			
11b	As healthy as anyone			
11c	Expect my health to get worse			
11d	Excellent health			
9a	Feel full of pep	Scale 5: Vitality		Mental dimension
9e	Have a lot of energy			
9g	Feel worn out			
9i	Feel tired			
6	Social-extent	Scale 6: Social-functioning		
10	Social-time			
5a	Cut down time	Scale 7: Role-emotional		
5b	Accomplished less than you would like			
5c	Not careful in work			
9b	Nervous	Scale 8: Mental- Health		
9c	Down in dumps			
9d	Calm and peaceful			
9f	Downhearted and blue			
9h	Happy			
2	Change in reported health past year			

RESULTS

Baseline patients' characteristics

Of the 404 patients treated at the Erasmus MC-Daniel den Hoed Cancer Center, 300 patients (responders, 74%) have participated in the QoL part of the study, filling out at least one QoL questionnaire. There were no differences between the responders and non-responders with respect to age, tumor stage, PSA, adjuvant HT, or presence of comorbidity. More patients among responders had higher Gleason scores as compared to the non-responders (p= 0.005). Among the responders, the patient characteristics were similar in both randomization arms (Table 2).

Table 2. Patient Characteristics of responders & non-responders and of both randomization arms

	Whole group (n=404)		Responders (n=300)	
	Responders (n=300)	Non-responders (n=104)	68-Gy arm (n=140)	78-Gy arm (n=160)
	%	%	%	%
Age, years				
Mean (years)	68	68	67	68
Range (years)	48-80	52-81	50-80	48-80
<= 65	34	35	42	26
66-70	28	25	23	34
>70	38	40	35	40
Tumor stage				
T1	16	20	16	16
T2	45	39	47	43
T3	37	39	34	41
T4	2	2	3	0
Gleason score *				
2-6	43	58	44	42
7	38	32	39	37
8-10	19	10	17	21
iPSA				
<4	9	10	9	9
4-10	36	36	34	38
10-20	34	34	32	35
>20	21	20	25	18
HT				
Yes	16	9	14	19
No	84	91	86	81
Comorbidity ^				
Yes	33	29	30	35
No	67	71	70	65
Pre-existing GI	2	3	1	3
Pre-existing GU	8	7	6	10

Abbreviations: iPSA: initial prostate-specific antigen; HT: hormonal therapy; GI: gastro-intestinal; GU: genito-urinary. *significantly more patients among responders had higher Gleason scores, as compared to non-responders (p=0.005), all other demographics were equally distributed among responders & non-responders and among both randomization arms. ^Comorbidity was scores "Yes" if patient had diabetes mellitus, cardiovascular and/or cerebrovascular disease.

Patient functioning by randomization arms

As shown in Table 3 and Figure 1, no statistically significant differences in any SF-36 scales were found between both randomization arms at baseline (P-Baseline). The SF-36 scores at baseline ranged from 65 to 89, which mean that the patient population functioned well within the tested domains. Also after RT there was no difference between the randomization arms in their scores on any of the scales (P-R). After 3 years, the average total summary-score physical-health was 73.2 for the 68 Gy arm (-4.9 compared to baseline) vs. 71.6 for the 78 Gy arm (-8.8 compared with baseline) (p= 0.81) and the average total summary-score mental-health was 76.7 for the 68 Gy arm (+0.1 compared with baseline) vs. 76.1 for the 78 Gy arm (-3.5 compared with baseline) (p= 0.97).

Table 3. Quality-of-life scores as measured by the SF-36 QoL-questionnaires by randomization arms

SF-36 scales	R-arms	SF-36 QoL scores by time points in months						P-values			
		Baseline	6	12	24	36	B-36^	Baseline*	Time*	R*	Time by R*
SSPH	68 Gy	78,1	75,4	77,6	74,4	73,2	-4.9	0,30	**< 0,001**	0,81	0,39
	78 Gy	80,4	75,5	76,9	73,1	71,6	-8.8				
SSMH	68 Gy	76,6	78,1	78,8	77,6	76,7	0.1	0,16	0,12	0,97	0,93
	78 Gy	79,6	77,6	79,2	78,1	76,1	-3.5				
PF	68 Gy	82,7	79,0	80,1	78,9	76,0	-6.7	0,13	**< 0,001**	0,69	0,11
	78 Gy	86,1	81,1	81,3	77,2	75,8	**-10.3**				
RP	68 Gy	76,5	68,4	74,7	72,5	71,9	-4.6	0,25	0,24	0,84	0,18
	78 Gy	81,6	69,1	75,2	69,3	66,4	**-15.2**				
BP	68 Gy	86,4	87,0	87,5	83,8	84,6	-1.8	0,23	**0,003**	0,50	0,56
	78 Gy	89,0	86,4	85,5	82,4	82,4	-6.6				
GH	68 Gy	66,0	67,2	67,8	62,3	61,1	-4.9	0,66	**< 0,001**	0,64	0,07
	78 Gy	65,0	65,2	65,5	63,6	62,4	-2.6				
VT	68 Gy	71,6	68,2	69,9	67,5	67,5	-4.1	0,19	**< 0,001**	0,77	0,37
	78 Gy	74,5	68,2	68,7	67,7	64,9	-9.6				
SF	68 Gy	85,9	86,5	86,7	84,1	85,3	-0.6	0,63	0,43	0,46	0,93
	78 Gy	84,8	84,0	85,6	83,9	83,0	-1.8				
RE	68 Gy	73,7	80,3	82,1	83,4	79,8	6.1	0,02	0,03	0,92	0,93
	78 Gy	83,3	80,0	82,7	81,2	80,1	-3.2				
MH	68 Gy	76,5	79,0	78,8	78,3	75,9	-0.6	0,92	**0,004**	0,81	0,66
	78 Gy	76,6	79,0	79,7	79,2	76,9	0.3				

Abbreviations: R: randomization; SSPH: summary-score physical-health; SSMH: summary-score mental-health; PF: Physical-functioning; RP: Role-physical; BP: Bodily-pain; GH: General-health; VT: Vitality; SF: Social-functioning; RE: Role-emotional; MH: Mental-health; B-36^: indicates difference in QoL-scores between scores at baseline and at 36-months (only a difference of > 10 points was regarded as clinically relevant, according to Osaba *et al.*(6). Clinically relevant differences were indicated in bold. The P-value in the Baseline column is for the test of no difference between the two arms at baseline. The P-value in the Time column is for the test of no difference between baseline and post RT scores and no trend over time in scores post RT. The P-value in the R (randomization arm) column is for the test of no difference in scores between both arms post RT. The P-value in the Time by arm column is for the test of no interaction between arm and time post RT. Note: statistically significant differences (P-value < 0.01) are indicated in bold.

Changes in patient functioning over time

Statistically significant changes over time were observed in both randomization arms in 6 scales (summary-score physical-health, physical-functioning, bodily-pain, general-health, vitality, and mental-health) (P-Time), while clinically relevant changes over time in the mean scores (> 10 points), according to the guidelines as outlined by Osaba et al. (6), were seen in only 2 scales in patients treated with 78 Gy (-15.2 for role-physical, and -10.3 for physical-functioning, compared with baseline). The scores on these 2 scales were also deteriorated over time in the low-dose arm, however less pronounced than in the high-dose arm (–4.6 for role-physical, and -6.7 for physical-functioning, compared with baseline). However, it should be noted that no statistically significant interactions were observed between time and arm on any of the scales (P-Time by R), which means that the apparent differences between the arms are within the sampling fluctuation.

Analysis by time points by scales (Table 3)

Summary-score physical-health

At 6-months, QoL-scores in both arms registered declines followed by a slight improvement at 12-months. Thereafter, the scores in both arms showed gradual deterioration, with the largest decline registered in the high-dose arm (-8.8 vs.-4.9 at 3-years, compared with baseline, $p< 0.001$).

Summary-score mental-health

Patients treated with 68 Gy registered a slight improvement at 6- and 12-months, while those treated with 78 Gy showed a decline at 6-months followed by a slight improvement at 12-months. Subsequently, a slight deterioration in QoL-scores was seen in both arms at 24- and 36-months. At 3-years, QoL-scores for patients treated with 68 Gy was +0.1 vs. –3.5 for 78 Gy, compared with baseline ($p= 0.12$).

Physical-functioning and Role-physical

Only in these two scales the deterioration in mean QoL-scores at 3-years were clinically relevant (> 10 decrease), compared with baseline. The pattern of changes over time on these 2 scales was also similar; the largest declines were registered at 6-months in both arms, with the greatest decrease seen in role-physical in patients treated with 78 Gy (-12.5, compared with baseline). While slight improvements were seen at 12-months in both arms at physical-functioning (+1 compared with baseline), the improvements at role-physical in both arms were tremendous at 12-months (+6 compared to 6-months). As in most scales, QoL-scores registered deterioration at 24- and 36-months on both scales and in both arms. After 3-years, patients treated with high-dose RT showed a clinically relevant decline, compared with baseline (-15.2 at role-physical and –10.3 at physical-functioning). Although the scores of patients treated with 68 Gy

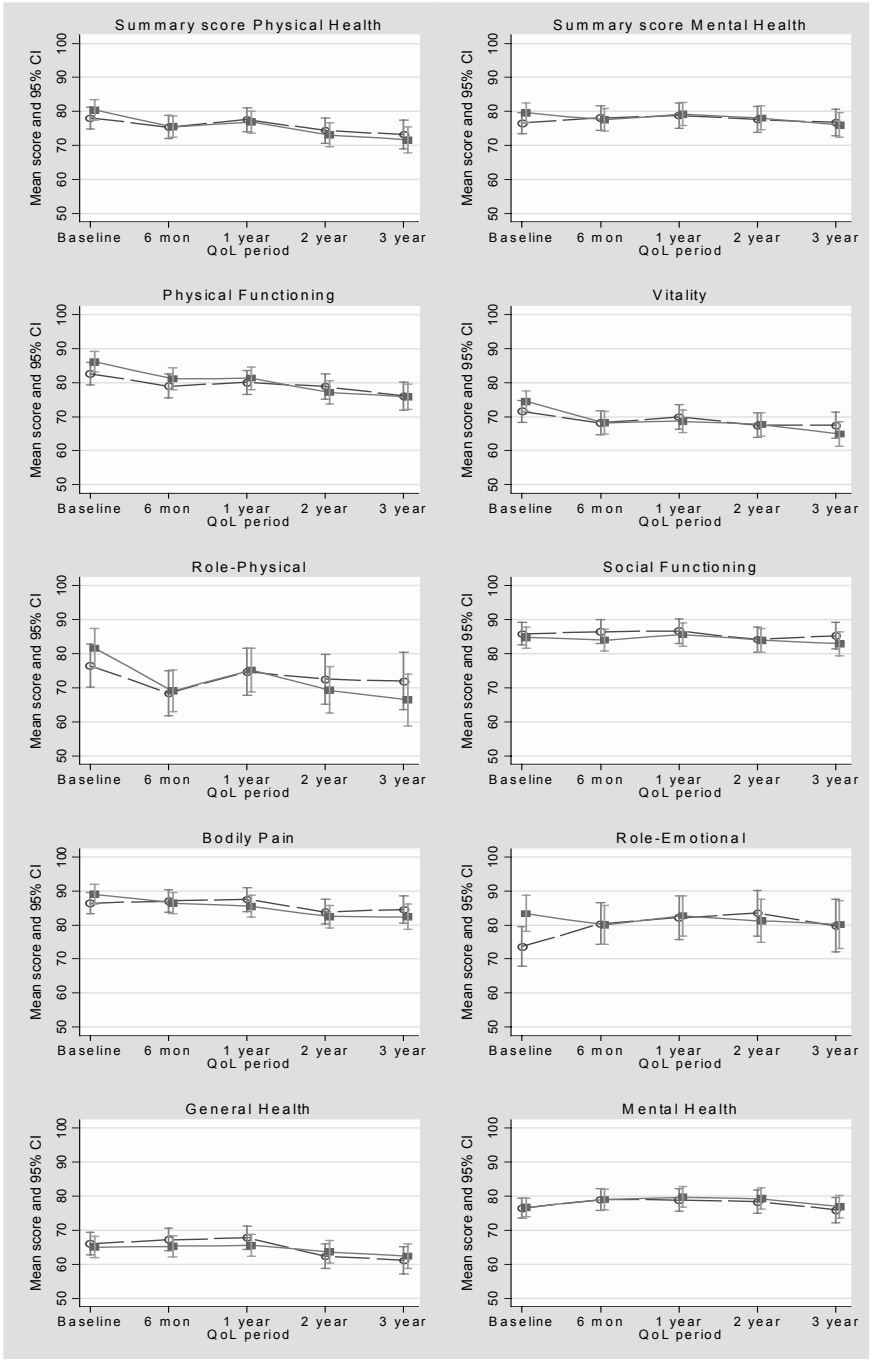

Figure 1. Quality-of-life scores of prostate cancer patients treated with 68-Gy (dashed line) or 78-Gy (solid line) of 3-demensional conformal radiotherapy. For all scales of the FS-36 questionnaire, a higher score reflects a better quality-of-life. The horizontal axis indicates the 5 times points where quality-of-life was scored (at baseline, 6, 12, 24, and 36 months). The vertical axis indicates the mean scores. Bars represent 95% confidence intervals.

at 3-years were also deteriorated, as compared with baseline (-4.6 at role-physical and –6.7 at physical-functioning), these declines were clinically non relevant.

Bodily-pain

Patients treated with 78 Gy showed a continuous but gradual deterioration in QoL-scores over time, with the largest declines observed at 6- and 24-months. Patients treated with 68 Gy showed a fluctuating pattern of changes over time, with slight improvements at the early stages after treatment. At both arms, the scores at 3-years were lower than baseline (-6.6 vs.-1.8 for 78 and 68 Gy arms, respectively) (p= 0.003).

General health

Both arms showed a similar pattern of changes over time, with slight improvements at 6- and 12 months, followed by slight deteriorations at 24- and 36-months. Again, the scores at 3-years were lower than baseline in both arms. However, the deterioration of scores on this scales (and on mental-health) were less pronounced in patients treated with 78 Gy than in those treated with 68 Gy (-2.6 vs. 4.9, respectively, p= <0.001).

Vitality

The most significant deterioration seen in both arms was registered at 6 months. These declines were followed by slight improvement at 12-months and subsequently by gradual deterioration at the last time periods. Beside the fact that changes over time were statistically significant at this scale (p< 0.001), the changes in patients treated with high-dose RT were almost clinically relevant (-9.6, compared with baseline).

Social-functioning

The changes in scores over time in both arms showed mild fluctuations from baseline. The scores at 3-years were slightly lower than at baseline (-0.6 and –1.8 for 68 and 78 Gy, respectively, p= 0.43).

Role-emotional

At baseline, patients treated with 78 Gy had higher QoL-scores than patients treated with 68 Gy (p= 0.02). Patients treated with 68 Gy registered improvements at first 3 time points, with the largest increase seen at 6-months (+6.6). Despite the deterioration seen at 36-months, these patients ended up with higher scores (+6.1), compared with baseline. Patients treated with high-dose RT showed a similar pattern of changes over time, as seen in summary-score physical-health, summary-score mental-health, physical-functioning and role-physical, and social-functioning. These patients had lower scores at 3-years compared with baseline (-3.2).

Mental-health

Both arms registered improvements at early time points followed by a gradual deterioration at later time points. The changes over time on this scale were statistically significant (p=0.004), but patients from both arms ended up with nearly similar scores (-0.6 for 68 Gy vs. +0.3 for 78 Gy), compared with baseline.

Relation between QoL and selected covariates

None of the tested covariates showed a statistically significant correlation with any scale of the SF-36 questionnaire. However, late GI and GU toxicity scores showed, as one would expect, a negative correlation with most QoL scales, i.e. higher grades of late GI or GU toxicity were associated with lower QoL-scores (Table 4).

Regarding the two scales (role-physical and physical-functioning) where deterioration of QoL over time was clinically relevant in the high-dose arm, a borderline significant correlation with late GI toxicity (p= 0.02) and GU toxicity (p= 0.05) was found for role-physical and with comorbidity and age (p= 0.02) for physical-functioning. In all other scales, no statistically significant correlation was found between the tested covariates and QoL.

Table 4. P-values for association between selected covariates and SF-36 scores

SF-36 scales	Age	Comorbidity	Hormonal therapy	GI toxicity	GU toxicity
SSPH p-value	0,65	0,14	0,54	0.07	0,10
beta	-0.071	-4.078	-1.57	-1.129	-0.969
SSMH p-value	0,78	0,91	0,24	0,57	0.07
beta	0.043	0.301	-3.012	-0.345	-1.014
PF* p-value	0,02	0,02	0,94	0,47	0,26
beta	-0.347	-6.482	0.196	-0.452	-0.646
RP* p-value	0,67	0,61	0,07	0,02	0,05
beta	0.118	-2.5	-7.979	-3.462	-2.757

Abbreviations: SSPH: summary-score physical-health; SSMH: summary-score mental-health; PF: Physical-functioning; RP: Role-physical; GI: gastro-intestinal, GU: genito-urinary. Notes: p-value < 0.01 was regarded as statistically significant. Beta: regression coefficient for the repeated measurements regression analysis. *These two scales were analyzed separately, because only on these 2 scales clinically relevant changes ($\geq$ 10 points) in QoL-scores over time were seen. In all other scales the changes in scores over time were clinically non relevant.

DISCUSSION

Several factors make the assessment of the impact of any treatment modality on QoL extremely important in patients with localized PC. Firstly, most patients are asymptomatic due to the early diagnosis because of the elevated PSA level. Secondly, there are several treatment modalities available and watchful waiting is an alternative option for early-stage PC, especially in elderly men with a short expected life-span. Thirdly, patients may survive for a considerable period even in the presence of metastatic disease. Finally, none of the published randomized studies

have shown a survival benefit (1-3). Accurate reporting of the side effects and the impact on QoL is, therefore, very essential to facilitate decision-making by both patients and clinicians.

To our knowledge, this is the first randomized dose-escalation trial reporting on the impact of increasing the dose of RT on QoL of patients with localized PC by using a validated QoL-questionnaire. The randomized dose-escalation trial of the M.D. Anderson Cancer Center showed, after 3-years follow-up, that rectal bleeding had improved, erectile function had decreased, and urinary urge incontinence had increased in both dose-arms (70 and 78 Gy). In that study, a radiation dose-effect on bowel and bladder functions was not seen (7).

In the present study, escalating the dose of RT from 68 to78 Gy did not significantly decrease the QoL-scores as measured by SF-36 questionnaire (P-value R-column at Table 3). Analysis of time trends revealed statistically significant deterioration in QoL-scores over time in both randomisation arms on 6 scales (P-value Time column at Table 3), but these changes were clinically relevant only in physical-functioning and role-physical (> 10 points). These clinically relevant deteriorations over time were seen only in the high-dose arm (-15.2 for role-physical, and -10.3 for physical-functioning, compared with baseline). The scores over time on these 2 scales were also deteriorated in the low-dose arm, however less pronounced than in the high-dose arm. However, no statistically significant interactions were observed between time and arm on any of the scales (P-value Time by R column at Table 3), which means that the apparent differences between the arms are within the sampling fluctuation.

In summary, the SF-36 questionnaire demonstrates a complicated and mixed pattern of changes following RT for localized PC. However, three general patterns of changes in QoL-scores could be distinguished. Firstly, the most appreciable treatment-related deteriorations in QoL measures were observed in physical-health domain. Secondly, in both randomization arms there was temporary improvement in almost all scales at 12-months, followed by gradual deterioration of scores at 24- and 36-months. The SF-36 scores of most scales at 3-years were lower than at baseline. Lastly, the deterioration in QoL-scores were, in general, less pronounced in the low-dose as compared to the high-dose arm, but the differences between the two arms over time were not statistically significant.

It should not be totally surprising that almost all items of QoL have temporarily improved at 12-months after the registered declines at 6-months. The first possible explanation for this temporary improvement is the identification of benefit from adversity, a phenomenon known as “benefit finding” (8). Evidently, most patients not only experience negative effects but also certain positive effects after an encounter with the diagnosis and treatment of cancer. Secondly, many patients have accepted the early side effects of RT as inevitable consequences of having been treated for PC, a disease that yet perceived by many people to be the most life-threatening event. However, the temporary improvements were followed by gradual deterioration of scores

at 24- and 36-months. At 3-years the scores of most scales were lower than at baseline. However, the deterioration was clinically relevant only in 2 scales (physical-functioning and role-physical). Possible explanations are: changes in perceived health-related QoL may lag behind the mergence of symptoms. The decrements in scores may develop slowly, as men live with these problems and readjust their appraisals of health-related limitations in their functional status. The longer follow-up in our study, compared to that of other investigators (9-11), had therefore the advantage to detect these late changes in QoL-scores. Furthermore, different factors as aging, comorbidity and the development of late GI and GU toxicities might have resulted into worse QoL-scores in these patients after 2-3 years of follow-up. Lips et al. (9) compared in a prospective and longitudinal study QoL after 70 Gy of 3-DCRT with QoL after 76 Gy of IMRT in patients with PC and concluded that IMRT seems to provide a possibility to escalate the dose of RT without deterioration in QoL. The same conclusions were drawn by Yoshimura et al. (10) and Kupelian et al. (11) after 1 and 2 year of follow-up, respectively, in patients treated with IMRT to a relatively high-dose. However, it is not fair to compare these studies with our study, because these studies are not randomized, the radiation dose was on average lower than 78 Gy, the follow-up is short (6, 12, and 24-months, respectively), and the number of patients is small (92, 60, and 51 patients, respectively). Furthermore, those patients were treated with IMRT with possibly less late side-effects.

To explore whether there was any correlation between selected clinical covariates and QoL, these covariates were added to the repeated measurements regression multivariate models. None of the tested covariates showed statistically significant correlation with QoL. However, late GI and GU toxicity showed a borderline significant correlation with both summary-score physical-health and summary-score mental-health, respectively (p= 0.07). Regarding the two scales where deterioration of QoL over time was clinically relevant in high-dose arm, there was a trend toward significant correlation with late GI toxicity and GU toxicity for role-physical and with comorbidity and age for physical-functioning.

In the present analysis, we did not study the late side-effects of dose-escalated RT (GI, GU or sexual functioning) separately since these late effects were thoroughly described by other investigators from our group (12, 13). The effect of dose-escalation on sexual function was studied by van der Wielen et al. (12). In that study, patients were censored at the moment they started with HT, in order to estimate the effect of RT only. They found a significant increase in the prevalence of erectile dysfunction after RT (38% cumulative incidence at 3-years in patients without erectile dysfunction prior to the RT). Escalating the dose of RT from 68 to 78 Gy did not significantly worsen the sexual function. The incidence of erectile dysfunction at 3-years was 39% and 37% for the low- and high-dose arms, respectively (12). Although raising the dose to the prostate from 68 to 78 Gy resulted in higher incidence of acute and late GI and GU toxicity, but these differences were not significant at 3-years. The 3-year cumulative incidence of late

grade ≥ 2 GI toxicity of patients treated within the Dutch randomized dose-escalation trial (CKTO 96-10) were 23.2% and 26.5% for low- and high-dose arms, respectively (p=0.3). The figures for late grade ≥ 2 GU toxicity were 28.5% and 30.2% (p=0.3) (13). Like others, we believe that clinicians should be aware of the fact that assessment of general QoL-dimensions as physical, mental, and social (as measured by SF-36 or other validated QoL-questionnaires) are of equal or even greater significance for QoL than specific organ-related morbidity (sexuality and bladder and bowel symptoms). Lilleby et al. (14) found that fatigue, physical and emotional functions (all are items of the SF-36 questionnaire) were the 3 independent parameters predictive for QoL, whereas the impact of specific organ-related morbidity did not reach the level of statistical significance in the multivariate analysis. Clark et al. (15) reported no decline in the SF-36 scores as a result of new urinary, bowel, or sexual problems during the follow-up.

CONCLUSIONS

QoL-scores in PC patients as measured by SF-36 questionnaire did not appear to be significantly decreased by escalating the dose of RT from 68 to 78 Gy. However, the decrease in QoL-scores, in general, was more pronounced in the high- than in the low-dose arm and in the physical- than the mental-health domain. In both randomization arms, statistically significant decrease in QoL-scores over time were seen in 6 scales, but the deterioration over time was clinically relevant only in role-physical and physical-functioning scales in patients treated in the high-dose arm. None of the tested covariates in the repeated measurements regression analysis correlated significantly with QoL changes over time. However, late GI and GU toxicity showed a trend toward significant correlation.

Given the slight deterioration in different QoL-scales, albeit statistically non-significant, seen by escalating the dose of RT from 68 to 78 Gy, the possible risks of complications and deterioration of QoL must, therefore, be carefully weighted against the risk of relapse during the patient's expected life span. When the expected toxicity of high-dose RT in that particular patient is high, the expected life span is relatively short and the risk of local recurrence is predicted to be low (based on iPSA, Gleason score, and T-stage), dose-escalation should, in our opinion, be avoided.

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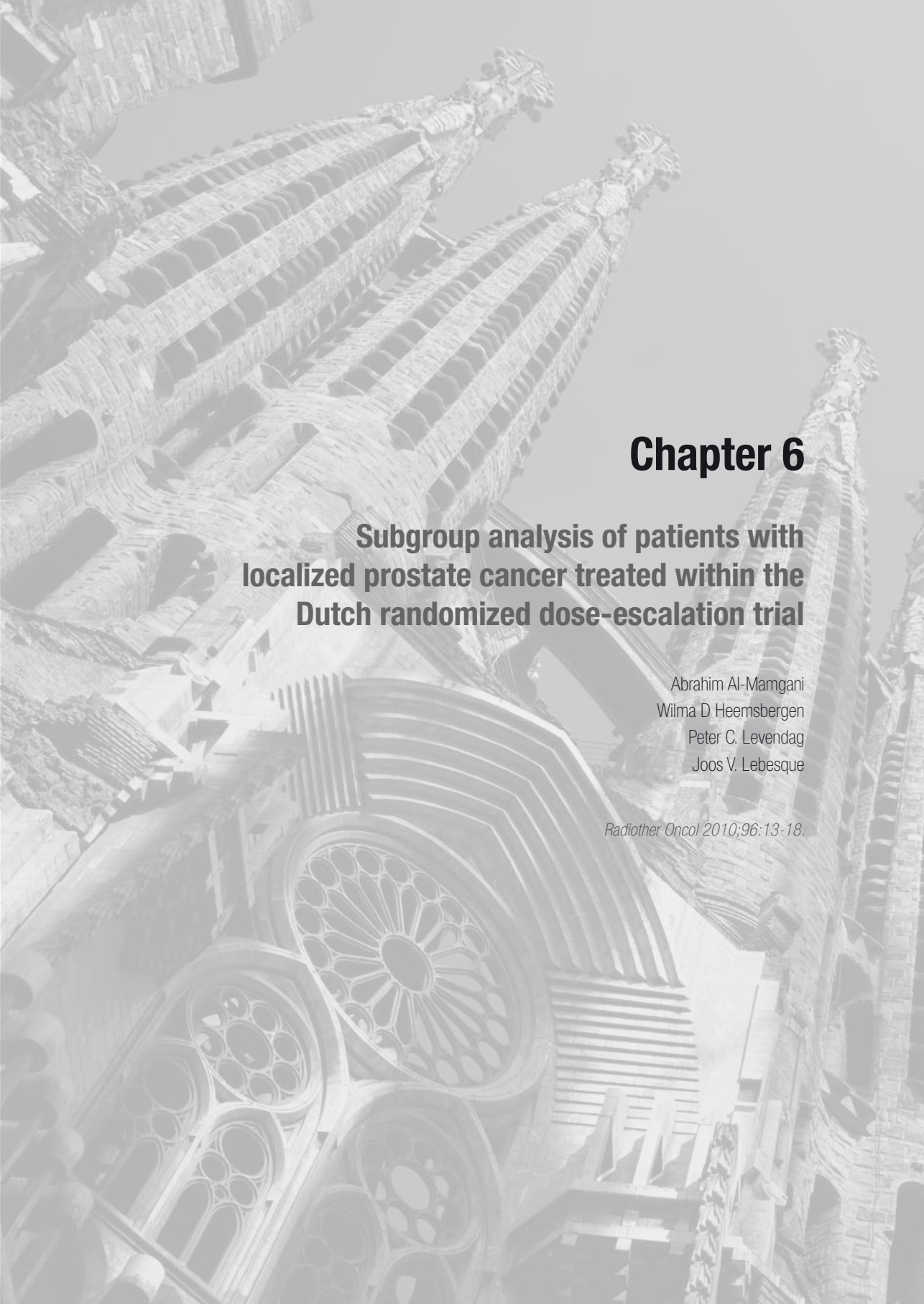

Chapter 6

Subgroup analysis of patients with localized prostate cancer treated within the Dutch randomized dose-escalation trial

Abrahim Al-Mamgani
Wilma D Heemsbergen
Peter C. Levendag
Joos V. Lebesque

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ABSTRACT

Purpose

To investigate the effect of dose-escalation within prognostic risk-groups in prostate cancer.

Patients and Methods

Between 1997 and 2003, 664 patients with localized prostate cancer were randomly assigned to receive 68- or 78-Gy of radiotherapy. Two prognostic-models were examined: a risk-group-model (low-,intermediate-,and high-risk) and PSA-level groupings. High-risk patients with hormonal therapy (HT) were analyzed separately. Outcome variable was freedom from failure (FFF) (clinical failure or PSA nadir + 2 μg/L).

Results

In relation to the advantage of high-dose radiotherapy, intermediate-risk patients benefited most from dose-escalation. However no significant heterogeneity could be demonstrated between the risk groups. For two types of PSA level groupings: PSA < 10 and ≥ 10 μg/L, and < 8, 8-18 and > 8 μg/L, the test for heterogeneity was significant (p= 0.03 and 0.05, respectively). Patients with PSA 8-18 μg/L (n = 297, HR= 0.59) derived the greatest benefit from dose-escalation. No heterogeneity could be demonstrated for high-risk patients with and without HT.

Conclusion

Intermediate-risk group derived the greatest benefit for dose-escalation. However, from this trial no indication was found to exclude low-risk or high-risk patients from high-dose radiotherapy. Patients could be selected for high-dose radiotherapy based on PSA-level groupings: for patients with an PSA < 8 μg/L high-dose radiotherapy is probably not indicated, but should be confirmed in other randomized studies.

INTRODUCTION

Prostate cancer currently is the most common malignant disease in western countries. Although the outcome of radiotherapy for localized prostate cancer has improved with dose-escalation, the risk of cancer recurrence remains substantial (1-5). The Dutch randomized trial (1) showed that freedom from failure (FFF) (clinical failure or PSA nadir plus 2) at 7-years was significantly better in the 78-Gy arm compared with the 68-Gy arm: FFF-rates 56% vs. 45%, respectively; p= 0.03). There were no differences between both arms in terms of freedom from clinical failure and overall survival. With the advent of screening programs and increased public awareness of the disease in the last decades, there has been a gradual stage migration with subsequently an increase in patient referral for radical treatment. The question which patients should receive high-dose radiotherapy has become a very important issue to be addressed, especially in view of the arguments in favour of observation. From the current literature, it is well-known that dose escalation is associated with a higher risk of complications and therefore an impact on quality of life (1-5). Furthermore, the lifetime risk of dying from prostate cancer is 3%, indicating that a significant proportion of patients die from intercurrent diseases or second cancer (6). Therefore, the selection of patients who should receive high-dose radiotherapy remains a common and vexing clinical problem.

In the current study, we performed an analysis to study whether subgroups of patients could be identified who might benefit from high-dose radiotherapy and who might not benefit. This subgroup analysis was done in patients with localized prostate cancer treated within the Dutch phase III trial randomizing between 68- and 78-Gy of three-dimensional conformal radiotherapy (3-DCRT). This subgroup analysis was performed in an intent-to-treat manner.

PATIENTS AND METHODS

Between June 1997 and February 2003, 664 patients with stage T1b-T4 localized prostate cancer with initial prostate-specific antigen (iPSA) < 60 μg/L were enrolled in the Dutch dose-escalation trial and randomly assigned to receive either 68-Gy (n = 331) or 78-Gy (n = 333) of 3-DCRT. Patients with cytologically or histologically proven positive regional lymph nodes were excluded. TNM-classification was done according to the AJCC-1997 guidelines. The details of the study design have been published previously (1,5). In brief, patients were stratified by hospital (A, B ,C , and D), use of hormonal therapy (HT) (yes vs. no), age (≤ 70 year vs. > 70 year), and treatment groups (I, II, III, and IV). These four treatment groups were defined depending on the risk of involvement of the seminal vesicles (SV), according to Partin et al. (7) (Table 1). Patients who belong to treatment group I have an estimated risk of SV involvement of < 10%, while patients in group II have an estimated risk of 10-25%. Patients in group III and IV have an estimated risk of SV involvement of > 25%, whereas this risk was 100% for the T3b patients in group IV.

Table 1. Treatment groups, according to the risk of involvement of the SV, Partin *et al.* #

		T1b, T1c, T2a*				T2b, T3a*	T3b, T4*
Gleason score	Differentiation grade	PSA 0-4	PSA 4-10	PSA 10-20	PSA 20-60	PSA 0-60	PSA 0-60
2-4	Good	I	I	I	II	III	IV
5-7	Moderate	I	II	II	III	III	IV
8-10	Poor	II	III	III	III	III	IV

* According to the American Joint Committee on Cancer 1997 guidelines. # Treatment groups defined by Partin: I = risk of seminal vesicles (SV) involvement of < 10%, II = risk of SV involvement of 10-25%, III and IV: risk of SV involvement of >25%.

For each treatment group, a specific planning target volume (PTV) was defined. The PTV included the prostate with or without the SV as clinical target volume (CTV), with a margin of 10 mm during the first 68-Gy and 5 mm (except toward the rectum: 0 mm) for the last 10-Gy in the high-dose arm. The CTV for treatment group I was defined as the prostate only, and for group IV, it was the prostate with SV. For treatment group II and III the CTV included the prostate with SV, but the SV was excluded from the CTV after 50-Gy and 68-Gy, respectively. The dose was specified to the isocenter (ICRU point). The dose to PTVs was between -5% and +7% of the prescribed-dose, and 99% of the PTVs were treated to at least 95% of the prescribed-dose. Institutions A, B and D used a three-field technique and institution C a four-field technique. For 41 patients in the high-dose arm, an IMRT-technique was used with the simultaneous integrated boost in institution B (8). All the patients in the 68-Gy arm received the prescribed dose. In the high-dose arm, however, 11% received a dose lower than 78-Gy, partly because of the dose constraints for rectum and small bowel (for details (5)).

Prognostic models

Two existing models of outcomes prediction were examined. The first was the single-factor risk-group model of Chism et al. (9), using three risk-groups: patients with T1-2 and Gleason ≤ 6 and PSA ≤ 10 μg/L, were at low risk, whereas patients with T3-4 or Gleason 8-10 or iPSA > 20 μg/L were at high risk. All the other patients were at intermediate risk. The second prognostic model was based on iPSA level, because iPSA is the strongest single pre-treatment predictor of FFF (2, 10, 11). We analyzed our data according to the most commonly used iPSA-cut-off value in the literature (< 10 and ≥ 10 μg/L). Furthermore, we studied in an exploratory analysis whether a patient group could be identified based on PSA level groupings, who benefited most from dose-escalation. In patients who received HT in combination with external-beam radiotherapy, we analyzed the FFF-rates separately in order to explore the independent role of dose-escalation in this group of patients.

Outcome variables

Failures were defined as clinical failures (CF) or biochemical failures (BF) according to the Phoenix definition (PSA nadir + 2 μg/L after RT) because of the recent recommendation in the

literature that this definition of biochemical failure is a better approximation of eventual CF than the ASTRO-definition (three consecutive rises in PSA with backdating to midway between the nadir and the first rise) (12). CF was defined as local relapse (palpable and/or biopsy-proven), regional relapse, or distant metastases. Initiation of salvage HT only because of a rising PSA level was also considered as a CF.

Statistical analysis

We summarized the subgroup analysis of the different models in Forest Plots. This method provides estimates of the Hazard Ratio's (HRs) (high-dose arm vs. low-dose arm) with its 95% confidence interval for each defined subgroup. Chi-square statistics for heterogeneity across the defined strata were calculated. We illustrated a number of subgroup analysis by calculating Kaplan Meier curves and we estimated the 6-year FFF rates with their 95% confidence interval. Software used was SPSS version 15.0.0 (SPSS Inc., Chicago, IL, USA). Review Manager was used to construct the Forest Plots (Rev Man, version 5.0, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). We considered p values of 0.05 or below, as statistically significant.

RESULTS

General characteristics

The distribution of baseline characteristics according to the randomization arms was well balanced (1, 5). The median age was 68 years and the median follow-up time was 70 months for both arms. Seventy nine patients (12%) had an iPSA of 0-5 μg/L, 179 (29%) an iPSA of 5-10 μg/L, 250 (38%) an iPSA of 10-20 μg/L and 156 an iPSA 20-60 μg/L. One hundred and nineteen patients (18%) were at low risk, 179 (27%) were at intermediate risk and the majority (366, 55%) were in the high risk group. (Neo)adjuvant HT was allowed and prescribed in 143 patients: mostly to high-risk patients (n=125) and rarely to intermediate- or low-risk patients (n=18). Institution A gave long-term neo-adjuvant HT (3 years) (n=79), while institution B used short-term HT (6 months) (n=64). Seventy-three patients (22%) in the low-dose arm and 70 patients (21%) in the high-dose arm received HT.

Interactions, Hazard Ratios and Kaplan Meier estimates

Risk groups

There was no significant (p=0.21) interaction between dose-arm and risk-group (Figure 1A). This result shows that high-dose radiotherapy is not more or less beneficial in either of these risk groups. The HRs were 1.26, 0.55 and 0.81 for the low-, intermediate- and high-risk groups, respectively. The HR for the whole group was 0.78 (95% CI: 0.61-0.99, p= 0.04).

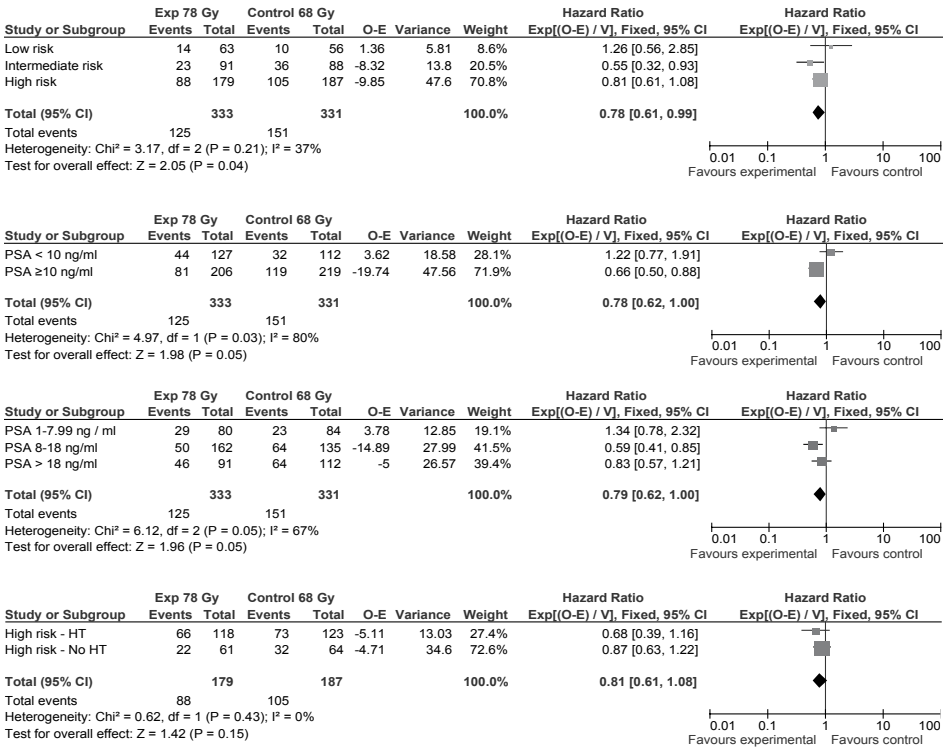

Figure 1. Forest plots with numbers of events and the corresponding hazard ratios (with 95% CI) showing the effect of radiation dose on (1A) freedom from failure (FFF) for low-, intermediate-, and high-risk groups according to Chism *et al*. (9), (1B) FFF for iPSA-groupings (< 10 and ≥ 10 μg/L), (1C) FFF for iPSA-groupings (< 8, 8-18, and > 18 μg/L), and (1D) FFF for high-risk patients treated with or without hormonal therapy.

The overall 6-years FFF-rates for the whole group were 51% (95% CI: 45-58%) and 63% (95% CI: 57-68%) for the 68- and 78-Gy arms, respectively. FFF-rates for low-risk group at 6-years were 84% (95% CI: 73-95%) and 80% (95% CI: 69-91%) for the low-dose arm and the high-dose arm, respectively (p= 0.57) (Figure 2A). Kaplan-Meier estimates for intermediate-risk patients were 54% (95% CI: 41-66%) and 78% (95% CI: 68-87%) for the 68 and 78-Gy arms, respectively (p= 0.023) (Figure 2B). The figures for high-risk group were 40% (95% CI: 31-48%) and 49% (95% CI: 41-57), respectively (p= 0.15) (Figure 2C).

PSA groupings

For patients according to an iPSA level < 10 μg/L or ≥ 10 μg/L, the test for heterogeneity was significant (p=0.03) (Figure 1B). The HRs were 1.22 and 0.66 for the iPSA level < 10 μg/L and ≥ 10 μg/L group, respectively. Patients with iPSA ≥ 10 μg/L who were randomized in the high-dose arm showed significantly (p= 0.005) better FFF (6-year FFF rate 62%, 95% CI: 55–69%) as compared to those in the low-dose arm (6-year FFF rate 40% 95% CI: 32–48%) (Figure 3B). For

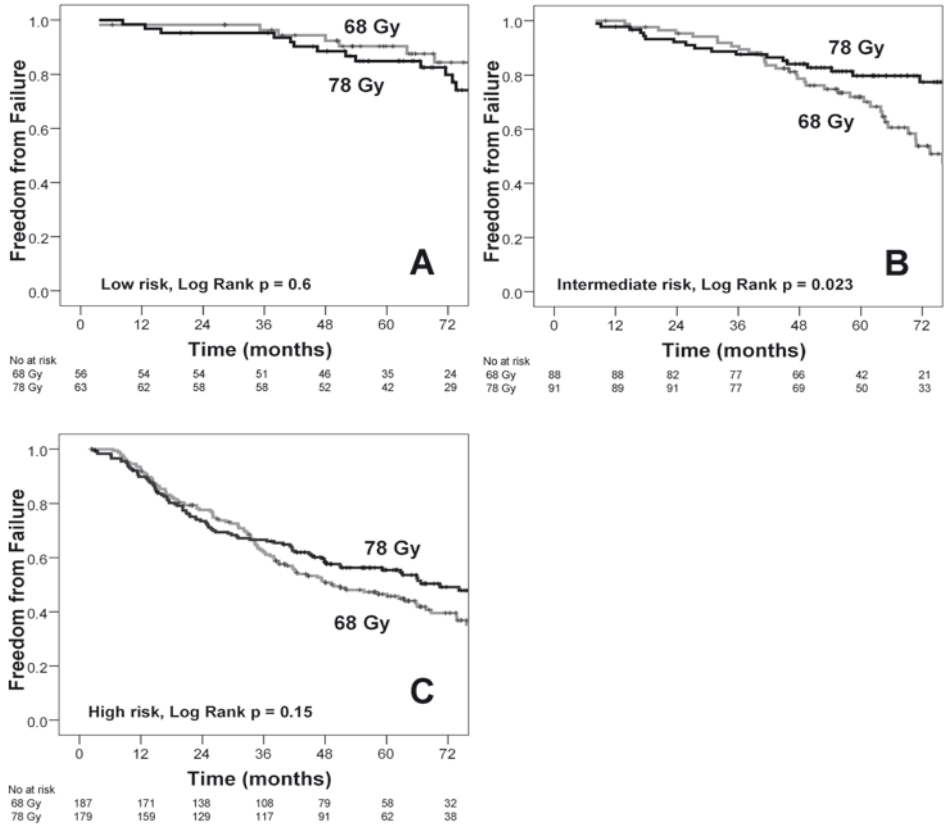

Figure 2. Freedom from failure for patients in the low-risk (2A), intermediate-risk (2B) and high-risk groups (2C) by randomization arm.

patients with iPSA < 10 μg/L, there was no significant (p= 0.4) difference in the 6-year FFF rates (Figure 3A).

An explorative analysis of our data showed the most optimal dose-effect for patients with an iPSA between 8-18 μg/L (297 patients, 45% of the study population). Therefore we decided to analyse our data with PSA level groupings according to three groups: < 8, 8-18 and > 8 μg/L. The test of heterogeneity was significant (p= 0.05) (Figure 1C). Patients with iPSA between 8 and 18 μg/L seem to derive the most benefit from high-dose radiotherapy, as compared to other the PSA-groups (HR= 0.59 for iPSA 8-18 μg/L, 0.83 for iPSA > 18 μg/L, and 1.34 for iPSA < 8 μg/L).

Patients with iPSA 8-18 μg/L who were randomized in the high-dose arm showed significant (p= 0.008) better FFF (6-year FFF rate 70 %, 95% CI: 62–78%) as compared to those in the low-dose arm (6-year FFF rate 52 %, 95% CI: 41–62%) (Figure 4B). For patients with iPSA <8

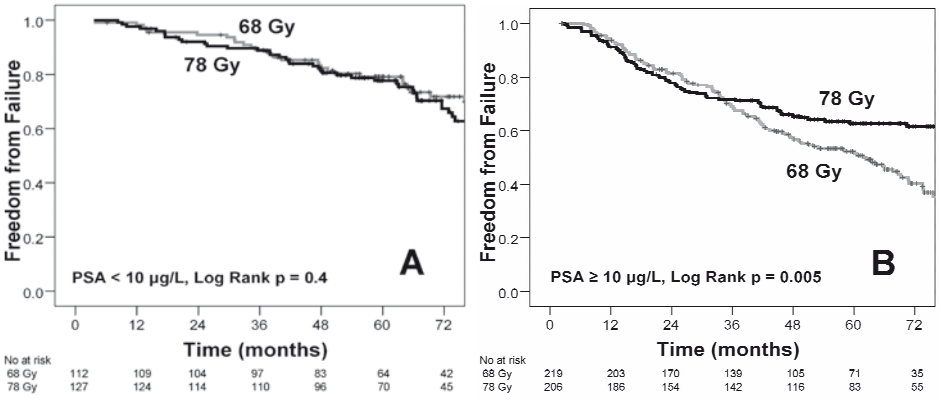

Figure 3. Freedom from failure for patients with iPSA< 10 (A) and ≥ 10 µg/L (B) by randomization arm.

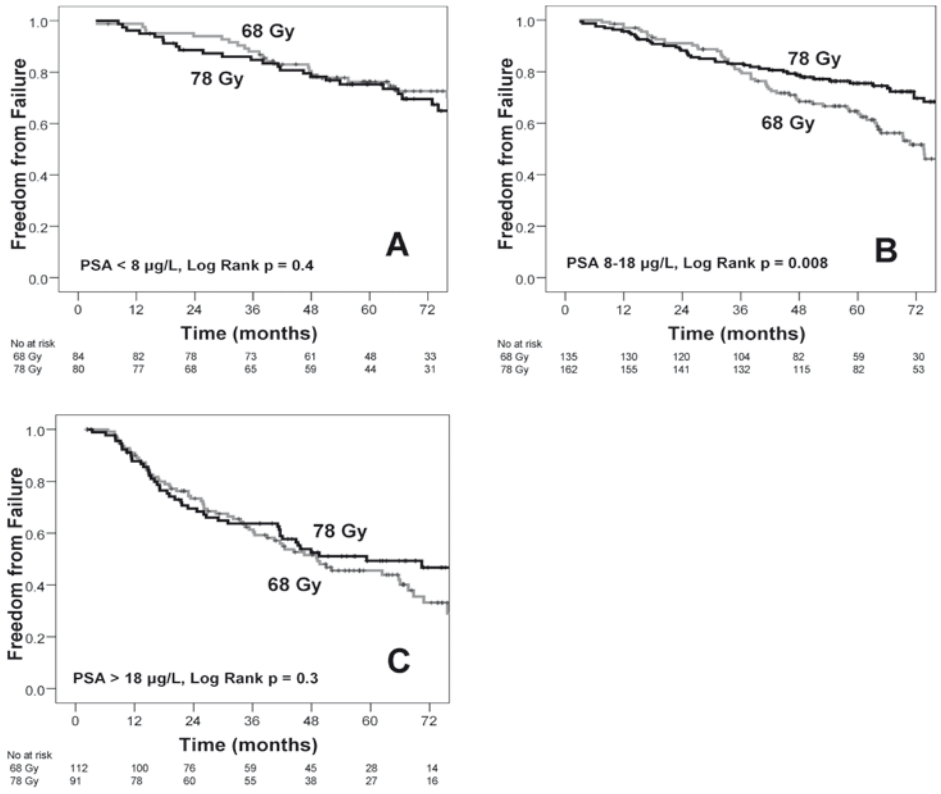

Figure 4. Freedom from failure for patients with iPSA < 8 (4A), 8-18 (4B), and > 18 µg/L (4C) by randomization arm.

μg/L and iPSA> 18μg/L, there were no significant (p= 0.4 and p= 0.3, respectively) differences in the 6-year FFF rates (Figure 4A and 4C).

With respect to the use of HT in high-risk patients, the test for heterogeneity was not significant (Figure 1D). FFF-rates were better in patients treated with HT and radiotherapy, compared to those treated with radiotherapy alone (HRs were 0.68 and 0.87, respectively).

DISCUSSION

In our trial, we found an overall significantly better FFF in patients treated with a higher dose for localized prostate cancer. We investigated in this study whether we could identify significant heterogeneity in dose-response among the trial patients, who had a wide range in expected tumor control based on their Gleason score, iPSA level and/or tumor stage. Separating patients on iPSA, we found similar results as reported in literature: patients with low iPSA levels do not seem to benefit from dose escalation. We found however an indication that the most optimal cut-off was around 8 μg/L instead of 10 μg/L and moreover that patients with relatively high iPSA levels did not profit either from dose-escalation in our trial. We also evaluated the effect of combined treatment of RT with HT for the high-risk patients and concluded that there was no indication that these patients would not profit from dose-escalation, which also confirms observations of other groups.

Low-, intermediate-, and high risk groups as defined by Chism et al.

The tests of interaction between risk group and dose-arm was not significant, indicating that based on our trial no risk-group should be excluded from high-dose radiotherapy. The Kaplan Meier curves were shown to illustrate FFF as a function of time (Figures 2A-C). It should be stressed here, that one should not conclude that high-dose radiotherapy is not indicated for the low- and high-risk patients (with p values of 0.4 and 0.15, respectively), since there was no significant interaction.

Dearnaley et al. (4) performed a similar subgroup analysis and found, as in our study, no heterogeneity of effect (p= 0.44). Therefore, neither of these analyses could exclude nor recommend high-dose radiotherapy in either of these risk-groups. In the MGH/LLUMC proton dose escalation trial (3), the overall significant differences persisted for low-risk (p< 0.001) and intermediate-risk (p= 0.02) patients, but was lost in the small number (n= 33) of high-risk patients (p= 0.49). However, in this study a test of interaction was not performed.

When the data from the MRC trial (4) and our trial were pooled, the test of interaction was still negative but the HR was improved from 0.78 in our study to 0.65 in the pooled data from both studies (p= 0.0001) (Figure 5). Therefore, a meta-analysis from the data of all mature

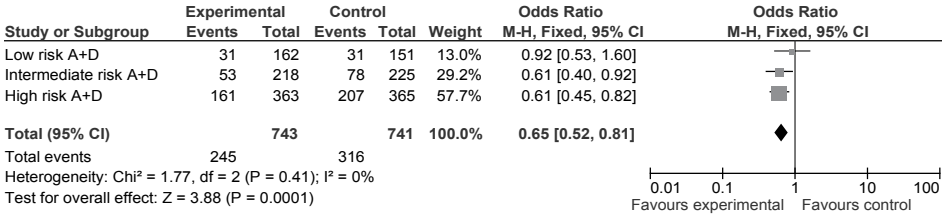

Figure 5. Forest plots with numbers of events and the corresponding hazard ratios (with 95% CI) showing the effect of radiation dose on freedom from failure for low-, intermediate-, and high-risk groups according to Chism *et al*. (9) in the pooled data from our study (A from Al-Mamgani et al.) and the MRC RT01 trial of the Institute of Cancer Research and Royal Marsden Hospital (D from Dearnaley *et al*. (4)).

randomized dose-escalation trials would help us to decide whether low-risk patients should receive high-dose radiotherapy or not.

In the literature, the role of dose-escalation in the intermediate-risk group is undisputed (1-5, 10, 13, 14), whereas the importance of high-dose radiotherapy for high-risk patients is definitively more complex, especially in studies were HT were allowed, as in our study. The use of HT in these studies makes it difficult to determine the role of dose-escalation separately. Because of the improved local control, distant metastases-free survival and even overall survival achieved with HT (10, 15), it is not justified to exclude high-risk patients using HT from high-dose radiotherapy. If we do so, we might withhold these patients from the essential synergistic role of RT and HT to control their disease in a proper way. In our study the FFF was better in those patients who received high-dose radiotherapy in combination with HT (HR= 0.68).

Only one prospective randomized trial (the MRC trial of the Institute of Cancer Research and Royal Marsden Hospital) showed a benefit of dose-escalation in patients treated with HT (4). One prospective non-randomized trial (16) demonstrated a 79% freedom from biochemical failure (FFBF) at 5-years in high-risk patients treated with HT and high-dose radiotherapy, comparable with the 5-year FFBF seen in the low-risk group (80%). Interestingly, these patients consistently experienced a significant benefit from higher radiation doses (63% for < 72 Gy vs. 84% for ≥ 72 Gy) (p=0.003). Zelefsky et al. (10) observed a benefit for HT in high-risk patients who also received higher doses of radiotherapy, but also concluded a strong interdependence on the use of neo-adjuvant HT and higher doses; patients who offered neo-adjuvant HT were significantly more likely to receive higher dose of radiotherapy than patients who did not receive HT (p< 0.0001).

Table 2 shows an updated overview of subgroup analyses from different randomized and non-randomized trials of dose-escalation of radiotherapy for localized prostate cancer. As illustrated in Table 2, all randomized-controlled trials (RCT) showed a benefit of dose-escalation in the

Table 2. Subgroup analyses, randomized and non-randomized trials of DE of radiotherapy for localized prostate cancer

Trial	Size	Dose (Gy)	Subgroup	FF(B)F; high-dose vs. low-dose	Statistics
RCT MD Anderson (2)	301	70 vs. 78	PSA >10	78% vs. 39% at 8-years	p= 0.001
			LRG	88% vs. 63% at 8-years	p= 0.042
			IRG+PSA >10	94% vs. 65% at 8-years	p= 0.076
			HRG	63% vs. 26% at 8-years	p= 0.004
RCT MRC RT01 (4)	843	64 vs. 74	LRG	85% vs. 79% at 5-yeras	HR= 0.78
			IRG	79% vs. 70% at 5-years	HR= 0.74
			HRG	57% vs. 43% at 5-years	HR= 0.60
RCT MGH/LLUMC (3)	393	70.2 vs. 79.2	LRG	98% vs. 85% at 5-years	p< 0.001
			IRG	91% vs. 79% at 5-years	p= 0.02
RCT Current Dutch study	664	68 vs. 78	PSA > 10	62% vs. 40% at 6-years	HR= 0.66
			PSA 8-18	70% vs. 52% at 6-years	HR=0.59
			IRG	78% vs. 54% at 6-years	HR= 0.55
			HRG	49% vs. 44% at 6-years	HR= 0.81
NRT Multicenter study (13)*	4,839	< 72 vs. ≥ 72	IRG	64% vs. 50% at 8-years	p< 0.0001
			HRG	36% vs. 27% at 8-years	p= 0.007
NRT MSKCC (10)	2,047	66-86.4	IRG	84% vs. 68% at 5-years	p< 0.001
			HRG	71% vs. 40% at 5-years	p< 0.001

Abbreviations: DE: dose-escalation; FF(B)F: freedom from biochemical failure or freedom from any failure; RCT: randomized controlled trial; NRT: non-randomized trial; PSA: prostate-specific antigen level; LRG: low-risk group; IRG: intermediate-risk group; HRG: high-risk group; HR: hazard ratio; MRC: Institute of Cancer Research and Royal Marsden Hospital; MGH/LLUMC: Massachusetts General Hospital and Loma Linda University Medical Center; MSKCC: Memorial Sloan-Kettering Cancer Center. * Kuban *et al.* (13) pooled and published the results from different centers including MD Anderson, MSKCC, Cleveland, Fox Chase Cancer Center, and more.

intermediate- and high-risk group, with the exception of the trial of the Massachusetts General Hospital and Loma Linda University Medical Center (3). A benefit from dose-escalation in low-risk patients were observed in all RCT, except in our study. Subgroup analyses were also performed in two large non-randomized studies. Zelefsky et al. (10) treated more than 2000 patients with localized prostate cancer to different dose levels ranged from 66 to 86.4-Gy and found a significant improvement in outcomes for patients with intermediate- and high-risk patients but no differences were observed among low-risk patients for the various dose-groups. Kuban et al. (13) pooled the results of 4839 patients from different institutions and showed a significant dose-effect relationship (doses < 72 vs. ≥ 72-Gy) in intermediate- and high-risk patients but not in the low-risk group.

PSA-level groupings

For the two studied types of PSA level groupings: PSA < 10 and ≥10 μg/L, and < 8, 8-18 and > 18 μg/L, the test for heterogeneity was significant (p= 0.03 and 0.05, respectively). These results indicate that patient selection for high-dose radiotherapy based on iPSA level might be indicated. The exact number(s) of iPSA cut-off points is still to be determined. Our data showed that patients with iPSA between 8 and 18 μg/L benefited most from dose-escalation; FFF-rates were significantly better in the high-dose arm as compared to the low-dose arm (p= 0.008).

Other groups analyzed their data as well, based on a cut-off value of 10 μg/L. The MDACC trial (2), reported a benefit from dose-escalation in patients with iPSA > 10 μg/L and no dose-response could be demonstrated for patients with iPSA ≤ 10 μg/L. However, no test of interaction was performed in this study. Pinover et al. analyzed the Fox Chase Cancer Centre cohort with iPSA ≤ 10 μg/L (n=488) (stratification < 72.5, 72.5-75.9 and ≥ 76 Gy) and found no significant dose-response for the entire group and for good prognosis patients. Only poor prognosis patients (> T2a and Gleason > 6) with iPSA ≤ 10 μg/L benefited from escalating the radiation dose to ≥76 Gy (17).

Since a relatively large part of prostate cancer patients has iPSA between roughly 7 and 10 μg/L, it is a clinically relevant question whether these patients might benefit from dose-escalation. Our data do not support the findings of other investigators that patients with iPSA <10 μg/L do not profit form high-dose radiotherapy (2, 17). From our data one could conclude that patients with an iPSA < 8 μg/L have no benefit of high-dose radiotherapy.

Our results also suggest that there could be an upper limit of iPSA, above which there is no advantage for high-dose radiotherapy. This finding should be confirmed by other studies.

General remarks

Despite the fact that our study has been carried out within the framework of a randomized trial, one should be aware of the weaknesses and pitfalls of such an exploratory analysis of prospectively collected data. We performed tests of heterogeneity to assess whether a treatment effect differed between subgroups. The test of interaction in our analysis was not significant between dose-arm and the prognostic risk groups. Therefore no conclusion could be made of the value of high-dose radiotherapy in any of these risk groups separately. However, based on the two iPSA level groupings, we found significant interactions. Therefore we might conclude that for patients with an iPSA < 8 μg/L high-dose radiotherapy is probably not indicated.

The results of our analyses suggest that iPSA grouping is probably a better predictor for a possible benefit of dose escalation rather than the risk grouping. The studied risk groups are however also partly based on iPSA-grouping. In a multivariate analysis of prognostic factors for FFF with iPSA as a continuous variable and risk-group, dose-arm and use of HT as co-variables (data not shown), the iPSA level and risk grouping both are significant factors. Therefore the iPSA level is probably of a higher importance than accounted for in the current risk grouping. Moreover, within the context of the value of high-dose radiotherapy, one might explore in the future other definitions of prognostic groups, including not only factors like iPSA, T-stage, Gleason sum and but also parameters like e.g. vascular or perineural invasion, multiple positive biopsies, or high iPSA level/velocity. Such a study should preferably be undertaken in a meta-analysis from the data of all mature randomized dose-escalation trials.

CONCLUSIONS

In our study, no conclusion could be drawn with regard to the value of high-dose radiotherapy in the three risk-groups and specifically no indication was found to exclude low-risk patients from high-dose radiotherapy. FFF-rates were improved in patients treated with hormonal therapy in combination with high-dose radiotherapy, compared to those treated with low-dose radiotherapy and hormonal therapy. PSA-level groupings showed significant interactions with the dose-arm. For patients with an iPSA < 8 μg/L high-dose radiotherapy is probably not indicated, but this should be confirmed in other studies.

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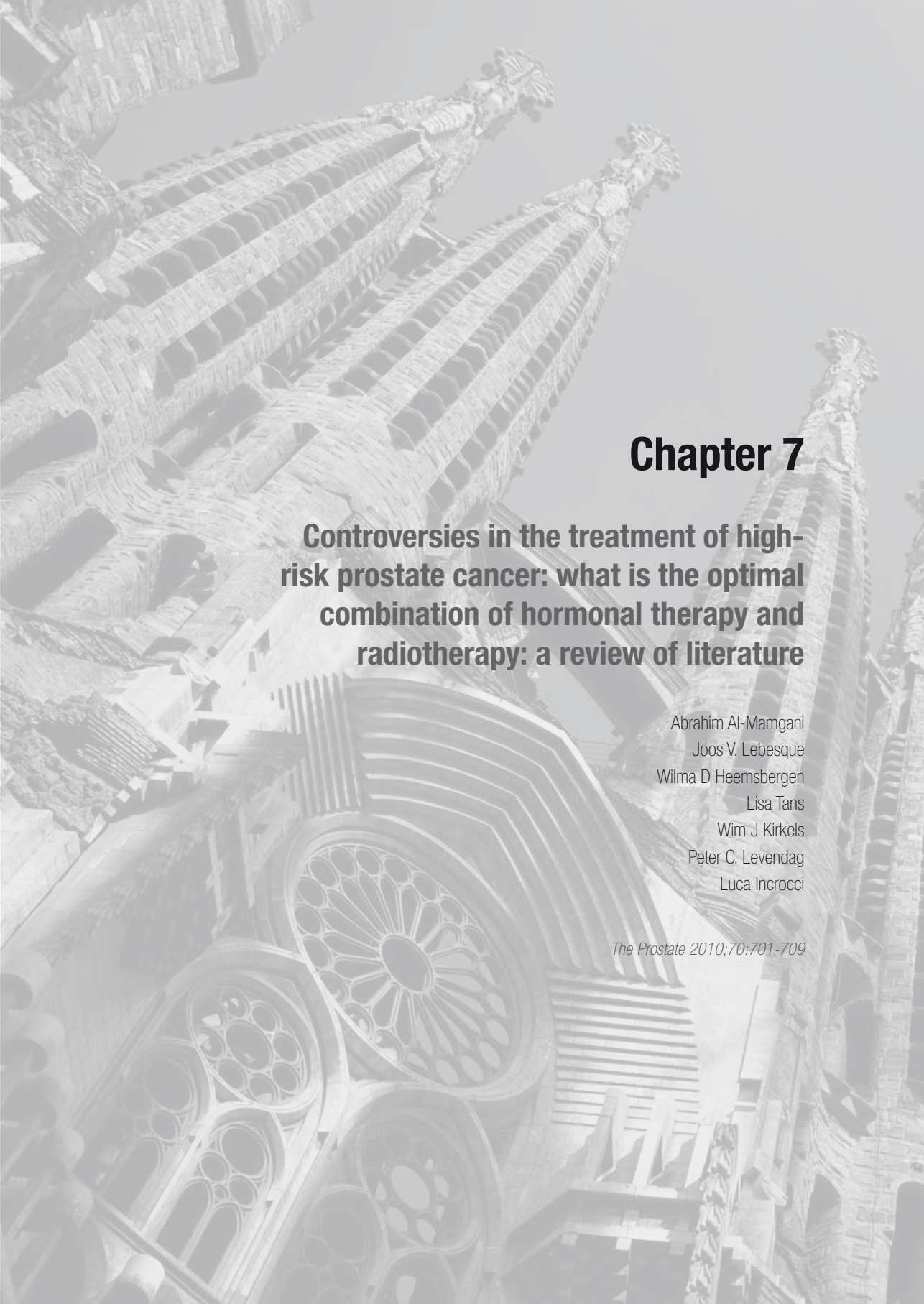

Chapter 7

Controversies in the treatment of high-risk prostate cancer: what is the optimal combination of hormonal therapy and radiotherapy: a review of literature

Abrahim Al-Mamgani
Joos V. Lebesque
Wilma D Heemsbergen
Lisa Tans
Wim J Kirkels
Peter C. Levendag
Luca Incrocci

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ABSTRACT

Background

In high-risk prostate carcinoma, there is controversy whether these patients should be treated with escalated-dose (≥ 74 Gy) or conventional-dose radiotherapy (< 74 Gy) combined with hormonal therapy. Furthermore, the issue of the optimal duration and timing of hormonal therapy are not well crystallized.

Patients and Methods

A search for evidence from randomized- and large non-randomized studies in order to address these issues, was therefore initiated. For this purpose, MedLine, EMbase, and PubMed and the data base of the Dutch randomized dose-escalation trial, were consulted.

Results and Conclusions

From this search it was concluded that the benefit of hormonal therapy in combination with conventional-dose radiotherapy (< 74 Gy) in high-risk prostate cancer is evident (Level 2 evidence); Level 2 and 3 evidence was provided by several studies supporting the use of escalated-dose radiotherapy in high-risk prostate cancer. For the combination of hormonal therapy with escalated-dose radiotherapy in these patients, there is Level 2 evidence for moderately escalated dose (74 Gy) and high escalated dose (≥ 78 Gy). The optimal duration and timing of hormonal therapy are not well defined. More randomized-controlled trials and meta-analyses are therefore needed to clearly determine the independent role of dose-escalation in high-risk patients treated with hormonal therapy and the optimal duration and timing of hormonal therapy.

INTRODUCTION

Since 2002, prostate cancer (PC) has overtaken lung cancer to become the most common cancer in men. Annually, in the USA, approximately 186,000 new cases of PC are diagnosed with 29,500 PC-related deaths [1]. Of the newly-diagnosed cases, at least 30% have high-risk disease [2]. The four randomized dose-escalation trials of radiotherapy (RT) [3-6] included 2,201 patients with localized PC. Of those patients; 39% were at high-risk for biochemical failure. The most commonly used definitions of high-risk PC are the single-factor risk-group model of Chism et al. [7] (stage T3-4 or iPSA > 20 μg/L, or Gleason-score 8-10) and the very similar National Comprehensive Cancer Network criteria [8] (stage T3 or Gleason score 8-10 or iPSA > 20 μg/L). High-risk PC is clinically a very heterogeneous group and, therefore, a challenge to the oncologists in terms of diagnosis, management and prognosis. This group contains a wide spectrum of diseases, ranging from patients with locally aggressive disease to those with widespread occult distant metastases (DM).

Different studies have shown that patients with high-risk PC have a higher incidence of biochemical and clinical failures when treated with monotherapy (hormonal therapy (HT) or RT) [9, 10]. Widmark et al. [9] recently published the results of the Scandinavian randomized-controlled trials (RCT) comparing HT-alone with the combination of HT and standard-dose RT in 875 patients with locally-advanced PC. In that study, the addition of local RT to HT halved the 10-year cancer-specific mortality (CSM) in high-risk PC and substantially improved local control and overall survival (OS) with a fairly acceptable toxicity profile. It is also well-known that long-term outcome after conventional-dose RT alone in locally-advanced PC is poor: treating those patients with 60-66 Gy of RT alone in the pre-PSA era resulted in poor disease-free survival (DFS) (15-30%), and OS (10-20%) at 15-years [11]. The need for increasing the dose of RT to above those levels was first suggested by dose-response observations by Perez et al. [12] and Hanks et al. [10] and confirmed, later on, by different RCTs [3-6].

PATIENTS AND METHODS

In this article, we will give an overview of the following issues for high-risk PC patients:

1. The use of HT in combination with standard-dose RT
2. The effect of dose-escalation of RT
3. The independent role for RT dose-escalation for patients on HT
4. Short- vs. long-course HT
5. Neoadjuvant, concomitant, adjuvant HT or in a combination of these

In order to address these issues, a thorough and critical literature review was performed through literature searches (in MedLine, EMbase and PubMed) for evidence from randomized and large non-randomized studies to support either the use of conventional-dose or escalated-dose RT in high-risk PC combined with HT. Data from the Dutch randomized dose-escalation trial were also used for this review [6]. Only relevant peer reviewed papers published in English after the era of combined-modality treatment (HT and RT) were included. The search terms used were: "high-risk PC", "locally-advanced PC", "radiotherapy", "hormonal therapy", and "dose-escalation".

According to National Cancer Institute (NCI) guidelines [13], the levels of evidence supporting recommendations for the different strategies are reported in the text and summarized as follow:

Level 1. Randomized controlled clinical trials:

- Double-blinded.
- Nonblinded treatment delivery. Subset analyses should be placed in the next lower category of study design (nonrandomized controlled clinical trials).

Level 2. Nonrandomized controlled clinical trials.

Level 3. Case series.

- Population-based, consecutive series.
- Consecutive cases (not population-based).
- Nonconsecutive cases.

RESULTS

Combining HT with conventional-dose RT in locally-advanced PC (Table 1)

First it should be mentioned that the RCTs mentioned in this paragraph were performed for locally-advanced PC. This group of patients only partly overlap with the high-risk patients group.

The Radiation Therapy Oncology Group (RTOG) has conducted three large RCTs to evaluate the role of combined-modality treatment (HT added to conventional-dose RT) in locally-advanced PC [14-16]. These trials enrolled almost 3000 patients between 1987 and 1995. RTOG 86-10 was the first RCT to evaluate the effect of neoadjuvant HT in combination with 65-70 Gy of RT [16]. In that study, 456 patients were randomly assigned to receive either RT-alone or RT in combination with HT starting 2 months before the RT and continued during the course of radiation. In that study, DFS (any kind of failure, death from any cause or starting salvage HT), freedom from distant metastases (FFDM), and cancer-specific mortality (CSM) were significantly better in the combined-modality arm without increasing risk of fatal cardiac events. OS was also better in the combined-modality arm, but did not reach statistical significance (Table 1).

In the second RTOG-trial (85-31) [15], 977 patients with locally-advanced PC were randomized to be treated with either RT and immediate HT (arm I), started in the last week of radiation course (65-70 Gy) and continued indefinitely or until signs of progression or RT and delayed HT at relapse (arm II). DFS (survival in the absence of locoregional or distant metastasis), and CSM were significantly better in patients treated with adjuvant HT (arm I) The absolute survival at 10 years was also significantly better in arm I compared with arm II (49% vs. 39%, respectively, p=0.002).

The largest RTOG-trial (92-02) included 1554 patients with locally-advanced PC [14]. All patients were treated with HT before and during the RT (4 months) and followed by randomization to either no further HT (arm I) or 24-months of goserelin (arm II). In that study, DFS was defined as survival without any kind of failure, including biochemical failure, starting additional HT or death. At 10-years, arm II showed significant improvements in all endpoints except OS. However, in the subgroup analysis, a significant OS benefit was observed in patients with Gleason score of 8-10 treated in arm II (45% vs. 32%, p=0.006).

Table 1. RCT of conventional-dose RT alone or in combination with HT in patients with locally-advanced prostate cancer

Trial	P (N)	Timing HT	Duration HT	Dose RT	Outcomes RT arm vs. RT + HT arm	P-value
RTOG 92-02 [14]	1,554	NHT/CHT vs. NHT/CHT/AHT	24 months	70 Gy	10-years OS 52% vs. 54%	0.36
					10-years DFS 13% vs. 23%	<0.0001
					10-years CSM 16% vs. 11%	0.004
RTOG 85-31 [15]	977	AHT	Indefinitely	65-70 Gy	10-years OS 39% vs. 49%	0.002
					10-years DFS 23% vs. 37%	<0.0001
					10-years CSM 22% vs. 16%	0.005
RTOG 86-10 [16]	456	NHT/CHT	4 months	65-70 Gy	10-years OS 34% vs. 43%	0.12
					10-years DFS 3% vs. 11%	<0.0001
					10-years CSM 36% vs. 23%	0.01
AMCM [17]	206	NHT/CHT/AHT	6 months	70 Gy	8-years OS 61% vs. 74%	0.01
					8-years CSM 14% vs. 4%	0.007
EORTC [18]	415	CHT/AHT	3 years	70 Gy	5-years OS 62% vs. 78%	<0.0001
					5-years DFS 40% vs. 74%	<0.0001
					5-years CSM 21% vs. 6%	<0.0001
TROG 96-01 [19]	818	NHT	3 months	66 Gy	5-years DFS 32% vs. 49%	0.0001
					5-years CSM 9% vs. 8%	0.7
			6 months	66 Gy	5-years DFS 32% vs. 52%	<0.0001
					5-years CSM 9% vs. 6%	0.04
Swedish [20]	91	Orchidectomy		65 Gy	17-years OS 13% vs. 24%	0.03
					17-years CSM 57% vs. 36%	0.02

Abbreviations: RCT: randomized-controlled trials; RT: radiotherapy; HT: hormonal therapy; P (N): patients' numbers; AHT: adjuvant HT; NHT: neo-adjuvant HT; CHT: concurrent HT, OS: overall survival; DFS: disease-free survival; CSM: cancer-specific mortality; RTOG: Radiation Therapy Oncology Group; AMCM: Academic Medical Centers Massachusetts; EORTC: European Organization for Research and Treatment of Cancer; TROG: Trans-Tasman Radiation Oncology Group;

D'Amico et al. [17] published the results of the RCT of 6-months of adjuvant HT plus RT (arm I) vs. RT-alone (arm II) for 206 patients with localized but unfavorable PC. In arm I, 70 Gy of RT was combined with 6-months of HT; started 2 months before, continued during and for 2-months after the RT. Combined-modality treatment showed significant improvements in CSM and OS. Only four patients died from PC in the combined modality arm compared to 14 patients in the RT- alone arm at 8 years (p=0.007).

Bolla et al. [18] reported significant improvements in DFS (locoregional or distant failures), and OS at 5-years in 415 patients with localized PC treated with either 70-Gy of RT-alone or combined with 3-years of adjuvant HT, started on the first day of irradiation. Of the whole study population, 129 patients (31%) were at high-risk. The improvements seen in all endpoints persisted in the high-risk patients in the subgroup analysis (Table 1).

The Trans-Tasman Radiation Oncology Group (TROG) [19] has randomized 818 patients with locally-advanced PC to receive either 66-Gy alone (arm I) or 66 Gy of RT in combination with 3-months HT starting 2 months before RT (arm II) or 6-months HT starting 5 months before RT (arm III). At 5-years, DFS (no evidence of clinical failure at any site, start of salvage HT, no biochemical failure or death) was significantly improved in arm II as compared to arm I. Regarding CSM at 5 years, the rates were comparable in both arms (9% for arm I vs. 8% for arm II, p=0.7). However, all endpoints of the study were significantly improved with increasing the duration of the adjuvant HT from 3 to 6 months plus RT (arm III), including reduction or delay in the appearance of DM (HR=0.67, p=0.04).

The long-term results of the Swedish RCT comparing orchidectomy and RT vs. RT-alone, showed that CSM at 17 years was significantly higher in the RT-alone arm (57% vs. 36%, p=0.02) [20]. OS was also significantly improved in the combined modality arm (24% vs. 13%, p=0.03).

In conclusion, the results of the seven RCTs comparing the use of conventional-dose RT-alone vs. the addition of HT to RT substantiate a powerful beneficial effect of adjuvant HT in patients with locally-advanced PC. Subgroup analysis in some of these studies showed that the adjuvant effect was also apparent in the high-risk patient subgroup. Therefore these studies provided Level 2 evidence supporting the use of HT in combination with conventional-dose RT as a standard of care in high-risk PC.

Dose-escalation of RT in high-risk prostate cancer

Non-randomized studies of dose-escalation in high-risk PC (Table 2)

Zelefsky at al. [21] reported the experience of MSKCC treating 2,047 patients with clinically localized PC with 3D-CRT or IMRT with different dose-levels ranged from 66 to 86.4 Gy. About half of the patients (48%) were treated with 3 months of neoadjuvant HT. Intermediate- and high-risk patients appeared to benefit most from escalating the dose of RT above conventional-levels. In patients with high-risk PC, multivariate-analysis showed that radiation dose is not only a significant predictor for freedom from biochemical failure (FFBF) (Phoenix definition [22]: an increase in PSA level of more than 2 μg/L above the post-treatment nadir) ($p<0.0001$), but also for FFDM ($p=0.01$). Because neoadjuvant HT and higher radiation doses were closely associated in this study, specific high-dose levels were not longer significant in the setting of neoadjuvant HT.

Kupelian et al. [23] reported the results of 9 institutions (n = 1,325). In that study, the 5-year FFBF (ASTRO definition [24]: 3 successive increases in PSA level, with the failure backdated to a point halfway between the first increase and the last non-increasing value) for the whole group of patients received a dose ≥ 72 Gy was significantly better as compared with those treated with < 72 Gy (69% vs. 63%, $p=0.046$). However, for the 221 high-risk patients the difference (46% vs. 38%) was no longer significant ($p=0.13$).

A moderately-strong evidence for the need of dose-escalation in high-risk PC was also provided by the group of William Beaumont Hospital [25]. They performed a prospective trial of pelvic external-beam RT (46 Gy) interdigitated with dose-escalating highly-conformal HDR-brachytherapy (BT), using two dose-levels (low BED <93 Gy and high BED >93 Gy). The 5-year FFBF (ASTRO definition) and CSM were significantly better in the high-BED group ($p<0.001$ and 0.014, respectively).

At the University of Michigan [26], 1473 localized PC were treated with 3D-CRT. Prescribed dose-levels ranged from 60 to 80.4 Gy. For intermediate-risk patients, the effect of the total dose on the FFBF (ASTRO definition) was significant (HR=0.92, $p=0.005$). However, for the high-risk patients (n=456), the effect of the total dose was not significant (HR=1.02, $p=0.3$).

Randomized-controlled studies of dose-escalation in high-risk PC (Table 3)

The first RCT of dose-escalation was undertaken by Pollack and colleagues from the M.D. Anderson Cancer Center. In the recent update of that study [3], FFBF (Phoenix definition), freedom from clinical failure (FFCF), and FFDM were significantly improved by escalating the dose of RT from 70 to 78 Gy. In the entire cohort, the 8-year FFBF was significantly improved in the high-dose arm (78% vs. 59%, $p=0.004$). In the subgroup analysis, high-risk patients (33% of the whole study population) benefited significantly from high-dose RT, with FFBF at 8-year of 63% for

the high-dose arm, compared with 26% for the low-dose arm (p=0.004). FFCF (93% vs. 82%, respectively) and FFDM (4% vs. 17%, respectively) were also significantly better in the high-dose arm. No OS benefit was seen in that study. However, more patients died of PC in the 70-Gy arm.

At the Massachusetts General Hospital and Loma Linda University Medical Center, 393 patients with localized PC were randomized to receive either 70.2- or 79.2 Gy [4]. The primary endpoint of that study was FFBF, defined using the ASTRO criteria. In the entire study population, the 5-year actuarial FFBF was 93% for the high-dose arm as compared with 81% for low-dose arm (p<0.001). These significant differences between both arms also persisted when patients were divided into low-risk (84.7% vs. 97.8%, p<0.001) and intermediate-risk (79.1% vs. 90.9%, p=0.02) subgroups, but lost in the small number (n=33) of high-risk patients (p=0.8).

In the RCT of Medical Research Council (MRC), 843 patients were randomly assigned to receive a standard-dose (64 Gy) or escalated-dose RT (74 Gy) [5]. All patients received neo-adjuvant and concomitant HT for 3-6 months. FFBF in that study was defined as increase in PSA concentration to greater than the nadir by at least 50% and >2 ng/mL 6 months or more after the start of RT. In the entire cohort, the 5-year FFBF was significantly improved in the high-dose arm (71% vs. 60%, HR=0.67, 95%CI = 0.53-0.85, p=0.0007). Of the whole group, 362 patients (43%) were at high-risk. The 5-year FFBF-rates for high-risk PC treated with high-dose vs. low-dose were 57% vs. 43%, respectively (HR=0.6, 95% CI = 0.44-0.81).

The Dutch RCT enrolled 664 patients; of those, 362 (55%) were at high-risk [6]. Of the high-risk patients, 125 patients (34%) received 6- or 36-months of HT. Of the whole group, the 6-year freedom from failure (FFF) (biochemical (Phoenix definition) or clinical) was improved from 51% in the low-dose arm to 63% in high-dose arm (p=0.04). In the subgroup analysis, the difference between both arms was not statistically significant in the high-risk group (49% vs. 40%, p=0.15) [27].

In conclusion, a significant benefit from dose-escalation was seen in high-risk patients in some randomized and non-randomized trials. These positive studies generate Level 2 and Level 3 evidence supporting the use of dose-escalation in high-risk PC. A meta-analysis of all mature RCTs would strengthen the level of evidence. The questions which emerge: Is high-dose RT really required in patients with high-risk PC on hormonal treatment?

Dose-escalation combined with HT in high-risk PC (Table 2)

Several studies have shown that conventional-dose RT in combination with HT yielded a significantly better outcome than RT-alone [15-20]. However, the mechanism mediating the better outcome in the combined-modality arm remains unclear. Whether the benefits observed are due to hormone-induced radiosensitization or due to the elimination of occult micrometastses remains to be proven. In order to identify a possible independent role of dose-escalation in

high-risk PC, we analyzed data from different non-randomized and randomized studies where this issue was addressed separately.

Table 2. Non-randomized studies of dose-escalation of RT with or without HT in patients with high-risk prostate cancer

Trial	P (N)	HRG (N)	HT	Duration HT	Dose RT	Outcomes	Statistics
Zelefsky [21]	2,047	752	No/Yes	3 months	< 70 Gy	5-years FFBF 40%	p<0.0001
					75.6 Gy	5-years FFBF 61%	
					81 Gy	5-years FFBF 66%	
					86.4 Gy	5-years FFBF 71%	
Kupelian [23]	1,325	221	No		< 72 Gy	5-years FFBF 38%	p=0.13
					≥ 72 Gy	5-years FFBF 46%	
Zapatero [28]	416	160	Yes	24 months	< 72 Gy	5-years FFBF 63%	p=0.003
					≥ 72 Gy	5-years FFBF 84%	
Nguyen* [29]	296	88	Yes for <75 Gy	3 months	< 75 Gy	5-years FFBF 35%	p=0.02
					≥ 75 Gy	5-years FFBF 57%	
Martinez [25]	207	207	No		46 Gy EBRT+ HDR BT:		p<0.001
					BED < 93 Gy	5-years FFBF 52%	
					BED > 93 Gy	5-years FFBF 87%	
Stone [30]	5,889	1078	No/Yes	3-9 months	45 Gy EBRT+ LDR BT:		p<0.001
					BED < 200 Gy	5-years FFBF 76%	
					BED 200-220 Gy	5-years FFBF 83%	
					BED > 220 Gy	5-years FFBF 88%	

Abbreviations: HT: hormonal therapy; P (N): number all patients included in that study; HRG (N): number of patients with high-risk included in that study; RT: radiotherapy; EBRT: external-beam radiotherapy; BT: brachytherapy; * Matched-pair analysis; FFBF: freedom from biochemical failure; HDR: high-dose rate; LDR: low-dose rate; BED: biological equivalent dose.

Non-randomized studies of dose-escalation of RT in combination with HT

The hypothesis that escalated-dose RT is also needed in high-risk patients treated with HT was already tested by different prospective and retrospective studies of external beam therapy (EBRT), brachytherapy (BT) or the combination of both modalities of RT (Table 2 and 3).

Only one prospective non-randomized study has addressed the independent role of dose-escalation in high-risk patients who also received HT. Zapatero and colleagues [28] treated 160 patients with high-risk PC with 3D-CRT (dose 64.2-82.6 Gy) combined with adjuvant HT (24-months). The results demonstrated a 84% FFBF (ASTRO definition) at 5- years in high-risk patients treated with HT and radiation dose ≥ 72 Gy, compared to 63% in patients treated with dose < 72 Gy (p=0.003).

Zelefsky et al. [21] reported in the recent update of their retrospective analysis (n = 2,047) a benefit for HT in high-risk patients who also received higher doses of RT. Because neoadjuvant HT and higher radiation doses were closely associated in this study, specific high-dose levels were not longer significant in the setting of neoadjuvant HT.

Table 3. Randomized-controlled trials of dose-escalation of RT with or without HT in patients with high-risk prostate cancer

Trial	Randomization arms	HT	Duration HT	P (N)	HRG (N)	FF(B)F high-dose vs. low-dose arm	Statistics
MDACC [3]	78 vs. 70 Gy	No		301		78% vs. 59% at 8-years	p=0.004
					101	63% vs. 26% at 8-years	p=0.004
MGH/LLUMC [4]	79.2 vs. 70.2 Gy	No		393		93% vs. 81% at 5-years	p<0.001
					33	Very small number of patients	0.8
MRC [5]	74 vs. 64 Gy	Yes	3-6 months	843		71% vs. 60% at 5-years	HR=0.67, 95%CI:0.53-0.85
					362	57% vs. 43% at 5-years	HR=0.60, 95%CI:0.44-0.81
Dutch trial [6]	78 vs. 68 Gy	Yes/No	6-36 months	664		63% vs. 51% at 6-years	p=0.04
					362	49% vs. 40% at 6-years	p=0.15

Abbreviations: RT: radiotherapy; FFF: freedom from failure; FFBF: freedom from biochemical failure; P (N): total number of patients treated in that trial; HRG (N): number of high-risk patients treated in that trial; HR: hazard ratio; MDACC: M.D. Anderson Cancer Center; MGH/LLUMC: Massachusetts General Hospital, Loma Linda University Medical Centre; MRC: Medical Research Council.

In order to address the question if short-term HT is a substitute for dose-escalation in high-risk PC, Nguyen and colleagues from Fox Chase Cancer Center [29] did a separate matched-pair analysis between high-risk patients treated with short-term HT and radiation dose < 75 Gy (group A) and those with a dose ≥ 75 Gy without HT (group B). FFBF (ASTRO definition) at 5-years was significantly better in group B (57% vs. 35%, p=0.02). The results in that small study suggest that short-term HT was not a substitute for a higher dose RT.

The benefit of dose-escalation of RT in high-risk PC was also suggested by a study were high-dose RT using BT (as a boost after EBRT) was given partly in combination with HT. Stone et al. [30] reported the data of 1078 high-risk (Gleason 7-10) patients collected from 6 cancer centers in the USA. In that study, patients were treated with high-dose RT consisted of 45 Gy of EBRT followed by BT. Of the whole group, 61.8% was treated with HT. FFBF (Phoenix definition) at 5 years was significantly better (p<0.001) as the BED increased from less then 200 Gy to larger then 220 Gy.

Randomized studies of dose-escalation of RT in combination with HT

From the 4 mature RCTs of dose-escalation of RT [3-6], a possible independent role of escalated-dose RT in high-risk patients treated with hormones was only be examined in the MRC trial [5]. In this trial HT was given to all patients and in the high-risk subgroup the effect of dose escalation was still present. In this trial however, the escalated dose was relatively low (74 Gy). In the first two RCT of the M.D. Anderson Cancer Center and Massachusetts General Hospital/ Loma Linda University Medical Centre [3, 4] the escalated dose was high (78 Gy and 79.2 Gy, respectively), but HT was not allowed.

The Dutch trial randomized 664 patients with localized PC to receive either 68 Gy (n = 331) or 78 Gy (n = 333) of 3D-CRT [6]. In the high-dose arm, 11% (n = 37) received a dose lower than the prescribed dose of 78 Gy. Therefore, we divided our study population into two non-overlapping dose-groups: patients who received < 73 Gy (median dose 68 Gy) and those received ≥ 73 Gy (median dose 78 Gy). Of the whole group, 362 patients (55%) were at high-risk. Of this high-risk group, 125 patients (35%) received HT.

We analyzed FFF-rates in high-risk PC who received combined-modality treatment (RT plus HT) separately in order to explore the independent role of dose-escalation in those patients. As shown in Figure 1, a trend towards a significant difference between both dose-levels was observed. The 6-year actuarial FFF-rates in high-risk patients who received HT and escalated-dose RT (≥ 73 Gy) were better than in patients who were treated with HT and conventional-dose RT (< 73 Gy) (66% vs. 50%, respectively) (p=0.07).

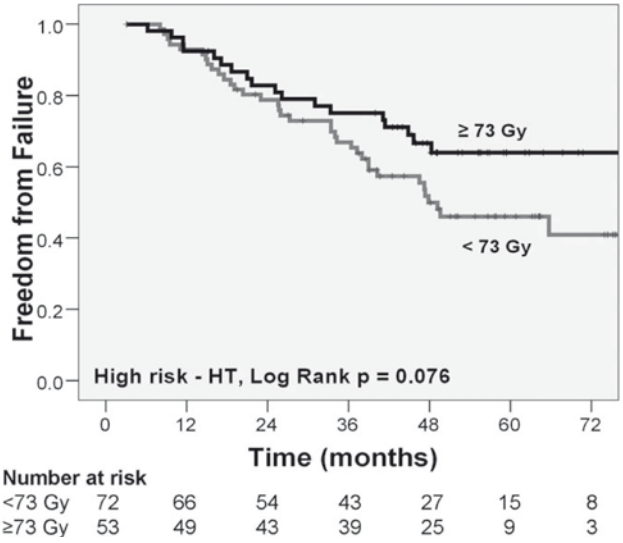

Figure 1. Kaplan-Meier estimates of freedom from failure for high-risk prostate cancer patients treated within the Dutch dose-escalation trial with hormonal therapy and either conventional-dose RT (< 73 Gy) or escalated-dose RT (≥ 73 Gy).

In conclusion, there is some evidence (Level 2 and 3) supporting the independent role of high-dose RT in high-risk PC treated with hormones. These results need, therefore, to be consolidated by a powerful RCT or addressing the exact role of high-dose RT in high-risk PC treated with hormones as well.

Duration of HT

The Canadian-trial [31] randomized 387 PC-patients to either 3- or 8-months of neo-adjuvant HT in combination with 66-Gy of RT. The DFS (defined as survival without biochemical failure (Phoenix definition), locoregional or distant failure) at 5-years was significantly improved for high-risk patients in the 8-months arm (71% vs. 42%, p=0.01), but not in intermediate- and low-risk

group, suggesting that high-risk patients are at higher risk of harboring micrometastases. The recently published subset analysis of this trial showed that the biochemical response to neo-adjuvant HT, but not duration, appeared to be the most significant predictor of outcome, especially in high-risk patients. That study suggests that tailoring neo-adjuvant HT, based on biochemical response before RT, would improve therapeutic gain by minimizing the duration of androgen deprivation therapy and its related toxicity [32].

Individually-tailored duration of neo-adjuvant HT based on clinical and biochemical response was also suggested by Heymann et al. [33]. In a Phase II study, 123 patients were treated with neo-adjuvant HT for 9-months. RT initiation was individualized to begin after a maximum response to androgen deprivation therapy as assessed by monthly rectal digital examination and PSA-level. At 5-years excellent FFBF (ASTRO definition), FFCF and OS were achieved (63%, 75%, and 89%, respectively). However, in the subgroup of patients were no maximum response was obtained, significantly lower FFBF and FFCF (RR 1.0, p=0.03) were observed.

In a retrospective study of high-risk patients treated with high-dose RT (23-Gy BT and 42-Gy EBRT) [34] 252 patients received RT in combination with and 308 patients without neo-adjuvant HT. In a multivariate analysis, neo-adjuvant HT was a borderline significant (p=0.03) risk factor for DM.

The meta-analysis of 5 RTOG-trials [35] has assessed the impact of short- and long-term HT on disease-specific survival (DSS) and OS in 2200 patients with localized PC treated with RT. Patients were stratified by prognostic risk groups. High-risk patients (T3/T4 or Gleason 8-10) were noted to have an 16% higher OS at 8-years with the addition of long-term HT (p=0.0004). OS at 8-years in patients with high-risk PC treated with long-term HT, vs. short-term HT vs. RT-alone were 44%, 36%, and 28%, respectively (p=0.03). The figures for DSS were 69%, 49%, and 42%, respectively (p=0.001).

Contrary to the aforementioned results supporting the use of long-term adjuvant HT, D'Amico and colleagues [36] pooled data from three RCTs of HT in combination with RT in high-risk PC and found no OS-benefit with 3-years compared with 6-months of HT. However, we cannot exclude in that study that unknown confounding factors might have affected these results, for instance the differences in radiation dose and field size used in those RCTs. Finally, there are parallels between breast and prostate cancers. In both diseases, long-term outcome was improved by the combination of HT and RT as compared with either alone. Since the long-term HT significantly improves OS in patients with breast cancer [37], one should, therefore, not be surprised if PC behaves similarly by using prolonged course of HT.

In conclusion, there is moderately-strong evidence (Level 2 and 3) that the duration of neo-adjuvant HT should be tailored by the biological response. There is level 2 evidence that

long-term adjuvant HT is preferred above short-term adjuvant HT. However, the optimal duration of long-term HT must be confirmed by RCTs by including patients in multiple-arms study. The answer to this question is quite essential, especially in view of the arguments of the cost and long-term side effects of a prolonged-course HT.

Timing of HT

The addition of 4-months (neo-adjuvant and concurrent) HT to the RT improved FFBF (PSA >2 ng/mL at ≥1 year from the date of randomisation), DFS (any kind of failure, death from any cause and starting salvage HT), and FFDM without OS-benefit in patients with unfavorable PC in the RTOG-8610-trial [16]. Adding another 2-years of HT adjuvantly to the 4-months (neoadjuvant and concurrent) in 1554 patients with locally-advanced PC treated within the RTOG-9202 trial, improved all endpoints, including OS in patients with Gleason score 8-10 [14]. The efficacy of combining neoadjuvant, concurrent with adjuvant HT was also demonstrated by D'Amico and colleagues [17]. In that study, as well OS as CSM were improved by adding two months adjuvant HT to the neoadjuvant and concurrent androgen deprivation therapy.

The question when should HT be administered in combination with RT (neoadjuvantly, concomitantly, adjuvantly or the combination of the 3), remains unanswered. In order to address this critical issue, RTCs including high-risk patients in multiple-arms studies are warranted.

CONCLUSIONS

In high-risk PC, the benefit of HT in combination with conventional-dose RT (< 74 Gy) is evident (Level 2 evidence). Level-2 evidence supporting the use of escalated-dose RT in high-risk PC was also provided by several RCTs. For the combination of hormonal therapy with escalated-dose radiotherapy in these patients there is Level 2 evidence for moderately escalated dose (74 Gy) and high escalated dose (≥ 78 Gy).

Regarding the optimal duration and timing of HT, there is moderately-strong evidence supporting the use of long-term adjuvant HT in high-risk PC. Further RCTs are, therefore, warranted to clearly determine the independent role of dose-escalation in high-risk patients using HT as well as the optimal duration and timing of HT. Until then, the treatment of high-risk PC is individualized and includes hormones in combination with conventional- or dose-escalated RT. When the expected risk of high-dose RT is high and the risk of local recurrence is predicted to be low, dose-escalation could be avoided.

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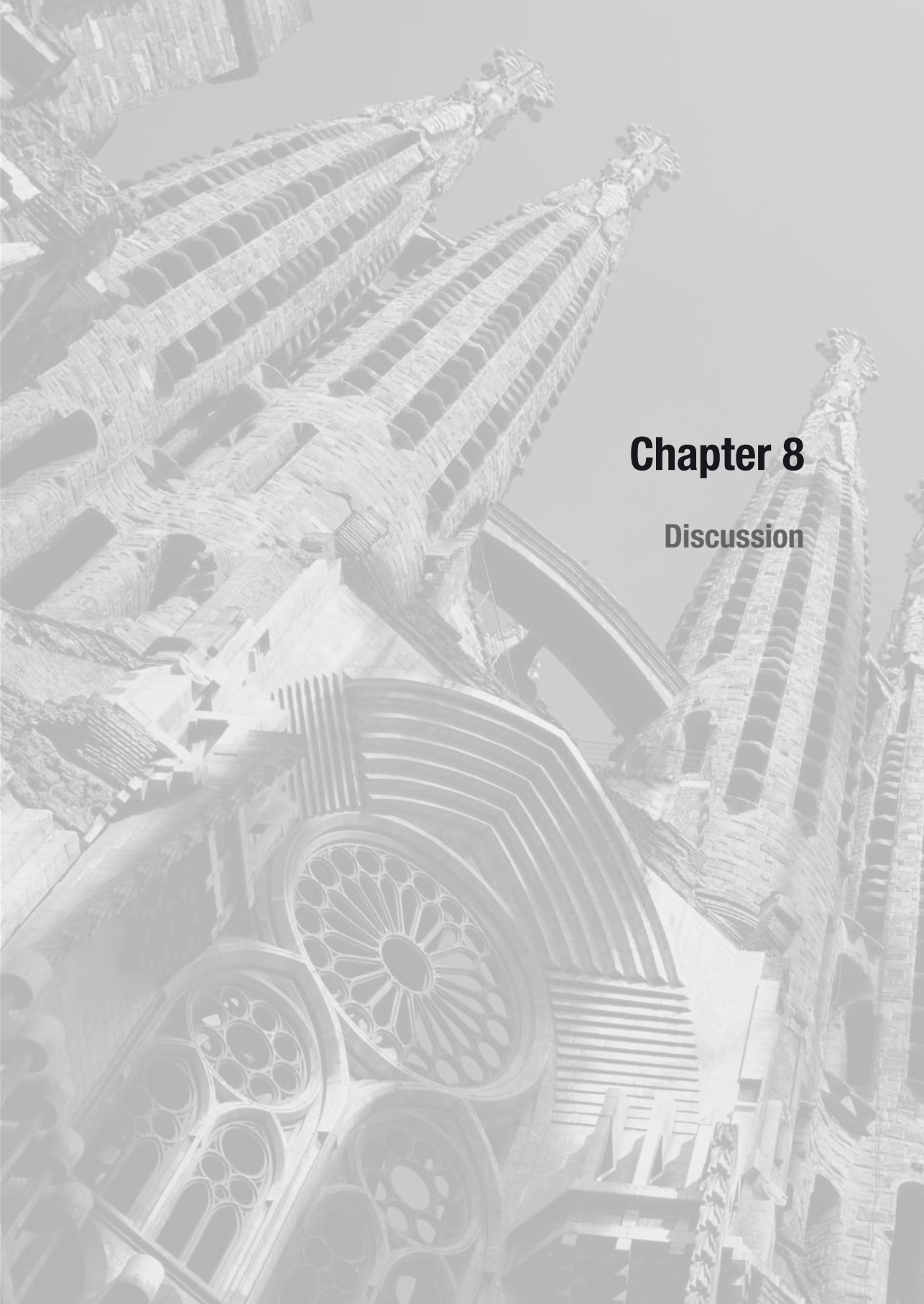

Chapter 8

Discussion

DISCUSSION

With the exception of skin cancers, prostate cancer has become the most common cancer in men in Western countries since 2002 (1). Radical prostatectomy and radiotherapy (RT) are currently standard treatment modalities for localized prostate cancer. Regarding RT, available data indicate a clear dose-response relationship for localized prostate cancer (2-4). These studies suggest that long-term outcome of localized prostate cancer critically depends on adequate radiation dose. Prostate cancer patients treated in the pre-PSA era with conventional-dose RT (60-66 Gy), showed a poor disease-free survival (DFS) (15-30%) and overall survival (OS) (10-20%) at 15-years (4). Few years after the first paper on dose-response correlations, it became evident that local control is of critical importance not only for the local treatment of the disease but also for overall survival, being a critical denominator for the occurrence of distant metastases (5). Although retrospective studies (4-6) have proven a better local control with dose escalation, increasing the dose over 66 Gy was limited by a rise in late toxicity. With the implementation of new treatment techniques such as 3-dimentional conformal RT (3DCRT) and intensity-modulated RT (IMRT) improved conformality was observed.

As a result of the promising high local control rates observed in different prospective dose escalation studies in the USA (7-9), a feasibility dose escalation study was performed in the NKI/AvL, The Netherlands. It was concluded that 3DCRT offers acceptable complication rates with high dose of radiation. However, randomized phase III studies were needed to validate these results. Therefore, the CKVO study 96-10 was initiated in The Netherlands in 1997 investigating the tumor control and toxicity as a consequence of dose escalation, comparing the standard dose of 68 Gy with the experimental dose of 78 Gy (10). This study was carried out in four cancer institutes in the Netherlands (Daniel den Hoed Cancer Center in Rotterdam, Nederlands Kanker Instituut-Antonie van Leeuwenhoek Hospital in Amsterdam, Radiotherapie instituut Friesland in Leeuwarden, Zeeuws radiotherapie instituut in Vlissingen).

The tumor control and toxicity of the Dutch phase III dose escalation trial after a median follow-up of 70 months, has been reported in **chapter 2**. As in other randomized dose-escalation trials (10-14), our study has also demonstrated improved biochemical control by increasing the dose to the prostate. Statistically significant improvement in freedom from failure (FFF) was seen in patients treated with 78 Gy but without improvement of OS and at the cost of increased late GI toxicity. Furthermore, none of the published individual dose escalation trials (9-11) have shown an OS benefit by increasing the RT dose above conventional dose levels, probably because of the competing risk of death from intercurrent diseases, the short follow-up period and/or because of lack of statistical power in these studies. One could, therefore, argue regarding the value of dose escalation in prostate cancer. Actually, the same problem was also seen initially by analyzing the data of different randomized controlled trials on the benefit of postoperative RT in breast cancer patients treated by breast-conserving surgery. None of the trials on its

own showed a significant OS benefit for the RT-arm. However, after a long follow-up period, a statistically significant benefit from postoperative RT in terms of OS was seen in the pooled data of 7,300 patients from 10 randomized controlled trials comparing breast-conserving surgery with or without RT (15-year breast cancer mortality risks 30·5% versus 35·9%; reduction 5·4%, SE 1·7, p=0·0002; overall mortality reduction 5·3%, SE 1·8, 2p=0·005) (15). Therefore, it is to be expected that the advantage of dose escalation in prostate cancer in terms of OS become evident only after long follow-up and/or after performing a meta-analysis of all mature dose escalation trials. Therefore, we still believe that dose escalation is necessary in patients with localized prostate cancer because biochemical control has been shown to correlate not only with local failure but also with distant metastases, cause-specific survival and disease-free survival (11, 16-18).

Besides our study, different other randomized trials have also shown that better local control rates are achieved with dose escalation at the cost of increased late GI toxicity. The radiation oncology community continues to struggle with the question how to further reduce these late complications of RT, because decreasing these complications has an important impact on the quality of life of prostate cancer patients. IMRT is a new conformal RT technique that produces highly conformal dose distributions, facilitating selective escalation to the target volume with lower dose to normal tissues. Different prospective studies showed lower GI toxicity rates in patients treated by means of IMRT, compared to those treated with 3DCRT with the same dose (19, 20). In **chapter 3**, we analysed the toxicity of 41 prostate cancer patients treated with IMRT. A very interesting finding was the significant reduction in acute GI toxicity by implementing IMRT in those patients, as compared to patients treated by means of 3DCRT to the same dose-level at the same hospital. IMRT was also of benefit in reduction of late toxicity, albeit statistically not significant. The explanation might be the short follow-up and/or the small number of patients treated with IMRT in our study (21). From a radiobiological point of view, the significant reduction of acute toxicity achieved by using IMRT should be translated in the future into a significant decrease in late toxicity. Heemsbergen et al. (22) concluded that acute GI toxicity is the most significant predictor of late toxicity, suggesting a consequential component in the development of late grade ≥ 2 GI toxicity. We believe that the recent implementation of image-guided RT (IGRT) at our institute will further enhance the safety and accuracy of IMRT and achieve, therefore, further decrease in the late toxicity.

In **chapter 4**, we specifically studied the relationship between different clinical and dosimetric variables and the occurrence of late urinary obstruction in our study population. The cumulative incidence of urinary obstruction at 7-years was 2.6% and 6.1% for the low- vs. the high-dose groups (p=0.2). Patients with pre-existing GU symptoms, those who experience acute GU toxicity during the RT, and patients with previous TURP were found to be at risk of urinary obstruction within 2 years after RT. An interesting dosimetric finding is that hotspots in the

bladder were also associated with urinary obstruction at early stages after RT. Events after a period of 2-7 years were associated with local dose in the trigonal area/bladder neck. Because of the serious nature of this RT-related complication, avoiding hotspots in the region of bladder neck and keeping the dose to the region of bladder neck/trigon as low as possible are quite challenging from treatment planning pint of view, because these issues were never used as constraints in treatment optimization (23).

Besides the achievement of excellent local control as primary goal of radical treatment of prostate cancer, toxicity and assessment of quality-of-life (QoL) have become very important secondary considerations in the design of clinical trials, especially given the arguments in favour of watchful waiting in patients with early-stage disease. The cohort studied at **chapter 5** contains 404 patients who were treated at the Erasmus MC-Daniel den Hoed Cancer Center in Rotterdam. The CKVO 96-10 is the first randomized dose escalation trial reporting on the impact of dose escalation on QoL of patients with localized prostate cancer by using a validated QoL-questionnaire (SF-36 questionnaires). QoL-scores did not appear to be significantly decreased by escalating the dose of RT from 68 to 78 Gy. However, the decrease in QoL-scores, in general, was more pronounced in the high- than in the low-dose arm and more in the physical- than the mental-health domain. Late GI and GU toxicity showed a trend towards significant correlation with decrease in QoL-scores. Given the slight deterioration in different QoL-scales, albeit statistically non-significant, seen by escalating the dose of RT from 68 to 78 Gy, the possible risks of complications and deterioration of QoL must, therefore, be carefully weighted against the risk of relapse during the patient's expected life span. When the expected toxicity of high-dose RT in that particular patient is high, the expected life span is relatively short and the risk of local recurrence is predicted to be low, dose escalation should, in our opinion, be avoided (24).

The increased rate of GI toxicity and the slight deterioration of QoL-scores in patients received higher dose RT raise the question which subgroup of prostate cancer patients really need a higher dose of RT in order to control their disease appropriately?. A subgroup analysis was performed within the framework of this randmozed trial in order to identify subgroups of patients who might benefit from high-dose RT and those who might not benefit (**chapter 6**). It was shown that intermediate-risk patients benefited most from high-dose RT. Because of the small number of low-risk patients treated in our trial, no indication was found to exclude this subgroup from dose-escalation, also because of the negative test of interaction found in the subgroup analysis. The results in high-risk patients were more complicated, because this group was very heterogeneous and contained patients who were treated with either RT alone or with combination of RT and hormonal therapy (HT). Furthermore, not all high-risk patients allocated to the high-dose arm received the intended high-dose RT; that is 11% of this group received a dose lower than 78 Gy. Regarding PSA-groupings, patients with PSA > 10 μg/L and those with

PSA between 8 and 18 μg/L benefited most from dose escalation. In patients with iPSA lower than these levels, high-dose RT is probably not indicated, but this should be confirmed in other randomized controlled trials (25).

In **chapter 7**, we performed a thorough literature review in order to investigate different controversial aspects of the management of high-risk prostate cancer, including the role of dose escalation with or without HT as well as the optimal time and duration of HT. In this review, we concluded that the role of dose escalation in patients with localized prostate cancer is undisputed. Although, there is not arguing about the need for a combined modality treatment (HT and RT) in this subgroup of patients, the exact role of high-dose RT in high-risk patients who receive HT as well is is not yet well-defined. There is a moderately strong evidence suggesting the necessity of long-term HT (of at least 2 years), beside high-dose RT (26).

FUTURE PERSPECTIVES

Because the significant improvement achieved in local control in different randomized dose-escalation trials was associated with increased late GI toxicity (10-14), radiation oncology community continues to search for strategies to reduce the rate of this radiation-induced complication. Modulating different aspects of the current treatment of localized prostate cancer were explored and subsequently implemented in our institute in order to achieve this purpose.

PROSTATE MOTION AND IMAGE-GUIDED RADIOTHERAPY

Integration of more conformal radiation techniques with smaller radiation fields into the clinical setting has necessitated a better understanding of the shape and the location of the prostate during treatment and between daily treatments. The fact that prostate motion could result in potential geographical misses and consequently can lead to worse clinical outcome, was demonstrated by de Crevoisier et al (32). They found that patients with a distended rectum at the time of treatment planning had > 30% worse PSA outcomes versus those that had a normal rectum filling. Radiation oncologists must thus design a treatment strategy that will account for prostate motion that occurs between daily treatments (interfraction motion) and that during the treatment itself (intrafraction motion); that is, a treatment strategy that limits geographical misses.

Implantation of 3 to 4 fiducial markers in and around the prostate is nowadays a daily routine for every prostate cancer patient treated by means of IMRT in our institute. This simple procedure subsequently enables us to digitize these markers before every fraction. Such stereographic targeting yields systematic and random prostate positioning errors of < 1mm. Differences of more than 2 mm with the pre-treatment position would be corrected immediately online with

< 1 min of added treatment time (33). Using such stereographic targeting technique made a reduction of the margin of the CTV to the PTV and towards the rectum feasible and safe without compromising the target coverage. This step would eventually achieve further reduction of the late GI toxicity at our institute.

With the ability to use on-board Computed Tomography (CT) imaging modalities; the prostate, bladder and rectum can be imaged before each treatment and the actual doses delivered to these organs can be computed using the "anatomy of the day". Using kilovoltage cone-beam CT, the treatment plans can be adapted based on the image feedback from daily scans, to allow the actual delivered doses to closely approximate the original planned doses. Drawbacks to the use of the cone-beam CT in IGRT are the inter-observer variation in delineation of the prostate on cone-beam CT, because of the low resolution and the fact that acquisition of cone-beam CT is time-consuming (34). This makes cone-beam CT less suitable for on-line positioning correction. However, with a new Linac control software, namely volumetric modulated arc therapy (VMAT, Elekta Synergy), in-treatment cone-beam CT-imaging become clinically feasible (35). Automatic soft tissue and non-rigid registration tools (36-38) have been developed. These tools could potentially eliminate the inter-observer variations.

Another possibility to reduce the radiation dose to the structures surrounding the prostate and seminal vesicles is by reducing the margin of the CTV to the PTV. Cyberknife (Accuray Incorporated, Sunnyvale, CA, USA) is an excellent device for administering hypofractionated schedules. This noval 4-dimensional IGRT system corrects for both patient and tumor motions during treatment. Another advantage of this advanced RT system is the ability to deliver a high biological dose to the tumor and a minimal dose to the surrounding normal tissue because of the rapid fall-off outside the target volume. In order to validate this approach, Aluwini et al. (39) from our institute performed a pilot study on 10 early-stage low-risk prostate cancer patients who were not suitable for the standard treatment with HDR brachytherapy. The prescribed dose was 38 Gy in four daily fractions of 9.5 Gy. They concluded that such regimen was well tolerated, is feasible with excellent dose coverage of the prostate. Data collection is ongoing for further assessment of tumor control, toxicity, and QoL.

Despite the tremendous gains achieved with IGRT, a strong quality control is still required for safety and proper prospective evaluation of the clinical benefit of IGRT. Other venues for investigation include the potential role of protons, of MRI to reduce the uncertainties caused by delineation of the prostate and seminal vesicles and the necessity of including the whole seminal vesicle in the CTV, and the feasibility of dose recalculation and dose-guide adaptive radiation therapy.

GENERAL CONCLUSIONS AND RECOMMENDATIONS FROM THE CKVO 96-10 STUDY

- The benefit of dose escalation of RT for localized prostate cancer in terms of freedom from failure is undisputed.
- Patients with intermediate-risk prostate cancer and those with iPSA between 8 and 18 μg/L seem to benefit most from high-dose RT. However, from the current knowledge, neither low-risk nor high-risk patients could be safely excluded from high-dose RT because of the negative test of heterogeneity. Randomized trials are warranted to answer this important issue.
- The associated increased late GI toxicity would be reduced by the recent implementation of image-guide intensity-modulated radiotherapy at our institute.
- Despite the increased late GI toxicity seen in patients treated in the high-dose arm, dose escalation did not appear to decrease QoL-scores significantly in these patients.
- Predictive models need to be developed in order to identify patients at high risk of toxicity from high-dose RT. The possible risks of complications and deterioration of QoL-scores must be carefully weighted against the benefit from dose escalation in terms of local control.
- The optimal combination of HT and RT in high-risk prostate cancer patients are not yet well-defined.
- More attention should be paid to the optimization of treatment planning, with regard to the dose of RT to the bladder neck and avoidance of hotspots in the bladder, in order to reduce the rate of late GU complications.

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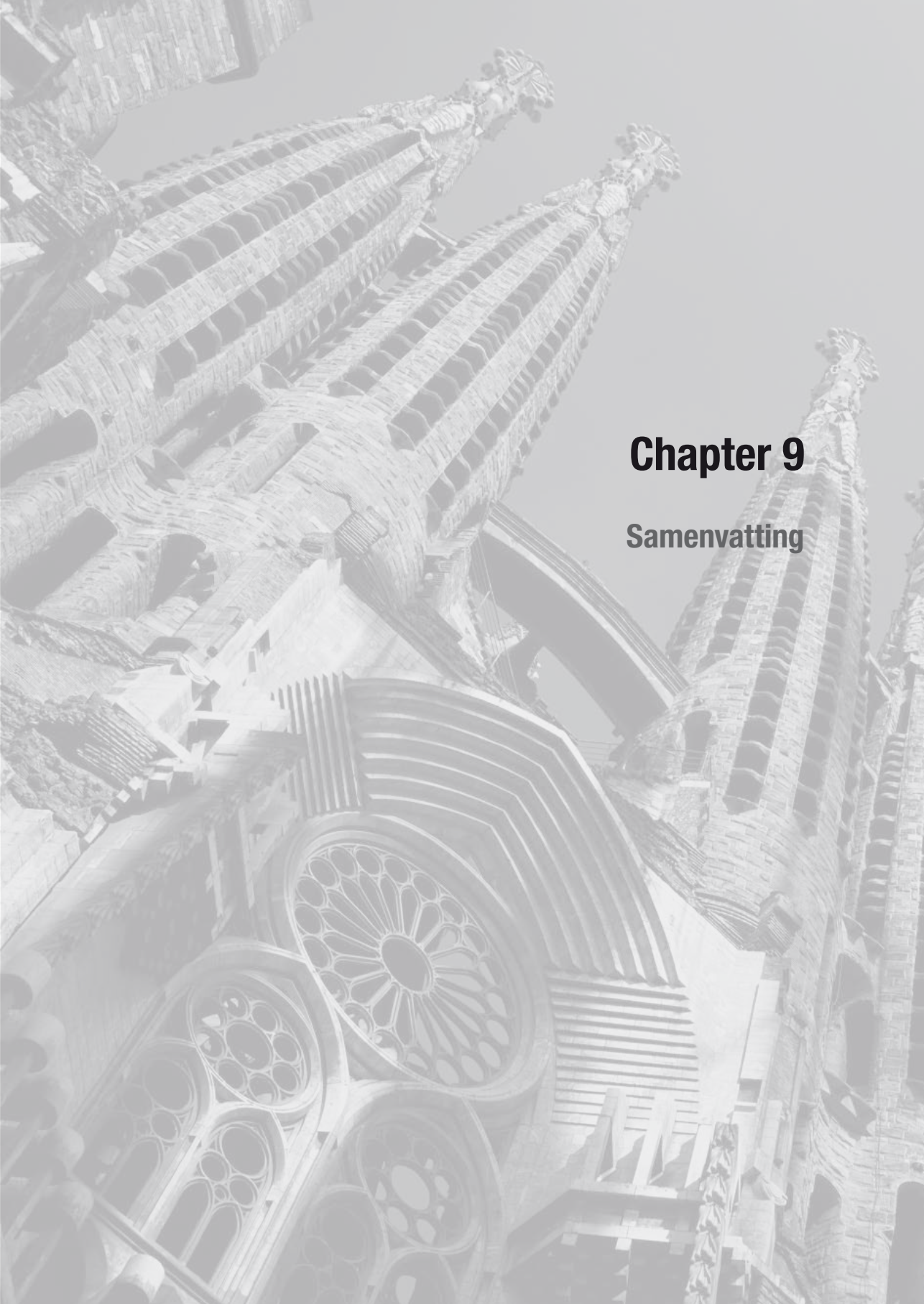

Chapter 9

Samenvatting

SAMENVATTING

Prostaatkanker is, na huidkanker, de meeste voorkomende soort kanker bij mannen in de Westerse wereld. Radicale prostatectomie en radiotherapie (RT) zijn de standaard behandelopties voor een gelokaliseerde prostaatkanker. In verschillende studies is een duidelijke dose-response effect aangetoond bij radiotherapie. Uit deze studies is gebleken dat lange termijn uitkomst van RT voor prostaatkanker sterk afhankelijk is van de adequate bestralingsdosis. Patiënten die in het verleden behandeld zijn met conventionele dosis RT (60-66 Gy), hebben 15 jaar na de RT een slechte ziektevrije overleving (15-30%) en overall survival (10-20%).

Verschillende retrospectieve studies hebben aangetoond dat hoge dosis RT tot een betere lokale controle zou kunnen leiden. Toch werd in het verleden, door de hoge kans op late bijwerkingen, nauwelijks een bestralingsdosis boven de 66 Gy (dosisescalatie) gegeven. Door het ontwikkelen en implementeren van nieuwe RT technieken zoals 3-dimensional conformal RT (3DCRT) en intensity-modulated RT (IMRT) werd het toedienen van hoge dosis RT (alsnog) mogelijk gemaakt.

In het NKI/AvL werd een haalbaarheidsonderzoek verricht, naar aanleiding van de belovende resultaten van de dosisescalatie studies uit de VS, waarbij verbetering werd gezien van de lokale controle door het toedienen van hoge dosis RT. Uit dit onderzoek is gebleken dat dosisescalatie middels 3DCRT goed mogelijk is met aanvaardbare bijwerkingen. Gezien de uitkomsten van deze studie, is in 1997 de Nederlandse gerandomiseerde studie (CKVO 96-10) geïnitieerd. In deze studie werden de uitkomst en de toxiciteit van de standaard arm (68 Gy) vergeleken met die van de experimentele arm (78 Gy). Voor deze studie werden patiënten uit 4 centra in Nederland geïncludeerd (Daniel den Hoed kliniek te Rotterdam, Nederlands Kanker Instituut-Antonie van Leeuwenhoek ziekenhuis te Amsterdam, Radiotherapie Instituut Friesland te Leeuwarden, Zeeuws Radiotherapie Instituut te Vlissingen).

Na de algemene introductie in **hoofdstuk 1**, worden de lokale controle en de toxiciteit van de Nederlandse fase III dosisescalatie studie beschreven in **hoofdstuk 2**. Zoals in andere gerandomiseerde studies, heeft ook de Nederlandse studie aangetoond dat freedom from failure (FFF) (zowel biochemische als klinische recidieven) significant verbeterde door het verhogen van de bestralingsdosis aan de prostaat. Na een mediaan follow-up van 70 maanden, was FFF significant beter in de 78-Gy arm t.o.v. de 68-Gy arm (respectievelijk 56% vs. 45%, p=0.03). De verbeterde lokale controle ging echter niet gepaard met verbetering van de overleving. Patiënten die een hogere dosis RT hebben gekregen (78 Gy), hadden hogere incidentie van late darmtoxiciteit. Er zijn meerdere redenen mogelijk waarom geen enkele dosisescalatie studie een verbetering van de overleving heeft aangetoond. Dit zijn namelijk het overlijden aan andere aandoeningen, de korte follow-up in deze studies en/of vanwege het beperkt aantal patiënten. Men zou daarom kunnen twijfelen over het nut van de dosisescalatie bij prostaatkanker. Echter, hetzelfde probleem had men ook gezien bij het analyseren van verschillende gerandomiseerde

studies over de winst van de postoperatieve RT na een mammasparende operatie. Geen van deze studies heeft een verbetering aan kunnen tonen in de overleving. Echter na het poolen van de data van 10 gerandomiseerde studies in een grote meta-analyse (7,300 patiënten), werd een significante verbetering gezien in de overleving van patiënten die postoperatieve RT hebben gekregen na de mammasparende operatie (15-jaar risico op mortaliteit van mammacarcinoom in de RT-groep was 30.5% t.o.v. 35.9% voor patiënten die geen RT hebben ontvangen, dit komt overeen met een mortaliteitsreductie van 5.4%, p=0·0002). Het valt daarom te verwachten dat dosisescalatie bij patiënten met prostaatkanker uiteindelijk zal leiden tot verbetering van de overleving na lange follow-up en/of na het verrichten van een meta-analyse van alle dosisescalatie studies die verricht zijn in de VS, GB en Nederland.

Naast de Nederlandse dosisescalatie studie, hebben ook andere gerandomiseerde studies aangetoond dat hoge dosis RT gepaard gaat met toename van late darmtoxiciteit. Men probeerde daarom RT technieken te ontwikkelen en vervolgens te implementeren zodat deze bijwerking gereduceerd zou kunnen worden. IMRT is een nieuwe behandeltechniek waarbij de RT-dosis gemoduleerd kan worden. Hierbij kan een hogere dosis aan de prostaat gegeven worden en tegelijk kan de dosis in de omringende organen zo laag mogelijk gehouden worden. In **hoofdstuk 3** wordt de toxiciteit van 41 prostaatkankerpatiënten, die behandeld werden met IMRT binnen onze studie, beschreven. Een belangrijke conclusie van deze studie is de significante reductie van acute darmtoxiciteit bij patiënten die behandeld zijn met IMRT vergeleken met de toxiciteit van patiënten die behandeld zijn met 3DCRT. De incidentie van late darmtoxiciteit was ook lager bij patiënten die behandeld zijn met IMRT, hoewel statistisch nog niet significant. Dit zou verklaard kunnen worden door het beperkt aantal patiënten en/of de korte follow-up. Radiobiologisch gezien zou, door het implementeren van IMRT, de significante reductie in acute toxiciteit zich moeten vertalen in een reductie van late toxiciteit. Uit eerdere publicaties van deze studie is gebleken dat acute toxiciteit de belangrijkste voorspeller is voor het optreden van late bijwerkingen (consequentiële bijwerkingen).

In **hoofdstuk 4**, werd de relatie tussen verschillende klinische en dosimetrische variabelen en het optreden van late urine obstructie uitvoerig bestudeerd. The cumulatieve incidentie van urine obstructie was 2.6% voor 68-Gy arm en 6.1% voor de 78-Gy arm (p=0.2%). Uit deze studie is verder gebleken dat patiënten met pre-existerende mictieklachten, patiënten met acute RT-gerelateerde mictieklachten, patiënten met recente TUR-prostaat en patiënten met hotspots in de blaas een hoger risico hebben op het optreden van urine obstructie binnen 2 jaar na de RT. Urine obstructie 2-7 jaar na de RT werd vaker gezien bij patiënten waar hotspots werden gezien in de blaashals. Gezien het belang van de reductie van deze ernstige complicatie, dient bij de planning meer aandacht besteed te worden aan het voorkomen van hotspots in de blaas(hals).

Het verhogen van de RT-dosis in onze studie zorgde niet alleen voor verbetering van de lokale controle, maar helaas ook voor hogere kans op late darmtoxiciteit, zoals werd beschreven in hoofdstuk 2. In **hoofdstuk 5** werd het effect van de dosisescalatie op kwaliteit van leven (QoL) van deze patiënten uitvoerig onderzocht. Alle patiënten die geïncludeerd en behandeld werden in het Erasmus MC- Daniel den Hoed kliniek (n=404) hebben deelgenomen aan een side-study, waarbij de QoL op verschillende tijdstippen werd onderzocht. Deze patiënten hebben de SF-36 QoL formulieren ingevuld vòòr starten van de RT (baseline) en 6, 12, 24, 36 maanden na het afronden van de behandeling. Uit deze side-study is gebleken dat er geen significante verslechtering van QoL is bij patiënten die 78 Gy hebben gehad ten opzichte van patiënten die 68 Gy hebben ontvangen. Echter, patiënten die behandeld werden in 78 Gy arm hadden over het algemeen wat lagere QoL-scores. Dit was met name het geval op het fysieke domein en minder op mentale domein van het SF-36. Late darm en blaas toxiciteit blijken enige invloed te hebben op de achteruitgang in de QoL-scores (trend maar niet significante correlatie). Gezien de lichte verslechtering van QoL-scores bij patiënten die hoge dosis RT hebben ontvangen, dient het nut van doesescalatie bij iedere prostaatkankerpatiënt voorzichtig afgewogen te worden tegen het risico van verhoogde darmtoxiciteit en de eventuele verslechtering van QoL-scores. Wanneer de kans op te verwachten bijwerkingen bij een patiënt hoog is, de levensverwachting relatief kort is en de kans op lokaal recidief laag is, dient doesescalatie vermeden te worden bij deze patiënt.

Gezien het feit dat dosisescalatie gepaard gaat met een verhoogd risico op late darmtoxiciteit en mogelijk ook enige verslechtering van QoL-scores, ontstaat een zeer belangrijke vraag die beantwoord dient te worden; welke subgroepen van prostaatkanker zullen baat hebben bij hoge dosis RT en welke niet? Teneinde een antwoord te kunnen geven op deze essentiële vraag, werd een subgroep analyse verricht binnen onze patiëntenpopulatie (**hoofdstuk 6**). Uit deze analyse is gebleken dat patiënten met intermediate-risk prostaatkanker de meeste baat zullen hebben bij hoge dosis RT. Echter, er werd geen indicatie gevonden uit deze subgroep analyse om patiënten met low-risk of high-risk prostaatkanker uit te sluiten van dosisescalatie. Het aantal low-risk patiënten die behandeld zijn in onze studie is te klein om daarover een degelijke conclusie te kunnen formuleren. In de high-risk groep, is de situatie nog ingewikkelder omdat 20% van high-risk patiënten naast de RT ook met hormonen zijn behandeld. Patiënten die hormonen en hoge dosis RT (78 Gy) hebben gekregen, hadden betere lokale controle ten opzichte van patiënten die naast de hormonale behandeling lage dosis RT (68 Gy) hadden gehad. Wat betreft het PSA gehalte, het is gebleken uit deze subgroep analyse dat patiënten met PSA > 10 μg/L en in het bijzonder patiënten met PSA tussen 8 en 18 μg/L, de meeste baat hadden bij dosisescalatie. Bij patiënten met een PSA gehalte < 8 μg/L is hoge dosis RT waarschijnlijk niet noodzakelijk. Dit moet echter in de toekomst bewezen worden in een groot gerandomiseerde studie.

In **hoofdstuk 7**, kunt u de resultaten van de review lezen aangaande verschillenden controversiële aspecten in de behandeling van high-risk prostaatkanker. We hebben de rol van dosisescalatie met en zonder hormonale behandeling in deze heterogenen groep patiënten, de optimale duur en timing van de hormonale behandeling geanalyseerd. Uit dit overzichtartikel kunnen wij concluderen dat de rol van dosisescalatie onomstreden is in patiënten met gelokaliseerde prostaatkanker. Ondanks het feit dat de combinatie van RT en hormonale therapie zeer noodzakelijk is in high-risk patiënten, dient de exacte rol van dosisescalatie in deze patiënten nog uitvoerig onderzocht te worden in een gerandomiseerde studie. Verder is uit deze studie gebleken dat er redelijk sterke aanwijzingen zijn dat hormonen voor een minimale periode van 2 jaar gegeven moeten worden aan patiënten met high-risk prostaatkanker.

NIEUWE ONTWIKKELINGEN

Uit verschillende gerandomiseerde studies is gebleken dat de lokale controle significant verbetert met dosisescalatie in vergelijking met lage dosis RT. Echter de verbeterde lokale controle (FFF) ging in deze studies gepaard met een hoge incidentie van late darmtoxiciteit. Men is daarom al jaren bezig met allerlei nieuwe ontwikkelingen om de darmtoxiciteit te kunnen verminderen en de uitstekende lokale controle te kunnen behouden.

Het is bekend dat de prostaat en de zaadblaasjes bewegen tijdens en tussen de bestralingen in. De beweeglijkheid wordt (ook) van buiten af beïnvloed door de vulling van de endeldarm. Wanneer men geen rekening houdt met deze beweeglijkheid, zou een deel van de prostaat gemist kunnen worden, terwijl een deel van de endeldarm onnodig bestraald wordt (dit fenomeen heet geographical misser waardoor de lokale controle slechter zou kunnen worden en endeldarmbelasting hoger zou kunnen uitvallen). Wanneer de beweeglijkheid van de prostaat en de zaadblaasjes tijdig opgespoord wordt, kan men het plan online zodanig aanpassen/corrigeren dat het bewegen van de prostaat geen negatieve invloed zal hebben op de uitkomst van de RT. Dit concept vormt de basis van het zogenaamd image-guided RT (IGRT).

In ons instituut wordt IGRT op verschillende fronten bedreven. Tegenwoordig worden bij alle prostaatkankerpatiënten 3-4 markers geplaatst in en om de prostaat. Deze markers kunnen vervolgens digitaal opgespoord worden. Gebruik makend van de zogenaamd “stereographic targeting”, kan men systematische en random fouten in de positie van de prostaat detecteren. Bij afwijkingen van > 2 mm zal men onmiddellijk een correctie toepassen zonder dat er sprake zal zijn van verlenging van de behandeltijd.

Het gebruik van de nieuwe imaging techniek (cone-beam CT; VMAT, Elekta Synergy) vòòr het toedienen van de bestraling geeft een uitstekend beeld van de “anatomy of the day”. Hierdoor kan men het plan dagelijks aanpassen aan de positie van de prostaat en de zaadblaasjes, maar ook aan de positie van kritieke organen, namelijk de endeldarm en de blaas.

Patiënten met “very low-risk” prostaatkanker kunnen tegenwoordig behandeld worden in ons instituut met de Cyberknife (Accuray Incorporated, Sunnyvale, CA, USA), een 4-dimensional IGRT systeem waarbij onmiddellijk een correctie voor beweging van tumor en organs at risk toegepast kan worden. In een pilot studie, zijn inmiddels 10 patiënten met “very low-risk” prostaatkanker behandeld in ons instituut met de Cyberknife (4 fracties van 9.5 Gy). Deze behandeling bleek haalbaar te zijn en werd goed getolereerd door patiënten. Men heeft ook een uitstekende coverage van het doelvolume kunnen bereiken met optimale sparing van de endeldarm, de blaas en de urethra.

Door het toepassen van verschillende image-guidance technieken (stereographic targeting, cone-beam CT en het gebruiken van de Cyberknife) wordt bestraling van prostaatkanker steeds veiliger. Hierdoor kunnen de marges van het CTV naar het PTV kleiner gemaakt worden waardoor de darm en de blaas minder belast worden. Vervolgens zullen de acute en late bijwerkingen van de RT verminderd worden.

Algemene conclusies and aanbevelingen van de CKVO 96-10 studie

- Het nut van dosisescalatie bij prostaatkankerpatiënten is onomstreden.
- Patiënten met intermediate-risk prostaatkanker en met een PSA gehalte van 8-18 μg/L hebben de meeste baat bij dosisescalatie. Echter, uit deze studie kan men noch low-risk noch high-risk patiënten hoge dosis RT veilig onthouden. Grote gerandomiseerde studies dienen deze vraag in de toekomst te beantwoorden.
- Door het implementeren van IGRT, zal de late darmtoxiciteit fors verminderd worden.
- Ondanks de toename van late darmklachten bij patiënten die behandeld zijn met hoge dosis RT, heeft dosisescalatie in onze studie niet geleid tot significante verlaging van de QoL-scores.
- Men dient “predictive models” voor toxiciteit te ontwikkelen om vervolgens patiënten te identificeren die hoog risico lopen op RT-gerelateerde bijwerkingen. Bij deze patiënten, dient het nut van dosisescalatie in termen van lokale controle voorzichtig te worden afgewogen tegen het risico op bijwerkingen en eventuele achteruitgang van QoL.
- De optimale combinatie van RT en hormonale behandeling in high-risk prostaatkanker is niet helemaal uitgekristalliseerd.
- Meer aandacht dient besteed te worden aan het optimaliseren van de RT-planning. Met het oog op het verminderen van incidentie van ernstige late urine obstructie dienen hotspots in de blaas(hals), wanneer mogelijk, voorkomen te worden.

CURRICULUM VITAE

Abrahim Al-Mamgani, born on 5th May 1963 in Iraq. In July 1987 I received my Bachelor in "Medicine and General Surgery". I've been graduated with Cum Laude at the University of Kufa-Iraq .

From august 1987-oktober 1994 I worked as Senior House Officer (SHO) in different departments of Baghdad Medical City. During this period I was in training for Internist with the subspeciality medical oncology and Haematology.

In 1994 I have emigrated to The Netherlands. In 1999 I've got my diploma for medicine at the Erasmus University in Rotterdam, again graduated with Cum Laude. Thereafter I worked in several functions as SHO at the departments of internal medicine, intensive care, medical oncology, and cardiology and for a while at the sector of community medicine before I started to work at the department of radiation-oncology of the Erasmus MC, Daniel den Hoed Cancer Center in Rotterdam.

As radiation oncologist, I am involved in the treatment of urological, head and neck, lung, and breast cancers.

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PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

Name PhD Student:	A. Al-Mamgani
Erasmus MC Department:	Radiation Oncology
PhD period:	01-02-2007 until 01-03-2010
Promotor:	Prof.dr. P. C. Levendag
Supervisors:	Dr. J. V. Lebesque and Dr. L. Incrocci

Presentations

- Update of the Dutch multicenter randomized phase III trial comparing 68 Gy with 78 Gy for localized prostate cancer.
  ECCO-14 in Barcelona, 2007

- Highlight session on the treatment of prostate cancer together with prof.dr. Thomas Wiegel from the University of Ulm Germany.
  ECCO-14 in Barcelona, 2007

- Results of the Dutch randomized dose-escalation trial of radiotherapy for prostate cancer.
  ASTRO-49 in Los Angeles, 2007

- The winner of the “Siemens Poster Award” at the ESTRO conference 2008 in Goteborg-Sweden to the subject of “Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects and baseline characteristics” (chapter 4), together with Wima Heemsbergen, Marnix Witte, Marcel van Herk, Floris Pos, and Joos Lebesque from the Dutch Cancer Society, The Antoni van Leeuwenhoek Hospital in Amsterdam.

- Overview of the results and toxicity from the CKVO 96-10
  Research meeting Erasmus MC-Daniel den Hoed Cancer Center 2009.