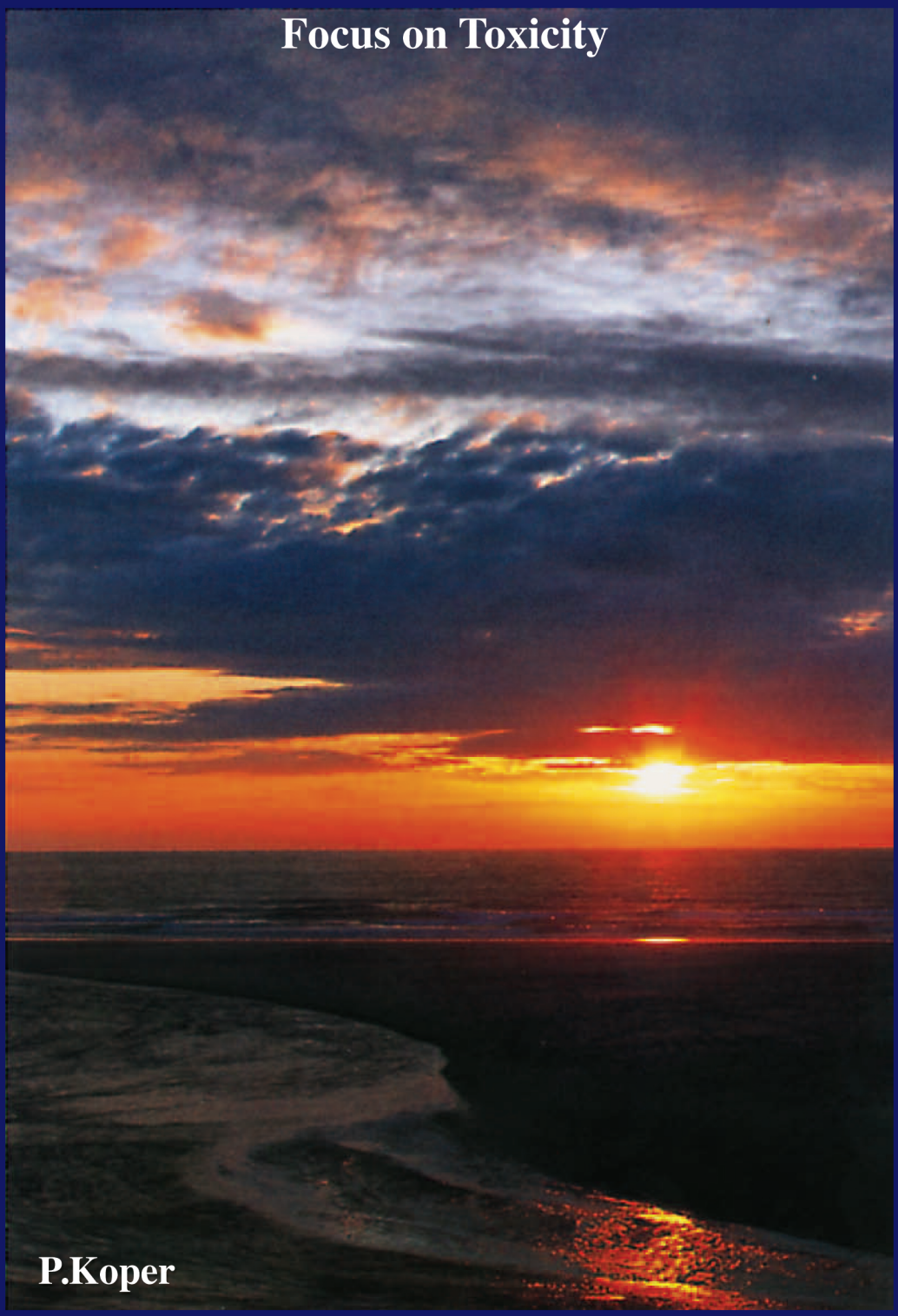
3D Conformal RadioTherapy for Prostate Carcinoma
Focus on Toxicity



P.Koper

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This thesis was financially supported by :
The Revolving Fund, Erasmus MC, Rotterdam
The Dutch Cancer Society ("Nederlandse Kanker Bestrijding")

This thesis was kindly supported by :
Astra Zeneca

Printed by :
Optima Grafische Communicatie, Rotterdam

3D Conformal RadioTherapy for Prostate Carcinoma
Focus on Toxicity

Drie dimensionale conformatie radiotherapie bij prostaat carcinoom
focus op toxiciteit

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de
Rector Magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 21 oktober 2004 om 13.30 uur

door

Petrus Clemens Maria Koper

geboren te Leiden

Promotiecommissie

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Introduction

Prostate carcinoma is the most common malignancy in men. Due to (un)controlled screening and patient awareness the incidence seems to be increasing with years. Many (treatment) options are available, that can be roughly divided in surgery ([laparoscopic] prostatectomy [including lymphadenectomy]), radiotherapy (brachytherapy [iodine^{125} seeds / palladium seeds / HDR Ir ^{192} afterloading] and / or external beam [+/- androgen ablation]) and for some patients even watchful waiting is advocated. The combination of prognostic factors like stage, Gleason score (differentiation grade), PSA and others e.g. the percentage of positive prostate biopsies, will give an indicate the chances for organ confined disease, seminal vesicle infiltration, lymph nodes metastases and ultimately for tumor control.

In less favorable patients, without evidence for regional and distant metastases, external beam radiotherapy will be the treatment of choice. Due to the position of the prostate and seminal vesicles being close to the rectum, anus, bladder, nerves and vasculature, this treatment is bound to affect these organs and as such the physiology of these organs. The maximum radiation dose to these organs at risk has to be limited, because of the increasing incidence of side effects with increasing dose. The exact dose volume relationships are however not clear. Sigmoidal dose and volume effect relationships are modeled and give us a (rough) estimate of the complication rates.
The retrospective analysis by Smit et al, is one of the first that studied the dose (volume) effect relationship for radiation induced proctitis. As a result of this analysis the treatment protocol in the Daniel den Hoed Cancer Center was adapted. Using so called conventional radiotherapy with open treatment fields, the total tumor dose was lowered from 70 Gy to 66 Gy to limit serious proctitis. With the introduction of the Scanditronics MM50 and 3D planning software (Cadplan) in the early 90's, it was hoped for that the introduction of 3D Conformal Radiotherapy (3DCRT) would reduce toxicity and possibly facilitate increased tumor dose to improve tumor control. It was decided to study the effects of 3DCRT on the incidence of complications in a randomized toxicity study. In literature the outcome of these techniques was reported only in cohort studies. Although is was felt that treating less (normal tissue) volume would ultimately result in less toxicity, definitive proof by a randomized study was not available. A randomized phase III study (DDHK 94/14) was designed to study the reduction of acute and late toxicity using 3DCRT compared to open fields with conventional treatment techniques. One should realize that both the dose (66 Gy) and the margins (15 mm) in this trial were quite conservative.
In an effort to reduce the GTV (gross target volume) to PTV (planning target volume) margins, a study using repeated CT scans was initiated to clarify some of the issues related to the choice of a margin. Megavolt Imaging (MVI) studies were implemented both locally and in collaboration with other centers in the Netherlands. A grant from the Revolving Fund of the Erasmus Medical Center – Daniel den Hoed Cancer Center, enabled us to accrue additional physics support to perform these studies. The results of this work have been included in this thesis as well in a previous thesis
(J. Stroom; "Safety margins for geometrical uncertainties in radiotherapy"; Erasmus Medical Center, Rotterdam, 2000).

In the last period of the DDHK 94/14 toxicity study, a collaboration with the radiotherapy department of The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, was initiated. In the Antoni van Leeuwenhoek Hospital 3DCRT was studied in a dose finding setting (phase II study), assuming that a volume reduction in the organs at risk would allow further dose escalation. A dose escalation up to a dose level of 78 Gy seemed feasible. A randomised phase III dose escalation study (CKVO 96/10 study) was designed, studying tumor control and toxicity. Linked to this dose escalation

study a grant (NKB 98-1830) was obtained from the Dutch Cancer Society to study the physical aspects.
In February 2002 the CKVO 96/10 study was closed, having accrued 669 patients. There is a limited number of randomized studies concerning this subject. For example, the MD Anderson study reported in 2002 a significant advantage in tumor control at the cost of more late toxicity. The coordinators of the international studies (CKVO, The Netherlands, MD Anderson Hospital, USA, and Medical Research Council, UK) concerning dose escalation in prostate cancer intend to combine data in a meta-analysis in the future.

Initially the CKVO study was open to the 2 centres in Amsterdam and Rotterdam. Two other radiotherapy centres participated in the study (Zeeuws Radiotherapeutisch Instituut, Vlissingen and Radiotherapeutisch Instituut Friesland, Leeuwarden). Quality control studies were performed to ensure a uniform contouring, treatment planning and data management. Having no access to the non-disclosed data of the dose escalation study (CKVO 96/10), the data of the DDHK 94/14 toxicity study were used to prepare future dose volume data analysis. Future analyses will concentrate on urological and intestinal toxicity and tumor control. Other important aspects of this treatment being (sexual) quality of life will be subject of other forthcoming studies.

This thesis describes the initial steps in our clinic regarding the implementation of 3DCRT for prostate cancer. Technical aspects to improve the irradiation technique will be dealt with in Chapters 1 to 4. The results of the toxicity study will be described in Chapters 5 to 8. In Chapters 9 and 10 the sexual quality of life aspects are discussed.
The first toxicity analysis of the CKVO dose escalation study is included in Chapter 11.
Hopefully these experiences, as a whole, will lead to a better understanding of radiotherapy related toxicity. With this knowledge tumor control will be improved with reduced morbidity.

Chapter 1

MULTIPLE TWO-DIMENSIONAL VERSUS THREE-DIMENSIONAL PTV DEFINITION IN TREATMENT PLANNING FOR CONFORMAL RADIOTHERAPY

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Radiotherapy and Oncology 47 (1998) 297–302

Abstract

Purpose:
To demonstrate the need for a fully three-dimensional (3D) computerized expansion of the gross tumour volume (GTV) or clinical target volume (CTV), as delineated by the radiation oncologist on CT slices, to obtain the proper planning target volume (PTV) for treatment planning according to the ICRU-50 recommendations.
Materials and methods:
For 10 prostate cancer patients two PTVs have been determined by expansion of the GTV with a 1.5 cm margin, i.e. a 3D PTV and a multiple 2D PTV. The former was obtained by automatically adding the margin while accounting in 3D for GTV contour differences in neighbouring slices. The latter was generated by automatically adding the 1.5 cm margin to the GTV in each CT slice separately; the resulting PTV is a computer simulation of the PTV that a radiation oncologist would obtain with (the still common) manual contouring in CT slices. For each patient the two PTVs were compared to assess the deviations of the multiple 2D PTV from the 3D PTV. For both PTVs conformal plans were designed using a three-field technique with fixed block margins. For each patient dose–volume histograms and tumour control probabilities (TCPs) of the (correct) 3D PTV were calculated, both for the plan designed for this PTV and for the treatment plan based on the (deviating) 2D PTV.
Results:
Depending on the shape of the GTV, multiple 2D PTV generation could locally result in a 1 cm underestimation of the GTV-to-PTV margin. The deviations occurred predominantly in the cranio-caudal direction at locations where the GTV contour shape varies significantly from slice to slice. This could lead to serious underdosage and to a TCP decrease of up to 15%.
Conclusions:
A full 3D GTV-to-PTV expansion should be applied in conformal radiotherapy to avoid underdosage.

Acknowledgements
The authors want to thank the Dutch Cancer Society (NKB-project 92-86) and the Revolving Fund of the University Hospital Rotterdam for sponsoring the research described in this paper. Furthermore, the support of John van Sörnsen de Koste during the various treatment planning sessions and the useful suggestions of Filicity Yorke during the writing of the paper are greatly appreciated

1. Introduction

To ensure a correct dose delivery to the tumour in radiotherapy treatment the ICRU has suggested a scheme for the determination of the planning target volume (PTV) that should be used for treatment planning [4]. Initially, the gross tumour volume (GTV), which is the visible and/or palpable volume of malignant growth, should be outlined in the diagnostic images. This volume is then extended to the clinical target volume (CTV) which contains the GTV plus areas of suspected subclinical microscopic disease. Finally, a margin is added to take into account geometrical uncertainties like patient and organ movement, resulting in the PTV.
Although the ICRU concepts for definition of a PTV are clear, their application can be problematic. The nature of the problem is demonstrated in Fig. 1. In Fig. 1a, a transversal CT slice through a prostate GTV is depicted. An isotropic 1.5 cm margin has been added in 2D around the GTV contour to get the PTV. The same has been done in all other slices, i.e. a multiple 2D PTV has been generated which reflects a normal manual outlining procedure. However, due to GTV contour differences in neighbouring slices this would yield margins that were too small in the cranial direction, as is indicated in a sagittal CT reconstruction through the prostate (Fig. 1b).

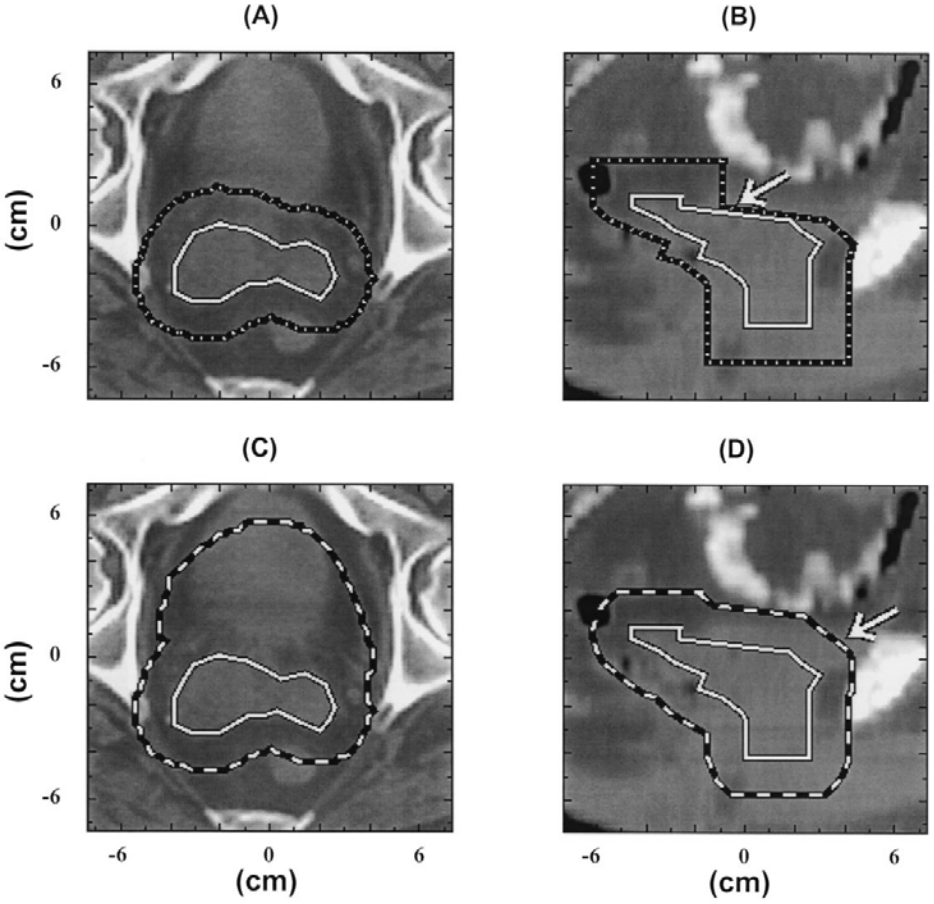


Fig. 1. Illustration of the problem discussed in this paper. Multiple 2D margins (dotted curves) around a prostate GTV (solid curves) in a transversal CT slice (A) may yield margins that are too narrow in the cranio-caudal directions as shown in a sagittal reconstruction (B). The 3D margins (dashed curves) may appear too large in a transversal CT slice (C) but are actually correct (D). The arrows in the sagittal reconstructions indicate the position of the transversal CT slice.

In Fig. 1c the correct 3D PTV has been generated by automatic expansion in all three dimensions. In the anterior part of the PTV the margin is clearly larger than 1.5 cm but the sagittal reconstruction (Fig. 1d) shows that this margin is correct. It is obviously all but impossible to accurately draw a 3D margin in 2D CT slices without the aid of software tools. Consequently, several groups have pointed out the importance of automatic 3D margin delineation [1, 2, 8]. In this paper we want to explore the geometrical and dosimetrical consequences of the still common but incorrect multiple 2D PTV generation by comparison with the correct 3D PTV calculation for a group of prostate cancer patients.

In the following `3D PTV' will stand for the full 3D PTV and `2D PTV' will refer to the multiple 2D PTV.

2. Materials and methods

Ten prostate cancer patients were selected for this study. Three of the patients had stage T1 tumours and the others had T2 tumours for which the vesiculae seminalis were part of the GTV. All patients were routinely CT-scanned in the supine treatment position with a 5 mm slice distance. The GTV was outlined in all relevant slices by a radiation oncologist. The position of the apex of the prostate was verified by the use of sagittal reconstructions through the prostate. The GTV-to-PTV margin for subclinical disease and geometrical uncertainties was taken to be 1.5 cm at the time of the study. For all patients 3D and 2D PTVs were automatically determined.

The algorithm for automatic margin generation has been described in a separate paper [8] and roughly works as follows. The GTV is represented in a 3D matrix grid with voxel values equal to the fraction of the voxel volume that is inside the GTV contours (i.e. in-between 0 and 1). It is expanded in three dimensions by centring an ellipsoid at every matrix element within the volume. The shape of the ellipsoid reflects the size of the margins in the three main directions. The PTV is subsequently obtained by extracting the 0.5 iso-value surface from the expanded volume. Depending on the size of the margin and the volume, the whole operation is generally performed within 1 min. The 3D PTV was generated by applying an isotropic margin to the GTV in all three dimensions, i.e. the ellipsoid in the expansion algorithm was actually a sphere with a radius of 1.5 cm. The 2D PTV was calculated by expanding each GTV voxel by a circle with a radius of 1.5 cm and orientation parallel to the CT slices. This procedure simulates the manual slice-by-slice contouring of the PTV (without taking the GTV shape in neighbouring slices into account). For the 2D PTV the GTV extension in cranial and caudal directions was obtained by copying the PTV contours at both ends of the GTV to the next three slices without GTV. The geometrical differences between the 3D PTV and the corresponding 2D PTV were assessed from sagittal and frontal CT reconstructions through the PTV and by comparison of the volumes.

For each patient our standard isocentric three-field treatment plan with conformal blocks was designed for both PTVs. It consisted of one anterior-posterior beam and two lateral-oblique beams. The lateral beams were partly delivered with a 60° motor wedge and were slightly tilted posteriorly in order to minimize rectum irradiation. Beam weights were such that each field contributed equally to the dose at the isocentre. For all plans the orientation-dependent block margins between the beam's-eye-view (BEV) PTV-projection and conformal blocks were 5 mm in the lateral direction of the AP fields, 9 mm in the ventro-dorsal direction of the lateral fields and 15 mm in the cranial-caudal direction of all fields at the time of the study [3]. All plans were made for the 25 MV photon beam of a Racetrack Microtron MM50 (Scanditronix) and complied with the ICRU recommendation for dose homogeneity in the PTV, i.e. the variation of the dose in the PTV is kept within +7 and -5% of the prescribed dose [4].

To analyze the consequences of the use of the 2D PTV in treatment planning, the dose distribution resulting from the beam shapes determined for that PTV was assumed to have been delivered to the (correct) 3D PTV. Differences in dose–volume histograms (DVHs) and tumour control probabilities (TCPs) with the treatment plan that was designed for the 3D PTV were calculated. The model that was used for TCP calculations is described by Munzenrider et al. [5]. The parameters for the TCP calculations were TCP_{66}=70% (based on data from our own institute), $_{pop}$=1 and $_{ind}$=8 [6]. Since the TCP values are mainly determined by the average dose, all plans were normalized so that the average dose in the original PTV became 66 Gy.

All treatment planning was performed on HP 9000/7xx work stations using the CadPlan planning system (Varian-Dosetek). The software for 3D extension of planning volumes delineated in CT slices

was developed to run with CadPlan and is now routinely used for most patients that are 3D planned. Part of the software has been integrated in the latest CadPlan version (2.7.7).

3. Results

In Fig. 2a,b sagittal and frontal reconstructions through the centre of the prostate in a plane near the isocentre are shown for all patients and the GTV, 2D PTV and 3D PTV are depicted. As expected, the 2D PTV generally follows the GTV at exactly 1.5 cm in lateral and ventro-dorsal directions. The seemingly larger margins that sometimes occur (especially near the seminal vesicles) are due to the data being presented as reconstructions in 2D planes; certain parts of the GTV responsible for a GTV-to-PTV extension as seen in the reconstruction may in themselves be invisible in that reconstruction. However, Fig. 2a,b clearly shows that for some patients the multiple 2D extension of the GTV results in extremely narrow margins between the GTV and the 2D PTV in the cranio-caudal direction (see for example patients 4, 7 and 10 in Fig. 2a). These deviations occur in areas with large GTV contour differences in neighbouring slices. The 3D PTV does not suffer at all from this problem due to the full 3D extension of the GTV. The spikes that are visible in the cranial part of some of the contours (see for example patient 7 in Fig. 2a) are due to a graphical artefact of the planning system. If the volume of interest divides into more than one branch (like the vesiculae), the planning system requires that the separate GTV contours that are delineated in one slice are connected with a line. These lines can appear as spikes in sagittal or frontal reconstructions but contain no volume and are subsequently ignored.

The average 3D PTV is 519±59 cm^3 (1 SD), whereas the average 2D PTV is 456±54 cm^3 (1 SD), i.e. there is a mean difference of 62±10 cm^3 (1 SD) (see Table 1). This implies that on average at least 12% of the 3D PTV is not included in the 2D PTV. Actually this percentage is slightly larger because the copying of the outer PTV slices of the 2D PTV somewhat overestimates the margin, and hence the volume, at the cranio-caudal edges

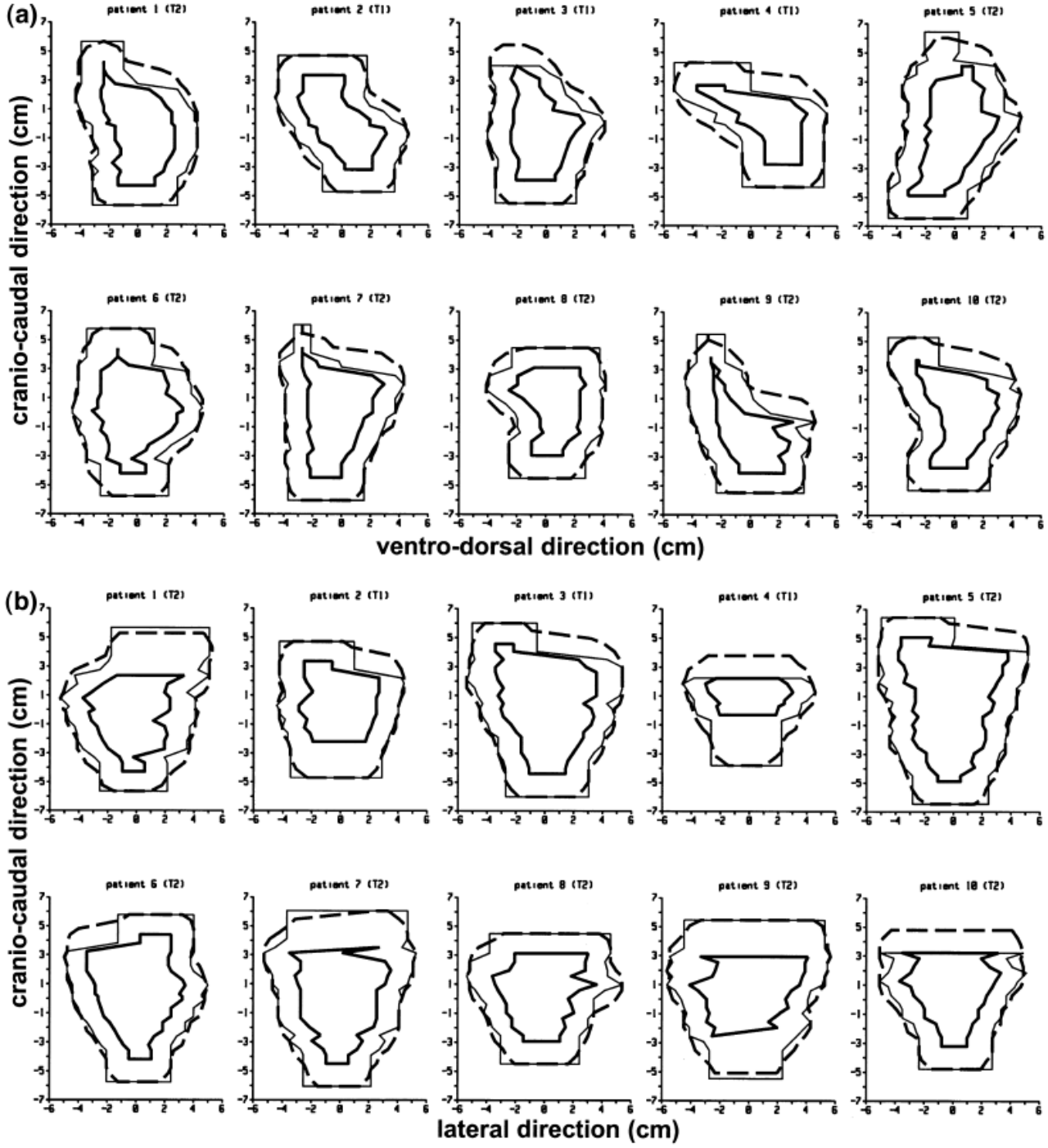
Table 1

Volume and TCP reduction for the 10 prostate patients described in this study

Patient	Stage	ΔV (cc)	ΔTCP (%)
1	T2	68	4
2	T1	55	11
3	T1	72	13
4	T1	68	15
5	T2	81	13
6	T2	57	8
7	T2	56	10
8	T2	58	4
9	T2	50	3
10	T2	67	7
Mean ± SD	–	62 ± 10	9 ± 4

ΔV is the volume difference between the 3D PTV and the 2D PTV. ΔTCP is defined as the TCP for the 3D PTV resulting from the plan designed for the 3D PTV minus the TCP for the 3D PTV resulting from the plan designed for the 2D PTV.

Fig. 2. Sagittal (A) and frontal (B) reconstructions through the centre of the prostate for 10 patients. The GTVs are indicated by the thick solid curves, the 2D PTVs are indicated by the thin solid curves and the 3D PTVs are indicated by the dashed curves. Large differences between 2D and 3D PTVs occur in areas with large GTV contour differences between neighbouring CT slices.



In Fig. 3 two BEV plots of the 3D PTV of patient 4 are shown together with the conformal blocks designed for irradiation of the 2D PTV. In large areas the blocks overlap or fit too tight around the 3D PTV, not leaving enough room to account for the beam penumbra. Applying these blocks will therefore result in underdosage of the 3D PTV. This is further illustrated in Fig. 4 by the average DVHs for the 3D PTV resulting from the treatment plans designed for the 2D and 3D PTVs, respectively. The average minimum dose in the 3D PTV decreases from about 62 Gy for the plan designed for the 3D PTV to about 51 Gy for the plan designed for the 2D PTV. The average TCP difference between the correct plan and the plan designed for irradiation of the 2D PTV was 9±4% (1 SD) (see Table 1).

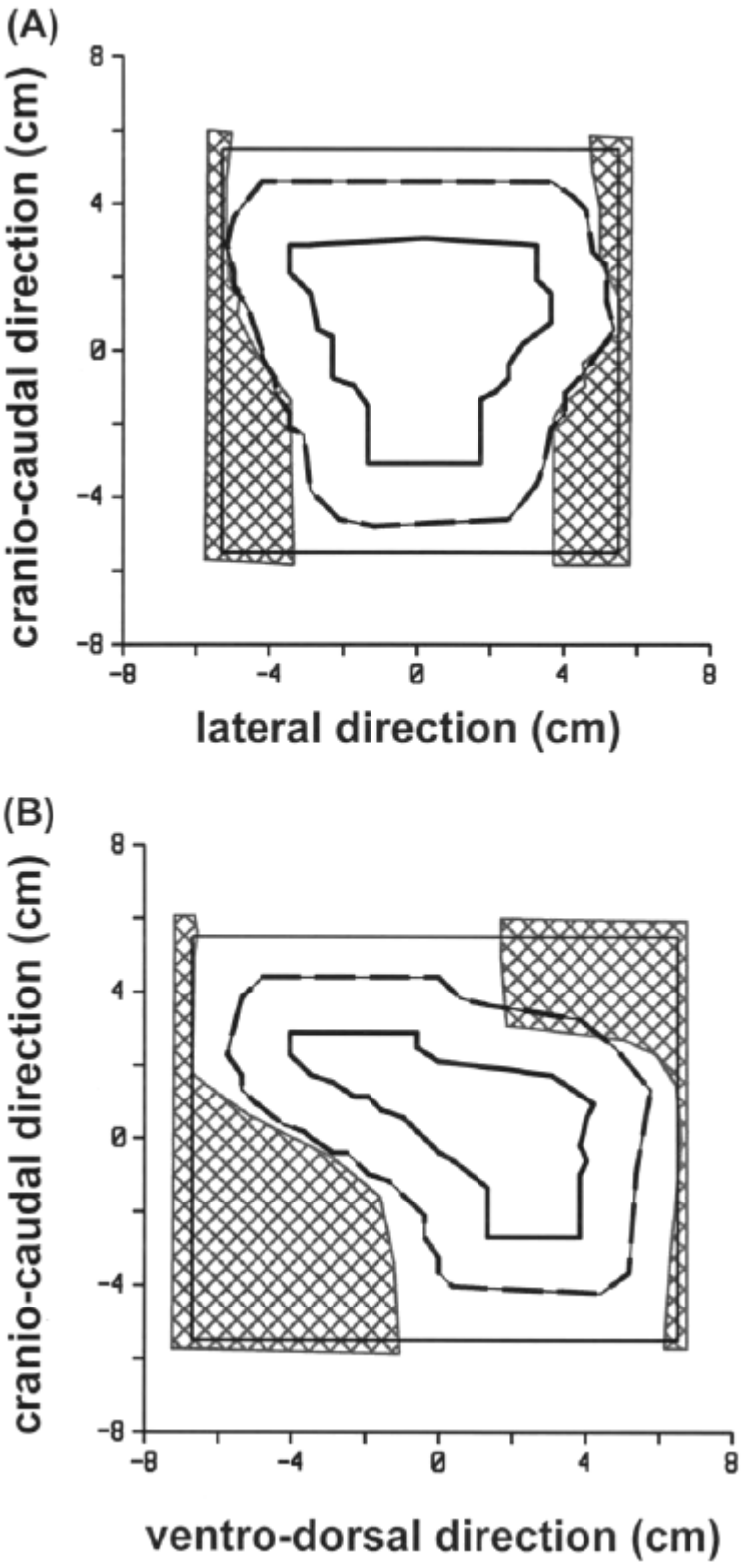


Fig. 3. AP (A) and lateral (B) beam's-eye-view (BEV) plots of the 3D PTV (dashed lines) with conformal blocks designed for the 2D PTV for patient 4. The solid lines are the BEV projection of the GTV. Over large areas the block margins are too narrow to account for the beam penumbra. In some areas the blocks even overlap the PTV.

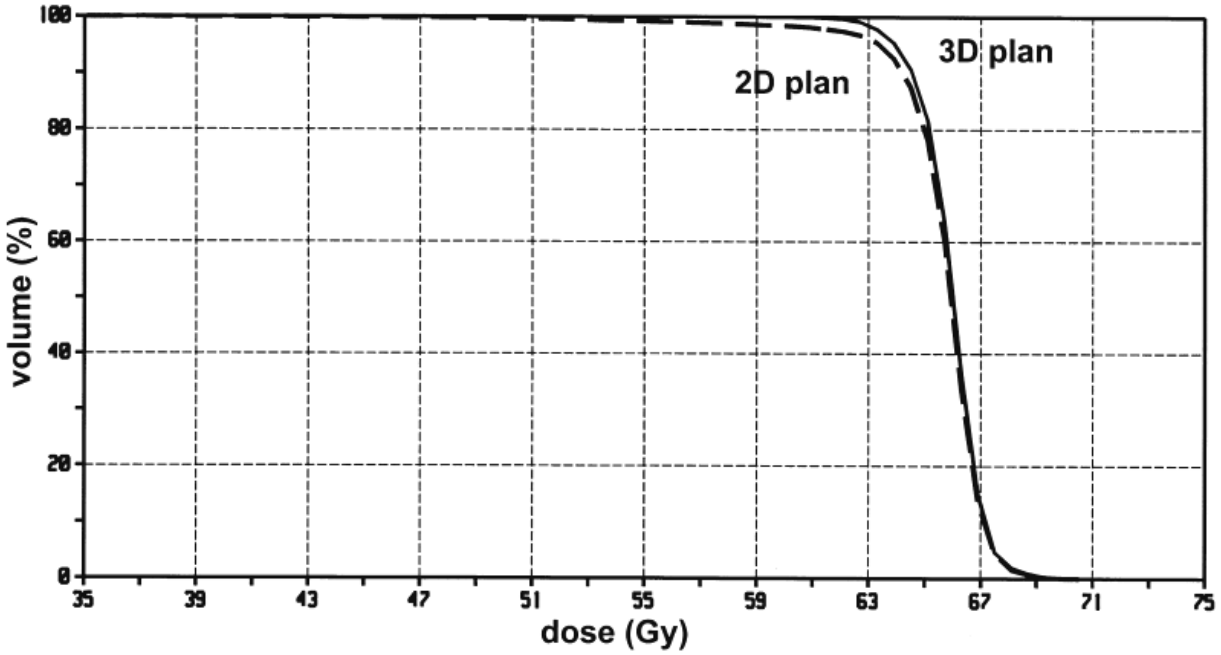


Fig. 4. Cumulative DVHs for the 3D PTV averaged over the 10 patients. The dashed curve represents the averaged DVH of the plans designed for the 2D PTV and the solid curve represents the averaged DVH of the plans designed for the 3D PTV. There is a systematic underdosage of the 3D PTV when planned with the beams designed for the 2D PTV.

4. Discussion

The magnitude of the observed TCP reduction when the PTV margins were assumed to be two-dimensional depended mainly on the shape of the GTV. There appeared to be a relation with the tumour stage as all patients with stage T1 tumours had TCP reductions of over 10%, whereas only one of seven patients with T2 tumours showed this phenomenon. One would expect large variations in GTV delineation especially with T2 tumours, where the seminal vesicles are part of the GTV. However, also in all T1 cases the most cranial GTV contours were significantly smaller than those in neighbouring slices.

Obviously, the TCP reductions depend on the dose distribution and hence on the treatment technique. The more conformal the 95% isodose volume that encloses the PTVs, the larger the errors will be when 2D PTVs are used instead of 3D PTVs. The difference between our three-field technique and, for instance, a four-field technique with similar block types would therefore be small. However, if rectangular fields were used instead of conformally-shaped fields, the multiple 2D procedure would not result in underdosage. The rectangular field size is normally determined by the outermost tumour extensions and these are the same for the 2D PTV and the 3D PTV. If the beams were shaped by multi-leaf collimators, the block margins around the PTV would on average be larger than for conformal blocks and hence the errors due to 2D PTV determination would be smaller. A possible 2D alternative for treatment planning based on a 3D PTV is beam's-eye-view (BEV) planning [7]. Using this technique the PTV and block margins around the BEV projection of the GTV are automatically calculated in 2D in the BEV plane. Consequently, the BEV technique does not result in a 3D PTV. Straightforward evaluation of the dose distribution in the PTV, as recommended by the ICRU [4], is

therefore not possible. Moreover, the projection of the GTV to one plane may yield over- or underestimation of the margin if the outermost extensions of the GTV are not at the level of the BEV plane, as is demonstrated in Fig. 5 for a hypothetical tumour. Due to the divergence of the treatment beams the magnitude of the required 3D margins is altered when projected to the BEV plane. This effect is not taken into account by the BEV method. In normal clinical situations (with the BEV plane through the GTV, a GTV `diameter' of about 10 cm and a focus-BEV plane distance of about 100 cm) the errors are relatively small (maximally 1 mm). A final objection to the BEV method is that it is quite impractical in the case of anisotropic margins and/or oblique fields, especially when the direction of the margins is not perpendicular to the field.

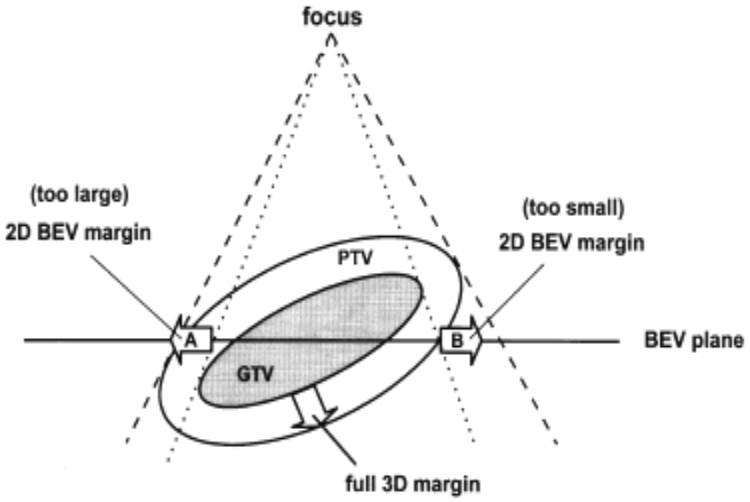


Fig. 5. Illustration of a drawback of 2D BEV planning (based on a BEV projection of the GTV) compared to planning based on a full 3D PTV. The GTV-to-PTV margins are indicated by the arrows and the dotted and dashed lines indicate the projection to the BEV plane of the GTV and 3D PTV, respectively. Due to the divergence of the beam two-dimensional extension of the GTV in the BEV plane may yield margins that are too large (A) or too small (B) compared to the (correct) margins that result from projections of the 3D PTV.

In conclusion, for 10 prostate cancer patients we have shown that multiple 2D calculation of PTV margins instead of full 3D calculations can lead to serious underdosage and TCP reductions of up to 15%. The same conclusion holds, of course, for other than prostate tumours. Delineated GTV or CTV contours normally vary from slice to slice and hence full 3D PTV margin calculations are required when conformal radiotherapy is used.

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Chapter 2

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FIELD MARGIN REDUCTION USING INTENSITY-MODULATED X-RAY BEAMS FORMED WITH A MULTILEAF COLLIMATOR

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Int. J. Radiation Oncology BioI. Phys.. Vol. 38. No. 5. pp. 1123-1129. 1997

Abstract

Purpose:
In axial, coplanar treatments with multiple fields, the superior and inferior ends of a planning target volume (PTV) are at risk to get underdosed due to the overlapping penumbras of all treatment fields. We have Investigated a technique using intensity modulated x-ray beams that allows the use of small margins for definition of the superior and inferior field borders while still reaching a minimum PTV - dose of 95 % of the isocenter dose.

Methods and Materials:
The applied intensity modulated beams, generated with a multileaf collimator, include narrow (1.1-1.6 cm) boost fields to increase the dose in the superior and inferior ends of the PTV. The benefits of this technique have been assessed using 3D treatment plans for 10 prostate cancer patients. Treatment planning was performed with the Cadplan 3D planning system (Varian-Dosetek). Dose calculations for the narrow boost fields have been compared with measurements. The application of the boost fields has been tested on the MM50 Racetrack Microtron (Scanditronix Medical AB), which allows fully computer-controlled setup of all involved treatment fields.

Results:
Compared to our standard technique, the superior-inferior field length can be reduced by 1.6 cm, generally yielding smaller volumes of rectum and bladder In the high dose region. For the narrow boost fields, calculated relative dose distributions agree within 2% or 0.2 cm with measured dose distributions. For accurate monitor unit calculations, the phantom scatter table used in the Cadplan system had to be modified using measured data for square fields smaller than 4 x 4 cm2. The extra time needed at the MMSO for the setup and delivery of the boost fields is usually about 1 min.

Conclusion:
The proposed use of intensity modulated beams yields improved conformal dose distributions for treatment of prostate cancer patients with a superior- inferior field size reduction of 1.6 cm. Treatments of other tumor sites can also benefit from the application of the boost fields.

Acknowledgements
This work was supported by a grant of the "Revolving Fund" of the University Hospital Rotterdam. Accepted for publication 28 March 1997
The authors want to thank P. Storchi and E. Woudstra for fruitful discussions on the dose calculation algorithms used in Cadplan.
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introduction

At present, in the Daniel den Hoed Cancer Center, prostate cancer patients are treated at the MM50 Racetrack Microtron with the 25 MV photon beam. An isocentric technique is used with one open anterior field and two lateral oblique fields, which are partly delivered with a 60° (motor) wedge inserted. The lateral oblique fields are slightly tilted posteriorly to minimize the irradiated rectal volume. All fields contribute equally to the dose in the isocenter. Beam shaping is performed with a multileaf collimator. The intention is to comply with the ICRU-50 recommendations for dose homogeneity (7) : the dose in the 3D PTV is aimed to be between -5 and +7% of the dose in the ICRU-point, Le., the isocenter. To avoid doses in the PTV of less than 95% resulting from beam penumbras, beam apertures are defined by adding field margins to the beam's-eye-view projections of the PTV. For all patients, field margins of 0.5 and 0.7 cm for, respectively, the lateral borders of the anterior field and the anterior and posterior borders of the lateral oblique fields are sufficient to meet the ICRU-50 recommendations. However, even a field margin of 1.5 cm for definition of the superior and inferior field borders of all fields still yields small under dosages (< 2%) in the superior and inferior ends of the PTV for nearly all patients. In these cases, 1.5 cm margins are used and the under dosages are accepted. Relatively large field margins for definition of the superior and inferior field borders for treatment of prostate cancer patients have also been reported by Leibel *et al.* (9).

Recently, Chen *et al.* (3) and Mohan *et al.* (14) have investigated the influence of phantom scatter on the design of optimized intensity modulated beams; phantom scatter is one of the main causes for the generally observed large 50-95% penumbra width of photon beams. They found that extra beam intensity near the beam boundaries could compensate for beam penumbra effects, yielding a more homogeneous irradiation of the PTV and providing a better protection for normal tissues. For multiple field axial treatments, extra beam intensity was especially needed near the superior and inferior field borders; this observation was attributed to the overlap of penumbras of all involved treatment fields at the superior and inferior ends of the PTV.

Several devices have been used to reduce the 50-95% penumbra width of x-ray beams. Biggs and Shipley (2) have described the use of lead filters in a 25 MV photon beam, which were positioned in the central part of the fields. In this way the dose in the center of the beam was attenuated relative to the dose in the beam edges, improving the 50-95% penumbra width with 0.4 to 0.7 cm, depending on the field size. For a 4 MV accelerator, improvements in the flatness and the penumbra of small fields (up to 10 x 10 cm2) have been reported using special tungsten alloy trimmers, attached to a tray below the accelerator head (15). The lead filters used by Biggs and Shipley have some disadvantages: for each patient and each treatment field, a separate filter has to be produced. Moreover, in between treatment fields the technicians have to enter the treatment room to change the filters. The use of the tungsten alloy trimmers is restricted to rectangular fields.

In this article we report on a method for treatment of prostate cancer patients applying intensity modulated (IM) x-ray beams with increased intensity near the superior and inferior field borders to reduce the distance between the 50 and 95% isodose surfaces. The intensity modulated beams, produced with a multileaf collimator, include narrow, low weight boost fields superimposed on the superior and inferior ends of regular flat fields. The development of the IM technique was aimed to achieve a reduction in the superior-inferior field length. The technique should meet three constraints: (i) the minimum dose in the entire PTV should be 95% of the isocenter dose; (ii) compared to our standard technique, increases in the maximum rectal and bladder doses should be avoided as much as possible; and (iii) treatment planning and clinical application of the IM technique should be simple, safe, and not time consuming.

Using 3D treatment plans, the benefits of the technique are demonstrated for 10 prostate cancer patients. The accuracy of the dose calculation algorithm in our treatment planning system for the

narrow boost fields has been determined by comparison with measurements. For treatments at the MM50 Racetrack Microtron, the extra time needed for delivery of the boost fields has been assessed.

methods and materials

Intensity-modulated x-ray beams for treatment of prostate cancer patients: the applied technique
With respect to our standard three-field technique, described in the Introduction, only two changes are made for the IM technique: I) for all three involved fields the field margin for definition of the superior and inferior field borders is fixed at 0.7 cm instead of the usual 1.5 cm, and 2) narrow, low-weight boost fields are superimposed on the superior and inferior ends of each of the two lateral oblique fields such that the minimum dose in the superior and inferior ends of the PTV just exceeds the 95% level. For field margins smaller than 0.7 cm, a minimum PTV dose of 95% could generally only be achieved at the cost of an increase in the maximum doses delivered to the rectum and the bladder.For both lateral oblique beam orientations, the superior and inferior boost fields are generally delivered simultaneously by closing leaf pairs in the central part of the beam while keeping the position of the

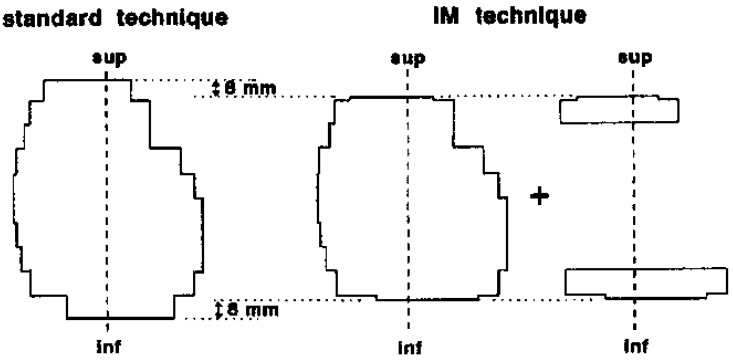

Fig. 1. Right lateral oblique fields for treatment of patient 4 in Table 1: (a) for the standard technique using field margins in superior–inferior direction of 1.5 cm; (b) for the IM technique, i.e., superior–inferior field margins of 0.7 cm and addition of a superior and an inferior boost field.

collimator blocks fixed (see Fig. 1 for an example).
To be able to compensate for variations in the patient contour in the superior-inferior direction, possibly yielding an increased maximum dose in the rectum or the bladder, the two fields can also be delivered sequentially (see also below). For each patient, all four boost fields have the same superior-inferior length *I,* obeying the equation $l = (L - n*w)/2,$ (Eq. 1)
with L the field length as defined by the collimator blocks, n the number of central leaf pairs that are closed, and w the leaf width (1.25 cm at isocenter for the MM50 Racetrack Microtron). L is fully determined by the superior inferior PTV length and the applied fixed field margin of 0.7 cm. As a consequence, for each patient, possible lengths l of the boost fields differ by multiples of w /2 cm, depending on the choice of n in the equation above. Based on a large number of treatment plans, it was concluded that l should preferably be in the range 1.1 to 1.6 cm. Often, a smaller field length yielded under dosages in the PTV in CT slices situated next to the most superior and inferior slices with PTV; larger lengths l could lead to unwanted increases in the maximum dose delivered to the rectum or the bladder. For each patient, only one lean fulfill both equation I and 1.1 cm $\leq l \leq$ 1.6 cm. For the patients in this study, each with a different PTV length, the length I of the applied boost fields -for the design of the final IM plan is presented in Table 1.

Table 1. The superior–inferior length of the applied boost fields as a function of the length of the PTV in superior–inferior direction

Patient	Length PTV (cm)	Length boost fields (cm)
1	7.5	1.3
2	8.0	1.6
3	8.5	1.2
4	9.0	1.5
5	9.5	1.1
6	10.0	1.3
7	10.5	1.6
8	11.0	1.2
9	11.5	1.5
10	12.0	1.1

The only real variables in treatment planning are the weights of the boost fields and the choice whether or not to deliver the superior and inferior boost fields simultaneously (see above). In practice, for each patient, the design of the IM technique starts with a treatment plan based on a simultaneous delivery of the superior and inferior boost fields for each of the two lateral oblique fields. The weight of the boost fields is such that for both the superior and the inferior ends of the PTV, the delivered dose is at least 95% of the isocenter dose. In case the obtained minimum PTV dose in the most superior or the most inferior part of the PTV is higher than 95% (e.g., due to variations in patient contour in superior-inferior direction), a modified plan, based on a sequential delivery of the superior and inferior boost fields for one of the two lateral oblique fields with slightly different weights, is considered.
At the MM50 Racetrack Microtron overtravel of the collimator blocks across the central axis is not possible. Therefore, a more flexible field length definition of the boost fields by using both collimator blocks for generation of each of the two boost fields, implying a sequential delivery of these fields, is impossible. The leaves of the multileaf collimator of the MM50 have a maximum overtravel of 14 cm, allowing more flexibility in the choice of I by rotating the collimator 90° prior to the delivery of the boost fields. These fields should then be delivered separately using the leaves for the definition of I and the blocks for definition of the width of the boost field. Because of the good results obtained with the relatively simple technique described above, we did not study this more complex and time-consuming technique with collimator rotation.

Evaluation of the IM technique based on 3D treatment planning
To assess the effectiveness of the proposed use of intensity modulated x-ray beams, 3D treatment plans have been made for 10 prostate cancer patients with PTV lengths ranging from 7.5 to 12 cm using the Cadplan 3D planning system manufactured by Varian-Dosetek (1, 18, 19). For each patient three plans have been compared: (A) our standard technique with field margins in the superior-inferior direction of 1.5 cm; (B) the same technique but with field margins in the superior-inferior direction of only 0.7 cm; and (C) the IM technique described in the previous subsection, based on field margins of 0.7 cm and application of superior and inferior boost fields.
For all patients, CT slices with 0.5 cm spacing were available. To improve the spatial resolution for penumbra analyses in the superior-inferior direction, dose calculations were also performed for CT slices generated by interpolation at intermediate positions; within each slice a grid size of 0.5 cm was used for the dose calculations.
For treatment planning, the gross tumor volume (GTV) (7), i.e., prostate (for patients 1, 2, and 6) or prostate + vesiculae seminalis (other patients) as delineated on CT slices by the physician, was

expanded in 3D (21) with a margin of 1.5 cm to render the PTV. For the bladder and the rectum, the outer surfaces were contoured. The rectum was contoured from 2.5 cm inferior of the PTV to 2.5 cm superior of the PTV.
Treatment plans were designed and evaluated using 3D planning tools such as Beam's-Eye-View (BEV), dose distributions in coronal and sagittal planes, and dose-volume histograms of the PTV, the rectum, and the bladder. Dose profiles along the superior-inferior axis through the isocenter have been used to quantify the superior and inferior reduction in distance between the 50 and 95% isodose surfaces, resulting from the applied boost fields in plan C. For each patient, the percentual changes between the IM plan and the standard plan in rectal and bladder volumes receiving a dose higher than 80% of the isocenter dose and in the maximum rectal and bladder doses have been quantified.

Accuracy of dose calculations
The high accuracy of the implemented dose calculation algorithms in Cadplan (version 2.62) for photon fields larger than 4 X 4 cm2 has been demonstrated (1, 18, 19). To assess the accuracy of these algorithms for the 25 MV narrow boost fields, calculated relative dose distributions for off-axis fields as small as 1.1 X 5.0 cm2 have been compared with distributions measured in a water phantom (RFA-300, manufactured by Scanditronix Medical AB), using a linear detector array consisting of 11 p-type diodes, and with distributions measured with film, irradiated horizontally in a polystyrene phantom at a depth of 3.5 cm (the depth of maximum dose for the 25 MV photon beam). In the latter case, measured optical densities were converted into doses by applying a sensitometric curve determined for the beam axis of a 10 X 10 cm2 field using the same setup. All measurements were performed with a source-to-surface distance of 100 cm.
Absolute dose calculations of Cadplan were checked by comparison with dose measurements performed on a depth of 3.5 cm in the center of the narrow boost fields, using a semiconductor detector (manufactured by Scanditronix Medical AB). The readings of the semiconductor were converted to dose by applying a conversion factor measured at the same depth on the beam axis of a 10 X 10 cm2 field. Required phantom scatter factors, needed to improve the accuracy of the monitor unit calculations of Cadplan for the small boost fields, were determined from measurements of the head-scatter factor (S<) and the total scatter factor (S<p) (23) for square fields of 4 X 4 down to 1 X 1 cm2. All scatter factors were determined relative to the 10 X 10 cm2 field. The head-scatter factors were measured with an RK chamber vertically positioned in a brass buildup cap with side walls of 2 g cm-2 (10, 25) and a front wall of 10 g cm-2. To ensure the 1 X 1 cm2 radiation field to fully encompass the used buildup cap, the source-to-surface distance was extended from 100 to 120 cm. Measurements of the total scatter factors were performed in water at a depth of 10 cm (20) using a semiconductor detector; a source-to-surface distance of 100 cm was used.

Implementation on the MM50 Racetrack Microtron
The dual-gantry MM50 Racetrack Microtron (5, 8, 11- 13, 24), in operation in our institution since March 1994, is a fully computer-controlled treatment unit, suited for advanced con formal radiotherapy techniques. Photon beams can be produced from 10 up to 50 MV in steps of 5 MV. The system is equipped with double focused multileaf collimators (MLC). Flat beam profiles are created by scanning of elementary beams according to fixed scanning patterns. Due to this beam scanning, flattening filters can be omitted or be very thin, yielding extremely flat beam profiles on all depths (8, 11). Intensity-modulated beams can be generated by computer-controlled superposition of MLC-defined fields, by scanning of elementary beams according to individualized scanning patterns and by dynamic multileaf collimation (4, 6, 16, 17, 22, 24).
The MM50 can be operated in a fully computer-controlled multi segment treatment mode (5,12). In this mode only the first segment (field) of a patient treatment is set up by the technicians. All parameters of the next segments, like the gantry and collimator angles, couch positions, field shapes,

beam energies, and monitor units, are set up and verified by the treatment computer. In between segments, the technicians do not enter the treatment room. Segments without dose ("dummy" segments) can be used to temporarily displace the treatment table to increase the distance between the patient and the treatment head before rotating the gantry. For treatment of prostate cancer patients we use two "dummy" segments. The extra time needed for delivery of the boost fields has been assessed using the fully computer-controlled multisegment treatment mode.

results and discussion

Evaluation of the IM technique based on 3D treatment planning
Dose profiles along the superior-inferior axis. For all patients, the dose profiles along the superior-inferior axis through the isocenter have been analyzed for plans A and C (see above) to assess the superior and inferior reduction in distance between the 50 and 95% isodose surfaces resulting from the application of the boost fields.

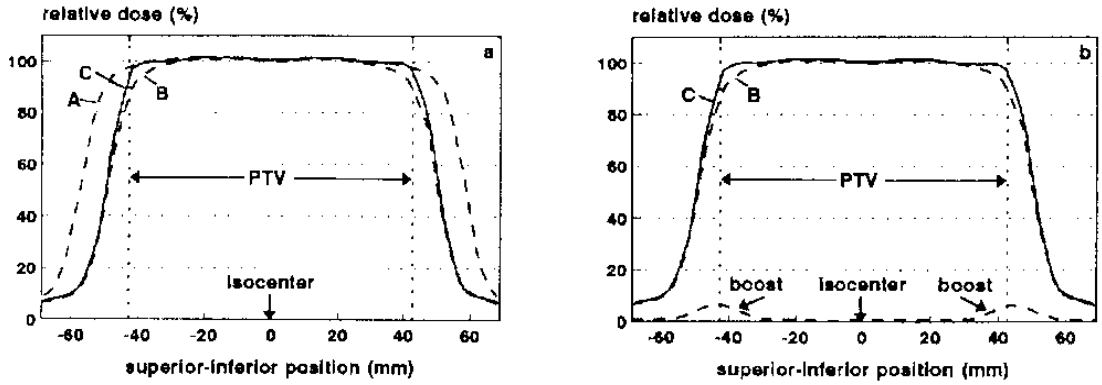

Fig. 2. (a) Dose profiles in superior–inferior direction through the isocenter for patient 3 in this study. Curve A: superior–inferior field margins of 1.5 cm; curve B: superior–inferior field margins of 0.7 cm; curve C: superior–inferior field margins of 0.7 cm and boost fields on the superior and inferior ends of the PTV. (b) Addition of the boost profiles to curve B yields curve C of the IM technique.

As an example, Fig. 2a shows the dose profiles for patient 3; Fig. 2b shows the dose distributions of the superior and inferior boost fields that are added to plan B, yielding plan C.
The average reduction in the superior and inferior 50-95% penumbra widths due to the application of boost fields is 0.66 ± 0.25 cm (1 SD) for all patients.

Dose distribution in the PTV.
For the 3D PTV, minimum doses and dose homogeneities, expressed as the standard deviation *(σ)* of the observed deviations from the average dose, are summarized in Table 2.

Table 2. Minimum PTV doses and dose homogeneities in the PTV for the three treatment plans described in the text

	A Field margin 1.5 cm		B Field margin 0.7 cm		C Field margin 0.7 cm + boost fields	
Patient	D_{min} (%)	σ (%)	D_{min} (%)	σ (%)	D_{min} (%)	σ (%)
1	95.6	1.3	88.5	2.4	95.6	1.1
2	93.6	1.3	88.5	2.1	95.0	1.2
3	94.5	1.9	89.5	2.7	95.0	1.8
4	92.6	1.8	86.5	2.5	95.0	1.5
5	94.5	1.3	87.6	2.0	95.6	1.2
6	93.6	1.4	89.5	2.2	95.6	1.2
7	93.5	1.6	86.7	2.1	95.6	1.1
8	94.5	1.4	89.6	1.9	95.6	1.2
9	94.5	1.3	88.6	1.9	95.6	1.2
10	93.6	1.3	89.5	1.7	95.6	1.3

Each dose distribution was normalized to 100% in the isocenter. The data show that for 9 of the 10 patients a field margin in superior-inferior direction as large as 1.5 cm (plan A) was not enough to fully comply with the ICRU-50 recommendations for dose homogeneity in the PTV (7), i.e., in some parts of the PTV (situated in the superior and inferior ends) the dose is still somewhat less than 95%. With field margins in superior inferior direction of 0.7 cm and no boost fields (plan B), the minimum dose in the PTV was on average 88.4% for the 10 patients; for patient number 4 the minimum PTV dose was only 86.5%. Using superior-inferior field margins of 0.7 cm in combination with boost fields (plan C, the IM technique) yielded a minimum PTV dose of 95% for all patients. This technique also yielded the best dose homogeneity, i.e, the smallest values for σ.

Dose distribution within rectum and bladder.

As demonstrated in Table 2, our standard technique (plan A) and the IM technique (plan C) allow, respectively, near and full compliance with the dose homogeneity recommendations mentioned in the ICRU-50 report. Due to the reduction of 1.6 cm in field length for the IM technique relative to the standard technique, reductions in rectal and bladder volumes in the high dose area could be expected for the *former* technique. In Table 3, observed percentual decreases in the rectal and bladder volumes that receive a dose higher than 80% of the isocenter dose are presented. For both the rectum and the bladder, the data show a large variation in the observed high dose volume reductions, depending strongly on the position and the shape of these critical organs relative to the most superior and inferior parts of the radiation fields.

Table 3. Differences between our standard technique and the IM technique with respect to rectal and bladder volumes receiving a dose of more than 80% (ΔV) and to the maximum dose delivered to these tissues (ΔD_{max})

	Rectum		Bladder	
Patient	ΔV (%)	ΔD_{max} (%)	ΔV (%)	ΔD_{max} (%)
1	4.5	−0.4	15.6	−0.4
2	11.3	−2.2	11.9	−3.0
3	2.5	0.1	14.7	0.3
4	4.1	−0.3	−0.2	−0.6
5	0.1	0.3	1.1	0.6
6	6.6	0.3	0.6	0.3
7	2.3	−1.0	9.0	0.2
8	3.1	0.3	0.5	0.3
9	7.8	0.1	0.4	0.3
10	8.1	−0.4	−0.9	0.5

Positive numbers point at reduced values for the IM technique.

As explained previously, attention has been paid to avoid increases in the maximum rectal and bladder doses due to the application of the boost fields. Table 3 shows that the differences in maximum rectal

and bladder doses between the IM technique and the standard technique are small (< 1 % of the isocenter dose for 9 of the 10 patients). The observed increases in maximum doses for the IM technique for patient 2 (2.2% in the rectum and 3.0% in the bladder) and the increase of 1 % in maximum rectal dose for patient 7 are due to the relatively large superior inferior length of the applied boost fields (1.6 cm) for these patients (see Table I). For both patients the increased maximum doses occurred in one or two CT slices adjacent to the most superior or the most inferior CT slice containing PTV (slice distance 0.25 cm). By choosing boost fields for these patients with a length of 1.0 cm instead of 1.6 cm, increased maximum rectal and bladder doses could be avoided. However, as a consequence the calculated minimum PTV dose went down to 94.5% for both patients.

Accuracy of dose calculations

Dose calculations of the Cadplan planning system for the narrow boost fields have been extensively verified by comparison with measurements. The field sizes that were studied ranged from 1.1 X 5.0 cm2 up to 1.6 X 10 cm2; the fields were positioned off-axis at distances of 3.2 to 6.1 cm from the isocenter. As an example, measured and calculated dose distributions for boost fields of 1.2 X 5.0 cm2 and 1.2 X 10 cm2, positioned at an off-axis distance of 4.4 cm, are depicted in Fig. 3. The measurements and calculations have been normalized to 100% on a depth of 3.5 cm. For all cases, measured and calculated relative dose distributions agreed within 2% or 0.2 cm.

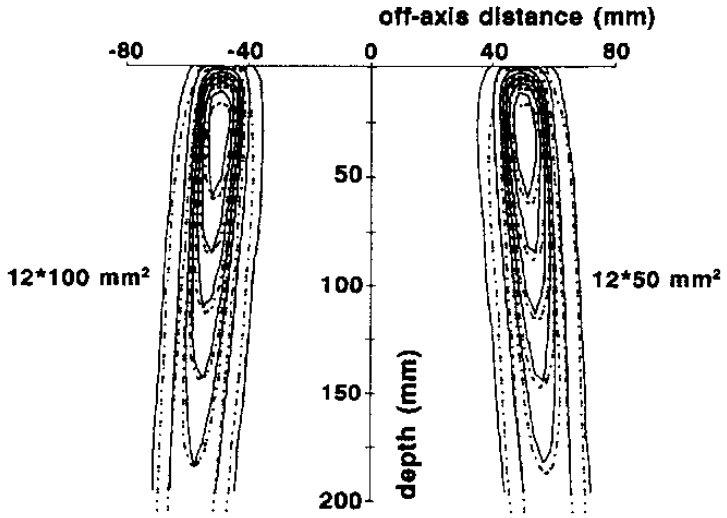

Fig. 3. Measured (dashed lines) and calculated (solid lines) isodose distributions for boost fields. Depicted isodose lines: 10, 30, 50, 60, 70, 80, and 90%.

Initially, the Cadplan planning system calculated too high absolute doses (up to 16%) in the normalization point of the boost fields. The largest deviations were observed for boost fields with the smallest lengths. To a very large extent, this discrepancy was caused by the table of phantom scatter factors (Sp) used in the Cadplan system. For fields larger than 4 X 4 cm2, this table is based on data presented by Storchi and van Gasteren (20). For smaller fields,the values in the table were obtained by a linear extrapolation. Based on measurements of head-scatter factors (Se) and total-scatter factors (Scp), we determined phantom scatter factors for square fields down to 1 X 1 cm2.

In Fig. 4, the results are depicted and compared with the original Cadplan table. For the larger fields, the Cad plan data agree very well with the measurements. However, serious deviations occur for fields smaller than 4 X 4 cm2. After modification of the Cadplan phantom scatter table according to our measurements, measured and calculated absolute doses for the boost fields generally agreed within 2%. Because the applied boost fields have a small weight the achieved accuracy of the dose calculations for boost fields is certainly adequate.

Implementation on the MM50 Racetrack Microtron

For all 10 patients, the increase in treatment time due to delivery of the boost fields has been assessed by simulation of the treatments using the fully computer-controlled multi segment treatment mode. For most patients, the observed extra time for delivery of the boost fields was about 1 minute. For patients 4, 5, and 7, the two boost fields in the left lateral oblique field were delivered sequentially (with different weights) to avoid an increase in the maximum dose delivered to the bladder and/or the rectum as much as possible (see also Methods and Materials). For these patients the extra time was about 1.5 minute. Most of the extra time needed for delivery of the boost fields is used by the MM50 computer for verification of the setup. A modification of the control software of the MM50, which is being developed by the manufacturer, will allow a significant reduction of this overhead time.

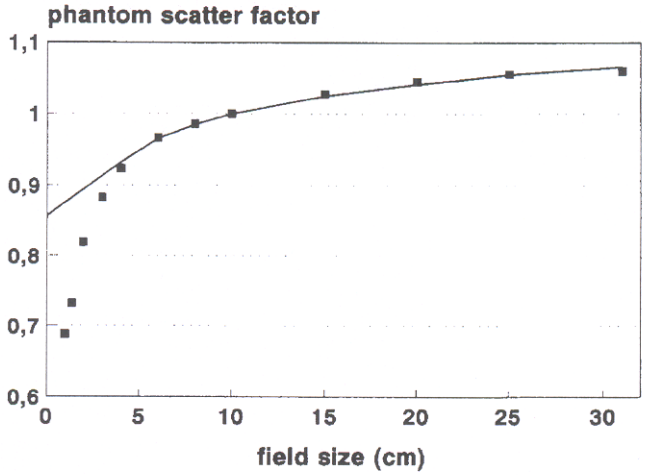

Fig. 4. Comparison of measured phantom scatter factors for the 25 MV x-ray beam of the MM50 (squares) with the values originally used in the Cadplan planning system (solid line).

summary and conclusions

In axial, coplanar treatments with multiple fields, often large field margins are needed for definition of the superior and inferior field borders to avoid under dosages in the superior and inferior ends of the PTV. We have investigated the use of intensity modulated beams, generated with a multileaf collimator, to allow reduction of these field margins while fulfilling the ICRU-50 recommendations for dose homogeneity. The intensity modulated beams consist of narrow, low-weight boost fields superimposed on the superior and inferior ends of treatment fields that enclose a BEV -projection of the PTV with well defined narrow field margins.

For 10 prostate cancer patients, computer-planning studies have shown that due to the proposed application of the intensity modulated fields the field length can be reduced by 1.6 cm, usually resulting in significant reductions in rectal and/or bladder volumes receiving a high dose. No differences were observed between patients planned to the prostate-only or to the prostate and seminal vesicles. The accuracy *of* the Cadplan planning system for calculation of relative dose distributions for the narrow boost fields is within 2% or 0.2 cm. After a small modification in the Cadplan system, calculated absolute doses *of* the boost fields at the depth *of* maximum dose generally agreed within 2% with measurements.

Using the fully computer-controlled multi segment treatment mode *of* the MM50 Racetrack Microtron, the application *of* intensity modulated beams would have led to an increase in treatment time of 1.5 minute maximum.

In this study, we have focused on prostate cancer patients treated with our three-field technique. However, we have observed that introduction of boost fields in the often applied four-field box and six-field techniques can also yield significant reductions in field length. Improved dose distributions have also been achieved for a cervix cancer patient. We expect that treatments of other tumor sites can also benefit from the proposed application *of* boost fields. In the meantime, we have started treating prostate cancer patients with the new technique described in this article.

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Chapter 3

INTERNAL ORGAN MOTION IN PROSTATE CANCER PATIENTS TREATED IN PRONE AND SUPINE TREATMENT POSITION

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Radiotherapy and Oncology 51 (1999) 237-248

Abstract

Background and Purpose:
To compare supine and prone treatment positions for prostate cancer patients with respect to internal prostate motion and the required treatment planning margins.
Materials and Methods:
Fifteen patients were treated in supine and fifteen in prone position. For each patient, a planning computed tomography (CT) scan was used for treatment planning. Three repeat CT scans were made in weeks 2, 4, and 6 of the radiotherapy treatment. Only for the planning CT scan, laxation was used to minimise the rectal content. For all patients, the clinical target volume (CTV) consisted of prostate and seminal vesicles. Variations in the position of the CTV relative to the bony anatomy in the four CT scans of each patient were assessed using 30 chamfer matching. The overall variations were separated into variations in the mean CTV position per patient (i.e. the systematic component) and the average 'day-to-day' variation (i.e. the random component). Required planning margins to account for the systematic and random variations in internal organ position and patient set-up were estimated retrospectively using coverage probability matrices.
Results:
The observed overall variation in the internal CTV position was larger for the patients treated in supine position. For the supine and prone treatment positions, the random components of the variation along the anterior-posterior axis (Le. towards the rectum) were 2.4 and 1.5 mm (1 standard deviation (1 SD), respectively; the random rotations around the left-right axis were 3.0 and 2.9 degrees (1 SD). The systematic components of these motions (1 SD) were larger: 2.6 and 3.3 mm, and 3.7 and 5.6 degrees, respectively. The set-up variations were similar for both treatment positions. Despite the smaller overall variations in CTV position for the patients in prone position, the required planning margin is equal for both groups (about 1 cm except for 0.5 cm in lateral direction) due to the larger impact of the systematic variations. However, significant time trends cause a systematic ventral-superior shift of the CTV in supine position only.
Conclusions:
For internal prostate movement, it is important to distinguish systematic. from random variations. Compared to patients in supine position, patients in prone position had smaller random but somewhat larger systematic variations in the most important coordinates of the internal CTV position. The estimated planning margins to account for the geometrical uncertainties were therefore similar for the two treatment positions.

Acknowledgements
The authors would like to thank the Revolving Fund of the University Hospital, Rotterdam for their financial support.

1. Introduction

In order to optimally gain from conformal radiotherapy, the planning target volume (PTV [12]) should be as small as possible. Since the PTV consists of the clinical target volume (CTV [12]) plus a margin for geometrical uncertainties in the treatment, these uncertainties, mainly caused by variations in the CTV-position relative to the treatment portals, should be minimised. For prostate cancer patients, deviations of the actual CTV-position from the planned reference position can be separated into errors in the set up of the patient relative to the isocentre (using markers on the patient's skin), and errors due to variations in the position of the CTV relative to the bony anatomy (i.e. internal organ motion). Reports in the literature indicate that internal organ motion [1,2,3,16,20,27,28] can be of the same magnitude as the set-up variations [5,9,11,21,26]. The difficulty in defining the CTV borders might be considered as another serious cause of geometrical uncertainty in the treatment of prostate cancer patients [6,8,19], but this paper is concerned with the actual CTV movements only.

Patient set-up variations are normally measured by matching the bony structures in portal images with corresponding structures in a digitally reconstructed radiograph or a simulator image. Since the CTV is not visible in portal images, more complicated procedures have to be followed to assess the internal organ motion. A possibility is to implant radio-opaque markers in the CTV so that portal images can still be used [1,2,28]. A disadvantage of this method is that it involves an invasive procedure. Furthermore, the CTV-position is measured indirectly (markers may move within the prostate) and incompletely (only a few markers in the whole prostate and no markers in the seminal vesicles). Recently, Kroonwijk et al. [13] have demonstrated that internal prostate motion due to large gas pockets in the rectum of patients can be detected with an electronic portal imaging device (EPID), but this method still needs quantitative validation. Internal organ motion can also be assessed with repeat CT scans [3,16,20,27]; CTVs are outlined in all scans and manual or automatic matching procedures are applied to determine the prostate positions relative to the bony structures. A drawback of this method is its cumbersomeness in clinical practice; in all reported studies only a few CT scans per patient were made and they were not acquired just prior to a treatment fraction. Therefore, the data could not be used for daily adjustments of the treatment according to the actual position of the CTV.

Recently, Zelefsky et al. reported that treatment in prone position reduces dose delivery to the rectum, compared to the supine treatment position [29]. However, their analyses were based on equal PTV margins for both set-up techniques, assuming equal patient set-up uncertainties and internal prostate motion. Most of the studies on internal prostate motion deal with patients treated in supine position [1,2,3,20,27,28]. Only Melian et al. [16] have described prostate movement in prone position. Quantitative comparison of the performed studies is often very difficult due to differences in applied protocols to control the rectum and/or bladder filling and due to differences in the applied measurement- and analysis techniques. Moreover, observed internal organ motion is sometimes reported in terms of rotations and translations and sometimes in terms of translations only.

In this paper we report on a systematic investigation based on repeat computed tomography (CT) scans, comparing the prone and the supine treatment position with respect to internal organ motion. Apart from the treatment position, all parameters for acquisition of the CT scans and for the analyses were kept constant. The variations in internal organ position can be systematic, i.e. the same for each measurement, as well as random, i.e. varying per measurement. Systematic deviations in the internal CTV position, which are due to a non-representative planning CT scan, have a larger impact on the required PTV-margin than random deviations. This is because a serious systematic deviation will cause a shift of the dose distribution with respect to the planned distribution, i.e. the tumour will be underdosed for all fractions of the treatment; random variations will only cause a smearing of the planned dose distribution [22]. Therefore, we have separated the systematic from the random component in the observed internal prostate movements in the CT scans. Time trends in internal prostate position, e.g. due to radiation induced proctitis and/or cystitis, were also investigated.

2. Materials and methods

2.1. *CT scans and patient treatment*

Thirty T3 prostate cancer patients participated in this study. Fifteen patients were treated in supine position and 15 in prone position. In supine position, which has been our standard treatment position until this study, only a knee-roll and home-made foot and arm supports were used,to position the patient on the treatment table. In prone position a homemade belly-board in combination with a prone pillow was used. The belly-board was expected to improve immobilisation (especially by minimising rotational variations), but a positive side effect might be a displacement of the (small) bowel in superior direction and hence a reduction in bowel exposure (not studied in this paper).
For all patients, a planning CT scan was used to design the 3D treatment plan. Following suggestions in the literature [17,25], the patients were asked to take mild laxative suppositories four hours prior to acquisition of the planning CT scan in order to minimise the rectal content. To study the internal CTV motion, three repeat CT scans in treatment position were made in weeks 2, 4 and 6 of the treatment. For all CT scans the CT pixel size was 2 mm and the slice distance was 5 mm (for most scans) or 3 mm. To avoid large variations in bladder volume, the patients were asked to empty the bladder and to subsequently drink half a litre of water 1 h prior to all CT scans and treatment sessions. In all CT scans, the outlines of .the CTV (prostate + seminal vesicles), rectum and bladder were manually contoured by the radiation oncologist (PK). The length of the delineated rectum was equal to the superior-inferior field length (i.e. the length of the CTV plus margins). The variability in the outlining of the CTV has been minimized by visual comparison and, if necessary, correction of the outlines in the four CT scans per patient, before the start of the registration procedure. In this way, all CTVs of one patient had similar shapes; possible errors that were made in the delineation were made in all scans of one patient and hence had limited effect on the calculated movements. This is not a realistic situation in clinical practice, but, as mentioned before, the subject of this paper is to calculate the prostate movements; the variability in the CTV delineation is a different subject [6,8,19].
To design the treatment plan, a recently developed algorithm [23,24] was used for a full 3D expansion of the outlined CTV in the planning CT scan with 1 cm, yielding the planning target volume (PTV). All patients were treated with an isocentric technique using an anterior field and two laterally oblique fields; beam intensity modulation was used to minimize the superior-inferior field length [7]. The patients were treated to a total isocentre dose of 66 Gy, delivered in 2-Gy fractions. For all patients, the minimum PTV dose was 95% of the prescribed isocentre dose; the maximum PTV-dose was always less than 107% [12].

2.2. *Measurement of internal CTV motion*

Differences in CTV position relative to the bony anatomy between two CT data sets of a patient (i.e: internal organ movements), were determined by subsequent, 3D chamfer matches of the two CTVs and of the two bony anatomies, followed by a subtraction of the translational and rotational displacements in the bone match from those in the CTV match. For the relatively small rotations that will occur, this method gives a good approximation of the 'true' internal CTV movement. Details of the application of chamfer matching for 3D registration of volumes in two different CT data sets have been given elsewhere [27]. Therefore, in this paper the explanation of the method is limited to the following summary that uses the match of two CTVs as an example. In one CT data set, the CTV is represented by a 3D set of contour points while the other data set (the reference) is used to calculate a 3D distance matrix. The voxel values in this matrix represent the distance from the voxel to the nearest CTV outline. Projection of the contour points of the first CTV in this distance matrix and averaging of the distance values under the points, yields the average distance of these points to the CTV contour of the

second (reference) scan. This difference indicates the goodness of the match and the similarity of the two matched volumes, and is called the cost function. The contour points are translated and rotated in three dimensions and a simplex search algorithm is applied to find the minimal cost function. The bone matches are similar except that automatically extracted bone edges instead of delineated CTV contours are used. The final result is a set of six parameters, three translations and three rotations, which describe the relative positions of the two CTVs.
In our analyses, the scaling parameters in the chamfer matches were kept constant because the CT pixel size was equal for all scans (2 mm). The three perpendicular rotation axes always intersected in the centre-of-mass (CM) of the delineated CTV, both for the bone and the CTV matches.

2.3. *Variations* in *CTV position*
In each CT scan, the position of the CTV relative to the bony anatomy is described by six parameters: the CM-coordinates along the left-right- (LR), the anterior-posterior(AP) and the superior-inferior (SI) patient axes, and the rotation angles around these axes. In Appendix A, a detailed description is given of the method to accurately determine for each CT scan of a patient the six coordinates, describing the CTV-position relative to the average CTV-position in the four available scans per patient. The four positions in all 15 patients were pooled to calculate standard deviations describing the overall variations (i.e. no separation in systematic and random variations) for the six coordinates (see Appendix B).
The same relative CTV-positions were also used to calculate the random and the systematic components of the observed position variations (see Fig. 1). For each patient the standard deviations in the six CTV coordinates during the three repeat scans were calculated. For each coordinate, the random variation (σ) for a patient group was then determined as the square root of the average of the variances for all patients. Per patient, the difference between prostate position in planning CT and the average position in the three follow-up CTs was calculated as well. The mean-of means (M) was then defined as the mean of the average movement for all patients; the systematic variation (∑) was determined as the standard deviation in these average movements. The internal organ movement for each set-up technique was thus characterized by M, ∑ and σ -values for the three translations and three rotations. A more analytical description of these parameters is given in Appendix B.

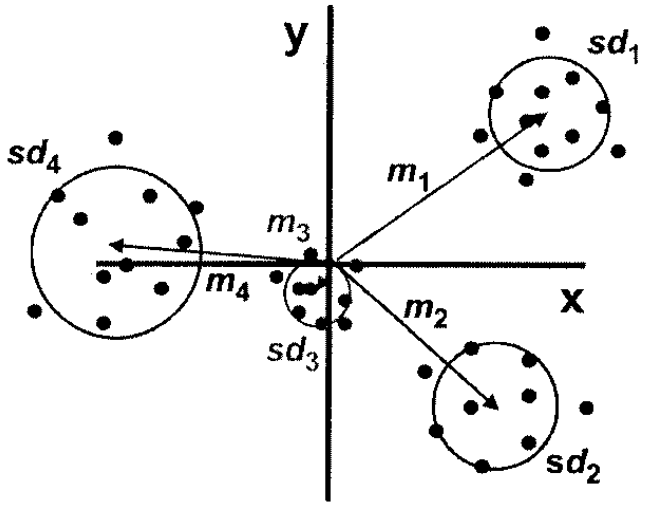

Fig. 1. Schematic 2D overview of the separation of the variation of CTV coordinates in a group of four (imaginary) patients into a systematic and random component. Indicated are observations (x,y) for several fractions. For each patient *i* the reference CTV position (i.e. the position in the planning CT) is situated in the origin. The average position in the repeat CT scans are indicated by m_i, and the standard deviation sd_i describes the variation around this average. A patient group is then characterised by the mean of the averages, M, the standard deviation of the averages, Σ and the square root of the average variance, σ.

The difference between supine and prone treatment position was established by testing the equality of the values for M, ∑ and σ and overall variations, using the Student's *t-test* for the equality of means and a standard deviation test described by Hoel et al. [10] for the equality of standard deviations. The same tests were used to verify whether M-values were significantly different from zero and whether ∑ and σ values were equal within one group.

2.4. *Time trends and correlations*

Without time trends, corrections, or specific differences in patient protocols and geometrical accuracy between CT and accelerator, theoretically *M* should be zero and ∑ should be equal to σ (see Appendix B). Therefore, special attention was given to the effect of the rectum laxation, which was given during the planning CT scan only, on the CTV-position. The intention was that minimization of the rectum volume would cause the prostate to be in its most dorsal position [17,25]. The prostate position during acquisition of the planning CT scan would then not be a random sample from the 'normal' distribution during treatment, but from a smaller distribution (around a more extreme position). The overall mean motion *M* would then deviate from zero, but the systematic variation ∑ might decrease (and become smaller than the random variation). This might justify significant reduction in PTV margins (see Section 2.6). On the other hand, the radiation treatment might cause a proctitis or cystitis which could reduce variations in bladder and rectum volume, and consequently in prostate position at the end of the treatment. In this case, the random variations might become smaller than the systematic variations. Time trends in CTV-positions were investigated by establishing whether the average positions of the 15 patients in weeks 2, 4 and 6 were significantly different from the planning situation.

To assess the influence of bladder and rectum volume changes on the internal prostate position, mutual correlations were determined. Combinations of bladder and rectum changes were also considered. In order to obtain the same dimension for rectum and bladder change as for the CTV translations and in order to obtain optimal correlations, rectum and bladder were represented by a diameter. The rectum volume in those slices that also contained CTV *(Vr)* was assumed to be cylindrical with length equal to the superior-inferior length (l) of the CTV; consequently the rectum diameter was taken to be $2.(Vr/(\pi\, l))^{1/2}$. The bladder volume *(Vb)* was approximated by a sphere with diameter $2.(3\, Vb/(4\,\pi))^{1/3}$. Correlations between bladder and rectum diameters in the planning CT scan and systematic prostate movements were calculated to investigate whether these diameters can be used to predict the average prostate position during treatment, as suggested by Lebesque et al. [14].

2.5. *Patient set-up accuracy*

Retrospective calculation of required treatment planning margins to account for geometrical uncertainties also implies knowledge of systematic and random patient setup errors. For all patients in this study the set-up accuracy was assessed using an EPID. Portal images were regularly acquired for each patient and observed deviations from the intended position, as indicated in a digitized simulator film, were measured. The deviations were used in an off-line setup correction protocol to minimize the systematic variations [4]. In this protocol the average set-up deviation in several fractions is compared with an action level that shrinks with the square root of the number of measured fractions. When the action level is exceeded, a set-up correction is applied in the following fractions and the protocol is restarted. For the patients in this study, the action level shrank from 8 to 4.6 mm in three fractions. After three successive measurements without corrections, images were acquired weekly; the action level remained 4.6 mm and was applied to the sliding average of the last three measurements. For the three main translations the final set-up accuracy in both groups of fifteen patients was again characterized by a mean-of means *M,* a systematic variation ∑ and a random variation σ (for definitions see Section 2.4 and Appendix B). From previous experience in our institute, rotations were estimated to be relatively small and are therefore not explicitly considered in the analyses.

2.6. *PTV margins*

PTV margins can be determined using coverage probability matrices, which have been introduced in a previous publication [22]. In short, for each patient separately, a 3D coverage probability matrix can be calculated by convolution of the CTV with the distribution of geometrical uncertainties due to internal organ motion and uncertainties in patient set-up. The distributions can either be sampled from actually measured CTV movements, or normal distributions characterized by standard deviations ∑ or σ can be

used. The advantage of the former method is that mutual correlations between the different movements are included as well [15]. The voxel values in a coverage probability matrix indicate the probability of the voxel being covered by the CTV (i.e. they vary from 0 to 1). For objects without sharp edges (which is usually the case for CTVs), a voxel value also indicates the probability that the CTV lies outside of that voxel. PTVs are chosen as iso-probability volumes in such a way that on average a large part of the CTV (e.g. >99%) is adequately covered. Previous research has indicated that adequate iso-probability values are 2.5% for systematic and 25% for random deviations [22]. In the absence of rotations and with the uncertainties described by normal distributions, this corresponds to a margin equal to about $2\sum$ tot + 0.7σ tot, with $\sum$ tot and σ tot the quadratically summed contributions of translational set-up uncertainty and internal organ motion. This means that the systematic variations are about three times more important than the random variations. In the case of significant rotations with non-spherical targets the required margins may become position dependent. The overall mean deviation *M* is a constant factor (i.e. not an uncertainty) and does not influence the size of the margins. However, in the case of *M* values significantly different from zero, the calculated PTV should be shifted as a whole accordingly.

3. Results

3.1. *Overall CTV motion and measurement accuracy*

Per treatment position group, 240 CTV movements have been determined (i.e. 16 per patient, see Appendix A). There was no significant difference in the chamfer match accuracy between the two groups. For both treatment positions, the average minimal cost function for the bone match was about 1.9 ± 0.3 (1 SD) mm and for the contour match 2.8 ±0.4 mm. This is adequate considering a pixel size of 2 mm and a slice distance of 3 or 5 mm. The minimal cost function also gives an indication of the similarity in shape of the two matched volumes. The cost function for the bone matches was lower than for the contour matches due to the random irregularities in the manual delineation of the prostate.

As described in Appendix A, four separate measurements of the internal prostate position in each CT scan of a patient were used to assess the internal CTV mobility for the two involved patient set-up techniques. For the CTV coordinates along the main axes and for the rotation angles around these axes, the observed average standard deviations in the four measurements, which also gives an indication of the accuracy of the registration procedure (see Appendix A), were about 0.5 mm and 0.9 degrees, respectively. The uncertainty in SI coordinate and lateral rotation angles were the largest because of the slice distance being larger than the CT pixel size.

The standard deviations describing the overall variations in internal CTV position, as calculated with Eq. (3) in Appendix B, are presented in Table 1.

Overall internal prostate motion was significantly smaller in prone than supine position for translations in the SI ($P = 0.04$) and AP ($P = 0.0002$) directions. The important rotation around the LR-axis was slightly larger (not significant) in prone position.

Table 1
Overall variations in the six coordinates describing the internal CTV position (1 SD) for the supine and prone set-up position in mm and degrees[a]

Position variation	Supine	Prone
LR translation	0.6 (−1.0–1.1)	0.5 (−0.9–1.2)
AP translation	**2.8** (−8.9–4.2)	**2.1** (−6.9–4.9)
SI translation	**2.8** (−6.8–7.2)	**1.7** (−3.6–2.6)
Rotation LR-axis	3.4 (−6.8–6.2)	3.9 (−10.1–6.1)
Rotation AP-axis	0.9 (−2.0–1.6)	0.9 (−1.5–2.7)
Rotation SI-axis	1.6 (−3.9–4.0)	1.3 (−3.0–2.8)

[a] Standard deviations that are significantly different between the two patient groups are shown in bold ($P < 0.05$). The range of the observed CTV coordinates is indicated between brackets.

3.2. *Correlations*

Correlations of CTV movements with rectum and bladder diameter changes are given in Table 2. Both the correlation of internal CTV displacements with bladder and rectum diameter changes separately, and correlations of CTV motion with the combined effect of changes in the rectum and the bladder are indicated. Mutual correlations between different CTV movements are shown as well.

In supine treatment position, the internal prostate position is only affected by rectum diameter changes; correlations with bladder variations are not significant. For patients treated in prone position, bladder and rectum diameter changes correlate with AP CTV translations equally well although the slope for rectum correlations is twice as steep as for bladder correlations; an increase in rectum diameter of e.g. 1 cm, has roughly the same effect on prostate position variation as a 0.5-cm decrease in bladder diameter. Since there is no correlation between rectum and bladder variations, a combination of the two diameter changes actually improves the correlations with AP translations in prone position. The optimal combination was equal to the rectum diameter change minus halve the bladder change. Looking at the slopes of the correlations, a 1-mm change in rectum diameter induces

Table 2
Significant correlations ($n = 45$, $P < 0.001$) of internal prostate position variations with rectum and bladder diameter changes in supine and prone treatment position[a]

Observation pair	Supine		Prone	
	Correlation coefficient	Slope	Correlation coefficient	Slope
AP translation/rectum diameter	−0.76	−0.36	0.51	0.22
SI translation/rectum diameter	−0.47	0.20	–	–
Rotation LR axis/rectum diameter	−0.61	−0.34	−0.65	0.5
AP translation/bladder diameter	–	–	−0.51	−0.11
AP translation/r&b diameter	−0.76	−0.36	0.67	0.19
SI translation/r&b diameter	0.52	0.20	–	–
Rotation LR-axis/r&b diameter	−0.65	−0.34	0.71	0.52
AP translation/rotation LR axis	–	–	0.56	0.57
AP translation/SI translation	−0.69	−0.76	0.55	0.64

[a] Indicated are the correlation coefficients and the slopes (in mm/mm or degrees/mm). The selected combination of rectum and bladder diameters (indicated by 'r&b diameter') was that combination that correlated best with the different CTV coordinates.

an AP prostate movement of about 0.2 (prone) and 0.4 (supine) mm, i.e. diameter changes and prostate displacements are not equal. For both set-up techniques, a correlation was found between AP and SI translations. This implies that the prostate tended to move in an oblique direction. In prone position there was also a strong correlation *(P* < 0.001) between AP translation and rotation around the LR-axis. In supine position this correlation was far less significant *(P* = 0.029, *r* = 0.325).

Rectum and bladder volumes, diameters, and diameter variations are presented in Table 3. Both the inter-patient variation and the intra-patient variation are for the rectum similar in both patient groups and are hence not the cause of the observed differences in prostate movement. Since prostate movement is not correlated to bladder diameter in supine position (Table 2),

Table 3
Average rectum and bladder diameters (M_{dia}) and diameter variations in mm for supine and prone patients[a]

Organ	Supine				Prone			
	M_{dia}	Σ_{dia}	σ_{dia}	V	M_{dia}	Σ_{dia}	σ_{dia}	V
Rectum	35	3	6	123	40	5	5	166
Bladder	74	17	9	252	71	11	8	207

[a] The variations have been split into inter-patient variation (Σ_{dia}) and intra-patient variations (σ_{dia}) similar to prostate movements (see Eq. (5) in Appendix B) except that the mean and standard deviation per patient were taken from the four absolute diameters instead of the three differences with the reference scan (see Eq. (4) in Appendix B). Mean volumes V (in cc) are also indicated.

the difference between the two set-up techniques in inter-patient bladder diameter variations does in itself not explain the smaller prostate movements in prone position (Table 1). There are also differences in average diameters. The reason for the average rectum diameter being larger in prone position might be explained by the differences in anatomy; in supine position the bladder and prostate weigh down on the rectum whereas in prone position the rectum may be able to sag more freely. The reason for the difference in average bladder volume between supine and prone position may be explained by the time trends as described in the next section. The average CTV volumes were about 90 cc in both patient groups. The average intra-patient variation was about 4 cc (1 SD) for both groups, i.e. the CTV delineations were sufficiently similar in the different scans of one patient, as was also indicated by the final cost functions of the chamfer matches.

3.3. *Time trends*

In Fig. 2, average organ motions and bladder and rectum variations relative to the planning CT scan are shown as a function of the CT scan number for the 15 supine and 15 prone patients. In supine position, there are obvious time trends in rectum diameter and prostate translations. The mean AP position in week 2 and the mean SI positions in weeks 2 and 4 are significantly different *(P* < 0.05) from their respective values during the planning CT scan. Due to the laxation for the planning CT scan, the rectum was relatively empty and the prostate was in a dorsal and inferior position. Since no laxation was applied in subsequent scans, the rectum diameter in weeks 2 and 4 was on average significantly larger *(P* < 0.05). Consequently, the prostate is moved in a superior and ventral direction. By week 6, the average rectum diameter and prostate position returned to the planning CT situation, which may have been caused by a proctitis resulting from the irradiation [17]. The significant *(P* < 0.05) change in the angle around the LR axis in week 6 cannot be correlated with diameter variations and is as yet not understood. The bladder diameter is never significantly different from its average value.

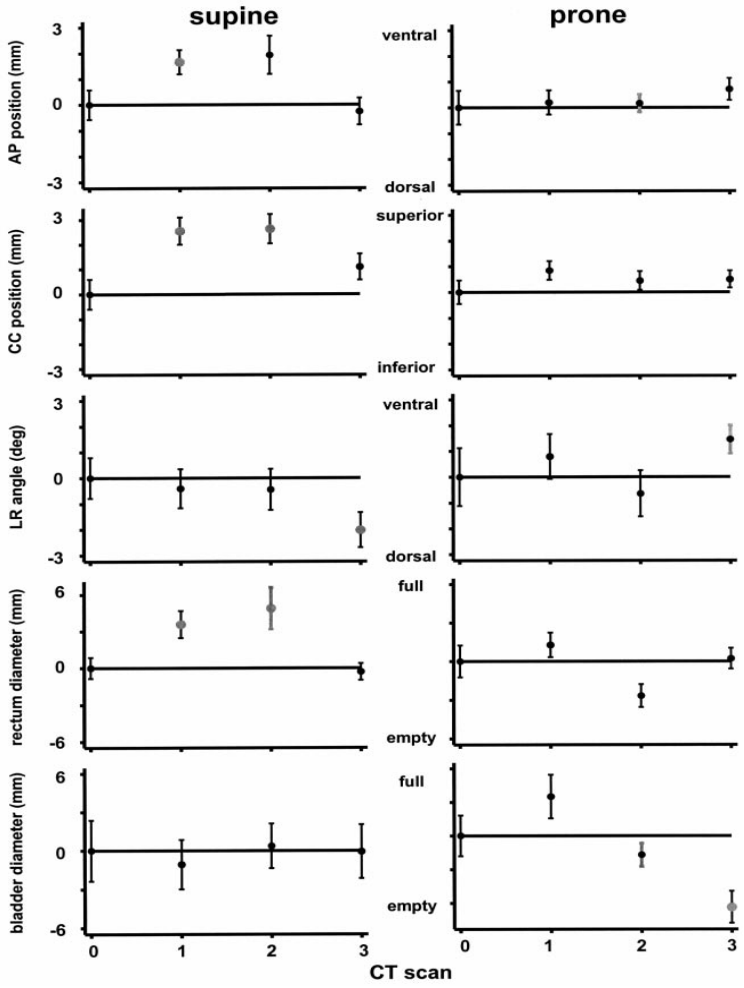

Fig. 2. Time trends for the average values (of 15 patients) of prostate position and of rectum and bladder diameters, in prone and supine treatment position. Indicated are the average values and standard errors (i.e. SD/$\sqrt{15}$) for the planning CT (scan 0) and the situation in the repeat CT scans (1, 2, and 3). For presentation purposes the averages in week 0 are taken to be zero. If the average values or the standard errors in the repeat CT scans are significantly different from the planning situation ($P < 0.05$), they are shown in grey bold type. For the rotation around the LR axis, *ventral* means that the rotation causes the *vesicles* to move in ventral direction. In supine position a significant change in average prostate position and rectum diameter with time is visible. In prone position there are no significant time trends in prostate location.

In prone position, there was no time trend in AP and SI prostate coordinates. The relatively stable prostate position, especially in the first

three scans, might be explained by similar but counteractive trends in bladder and rectum diameters in the first three scans (although there is no significant correlation between the two); full bladders, which would push the prostate in dorsal direction, seemed to go hand in hand with full rectums, which would push the prostate in ventral direction. The average angle around the LR axis displays a zigzag behaviour that corresponds to rectum diameter variations but they are not significantly different from the planning situation. The trends in rectum and bladder diameter clearly differ from those for supine patients which is possibly explained best by differences in dose delivery to rectum and bladder [29], which in turn might cause differences in the occurrence of proctitis and cystitis. An increased bladder exposure in prone position could also explain the gradual decrease of the bladder diameter in the course of treatment (in week 6 significantly less than in week 0, $P = 0.03$) and hence the smaller average volume

3.4. *Systematic and random CTV position variation*

The results of the separation of the overall CTV position variations in systematic and random variations are shown in Table 4. In contrast to the prone position, the time trends in supine position result in a mean-of-means M that is significantly different from zero for SI translations ($P = 0.02$). The 1.1-mm overall mean shift in ventral direction is not significant. On the other hand, in prone position the systematic variations are significantly larger than the corresponding random variations, i.e. the variation of the average position in the follow-up scan with respect to the planning situation is larger than the variation within the follow-up scans.

The prostate movement in prone position appears to decrease somewhat in the second half of the treatment, possibly due to inflammations of bladder and rectum. At the moment of the planning CT scan, the variations are larger which is indicated by the error bars in Fig. 2; in prone position, the standard error of the average values at the planning CT scan are generally larger than the standard errors at the follow-up scans. In supine position they are about equal, so the gain of the laxation might actually be that in supine position the variation at the planning CT scans has been reduced to average values as shown in Table 3.

Table 4
CTV coordinate variations split into overall means (M), systematic variations (Σ), and random variations (σ), in mm and degrees, for patients treated in supine and prone position[a]

	Supine			Prone		
	M	Σ	σ	M	Σ	σ
LR translation	**0.4**	0.5	0.6	0.1	0.4	0.5
AP translation	−1.1	2.5	**2.8**	0.4	**3.3**	**1.7**
SI translation	**2.1**	2.7	2.5	0.6	**2.2**	1.5
rotation around LR axis	1.0	3.6	3.3	0.5	**5.5**	3.4
rotation around AP axis	−0.1	0.8	0.9	−0.1	**1.1**	0.8
rotation around SI axis	0.7	1.7	1.5	0.0	0.8	1.4

[a] Overall mean values that are significantly different from zero, systematic variations that are significantly different from the corresponding random variations, and random variations that are significantly different between the two patient groups are shown in bold ($P < 0.05$).

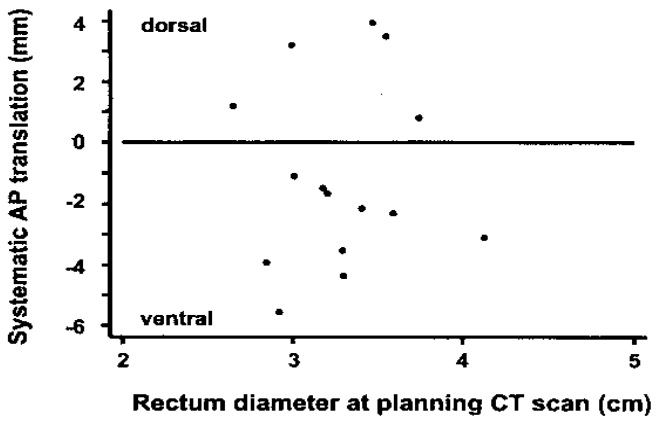

Fig. 3. Illustration of the effect of the laxative suppositories taken before the planning CT scans only. The average CTV movements in AP direction for the 15 patients treated in supine position are plotted as a function of rectum diameter at the time of the planning CT scan. One would expect only ventral movements because the suppositories are supposed to empty the rectum and cause the CTV to be in a maximum dorsal position. However, 5 of the 15 patients display on average a dorsal translation.

In both treatment positions there was no correlation between absolute rectum and bladder diameters during planning CT scan and subsequent systematic prostate position deviations, i.e. it was not possible to predict the average prostate position during

treatment based on the situation during the planing CT scan (see Fig. 3 for correlations with rectal diameter of the patients treated in supine position). It appeared that there was too much variation between the individual patients, even though on average the laxation resulted in a small rectum diameter (see Fig. 2) and in a mean position of all patients during the planning CT (i.e. M) in cranial-posterior direction from the average position (see Table 4). Fig. 3 also shows that five out of the 15 patients had a systematic translation in the repeat CT scans in the dorsal direction despite the use of laxative suppositories.

3.5. *Set-up variation*

In Table 5, the patient set-up variations for the three main translations are given for the supine and prone treatment positions. The systematic set-up variations are smaller than the systematic internal organ movements, which is partly due to the applied correction protocol. In supine and prone position on average 9 and 10 fractions per patient were analyzed, respectively. The number of set-up corrections was different between the groups: 6 for supine and 20 for prone treatments.

The (retrospectively calculated) uncorrected set-up accuracy was clearly worse in prone than in supine position (as reflected by the random variations), which is possibly due to the difference in experience with the two techniques; the supine set-up technique has been in use for many years whereas the prone technique with the belly-board was first used on the 15 patients described in this paper. However, the larger number of corrections for the patients in prone position effectively reduced the systematic deviations such that the final systematic variations were even smaller than in supine position (this is inherent in the protocol). There is no satisfying explanation for the mean-of-means in AP and SI direction in supine position being significantly different from zero.

Table 5
Set-up variation data (in mm) for patients treated in supine and prone position[a]

	Supine			Prone		
	M	Σ	σ	*M*	Σ	σ
LR translation	0.4	**1.3**	**1.6**	−0.4	**0.8**	**2.7**
AP translation	**−1.0**	**1.5**	2.2	−0.1	**0.8**	2.4
SI translation	**−1.0**	1.4	**1.5**	−0.6	**0.8**	**2.4**

[a] Just as for internal organ motion (Table 4), overall mean values that are significantly different from zero, systematic variations that are significantly different from the corresponding random variations, and random variations that are significantly different between the two patient groups are shown in bold ($P < 0.05$). The small systematic variations are due to the use of a set-up correction protocol.

3.6. *PTV margins*

Combination of observed variations for internal organ motion and patient set-up, and application of the $2\sum + 0.7\sigma$ -rule for the PTV margin [22], yields, for translational deviations only, the margins as shown in Table 6.

Table 6
CTV-to-PTV margins (in mm) required for internal organ motion and set-up deviations and ignoring the rotations, for patients treated in supine and prone position

Direction	Supine	Prone
Left–right	4.0	3.7
Anterior–posterior	8.3	8.8
Superior–inferior	8.2	6.6

In supine position the whole PTV should be shifted 2 mm in ventral and 1 mm in superior direction to correct for the mean-of mean internal organ motions and set-up deviations (the 1mm AP translation for organ motion was included although it was not significant). Due to the larger impact of the systematic variations, the differences between margins in supine and prone treatment position are small despite the observed differences in random variations. Furthermore, in both positions the margin in LR direction is significantly smaller than in the AP and SI directions, due to the negligible organ motion in

the LR direction. In order to take the significant rotations into account as well, coverage probability calculations have been applied to calculate the margins needed in supine and prone treatment position, for internal organ motions only. The actually measured prostate displacements were used in the calculations, for both the random (45 observations per group) and the systematic deviations (only 15 observations per group). A 2.5% iso-probability level was selected for the systematic variations, and 25% for the random deviations. An indication of the resulting margins is shown in Fig. 4.

Quantitative conclusions should be drawn from this figure with some caution since only 15 observations were used to the determine the main part of the margins (systematic variations are three times more significant than random variations); the 2.5% iso-probability volume is for 15 measurements actually equal to the enveloping .volume of all 15 CTV positions, which gives extreme positions a relatively great weight. Nevertheless, especially in the sagittal slice some differences between supine and prone margins become visible. The supine margin in the SI direction is larger than the prone margin and is also shifted in superior direction. The effect of the rotations is, as expected, larger for the prone margin; at the superior CTV end the margin can become twice as large as at the inferior end. In the transversal slice, the PTV is very close to the CTV in the lateral direction. This is due to the very small variation in lateral direction (see Table 4) and the discrete voxel size (2 mm in LR and AP, and 3 mm in SI direction).

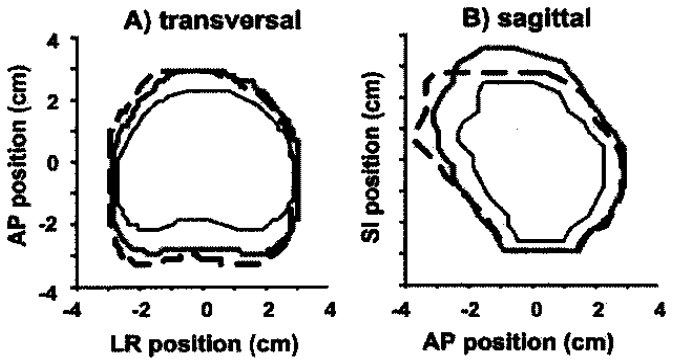

Fig. 4. CTV (thin solid lines) with PTV margins as determined by coverage probability calculations [22] for the prone (thick dashed lines) and supine (thick grey lines) internal organ motions. Systematic and random variations are included. The 15 systematic motions were the mean CTV positions with respect to the planning situation (as determined from Eq. (4) in Appendix B), the 45 random variations were the individual positions of the prostate in the repeat CT scans relative to the corresponding planning CT scans. Especially in the sagittal slice, the differences and agreements between the two margins are obvious.

4. Discussion

4.1. *Comparison with other studies*

In most other studies on internal prostate motion [2,16, 20,27,28], overall standard deviations of prostate movements in AP and SI directions are in the order of 3 to 4 mm, and in LR direction about 1 mm. Only Althof et al. [1], who used implanted 1251 seeds and multiple simulator images, appear to have significantly smaller values: standard deviations of 1.1 mm in AP and SI direction. They were, however, the only group who conducted the study about (on average) 2 years after the irritation treatment had been given. The prostate movement might have been less due to smaller rectum variations or due to a radiation induced fibrosis that could have restricted the prostate movement. The values in the other studies compare reasonably well to our own values as showed in Table 1. It should be noticed however, that in Table 1 standard deviations of prostate positions are given. To obtain the standard deviations of the movements (i.e. the differences in position) which are calculated in most other studies [1,2,16,20,28], our values should be multiplied by $\sqrt{2}$. In none of the previously published studies was an attempt made to separate systematic from random prostate motions.

Regarding the supine treatment position, the study most alike our own was performed by van Herk et al. [27] analyzing multiple CT data of 11 patients with chamfer matching. In contrast to our study, femurs were excluded in the bone match in order to minimize the cost function and reduce the uncertainty in the match results. But considering that the whole of the pelvic bone is used in the match, misalignment of the relatively small leg bones is less significant. Furthermore, they used a slightly different cost function for the CTV matches and instead of subtracting the bone match from the CTV

match, they acquired the CTV movement by matching the CTVs using the bone match as starting point. They also treated with a full bladder but did nothing to influence the rectum filling. The overall prostate movement, volume variations, and correlations are very similar to our supine data. Our position variation in SI direction was larger than theirs (1.7 mm) which might be due to their smaller CT slice distances (3 mm in the prostate region for all patients), differences in the registration procedure, or to our laxation for the planning CT scan. Their AP position variation (2.7 mm) was similar and the rotational variations (4.0, 1.3, 2.1 degrees around LR, AP and SI axes, respectively) were slightly smaller in our institute which might be due to the data averaging that we performed to decrease the measurement errors (see Appendix A).

To our knowledge, only Melian et al. have performed a study on internal prostate movement in prone treatment position [16]. They also used multiple CT data and found, for 13 patients, overall standard deviations for translations in LR, AP, and SI directions of 1.2, 4.0 and 3.1 mm, respectively. This is larger than our values (even taking into account the $\sqrt{2}$ correction factor). There were, however, several differences with the study described in this paper: they did not use laxation, they treated some patients with empty bladders, they could not perform automatic 3D matches, they used translational coordinates to determine rotations, and they made one of the three follow-up scans with an artificially expanded rectum. In agreement with our data, they also found correlations between prostate movements and bladder and rectum volume variations.

4.2. *Systematic and random variations, time trends, and margins*

Compared to the aforementioned studies, which did not consider time trends, the most remarkable finding of this study were the differences between systematic variations $\sum$ and random variations σ. It appeared that the planning CT situation was not just a random sample of the distribution of situations that occur during the rest of the treatment. In prone position, the prostate position variation at the planning situation was significantly larger than the variation in the course of treatment (see Table 4), despite the rectum laxation (if all patients have indeed taken their laxative suppositories, there is no reason to believe that the laxation might actually be the cause of an increase of the variation in prone position). Since the uncertainty in prostate position at the planning CT scan determines the systematic variation $\sum$, which in turn is largely responsible for the CTV-to-PTV margins, our currently applied margins of 1 cm cannot be decreased. One might even argue that they are too small in the superior region of the CTV (near the vesicles). To get the same coverage there as in the rest of the PTV, the margins should be increased to 1.5 cm or more as indicated in Fig. 4. There is, however, some discussion on the relevance of a small underdosage in part of the vesicles (see for instance Pisansky et al. [18]).

Another noteworthy result of this study is the significant time trend in CTV position for the patients treated in supine position (see Fig. 2). Near the end of the treatment the average rectum diameter seems to decrease and return to the (laxated) rectum diameter of the planning CT. The CTV position in AP and SI follow this trend. At the moment, PTV margins are based on measured systematic and random variations. In theory, one could go further and adjust the PTV margins on a weekly basis; the average prostate location changed from ventral to dorsal in the course of treatment and the standard deviations, which are responsible for the size of the margins, changed as well. As with all CT based studies however, the number of measurements per patient in this study is rather low, in our case due the limited availability of the CT scanner for research purposes. If more patients and more CT scans per patient can be measured, the trends, and therefore time-dependent PTV margins, can be determined with a better accuracy.

The small number of CT scans per patient is not fully representative for a prostate treatment of 33 fractions. Therefore only large differences in the measurement data are also statistically significant, like for example the difference between systematic and random variations for the internal organ motion in patients treated in prone treatment position (see Table 4). Based on the results of this study,

however, there is no reason to prefer one positioning technique above the other; Table 6 shows that there is hardly any difference in planning margins for the translational variations. The differences as shown in the more 'qualitative' Fig. 4, which include the rotational variations, also do not clearly favour one technique; in prone position the rotations appear to necessitate a larger margin in posterior direction (near the rectum), whereas in supine position the cranial margin is larger. Therefore, considering the equality of the PTV margins, the decision to treat in prone or supine position might actually be decided by planning' studies. Zelefsky et al. [29] concluded that prone position was to be preferred over supine position, but since the results may depend on hospital specific issues like protocols for rectum and bladder filling, we are currently conducting our own planning study.

4.3. *Patient databases and protocols*

In both treatment positions, mutual correlations of the different CTV movements make independent margin determination in the different directions less accurate. The measurements showed that the prostate tends to move obliquely from dorsal-inferior to ventral-superior direction, as also observed by van Herk et al. [27]. Furthermore, Fig. 4 indicates that the axis of rotation is not at the centre of mass of the prostate but more likely at the inferior apex, as has been reported before [27]. The simple rule for independent margins in LR, AP and SI direction is then only a first-order approximation. Mageras et al. [15] suggested generation of a large database of prostate movements, which can be sampled at the time of planning so the expected treatment can be simulated. The question is whether this database could be used universally or if every institute should create its own, considering the complexity of the movement and the dependency on institute specific treatment protocols. Although the overall variations from separate institutes may appear similar, as indicated in a previous section, detailed study of, for instance, systematic and random variations might yield significant differences.

Considering the variation of rectum filling at the planning CT scan (see Fig. 3), one might ask if the laxative suppositories used in this study were effective enough. Patients were asked to take them 4 h before the CT scan but the application and its effect might be too variable for individual patients. To be really sure that the rectum is empty and the prostate at its most dorsal position, other laxation methods like a rectal enema might be a more reliable (but more cumbersome) solution [17]. Furthermore, the time of day on which the patients are treated might be important. Due to the aforementioned limited availability of the CT scanner, all CT scans in this study were made early in the morning. This is, however, not always representative for the irradiation sessions of prostate cancer patients which can be carried out at all times during the day. Assuming regular bowel movements, particularly in the beginning of the treatment, ideally all treatments, simulations and acquisitions of the CT scans should be carried out at the same time of day.

The more elaborate analysis of our prostate movement data yielded significant differences with previously published studies. Although at first glance the overall prostate movement appeared to be less in prone than in supine position, separation of systematic and random variations showed that this was predominantly because of the smaller random variations. The systematic variations are about equal for both treatment positions. Since systematic variations are largely responsible for the PTV margins, a margin reduction cannot be justified by treating the patient in prone instead of supine position. More measurements should be performed to further confirm this conclusion and obtain more certainty in the observed time trends for patients in supine position.

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Appendix A. Data and error reduction

Assuming that the CTV of a patient is basically a rigid body, its position relative to the bony anatomy is fully described by six coordinates: the CM-coordinates along the AP-, LR-, and the SI-axes, and the rotation angles around these axes (the three axes intersect in the CM of the prostate). As explained in Section 2, internal CTV movement was established by subtraction of 3D chamfer match results for bony anatomy from the results of the corresponding CTV match.

Due to (small) differences in delineated CTVs in the different CT scans of a patient and due to the inability of the applied search algorithm to always find exactly the same optimum match, there is some uncertainty in the results. Moreover, the two CT-data sets in a matching procedure are used in rather different ways; the reference CT scan is used to calculate a distance transform matrix while the other data set is used to construct a 3D set of contour points (see Section 2). In this appendix, a description is given of the method that was used to calculate for each CT scan of a patient the CTV-coordinates relative to the average CTV-coordinates of the patient. With this method the effects of the above mentioned uncertainties can be minimised.

The method is based on the results of 4×4 matches per patient; all CT scans are subsequently used as the reference scan r and matched with the three other scans and with itself, yielding four sets of CTV displacements, each calculated with a different CT scan as the reference scan. Application of Eq. (1) given below yields for each CT scan k of a patient four estimates $p_{av,k}^{(r)}$ (one for each r) of the CTV position relative to the average CTV position. (For convenience, no patient- and CTV-coordinate labels are used in the formulas; the formulas are to be applied separately for every patient and for each of the six CTV-coordinates).

$$p_{av,k}^{(r)} = p_{r,k} - p_{r,av} = p_{r,k} - \frac{1}{4}\sum_{k=0}^{3} p_{r,k} \tag{1}$$

with $p_{r,k}$ the position in scan k relative to the reference r (i.e. the result of one bone match for scans r and k subtracted from the corresponding CTV match), and $p_{r,av}$ the average CTV-position relative to the CTV-position in the reference scan r. The four estimates of the CTV-position in scan k relative to the average position are finally averaged

$$p_k = \frac{1}{4}\sum_{r=0}^{3} p_{av,k}^{(r)} \tag{2}$$

Hence, p_k (or p_k^{ij} if the labels for coordinate i and patient j are denoted as well) is the CTV position for an individual scan k with respect to the average CTV position of that patient (i.e. $\sum_{k=0}^{3} P_k = 0$). In this manner, the 16 measured prostate movements per patient are reduced to four prostate positions (one for each CT scan).

An estimate of the measurement accuracy is given by the standard deviation of the four measurements, multiplied by a factor ($\sqrt{4/3}$) because the four measurements contain the same average and are therefore not fully independent. It should be noted that the effect of uncertainty in CTV delineation is not included in this standard deviation; the same outlines were used for the different matches. The delineation accuracy has been optimised by visual comparison and correction of the CTV outlines in the different scans of one patient, as explained in Section 2.

Appendix B. Overall systematic and random position variations

The coordinates p_k^{ij}, as derived in Appendix A, were used to calculate parameters describing the overall CTV position variations and the random and systematic components. For both patient groups, the overall variations in the six CTV-coordinates were quantified using:

$$SD^i = \sqrt{\frac{1}{15}\sum_{j=1}^{15}\frac{1}{3}\sum_{k=0}^{3}\left(p_k^{ij}\right)^2} \tag{3}$$

with SD^i the standard deviations for CTV-coordinate i (e.g. the CM-position along one of the axes) for all patients j and all scans k, describing the overall variation of this coordinate. Again the normal standard deviation is corrected by a factor ($\sqrt{4/3}$) because the four measurements of each patient contain the same average.

The CTV position variations p_k^{ij} were also used to calculate, for each patient j and coordinate i, the average deviation m^{ij} of the three repeat CT scans ($k = 1, 2, 3$) with respect to the planning CT scan ($k = 0$) and to determine the variation sd^{ij} within the three repeat CT scans:

$$m^{ij} = \frac{1}{3}\sum_{k=1}^{3} p_k^{ij} - p_0^{ij} \text{ and } sd^{ij} = \sqrt{\frac{1}{2}\sum_{k=1}^{3}\left(p_k^{ij} - p_0^{ij} - m^{ij}\right)^2} \tag{4}$$

Both patient groups were then characterised by their mean-of-means M, the systematic variation Σ; and the random variation σ for each coordinate i, according to:

$$M^i = \frac{1}{15}\sum_{j=1}^{15} m^{ij},$$

$$\Sigma^i = \sqrt{\frac{1}{14}\sum_{j=1}^{15}\left(m^{ij} - M^i\right)^2},$$

and

$$\sigma^i = \sqrt{\frac{1}{15}\sum_{j=1}^{15}\left(sd^{ij}\right)^2} \tag{5}$$

For the random variation σ, the square root of the average of the variances is taken. This value gives a better estimate of the population's distribution than the average standard deviation. In Fig. 1 the occurrence of systematic and random variations is explained in a graphical manner. Since the systematic deviation per patient (m^{ij}) was determined by only three observations, a relatively large error equal to $sd^{ij}\sqrt{3}$ was made. This will also manifest itself in the systematic variation Σ; which was therefore corrected according to:

$$\Sigma_{new}^i = \sqrt{\left(\Sigma_{old}^i\right)^2 - \left(\sigma^i/\sqrt{3}\right)^2} \tag{6}$$

As a first approximation, one can assume equal distributions of possible prostate positions during planning CT scan and during treatment. If it is then assumed that all patients have about the same variations in prostate position, the prostate position during the planning CT scan, which will determine the average deviation m, can be considered as just one sample of the distribution of prostate positions during the treatment, which will determine the variation sd. The standard deviation of the average deviations (i.e. Σ) should then be equal to the average of the variations sd (i.e. σ) and M should theoretically be zero.

Chapter 4

DETECTION OF INTERNAL ORGAN MOVEMENT IN PROSTATE CANCER PATIENTS USING PORTAL IMAGES

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Med.Phys.2000 Mar;27(3); 452-461

Abstract

Previous research has indicated that appearance of large gas pockets in portal images of prostate cancer patients might imply internal prostate motion. This was verified with simulations based on multiple CT data for 15 patients treated in supine position. Apart from the planning CT scan, three extra scans were made during treatment. The clinical target volume (CTV) and the rectum were outlined in all scans. Lateral portal images were simulated from the CT data and difference images were calculated for all possible combinations of CT scans per patient; each scan was used both as reference and repeat scan but gas pockets in the reference scan were removed. Gas pockets in a repeat CT scan then show up as black areas in a difference image. Due to gravity, they normally appear in the ventral part of the rectum. The distances between the ventral edge of a gas pocket in a difference image and the projection of the delineated ventral rectum wall in the reference scan were calculated. These distances were correlated with the "true" rectum wall shifts (determined from direct comparison of the rectum delineations in reference and repeat scan) and with CTV movements determined by 3D chamfer matching. Gas pockets occurred in 23 % of cases. Nevertheless, about 50 % of rectum wall shifts larger than 5 mm could be detected because they were associated with gas pockets with a lateral diameter > 2 cm. When gas pockets were visible in the repeat scan, rectum wall shifts could be accurately detected by the ventral gas pocket edge in the difference images ($r=0.97$). The shift of the rectum wall as detected from gas pockets also correlated significantly with the AP shift of the center-of-mass of the CTV ($r=0.88$). In conclusion, the simulations showed that lateral pelvic images contain more information than the bony structures that are normally used for set-up verification. If large gas pockets appear in those images, a quantitative estimate of the position of prostate and rectum wall can be obtained by determination of the ventral edge of the gas pocket.

Acknowledgements

The authors wish to thank the revolving fund of the University Hospital Rotterdam and the Dutch Cancer Society (project 98-1681) for their financial support.

Gert Korevaar, Marjolein van Os, and Marjolein Janssen are gratefully acknowledged for their work in the acquisition and preparation of the CT scans, and Hans de Boer for discussing the subject and for his help in the preparation of some of the figures.

Introduction

Geometrical uncertainties

In order to optimally use the advantages of conformal radiation therapy, the geometrical uncertainties during treatment should be known (to apply adequate safety margins) and minimized where possible (to reduce the size of the safety margins). The geometrical uncertainties consist for a large part of set-up errors and internal organ motion. Set-up deviations can be derived from portal images acquired during the radiation session. The gray shades in those images reflect the irradiated radiological thicknesses and bony structures are therefore highly visible. Calculation of the position of the bony anatomy relative to the reference situation yields the set-up deviation. In the last two decades several electronic portal imaging (EPID) systems have been developed for computerized acquisition and analysis of portal images.[1-3] Either off-line[4,5] (before the next treatment session) or on-line[6,7] (while the patient is still on the treatment couch) set-up correction protocols can then be used to minimize the set-up errors. On-line corrections yield better accuracies than off-line corrections but generally take more time. In recent years, the focus of the research is shifting towards determination of internal organ movement, especially for prostate cancer patients.

Measuring prostate movement

Several methods for measuring internal prostate movement have been reported in the literature. One possibility is to make a number of CT scans for each patient in the study.[8-14] In all scans the prostate is delineated, and manual or (semi-)automatic registration techniques are used to determine the prostate movement between the different scans. An advantage of this method is that the whole volume is used in the match and that 3D rotations can be measured. A disadvantage is its cumbersomeness, which at the moment restricts the use of on-line analysis and correction. Some groups are trying to overcome this problem by integrating CT and accelerator.[15,16]

Instead of CT, other imaging techniques can be used visualize the position of the prostate. For instance, ultrasound imaging can be a save and quick alternative. However, the normal transrectal placement of the ultrasound probe is too uncomfortable to be used for all or many sessions of the radiotherapy treatment. Therefore Troccaz *et al* decided to place the probe on the belly of the patients at the cost of reduced prostate visibility.[17] They claim however that the image quality is still adequate enough to make on-line corrections of the prostate possible. A clinical study comparing CT and suprapubic ultrasound images has recently been performed with a commercial ultrasound system for prostate localization.[18]

A third method to detect internal prostate motion makes use of the aforementioned portal imaging. Since the prostate itself has a similar density as its surroundings, it is not visible in those images. Therefore radio-opaque markers can be implanted in the target volume.[19,20] If the markers can be distinguished in the images, rapid analysis of the prostate position and possible on-line correction can be performed similar to set-up corrections. A disadvantage of this invasive procedure is the extra burden for the patient. Furthermore, markers might migrate and since they can only be implanted in the base of the prostate, not all parts of the target volume (like e.g. the vesicles) can be imaged. Instead of putting radio-opaque markers in the prostate itself, they can also be placed in an urethral catheter.[21] However, side effects of the irradiation inhibit the use of bladder catheters after a few fractions of the irradiation; at the moment this method can only be used for the first few fractions.

Indirect detection of prostate movement

Since the prostate is located directly ventral to the rectum, many groups have been able to demonstrate the relation between *rectum volume* and prostate position.[8-13] The correlation coefficients are rather low because other factors like bladder volume are also involved. However, with portal imaging the position of *ventral rectum wall* might be determined. In routine portal images of pelvic fields, the most

visible objects besides bony structures are gas pockets in the rectum. These gas pockets might indicate the position of the ventral rectum wall, which is expected to have a better correlation with the prostate position than the rectum (and/or bladder) volume. In Fig. 1 the rationale behind this correlation is visualized.

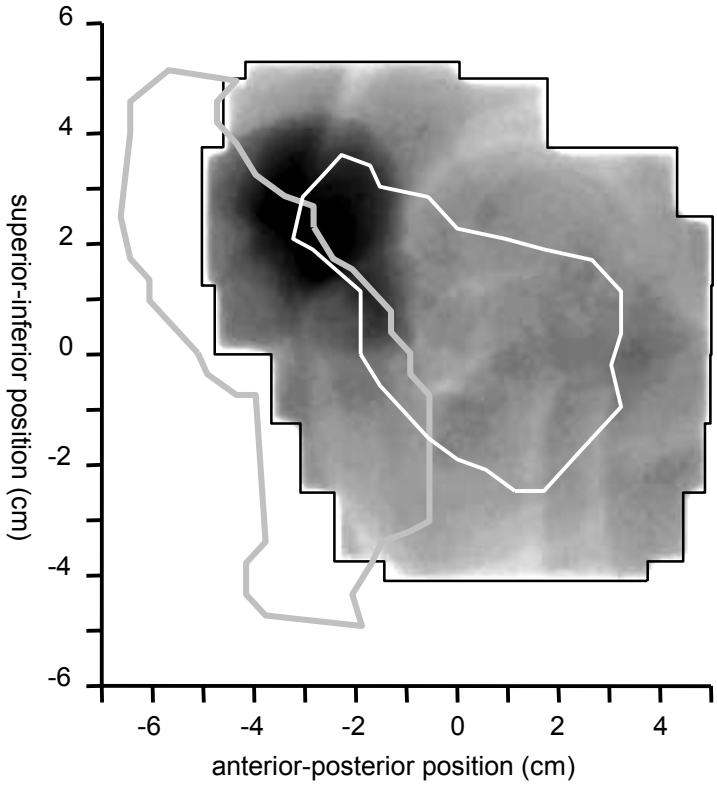

Fig.1. The rationale of the use of lateral portal images and naturally occurring gas pockets in the rectum of prostate cancer patients to determine internal rectum and prostate movement relative to the planning CT scan. The beams-eye-view contours of the rectum (thick gray line, filled semitransparently) and CTV (thin white line) in the planning CT scan of a prostate patient are superimposed on a clinical lateral portal image. The dark spot in the image, indicating a gas pocket, clearly extends outside the delineated rectum. This implies that during treatment the rectum wall, and probably the prostate, were moved in a ventral direction.

The beams-eye-view contours of the planned rectum and clinical target volume (CTV) of a prostate cancer patient are superimposed on a lateral portal image that was used for set-up verification. The portal image clearly shows a dark spot indicating a gas pocket that extends outside the rectum as delineated in the planning CT scan. This implies that the local rectum wall, and probably the prostate, has moved in a ventral direction. The use of gas pockets to detect internal organ movement would not increase the treatment time because portal images are already routinely acquired for set-up verification. Furthermore, it would be a non-invasive technique since rectum gas occurs naturally in prostate cancer patients. Kroonwijk *et al* already showed that gas pockets in portal images can reveal internal organ motion.[22] They did however not specify how this could be used in practice. In this paper, a method is proposed for using gas pockets in the rectum for quantitative determination of the rectum wall and, indirectly, the prostate position. The validity of the method is verified by simulations based on multiple CT data.

Methods and materials

Study outline

In order to verify whether gas pockets in clinical portal images can be used to predict the amount of rectum wall and prostate movement, simulations have been performed using previously obtained data of fifteen prostate cancer patients of which multiple CT scans were acquired during treatment.[10] In Fig. 2 a schematic outline of the study set-up is depicted. Firstly, the 4 CT data sets per patient were matched and resliced in 3D to remove the set-up deviations. Secondly, portal images for the left lateral beams were simulated from the resliced data sets. In order to automatically detect gas pockets, difference images between two scans were created for all combinations per patient. The gas pocket edges visible in the difference images were subsequently used to estimate the local rectum wall shifts between two scans. Thirdly, the "true" rectum wall shifts between two scans were measured by comparing rectum delineations in reference and repeat CT scan. Corresponding prostate movements

were determined from 3D matching. Finally, the rectum wall shifts as determined in the portal images were correlated with the true rectum wall shifts and with the prostate movements.
In the following paragraphs in this section, the set-up of the study will be explained in more detail.

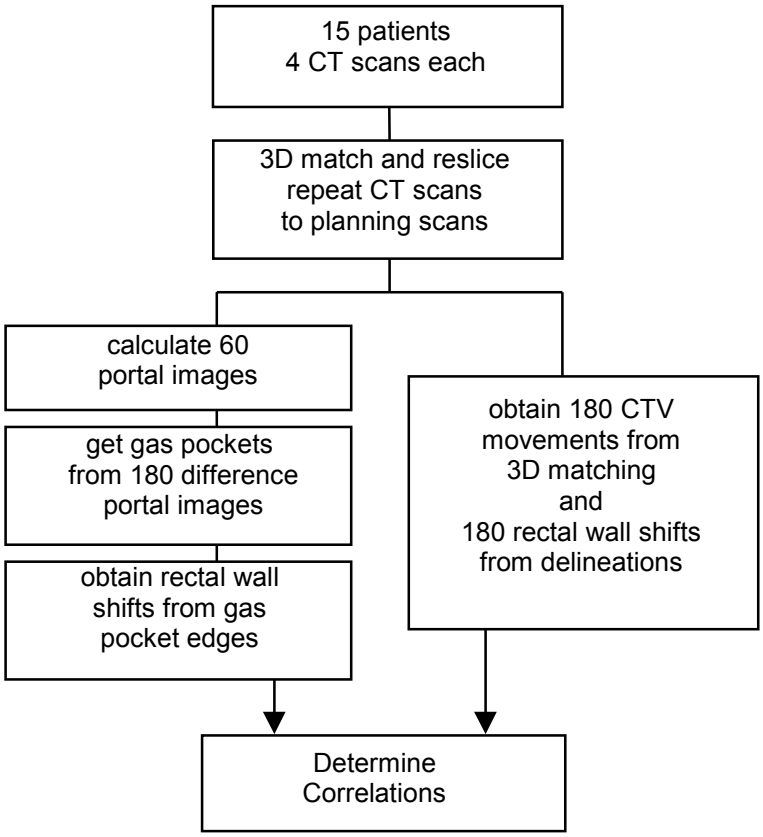

Fig 2. Schematic outline of the set-up of the study. A multiple CT data set is used to determine the rectum wall shift from gas pockets in simulated portal images. To verify whether this can be used to predict the true rectum wall movement and the prostate movement, the same data set is used to calculate these movements from delineations and by 3D matching, and a correlation analysis is performed. For more detailed information see the Methods and Materials section.

Patient data

In a previous study, the differences in prostate movement between 15 patients treated in supine and 15 in prone position were investigated.[10] The data of the 15 patients treated in supine position were also used in the current study. For each patient, four CT scans in the supine treatment position were acquired: one planning CT and three repeat CT scans in week two, four, and six of the treatment. Before the planning CT only, mild laxative suppositories were applied to minimize rectum volume. The patients were asked to empty the bladder and subsequently drink half a liter of water before all CT scans (and therapy sessions). In all scans the CTV (i.e. prostate and seminal vesicles), rectum, and bladder were manually contoured by the radiation oncologist. All patients were treated with an isocentric technique using an anterior field and two partly wedged laterally oblique fields; beam intensity modulation was used to minimize the superior-inferior field length.[23] The patients were treated to a total isocenter dose of 66 Gy, delivered in 2 Gy fractions.
Since we were only interested in the internal organ motion between the different CT scans, the set-up differences between the scans of each patient were corrected. 3D chamfer matching was used to match the bony anatomy in the repeat CT scans to their respective planning CT scans. The four CT sets per patient were subsequently aligned to the coordinate system of the planning scan by reslicing of the repeat CT scans. Details of the 3D chamfer matching algorithm and application can be found elsewhere.[9,10] The CT slice distance was 5 mm in most scans and 3 mm in some, the pixel size within the slices was 2 mm in all scans.

Radiological thickness images (RTIs)

Portal images for the aligned CT scans were simulated by calculation of radiological thickness images (RTIs). RTIs are a simplified form of digitally reconstructed radiographs, the difference being that a pixel value in an RTI is simply the sum of the electron densities in CT voxels along a ray line. Consequently the unity of the pixel values is easily interpretable: cm radiological thickness. In this study, only the RTIs of the left lateral prostate fields were used because the prostate movements of

interest occur predominantly in the sagittal plane; the lateral translation of the prostate is negligible and the rotation around the lateral left-right axis is by far the most significant.[8-14] Furthermore, in a lateral image the prostate and rectum are projected separately so that detection of the ventral rectum wall might indicate the dorsal prostate border, whereas in AP images the two organs are projected on top of each other. The lateral RTIs were obtained for all 60 CT scans with pixel size equal to the CT pixel size (2 mm) at isocenter.

Automatic detection of gas pockets in lateral RTIs appeared to be handicapped by the presence of other pixel gradients in these images due to variation in body contour and due to the visibility of the femoral heads. Especially the femoral heads were frequently in the region where the gas pockets appear. To diminish the effect of these gradients, difference RTIs (dRTIs) were calculated; the pixel values in a reference RTI were subtracted from those in the repeat RTIs. The relatively flat background in the dRTIs made the gas pockets in a repeat CT scan appear as distinctive dark spots. Only the gas pockets in the *repeat* CT scan are useful since they give information about a possible change from the reference situation. To avoid that a gas pocket in the repeat CT scan is neutralized by a similar gas pocket in the reference CT scan, the rectum in the *reference* scan was automatically filled with water-equivalent CT values before calculation of the reference RTI (i.e. gas pockets were removed). In order to study as many internal organ movements as possible, all scans were used both as reference and repeat scan. This yielded 12 dRTIs per patient, i.e. 180 in total. Since every CT scan had two RTIs (one normal and one without gas pockets that was always used as reference), inversion of two CT scans did not automatically yield exactly inverted dRTIs.

Rectum wall shift determination using gas pockets in dRTIs

The gas pockets were automatically determined by searching for the dark spots in a specific region in the dRTIs. Since there was some a priori knowledge about the location of the gas pockets and because there were some practical restrictions, this region could be limited in several ways. All dRTIs were overlaid with the beams eye view (BEV) projections of the corresponding reference prostate and reference rectum. The search region was then composed as follows: 1) In clinical portal images, only the area within the field defining blocks is visible. Therefore, the search region was restricted to the prostate projection in the dRTI, expanded with a 2D margin of 1.5 cm because that was the usual margin from the CTV to the field borders in our institute. 2) The resulting region was further limited in the ventral direction because of the known limitations in prostate movement, which is seldom more than 1.5 cm. Therefore, the search region was restricted to maximally 2 cm ventral from the rectum wall projection.[10] 3) Finally, in cranio-caudal direction the search region was limited by the cranial and caudal ends of the prostate; the gas pockets showing up outside that region (i.e. frequently in or near sigmoid or anus) did not have an effect on the prostate motion. An example of the resulting search region is shown in Fig. 3a. Within the search region the minimum pixel value in the dRTI was determined. If the minimum exceeded a certain (thickness) threshold, a gas pocket might have been detected. The extensions of the gas pocket were then determined by searching for all neighboring pixels with values below the threshold, using the position of the minimum as a starting point (see Fig. 3b). Hence a selected threshold can be considered as the minimal required lateral dimension of a gas pocket. If the gas pocket in the dRTI was positioned in the outermost cranio-caudal centimeter of the search region and if its size was smaller than about 0.5 cm^2, the pocket was discarded because there was a high probability that it was an artifact resulting from e.g. an imperfect alignment of bony structures. The applied radiological thickness threshold was varied to find an optimum value; too small thresholds resulted in picking up too many artifacts in the dRTIs, too large values resulted in the miss of genuine gas pockets.

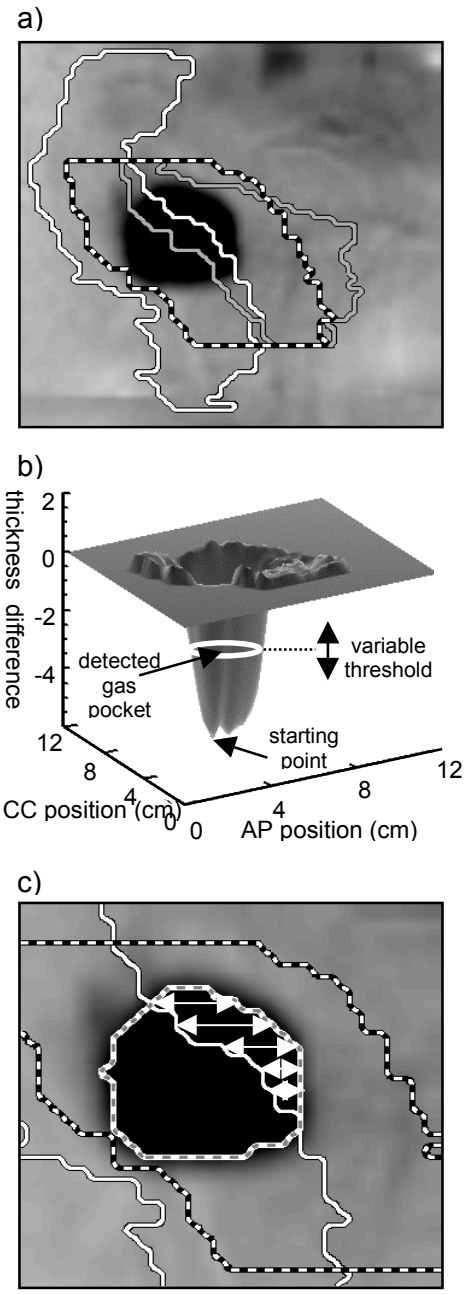

Fig. 3. Determination of the rectum wall shift in a dRTI. In (a) the construction of the search area (dashed contour) used to find gas pockets in the dRTI from the reference prostate (gray contour) and rectum (white contour) BEV projections is indicated. The search area is limited to the cranio-caudal length of the prostate, and extends 1.5 cm from the dorsal prostate edge and 2.0 cm from the ventral rectum edge. In (b) the gas pocket detection in the same dRTI is illustrated. If the maximum radiological thickness difference in the search area exceeds a user-defined threshold, the position of that maximum is used to start the search for connecting pixel values that also exceed the threshold. In (c) the automatically detected gas pocket is indicated by the lightly dashed contour. The rectum wall shift is estimated as the average AP shift along the cranio-caudal length of the gas pocket, as indicated by the arrows.

In Fig. 3c the detected gas pocket edge, using a threshold of 2 cm, is depicted. Also indicated in Fig. 3c is the method to estimate the local rectum wall shift from the detected gas pocket. Due to gravity, the gas pockets normally appear in the ventral part of the rectum for patients treated in supine position. The ventral edge of the detected gas pocket was therefore expected to correlate with the position of the ventral rectum wall in the repeat CT scan. Consequently, the local rectum wall shift was measured by comparing the position of the ventral gas pocket wall in the dRTI to the position of the reference rectum wall projection (see Fig. 3c). Only the shifts in AP direction were considered because that was the clinically most relevant direction. To get as much information as possible, average shifts along the horizontal pixel lines in the cranio-caudal reach of the gas pocket were calculated.

Rectum wall shift validation

To validate the local rectum wall shifts as measured from gas pocket edges in dRTIs, they were correlated with the "true" local rectum wall shifts. The true local rectum wall shifts could be determined from the position of the rectum projection in the repeat CT scan relative to the rectum projection in the reference CT scan. Again the shifts were averaged over all horizontal pixel lines in the cranio-caudal extent of the gas pocket. Correlation coefficients, statistical significance, and the slope of the fit were determined for the relation between rectum wall shifts estimated from gas pocket edges in dRTIs and true rectum wall shifts. Since all 12 possible dRTIs per patient were used in the correlation, it might seem that some data are counted double, which would incorrectly improve the statistical significance.

However, the dRTIs are determined from subtraction of two images, and since the reference image (A') in this subtraction is different from the original (A) because the gas pockets have been removed, the subtraction image A-B' is not directly correlated to B-A'. Similarly, C-A' is not a simple combination of C-B' and B-A'. The reference image is only equal to the repeat image when there are no gas pockets in the rectum and in that case they are not counted in the correlation anyway.

Prostate shift prediction

Since the prostate normally rests on the rectum and is at the base actually physically connected to it, a measured shift of the ventral rectum edge could well be a predictor of prostate shifts. Therefore the rectum wall shifts derived from gas pockets in dRTIs were also correlated with the AP translations of the center-of-mass (COM) of the CTV that were determined in a previous study with chamfer matches.[10] In short, differences in CTV position relative to the bony anatomy between two (not aligned) CT data sets of a patient, were determined by subsequent, 3D chamfer matches of the two CTVs and of the two bony anatomies, followed by a subtraction of the translational and rotational displacements in the bone match from those in the CTV match. Each scan was used as a reference to calculate the prostate position in the three other scans of a patient, which yielded a total of 180 3D prostate translations and rotations, identical to the number of dRTIs. Correlations of the rectum wall shift with the other significant prostate movements (i.e. COM translations in cranio-caudal direction and rotations around the lateral axis) and with combinations of those movements were also investigated. Since they yielded far less significant results, they are not considered any further in this paper.

In order to use the estimated rectum wall shifts as a predictor for AP prostate COM movements, two corrections were applied. Firstly, gas pocket edges never exactly coincide with the *outer* rectum wall edges since the rectum wall itself was not taken into account. Moreover, the choice of the threshold also influenced the exact position where the gas pocket edge was detected; higher threshold values resulted in smaller detected gas pocket cross sections, with ventral gas pocket edges that moved in dorsal direction (see the slope of the gas pocket in Fig. 3b). Therefore the differences between gas pocket edges in the dRTI and true rectum edges in the repeat scans were averaged for all data for a specific threshold, and a threshold-dependent correction was applied on the estimated rectum wall shift. Secondly, in case of an angle α between the reference rectum wall and the SI-axis, the rectum wall shift as derived from gas pockets was multiplied by a factor $\cos^2 \alpha$ to predict the AP shift of the prostate COM (see Fig. 4). Angles larger than 45 degrees were found, yielding correction factors smaller than 0.5.

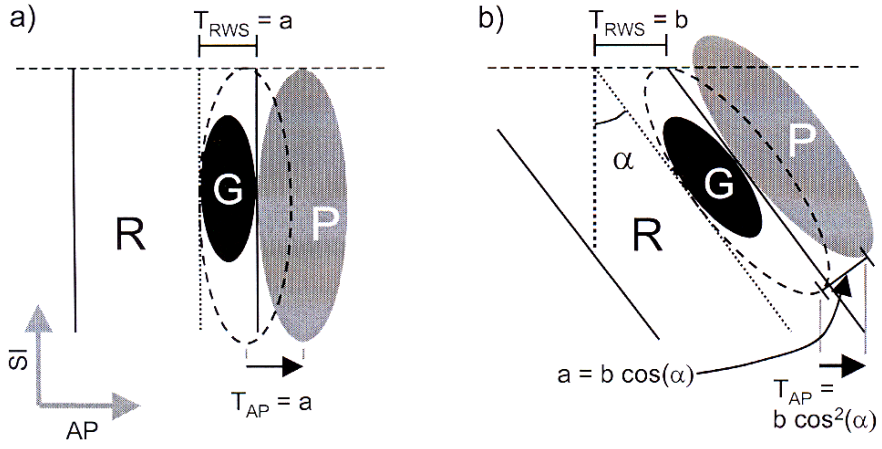

Fig. 4. A geometrical correction factor for transforming detected rectum wall shifts in AP direction (T_{RWS}) into prostate COM shifts in AP direction (T_{AP}). Schematic illustrations of rectum (R), gas pocket (G), and prostate (P) are depicted in a situation without (a) and with correction (b). Dotted and dashed lines indicate the reference rectum and prostate, respectively; solid lines represent the repeat situation. Since it is assumed that the prostate is solidly connected to the rectum, a correction equal to $\cos^2(\alpha)$ is needed if there is an angle (α) between rectum wall and the vertical SI axis.

Efficacy of the method

An obvious drawback of the described method to determine prostate shifts is that it relies on naturally occurring gas pockets; there may be rectum wall and prostate shifts from the reference position without a noticeable gas pocket in the dRTI (i.e. false negatives). The efficacy of the method was therefore investigated by answering the following questions. 1) How often did gas pockets occur? For all 60 scans a sagittal CT reconstruction through the rectum and the center of the prostate was calculated. The number of potentially useful CT scans (of the 60 scans present) was determined by automatic and

visual inspection of the presence of gas pockets in the relevant part of the rectum. 2) How many of the occurring gas pockets were actually detected with the described method? Each occurring gas pocket should have been measured in three dRTIs because each repeat scan was combined with three different reference scans. 3) How many and what type of prostate movements could be detected by the method? This was the main question because ultimately the method should detect organ movements. If there is no significant change from the reference situation, there is no need for detection. Therefore, the percentage of prostate movements that was detected by the gas pockets was determined as a function of the size and direction of the prostate translation.

Results

In Fig. 5 an example of a significant prostate shift between two CT scans of the same patient, due to the appearance of a gas pocket, and its effect on the RTIs is demonstrated. In this figure six images are shown, two normal RTIs (a and b), two RTIs without gas pockets that are used as reference (c and d), and the two dRTIs of these images (e and f).

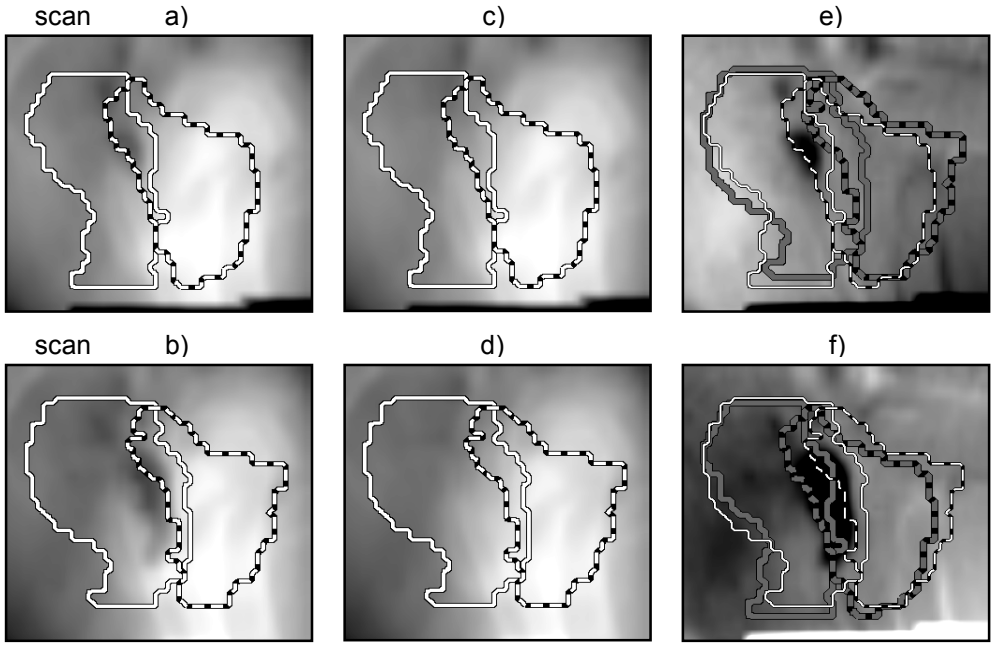

Fig.5. Demonstration of correlation of ventral rectum wall shift, gas pocket appearance, and prostate movement, as measured in radiological thickness images obtained from multiple CT data. For two CT scans, the normal RTIs (a, b), the reference RTIs with the gas pockets removed (c, d), and the dRTIs are indicated. Figure (e) is the difference between (a) and (d), figure (f) is the difference between (b) and (c). BEV projection of rectums are indicated by solid lines, prostates by dashed lines. In the dRTIs the reference organs are indicated by thick gray lines, the repeat organs by thin white lines. There is a good correlation between gas pocket wall, rectum wall and prostate position for both the ventral and the dorsal shift

Furthermore the BEV projection of the respective prostates and rectums are indicated. In scan 2 the rectum is clearly larger than in scan 1. In the difference image with *scan 1 as reference and scan 2 as repeat scan* (f), a rather large gas pocket is visible, the ventral edge of which corresponds nicely to the rectum wall in scan 2. Hence the edge of the gas pocket gives in this case a good estimate of the position of the rectum wall. Moreover, comparing the two prostate projections yields a clear ventral shift of the prostate, which in turn corresponds nicely to the rectum wall shift. In the difference image with *scan 2 as reference and scan 1 as repeat scan* (e), a small gas pocket can be discerned. The edge of this pocket also aligns nicely with the corresponding repeat rectum edge of scan 1. So even though

the rectum wall and the prostate have moved dorsally, it could be detected by a gas pocket. This example also shows why the gas pockets are removed for calculation of the reference RTIs; if the large gas pocket in scan 2 had not been removed, the small gas pocket from scan 1 would not have been detected in the dRTI. Also visible in the difference images (e and f) are some black and white shadows that indicate the legs. Although the bony structures in the two CT images were aligned before the generation of the RTIs, it is impossible to align every bone if the legs have moved with respect to the pelvic rim. Hence there are some black and white areas that might be mistaken for gas pockets if a too low threshold has been selected.

Local rectum wall shift

In Fig. 6 is verified whether the relation between gas pocket edge and rectum wall is always as straightforward as appeared from the example shown in Fig. 5. The rectum wall shift as derived from gas pockets in dRTIs, is plotted against the true rectum wall shift (see section 0). The thickness threshold that was used for gas pocket detection was equal to the optimal value of 2 cm. Lower values generated too many false positive gas pockets (i.e. artifacts), which were mostly due to imperfect alignment of the bony structures. Another reason for the occurrence of false positives is that the smaller gas pockets are not always positioned at the ventral border of the rectum but can be found anywhere in the rectum. Threshold values larger than 2 cm reduced the number of detected gas pockets, i.e. increased the number of false negatives, and hence decreased the efficacy of the method. Fig. 6 shows an excellent correlation between true and estimated rectum wall shift, r = 0.97. This implies that if a sufficiently large gas pocket is detected in a lateral portal image, one is able to predict the position of the local rectum wall with great certainty. The offset of the straight fit from zero is due to the fact that the gas pocket edge is always more dorsal then the true rectum wall due to the thickness of the wall itself and due to the threshold that is used to detect the gas pocket.

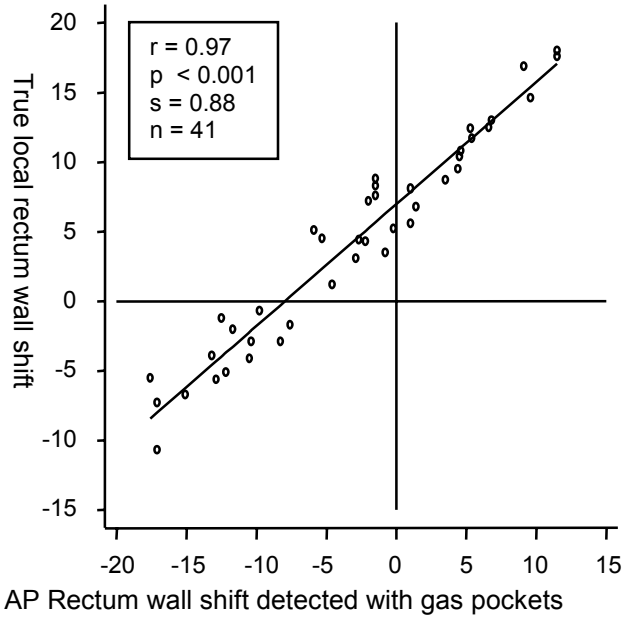

Fig. 6. *The correlation between true local rectum wall shifts and rectum wall shifts detected using gas pockets in dRTIs. Ventral shifts are positive and dorsal shifts negative.*

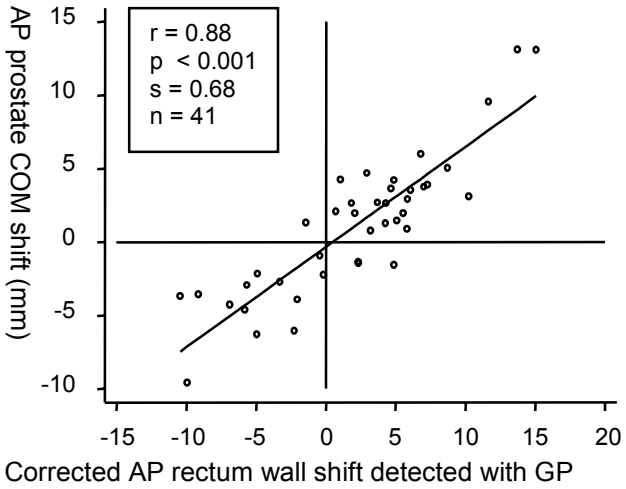

Fig. 7. *The correlation between AP movements of the COM of the prostate, as measured with 3D chamfer matching, and rectum wall shifts detected from gas pockets in the dRTIs. The applied rectum wall shifts were corrected for the slope of the rectum wall near the gas pockets and the threshold dependent distance between the true rectum wall and the gas pocket edge.*

For a 2 cm threshold, the combination of these two factors yields an offset of about 7.5 mm. The slope of the fit (0.88) is somewhat smaller than the expected value of 1. The limited number of data points, i.e. 41 out of a possible 180, will be discussed below.

AP prostate COM movements

The remaining question is whether a rectum wall shift that has been detected with a gas pocket can also predict prostate COM movements. In Fig. 7 the measured AP rectum wall shifts (with threshold equal to 2 cm) that were corrected for offsets and tilted rectum walls (see section 0), are plotted versus the corresponding AP translations of the COM of the prostate that were measured with 3D chamfer matching. The correlation coefficient of 0.88 is highly significant, the slope of the fit equals 0.68. One possible explanation for the correlation and the slope not being equal to 1 is that the translation of the prostate *center of mass* has been plotted against a local rectum wall shift, and for instance prostatic rotations have not been taken into account. Furthermore, especially near the cranial part of the prostate (where most gas pockets are observed), there can be a relatively wide separation between prostate and rectum, i.e. the rectum may shift locally without moving the prostate with it. This can cause an overestimation of the expected prostate translations and consequently a decrease of the slope in Fig. 7. The offset of the linear fit through the data points actually becomes zero, which implies that the threshold dependent correction was adequate.

Efficacy of the method

As shown in Figs. 6 and 7, the number of internal organ motions detected by gas pockets was 41, i.e. 23 % from a possible total of 180 internal motions. At maximum, 51 rectum wall shifts might have been detected because visual inspection indicated that 17 of the 60 CT scans contained a gas pocket in the relevant part of the rectum, and each gas pocket should be visible in 3 dRTIs. This implies that the method found 80 % of the occurring gas pockets.

In Fig. 8 the percentage of detected AP prostate movements is plotted as a function of the minimal size of the movement (i.e. data with absolute prostate translations smaller than the minimum are discarded).

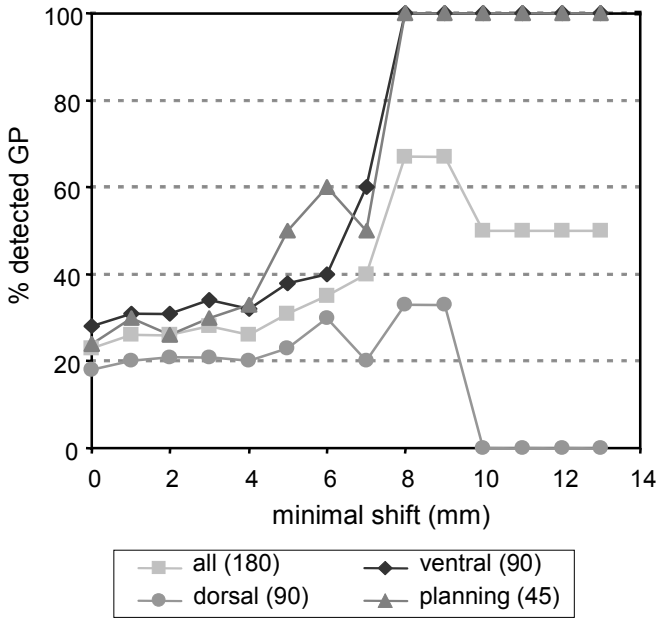

Fig. 8. Effectiveness of the method described in this paper. The percentage of prostate movements actually detectable by gas pockets is plotted as a function of the minimum AP prostate translation, considering 1) all data, 2) only those data with shifts in ventral direction, 3) only those data with shifts in dorsal direction, and 4) only those data with the original planning CT as reference. For the latter (clinical) category, about 50 % of translations larger than 5 mm was detected.

If all 180 prostate shifts are considered, the previously mentioned 23 percent can be detected. With increasing minimum AP shift, the detection probability increases to about 50 %. When only the ventral prostate shifts are considered, 40 % (4 of 10) larger than 5 mm was accompanied by a detected gas pocket, and all shifts (3) larger than 7 mm were detected.

This trend is due to the fact that large ventral shifts imply a large increase in rectum volume which are more likely to be accompanied by gas pockets. For the same reason, dorsal prostate movements are far less likely to be detected (although they can, see the example in Fig. 5).

This also explains the asymmetrical shape of Fig. 7. In clinical practice one might be particularly interested in ventral shifts because those imply movement of the rectum, which is the most critical structure for prostate treatments, into the treatment field.
In our institute, the ventral shifts dominate because rectum laxation is used before acquisition of the planning CT scan. The detection probability for the 45 shifts with respect to the clinical planning CTs only, confirm this: 50 % (3 of 6) of shifts larger than or equal to 5 mm is detected.

DISCUSSION

Clinical portal images

In order to use clinically acquired portal images to quantify internal organ movement, the "repeat" portal image as acquired with e.g. an EPID should be comparable to the reference image as acquired from the CT data. This implies that the clinical portal dose image should be converted to a reference RTI, or vice versa. Pasma *et al* have indicated that RTIs can be derived from portal images obtained with a CCD camera based fluoroscopic EPID.[25] In short, a transmission image can be obtained from the ratio of a portal image acquired with the patient in the beam and a portal image acquired without the patient in the beam. The raw EPID images are only corrected for the non-linear response of the system.[26] The radiological thicknesses are then determined from the primary component of the transmission, which is obtained by correcting the transmission image for scatter from the patient onto the EPID.
The clinical images will generally be noisier than the simulated RTIs used in this study, which might make the smaller gas pockets invisible. Furthermore, small artifacts due to e.g. misalignment of bony structures might occur more frequently in clinical images since matching of bony structures will normally be done in 2D, instead of 3D as in this study. If too many artifacts appear, the threshold for gas pocket detection might have to be increased. This would decrease the number of detected gas pockets, but the largest and most significant ones would still be caught. Fig. 9 shows that the basic principle of the method, determination of a rectum wall in a difference image of two portal images, also works for clinical megavoltage images. The gas

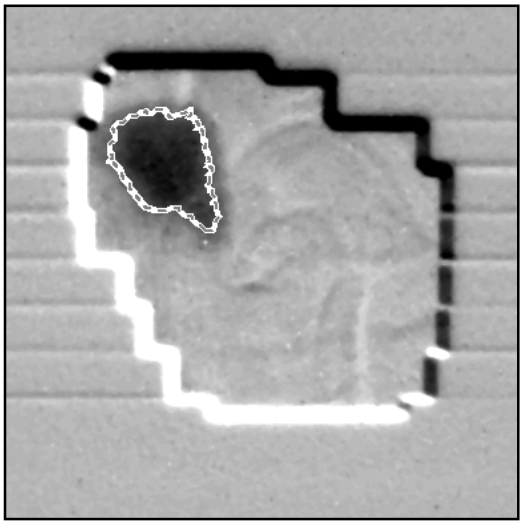

Fig.9. Simulation of a dRTI by subtraction of two clinical portal images. A reference portal image without significant gas pockets has been subtracted from the portal image that was shown in Fig. 1. The difference image makes the edge of the gas pocket more pronounced which enables accurate automatic detection of the edge of the gas pocket (dashed line). The bony structures of the images were matched before the subtraction (as is demonstrated by the black and white edges at the field borders), to be able to focus on the internal organ motion only.

pocket clearly shows up as a dark spot in an overall relatively flat difference image which enables automatic detection. This indication is further supported by clinical portal images that were available for nine of the fifteen patients in this study. The two patients which showed the most variation in the clinical images due to appearance and disappearance of gas pockets, also had on average the largest gas pocket size in the CT data, and vice versa.

Clinical application of the method

Although the method does not detect all shifts, an important advantage of the proposed method for internal organ motion detection over other methods is that it is non-invasive and no extra work during treatment is required. Portal images are already routinely made for set-up verification in our institute. Why not use the extra information that can be obtained from the occasionally occurring gas pockets in images to improve the set-up in some fractions of the treatment? In clinical practice, the method seems therefore mainly useful for *on-line* corrections of internal organ positions. In this case the images are acquired using only a small fraction of the total irradiation, which is subsequently interrupted, and the set-up deviation is determined by matching the bony structures in the portal image with the reference image. The portal image is then aligned with the reference image and a dRTI is calculated after conversion of the portal dose image into a RTI (see previous section). If a rectum wall shift from the reference situation is found in the dRTI, two different strategies may be followed before the rest of the fraction is given.

The first strategy is aimed at sparing the rectum. Especially the local rectum wall position can be predicted accurately with the described method (see Fig. 6). At some (boost) stage of the prostate treatment, sparing of the rectum volume might get a higher priority than adequate irradiation of the tumor.[27] Hence, in case the ventral gas pocket wall in the dRTI indicates that a significant part of the rectum wall has moved into the treatment field, a correction of the table position or the lateral treatment field can be applied so that the rectum wall is better shielded (even though the prostate might then be partly shielded as well). If the fields are shaped with multi leaf collimators, improved local shielding of the rectum might be obtained by moving only some of the leaves. After the correction, a second portal image can be obtained to verify the correction.

The second strategy primarily aims at an accurate irradiation of the prostate. If a rectum wall shift is observed, the fit in Fig. 7 can be used to determine the probable prostate movement. The isocenter of the lateral beams can then be moved accordingly before the rest of the fraction dose is applied. The prostate position is less accurately predicted than the rectum wall position, but if action is undertaken only in case of larger prostate shifts (e.g. > 5 mm), the benefits will be greater than the damages. Even if only a limited percentage of prostate movements is correctable (i.e. accompanied by gas pockets), the size of the safety margins and treatment portals might be decreased. For instance, the overall standard deviation of the AP prostate COM movements for the 45 shifts from the planning CT scans in this study was 3.8 mm. In the (hypothetical) case that all 11 detected gas pockets would have been used to perfectly correct the prostate position, this standard deviation would reduce to 2.8 mm. If we assume the planning margin equal to about 2 times this overall standard deviation[28] (and if we neglect other sources of uncertainties), a significant margin reduction of 2 mm would be justified.

Possible improvement and future developments

Half of the AP translations of the CTV from the planning CT scan situation larger than or equal to 5 mm were detected with the described method (Fig. 8). The laxation before the planning CT scan causes the rectum to be on average relatively empty, so larger shifts will occur if the rectum is full in the repeat situation. Because gas pockets are more likely to be found in fuller rectums, laxation results in a relatively high detection probability of large shifts. In theory there is ample room to improve the detection probability but different treatment protocols or patient instructions which might establish this seem not so realistic. For instance, possible injection of air in the rectum before the irradiation session will seriously complicate the otherwise so simple and quick method. Furthermore it can only be considered for a prostate boost at the beginning of the treatment,[21] because proctitis will hamper it at the end.

To increase correction accuracy, the correlation of rectum wall shifts with prostate translations might be improved. Additional information from the lateral and AP dRTIs, like size, position, and the

extreme pixel values in the gas pockets in dRTIs, has already been added to the regression analysis but it appeared that at least three variables were needed to really improve the correlation, which prevents a clear physical understanding of what is going on. In section 0 was already mentioned that correlations with other movements than AP COM translations led to nothing. Alternatively, from sagittal CT reconstructions the gap between prostate and rectum in the cranial part of the prostate in the reference situation can be measured (see section 0). In the BEV projections of rectum and prostate this is normally not visible because of the frequent overlap of the prostate and rectum. If such a gap exists, a rectum movement in the ventral direction might have a reduced effect on the prostate, which may be corrected for. This correction can however not be applied for the inverse (dorsal) rectum wall motions because in clinical practice it seems not possible to predict from one planning CT scan if a gap between rectum and prostate will develop or not.
Before preparing a possible clinical introduction of the method, available clinical portal images will be checked for gas pockets to verify whether they appear as frequent as in the 60 CT scans used in this study (28 %). There might for instance be time trends in the gas pocket formation, which were not detectable in the limited amount of data points available in this CT based study. Treatment fractions from which multiple portal images have been acquired can be used to determine the likelihood of intra-treatment motion. Furthermore, a clinical test of the method should be done by comparing CTV movement as measured by gas pockets with CTV movement as measured from the same images using radio-opaque markers. Such a study is currently being performed.

CONCLUSION

A quick and non-invasive method has been proposed for determination of internal organ motion in prostate cancer patients with an EPID. A study based on multiple CT data indicated that gas pockets in the rectum that are visible in normal portal images (i.e. without radio-opaque markers etc.) might be used to detect the ventral rectum wall and the prostate COM position. Since not all portal images display gas pockets not all movements can be detected, but the method is especially sensitive for the larger movements because they are more likely to be accompanied by gas pockets in the rectum. The accuracy of the method to quantify the AP movement of the prostate and especially the local rectum wall is more than adequate. Hence clinical portal images, which were up till now only used for set-up correction, might simultaneously be used to correct field shapes for internal organ motions.

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Chapter 5

ACUTE MORBIDITY REDUCTION USING 3DCRT FOR PROSTATE CARCINOMA: A RANDOMIZED STUDY

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Int. J. Radiation Oncology Biol. Phys., Vol. 43, No. 4, pp. 727–734, 1999

Abstract

Purpose:
To study the effects on gastrointestinal and urological acute morbidity, a randomized toxicity study, comparing conventional and three-dimensional conformal radiotherapy (3DCRT) for prostate carcinoma was performed. To reveal possible volume effects, related to the observed toxicity, dose–volume histograms (DVHs) were used.
Methods and Materials:
From June 1994 to March 1996, 266 patients with prostate carcinoma, stage $T_{1-4}N_0M_0$ were enrolled in the study. All patients were treated to a dose of 66 Gy (ICRU), using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure. However, patients in the conventional treatment arm were treated with rectangular, open fields, whereas conformal radiotherapy was performed with conformally shaped fields using a multileaf collimator. All treatment plans were made with a 3D planning system. The planning target volume (PTV) was defined to be the gross target volume (GTV) + 15 mm. Acute toxicity was evaluated using the EORTC/RTOG morbidity scoring system.
Results:
Patient and tumor characteristics were equally distributed between both study groups. The maximum toxicity was 57% grade 1 and 26% grade 2 gastrointestinal toxicity; 47% grade 1, 17% grade 2, and 2% grade > 2 urological toxicity. Comparing both study arms, a reduction in gastrointestinal toxicity was observed (32% and 19% grade 2 toxicity for conformal and conventional radiotherapy, respectively; $p = 0.02$). Further analysis revealed a marked reduction in medication for anal symptoms: this accounts for a large part of the statistical difference in gastrointestinal toxicity (18% vs. 14% [p = ns] grade 2 rectum/sigmoid toxicity and 16% vs. 8% [$p < 0.0001$] grade 2 anal toxicity for conventional and conformal radiotherapy, respectively). A strong correlation between exposure of the anus and anal toxicity was found, which explained the difference in anal toxicity between both study arms. No difference in urological toxicity between both treatment arms was found, despite a relatively large difference in bladder DVHs.
Conclusions:
The reduction in gastrointestinal morbidity was mainly accounted for by reduced toxicity for anal symptoms using 3DCRT. The study did not show a statistically significant reduction in acute rectum/sigmoid and bladder toxicity.

Acknowledgements
Supported by the "Revolving Fund" of the University Hospital Rotterdam
The authors wish to thank Mrs. P. Hoynck van Papendrecht, Mr. P. van Assendelft, Mrs. M. van Os, and Mrs. M. Janssen for their technical assistance, and Ms. I. Dijkstra for her assistance in preparing the manuscript.

Introduction

In 1990, a report from the Daniel den Hoed Cancer Center (DDHCC) was published [1] concerning late toxicity observed after treatment of prostate carcinoma with a tumor dose of 70 Gy. The rate of proctitis—30% in some patient groups—was found to be related to the maximum (point) dose calculated in the rectum. After this publication the tumor dose was lowered to 66 Gy to reduce the relatively high percentage of proctitis observed when using the conventional open, rectangular radiotherapy technique. As no randomized study had been published at the time of full implementation of three-dimensional conformal radiotherapy (3DCRT) in our department in 1993/1994, it was decided to investigate a possible reduction in (acute) toxicity, in order to gain experience for future dose escalation studies.

The introduction of 3DCRT has led to the expectation that exposure of less normal tissue would reduce toxicity [2]. Retrospective and prospective analyses of conformal radiotherapy in prostate cancer published in recent years suggested a low percentage of serious toxicity even when using high tumor doses [3, 4, 5, 6, 7, 8, 9, 10 and 11]. In the study by Hanks *et al.* [3] a 20% reduction in grade 2 acute toxicity was found. In another study [10], comparing historical patient groups, a 20% and 27% reduction of grade 2 acute toxicity was suggested for intestinal symptoms using computed tomography (CT)-based and beam's eye view–based radiotherapy techniques instead of conventional techniques.

However, in two randomized studies [7 and 9], these differences in acute toxicity have not been confirmed. In the preliminary report of the M.D. Anderson Hospital [7] acute toxicity (grade > 2) after conventional radiotherapy (RT) (70 Gy, $n = 31$) vs. conformal therapy (79 Gy, $n = 29$) was 0% and 10%, respectively, for bladder symptoms ($p > 0.4$) and 0% and 3%, respectively, for rectal symptoms ($p > 0.4$). In the Royal Marsden study [9] including prostate ($n = 138$), bladder ($n = 110$), and rectal cancer ($n = 11$), acute toxicity was identical using a patient questionnaire. Fifty percent and 23% of patients, respectively, reported more than "quite a bit" of bowel and bladder toxicity ($p = 0.3$ and 0.6). The authors were not able to score toxicity, for example, according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) toxicity scoring systems. Another problem in this study was the nonuniform fractionation scheme and dose. Our study was performed in a homogeneous group of patients treated with a homogeneous tumor dose and fractionation scheme. In the presented analyses a possible volume–toxicity correlation was studied using the EORTC/RTOG score, with special attention to the medication prescribed. We therefore feel that this study provides additional information to clarify possible mechanisms of acute toxicity caused by the conservatively dosed radiotherapy schemes.

Methods and materials

General information

From June 1994 to March 1996, 266 patients were enrolled in a randomized study. Inclusion criteria were: $T_{1\text{-}4}N_0M_0$ prostate carcinoma without prior radiotherapy to the pelvic region. Patients with a history of other malignancies were excluded. As the primary aim of this study was to investigate a possible reduction in toxicity, any tumor stage, grade, and prostate-specific antigen (PSA) level was accepted. Hormonal (neo) adjuvant therapy was not used at the time of this study. The pelvic lymphatics were not treated intentionally. There are no significant differences in patient characteristics for both study arms (Table 1). Three patients were excluded from further analysis, as they refused further treatment or because they appeared to have regional and/or distant metastases during pretreatment screening.

Radiotherapy protocol

All patients were treated to a dose of 66 Gy in the International Commission on Radiation Units and Measurements (ICRU) reference point [12], using the same treatment planning procedure, treatment technique, linear accelerator, and portal imaging procedure. Patients in the conventional arm were treated with rectangular, open fields; conformal radiotherapy was performed with conformally shaped fields using a multileaf collimator (MLC). Patients were asked to have a full bladder and empty rectum at the time of the planning CT scan and during treatment. For the CT scan 5-mm slices were used with a 5-mm width. The responsible radiation oncologist contoured the gross target volume (GTV), the lower intestinal structures, and the bladder. The GTV was limited to the prostate in T1 tumors, whereas in all other patients it encompassed both the prostate and the seminal vesicles. The length of the intestinal structures analyzed was limited by the superior and inferior field borders. The anus was reconstructed from these contours being (by definition) the most caudal 3.0 cm. The remaining intestines were defined to be the rectum/sigmoid (Fig. 1). The bladder was contoured entirely. The planning target volume (PTV) was constructed using an automated (uniform) 3D expansion of the GTV volume [13], adding 5 mm for microscopic disease (clinical target volume [CTV]) and another 10 mm for positioning errors and CTV mobility. These margins were chosen on the basis of the first reports on the internal movement of the CTV [14, 15, 16, 17, 18, 19 and 20]. All contours were checked by the study coordinator, to guarantee a uniform description of the contoured volumes.

Table 1. Comparison of conventional and conformal radiotherapy study arms for patient characteristics and dose information

		Conventional	Conformal
No. of patients		134	129
Mean age		69 (SD 7)	69 (SD 6)
T classification	T1	16	15
	T2	66	57
	T3	47	54
	T4	5	3
Histology	grade I	44	37
	grade II	65	59
	grade III	22	28
	grade x	3	5
PTV dose	mean	66.3 (SD 0.8)	66.2 (SD 0.7)
PSA at start		26 (SD 38)	21 (SD 20)
iPSA	<10	41	41
iPSA	10–20	39	40
iPSA	>20	50	47
iPSA	unknown	4	1

iPSA = initial PSA.

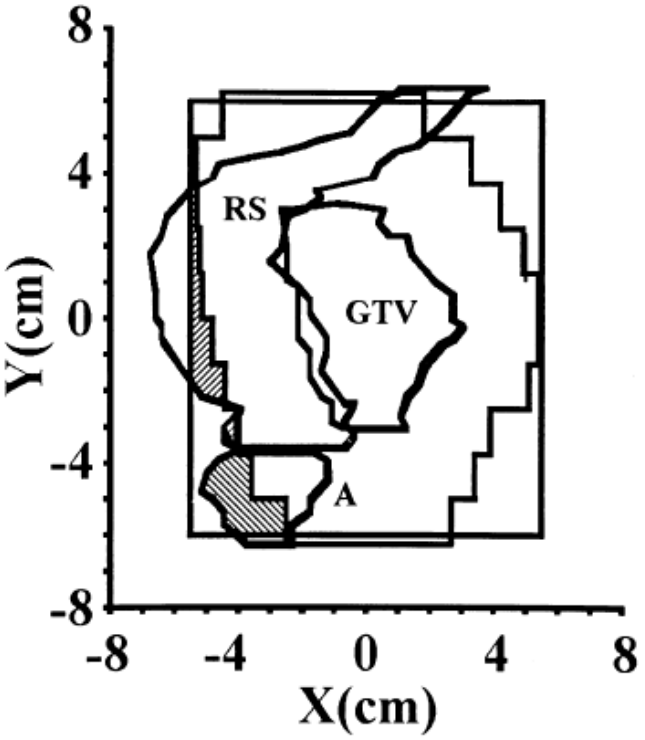

Fig. 1. Beams eye view presentation of one of the lateral oblique treatment fields for a typical patient. A = anus; RS = rectum/sigmoid; GTV = gross target volume. Reduction of irradiated volume indicated by the shaded area.

In the planning protocol a strict planning procedure was prescribed to guarantee a standard treatment plan for both treatment groups. A three-field technique (one anterior and two oblique laterals) was used. All treatment plans were made with a 3D treatment planning system (CADPLAN). In most patients, the recommendations of the ICRU 50 Report [19] were realized, allowing a -5%/+7% inhomogeneity over the PTV. However, for 17/265 (6.4%) of patients even a block to the PTV margin of 15 mm in the craniocaudal direction was not enough to avoid PTV doses somewhat less than 95% of the prescribed dose [21]. In these patients, a maximum block to the PTV margin of 15 mm was used and a small underdosage (minimum 92.4%) was

accepted. The total prescribed dose was 66 Gy in 33 fractions. All fields were treated daily in 5 fractions a week. There was no difference in median (Table 1), minimum, and maximum dose in both study arms. All patients were treated with the Scanditronix Racetrack Microtron (MM50) with a photon energy of 25 MV. As the patients were treated in supine position without a cradle or cast, regular setup verification with an electronic portal imaging device (EPID) was performed, using a "setup correction protocol" [19 and 22]. This protocol aims at reducing the influence of systematic positioning errors. Due to the protocol, the standard deviation (SD) of the systematic error could be limited to 1.5 mm in all directions. The average random error was 2.5 mm (1 SD).

Toxicity evaluation

The medication needed to treat excessive morbidity was prescribed by the responsible radiation oncologist. Attention was paid to the consequent description of the medication prescribed. The radiation oncologist used the EORTC/RTOG toxicity scoring system (Table 2) to monitor the gastrointestinal and urological morbidity.

Table 2. EORTC/RTOG acute scoring system

	Lower gastrointestinal incl. rectum	Genitourinary	Anal
Grade			
0	No change	No change	No change
1	Increased frequency or change in (quality of) bowel habits not requiring medication/rectal discomfort not requiring analgesics	Urination frequency or nocturia twice the pretreatment habit/dysuria, urgency not requiring medication	Discomfort or pain not requiring analgesics
2	Diarrhea requiring parasympatolytic drugs/mucus discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Urination frequency or nocturia less frequent than every hour. Dysuria, urgency, bladder spasm requiring medication	Discomfort or pain requiring analgesics
3	Diarrhea requiring parenteral support/ severe mucus or blood discharge necessitating sanitary pads/abdominal distension	Urination frequency and nocturia hourly or more frequent, dysuria, pelvic pain or bladder spasm requiring regular frequent narcotics, gross hematuria	Discomfort or pain requiring narcotics
4	Acute or subacute obstruction or perforation/GI bleeding requiring transfusion/abdominal pain or tenesmus requiring tube decompression or bowel diversion	Hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage, ulceration or necrosis	

At a later stage during analysis, both rectum/sigmoid and anal toxicity were separated. Rectum/sigmoid toxicity was graded according to the EORTC/RTOG toxicity scoring system. Anal toxicity, grade 1, was defined as anal discomfort for which only simple treatment (e.g., ointments) was needed. Grade 2 anal symptoms were scored when the patient needed anesthetic suppositories to ease the anal pain. Gastrointestinal toxicity is the combined score for rectum/sigmoid and anal symptoms.

Statistics

As we considered the tumor dose to be important for the development of acute toxicity, patient data were ordered by the dose delivered (pre RT, 25%, 50%, 75%, and 100% of the prescribed tumor dose). As a result, we were also able to correct for the differences in overall treatment time due to weekends, public holidays, and machine breakdown. The exact scores at these dose points were derived by interpolation from the scores 1 week before and after the time point. The mean overall treatment time was 49 days, with a standard deviation of 4 days.

As can be seen from Figs. 2a, 2b, and 2c, the general development pattern of acute toxicity was a monotone stepwise increase in toxicity grade with a maximum reached after administration of 75 % of the treatment dose. Only in a few patients an incidental increase and reduction in toxicity was observed.

Toxicity scores describe maximum toxicity. Dose–volume histograms (DVHs) were made of PTV, bladder, rectum/sigmoid, and anus, to investigate a correlation with observed toxicity. For each volume of interest the measures of exposure were derived from the DVH. DVH50 was defined as the percentage of the volume exposed to 50% or more of the planned treatment dose. Similarly, DVH90 and DVH95 were defined. An ordered logistic regression analysis was applied to study the relationship between the graded toxicity score and treatment arm and exposure measures. The target number of patients for this study was calculated to be at least two times 102 patients. Power calculations showed that this number would be sufficient to detect a proportional decrease in acute toxicity (with an odds ratio of 0.37) using the proportional odds model of Whitehead [23]. This number would be sufficient in a more conventional analysis to show an incidence reduction of grade 1–3 toxicity of an assumed 80% in the conventional treatment arm to 60% in the 3DCRT arm of the study, with a significance level of 5% and a power of 80%.

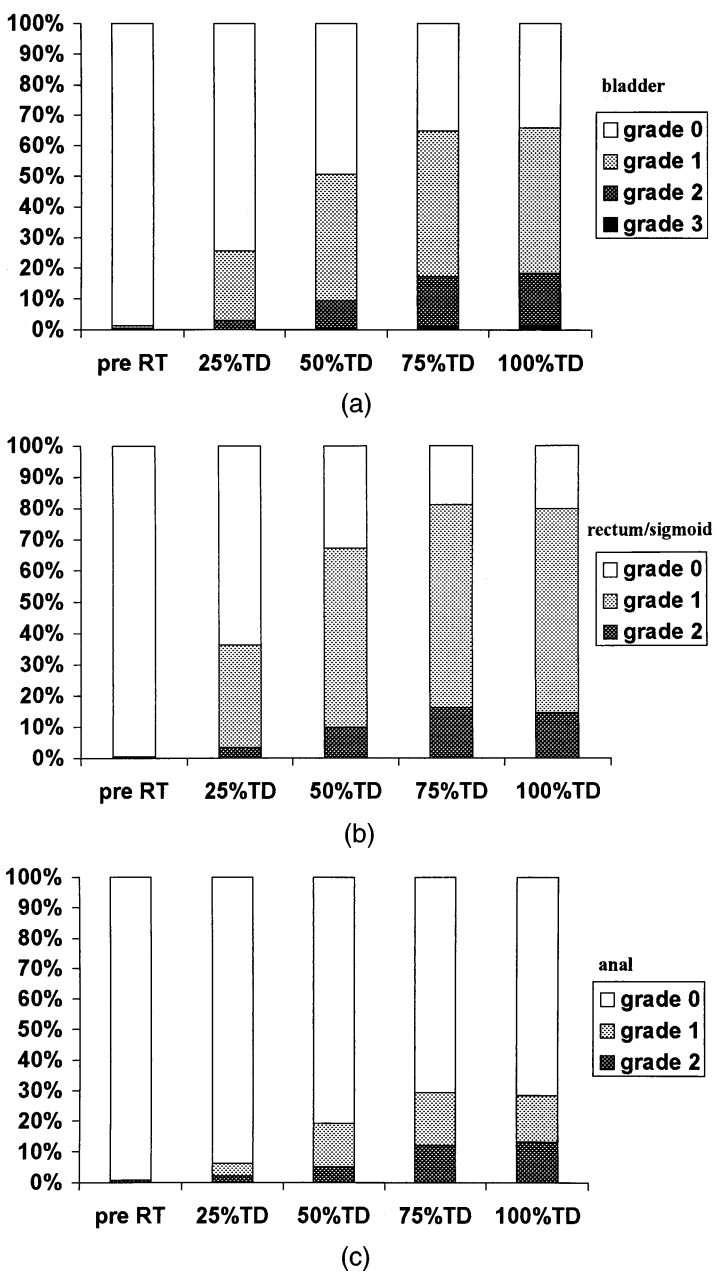

Fig. 2. Observed percentage of acute urological (a), rectum/sigmoid (b), and anal (c) EORTC/RTOG toxicity grades as a function of prescribed tumor dose.

Results

From the start of treatment, both gastrointestinal and urological toxicity increased to a maximum. Urological toxicity, grade 1 and 2 increased to 47% and 17%, respectively. Grade 3 and 4 toxicity have been scored in 2% of the patients needing a catheter because of urinary obstruction. Comparing the radiotherapy techniques for urological toxicity, 17% and 18% (EORTC/RTOG) grade ≥2 were observed for the conventional and conformal technique, respectively (Fig. 3a). There is no statistically significant difference between both study arms. Compared to the conventional technique there was a highly significant reduction in volume exposed (Fig. 3b) for the conformal technique for the dose levels studied: DVH50 21%, DVH90 28%, and DVH95 32% reduction, with $p < 0.0001$ at all dose

levels. However, the relatively large difference in DVH does not result in a marked reduction in bladder symptoms.

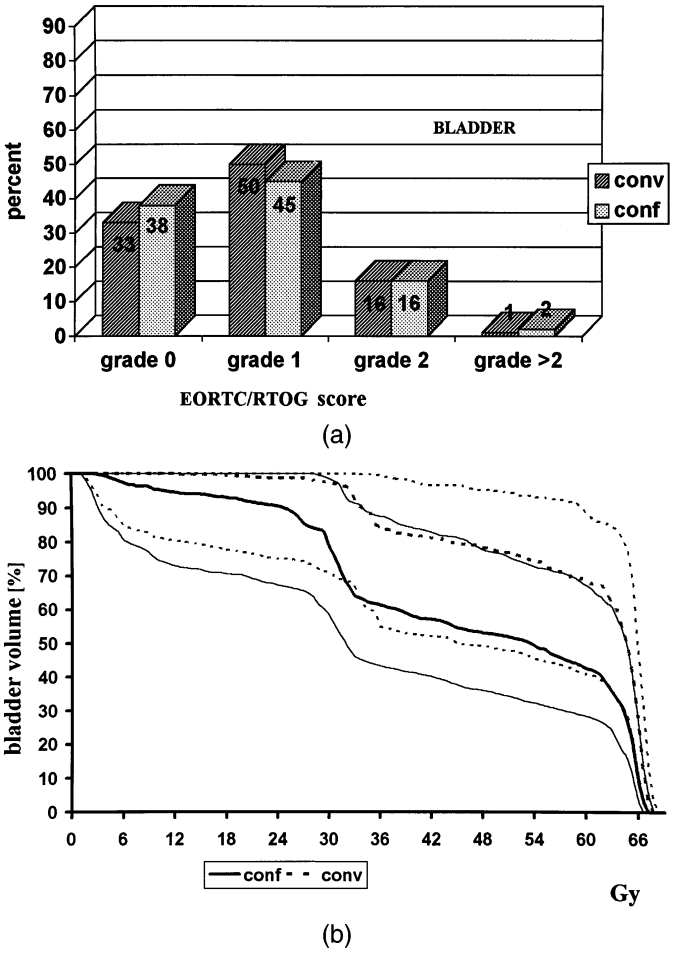

Fig. 3. (a) Observed percentage of urological EORTC/RTOG toxicity grades for conventional (conv) and conformal (conf) radiotherapy; no statistical difference. (b) DVH (median) for conventional (conv) and conformal (conf) radiotherapy, including the 66 percentile data, for bladder, $p < 0.0001$ at 50%, 90%, and 95% tumor dose.

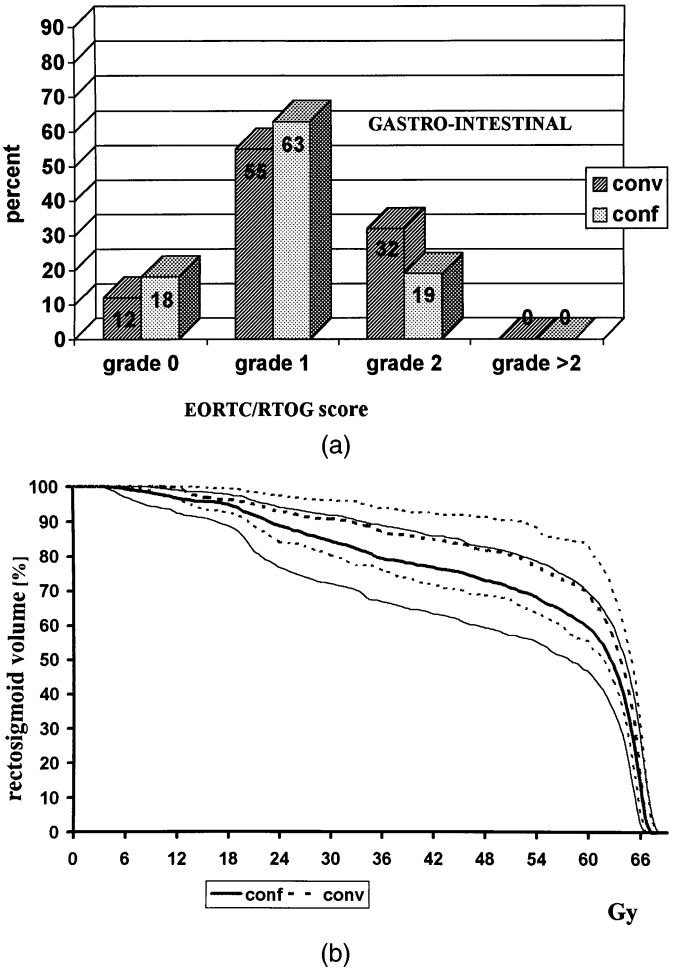

Fig. 4. (a) Observed percentage of gastrointestinal EORTC/RTOG toxicity grades for conventional (conv) and conformal (conf) radiotherapy, $p = 0.02$. (b) DVH (median) for conventional (conv) and conformal (conf) radiotherapy, including the 66 percentile data, for rectum/sigmoid and anus, $p = 0.25$ at DVH50, $p = 0.01$ at DVH90, and $p = 0.003$ at DVH95.

For gastrointestinal symptoms the maximum toxicity was 57% grade 1 and 26% grade 2 toxicity. Grade ≥3 toxicity was not observed. Comparing radiotherapy techniques, 32% and 19% grade 2 gastrointestinal toxicity were observed for conventional and conformal radiotherapy, respectively (p = 0.02, Fig. 4a). Although there was a statistically significant volume reduction, this difference was small (Fig. 4b). Compared to the conventional technique there was an 8% volume reduction at DVH50 (p = 0.25), 13% at DVH90 (p = 0.01), and 14% at DVH95 (p = 0.003) for the conformal radiotherapy technique.

An analysis of measures taken to treat the moderate to severe gastrointestinal side effects revealed a relatively high frequency of prescription of anesthetic suppositories for anal symptoms. Both anesthetic suppositories and loperamide were used in 13% and 11% of the patients, respectively. A detailed analysis of the toxicity of rectum/sigmoid and anus separately revealed a statistically nonsignificant reduction of grade 2 toxicity for rectal symptoms (18% and 14% for conventional and

conformal radiotherapy, respectively) and a statistically significant reduction of anal grade 2 toxicity (16% and 8% for conventional and conformal radiotherapy, $p < 0.0001$ [Fig. 5a]).
The reduced anal toxicity in the conformal treatment arm is explained by a statistically significant reduction in exposure of the anus (Fig. 5b, $p < 0.0001$ at all dose levels).

Therefore, the conclusion must be that the observed reduction of gastrointestinal toxicity was largely due to a reduction in anal morbidity. The beams eye view projection (Fig. 1) of one of the lateral oblique treatment fields for a typical patient indicates that a major part of the anus was blocked by the MLC, whereas the rectum/sigmoid itself was only blocked for a limited portion. A possible interaction for both rectal/sigmoidal and anal symptoms is presented in Table 3. It is concluded that there is not a statistically significant correlation; in other words it is not likely that anal toxicity was influenced by rectum/sigmoid toxicity or vice-versa.
As the DVH analysis confronted us with a wide range in bowel and bladder exposed in both arms, we decided to test the assumption that exposure of more normal tissue would cause more toxicity. The grade of toxicity was correlated with the volume of bladder, rectum/sigmoid, and anus exposed at three different dose levels in all patients, irrespective of the treatment technique used. The data for the different dose levels were found to be strongly correlated to each other. A large volume exposed to a 50% tumor dose (TD) will generally correspond to a large volume exposed to a 90% TD and a 95% TD. Therefore, the DVH90 data are presented in Fig. 6 and Fig. 7.

For the bladder and rectum/sigmoid there was no statistically significant relation for grade and exposed volume at all dose levels. For the anus there was a highly significant correlation for exposed volume and toxicity grade at all dose levels ($p < 0.0001$).

Figure 7 shows the fitted probabilities of toxicity (grade 0–2), as a function of anal exposure expressed in DVH90. It is evident that a large anal volume exposed leads to more (serious) toxicity.

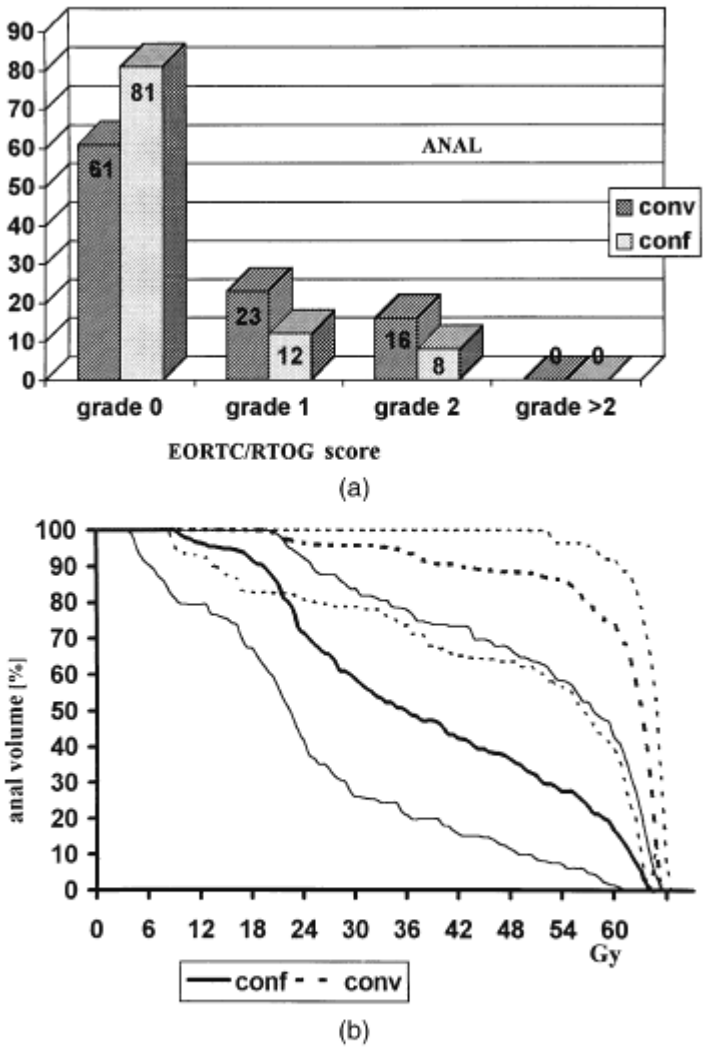

Fig. 5. (a) Observed percentage of anal toxicity grades for conventional (conv) and conformal (conf) radiotherapy, $p < 0.0001$. (b) DVH (median) for conventional (conv) and conformal (conf) radiotherapy, including the 66 percentile data, for anus (most caudal 3.0 cm of the rectum/sigmoid), $p < 0.0001$ at all dose levels.

Table 3. Relationship between rectum/sigmoid and anal symptoms

Rectum/ sigmoid toxicity	Anal toxicity		
	Grade 0	Grade 1	Grade ≥2
Grade 0	22%	12%	13%
Grade 1	60%	81%	70%
Grade 2	18%	7%	17%
Total	100% (n = 175)	100% (n = 43)	100% (n = 30)

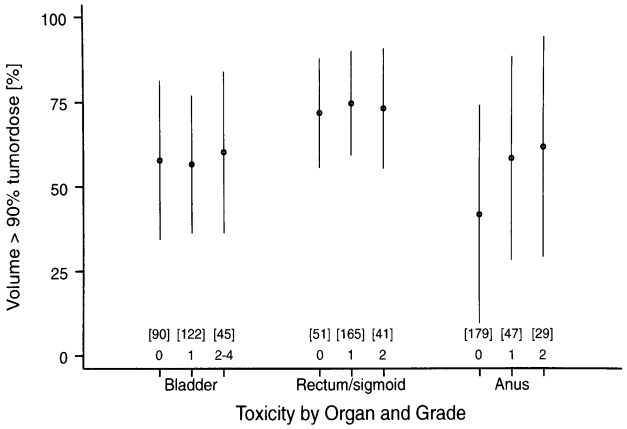

Fig. 6. Mean percentage of organs exposed (± 1 SD) to 90% tumor dose in relation to grade of toxicity. Bladder ($p = 0.8$); rectum/sigmoid ($p = 0.9$); anus ($p < 0.0001$). [ ]: number observed.

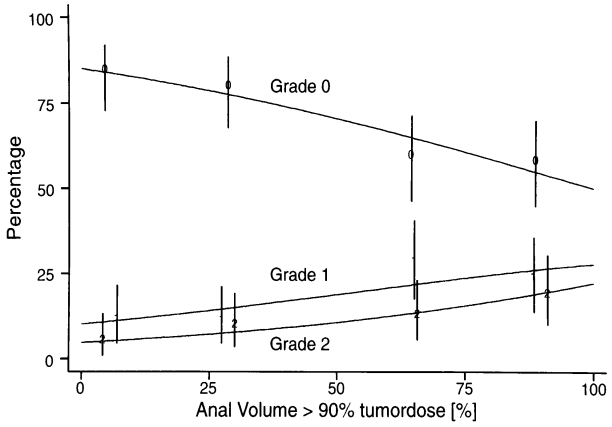

Fig. 7. Ordered logistic regression, fi ttedand observed percentage of anal toxicity (95% confi dence limits), as a function of anal volume exposed to > 90% tumor dose ($p < 0.0001$).

Discussion

In this report, we present the analysis on acute toxicity in a randomized study comparing the conventional open, rectangular radiotherapy technique and a conformal radiotherapy technique for prostate carcinoma. The analysis revealed a relatively low incidence of severe toxicity, comparable with other reports. In a similar randomized study in the Royal Marsden Hospital [9], a patient morbidity questionnaire was used to analyze the effects of conformal radiotherapy. In our study, a patient morbidity questionnaire was used together with the EORTC/RTOG toxicity scoring system. However, the observation that morbidity scored by the patient was highly influenced by medication prescribed (data not shown) made us decide to use the EORTC/RTOG score only for further analysis. The comparison between the Royal Marsden study and our study is complicated because of this observation. A detailed analysis to determine the role of a patient morbidity questionnaire in comparison with the EORTC/RTOG toxicity score will be the subject of a future report.

The DVH analysis for bladder did show a marked decrease in exposed volume, in favor of the conformal radiotherapy technique (Fig. 3b). The toxicity analysis, however, did not show a statistically significant difference (Fig. 3a). A further DVH analysis for all patients, irrespective of the radiotherapy technique, failed to show any significant correlation between exposed volume and toxicity grade. The urological toxicity is not easily explained by exposed volume as analyzed by the DVH. This observation is identical with the study published by Lebesque *et al.*[24]. Probably, urological toxicity is caused by the radiotherapy effects on the bladder base and urethra, both closely related to the prostate. This might explain a large number of complaints such as urge, frequency, and dysuria in both external beam radiotherapy and interstitial radiotherapy studies [25 and 26].

In two randomized studies [7 and 9], the authors could not find a statistically significant difference in acute toxicity for standard or conformal radiotherapy. The toxicity reduction for gastrointestinal symptoms in our study was found to be significant (Fig. 4a). The relatively frequent prescription of anesthetic suppositories has resulted in a further analysis of the role of anal toxicity. As can be seen in Fig. 5b, there was a marked reduction in anal volume exposed. This corresponds with a significant reduction in acute anal toxicity in favor of the conformal radiotherapy technique ($p < 0.0001$; Fig. 5a). It appears that the reduction in acute gastrointestinal toxicity can be explained by a reduction in anal toxicity and not in rectum/sigmoid toxicity.

The (limited) DVH analysis in the Royal Marsden study [9] revealed an average reduction of 13% in the "high dose volume." Despite this reduction (and a 10-mm margin) no difference in acute toxicity was observed. The volume reduction in the "high dose volume" seems to be identical with the data of our study.

In the analysis of Pollack *et al.* [7] there was no relation between toxicity grade and the volume of rectum and bladder receiving more than 60 Gy. In their study, the margin was 7.5 mm for the posterior direction, to avoid excessive inclusion of rectal volume. Although a reduced exposure would be expected compared to our protocol, especially in the high dose regions, the toxicity reported is almost the same. As the tumor doses given in both studies are different (70 Gy or 78 Gy, and 66 Gy, respectively), it is not easy to draw any conclusions. The comparison might suggest that the high-dose region is not a good indicator for acute toxicity. Another explanation might be that a high dose in a small volume will yield the same acute toxicity as a lower dose in a large volume. An alternative explanation might be a certain threshold volume. As long as a certain volume is exposed to a critical dose, no reduction of toxicity can be expected. This might also explain why we did not find a difference in toxicity, despite a wide range of volumes (DVHs) exposed. At this moment we cannot clarify the mechanism involved.

These observations also raise another question: can a DVH, based on an initial planning CT scan, be used as a predictor for acute and late effects? We realize that not all patients in this study had empty bowels at the time of this scan. This is illustrated by the mean volume and standard deviation for rectum/sigmoid and anus (165 ± 63 cc [1 SD]). It might be that the empty rectum (purged naturally or forced by medication) will give a better average estimate of the treatment position and state of the rectum. Part of our research now is to investigate if the strategy as proposed by Roach and Pickett [27 and 28] (laxative medication before the planning CT scan) can realize a better prediction for the total treatment. On the other hand, it might well be that the mobility of the rectum/sigmoid obscures the actual exposure. Without information about this mobility, the DVH calculated will always be a rough estimate. Our ongoing research aims to clarify these aspects of rectum/sigmoid toxicity.

However, is acute toxicity really important? Although treatment of acute toxicity is not difficult and often effective, the urological and intestinal effects were judged to be troublesome in 30% of the patients. The interaction of acute and late toxicity has long been debated. It was suggested that the target cells for acute and late morbidity were different, having a mucosal and a fibrotic origin, respectively. Recent publications [4 and 29] on animal models suggest, however, that some part of acute damage may be responsible for late damage as well (consequential late damage). In a recent publication [30], this theory seems to hold for patients treated for prostate cancer. Those who had moderate to severe acute toxicity were found to have a 2–3 times higher chance of moderate/severe late toxicity. This observation needs to be confirmed by other studies, but might face us with the need to reduce as much acute toxicity as possible to prevent consequential late toxicity.

More volume reduction seems to be necessary to overcome the wide anatomical variations and to realize a statistical benefit. We realize that the margins used in our study (5 mm for microscopic disease and 10 mm for positioning and CTV mobility) are not very tight. Tighter margins should in the end lead to less toxicity. This requires optimal positioning, but above all understanding, modeling, prediction or control of the CTV mobility, in order not to jeopardize the dose homogeneity of the PTV with a possibly lower chance of tumor control. A first step towards optimization of the radiotherapy technique has been the introduction of static intensity modulated beams as published by Dirkx *et al.* [21]. Continuous research is ongoing to define the minimum margin required, taking into account the positioning errors (systematic and random) and CTV mobility during treatment. The reduced margins found will be used in new studies and compared with the data as presented here. Acute toxicity will again be one of the endpoints analyzed. Meanwhile, we will focus our attention on late toxicity in the patients from this study.

Conclusions

Conformal radiotherapy for prostate carcinoma leads to a statistically significant reduction in acute gastrointestinal toxicity. This was mainly due to a reduction in anal toxicity, which can be explained by the reduction in exposure of the anus. There was, however, no statistically significant reduction in rectum/sigmoid symptoms, nor was a clear correlation between rectum/sigmoid volume exposed and grade of toxicity observed. Despite a statistically significant reduction in bladder volume exposed, there was no significant reduction in toxicity.

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Chapter 6

GASTRO-INTESTINAL AND GENITO-URINARY MORBIDITY AFTER 3D CONFORMAL RADIOTHERAPY OF PROSTATE CANCER: OBSERVATIONS OF A RANDOMIZED TRIAL

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Accepted for publication in Radiation Oncology

Abstract

Purpose:
The late morbidity of a randomized study was analyzed after a follow up of 2 years.
The difference in intestinal morbidity was analyzed as a function of the treatment arm and dose volume parameters. The correlation with acute toxicity and (pre-existing) bowel complaints was investigated.
Methods and materials:
266 T1-4N0M0 prostate cancer patients were randomized for conventional (open fields) and 3D conformal radiotherapy using beams eye view blocked fields with the same dose (66 Gy) and gross target volume-planning target volume margin (15 mm). Apart from the RTOG toxicity scoring system a patient self-assessment questionnaire was used to obtain detailed information on morbidity.
Results:
At 2 years there is only a trend for less rectal toxicity (grade $\geq$ 1) in favor of the conformal radiotherapy (grade 1, 47% versus 40% and grade 2, 10% versus 7% for conventional and conformal radiotherapy respectively ($p=0.1$). A significant relation was found between late rectal toxicity (grade $\geq$ 1) and the volume of the anus and rectum exposed to $\geq$ 90% tumor dose (TD). A highly significant relationship is observed between acute rectum and anal toxicity and late rectal toxicity. The patient self-assessment questionnaire analysis revealed that patients are most bothered by compliance related symptoms like urgency, soiling and fecal loss. In a multivariate analysis all other variables loose significance, when anal volume exposed to $\geq$ 90% TD and pre-treatment defaecation frequency are accounted for. Late anal toxicity is low and related only to acute anal toxicity. Late bladder toxicity is related solely to pre-treatment frequency and overall urological symptoms. The incidence of grade 2 toxicity increases with a factor 2.5-4 when (stool or urine) frequency is unfavorable at the start of treatment.
Conclusions:
Conformal radiotherapy at the dose level of 66 Gy does not significantly decrease the incidence of rectal, anal and bladder toxicity compared to conventional radiotherapy. There is a significant relationship between acute and late toxicity and the anal volume exposed to 90% TD. Intestinal (and urological) symptoms at start have a major impact on late toxicity.

Introduction

In the literature many studies have been published that report on acute and late toxicity in the treatment of prostate cancer. [4,6,9,18,38,41,47] It has been demonstrated that high doses of radiotherapy by Three Dimensional Conformal Radiotherapy (3DCRT) or Intensity Modulated Radiotherapy (IMRT) can be delivered to the planning target volume (PTV) without causing serious toxicity. Dose effect relationships have been published for proctitis/bleeding at doses as low as 46 Gy [14,15,24,40]. Currently dose escalation studies are maturing (RTOG, Royal Marsden / MRC and the Dutch phase III dose escalation study). Only the MD Andersen Hospital (MDAH) study has been published so far indicating that a dose escalation up to 78 Gy is superior to a conventional dose of 70 Gy for the failure free survival (including PSA failures) of intermediate risk patients at the cost of a higher percentage of late morbidity [36]. The optimal dose for both favorable and unfavorable patients is still a subject of debate. Frequently, treatment planning for IMRT is implemented using multiple treatment fields therewith spreading the dose. As indicated by Jackson et al. and Skwarchuk et al. [24,40] normal tissues will be treated to low doses for a relatively high volume. Dose effect relationships for these relatively low doses and large volumes are therefore of particular interest for the dose escalated conformal or IMRT plans. Conformal radiotherapy as a general concept is one way to reduce the volume of normal tissues exposed to the high doses in order to lower the chances of serious late toxicity. Although conventional techniques are thought to be inferior to conformal radiotherapy techniques, the Royal Marsden study [9], the MD Anderson Study [36] and the Rotterdam study [27] are the only clinical studies that deal with this subject in a randomized setting. In a previous report we have demonstrated the beneficial effects of the conformal radiotherapy technique for acute intestinal symptoms [27]. In this paper late toxicity is investigated. The effects related to treatment technique and irradiated volume will be analysed. Also, the data from a patient self-assessment questionnaire and the consequences for late toxicity score will be presented.

Methods and materials

A randomized study was performed in the Erasmus Medical Center / Daniel den Hoed Cancer Center to investigate the possible reduction of toxicity using conformal radiotherapy for prostate carcinoma. The study was approved by the local ethical committee. All patients referred for curative radiotherapy, without evidence (CT scan or bone scan) for lymph node or distant metastases, were asked to participate. After informed consent randomization was performed. In total 266 T1-4 N0M0 prostate carcinoma patients were included. There were no significant differences in patient and tumor characteristics for both study arms [27]. Two patients randomized for conformal radiotherapy were treated with the conventional technique, but were analyzed according to the intention to treat principle.

Radiotherapy protocol

All patients were treated to the conventional dose of 66 Gy tumor dose (TD) in 33 fractions in the ICRU reference point [21]. The planning, treatment technique, linear accelerator and portal imaging procedure were identical. Patients in the conventional treatment arm were treated with rectangular, open fields. Patients in the conformal treatment arm were treated with conformal
(beams eye view [BEV]) shaped treatment fields using the multi leaf collimator (MLC) of the Scanditronix MM50 with a leaf width of 1.25 cm. A three-field technique was used with one anterior and two lateral oblique treatment fields. Patients were treated supine, without special instructions for bladder or bowel filling. For the planning CT scan 5-mm slices with a thickness of 5 mm were contoured. In 6% of the patients the planning target volume (PTV) dose was less than the prescribed ICRU constraints with a minimum of 92.4% TD.

Randomization was performed stratifying for Gross Target Volume (GTV) and not for tumor grade and prostate specific antigen (PSA) level. In T1 tumors the GTV was defined to be the prostate, in all other tumor stages the prostate and seminal vesicles were considered to be the GTV. The delineated GTV was three-dimensionally expanded with 5 millimeters to create a Clinical Target Volume (CTV) and an additional 10 mm to create the Planning Target Volume (PTV) to correct for positioning errors and GTV mobility.
The most caudal part of the prostate was contoured at the pelvic diaphragm. The delineated length of the intestinal structures was limited to the cranial and caudal field borders. As it is not clear which part of the exposed intestine is responsible for the acute and late effects different structures were defined (rectum, sigmoid and anus). The rectum was defined to be the part of the large intestine in close proximity to the sacrum; the ventral part was defined to be the sigmoid. The anus or anal canal was defined as the most caudal 3 cm of the intestine. The total volume of the bladder was contoured. Both bladder and intestinal structures were analyzed including filling.
During treatment regular EPID mega voltage imaging was performed using a set-up correction protocol [5]. With this protocol the systematic positioning inaccuracy could be limited to 2mm +/- 2 mm (SD). Androgen depletion was used in adjuvant setting in 15% of the patients.

Toxicity analysis
Toxicity was scored by the responsible radiation oncologist in the patient charts. From these charts the toxicity grades according to the RTOG guidelines [28] were generated. The SOMA/LENT scores were not scored, as they were not used in our clinic at the time of the start of this protocol. For this study the late urological and intestinal toxicity was followed for a follow up of two years.
Grade 1 was scored for minor symptoms that required no treatment. Grade 2 was scored if these symptoms needed simple outpatient management (not affecting the life style). Grade 3 for distressing symptoms that did affect the life style, necessitating minor surgery, laser treatment, transfusion or a short admission in hospital. Grade 4 and 5 (major surgery, long term hospital admission and death due to a fatal complication) were not observed. This scoring system was used for all organs at risk (bladder, rectum and anus). Complaints related to the anus were graded as grade 1, for itching or pain, and grade 2, when analgesic ointment / suppositories were used to ease them. Rectum grade 2 was scored mainly in case of prescription of corticosteroids and/or anti-diarrhea medications.
Apart from this grading, the patients themselves scored (prospectively) their perceived morbidity using a patient self assessment questionnaire (modified and translated version of Tait and Fransson [16,43] grading their complaints in 4 grades: no, slight, moderate and severe. Questions asked and relevant for this report regard abdominal cramps, loss of faeces or blood, mucus discharge, urgency and staining or soiling, faecal consistency, faecal frequency and urological symptoms like dysuria, haematuria, incontinence and urinary frequency. Overall intestinal symptoms were defined by the maximum score of any of the intestinal items of the patient self-assessment questionnaire. Overall urological symptoms were defined likewise for urological symptoms.

Statistical methods
Primary endpoints for late toxicity were the RTOG grades at 2 years for urological, rectal and anal toxicity. For 32 patients lacking toxicity scores at 2 years, the scores at 1 year were used as endpoint, since no systematic differences were observed between the scores after 1 and 2 years (details not shown).
Dose Volume Histograms (DVH) were calculated for the following volumes: the rectal volume, the anal volume, and the bladder volume, all including the filling. For each of these volumes the fraction exposed to 90% of the tumor dose or more were estimated from the DVH and expressed as a volume percentage (range 0-100%). This was also done for the fractions of the volume exposed to at least 50% and at least 95% of the tumor dose.

Logistic regression analysis was applied to study the relationship between the 2-year toxicity scores and treatment arm, these DVH ≥ 90% exposure measures and other parameters. The analysis was also done with the DVH ≥ 50% and DVH ≥ 95% exposure measures, with similar results because of the very strong correlation between the DVH≥ 50%, ≥ 90% and ≥ 95% exposure measures. Details of the analyses with the DVH ≥ 50% and DVH ≥ 95% measures will not be shown. Since no grade 3 toxicity was observed and the incidence of grade 2 toxicity was very low (less than 10% for all the endpoints) the grade 1 and 2 scores were pooled together for the logistic regression analysis. Other parameters considered in the logistic regression analysis were the grade of acute toxicity and the scores on several symptoms on the patient questionnaire.
The strength of the association of a parameter with the incidence of late toxicity is expressed by the Odds Ratio (OR). For a parameter with more than 2 levels, like a DVH exposure measure with range between 0 and 100%, the OR is the estimated average odds ratio associated with an increase of one unit of the parameter, i.e. for the DVH exposure measures it reflects the OR associated with an increase of one percent. In addition the scores on several symptoms on the patient questionnaire at 2 years, or if not available at 1 year, were compared between both treatment arms and correlated with the RTOG toxicity scores and the scores on several symptoms on the patient questionnaire before the start of radiotherapy.

Results

The actuarial overall survival was 98% at 1 year and 93% at 2 year. The data of 248 out of 266 patients were available for the late toxicity analysis. Eighteen patients were excluded for death (NED) (3), loco regional tumor recurrence (7) and missing data in follow up or missing DVH data (8). As published before [27] prognostic factors were equally divided over both randomization arms. Additional prognostic factors for late toxicity/ morbidity are illustrated in table 1

Table 1
Description of patient characteristics for both randomization arms concerning prognostic factors for late grade ≥ I rectal toxicity

	Conventional	Conformal	*P*-value
Randomization arm	*n* = 125	*n* = 123	
Age, mean (SD)	70.0 (6.4)	69.5 (6.1)	0.51
Pre-treatment symptoms			
Defecation frequency/day, mean (SD)	1.5 (0.8)	1.4 (0.7)	0.87
Overall intestinal symptoms	24%	25%	0.90
Urological frequency/day, mean (SD)	8.2 (2.8)	9.2 (3.6)	0.09
Overall urological symptoms	26%	24%	0.62
Dose volume parameters			
DVH ≥ 90% rectum, mean % (SD)	76.3 (16.3)	71.6 (15.2)	0.01
DVH ≥ 90% anus, mean % (SD)	70.2 (24.9)	24.2 (22.8)	< 0.001
DVH ≥ 90% bladder, mean % (SD)	67.6 (20.5)	48.6 (19.8)	< 0.001
Acute toxicity			
Rectum grade ≥ 1	83%	79%	0.24
Anus grade ≥ 1	37%	19%	0.003
Bladder grade ≥ 1	68%	74%	0.74

Overall intestinal symptoms = maximum score in patient self-assessment questionnaire (graded slight, moderate or severe) for intestinal symptoms like cramps, faecal loss, blood, mucus, urge and staining/soiling. Overall urological symptoms = maximum score in patient self-assessment questionnaire (graded slight, moderate or severe) for urological symptoms like pain, urge, incontinence and blood.

1. Rectum

1.1 Conventional versus conformal radiotherapy technique

At 1 year follow up a statistical reduction for rectal toxicity is found in favor of those patients treated with conformal radiotherapy (32% versus 52% grade <1 [p< 0.001]). At 2 year follow up a trend is observed in favor of the conformal radiotherapy (grade 1 47% versus 40% and grade 2 10% versus 7% for conventional and conformal radiotherapy respectively (p=0.1) There was no grade 3 or higher toxicity in both randomization arms. (table 2)

1.2 Dose Volume Relationship

There is a statistically significant reduction of rectum and anal volume exposed to ≥ 90% tumor dose (TD) (DVH ≥ 90%) in the conformal radiotherapy arm (table 1). In the univariate analysis both the DVH ≥ 90% of the rectum and anus are significantly related to grade ≥ 1 rectal toxicity (respectively p=0.007 and p= 0.001). The observed incidence of rectal grade ≥ 1 increases from 38% (first quartile of anus exposed to ≥ 90% TD) to 65% (last quartile of anus exposed to ≥ 90% TD). The observed incidence of rectal grade ≥ 1 increases from 39% (first quartile of rectum exposed to ≥ 90% TD) to 65% (last quartile of rectum exposed to ≥ 90% TD).

A highly significant relation is observed between acute and late rectal toxicity (p= 0.0008) and acute anus toxicity and late rectal toxicity. (p=0.003). As illustrated in figure 1 at 2 year follow up, late grade 2 rectal toxicity is observed mainly in those patients that had grade 1 and 2 acute (rectal and anal) toxicity. At 2 year follow-up only 45% and 32% of patients, that had acute grade 1 and 2 (rectal and anal) toxicity respectively, reported to have no late rectal toxicity.

Table 2
Toxicity (RTOG and patient self-assessment questionnaire) scores at 2 year follow up for both randomization arms

Late toxicity	Conventional	Conformal	*P*-value
Rectum toxicity			0.10
Grade 1	47%	40%	
Grade > 1	10%	7%	
Anus toxicity			0.59
Grade 1	13%	15%	
Grade > 1	2%	2%	
Bladder			0.84
Grade 1	26%	28%	
Grade > 1	11%	9%	
Overall intestinal symptom			0.07
Slight	50%	40%	
Moderate/severe	16%/0%	11%/2%	
Defecation frequency/day	2.1 (1.2)	2.4 (1.7)	0.71
Urological frequency/day	8.3 (3.4)	8.2 (3.5)	0.75

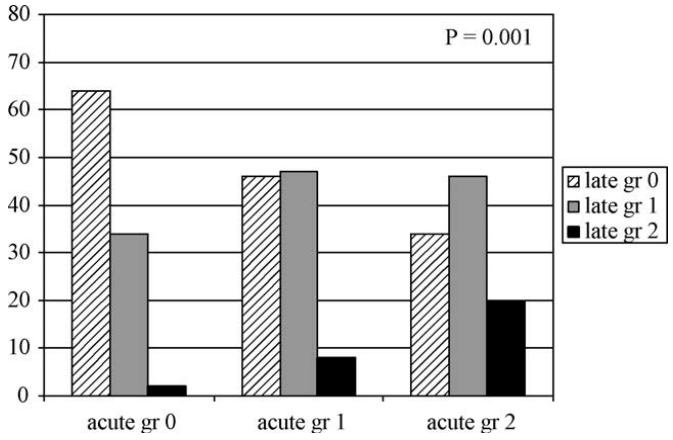

Fig. 1. Relation of acute (rectal + anal) and late rectal toxicity observed at 2 years of follow up. Grade 0, 1 and 2 late toxicity for patient groups with no acute toxicity ($n=47$), acute grade 1 toxicity ($n=157$) and acute grade 2 toxicity ($n=41$).

Table 3
Percentage of patients reporting intestinal symptoms in a patient self-assessment questionnaire. Pre-treatment symptoms and late intestinal symptoms

	Cramps (%)	Faec. loss (%)	Mucus (%)	Urge (%)	Soiling (%)	Blood (%)	Overall (%)
Pretreatment ($n=241$)							
Severe	0	0	0	0	0	0	0
Moderate	2	0	0	1	0	0	3
Slight	11	3	3	11	8	1	22
2 Year ($n=128$)							
Severe	0	0	1	0	2	0	2
Moderate	5	5	3	2	3	5	12
Slight	9	21	20	14	28	14	43

Overall intestinal symptom score = maximum of cramps, faecal loss, mucus discharge, urgency, soiling and bleeding.

1.3. Patient self assessment questionnaire analysis

In table 3 the patient self-assessment questionnaire symptoms before the start of treatment are illustrated. Twenty five percent of patients had pre treatment intestinal symptoms, mainly consisting of cramps, urge, soiling, faecal loss, mucus and bleeding (in order of appearance). In a sub analysis the relation of pre-existing intestinal symptoms and toxicity (acute and late) were studied. The incidence of acute and late intestinal symptoms (figure 2) is illustrated for those patients having **no** complaints at start compared to patients having some degree **(yes)** of intestinal symptoms. A highly significant difference is observed for acute ($p<0.002$) and late intestinal symptoms ($p=0.005$) in favor of those patients starting off with no complaints. The main difference in late intestinal symptoms is the high percentage of moderate to severe symptoms scored, 20% and 5% respectively, for patients with symptoms at start, compared to 8% and 0% for patients without symptoms at start. There is a trend for a better overall intestinal score for the conformal treatment technique ($p=0.07$ table 2). In the patient self-assessment questionnaire, 84-87% of the patients reported no or slight overall intestinal symptoms (maximum of all different intestinal items scored) at 2 years of follow up. (table 3). Two percent of the patients reported severe intestinal symptoms. Soiling, faecal loss and mucus discharge (compliance related symptoms) bothered the patients most (up to 29% slight problems and 5% moderate to severe problems). Blood loss, urge and bowel cramps (proctitis related symptoms) were less dominant (7-14% slight problems and 2-5% moderate and severe problems) (table 3). There is a highly significant relation for the questionnaire items and the RTOG toxicity score at 2 year follow up
($p< 0.0001$ for mucus, defaecation frequency and overall intestinal score;
$p< 0.001$ for bleeding, need to rest and tiredness; $p< 0.01$ for urge, faecal consistency and urinary frequency)

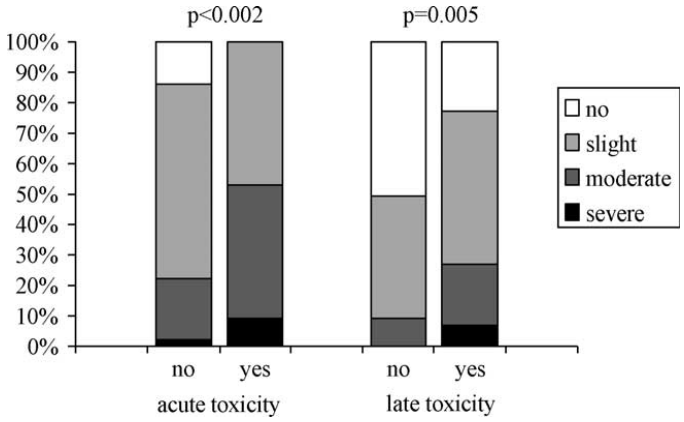

Fig. 2. Percentage of patients reporting acute and late (overall intestinal) symptoms in a patient self-assessment questionnaire in relation to pre treatment (overall intestinal) symptoms. Overall intestinal symptoms: cramps, faecal loss, mucus discharge, urgency soiling and bleeding (no = no intestinal symptoms at start of radiotherapy, yes = any symptom at start of radiotherapy).

1.4. Multivariate analysis

In a multivariate analysis all other variables fail to have a significant influence when the anal volume exposed to ≥ 90% TD ($p=0.008$), pre treatment defecation frequency ($p=0.0004$) and the rectal volume exposed to ≥ 90% TD ($p=0.1$) is accounted

Table 4
Univariate and multivariate analysis for prognostic factors for late grade ≥ I rectal toxicity

Univariate analysis	Odds ratio	95% Conf. limits	*P*-value
Randomization arm	0.66	0.40–1.08	0.1
Pre-treatment symptoms			
Defecation frequency/day	2.18	1.42–3.34	<0.0001
Overall intestinal symptoms	1.68	1.04–2.71	0.03
Dose volume parameters			
DVH ≥ 90% rectum	1.02	1.006–1.039	0.007
DVH ≥ 90% anus	1.01	1.005–1.020	0.001
Acute toxicity			
Rectum	1.82	1.18–2.84	0.006
Anus	1.63	1.09–2.43	0.01
Multivariate analysis			
DVH ≥ 90% rectum	1.015	0.997–1.033	0.10
DVH ≥ 90% anus	1.012	1.00–1.02	0.008
Defecation frequency/day	2.22	1.42–3.44	0.0004

Multivariate analysis: when corrected for anal DVH ≥ 90% TD, rectal DVH ≥ 90% TD and pre-treatment defaecation frequency all other factors loose significance ($P \geq 0.1$).

for (table 4). In figure 3a and 3b the fitted probability of late rectum grade ≥ I toxicity (univariate logistic regression analysis) is illustrated for both the DVH ≥ 90% of the anus and rectum.

In table 5 the observed rectal toxicity is presented for defecation frequency (and overall intestinal symptom score). For patients with a pre treatment frequency of more than once daily the incidence of late grade 2 toxicity increases from 4% to 16% ($p < 0.0001$).

2. Anus

For the reported anal toxicity no significant difference was found between the treatment arms. ($p = 0.59$ table 2) The incidence of grade 1 toxicity (itching and pain) was 13.8% while the incidence of grade 2 toxicity (analgesic ointment or suppositories) was 1.6%.

In a logistic regression analysis pre treatment symptoms, dose volume parameters and acute toxicity were studied for a possible relationship with late anal toxicity. With the exception of acute toxicity no other prognostic factor reached significance (minimum p-value 0.1). Those patients having grade 2 acute toxicity (n=27) have 36% grade ≥ 1 late toxicity, compared to 14 % for those with acute grade ≤ 1 ($p=0.02$). There is no statistical significant relation between anal volume exposed to ≥ 90% TD and anal toxicity grade ≥ I ($p=0.6$).

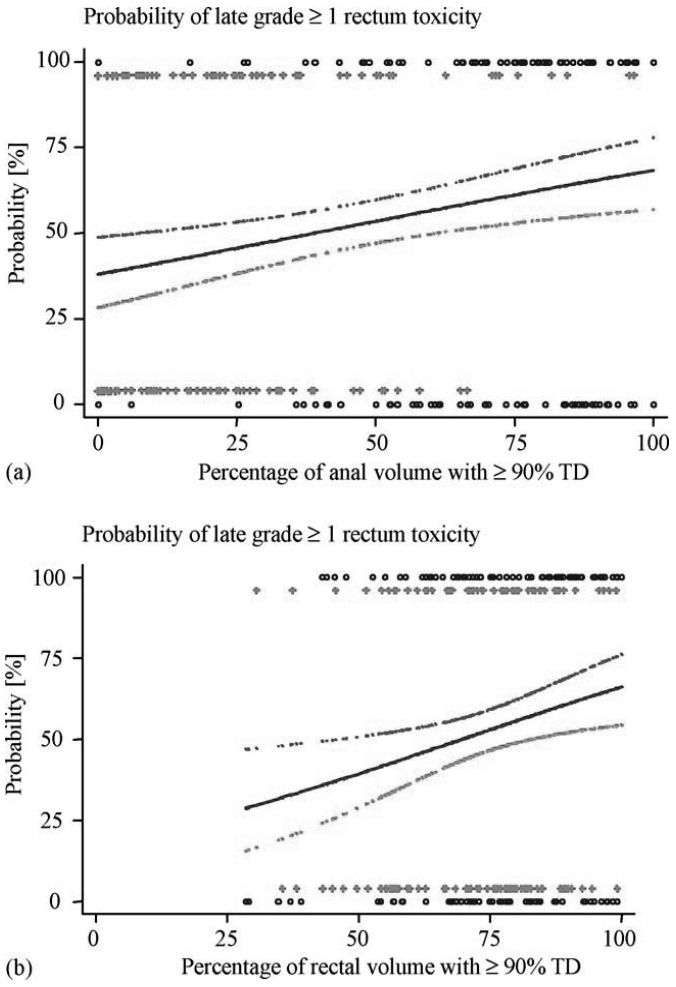

Fig. 3. Probability of late rectum toxicity grade≥I (univariate logistic regression analysis), with the 95% confidence region, for anal volume exposed to≥90% of tumor dose (a) and rectal volume exposed to≥90% of tumor dose (b). Points at the bottom indicate patients without late toxicity, while points at the top indicate patients with late toxicity. O, patients with conventional RT; +, patients with conformal RT.

3. Bladder

For bladder toxicity there was no statistical significant difference between the treatment arms. After 2 years of follow up 26% and 28% grade 1 and 11% and 9% grade >I was observed for the conventional and conformal radiotherapy technique respectively ($p=0.84$; table 2).

In the logistic regression analysis pre treatment symptoms, dose volume parameters and acute toxicity were tested for a relationship with late bladder / urological toxicity. The relationship between acute and late bladder toxicity was non-significant ($p=0.6$). The DVH ≥ 90% of the bladder was not related to late urological toxicity ($p=0.33$). Late urological toxicity was significantly influenced by the urological symptoms at start of treatment and the urological frequency (table 5)

Discussion

With the clinical introduction of conformal radiotherapy a randomized toxicity study was started. A statistical significant advantage with less acute intestinal toxicity was observed for the conformal radiotherapy technique as opposed to the conventional technique [27].

In this analysis, concerning late morbidity, we focus mainly on the intestinal toxicity. Bladder toxicity was analyzed, but no statistical significant difference was observed between the radiation techniques. Also no relation was found for dose and volume and late bladder toxicity. Late urological toxicity is mainly influenced by urological symptoms and/or frequency before the start of treatment (table 5).

Table 5
Relation of pre-existing symptoms and late rectal and urological toxicity, grade ≥ I and grade > I, at 2 year follow up

		Late grade ≥ 1 (late grade ≥ 2)	Significance
Overall intestinal questionnaire score			
No complaints	$n=179$	49% (6%)	$P=0.03$ #
Complaints	$n=59$	64% (13%)	
Stool frequency			
≤ Once daily	$n=158$	44% (4%)	$P<0.0001$
> Once daily	$n=80$	61% (16%)	
Overall urologic questionnaire score			
No complaints	$n=175$	31% (7%)	$P=0.002$
Complaints	$n=59$	54% (21%)	
Urinary frequency			
≤8/24 h	$n=127$	27% (7%)	$P<0.0004$
>8/24 h	$n=102$	51% (16%)	

No complaints at start versus any complaint (slight, moderate and severe) at start #=significant in univariate, but not significant in multivariate analysis. Overall intestinal questionnaire score=maximum score in patient self-assessment questionnaire for intestinal symptoms like cramps, faecal loss, blood, mucus, urge and staining/soiling. Overall urologic questionnaire score=maximum score in patient self-assessment questionnaire for urological symptoms like pain, urge, incontinence and blood.

The reported anal toxicity was low (grade 1 11%; grade 2 toxicity 1% at 2 year follow-up) with no difference between the treatment arms. There was no significant relationship between dose/volume and late anal toxicity either. Of interest anal toxicity is not related to anal or rectal volume exposed to ≥ 90% TD.

Although a statistical significant reduction for rectal toxicity was found at 1 year of follow up, in favor of conformal radiotherapy (32% vs. 52% grade<1, ($p<0.001$)), at 2 years of follow up, this difference disappeared (grade <1 43% vs. 53%, p=0.10). When one focuses to the intestinal toxicity the results in the Rotterdam series are quit similar with the Royal Marsden Hospital [9] data estimated at 2 year follow up, when expressed in RTOG toxicity grades for "worst rectal toxic effects" (40% vs. 59% grade <1). In the Royal Marsden study the most common bowel side effect was proctitis, appearing as rectal bleeding (bleeding in 51% vs. 34% for conventional and conformal radiotherapy respectively [p=0.009]). According to the patient self-assessment questionnaire, patients seldom report bleeding in our study. At 2 years of follow up 5% of patients complain of moderate to severe bleeding. Another 14% report slight rectal bleeding (total 19%). Moreover one should realize that bleeding, as stated by the patient, might include bleeding from hemorrhoids, so the percentage of actual proctitis bleeding might be overestimated. A possible explanations for the different observations for bleeding of the two studies might be the differences in radiotherapy technique or the use of androgen deprivation [37].

In the Rotterdam study the anal volume exposed was found to be a major predictive dose volume (DVH) factor for late rectal toxicity grade ≥ 1.The DVH ≥ 90% of the rectum, highly significant in the univariate analysis (p=0.007), becomes marginally significant related with rectal toxicity when the DVH ≥ 90% of the anus and the pre treatment defecation frequency is accounted for (p=0.1; table 4). The importance of relatively low doses in this report (the DVH ≥ 90% TD; 59.4 Gy) was observed in other studies as well [14,24,40]. A large volume of rectum (and/or anal canal) exposed to an intermediate dose (46, 57 or 59.4Gy) results in a high percentage of intestinal toxicity.
Both the rectum and anus volumes (DVH ≥ 90%) were found to be significantly related to late rectum toxicity (table 4). In figure 3a/3b the probability of late rectal toxicity and the percentage of anal volume and rectal exposed to ≥ 90% TD is graphically depicted. From this figure one can appreciate, that patients treated conformally have a tendency for less exposure. Due to anatomical variance there is, however, a wide spread and overlap with those patients treated with the conventional technique. As such there is no significant difference in late rectal toxicity for both randomization arms.

One explanation for the relation of anal exposure and rectal toxicity is the close anatomical relation of the caudal part of the rectum and the prostate. The cranial part of the rectum is less tightly fixed, mobile and maybe more voluminous. The more fixed caudal part of the rectum or anus will as a consequence be exposed to higher doses and to a substantial volume or part of the circumference. Another possible explanation can be found in the nature of late intestinal toxicity: 1. toxicity related to proctitis (mucus and blood) and 2. toxicity related to compliance (urgency, soiling, fecal loss and cramps). Especially the latter toxicity group is predominant and will dominate the intestinal/rectal grade to ≥ I toxicity. These complaints are most likely the consequence of the diminished compliance of the most distal part of the rectum (by definition called anus in this report). So the reduced anal exposure may explain the reduction in rectal complaints, mainly through the reduction of compliance related symptoms. This last possibility is amplified through the reduction of acute toxicity, as a consequence of the reduced exposure of the anal region by the conformal technique (table 1). In this study acute (anal and rectal) toxicity is related to late intestinal toxicity. This is an important difference between the Rotterdam study and the Royal Marsden study [9]. Other studies [7,24,33,38,41] have also observed the relationship of late and acute toxicity. One possible explanation is the so-called "consequential late damage theory" [10,12,22,33,46]. Some levels of acute toxicity seem to cause inflammation, leakage of intestinal content etc and finally lead to fibrosis, which, probably together with the actual late damage, present as late morbidity. Efforts to reduce the influences of acute damage might thus be of greater importance than just preventing the acute symptoms of the treatment. Intensity modulation will be the next step in further improving the results. In fact the data from the Memorial Sloan Kettering Cancer Center [48] show that this radiotherapy technique reduces the toxicity (10% grade 2/3 for 3DCRT and 2% for IMRT) while giving a tumor dose of 86,4 Gy.

In some studies measures other than radiotherapy technique have been unsuccessfully studied to diminish the consequences of acute damage [20,26,31,34]. The possible radio protective effect of sucralfate on rectal toxicity was not observed in histopathological research and clinical outcome [33, 22]. Only in a limited study, misoprostol seemed to protect for acute and late toxicity. [25]. There may also be other important prognostic factors as well like diabetes [24,40,47], a lower surviving fraction (SF2) [3] and ataxia-teleangiectasia [17,23], but also smoking habits [13] or confounding factors (intercurrent diseases e.g. abdominal surgery and medication) [1] can further complicate the picture.

The clinician assessment results might have been more precise if the symptoms were scored prospectively using a pre determined CRF system. For more toxicity details the data from the Patient self-assessment questionnaire were quite informative. For those patients that start with intestinal symptoms before treatment 23% will have no late toxicity and 25% report moderate to severe intestinal symptoms. In patients without complaints at start 51% report no late toxicity and only 8% moderate symptoms (p=0.005). O'Brien et al [33], Yeoh et al and Vordermark et al [44,46] report likewise: patients with deviations in bowel activities, squeeze and basal anal pressure were reported to have a higher chance of incontinence after radiotherapy. In fact, up to 20% of all people (including our prostate patients) are bothered by a so-called irritable bowel syndrome. [2,19,29,30]. Compliance related symptoms increase with age [35] (e.g. soiling in 18% in the age group of 70-79 years of age). In our material 25% of patients start off with intestinal symptoms.

One can also take from these self-assessment questionnaire data that patients are bothered most by soiling and faecal loss. Only a minority of patients is bothered severely by intestinal symptoms. In this study (table 3) 85% of patients report no or slight intestinal problems. Bleeding is, for example, in the eyes of the patients, not the most disturbing symptom. There is no doubt, that using the conventional radiotherapy technique at a dose level of eg. 78 Gy, would lead to a high percentage of moderate to severe toxicity. One would suspect that better treatment techniques and higher doses would change the conclusions of this report. In our succeeding dose escalation study (phase III randomized; 68 Gy vs. 78 Gy tumor dose, a cooperation of the Erasmus MC, Rotterdam and the Netherlands Cancer Institute /

Antoni van Leeuwenhoek Hospital, Amsterdam) using a conformal radiotherapy technique in both treatment arms, with tighter margins [11,42], there is only a trend for more toxicity in the high dose treatment arm. Only bleeding requiring laser treatment or transfusion was found to be significantly higher in the 78 Gy arm. Both proctitis and compliance related symptoms rise with dose and are equally frequent observed (personal communication). In the MD Anderson dose escalation study [32] moderate to severe changes in bowel movement rise from 10% to 34% and urgency from 18% to 37% for 70 and 78 Gy respectively. Bleeding was uncommon, occurring 7% once a week and 4% daily. Both Crook [8] and Denham [10] confirm this observation. Denham states: "the assessment of the incidence of bleeding (alone) underestimates the impact of late rectal morbidity". In the article of Vordermark [45] the importance of impaired faecal continence is further illustrated, as it is correlated to increased fatigue scores. Many late toxicity reports focus however on the (severe) bleeding percentage. Patient questionnaires focus our attention to other symptoms as well that are as frequent as bleeding. These symptoms may bother them even more, but are not well translated in the formal toxicity scales. Although the patient self-assessment questionnaire scores might be considered to be the "golden standard" one should realize that these scores are influenced by the measures taken by the physician as a response on the complaints mentioned by the patients. On the other hand the opinion of the physician might be different from the patients. [39] This does suggest that both scoring systems should be integrated to get a full perception of the actual toxicity. In our dose escalation study an integrated approach using the data of the formal score and patient self-assessment questionnaire is used and studied. A future analysis combining the data of the presented (toxicity study) and the maturing (phase III dose escalation) study will be done to refine the predicted (dose) volume effect relationship.

Conclusions

Conformal radiotherapy at the dose level of 66 Gy does not significantly decrease the incidence of rectal, anal and bladder toxicity compared to conventional radiotherapy technique. The exposure of the anal region (defined to be the most caudal 3-cm of the rectum) was found to be of relevance for developing late toxicity. Those patients with a relative large proportion of the anal region treated with doses of 59,4 Gy and higher were found to have more moderate to severe late intestinal toxicity. Late intestinal toxicity was found to be more prevalent in those patients that had more acute toxicity. Patient self-assessment questionnaire analysis revealed that patients are most bothered at this dose level by complaints concerning compliance (cramps, urge, soiling and faecal loss)and not so much by proctitis (mucus discharge and bleeding). Patients with intestinal symptoms at the start of treatment will experience significant worse acute and late toxicity. The incidence of serious toxicity (grade > 1) is increased with a factor 2-4 for patients with pre treatment intestinal / urinary symptoms or a stool frequency more than once daily or a urinary frequency of more than 8 daily.

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Chapter 7

IMPACT OF VOLUME AND LOCATION OF IRRADIATED RECTUM WALL ON RECTAL BLOOD LOSS AFTER RADIOTHERAPY OF PROSTATE CANCER

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Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 4, pp. 1072–1082, 2004

Abstract

Purpose
To identify dose–volume parameters related to late rectal bleeding after radiotherapy for prostate cancer.
Materials and methods
Clinical complication data from a randomized trial were collected and linked to the individual dose–volume data. In this trial, patients with prostate cancer were treated with either conventional (with rectangular fields) or three-dimensional conformal radiotherapy to a dose of 66 Gy. Patient complaints, including rectal blood loss, were collected for 199 patients, using questionnaires. Absolute and relative dose–volume histograms (DVHs) of the rectal wall (with and without the anal region) were calculated with and without rectal filling. A proportional hazard regression (PHR) model was applied to estimate the probability of any rectal blood loss within 3 years, as a function of several DVH parameters. In a multivariable analysis, dose–volume parameters were tested together with patient- and treatment-related parameters (age, smoking, diabetes, cardiovascular disease, tumor stage, neo-adjuvant androgen deprivation, conformal vs. conventional and rectal bleeding during treatment).
Results
The estimated incidence of any and moderate/severe rectal bleeding at 3 years was 33% and 8%, respectively. Differences between the conventional and conformal technique were small and not significant. The analysis of relative DVHs of the rectal wall (with and without the anal region), showed significant ($p < 0.01$) relations between the irradiated volume and the probability of rectal blood loss within 3 years for dose levels between 25 Gy and 60 Gy. This relationship was shown in subgroups defined by dose–volume cutoff points as well as in the PHR model, in which a continuously rising risk was seen with increasing volumes. For absolute DVHs and DVHs of the rectum including filling, less or no significant results were observed. The most significant volume-effect relation ($p = 0.002$) was found at 60 Gy for the rectum wall excluding the anal region. The probability of rectal bleeding increased from 10% to 63% when the irradiated rectum volume at 60 Gy increased from 25% to 100%. Other factors, including age, smoking, diabetes, cardiovascular disease, tumor stage, neo-adjuvant androgen deprivation, conformal vs. conventional, rectal bleeding during treatment, rectum length. and whole rectum volume. did not have a significant effect in the multivariable analysis. When controlling for the volumes at 60 Gy, the volumes at lower dose levels (25–55 Gy) were no longer significant ($p = 0.5$).
Conclusions
For any rectal bleeding within 3 years, an overall incidence of 33% was observed for patients treated to 66 Gy. For this endpoint, a volume-effect relation was found for DVH parameters of the relative rectal wall volume. This relationship appeared to be most significant for the rectum without the anal region and for the higher dose levels (50–60 Gy).

Acknowledgements
We thank W. van Putten and P. Hoynck van Papendrecht for their statistical and data management support.

Introduction

In recent years, intensity-modulated radiotherapy (IMRT) and dose escalation have been introduced in the treatment of prostate cancer. Retrospective and prospective cohort studies have shown these concepts to be possible [1, 2, 3 and 4]. With IMRT techniques, doses up to 86.4 Gy are proven to be feasible [3]. In a randomized study [5], the tumor control was found to be higher with doses of 78 Gy compared with 70 Gy.

On the basis of literature recommendations [6 and 7] and local clinical experience [8, 9 and 10], dose–volume constraints have been used to guide the optimization process of IMRT planning. In general, these techniques aim to control the volume exposed to high doses to limit serious late toxicity. Recent publications indicated, however, that doses in the range of 35–57 Gy might be at least equally important [4, 11, 12 and 13]. Therefore, a better understanding of the relationships between complications and dose–volume parameters over the whole dose range, including other prognostic factors, might help us in the optimization of IMRT techniques.

In most studies, these late complications are being scored using a composite score, such as the Radiation Therapy Oncology Group (RTOG) and Late Effect Normal Tissues (LENT)/SOMA (Subjective, Objective, Management, and Analytic) score. In these scoring systems, compliance-related symptoms (such as stool frequency) and proctitis-related symptoms (such as rectal bleeding) are combined to one overall score. The use of such an overall score might obscure the relation between dose–volume parameters and complications; therefore, it is probably better to study the subitems of the composite score, such as rectal bleeding in relation to the dose–volume parameters. For this analysis, the data on rectal bleeding as reported in a patient questionnaire were used.

Therefore, the main objective of this study was to evaluate in detail the relation between rectal bleeding and rectal dose–volume parameters together with other possible prognostic factors. Rectal dose volume parameters will be evaluated, including and excluding bowel content and anal part of the rectum.

Patients and methods

The patients for this study were taken from a Phase III randomized toxicity study comparing conventional radiotherapy and conformal radiotherapy. In total, 265 T1-4 N0M0 prostate carcinoma patients were included in this trial between 1994 and 1996. There were no significant differences in patient and tumor characteristics (Table 1) for both study arms [8].

Table 1. Patient and treatment data

		Total group (n = 199)
Age: mean (SD), year	70	6.2
Tumor stage		
T1	25	13%
T2	99	50%
T3	69	35%
T4	6	3%
Neo-adjuvant hormonal therapy		
Yes	34	17%
No	165	83%
Radiotherapy technique		
Conventional	99	50%
Conformal	100	50%

After informed consent, randomization was performed stratifying for gross target volume (GTV) definition and not for tumor grade or prostate-specific antigen level. For T1 tumors, the GTV was defined to be the prostate. For the other tumor stages, prostate and seminal vesicles were considered to be the GTV. Patients were treated in the supine position without special instructions for bladder or bowel filling. A conventional dose of 66 Gy was applied in both study arms.

Planning procedure/treatment

All patients were treated to a dose of 66 Gy in the International Commission on Radiation Units and Measurements reference point in 33 daily fractions [9, 10 and 11]. The GTV was expanded in three dimensions with 5 mm to create a clinical target volume. The clinical target volume was further expanded with 10 mm to create the planning target volume to take positioning errors and GTV mobility into account. The planning, treatment technique, linear accelerator, and portal imaging procedure were identical for both treatment arms of the trial. Patients in the conventional treatment arm were treated with rectangular, open fields. Patients in the conformal treatment arm were treated with conformally shaped treatment fields using a multileaf collimator. A three-field technique was used with one anterior and two lateral (oblique) treatment fields. During treatment, regular megavoltage imaging was performed, including a setup verification and correction protocol [12]. Because of this protocol, the systematic positioning inaccuracy could be limited to 2 mm (1 standard deviation).

The outer wall of the bowel was delineated from (and included) the anal region to the level of the inferior border of the sacroiliac joints. From this delineation, different intestinal structures were extracted—namely rectum, sigmoid, and anal region. The anal region was defined, more or less arbitrarily, as the most caudal 3 cm. The rectum, which excluded the anal region, was defined cranially as long as it had a close relation to the sacrum. The position where the bowel moved ventrally away from the sacrum was defined to be the sigmoid. We analyzed rectal bleeding as a function of dose–volume histogram (DVH) parameters of the rectum (without the anal region) of the rectum including the anal region and of the anal region alone for two reasons. First, because of the arbitrary cutoff level of 3 cm, and second, because it is, *a priori*, not evident from which region rectal bleeding, as reported by patients, is originating.

The contouring protocol resulted from a study on the delineation accuracy of prostate and organs at risk within the context of a randomized trial [13]. The inner bowel wall was estimated from the delineated outer wall surface using the methodology of Meijer *et al.* [14] and taking a rectal wall area in each perpendicular slice of 2.1 cm^2. Consequently, we were able to calculate DVHs for the rectum and anus with and without filling (walls). The length of the rectum was defined as the length along the central axis of the rectum. It was calculated by summing the lengths of the vectors between the centers of the delineated contours. Dose volume histograms were calculated for the rectum excluding and including the anal region and for the anal region. For all three structures, we calculated DVHs with (if present) and without filling and in relative and absolute volumes. Thus, we obtained in total 12 data sets.

Clinical endpoint

Some aspects of acute and late intestinal toxicity have been reported. Acute intestinal toxicity was reduced in the conformal treatment arm in this trial because of a reduction in anal exposure and, consequently, anal toxicity [8]. For RTOG Grade 2 [15] (scored prospectively defined by the clinician) late intestinal toxicity, a trend for less toxicity was observed in favor of the conformal technique mainly because of a reduction of compliance related symptoms [submitted for publication]. In this study, late (more than 180 days after radiotherapy) rectal bleeding as reported by the patients was the clinical endpoint. The information on this bleeding was taken from patient questionnaires. The patients themselves filled in these questionnaires at regular hospital visits to evaluate their perceived morbidity. The patients scored their complaints in four grades: no, some, moderate, and severe. One of these questions, "rectal blood loss" was used in this study. For 199 patients (Table 1), patient self-assessment questionnaires up to 3 years of follow-up (range 1–3 years) were available for analysis. For 1 patient, the acute morbidity data were missing.

Statistics

The Kaplan-Meier method was used to estimate the incidence of reported bleeding (any and moderate/severe) at 1, 2, and 3 years of follow-up for all groups of patients in this study.

We calculated average DVHs and the standard deviation at each dose level of different patient groups (i.e., conformal vs. conventional and bleeders vs. nonbleeders). To test if the differences between the average DVHs were significant, we evaluated the area under the DVH curve (AUCs) as the parameter, using the unpaired *t* test assuming equal variances of the AUCs. This AUC is mathematically equal to the mean dose [23].

In a number of published studies on rectal bleeding [4, 16, 17, 18 and 19], significant volume effects were found at various dose levels in the DVH. Therefore, for a number of dose levels in the DVH, the rectal volumes were divided into two groups using different volumes as cutoff level. Only cutoff points were used, which resulted in subgroups of at least 30 patients. For each subgroup, the incidence at 3 years was calculated (Kaplan-Meier). A series of these cutoff points was tested on their ability to discriminate between high and low risk for developing rectal bleeding, using log–rank statistics. Each cutoff point with a p value < 0.01 (log–rank) was considered significant. A proportional hazard regression (PHR) model was applied to estimate the probability of rectal blood loss within 3 years as a function of the percentage rectal wall at least irradiated to a certain dose level. Because of the large time intervals between the different moments of follow-up, an interval-censoring method was used, as described by Collett [20]. We used the SAS package (SAS, release 8.1; Cary, NC) to fit the complication probability C(t, V):

$$C(t, V) = 1 - \exp[-H_0(t) \times d \exp(\beta V)]$$

where $H_0(t)$ is the cumulative hazard at the time t, β is the regression coefficient, and V the percentage of rectal wall volume at least irradiated to a certain dose level.

In this study, we report the results at the time point of 3 years. To test whether other published [4, 16, 17, 18 and 19] patient- or treatment-related factors had a significant impact on bleeding, these factors were also tested in a similar univariable PHR model. To investigate the effect of a number of variables in a multivariable analysis, we added additional terms to X in the argument of the second exponent of Eq. 1.

Results

Intestinal complications

For the 199 patients in this study, intestinal toxicity Grade 2, according to the RTOG scoring system, occurred for 6%, 12%, and 10% of the patients at 1, 2, and 3 years of follow-up, respectively. For the cumulative incidences, these figures were 6%, 13%, and 16%, respectively. During the follow-up period of the study, no laser treatments or blood transfusions were given for the treatment of rectal blood loss. In the patient self-assessment questionnaires, no patients reported blood loss before the start of radiotherapy, whereas 34% of the patients mentioned blood loss during radiotherapy. At 1, 2, and 3 years of

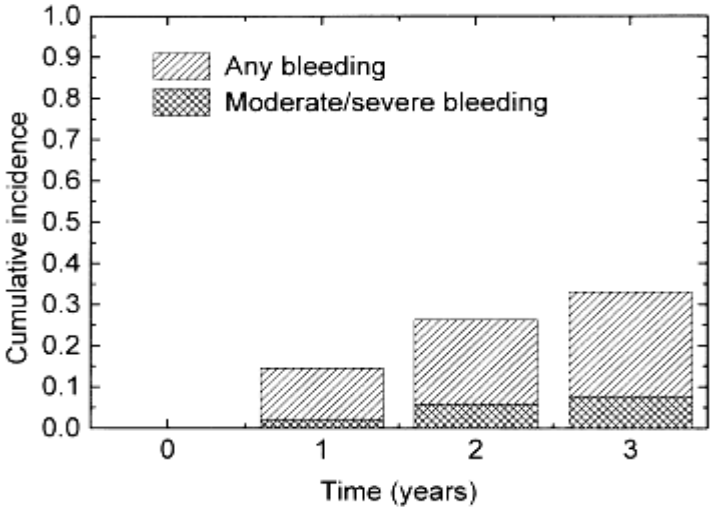


Fig. 1. The cumulative incidence of any and moderate/severe rectal bleeding at 1, 2, and 3 years of follow-up.

follow-up, the (any) blood loss incidences were 16%, 19%, and 19%, respectively. The cumulative incidences were 16%, 26%, and 33% at 1, 2, and 3 years of follow-up, respectively (Fig. 1).For moderate/severe blood loss, these figures were much lower (Fig. 1). For the conventionally and conformally treated patients, the incidences were not different (p = 0.5) at all follow-up periods. The cumulative incidences at 1, 2, and 3 years were 17%, 29%, and 32%, respectively, for the conventional group, and 12%, 23%, and 34% for the conformal group.

Dose and volume parameters

The distribution of the wall volumes and volumes, including filling of the rectum without the anal region, showed a wide variation (Fig. 2). The wall volume varied between 12.6 and 44 cm^3, with an average of 27.1 cm^3. This volume was strongly correlated (r = 0.81) with the length of the defined rectum (Fig. 2a). The volume including filling varied between 18.1 and 273 cm^3. Because of the variation in filling, the correlation between this rectum volume and length was poor (r = 0.30, Fig. 2b). Similar correlations were found for the rectum including the anal region.

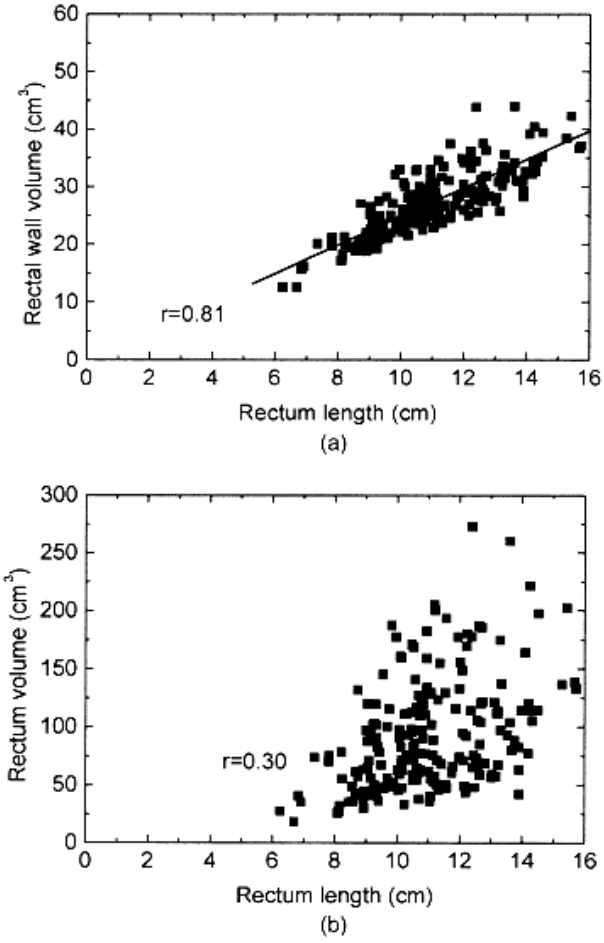


Fig. 2. Relation between rectum length (without anal region) and rectal wall volume (a) and rectum including filling (b).

The average relative DVHs of the rectum wall including the anal region for the conventionally and conformally treated patients showed lower volumes at each dose level for the conformally treated patients (Fig. 3a). The difference of the average DVHs was evaluated by the AUC, which is equal to the mean dose. Using this AUC, the difference (4.1 Gy) with a standard error (SE) of 0.8 Gy was statistically highly significant (p < 0.001). In accordance with earlier results for all randomized patients [8], this difference was mainly caused by differences (14.9 Gy, SE 1.2 Gy) of the DVHs in the anal region (p < 0.001, Fig. 3c); the DVHs of the rectum excluding the anal region (Fig. 3b) were not significantly (p = 0.09) different (1.6 Gy, SE 0.9 Gy).

Prognostic factors for late rectal blood loss (univariable analysis)

Patient- and treatment-related factors

First, we tested in a univariable PHR analysis the association of age, diabetes, cardiovascular disease, and tumor stage with the studied clinical outcome (any bleeding). No association was found (p ≥0.1). Treatment-related items (neoadjuvant androgen deprivation, conformal vs. conventional, length of rectal canal, rectal wall volume, and rectum volume including filling [all with and without the anal region]) were also tested and no associations were found. Only for the presence of rectal bleeding during the treatment (p = 0.06) and smoking (p = 0.08), some suggestion was found for an association with rectal blood loss, indicating less rectal bleeding for patients without rectal bleeding during treatment and for smokers. Of the nonsmokers (n = 145), 37% reported rectal blood loss, whereas only 14% of the smokers (n = 51) mentioned blood loss at 3 years of follow-up (cumulative incidences as estimated with the Kaplan-Meier method). Of the patients without bleeding during treatment (n = 131), 32% reported rectal blood loss during follow-up vs. 36% for patients with bleeding during treatment

(n = 67). The small difference of 4% between these subgroups at 3 years was more evident at 1 and 2 years, where the cumulative incidences of late rectal bleeding was 10% vs. 22% (1 year) and 21% vs. 36% (2 years), respectively.

Dose–volume parameters

To investigate the relation between dose–volume parameters and rectal bleeding, we first compared average relative DVHs of bleeders and nonbleeders (Fig. 3). We chose here to look at relative DVHs, because the relative DVHs correlated better with rectal bleeding than with absolute DVHs (see the following section).

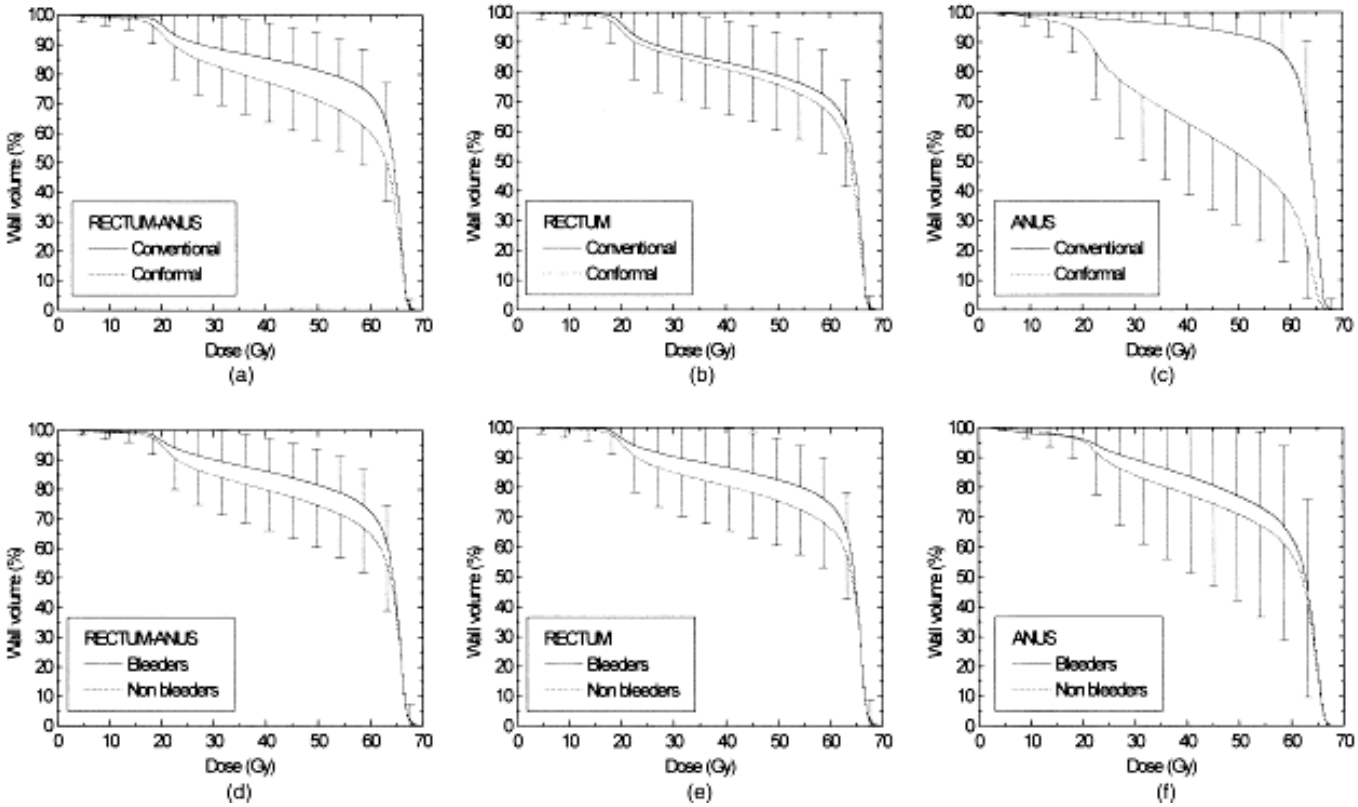
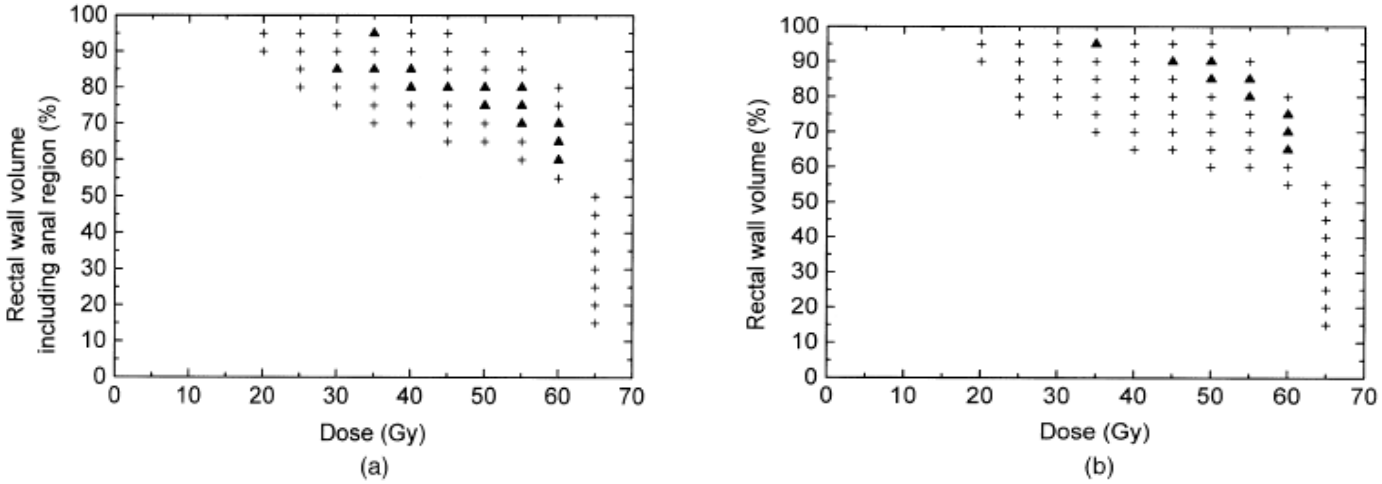


Fig. 3. Average relative dose–volume histograms of rectum including the anus, rectum without the anal region and the anus, for conventional and conformal treated patients, and for bleeders and non-bleeders. The error bars represent the standard deviations at each dose level

The average DVH of the wall structures of the bleeders was compared with the average DVH of the nonbleeders (Figs 3d, 3e, and 3f). For the rectum with and without the anal region, the average DVH of bleeders (Figs 3d and 3e) was significantly higher (2.9 Gy, SE 1.0 Gy; 2.9 Gy, SE 1.1 Gy, respectively) compared with the average DVH of the nonbleeders (p = 0.004 and 0.006, respectively). For the anal region (Fig. 3f), this difference (2.3 Gy, SE 1.8 Gy) was not significant (p = 0.2). .

For the same data sets, a series of dose–volume cutoff points was tested (Fig. 4) for significance of discriminating between bleeders and nonbleeders. Each cutoff point with $p < 0.01$ was considered to be significant. For the anal region, no significant cutoff points could be found. For the rectum wall including the anal region, significant volume cutoff points were found for all dose levels between 30 Gy and 60 Gy, with the most significant (p = 0.0002) cutoff point at 60 Gy and 70% volume (Fig. 4a). Patients with DVHs below this point had a 21% incidence of rectal bleeding compared with a 52% incidence above this cutoff point.

Fig. 4. Cutoff points (which resulted in subgroups of at least 30 patients) for the dose–volume histograms of rectum including the anal region (a) and rectum without the anal region (b). +: p ≥0.01, ▲: p < 0.01.



For the rectum without the anal region, significant cutoff points were found for 30 Gy and between 45 Gy and 60 Gy (Fig. 4b). Again, the most significant cutoff point (p = 0.0005) was at 60 Gy and 70% volume. Rectal bleeding incidence was 20% below and 52% above this cutoff point. For the patients with moderate/severe late rectal bleeding, no significant cutoff points could be determined because of a low number of cases. The average incidence of bleeding above all significant cutoff points was 45–69%, whereas it was 19–25% below these points.

For the dose levels between 25 Gy and 60 Gy, we further analyzed the relation between the volume parameters and the incidence of rectal bleeding, using the univariable PHR model. For this analysis, we studied all 12 data sets: rectum, anus, and rectum including the anal region for absolute and relative volumes, both with and without filling. For the four anal data sets, no associations were found. For the other eight datasets including the rectum, significant correlations were found. The relation for the absolute volumes was weaker compared with the relative volumes. Including filling weakened the relation between bleeding and relative volume. For the relative rectum wall DVHs, at all dose levels a significant relation was found, with a p value varying between 0.03–0.04 for 25 Gy and 0.002–0.004 for 60 Gy (Table 2). The most significant volume relation (p = 0.002) was found at 60 Gy for the relative rectal wall excluding the anal region. Therefore, we will restrict ourselves to this anatomic entity for the further results in this section.

Table 2. p values of the proportional hazard regression model for the relative rectal wall volumes with and without the anal region at different dose levels

Dose level (Gy)	Relative rectal wall including anal region, p value	Relative rectal wall excluding anal region, p value
25	0.03	0.04
30	0.02	0.03
35	0.01	0.02
40	0.01	0.02
45	0.009	0.01
50	0.006	0.006
55	0.004	0.003
60	0.004	0.002

In Fig. 5, the estimated volume-effect relations for the cumulative incidence of rectal bleeding after 3 years (with its 95% confidence intervals) are shown for 30, 45, and 60 Gy. These volume-effect relations compared well with the underlying data, presented by the estimated cumulative incidences in quartiles, each with approximately 50 patients. For the 30 Gy level (Fig. 5a), the probability rose from 10% to 43% when the rectal wall volume increased from 40% to 100%. For 60 Gy, the volume-effect

relation was steeper. The rectal bleeding probability increased from 10% at a relative rectal wall volume of 25% to 63% for a relative rectal volume of 100% (Fig. 5c). This volume-effect relation with the full range of incidence levels was more descriptive for the data than the earlier found significant cutoff level of 70% (see arrow in Fig. 5c) with only two incidence levels (20% and 52% below and above this cutoff point, respectively).

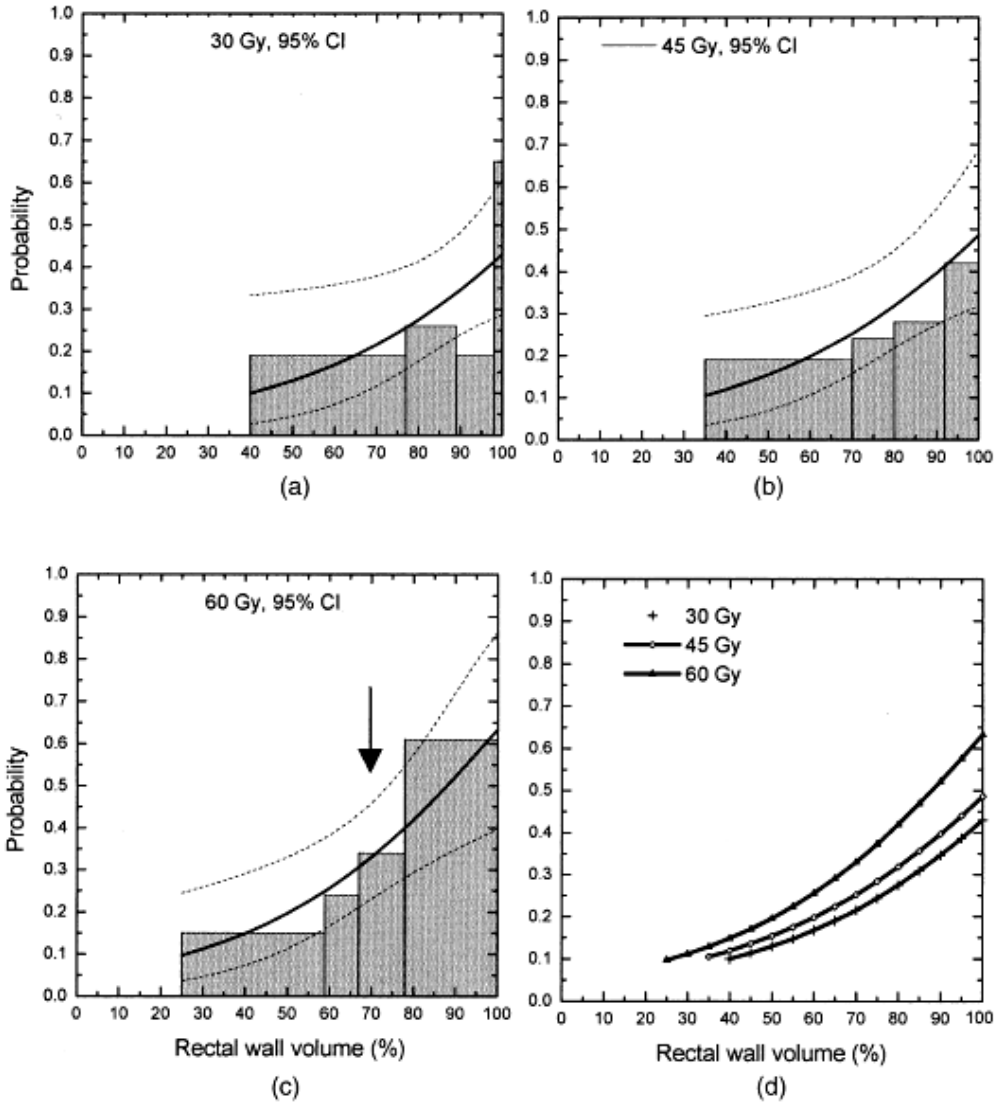


Fig. 5. The probability of rectal bleeding as a function of the relative rectal wall volume (without anal region) at three dose levels. The four bars in Panels a, b, and c represent the cumulative incidences in four volume bins with approximately 50 patients each. The drawn lines represent the fits to Eq. 1 of the proportional hazard regression model together with the 95% confidence intervals. (c) Arrow indicates the most significant cutoff level at 70% (see Fig. 4b).

Prognostic factors for late rectal blood loss (multivariable analysis)

In the subsequent multivariable PHR analysis, other variables were tested in combination with the relative rectal wall volume at 60 Gy. Age, tumor stage, conformal vs. conventional, neo-adjuvant androgen deprivation, smoking, diabetes, and cardiovascular disease were tested. Furthermore, other volume parameters were tested, such as length of rectal canal, rectal wall volume, and rectum volume including filling. No significant parameters were found. For acute rectal bleeding and for smoking, the p values increased ($p = 0.10$ and $p = 0.09$, respectively). When we included the volumes at an intermediate dose of 30 Gy together with the volumes at 60 Gy in the PHR analysis, the volumes at 30

Gy became completely insignificant ($p = 0.5$), whereas the volumes at 60 Gy remained significant ($p = 0.03$).

Discussion

Patients reported any bleeding in 33% and moderate to severe bleeding in 8% at 3-year follow-up in the patient self-assessment questionnaire. The significant difference of the DVHs of the rectum including the anal region between conformal and conventional treated patients (Fig. 3a) did not result in a significant difference in rectal bleeding. The reason for this finding was that the difference of the DVHs of the rectum including the anal region was mainly caused by a difference of DVHs of the anal region (Fig. 3c) and not by a difference of the DVHs of the rectum without the anal region (Fig. 3b). For the anal region alone, no relation was found between the average DVHs and rectal bleeding (Fig. 3f). Also, in the proportional hazard model, no relation between anal DVH parameters and rectal bleeding was found.
For the rectum wall with and without the anal region, a number of DVH parameters were significantly related to rectal bleeding (Fig. 3 and Fig. 4). Including filling gave less or no significant relations. Although the filling would not contribute to toxicity by itself, filling might be important because changes in filling will displace the rectum in or out of the treatment fields. When the rectum filling in the planning CT scan is larger than the rectal filling during treatment, the anterior rectal wall will be displaced dorsally during treatment. With an empty rectum in the planning scan, the anterior rectal wall can be displaced ventrally [21].

Applied methodology to study dose–volume effects
The volume-effect relationship was studied in different ways. First, the AUC of the DVH (or mean dose) showed a significant difference between bleeders and nonbleeders (Figs 3d and 3e). Second, in the approach with cutoff points, significant volume cutoff points at $p < 0.01$ were observed for dose points between 30 and 60 Gy (Figs 4a and 4b). The strongest predictor was the cutoff point at 60 Gy for 70% of the rectal wall volume with 52% and 20% of rectal bleeding above and below this cutoff point, respectively.

The third analysis was based on the PHR model (Eq. 1), because this allows the incidence of rectal bleeding to continuously rise as the irradiated volume increases (see Fig. 5). This is illustrated in Fig. 6 at a dose level of 60 Gy. The observed incidence of rectal bleeding was presented in quartiles (Fig. 6a) as in Figs 5a, 5b, and 5c. Fiorino *et al.* [16] also used quartiles to define cutoff levels, which they subsequently tested for significance. This method is illustrated for our patient group in Figs 6b, 6c, and 6d. We selected cutoff points simply by testing with volume intervals of 5% (see Fig. 5 and Fig. 6). The loss of information using cutoff points instead of using the incidences in quartiles or even the full information of each individual patient with the PHR model is illustrated by comparing the two bars in Figs 6b, 6c, and 6d with the four bars in Fig. 6a and the solid lines in these figures, respectively. Furthermore, the PHR model should be preferred above a threshold model, because it seems rather unlikely that the cumulative incidence of rectal bleeding should rise steeply around some threshold and be relatively constant below and above that point. Indeed, we found some evidence against this steep rise. In Eq. 1, only a linear component of volume was used. In a preliminary analysis, we tested whether this model was contradicted by the data by comparing its fit with a more complex model based on restricted splines [22]. At no dose level the fit was significantly better in the nonlinear model as one would have expected in the presence of an irradiated volume threshold above which the incidence of rectal bleeding sharply increases. This finding was in favor of a more gradual increase over the volume range. As described previously, we analyzed the relation between DVH parameters and rectal blood loss in a number of ways. When doing multiple comparisons, it could be that one is

likely to find a significant effect for a specific parameter, even if in fact no such relation exists. Still, we consider our results to be proof of a DVH-effect relationship. This conclusion is based on the following considerations. First, the analysis based on average DVHs was considered by us to be the primary analysis and this gave a highly significant p value (<0.006). Second, all DVH parameters tested were highly correlated (r > 0.86). Hence, the effective number of independent tests, on which, for instance, a Bonferroni correction should be based, is much smaller than the number of tests actually performed (around 200). Third, in most analyses, small p values (<0.01) were found, which one would not expect when no relation exists. Finally, the smallest p-value found (0.0002 for a cutoff point of 70% volume at 60 Gy) would still be significant even when the highly conservative Bonferroni correction of a multiplication by 200 was applied.

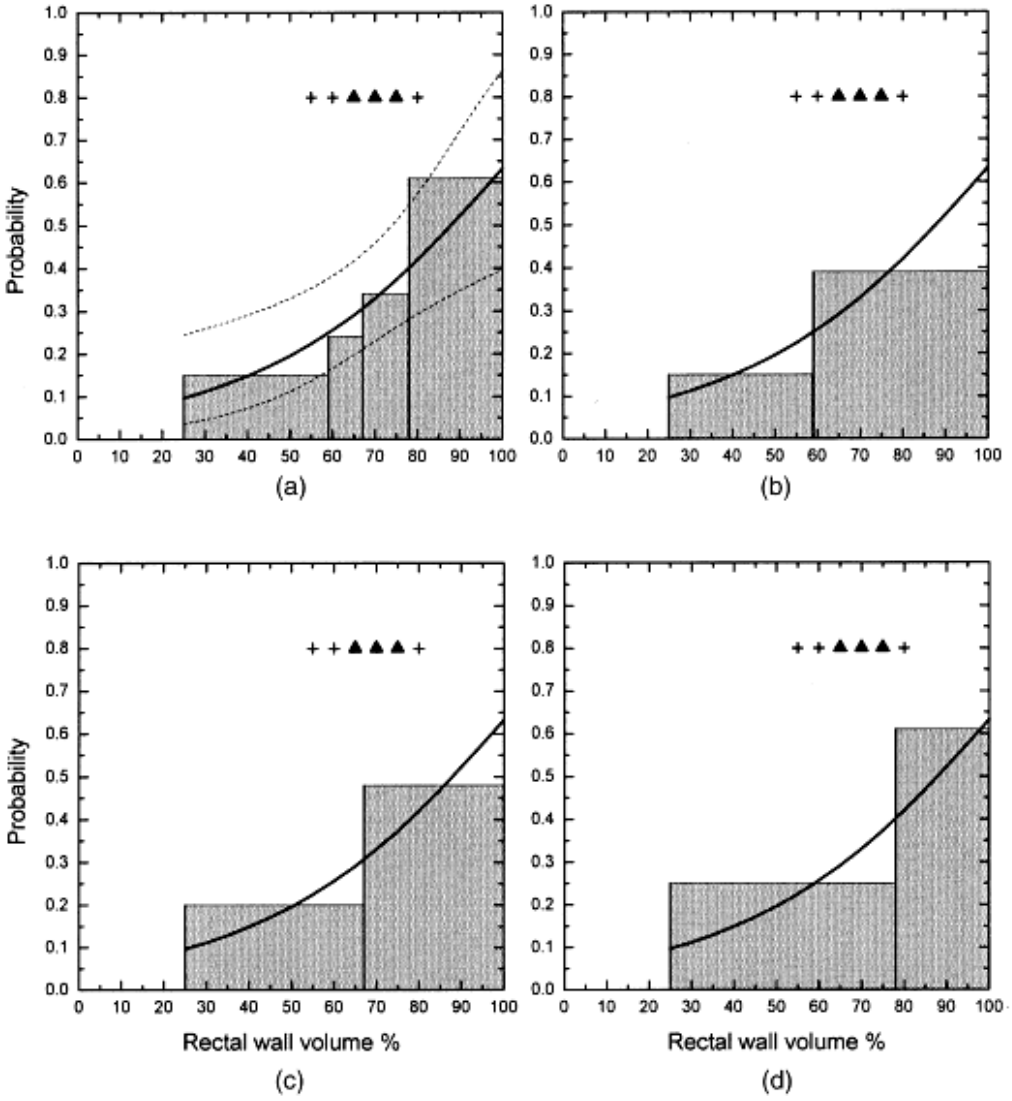


Fig. 6. The probability of rectal bleeding as a function of the relative rectal wall volume (without anal region) at 60 Gy. The solid lines represent the fit to Eq. 1 of the proportional hazard regression model; the dashed lines represent the 95% confidence interval of this fit. The crosses and triangles (at 65%, 70%, and 75%) indicate nonsignificant and significant cutoff levels, respectively (see Fig. 4b). The four bars in (a) indicate the cumulative incidences in four quartiles. The use of cutoff points based on these quartiles at 59%, 67%, and 78% is illustrated in (b), (c), and (d), respectively.

Our conclusion that the high-dose volumes at 60 Gy are most predictive for rectal blood loss is of a more speculative nature. However, it seems supported by the fact that it was found in both types of analysis—volume cutoff point as well as PHR analysis—and by the fact that in the PHR analysis including volumes at both the 30 and 60 Gy levels, only the latter retained a p value <0.05.

The comparison of the data from the Fiorino study [16] and this study was hampered by a number of differences. They published the results of a retrospective multicenter study. Confounding factors were the large number of patients treated postoperatively and different treatment procedures and doses, creating a somewhat inhomogeneous population. The definition of the rectum included the anal canal (personal communication) and rectal filling. They excluded 18% of their patients having more than 100 cm^3 of rectal volume in the planning computed
tomography scan. In our study, this criterion would have excluded 40% of the patient population. Probably an even more important difference was the range of tumor doses between 70 and 76 Gy
in their study, whereas in our study all patients had a tumor dose of 66 Gy. In Fiorino's study, the volumes at 50 Gy and 55 Gy (V50 and V55) were found to be the two most important prognostic factors, with volume cutoff points of 58% and 50%, respectively. These cutoff points are lower compared with the cutoff points found in our study (Fig. 4b). These differences can be explained by a number of factors. Fiorino *et al.* reported on Grade II and III rectal bleeding, whereas we analyzed any bleeding. We were not able to find a clear relationship for moderate/severe toxicity because of the small number of events. Another explanation might be the higher tumor dose (70–76 Gy) in their study compared with the tumor dose in our study (66 Gy).

The recent results from the Memorial Sloan Kettering Cancer Center [4 and 23] indicated a number of significant factors for rectal bleeders. Patient-related factors were age, diabetes, rectal wall volume, and acute toxicity. We tested these factors as well, but we found them not to be significant in the multivariable analysis. Acute toxicity was only of borderline significance ($p = 0.06$) in the univariable analysis. For the dose–volume parameters, they found the volume at high doses (102% of prescription dose, which was closely related to the maximum dose) and the volume at intermediate doses (62% of prescription dose), which was closely correlated to enclosure of the outer rectal contour by the 50% isodose. In the multivariable analysis of our study, the volumes at intermediate doses became insignificant if we controlled for the volumes at 60 Gy. This was, as mentioned before, the result of the high correlation between the irradiated rectum wall volumes at different dose levels.

The analysis of the data from the M.D. Anderson group [5, 17 and 24] indicated that volumes at relative high dose levels were of major importance. The percentage grade II/III toxicity (modified RTOG/LENT) at 3-year follow-up decreased from 28% to 12% if less than 25% of rectum volume was exposed to 70 Gy [24]. Huang [17] added volume cutoff points at other dose levels (60 Gy: 41%, 75.6 Gy: 16%, and 78 Gy: 5%). Unfortunately, they did not test in a multivariable analysis if these cutoff levels at different dose levels were independently associated with the observed toxicity. Of the clinical factors tested, only hemorrhoids had an additional effect on the incidence of late rectal bleeding.

In the study published by Boersma [19], the data indicated that severe rectal bleeding was related to both radiation dose and volume; patients with a rectal wall volume receiving at least 65 Gy for more than 40%, 70 Gy for more than 30%, and 75 Gy for more than 5% of the rectal wall were at a higher risk of developing severe rectal bleeding than patients in whom these volumes were smaller. In this study, tumor doses were applied between 70 Gy and 78 Gy, which might explain the different percentages of bleeders above and below the cutoff points.

A major drawback of our study is the relative conservative tumor dose applied. Two other studies [18, 25 and 26] have reported the volume effect for tumor doses similar to ours. Fenwick *et al.* evaluated the results of the Royal Marsden randomized study at a dose level of 60–64 Gy [18]. The rate of bleeding fell significantly as the fraction of the rectal wall irradiated to a dose of 57 Gy or more was reduced. In the study of Wachter *et al.* [25 and 26] (with a tumor dose of 66 Gy), a significant cutoff point was found at 57% of the rectal volume exposed to 60 Gy. It is not clear if the contouring (outer contour limited by the field edges), the use of an inflatable rectal balloon, or the more generous margins used (1.5–2.0 cm) in their study were responsible for a different cutoff point compared with

our study. The mean V60 (110 ± 50 cm^3 in the Wachter study compared with 93 ± 48 cm^3 in our study) might partly explain the observed difference.

Future studies

The data, as presented in this article, may be useful as a starting point to set the dose–volume constraints for the optimization process of IMRT planning. However, the most relevant DVH parameter is still not determined, and we could only include data with a moderate tumor dose of 66 Gy. Therefore, we will validate the observations in this study and expand them to higher dose ranges with the data from the Dutch randomized dose escalation study (68 Gy vs. 78 Gy), which has accrued more than 650 patients. In this future analysis, we will try to find the most relevant DVH parameter(s) to describe the volume effect using more elaborate statistical methods, such as m-fold cross validation, permutation testing, and bootstrapping. Because we found that not only the irradiated volume, but also the location of the irradiated volume, was important (the anal region did not contribute to rectal blood loss), we will also present the results of an analysis using rectal dose map. This method [27, 28 and 29] fuses spatial and dosimetrical information that is lost in the DVH. Using this method, the dose to the posterior part of the rectum and the influence of exposure of different parts of the rectum and anus will be related to the different aspects of the intestinal toxicity as reported in the patient questionnaires.

Conclusions

A significant relationship between relative rectal wall volume (with and without the anal region) and late rectal bleeding was found. The anal region did not contribute to rectal bleeding in this study. The most significant relation seemed to be present for the higher dose levels. Absolute volumes, rectum including filling, rectum length, rectum wall volumes, radiotherapy technique, and acute rectal bleeding seem to have less predictive power.

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Chapter 8

GASTROINTESTINAL TOXICITY AND ITS RELATION WITH DOSE DISTRIBUTIONS IN THE ANORECTAL REGION OF PATIENTS TREATED WITH RADIOTHERAPY FOR LOCALIZED PROSTATE CARCINOMA.

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Accepted for publication in Int.J.Radiation Oncology Biol. Phys.

Abstract

Purpose:
To study correlations between dose distributions in the anorectal region and late gastrointestinal symptoms in patients treated for localized prostate carcinoma.
Methods and Materials:
Data from a randomized study were analyzed. In this trial patients were treated with either rectangular or conformal fields with a dose of 66 Gy. Gastrointestinal (GI) symptoms were collected from questionnaires of 197 patients. Distributions of the anorectal region were projected on maps and dose parameters were calculated. Incidences of complaints were studied as a function of dose-area parameters and clinical parameters, using a proportional hazard regression model. Finally, we tested a series of dose parameters originating from different parts of the anorectal region.
Results:
Analyzing the total region, only a significant dose-area effect relation for bleeding was found ($p<0.01$). Defining sub-areas, we found effect relations for bleeding, soiling, faecal incontinence and mucus loss. For bleeding and mucus loss the strongest correlation was found with the dose received by the upper 70 % - 80 % of the anorectal region ($p< 0.01$). For soiling and faecal incontinence we found the strongest association with the dose to the lower 40 % - 50 % ($p<0.05$).
Conclusions:
We found evidence that complaints originate from specific regions of the irradiated lower GI tract. Bleeding and mucus loss are probably related with irradiation of the upper part of the rectum. Soiling and faecal incontinence are more likely related to the dose of the anal canal and the lower part of the rectum.

Acknowledgements:
This study was supported by Grant no 98-1830 from the Dutch Cancer Society.
We thank W. van Putten and P. Hoynck van Papendrecht for their statistical and data management support.

Introduction

As a consequence of radiation therapy for prostate cancer, patients might suffer from gastrointestinal (GI) complications afterwards. Since a significant volume of the bowel (i.e. the rectal wall and anal canal) is close to the target volume, every patient is at risk even when conformal fields are applied. The side effects occurring after radiation treatment of the rectum and anal canal are diverse, as can be expected from its function. As described by the RTOG/EORTC toxicity scoring system, late reactions to be expected after irradiation of the lower GI tract are proctitis related symptoms like bleeding and mucus loss, increased stool frequency, cramping and diarrhea (1).
A number of studies have been published investigating the underlying mechanisms of observed side effects, mainly aiming at the assumed dose volume effect relationships. Linking the clinical data of rectal toxicity to individual dose volume data has yielded interesting results, learning us more about the significance of irradiated volumes of the rectum. Especially the relationship between irradiation of the rectum and bleeding has been subject of many studies (2-9). The relationship between dosimetric parameters and overall RTOG/EORTC scores has been reported in other studies, where significant volume effects were found (10-11). Boersma *et al* did however not find a relationship between overall GI toxicity scores and dose volume parameters (2). Similar dose volume analyses involving specific GI symptoms other than bleeding as end points are not frequently published.
Apart from dose volume data, also dose surface data can be used to study dose-effect relations (12). At our institution a method was developed to use dose maps to describe the dose received by the outer area of the rectum (13). In these dose maps the dose to the outer rectal wall is projected onto a 2D normalized angular map. In our study we used this method to analyze the patient data of a clinical trial in order to study GI symptoms and their supposed relationship with the dose area maps. The main goal was to correlate these clinical data to the dose map data in order to generate hypotheses, which explain the origin of patient symptoms. Our hypothesis beforehand was that the dose to the rectum and to the anal canal could cause different complaints, since the anatomy and its functioning are different.

Patients and methods

Study population

We reviewed data from a phase III randomized clinical trial performed at the Daniel den Hoed Clinic / Erasmus Medical Center in Rotterdam, the Netherlands. This study recruited 266 T1-4 N0M0 prostate carcinoma patients in the period 1994-1996. After informed consent, randomization was performed between conventional and conformal irradiation fields. More details of this study population are described elsewhere (14).
One hundred and ninety seven patients were eligible for our study: they filled out a baseline questionnaire and at least one questionnaire during follow-up concerning GI complaints. For every patient we selected records with yearly intervals for a follow-up period of maximal 3 years. Characteristics of the selected group are summarized in Table 1.

E*nd points of interest*

The patients scored their perceived morbidity at regular intervals during the trial. They filled out a patient self-report questionnaire grading their complaints on a four point scale: ‘not at all’, ‘a little’, ‘quite a bit’ and ‘very much’, as described by Tait *et al.* (15). Only diarrhea was not scored on a grading scale; the patient had to indicate whether he had watery stools. This questionnaire was developed as a checklist to identify the symptoms mentioned on the RTOG/EORTC GU and GI toxicity scoring system (1). A similar questionnaire was published by Goldner *et al.* (16).

Table 1 *Patient and treatment data*

Variable	Total group (N = 197)
Mean age (y)	70 (6.2 1SD)
Tumor stage:	
T1	25 (13 %)
T2	98 (50 %)
T3	68 (35 %)
T4	6 (3 %)
Neo-adjuvant hormonal therapy:	
yes	33 (17 %)
no	164 (83 %)
Smoking	
yes	51 (26 %)
no	146 (74 %)
Radiotherapy technique:	
conventional	98 (50 %)
conformal	99 (50 %)
Anorectal wall volume (cm^3)	32.9 (5.8 1SD)
Length of anorectal structure (cm)	14.7 (1.8 1SD)

The bowel symptoms evaluated by the patient were: rectal bleeding, mucus loss, increased stool frequency, diarrhea (watery stools), urge without stools, painful abdominal cramps, faecal incontinence, and soiling (spots in underwear). All questions referred to the patients experience with regard to the preceding week. In this study we analyzed whether a complaint was present or not, regardless the grading reported.

Planning procedure and treatment

The prescribed dose to the Planning Target Volume (PTV) was 66 Gy in 33 daily fractions of 2 Gy. For T1 tumors the Gross Tumor Volume (GTV) was defined as the prostate. For other stages prostate and seminal vesicles was defined as the GTV. The GTV was 3D expanded with 15 mm to a PTV. A three-field technique was used with one anterior and two lateral (oblique) treatment fields (14). In the conventional arm, patients were treated with rectangular fields. Within the conformal arm, patients were treated with conformally shaped treatment fields using a multi leaf collimator. Patients were treated supine, without special instructions for bladder or bowel filling.

Contouring and construction of dose maps

The planning CT scan was used to obtain individual 3D dose volume data of the anorectal wall. The outer wall of the bowel was delineated from the anal region till the level of the inferior border of the sacroiliac joints. The anorectal region was defined cranially as long as it had a close relation to the sacrum. Where the bowel moved ventrally away from the sacrum, it was defined as sigmoid. On average the delineated anorectal region was 15 cm long (1.8 cm 1SD) with a minimum of 10 cm and a

maximum of 20 cm. The inner rectal wall was generated from the outer rectal wall and contours, using the method of Meijer *et al* (17).

We used a previously developed method to virtually unfold the delineated rectal wall and project the dose to the outer rectal surface onto a 2D angular map (13). To make a map, first a central axis was computed through the rectum and this central axis was divided in segments of 0.5 cm. Perpendicular to each segment we constructed a planar cross section. We assumed that the amount of rectal wall tissue was a constant in all orthogonal cross sections throughout the entire rectum (17). The orthogonal cross sections were unfolded at the dorsal side and the associated dose was projected onto the map. The vertical axis of the maps, i.e. the length of the rectum, was normalized to 100 %.

Descriptive statistics

The life table method was used to estimate the overall cumulative incidences of complaints at 3 years. For these estimates, complaints were only scored as present when the symptom was reported as worse with regard to baseline. The tetrachoric correlation coefficient was calculated to test whether there were associations between the reported symptoms. The life table method was also used to estimate the cumulative incidence at 3 year for each complaint within defined dose bins, each bin containing about 25 % of the population.

Statistical modeling of dose-effect relationships

Relative areas receiving a certain dose or more were calculated, with the dose varying between 20 Gy and 60 Gy (dose steps of 10 Gy). A proportional hazard regression (PHR) model was applied to estimate the probability of a complaint within 3 years, as a function of the calculated dose map parameters. These dose map parameters were extracted from different regions of the total dose map. An interval-censoring method was used as described by Collett (18) in order to correct for the large time intervals between the different moments of follow up. In this study we calculated and reported cumulative risks at three years. The SAS package was used for fitting the PHR model (SAS, release 8.1; Carry, NC).

Patient and treatment characteristics were also tested in a similar way (univariable), to study whether these factors had a significant impact on the complaints. The effect of univariably significant variables was also tested in multivariable analysis.

Mean dose maps

For each symptom two average dose maps were constructed: an average absolute dose map of the patients with the symptom and an average absolute dose map for the patient subgroup without the symptom. In this way differences in dose distributions were visualized. In these mean dose maps, the variation in follow-up between patients cannot be taken into account. Therefore the results of the PHR model are more valid in this study.

Results

Selected population

The study group consisted of 98 patients treated with rectangular fields and 99 patients treated with conformal fields. The variables GTV definition, age, hormonal therapy, anorectal wall volume and length of anorectal structure, were well balanced. With regard to tumor stage and smoking habits, there was a slight unbalance. The conventional group contained more patients with T2 tumors (n=54 against n=44) whereas the conformal group contained more patients with T3 tumors (n=39 against n=29). The conformal group also contained more smokers (n=29) than the conventional group (n=22).

Incidence of complaints

The incidences of complaints at baseline are shown in Table 2. The most frequent symptoms reported were: painful cramps (16 %) and urge (12 %). The cumulative incidences of baseline-corrected GI complaints at 3 years of follow-up (life table method) are shown in Table 2. It shows cumulative incidences in the range of 5 % (diarrhea) up to 58 % (increased stool frequency and soiling). Diarrhea appeared to be a rare late complaint and was therefore not further analyzed.

Table 2. *Prevalence of reported complaints at baseline and the cumulative incidence of each complaint at 3 years corrected for baseline, with its standard error (life table estimates). These cumulative estimates also include mild complaints. Incidences of moderate/ severe complaints only were much lower: in the range of 1 % - 6 %.*

Complaint	**Baseline** (n=192)	**Year 3*** (n=197)	**Standard Error**
Rectal bleeding	1 %	43 %	6 %
Frequency ≥ 3	8 %	58 %	6 %
Soiling	8 %	58 %	6 %
Faecal incontinence	4 %	57 %	6 %
Painful cramps	16 %	28 %	6 %
Mucus loss	4 %	55 %	6 %
Urge	12 %	35 %	6 %
Diarrhea	2 %	5 %	4 %

Cumulative at 3 years

It must be noted that the prevalence throughout the follow-up period, was much lower than the cumulative incidence at 3 years. At 2 years the prevalence of complaints was: 19 % for rectal bleeding, 31 % for increased stool frequency, 34 % for soiling, 26 % for faecal incontinence, 15 % for painful cramps, 23 % for mucus loss and 16 % for urge. There were much less moderate and severe complaints. At 2 years, the prevalence of moderate/severe complaints was: 5 % for cramps, 5 % for faecal incontinence, 5 % for soiling, 5 % for rectal bleeding, 4 % for mucus loss, 2 % for urge and 5 % for stool frequency at least 5 times a day.

Most clinical end points investigated showed mutual positive associations. All end points were significant positively associated with each other except bleeding with cramps and bleeding with increased frequency. The most outspoken association was seen between faecal incontinence and soiling: 80 % of the patients reported both symptoms either absent of present (tetrachoric correlation coefficient = 0.80, $p<0.001$).

Proportional Hazard Model

Within the PHR model clinical characteristics and dose parameters were included as independent variables. The results are summarized in Table 3 and Table 4 (univariable analysis). The presence of the corresponding symptom during the acute phase of radiotherapy appears to be the most outspoken clinical factor, which is significant ($p<0.05$) for every end point except for abdominal cramping and bleeding ($p=0.06$). In view of the number of tests performed, no strong evidence was found here for an association between any of the other clinical characteristics and the end points.

Table 3. *Results of univariable testing of clinical characteristics within the PHR model. P values ≤ 0.01 are written in bold italics.*

	Univariable PHR models, p values of symptoms tested Depending variable:						
Independent variable:	**Urge**	**Cramp**	**Blood**	**Mucus**	**Inconti-nence**	**Soiling**	**Freq 3+**
Age	0.37	0.8	0.7	0.5	0.2	0.8	0.03
Acute complaint y/n	***0.007***	0.06	0.06	***<0.001***	0.02	***0.001***	***<0.0001***
Hormones pre-RT y/n	0.3	0.7	0.2	0.8	0.6	0.3	0.2
Treatment	0.3	0.4	0.5	0.4	0.2	0.1	0.7
Smoking y/n	0.3	0.3	0.07	0.3	0.1	0.08	0.8

Univariable (UV) testing of areas receiving at least a certain dose was performed for dose levels between 20 Gy and 60 Gy with dose steps of 10 Gy. These dose parameters are highly correlated (Pearson correlations between 0.70-0.97, all p values < 0.001).
In Table 4 the results of a low dose (30 Gy), a high dose (60 Gy) and the mean dose are presented. These results show that testing the total anorectal area map, only significant results for bleeding are found (UV p values in the range of 0.008 – 0.01).

Table 4. *Results of univariable testing of general dose parameters within the PHR model (calculated area for the total anorectal region). P values ≤ 0.01 are written in bold italics*.

	Univariable PHR models, p values of symptoms tested Depending variable:						
Independent dose variable:	**Urge**	**Cramp**	**Blood**	**Mucus**	**Inconti-nence**	**Soiling**	**Freq 3+**
Area > 60 Gy	0.2	0.9	***0.008***	0.1	0.2	0.1	0.3
Area > 30 Gy	0.3	0.9	0.01	0.2	0.3	0.1	0.4
Mean dose	0.2	1.0	***0.01***	0.1	0.2	0.1	0.3

Multivariable (MV) testing was performed for all end points with 2 or more covariables with an UV p value < 0.1. Multivariable testing with bleeding as end point was performed for smoking, acute bleeding complaints and area receiving a dose ≥ 60 Gy. Only the latter covariable was significant (MV p=0.02) while for smoking and acute complaints the p value was 0.1 and 0.2, respectively. Multivariable testing with soiling as end point was performed with smoking and acute soiling complaints as covariables. In this analysis the acute complaints remained significant (MV p=0.003) and smoking became significant (UV p=0.08, MV p=0.01), indicating a lower risk for soiling complaints in the smoking group. Acute complaints and age were tested multivariable with increased stool frequency (3 or more times a day) as end point. Multivariable p values were: < 0.0001 for acute complaints (UV <0.0001) and 0.05 for age (UV 0.03). A higher age was associated with a higher incidence of increased stool frequency.

Mean dose maps

For "bleeding and no bleeding", "soiling and no soiling", the average dose maps are shown in Figure 1. These maps show a difference in the superior area for bleeding versus no bleeding, and in the inferior area for soiling versus no soiling. The dose map patterns for mucus loss were similar to the maps of the bleeders and the maps for faecal incontinence showed similar patterns as for soiling. The dose maps have to be interpreted with caution since it is not possible to correct for the variation in follow-up between patients (variation between 1 and 3 years) within these dose maps.

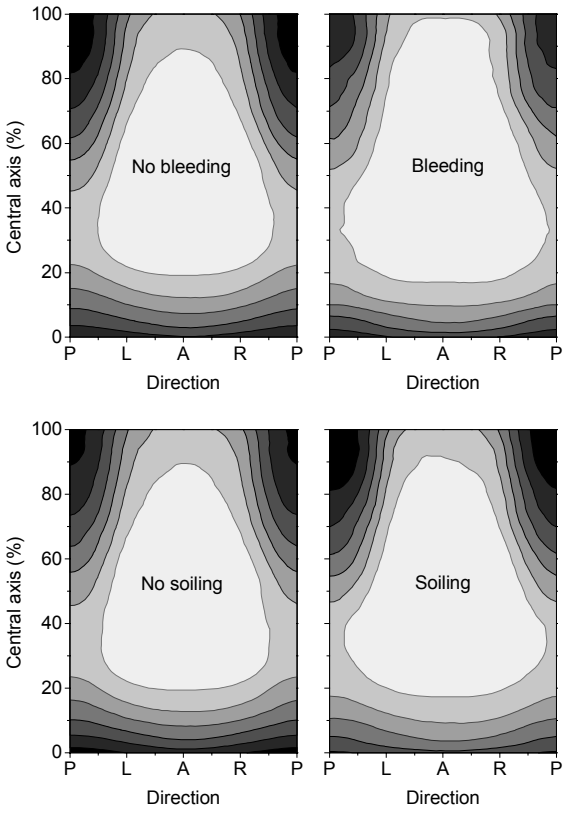


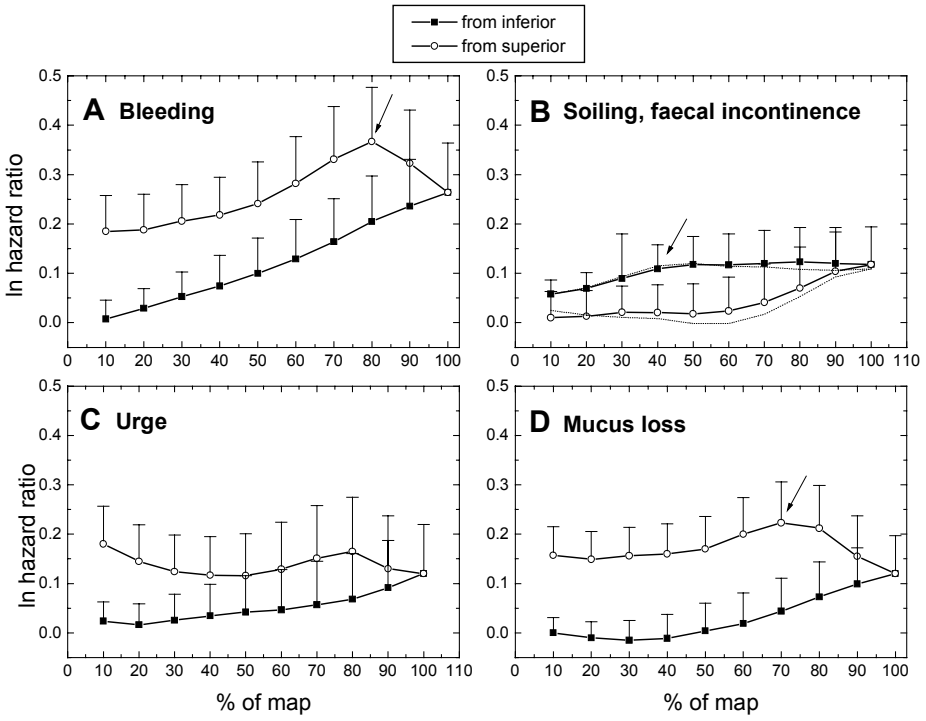
Figure 1.
Absolute dose maps of the total anorectal outer wall for different patient groups. The horizontal axis indicates the position along the circumference of the rectum: P stands for posterior, A for anterior, L for left and R for right. At the vertical axis the relative position to the anus (at the bottom: 0 %) and the most cranial part of the rectum (at the top: 100 %) is plotted. The upper maps represent the patients reporting bleeding during follow up (right) and the patients without bleeding (left). The lower maps represent the patients reporting soiling (right) and patients who did not report soiling (left).

Testing of sub-areas in the PHR model

Based on the information of the dose maps, we defined series of sub-areas, for which the area receiving a dose ≥ 60 Gy were tested (univariable) in the PHR model. A series starting from superior and another from inferior were defined; 10% of the total dose map, 20 %, 30 % etcetera, until 100 % was included (total map). They were tested for all symptoms separately as end points. For every combination of end point and sub-area, the natural logarithm (ln) of the hazard ratio was calculated for the % of the area irradiated to at least 60 Gy. The ln hazard ratios plotted in Figure 2 are the ratios for each 10 % of the area irradiated to at least 60 Gy. The hazard ratio expresses the increase in the complication rate for each increase of 10 % area receiving the defined dose. The results for bleeding, soiling, faecal incontinence, urge and mucus loss are shown in Figure 2. Together with the ln hazard ratios its standard error is plotted in each graph. In each graph, the series starting from inferior and superior, are both starting at the left side of the graph until they both contain 100 % of the dose-area map: at that particular point the 2 series are identical.

For bleeding (Figure 2A), the series starting from inferior show low hazard ratios, which are not significant, until the inferior 70 % - 100 % is included in the dose-area tested; from 70 % to 100 % superior the results are significant (p values < 0.05). The other way around starting from superior, the tested dose-areas remain significant all the way through the final point of 100. The graph for bleeding clearly shows a maximum in the ln hazard ratio at the superior 80 % of the map, indicated with an arrow (p value is 0.0012). Including another 10 % (to a total of 90 %) after this point causes a clear decrease in the hazard ratio.

Figure 2



Results of Proportional Hazard Regression (PHR) analyses concerning the end points bleeding (2A), soiling & faecal incontinence (2B, solid lines and dotted lines respectively), urge (2C) and mucus loss (2D). The rectal map is analyzed in different pieces: a series of 10 relative cut-off points are tested, starting from inferior (10 % of map until a 100 %) and another similar series starting from superior. The tested covariate is in all cases: % area receiving at least 60 Gy. The ln hazard ratios of the corresponding tested PHR models are plotted on the y axis together with its standard error (only plotted for the plus direction). The arrows indicate the cut-off values taken for the depicted graphs in Figure 3.

For soiling (Figure 2B), the series starting from superior show low levels of the ln hazard ratio, which are not significant. Starting from inferior, the first 5 tested dose-areas (inferior 10 % - inferior 50 %) are significant models ($p<0.05$). Passing the point of the inferior 40 % (indicated with an arrow), the tested dose-areas become less significant and passing the inferior 50 % the tested areas becomes not significant ($p>0.05$) while the estimated hazard ratio is still at the same level. In graph 2B, the results for faecal incontinence are also plotted with two thin dotted lines. The ln hazard ratios and corresponding p values found for this end point are very close to the results of the end point "soiling".
For the end point "urge" (Figure 2C), almost every tested dose-area was not significant, except the most superior 10 % and 20 % ($p<0.05$). For mucus loss (Figure 2D), a similar pattern as for "bleeding" was found. For this end point the results show a maximum of the hazard ratio at 70 %, indicated with an arrow (corresponding $p=0.007$). For increased stool frequency only a weak association was found (ln hazard ratio of only 0.09) with the inferior 60% of the anorectal map ($p=0.16$).
For the optimal sub-area related with bleeding (superior 80 %), soiling (inferior 40 %) and mucus loss (superior 70 %), graphs were constructed showing the volume effect of irradiation on the probability of developing the complaint at risk within 3 years (Figure 3). In this figure the estimated incidence at 3 years (solid line) of a complaint as a function of the area receiving a dose > 60 Gy is shown. The actual cumulative incidence at 3 years is also shown for four fixed bins (quartiles). If we repeat this for other dose levels (e.g. area irradiated to at least 40 Gy, 50 Gy and 65 Gy), similar probability lines are found, which are shifted to the left (lower dose levels) or to the right (higher dose levels).

Analyses of isolated sub-areas

Besides the division into superior and inferior parts, we also cut the anorectal map into isolated sub-areas. Each dose map (similar to Figure 1) was cut into 4 regions from superior to inferior, and 4 regions from posterior to anterior (left, anterior, right, posterior). The created 16 isolated pieces of rectum or anal canal were tested in explorative analyses. These analyses revealed no new information on local dose-effect relations (results not shown).

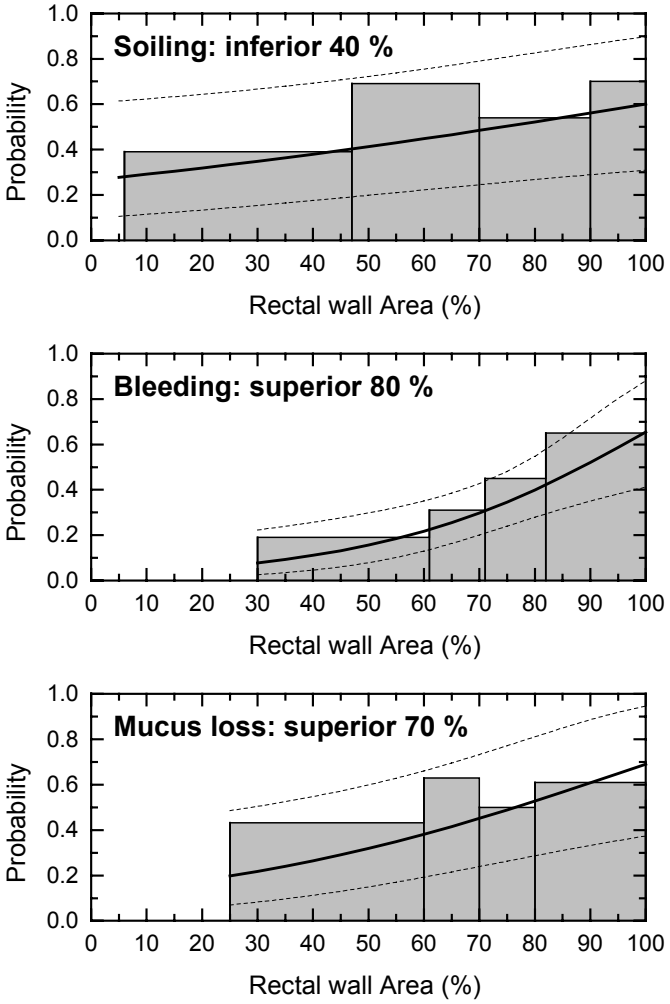


Figure 3.
Estimated incidences within 3 years (fitted lines) of soiling, bleeding and mucus loss as a function of the area receiving a dose ≥ 60 Gy. For soiling the inferior 40 %, for bleeding the superior 80 %, and for mucus loss the superior 70 % of the dose maps is taken for the fit. Confidence intervals (95 %) and life table estimates at 3 years (quartiles) are shown for each fit.

Discussion

In this study we found evidence that specific symptoms were related with dose-area parameters of different regions of the lower gastrointestinal (GI) tract. Analyzing 'rectal bleeding' revealed that the best prediction was found from the dose in the superior 80% of the anorectal map (p=0.001). Similar results were found for mucus loss (p=0.007 for the upper 70 %). These results have to be interpreted with caution with regard to its explorative nature and the large standard errors found (Figure 2). A visual inspection of the mean dose maps confirms the results found in statistical analysis for bleeders: in the region of the anal canal no clear differences in the dose pattern were found between the patient group 'bleeding' and the patient group 'not bleeding' while there clearly was a difference in the dose pattern at the superior side of the map (Figure 1).

Some evidence for a dose-effect relation for soiling and faecal incontinence was found within the inferior 40 % - 50 % of the dose map, situated in the anal region and the lower part of the rectum (p=0.03 for both end points). The width of the confidence intervals however indicated that these relationships were not be obtained accurately. Although less significant, this observation is relevant as the majority of the patients is bothered with compliance related symptoms (Table 2). Looking at the mean dose maps of the patient group reporting soiling vs. the group not reporting soiling (Figure 1), there is a difference at the average dose received by the most inferior part of the dose map (i.e. the anal canal), which confirms the results of the PHR analysis. For the more high dose regions (> 60 Gy) there is however a less clear difference between the high-dose areas for the group reporting soiling versus the group not reporting soiling.

For the observed increase in the incidence of urge and stool frequency no explanatory dose-area effect relation could be described within the studied lower GI tract. For urge we did find a significant association with the most upper part of the delineated rectum, close to the colon and the sacrum (p=0.02 for the superior 10 % of dose map), indicating a higher risk for larger areas. However, we cannot explain this. Given the number of tests we performed, it might be due to chance.
Dale *et al.* (19) investigated the correlation between dose-volume data of the rectum and several complaints scored on patient questionnaires in a small group of 52 prostate cancer patients. They found

that the high-dose levels were best correlated with the late side effects studied (i.e. diarrhea, cramps, gas, blood, mucus, pain). The correlation coefficients they found were however small and only significant for "cramps" ($p<0.01$).
Yeoh *et al* (20) investigated the anorectal functioning after radiotherapy (motility and sensory function) and found an association of radiotherapy with objective changes of the rectal sensitivity. An analysis including dose-volume data was however not reported. Other studies concerning anorectal function after radiotherapy, also found affected functioning of rectum and anus even when conformal techniques were applied. (21-22). Hayne *et al.* (23) published a review of the literature concerning anorectal injury after pelvic radiotherapy. This concerned prostate patients as well as patients treated for cancer of the rectum or cervix. The maximum tolerated rectal volume was decreased in all studies investigating this end point, indicating that the rectal capacity was affected.
Vordermark *et al*. (24) studied faecal incontinence in relation with dose-volume histogram data and reported no significant correlations. They did however find higher minimum doses to the anal canal for patients with severe complaints. They also compared the complaints of 44 patients treated 0.6 - 4.5 years ago for prostate cancer with the complaints in a control group of 30 untreated prostate cancer patients and found significantly worse scores in the treated group. In this study, faecal incontinence, as well as increased bowel movements, urge and soiling, were included in the continence score. In our study we also did not find a very strong relationship between continence problems and dose data.
The separation into superior and inferior parts corresponds with the anatomical and functional region of the rectum on one hand and the anal canal on the other. This is in agreement with the results indicating that bleeding and mucus loss originates from the rectum and complaints concerning soiling and faecal incontinence are a consequence of irradiating the anal region and probably the lower rectal region. It must be said however that faecal incontinence is likely to be a result of a number of underlying factors like soft stools, increased stool frequency, cramps, capacity of the rectum and the sphincter function. These factors are obviously not exclusively related to the anal canal, which makes it more complicated.
A number of analyses reported in this study, would have been possible with dose- volume data instead of dose-area data. In fact, for every projection of dose distributions on the outer rectal wall it is possible to obtain the corresponding dose-volume data. We choose to use the dose-area data since we already obtained the dose-area data to construct the dose maps. With regard to dose-volume data it can be noted that the correlation between the dose-area data and the dose volume data was high in this dataset: Pearson correlation coefficient 0.94 - 0.96 for dose levels of 20 Gy and higher.
The number of reported moderate to severe symptoms was low. Into these small subgroups no indications for a dose-effect relation were found. However, in this study 66 Gy was prescribed to the tumor. With regard to the current developments of describing a higher dose to a more tightly PTV, it would be very interesting to repeat these analyses in a large patient group. Therefore we plan to do further investigations in our trial randomizing between 68 Gy and 78 Gy, with conformal fields and with a more extensive follow up.

Conclusions
Irradiation of the anorectal region is associated with several side effects, showing a continuously rising risk with an increasing irradiated volume. Incorporating the spatial information of the dose distribution in our analyses indicated that different complaints origin from different regions. Rectal bleeding and mucus loss were related with irradiation of the more upper part, i.e. the rectal region. Faecal incontinence and soiling showed both a stronger association with the lower part of the GI tract, i.e. the lower part of the rectum and the anal canal.

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Chapter 9

SEXUAL FUNCTIONING IN PATIENTS WITH LOCALIZED PROSTATE CANCER AWAITING TREATMENT

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Journal of Sex & Marital Therapy, 27:353-363, 2001

Abstract

This paper evaluates current sexual functioning in patients with prostate cancer awaiting treatment. One-hundred-fifty-eight patients filled out a 15-item questionnaire regarding current sexual functioning. Median age was 67 years. Sixty per cent reported to have spontaneous erections at least once a week with a good firmness in 37%. During sexual activity, 35% reported no difficulty in getting erections and 33% in maintaining an erection.
After diagnosis, all patients reported a decrease in sexual interest, activity and pleasure. Diagnosis of prostate cancer does have an impact on sexual functioning, therefore sexual counseling prior to treatment is advised.

Acknowledgments
To Prof A. Koos Slob, Ph.D., sexologist, Erasmus University Medical Center Rotterdam and to Mrs Nicole C.E. Bootsma, M.D. for their help and critical comments on an earlier version of the manuscript.

Introduction

Prostate cancer (PC) has become the most frequent malignancy in men in Western countries. Over recent years the number of diagnosed patients has increased dramatically because of routine prostate specific antigen (PSA) tests and the awareness of possibility of cure of early disease, with a 5-year relative survival rate of 98% (Parker, Tong, Bolden, & Wingo, 1996). Standard treatments in The Netherlands comprise radical prostatectomy (RP), external beam radiotherapy (RT) or observation. Randomized trials are in progress to investigate whether RP and RT are superior to observation for long-term survival rates. Treatment choice is often determined by tumor staging, patient's age and co-morbidity, urologist's and patient's preferences. Patient's health related quality of life including sexual functioning is very important in decision making. As reported by Singer, Tasch, Stocking, Rubin, Siegler, & Weichselbaum (1991) some men may choose a treatment with lower long-term survival to increase their chance of remaining sexually potent. The occurrence of erectile dysfunction (ED) after RP varies in the literature from 30% with sparing both neurovascular bundles (Catalona & Bigg, 1990) to 50% when only one bundle is spared (Walsh, Epstein, & Lowe, 1987) and reaches 98% in non-nerve-sparing techniques (Lim, Brandon, Fiedler, Brickman, Boyer, Raub, & Soloway, 1995). After external RT, ED occurs in up to 77% of patients (Mantz, Song, Farhangi, Nautiyal, Awan, Ignacio, Weichselbaum, & Vijayakumar, 1997; McCammon, Kolm, Main, & Schellhammer, 1999; Shrader-Bogen, Kjellberg, McPherson, & Murray, 1997; Turner, Adams, Bull, & Berry, 1999). However, time is important after RT: erectile function continues to decline after 12 months and reaches a plateau after 24 months (ED in 38% and 59%, respectively) (Mantz, Song, Farhangi, Nautiyal, Awan, Ignacio, Weichselbaum, & Vijayakumar, 1997; Turner, Adams, Bull, & Berry, 1999). The impact of treatment on potency is difficult to determine unless a baseline, pretreatment assessment of erectile function is included. The present study was carried out to determine pre-treatment sexual functioning in PC-patients awaiting treatment and to evaluate whether the diagnosis of PC had an impact on sexual functioning. Furthermore these data were collected to be used for comparison one and two years later in the same patients following PC-treatment.

Patients and Methods

In the period 1996-1998 166 patients with localized PC were referred to our hospital for treatment. Eighty-five subjects were to be treated with RP and 81 with RT. Treatment choice had been previously determined by urologist's and patient's preferences. All subjects were asked to fill out at home a 15-

item questionnaire with items regarding various aspects of sexual functioning of the past two weeks. The questions referred to sexual interest, pleasure and activity and problems with getting erections following PC diagnosis (Appendix A). The questionnaire was adapted from a previously used version (Incrocci, Hop, & Slob, 1996; Slob, Blom, & van der Werff ten Bosch, 1990). The response rate was 91%: 158 out of 166 patients accepted to fill out the questionnaire.

Statistical methods
The statistical analysis was primarily descriptive. Differences between the RP and RT patients in the answers to the different questions and in the distribution of age were tested with the Kruskal-Wallis test and logistic regression.

Results

Median time between diagnosis and survey was 6 weeks (range 4-9 weeks). Patients' characteristics are summarized in Table 1. Median age was 67 years (range 50-80 years). Co-morbidity (diabetes and/or cardiovascular history) was reported in 21 % of the patients. Sixty-five patients (41 %) indicated to have (very) much sexual desire. Sex was (very) important to 124 men (78%). Sixty per cent reported spontaneous erections (= outside sexual activity), at least once a week. Firmness of these erections was good in 57 subjects (37%). Fifty-five patients (35%) reported no difficulty in getting and 52 (33%) no difficulty in maintaining an erection. For 56 patients (35%) these erections were firm enough for sexual activity (masturbation or intercourse). Overall satisfaction with sexual life was (very) high in 84 patients (53%). We found no statistically significant differences in sexual functioning between subjects with or without co-morbidity (all p values> 0.1).

Impact of cancer diagnosis
Receiving the diagnosis of PC (4-9 weeks earlier) had caused an important decrease in sexual activity in 31 patients (20%), in sexual interest in 12 patients (15%), in sexual pleasure in 20 patients (12%) and there was an increase in problems with getting an erection in 16 patients (10%). Before diagnosis 105 subjects (66%) were sexually active; after diagnosis, over the past two weeks, 88 patients (56%) were sexually active; this difference is highly statistically significant (p=0.008). The reason of not being sexually active was ED in only 15 men (10%); other reasons were absence of partner or no sexual desire in the partner.

Differences between RP and RT patients
The choice of treatment was not random, but determined by urologist's and patient's preference. As can be seen in Table I, RP patients were significantly younger than RT patients (median age 63 vs 69 years), PSA was significantly lower (4 µg/l vs 8 µg /l) and there were less cardiovascular diseases (14% vs 23%). To make comparisons in ED rates after treatment one should be aware of the differences between these two groups of patients. RP and RT patients differed in their current level of sexual activity (77% versus 57%, respectively; p=0.01). About half of the RP patients reported no problems in getting (45%) or maintaining an erection (42%) versus only a quarter of the RT patients (25% and 26% respectively), a statistically significant difference (p=0.01).
More RP patients (60%) than RT patients (46%) indicated high or very high overall satisfaction with sexual life (p=0.004). A logistic regression analysis with adjustment for age and the following independent variables: sexual desire, spontaneous erections, sexual activity, significance of sex and satisfaction with sexual life, showed no statistically significant differences between the RP and RT patients, except for satisfaction with sexual life (lower in RT patients than in RP patients, p=0.04).

Table 1. Characteristics of *n=158* patients with localized prostate cancer awaiting treatment, either radical prostatectomy (RP) or external beam radiotherapy (RT)

	Total *(n=158)*	*RP(n=77)*	*RT(n=8l)*
Median age (range) years	67 (50-80)	63* (50-73)	69 (55-80)
	n (%)	*n* (%)	*n* (%)
Diabetes Mellitus	5 (3)	1 (1)	4 (5)
Cardiovascular disease	30 (18)	11 (14)	19 (23)
TNM classification:			
T1	20 (13)	11 (14)	9 (11)
T2	97 (61)	52 (68)	45 (56)
T3	34 (22)	14 (18)	20 (25)
T4	3 (2)	0 (0)	3 (4)
unknown	4 (2)	0 (0)	4 (4)
NO	127 (80)	46 (60)	81 (100)
NX	31 (20)	31 (40)	0 (0)
MO	158 (100)	77 (100)	81 (100)
Differentiation grade:			
G1 (good)	78 (49)	40 (52)	38 (47)
G2 (moderately)	60 (38)	29 (38)	31 (38)
G3 (poor)	19 (12)	8 (10)	11 (14)
unknown	1(1)	0 (0)	1 (1)
Median PSA (range) J.lg/l	9 (1-59)	4* (1-30)	8 (1-59)

* $p<0.0001$ versus RT patients

Discussion

A very commonly ignored aspect of PC therapy is the impact on sexual activity and sexual functioning (McCammon, Kolm, Main, & Schellhammer, 1999; Ofman, 1995). Although the use of advanced surgical techniques as the nerve-sparing RP and the introduction of conformal RT, sexual functioning after PC treatment remains a concern. In order to carefully evaluate the impact of PC diagnosis and treatment on sexual life it is necessary to assess sexual functioning prior to treatment (Stock, Stone, & Iannuzzi, 1996; Zinreich, Derogatis, Herpst, Auvil, Piantadosi, & Order, 1990). Many published studies used retrospective assessments of sexual functioning prior to treatment (Lim, Brandon, Fiedler, Brickman, Boyer, Raub, & Soloway, 1995; Mantz, Song, Farhangi, Nautiyal, Awan, Ignacio, Weichselbaum, & Vijayakumar, 1997; Shrader-Bogen, Kjellberg, McPherson, & Murray, 1997). Some studies evaluated pre-treatment sexual functioning with a prospective design (Litwin, Flanders, Pasta, Stoddard, Lubeck, & Henning, 1999; Stock, Stone, & Iannuzzi, 1996; Turner, Adams, Bull, & Berry, 1999). Often PC patients are impotent before treatment. Therefore, assessment of this condition is necessary to predict sexual functioning after therapy (Robinson, Dufour, & Fung, 1997;

Stock, Stone, & Iannuzzi, 1996; Zinreich, Derogatis, Herpst, Auvil, Piantadosi, & Order, 1990). Preservation of potency is more likely to occur if there is no or minimal impairment before treatment (Turner, Adams, Bull, & Berry, 1999).

Of the 600 articles reviewed by Robinson, Dufour & Fung (1997) on ED in men after PC treatment only 40 (15%) comprised papers in which pre-treatment erectile functioning was assessed. They stated that this is the most important criterion to provide meaningful end comparisons of ED after RP or RT. The lack of consistency in definitions of potency makes it difficult to compare the results from different studies. In our study, potency was defined as the ability to achieve erections sufficient for sexual activity (masturbation or intercourse). Ideally, besides the questionnaire and in order to possibly differentiate between psychological and organic erectile dysfunction, we would have used also objective measurements as penile Doppler ultrasonography, Visual Sexual Stimulation or Nocturnal Penile Tumescence recording with the Rigiscan, but we felt this to be too time consuming and too cumbersome for our patients.

Because of the multifactorial nature of sexual dysfunction not only erectile function but also libido, satisfaction with sexual life and interest in sex should be assessed (Schover, 1993). Therefore, we adapted a 15-item questionnaire regarding many aspects of sexuality, routinely applied to all new ED patients (Incrocci, Hop, & Slob, 1996; Slob, Blom, & van der Werff ten Bosch, 1990). More recently an international questionnaire, also validated in our country, the International Index of Erectile Function (IIEF) has been introduced (Rosen, Riley, Wagner, Osterloh, Kirkpatrick, & Mishra, 1997), but unfortunately this was not yet available at the moment of our study. Sexual dysfunction in PC patients can be due to different factors such as age, medical therapy, co-morbidity, use of tobacco, alcohol, previous pelvic surgery or the prostate carcinoma itself (Helgason, Adolfsson, Dickman, Arver, Fredrikson, & Steineck, 1997; Melman & Gingell, 1999). Helgason, Adolfsson, Dickman, Arver, Fredrikson, & Steineck (1999) reported ED in 57% of patients with PC after RT and 53% in the not-treated men, assessed at 1.5-2.5 years after diagnosis. This suggests that PC itself was associated with an increased risk of sexual impairment. In our study the diagnosis PC resulted in decreased sexual activity. Although sexual functioning prior to diagnosis was assessed retrospectively (it is actually impossible to do this prospectively), the possibility of recall bias was rather limited because of the short time between diagnosis and survey (median 6 weeks). The prostate gland itself is not essential for normal sexual function but most men express anxiety after diagnosis of PC thinking of losing erectile capacity because of treatment (Schover, 1993). Fear of death and worries about family can also play a role in impairing sexual functioning when men are told they have cancer.

We are aware that a control group of patients without PC would have been interesting, but this was not possible in our case. Of our patients only 35% expressed no problem with getting or maintaining an erection. Reports on the Dutch population reveal that in men 60-69 years and 70 years and older the percentage of problems in getting an erection is 22% and 38%, respectively (Meuleman, Donkers, & Kiemeney, 2000). Thus, the incidence of ED in a normal population seems to be lower than in our PC patients. In the Meuleman et al. (2000) study 35% of subjects 60-69 years and in 53% in 70-79 years were satisfied with their sexual life; these figures are similar to our PC-patients data. Bosch, Groeneveld, Bohnen, Prins, & Hop (1999) reported an incidence of ED in 49% of men 70-74 years, in a community-based sample of 1661 men. This percentage is much lower than in the present study (65%). Forty-one per cent of our patients expressed a high level of sexual desire and 78% considered sex very important. Helgason, Adolfsson, Dickman, Arver, Fredrikson, G6thberg, & Steineck (1996) reported similar percentages in men without PC: 83% stated that sex was (very) important and 76% of men aged 60-69 years were potent. Before diagnosis, 66% of our patients were sexually active. These percentages are similar to those of Janus & Janus (I993) who reported that 69% of 212 men 65 years and older had weekly sexual activity, and of Brecher (1984) who reported that 79% of 598 men 70 years and older were sexually active. Diabetes and hypertension are significantly associated with ED, as well certain medications and the use of tobacco (Fe1dman, Goldstein, Hatzichristou, Krane, &

McKin1ay, 1994). We found no statistically significant difference regarding sexual functioning in patients with or without co-morbidity, possibly because of the small numbers (only 21 % of patients with co-morbidity). None of our patients were on hormonal therapy; use of tobacco or alcohol was not always reported. A significant difference in age was found between RP and RT patients, similar to earlier published studies (Lim, Brandon, Fiedler, Brickman, Boyer, Raub, & Soloway, 1995; McCammon, Kolm, Main, & Schellhammer, 1999; Shrader-Bogen, Kjellberg, McPherson, & Murray, 1997). Age difference is the main reason of all differences encountered in sexual functioning, therefore the differences in sexual functioning between patients undergoing RT or RP are mostly related to the doctor's preference for surgical treatment in younger men.
We are aware of the limited value of these mainly descriptive data, but such information is useful to make comparisons of treatment morbidity. Currently, data are been collected on sexual functioning in the same patients, one and two years after therapy.

Conclusions

There is a decrease in all aspects of sexual functioning after the diagnosis of Pc. Because of the impact of diagnosis and treatment of PC on sexual function, patients with PC may benefit profoundly from sexual counseling before (and presumably following) treatment. Baseline data on sexual functioning prior to treatment are relevant for later comparison with data after treatment and to detect treatment related morbidity.

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1. How much sexual desire (sexual thoughts or feelings) did you have in the past 2 weeks?
None at all
Some
Moderately
Quite a bit
Very much

2. How often did you have a spontaneous erection (partly or complete, not during sexual activity) at night or in the morning in the past 2 weeks?
Never (skip next question)
About once
More than once
About once a day
More than once a day

3. How would you rate the quality of those spontaneous night or morning erections?

1	2	3	4	5
rather soft		half soft/half hard		very firm

4. How important is sex to you?
Very unimportant
Unimportant
Somewhat important
Important
Very important

5. How satisfied are you, in general, with your current sexual life?
Very satisfied
Satisfied
Somewhat satisfied
Unsatisfied
Very unsatisfied

6. Were you sexually active (i.e. masturbation or intercourse) before you were informed to have prostate cancer?
Yes, continue with question 7
No, skip questions 7-10

7. Since you were informed to have prostate cancer, were you less interested in sex than before your illness?
Not at all
A little
Quite a bit
Very much

8. Since you were informed to have prostate cancer, were you less sexually active than before your illness?
Not at all
A little
Quite a bit
Very much

9. Since you were informed to have prostate cancer, did you have more difficulty in getting or maintaining an erection than before your illness?
Not at all
A little
Quite a bit
Very much

10. Since you were informed to have prostate cancer, was sex less enjoyable for you than before your illness?
Not at all
A little
Quite a bit
Very much

11. Were you sexually active (i.e. masturbation or intercourse) in the past 2 weeks?
Yes, go to questions 13-15
No, go to question 12, skip questions 13-15

12. I was not sexually active in the past 2 weeks because. ...
I had no sexual desire
I do not have a partner
My partner did not have sexual desire
I could not get an erection
Otherwise, (please describe)

13. Did you have difficulty in getting an erection in the past 2 weeks?
Yes, (almost) always
Yes, sometimes
No, (almost) never

14. Did you have difficulty in maintaining an erection in the past 2 weeks?
Yes, (almost) always
Yes, sometimes
No, (almost) never

15. How would you rate the quality of your erections during sexual activity in the past 2 weeks?

1	2	3	4	5
rather soft		half soft/halfhard		very firm

Chapter 10

SILDENAFIL CITRATE (VIAGRA) AND ERECTILE DYSFUNCTION FOLLOWING EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY

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Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 5, pp. 1190–1195, 2001

Abstract

Purpose:
To determine the efficacy of sildenafil citrate (Viagra) in patients with erectile dysfunction after three-dimensional conformal external beam radiotherapy (3D-CRT) for prostate cancer.
Methods and Materials:
406 patients with complaints of erectile dysfunction and who completed radiation at least 6 months before the study were approached by mail. 3D-CRT had been delivered (mean dose 68 Gy). Sixty patients were included and entered a double-blind, placebo-controlled, cross-over study lasting 12 weeks. They received during 2 weeks 50 mg of sildenafil or placebo; at Week 2 the dose was increased to 100 mg in case of unsatisfactory erectile response. At Week 6, patients crossed over to the alternative treatment. Data were collected using the International Index of Erectile Function (IIEF) questionnaire, and side effects were recorded.
Results:
Mean age was 68 years. All patients completed the study. For most questions of the IIEF questionnaire there was a significant increase in mean scores from baseline with sildenafil, but not with placebo. Ninety percent of the patients needed a dose adjustment to 100 mg sildenafil. Side effects were mild or moderate.
Conclusion:
Sildenafil is well tolerated and effective in improving erectile function of patients with ED after 3D-CRT for prostate cancer.

Acknowledgements
To Mrs L. Bakri, medical student, for collecting the data and to G. Dohle, M.D., urologist, for his comments on the study protocol.
This study has been supported by an unrestricted grant from Pfizer B.V., The Netherlands.

Introduction

Prostate cancer (PC) has become the most frequent non-skin male malignancy in Western countries. Over recent years the number of PC-diagnosed patients has dramatically increased because of routine prostate-specific antigen (PSA) testing, though erectile dysfunction (ED) after radiation for PC is becoming a concern. Published rates of ED following external beam radiotherapy (ERT) vary from 7% to 64% [1, 2 and 3]. In noncontrolled studies, sildenafil citrate (Viagra) has been reported to be effective in up to 77% of patients 2 years or longer after ERT [4, 5, 6 and 7]. We performed a randomized, double-blind, placebo-controlled, cross-over study to evaluate the efficacy of sildenafil citrate in treating ED in patients who had received three-dimensional conformal external beam radiation (3D-CRT) for PC.

Methods and materials

The medical records of subjects treated with 3D-CRT for PC in the period 1996–1999 were reviewed. A letter in which a study was announced to treat ED with sildenafil was sent to 406 patients with no sign of metastases, no postradiotherapy rise in PSA, who were not on hormonal therapy, who were not using nitrates, with no history of myocardial infarction or cerebral vascular accident and with no prior radical prostatectomy. Eighty-two patients showed interest in the study. After reviewing the inclusion criteria, 60 patients could be included. All patients claimed normal erectile functioning before radiation and had experienced progressive ED after treatment. ED was defined as the inability to attain or to maintain penile erection sufficient for satisfactory sexual activity (intercourse or masturbation). None of the patients used treatment for their ED, all were in a stable relationship, and all gave written informed consent to participate in the present study and to perform sexual activity at least once a week.

Patient characteristics

Patient characteristics are summarized in Table 1. All patients were treated on average 39 months earlier using a linear accelerator, mean energy 23 (range 6–25) MV with a mean dose of 68 (range 66–78) Gy, prescribed to the planning target volume. A 3D-CRT approach with a 3-field technique was used, the clinical target volume being the prostate gland, with or without the seminal vesicles, as seen on the planning computer tomography scan and adding 10 to 15 mm for the planning target volume.

Table 1. Patients (n = 60) with erectile dysfunction following radiotherapy: patient characteristics

Mean (range) age at radiation (yr)	65 (53–77)
Mean (range) age at trial entry (yr)	68 (56–79)
Mean (range) time after radiation (mo)	39 (15–55)
	%
Hypertension	10
Diabetes mellitus	3
TURP	18
Tumor stage	
T1c	33
T2a	17
T2b	15
T3a	18
T3b	17
Differentiation grade	
G1 (well)	43
G2 (moderately)	43
G3 (poor)	14
Median (range) PSA/μg/L	8.5 (1–227)

Abbreviations: TURP = transurethral resection of the prostate; PSA = prostate-specific antigen

Study design

After a 4-week, no treatment run-in period during which baseline data on sexual functioning were collected, patients entered a 12-week, double-blind, placebo-controlled treatment period. Patients received 50 mg of sildenafil citrate (n = 30) or placebo (n = 30) during 2 weeks. Drug or placebo was taken approximately 1 h before sexual activity, at least once a week and no more than once per day. After 2 weeks, all patients claiming inadequate erectile functioning received 100-mg tablets (sildenafil citrate or placebo) for the remaining 4 weeks. At Week 6, patients crossed over to 50 mg placebo or sildenafil citrate for another 2 weeks. In the event of unsatisfactory erectile response, at the end of Week 8, patients received 100-mg tablets (placebo or sildenafil citrate). If patients experienced adverse events, the dose could be decreased to 25 mg.

Patients were asked to fill out the International Index of Erectile Function (IIEF), an international, validated, self-administered, 15-item questionnaire [8] (Appendix), at the end of the run-in period, and at each visit to the clinic: after 2, 6 (before cross-over), 8, and 12 weeks. Responses on the IIEF questionnaire were graded on a scale of 1 (almost never or never) to 5 (almost always or always), 0 being no sexual activity. Mean baseline scores to the 15 IIEF questions were calculated at the end of the run-in period before treatment and compared with mean final scores after 2 and 6 weeks treatment of sildenafil or placebo. Two more questions were added for a global efficacy assessment to which patients could respond either positively or negatively: "Has the treatment you have been taking improved your erections?" and "Has the treatment you have been taking led to successful intercourse?" Furthermore, a side effects recording questionnaire was used. The study was performed according to the Declaration of Helsinki and was approved by the Hospital Medical Ethical Committee.

Statistical analysis

Comparison between sildenafil scores and placebo scores was done using Wilcoxon's matched pairs test. The same test was used to compare baseline scores and sildenafil scores, and baseline scores and placebo scores. For within-group and between-group comparison of percentages, McNemar's test and Fisher's exact test were used, respectively. Correlation coefficients given (r) are Spearman's; $p = 0.05$ (two-sided) was considered the limit of statistical significance. Items 3 and 4 of the IIEF were considered the primary outcome variables in this study. Power calculations had led to a study size of 50 patients; to compensate for possible dropouts, 60 patients were included.

Results

All patients completed the study. Mean time between completion of radiation treatment and initiation of the study was 39 (range 15–55) months. Both treatment sequences were well balanced regarding all baseline scores of the IIEF (all p values > 0.36). Also distribution of time from completion of radiation was the same. A comparison of mean scores of the IIEF questions before and after 6 weeks of treatment with sildenafil or placebo is reported in.

For all items of the IIEF questionnaire (except #12) there was a significant increase in mean scores from baseline with sildenafil, but not from baseline with placebo (except #6, #10, and #15). Forty-five percent of the patients after sildenafil and 8% after placebo responded positively to the global efficacy assessment question about improvement of erections ($p < 0.001$). Successful intercourse was reported in 55% of the patients after sildenafil versus 18% after placebo ($p < 0.001$). For all items of the IIEF questionnaire there was a positive significant correlation (r values ranging from 0.35 to 0.58) between baseline scores and scores after sildenafil. No statistically significant correlations were found between efficacy of sildenafil and the following: age at treatment, prostate cancer stage, use of antihypertensives, and time between radiation treatment and initiation of study. An analysis of the IIEF scores after 2 and 8 weeks (at 50-mg dose) also showed a significant difference between sildenafil and placebo for all items, except for item #11 (p = 0.06). Most of the patients (90%) increased the sildenafil dose to 100 mg, and no patient decreased the dose to 25 mg.

Table 2. Mean scores (SD) of the IIEF questionnaire before and after 6 weeks of treatment with sildenafil citrate or placebo

Questions	Baseline score	Score after sildenafil*	Score after placebo†
1. Erection frequency	1.7 (1.6)	2.9 (1.6)	1.8 (1.1)
2. Erection firmness	1.5 (1.5)	2.8 (1.8)	1.5 (1.1)
3. Penetration ability	1.5 (1.4)	2.8 (1.7)	1.6 (1.1)
4. Maintenance frequency	1.3 (1.4)	2.6 (1.7)	1.5 (1.0)
5. Maintenance ability	1.6 (1.7)	2.8 (1.7)	1.8 (1.4)
6. Intercourse frequency	1.2 (1.1)	2.8 (1.1)	2.4 (1.0)‡
7. Intercourse satisfaction	1.9 (1.9)	2.7 (1.6)	1.9 (1.3)
8. Intercourse enjoyment	1.6 (1.5)	2.8 (1.4)	1.9 (1.1)
9. Ejaculation frequency	2.1 (1.9)	3.0 (1.6)	2.4 (1.6)
10. Orgasm frequency	2.1 (1.8)	3.0 (1.7)	2.5 (1.6)‡
11. Desire frequency	2.8 (1.2)	3.0 (1.1)	2.8 (1.2)
12. Desire level	2.7 (1.0)	3.0 (1.0)	2.6 (1.0)
13. Overall satisfaction	2.3 (1.3)	3.0 (1.4)	2.3 (1.2)
14. Relationship satisfaction	2.7 (1.3)	3.2 (1.4)	2.8 (1.4)
15. Erection confidence	2.1 (1.1)	3.0 (1.1)	2.4 (1.3)‡

* Between baseline and sildenafil treatment $p < 0.001$, except for #11 ($p = 0.04$) and #12 ($p = 0.06$)

† Between sildenafil treatment and placebo $p < 0.01$, except for #6 ($p = 0.04$) and #14 ($p = 0.03$).

‡ Significant difference between baseline score and placebo ($p < 0.04$).

Side effects

All side effects (see Table 3) were mild or moderate, transient, and did not result in drug discontinuation. Except for headache, flushing, and dyspepsia, all other reported adverse events did not differ significantly between the two treatments.

Table 3. Side effects after 6 weeks of treatment with sildenafil or placebo

Side effect	Sildenafil (%)	Placebo (%)	*p*-value*
Headache	42	15	<0.001
Flushing	13	2	0.04
Myalgia	15	13	1.00
Nasal congestion	22	12	0.10
Dyspepsia	32	8	<0.001
Vision disturbances	17	8	0.18
Dizziness	17	10	0.29

* McNemar's test.

Discussion

Sildenafil citrate (Viagra) is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5, and hence inhibits the degradation of cGMP in the cavernosal smooth-muscle cells, restoring erectile response to sexual stimulation in patients with ED of different etiologies [9 and 10]. To our knowledge, no randomized, placebo-controlled, double-blind trials have been performed to assess the efficacy of sildenafil to treat ED after radiotherapy for PC. Previous,

noncontrolled reports indicated that sildenafil is effective and well tolerated in PC patients following radiotherapy. Main findings of the present study are the good tolerability of sildenafil even in the higher dose (100 mg) and its efficacy to have successful intercourse in 55% of the patients. Zelefsky *et al.* [5] reported on 50 patients with progressive deterioration of sexual functioning after 3D-CRT for PC. At a median time of 19 months, sildenafil treatment resulted in an improvement in the firmness of erections in 74% of the patients and a partial improvement in 4%. Kedia *et al.* reported on 21 patients [4]; using the IIEF questionnaire, an improvement of erectile function with sildenafil was reported by 71% of the patients. Weber *et al.* [6] performed an open-label study in 35 patients treated by ERT; erectile function was assessed using the IIEF questionnaire before study entry and at 6 weeks after using 100 mg of sildenafil. Of the 30 patients who completed the study, 23 (77%) reported significantly improved erectile function. The most recent and prospective study by Valicenti *et al.* [7] reported on 23 patients, with pre-ERT data on sexual functioning; 100 mg sildenafil (post-ERT median time 12 months) restored sexual functioning to pre-ERT levels in 21 of 23 patients.

In the present study, we found sildenafil to be effective in approximately 50% of our patients. A potential limitation of our study is the absence of data on erectile functioning before ERT. The efficacy of sildenafil in the present study is lower than in the open-label studies. However, our percentage is similar to the efficacy of sildenafil as reported in patients after radical prostatectomy or with diabetes [11 and 12]. Both treatment sequences were well balanced for sexual function baseline scores and time after completion of radiation. We found a positive significant correlation between baseline scores and scores after sildenafil; thus, erectile functioning before therapy can predict treatment outcome with sildenafil. We found no statistically significant correlations in efficacy of sildenafil with age, concomitant medication, time after radiation treatment, and previous transurethral resection of the prostate (TURP). These findings are in accordance with the data presented by Weber *et al.* [6]. In the present study no patients discontinued because of side effects. This is in contrast with the Weber *et al.* study [6] in which 24% of the patients did not complete the study. In the present study the side effects always graded mild or moderate, and they were transient; headache was reported by 42% of the patients and dyspepsia by 32%. These percentages seem to be higher than in other studies [4 and 5], but similar to those reported in clinical practice [13].

The higher dose of 100 mg seems to be necessary to treat ED after radiotherapy; 90% of our patients used 100 mg of sildenafil. This corroborates earlier reports [4 and 6].

Zelefsky and Eid [14] showed that ED in patients treated with radiotherapy is more often associated with an arteriogenic origin. Sildenafil induces relaxation in the corpora cavernosa smooth muscles and subsequently an inflow of blood, thus this could explain its efficacy in treating ED after radiotherapy. Furthermore, sildenafil taken at bedtime has been found to significantly increase nocturnal erectile activity, especially in patients with presumed vasculogenic ED [15]. We could hypothesize that this might be a potential way of minimizing the vascular deterioration that usually occurs after radiation therapy.

Conclusions

Sildenafil citrate (Viagra) is an effective and well tolerated oral treatment in men with ED after 3D-CRT for prostate cancer. In the present study, side effects were mild or moderate and never led to discontinuation of the drug. Because of the simplicity of delivery and the acceptable side effects, sildenafil should be the first treatment option for patients complaining of erectile dysfunction following radiotherapy for prostate carcinoma, but not using nitrates.

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APPENDIX. International index of erectile function

These questions ask about the effects your erection problems have had on your sex life over the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

- *sexual activity* includes intercourse, caressing, foreplay, and masturbation
- *sexual intercourse* is defined as vaginal penetration of the partner (you entered your partner)
- *sexual stimulation* includes situations like foreplay with a partner, looking at erotic pictures, etc.
- *ejaculation*: the ejection of semen from the penis (or the feeling of this)

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?
Please check one box only
[ ] No sexual activity
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?
Please check one box only
[ ] No sexual stimulation
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

The next three questions will ask about the erections you may have had during sexual intercourse.

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
Please check one box only
[ ] Did not attempt intercourse
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
Please check one box only
[ ] Did not attempt intercourse
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
Please check one box only
[ ] Did not attempt intercourse
[ ] Extremely difficult
[ ] Very difficult
[ ] Difficult
[ ] Slightly difficult
[ ] Not difficult

6. Over the past 4 weeks, how many times have you attempted sexual intercourse?
Please check one box only
[ ] No attempts
[ ] 1–2 attempts
[ ] 3–4 attempts
[ ] 5–6 attempts
[ ] 7–10 attempts
[ ] 11+ attempts

7. Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?
Please check one box only
[ ] Did not attempt intercourse
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?
Please check one box only
[ ] No intercourse
[ ] Very highly enjoyable
[ ] Highly enjoyable
[ ] Fairly enjoyable
[ ] Not very enjoyable
[ ] No enjoyment

9. Over the past 4 weeks, when you had sexual stimulation intercourse, how often did you ejaculate?
Please check one box only
[ ] No sexual stimulation/intercourse
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

10. Over the past 4 weeks, when you had sexual stimulation intercourse, how often did you have the feeling of orgasm (with or without ejaculation)?
Please check one box only
[ ] No sexual stimulation/intercourse
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

The next two questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (for example masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.
11. Over the past 4 weeks, how often have you felt sexual desire?
Please check one box only
[ ] Almost always/always
[ ] Most times (much more than half the time)
[ ] Sometimes (about half the time)
[ ] A few times (much less than half the time)
[ ] Almost never/never

12. Over the past 4 weeks, how would you rate your level of sexual desire?
Please check one box only
[ ] Very high
[ ] High
[ ] Moderate
[ ] Low
[ ] Very low/none at all

13. Over the past 4 weeks, how satisfied have you been with your overall sex life?
Please check one box only
[ ] Very satisfied
[ ] Moderately satisfied
[ ] About equally satisfied and dissatisfied
[ ] Moderately dissatisfied
[ ] Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?
Please check one box only
[ ] Very satisfied
[ ] Moderately satisfied
[ ] About equally satisfied and dissatisfied
[ ] Moderately dissatisfied
[ ] Very dissatisfied

15. Over the past 4 weeks how do you rate your confidence that you could get and keep an erection?
Please check one box only
[ ] Very high
[ ] High
[ ] Moderate
[ ] Low
[ ] Very low

Chapter 11

ACUTE AND LATE COMPLICATIONS AFTER RADIOTHERAPY FOR PROSTATE CANCER: RESULTS OF A MULTI-CENTER RANDOMIZED TRIAL COMPARING 68 GY TO 78 GY

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Accepted for publication in Int.J.Radiation Oncology Biol.Phys.

Abstract

Purpose:
To compare acute and late gastro-intestinal (GI) and genitourinary (GU) side effects in prostate cancer patients randomized to receive 68 Gy or 78 Gy.

Materials and methods:
Between June 1997 and February 2003, 669 prostate cancer patients were randomized between radiotherapy with a dose of 68 Gy and 78 Gy, in 2 Gy per fraction and using 3D-conformal radiotherapy. All T-stages with a PSA < 60 ng/ml were included, except any T1a and well-differentiated T1b-c tumors with a PSA ≤ 4 ng/ml. Stratification was done for four dose-volume groups (according to the risk of seminal vesicles (SV) involvement), age, hormonal treatment and hospital. The CTV consisted of the prostate with or without the SV, depending on the estimated risk of SV invasion. The CTV-PTV margin was 1 cm for the first 68 Gy and was reduced to 0.5 cm (0 cm towards the rectum) for the last 10 Gy in the 78 Gy-arm. Four Dutch hospitals participated in this phase III trial. Evaluation of acute and late toxicity was based on 658 and 643 patients, respectively. For acute toxicity (<120 days) the RTOG scoring system was used and the maximum score was reported. Late toxicity (>120 days) was scored according to the slightly adapted RTOG/EORTC criteria.

Results:
The median follow-up time was 31 months. For acute toxicity no significant differences were seen between the two randomization arms. GI toxicity grade 2 and 3 was reported as the maximum acute toxicity in 44% and 5% of the patients, respectively. For acute GU toxicity these figures were 41% and 13%. No significant differences between both randomization arms were seen for late GI and GU toxicity, except for rectal bleeding requiring laser treatment or transfusion ($p=0.007$) and nocturia ($p=0.05$). The 3-year cumulative risk of late RTOG/EORTC GI toxicity grade ≥ 2 was 23.2 % for 68 Gy, and 26.5% for 78 Gy ($p=0.3$). The 3-year risks of late RTOG/EORTC GU toxicity grade ≥ 2 were 28.5% and 30.2% for 68 Gy and 78 Gy, respectively ($p=0.3$).
Factors related to acute GI toxicity were hormonal treatment (HT) ($p<0.001$), a higher dose-volume group ($p=0.01$) and pretreatment GI symptoms ($p=0.04$). For acute GU toxicity prognostic factors were: pretreatment GU symptoms ($p<0.001$), HT ($p=0.003$) and prior TURP ($p=0.02$). A history of abdominal surgery ($p<0.001$) and pretreatment GI symptoms ($p=0.001$) were associated with a higher incidence of late GI grade ≥ 2 toxicity, while HT ($p<0.001$), pretreatment GU symptoms ($p<0.001$) and prior TURP ($p=0.006$) were prognostic factors for late GU grade ≥ 2.

Conclusions:
Rising the dose to the prostate from 68 Gy to 78 Gy resulted in higher incidences of acute and late GI and GU toxicity, but these differences were not significant, except for late rectal bleeding requiring treatment and late nocturia. Other factors than the studied dose-levels appeared to be important in predicting toxicity after radiotherapy, especially previous surgical interventions (abdominal surgery or TURP), hormonal therapy and the presence of pretreatment symptoms.

Acknowledgements:
This project has been supported by the Dutch Cancer Society (NKB Grant NKI 98-1830 and CKTO 96-10)
The authors are grateful to the datamanagers for their valuable contributions to this project: Paula Hoynck van Papendrecht, Gerda van Wijhe, Piet van Assendelft, Ingrid Mandjes, Danny Baars, Karen vanden Elsaker and Sippie Roukema.

1. Introduction

In the last decade a lot of attention has been paid to dose-escalation for radiotherapy of prostate cancer because of unsatisfactory local control and survival results with the past treatment doses (1,2). In this attempt to improve outcome in prostate cancer other approaches regarding radiotherapy have been examined, such as the use of neo-adjuvant, concomitant and/or adjuvant hormonal treatment (HT) combined with external beam irradiation (3,4,5), brachytherapy of the prostate in monotherapy (6) or as a boost (7), or boosting with proton (8,9) or neutron beams (10).
Encouraging results of improved outcome with higher radiation doses have already been reported in several non-randomized (7,11,12,13) and randomized studies (8,14). Many studies tried to identify the patient group that would benefit most from a higher radiation dose to the prostate. In the MD Anderson Cancer Centre (MDACC) randomized trial, intermediate-risk, and to lesser extent high-risk patients, benefited from higher doses (14), while low-risk patients showed a dose-response when going from doses of 64-66 Gy to 68-70 Gy, but not beyond that dose-level (15). Others also reported improved outcome in intermediate (11,13,16) or high-risk patients (8,11). Less frequently, even low-risk patients have been reported to show a dose-response (17,18). Most studies however do not show a dose-response effect in low-risk patients, but one can argue that a longer follow-up may be necessary to observe any benefit in these favorable patients. In contrast, some authors advocate watchful waiting (or deferred therapy) as initial management in selected low-risk patients (19). We also have to keep in mind that the definitions of risk groups are different in many studies. Classifications into two or three risk groups are based on PSA alone, or more frequently on combinations of two or three of the following factors: PSA, Gleason score and T-stage. Together with the rather frequent modifications of the TNM-staging this can hamper outcome comparison of risk groups between different studies.
In 1997 we initiated a multi-institutional randomized phase III-trial in order to investigate if an additional boost of 10 Gy improves biochemical NED and overall survival. Moreover we wanted to explore which patient group in particular might benefit from higher radiation doses. However, an increase of the radiation dose to the tumor implicates an increase of the dose to the surrounding normal tissue, which is the dose-limiting factor. And as prostate cancer patients have a potentially long survival, assessment of late toxicity is of major importance. Like others (12,20,21,22), we first performed a phase I dose-escalation trial to demonstrate the feasibility of irradiating the prostate to 78 Gy (23). Few phase III-trials comparing higher doses with conventional doses using external beam radiotherapy have been performed or are on their way (14,24, RTOG P-0126, MRC trial RT01). In our phase III randomized trial we compared radiation doses of 68 Gy and 78 Gy. This first analysis was performed to compare both randomization arms concerning acute and late toxicity in relation to general treatment factors and patient-related factors.

2. Methods and materials

2.1 Protocol entry criteria and stratification

Between June 1997 and February 2003, 669 patients with a localized adenocarcinoma of the prostate were entered in this phase III trial, randomizing patients between 68 Gy and 78 Gy. Four different centers in the Netherlands participated. Pretreatment evaluations included clinical history, physical examination, transrectal ultrasound of the prostate (TRUS), laboratory studies (full blood count, creatinine, alkaline phosphates, gamma-GT and PSA), a bone scan and optionally a pelvic CT-scan. The initial total PSA of each patient was determined, before digital rectal examination (DRE) and/or 10 days after biopsy or transurethral resection of the prostate (TURP), and use of Abbott IMx assay was recommended. TNM-staging was scored according to the American Joint Committee on Cancer 1997. At histological evaluation Gleason score and/or differentiation grade were assigned, and patients were divided into 3 groups: well differentiated or Gleason score 2-4, moderately differentiated or

Gleason score 5-7, poorly differentiated or Gleason score 8-10. All T-stages with a PSA < 60 ng/ml were eligible, except any T1a prostate tumor and well-differentiated (grade 1 or Gleason score<5) T1b–c tumors with PSA-levels ≤ 4ng/ml. Patients with positive regional lymph nodes, with distant metastases, on anticoagulant therapy, with a Karnofsky Index below 80, with a previous radical prostatectomy or pelvic irradiation were excluded. Hormonal therapy (HT) was allowed and was (commonly) prescribed to high-risk patients. In hospital A, HT was started approximately 1-6 months prior to radiotherapy and was prescribed for 3 years. In hospital B, HT was administered 3 to 4 months before radiotherapy and was continued for a total period of 6 months. Generally, a LHRH-agonist preceded by an anti-androgen was prescribed. In hospital C and D no HT was given, except for 1 patient.

Patients were stratified for hospital, HT, age (≤ 70 vs. > 70 years) and dose-volume groups. Four dose-volume groups were defined according to the estimated risk of seminal vesicles (SV) involvement (Table 1), according to Partin *et al* (25). Group I included T1b, T1c and T2a patients with an estimated risk of SV involvement of less than 10%. Group II included T1b, T1c and T2a patients with an estimated risk between 10% and 25%, while group III contained T1b, T1c and T2a patients with a risk larger than 25%, and all T2b and T3a patients. Group IV finally, comprised all T3b and T4 patients. For patients of dose-volume groups II, III and IV, lymph node evaluation was obligatory by diagnostic pelvic CT scan or ultrasound, and/or surgical or cytological sampling. T3a patients were initially included into dose-volume group IV, but we changed policy during the study (since February 1998) by classifying them into group III. We estimated that a boost on the SV was not indicated for these patients, as invasion of the SV was not proven, although classification as a T3a implies a high risk of SV invasion. Fourteen patients with a T3a prostate cancer, treated before this date, were treated following the directions of group IV instead of group III. Eight of them were randomized in the high-dose treatment arm.

Approval of the Ethical Committee of each institution was obtained and every patient gave an informed consent.

2.2 Dose schemes and Contouring

For each dose-volume group (Table 1), specific planning target volumes (PTV) were defined. Until 68 Gy, margins of 10 mm were added to the CTV to obtain the PTV. For patients included in the high-dose treatment arm, the margins were reduced to 5 mm to obtain the PTV for the last 10 Gy, except for the interface between CTV and rectal wall where no margin was taken to spare the rectum. CTV1 and CTV2 were defined as the prostate only and the prostate with seminal vesicles, respectively. In dose-volume group I, PTV was based on CTV1 during the whole treatment and in both randomization arms. In dose-volume group II, PTV was based on CTV2 for the first 50 Gy, on CTV1 for the following 18 Gy, and for patients in the 78 Gy-arm on CTV1 for the last 10 Gy. In dose-volume group III, PTV was based on CTV2 until 68 Gy, and for those included in the
high-dose treatment arm on CTV1 for the last 10 Gy. Finally, for dose-volume group IV, the PTV was based on CTV2 for the whole treatment in both randomization arms.

The rectum was delineated from the level of the tuberosities till the level of the inferior border of the sacro-iliacal joints, or when the rectum is no longer adjacent to the sacrum. This definition results from a quality control study performed at the beginning of the trial (28). In some patients the anal canal was drawn separately if the anal canal was not already included in the rectum delineated according to the definition. If the rectum volume including filling exceeded 150 cm^3, rescanning was advised. In view of a future analysis with dose-volume parameters, the coordinating centre (hospital B) reviewed all delineated structures, including CTV, PTV and

organs at risk for consistency with the protocol, in order to achieve a more homogeneous delineation and reduce interobserver variability. When a deviation was found for the organs at risk, the delineated structure was adapted according to the guidelines.

Table 1: Grouping criteria and identification of the 4 corresponding patient 'dose-volume groups', according to the estimated risk of seminal vesicles involvement.

		T1b, T1c, T2a				T2b, T3a	T3b, T4
Gleason score	Grade of differentiation	PSA (µg/l)				PSA (µg/l)	
		0-4	4-10	10-20	20-60	0-60	
2-4	Well-differentiated	I	I	I	II	III	IV
5-7	Moderately differentiated	I	II	II	III	III	IV
8-10	Poorly differentiated	II	III	III	III	III	IV

2.3 Radiotherapy techniques

All patients were scanned in treatment position (supine), with a slice thickness of 3 to 5 mm, and were treated with 3D conformal therapy using a multileaf collimator. Patients were instructed to urinate about 1 hour before the CT scan and every treatment fraction, then to drink ¼ liter liquid and not to urinate till after CT-scan or radiotherapy. Treatment planning was done after randomization. The treatment technique was left to the discretion of the participating institution. The techniques used were a 4-field technique (hospital C), 3-field techniques using one anterior and 2 lateral (hospital B, D), or 2 posterior oblique, wedged fields (hospital A). For the boost of 10 Gy in the high-dose treatment arm, similar techniques were used. The boost was given sequentially with 3D-CRT, except for the 41 patients in institution B, where a simultaneous integrated boost was given using intensity-modulated radiation therapy (IMRT) (26). Dose was specified to the ICRU (International Commission on Radiation Units and Measurements) reference point (27) and was delivered at 2 Gy per fraction per day with a megavoltage linear accelerator with ≥ 6 MV photons. Each participating centre used its own method for tissue inhomogeneity correction. According to ICRU, the dose to the PTV was within –5% and +7% to the prescribed dose. At least 99% of the PTV was treated to at least 95% of the prescribed dose in the ICRU reference point.

2.4 Treatment plan and treatment evaluation

The dose constraint for the rectum stipulated that the percentage of rectum receiving ≥ 74 Gy should not exceed 40%, similar to the constraint used in the Memorial Sloan Kettering Cancer Centre (11). The dose to the small bowel should not be higher than 68 Gy. This constraint was arbitrarily chosen based on former clinical experience with treatment doses of 68 Gy to the prostate. In the low-dose treatment arm all patients received the prescribed 68 Gy, while in the high-dose treatment arm, 36 patients received a dose lower than 78 Gy. One patient died after 16 Gy from a disease-unrelated cause, the other 35 patients received a dose ranging from 68 to 76 Gy. Nineteen of these patients were planned with a lower dose because of small bowel (11 patients) or rectal (8 patients) dose constraints. In 16 patients the dose was lowered during radiotherapy because of toxicity, on patient's request, or because of a technical problem. Only 3 of these patients had a maximal acute toxicity grade 3 (GU). The analyses presented here are based on the intention to treat.

Multiple portal images or portal films of each field were obtained in the first week. In the subsequent weeks orthogonal views were obtained weekly, and compared with corresponding Digitally Reconstructed Radiographs or simulation images. A verification procedure with decision rules for

setup corrections was specified by each institution according to the guidelines published by a collaborative study in the Netherlands (29). By using this protocol, systematic errors did not exceed 5 mm.

2.5 Follow-up schedule

All patients were evaluated once a week during radiotherapy and had a follow-up every three months in the first year, every four months in the second year, biannually in the following three years and yearly thereafter. At each follow-up visit a physical examination, including a DRE, full blood count, PSA, alkaline phosphates and creatinine levels were determined (prior to DRE). At PSA-relapse, defined according to the ASTRO-definition (30), a bone scan, a CT abdomen and a prostate biopsy were advised. In case of a PSA >1 ng/ml at 2 years of follow-up without PSA-relapse a TRUS was advised to obtain random biopsies.

2.6 Toxicity scoring

To determine the incidence and severity of the gastro-intestinal (GI), and genitourinary (GU) complaints, patients completed a detailed self-assessment questionnaire, concerning these GI and GU complaints, at the start of the therapy, weekly during therapy and at each follow-up visit. This patient self-assessment questionnaire included 22 questions, and was comparable to the questionnaires used by Tait et al (31). Together with the physician's notes, including the use of medication, they were used to classify the GI and GU symptoms according to a modified RTOG scoring system (Radiation Therapy Oncology Group) for the acute radiation morbidity (Appendix Table A1), and to the RTOG/EORTC (European Organization for Research and Treatment of Cancer) (Appendix Table A2) (32) and SOMA/LENT (Subjective, Objective, Management and Analytic/Late Effect Normal Tissue) scoring systems for the late radiation morbidity. The RTOG/EORTC and SOMA/LENT scales were both slightly adapted according to the scales used in the dose-escalation study preceding this randomized study (23). In this analysis we only reported the RTOG/EORTC scores. The pretreatment score is defined as the RTOG score obtained before radiotherapy. Side effects occurring within 120 days from start of radiotherapy were considered acute toxicity. Late toxicity was scored from 120 days after start of the treatment. For the evaluation of late toxicity we also analyzed 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. Seven indicators were defined for the GU symptoms, and 5 for GI toxicity (Appendix Table A3). When patients were diagnosed with a loco-regional recurrence, further assessment of complications was omitted from that moment on, as distinction between treatment- or recurrence-related symptoms can be difficult. Patients with biochemical relapses or distant metastases were not censored from the analysis.

2.7 End points and statistical analyses

Factors analyzed for their possible relationship with the endpoints were: randomization arm, dose-volume group, TURP before radiotherapy, hormonal treatment, pretreatment symptoms, age at diagnosis (continuous variable), diabetes mellitus, cardiovascular history, a history of abdominal surgery, smoking and use of acetyl salicylic acids (=covariates). The maximal acute toxicity was not included as a covariate in the analysis of late toxicity because it represents an effect of treatment, and not an independent variable.

Primary endpoints for acute toxicity were the maximum score on the RTOG toxicity scales for GI and GU adverse events. Possible interaction of the covariates and their joint effect on maximal acute toxicity were analyzed with ordered logistic regression. All covariates were first analyzed in a baseline model including the randomization arm, hospital of treatment and the dose-volume group. After that a

multivariate ordered logistic regression analysis was performed including all covariates that appeared to be associated with the endpoint in the first analysis. The Odds Ratio was used to express the strength of the association of a parameter with the incidence of maximal acute toxicity.

Primary endpoints for late toxicity were the GI and GU RTOG/EORTC toxicity grade ≥ 2 and ≥ 3. Secondary endpoints for late toxicity were the GI and GU indicators (Appendix Table A3). The Kaplan Meier method was used to calculate cumulative incidences of late side effects by arm and subgroups, and the log rank test was applied to compare the incidences by arms and subgroups. The Kaplan Meier curves were cut off at 4 years, but the log rank values were calculated on the total number of events. The Cox proportional hazards regression (PHR) model was used to determine the independent effect of the covariates on each studied endpoint of late toxicity. The results of the regression analyses are presented in the form of relative hazard rates. All covariates were first analyzed in a Cox PHR baseline model including the randomization arm, hospital of treatment and the dose-volume group in order to adjust for these factors. Subsequently, a multivariate Cox regression analysis was performed to test whether significant covariates remained significant. In this multivariate analysis, all covariates were included that appeared to be associated ($p<0.1$) with the endpoint in the former analysis, together with the covariates of the baseline model.

Two-tailed tests were used. A p-value ≤ 0.05 was considered statistically significant. No adjustment was done for the multiple endpoints and multiple testing. When pretreatment data were missing, the evaluation on day 7 was considered as the pretreatment toxicity score, or if this form was missing too, these values were treated as missing and included separately in the multivariate analysis.

Table 2: Distribution of patients by randomization arm and pretreatment characteristics

	68 Gy arm (n=331)		78 Gy arm (n=333)	
Age (years)				
Mean age	68.6		68.8	
Range	50.3-82.9		48.7-83.6	
Dose-volume groups				
Group I	54	(16%)	52	(16%)
Group II	65	(20%)	67	(20%)
Group III	157	(47%)	163	(49%)
Group IV	55	(17%)	51	(15%)
T-stage				
T1b	3	(1%)	5	(2%)
T1c	54	(16%)	62	(19%)
T2a	87	(26%)	77	(23%)
T2b	64	(19%)	64	(19%)
T3a	71	(22%)	81	(24%)
T3b	45	(14%)	42	(13%)
T4	7	(2%)	2	(1%)
Differentiation grade				
I (or Gleason score 2-4)	106	(32%)	93	(28%)
II (or Gleason 5-7)	170	(51%)	194	(58%)
III (or Gleason 8-10)	56	(17%)	45	(14%)
Initial PSA				
Mean (µg/l); SD	17.0; 12.8		15.3; 10.7	
Range (µg/l)	1.7-59.0		0.4-57.0	
< 4 µg/l	25	(8%)	19	(6%)
4-10 µg/l	95	(29%)	119	(36%)
10-20 µg/l	125	(38%)	125	(38%)
> 20 µg/l	86	(26%)	70	(21%)
(Neo-)adjuvant HT	73	(22%)	70	(21%)
TURP	41	(12%)	34	(10%)
Abdominal surgery	91	(27%)	92	(28%)
Diabetes mellitus	20	(6%)	18	(5%)
Cardiovascular history	105	(32%)	113	(34%)
Smoking	51	(15%)	57	(17%)
Use of acetylsalicylic acid	55	(17%)	65	(20%)
Hospital A	201	(61%)	203	(61%)
B	86	(26%)	85	(26%)
C	35	(11%)	35	(11%)
D	9	(3%)	10	(3%)

3. Results

3.1 Patient data

Five of the 669 randomized patients were excluded from the analysis because they were ineligible (3 patients) or because they were not irradiated (2 patients). Table 2 shows a well-balanced distribution of the patient characteristics for both randomization arms. Small differences between both arms were seen for differentiation grade and initial PSA. The high-dose treatment arm had more grade II prostate cancers, while the 68 Gy treatment arm included more grades I and III, and slightly more patients with

a PSA-levels > 20 ng/ml. The mean age at diagnosis was 68.7 years. The median follow-up time was 31 months (range 2–71 months) in both randomization arms. The mean initial PSA amounted to 16.1 µg/l (range 0.4-59.0) for all patients. PSA was determined in all patients, and in 432 cases the Abbott IMx assay was used. Abdominal surgery included appendectomy (42%), repair of inguinal hernia (32%), cholecystecomy (10%), surgery to the stomach (7%), iliacal lymph node dissection (5%) and other abdominal surgery (15%). Hormonal therapy (HT) was administered to 78 patients of hospital A, to 64 patients of hospital B and to 1 patient of hospital D. For acute toxicity, 658 patients were assessable for analysis, because 6 patients had no acute toxicity evaluation form. Due to lacking follow-up data, late toxicity analysis was based on 643 patients (68 Gy: 320; 78 Gy: 323 patients). Seventy-nine of the analyzed patients (12%) had a follow-up of less than one year.

3.2 Acute toxicity

The GI and GU scores gradually increased during treatment, leveling off after 5 weeks, and reaching a maximum at 7 weeks (Fig. 1). No significant differences were seen between the two dose levels when comparing for maximum acute GI (p=0.5) and GU toxicity (p=0.5). In the 68 Gy-arm, the incidences of grade 2 and 3 acute GI toxicity were 41% and 6%, respectively. For the 78 Gy-arm these figures were 47% and 4%. For acute GU toxicity in the standard treatment arm, grades 2 and 3 were reported as the maximum toxicity in 40% and 13 % of the patients, respectively. In the high-dose arm these incidences of GU toxicity were 42% and 13%. No grade 4 or 5 toxicity occurred.

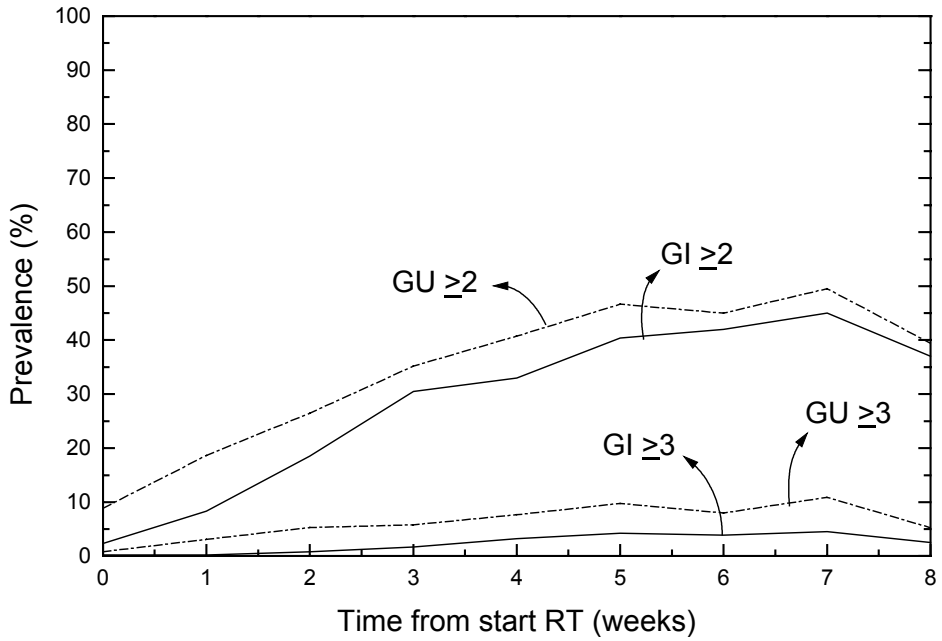

Figure 1: Evolution in time of acute RTOG GI and GU toxicity grade ≥ 2 and grade ≥ 3.

Overall, 51% of the patients experienced no or mild *gastro-intestinal* symptoms (grade 0/1) during radiotherapy, while grade 2 and grade 3 was recorded as the maximum acute GI toxicity in 44% and 5% of the patients, respectively. At ordered logistic regression analysis, using the baseline model, pretreatment GI symptoms, hormonal treatment (HT) and the dose-volume group were significant prognostic factors for acute GI toxicity (Table 3). The pretreatment score was significantly related to acute GI symptoms, but only 2% of the patients scored a pretreatment GI grade ≥ 2 (Fig. 1). When comparing dose-volume groups II, III or IV with group I (as categorical variable), no difference was seen for group II. Groups III and IV on the contrary showed significantly more acute toxicity compared to group I with an odds ratio of 1.8 and 1.7, respectively.

Table 3: Ordered logistic regression analysis for acute GI and GU toxicity

	Ordered logistic regression			
	GI		GU	
	p-value	OR	p-value	OR
Randomization Arm (78Gy vs. 68Gy)	0.5	1.1	0.5	1.1
Dose-volume group (continuous)	0.01*	1.3	0.7	1.0
Hormonal treatment (yes vs. no)	<0.001*	0.5	0.003*	1.8
Pretreatment score (grade = 2 vs. grade < 2) †	0.04*	2.6	<0.001*	7.4
TURP (yes vs. no)	0.5	1.2	0.015*	0.6

Estimates are based on ordered regression analysis using the baseline model; OR = Odds Ratio; GI = Gastro-intestinal; GU = Genitourinary; *: p-values considered significant; †: Pretreatment GI score for acute GI, and pretreatment GU score for acute GU toxicity.

Finally, patients receiving HT experienced less acute GI toxicity. Other analyzed factors, such as prior TURP, age, diabetes mellitus, cardiovascular history, history of abdominal surgery, smoking and use of acetyl salicylic acids were not associated with acute GI toxicity.

Overall, 46% of the patients experienced no or mild *genitourinary* complaints (grade 0/1) during radiotherapy, 41% had a grade 2 and 13 % had a grade 3 as maximum acute GU score. Prognostic factors for acute GU toxicity at ordered logistic regression, using the baseline model, were: the pretreatment GU score, prior TURP and HT (Table 3). A higher pretreatment GU score and use of HT were associated with more acute GU complications, while a TURP prior to radiotherapy was associated with less acute toxicity. Eight percent of the patients scored a GU grade ≥ 2 before radiotherapy (Fig. 1), and 94% of them also scored a grade ≥ 2 as maximal acute GU toxicity. Dose-volume group, age, diabetes mellitus, cardiovascular history, history of abdominal surgery, smoking and use of acetyl salicylic acids were not associated with acute GI toxicity.
In the multivariate ordered logistic regression analysis, all the covariates significantly associated with acute GI and GU toxicity remained statistically significant.

3.3 Late toxicity

3.3.1 Late gastro-intestinal toxicity

When comparing both randomization arms, the incidences of late GI symptoms were higher in the high-dose treatment arm for the overall scores (Fig. 2A) and for the GI indicators (Fig. 3). But these differences were not significant, except for the indicator 'Rectal bleeding requiring laser/transfusion' (p=0.007) (Fig. 2C). Twenty-three patients (68 Gy: 5 patients; 78 Gy: 18 patients) required at least one blood transfusion and/or laser treatment because of rectal bleeding. The cumulative incidences of RTOG/EORTC GI grade ≥ 2 at 3 years were 23.2% in the standard dose arm, and 29.7% in the high-dose arm. For RTOG/EORTC GI grade ≥ 3 these figures were 2.3% and 4.7%, respectively. Two patients experienced a late GI toxicity grade 4, one in each treatment arm. One patient (68 Gy) had a laparoscopic lymph node dissection and was subsequently planned for a prostatectomy. During this procedure the patient turned out to be technically inoperable. Radiotherapy started 2 months later and five months after completion of this treatment he had a perforated sigmoid and required urgent surgery. The second patient (78 Gy), with a history of appendectomy and gastric hemorrhage, had a temporary bowel diversion because of severe radiation proctitis and sigmoiditis. An exacerbation of the symptoms by a diverticulitis could not be excluded.

The data also show an increase of GI toxicity during the first three years, followed by stabilization (Fig. 2). But, the number of patients at risk after three years is too small to draw definite conclusions after three years, although these results are consistent with data in the literature.

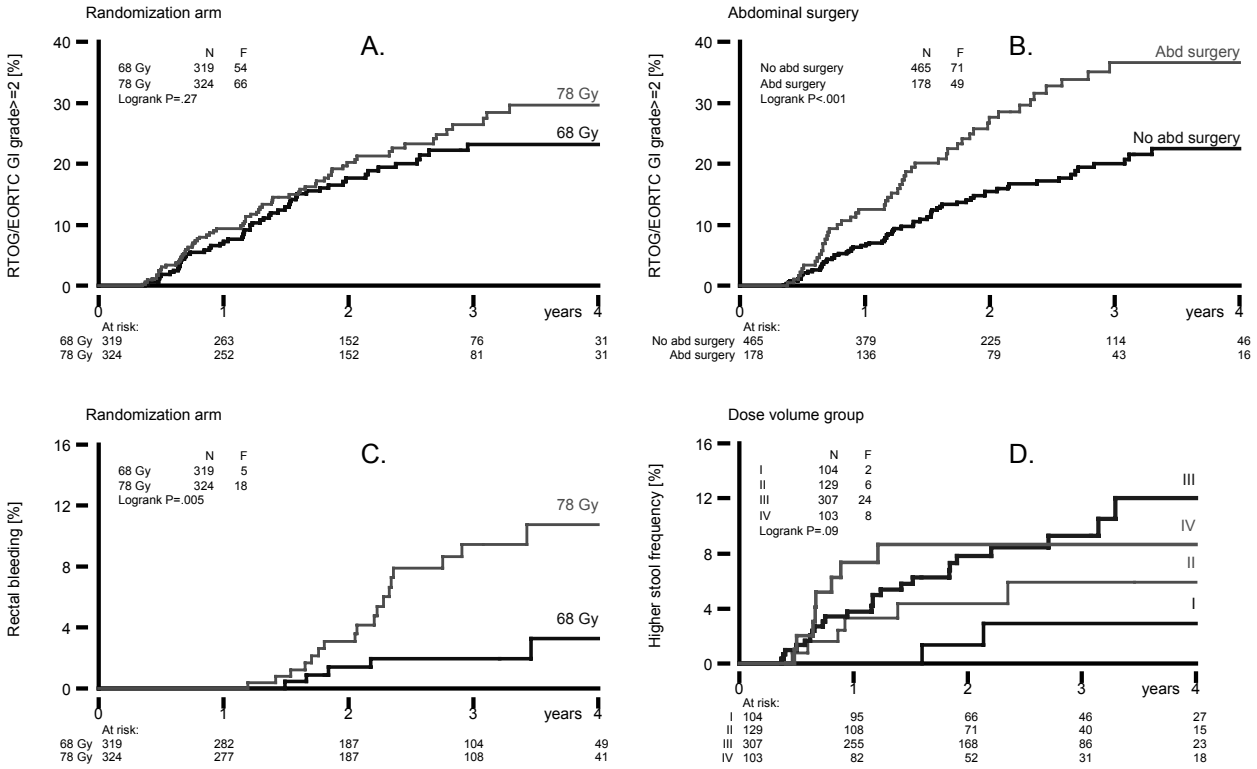

Figure 2: Kaplan-Meier plots of late GI toxicity. A: Comparison of both randomization arms for RTOG/EORTC grade ≥ 2. B: Comparison of patients with and without a history of abdominal (abd) surgery for RTOG/EORTC grade ≥ 2. C: Comparison of both randomization arms for 'Rectal bleeding requiring laser treatment or transfusion'. D: Comparison of the four dose-volume groups for 'Higher stool frequency'. The numbers of patients at risk are mentioned at the foot of each graph. N = total number of patients;F=number of events

Prognostic factors for late RTOG/EORTC GI toxicity in the Cox PHR baseline model were: history of abdominal surgery and the pretreatment GI score (Table 4). Patients with a history of abdominal surgery scored significantly more GI toxicity grade ≥ 2 (Fig. 2B) as well as grade ≥ 3. The higher incidences of GI toxicity in patients with previous surgery concurred with significantly higher incidences of three indicators: 'Bleeding requiring laser/transfusion' (p=0.002), 'Use of incontinence pads because of rectal loss of blood, mucus or stools' (p=0.008) and 'Proctitis and use of steroids' (p=0.05). A higher pretreatment GI toxicity was also predictive for more late GI toxicity ≥ 2. The association with GI toxicity grade ≥ 3 was only borderline significant (p=0.05). The higher GI toxicity in patients with a higher pretreatment score concurred with a higher incidence of two indicators, namely 'Pain/cramps/ tenesmus requiring medication' (p<0.001) and 'Use of incontinence pads because of blood/mucus/stool loss' (p=0.02).
But, only 14 patients had pretreatment GI symptoms grade ≥ 2, and 6 of them developed a late GI grade ≥ 2 so far. Also patients with diabetes mellitus needed more frequently 'Incontinence pads for rectal discharge' (p=0.02). Finally, the dose-volume group had a significant impact on the stool frequency (p=0.02), with higher incidences of risen stool frequency in patients of dose-volume groups III and IV (Fig. 2D).

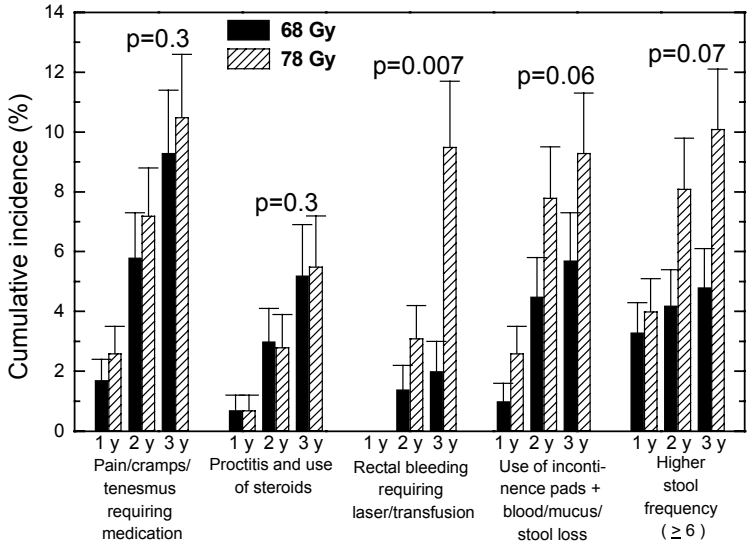

Figure 3: Late GI toxicity: cumulative incidences of the indicators at 1, 2 and 3 years from start of radiotherapy, in both randomization arms. The error bars indicate the standard error. The p-values compare both randomization arms and are obtained from the Cox PHR analysis using the baseline model.

In the multivariate Cox PHR analysis, all the covariates associated with GI endpoints remained statistically significant. Hormonal therapy, age, cardiovascular history, smoking, use of acetyl salicylic acids and prior TURP were not predictive for late GI toxicity.

Table 4: Cox proportional hazards analysis showing the prognostic factors for the end-points late GI and GU RTOG/EORTC grade = 2 and grade = 3

Variable	p-value for grade = 2	HR	p-value for grade = 3	HR
Gastro-intestinal				
Randomization arm (78 Gy vs. 68 Gy)	0.3	1.2	0.6	1.3
Dose-volume group (continuous)	0.9	1.0	1.0	1.0
History of abdominal surgery (yes vs. no)	<0.001*	1.9	0.01*	4.2
Pretreatment GI symptoms (grade = 2 vs. < 2)	0.001*	4.1	0.05*	8.4
Genitourinary				
Randomization arm (78 Gy vs. 68 Gy)	0.3	1.2	0.4	1.3
Dose-volume group (continuous)	0.6	1.0	0.3	1.2
Prior TURP (yes vs. no)	0.006*	1.7	0.001*	3.1
Hormonal treatment (yes vs. no)	<0.001*	2.2	0.03*	2.3
Pretreatment GU symptoms (grade = 2 vs. < 2)	<0.001*	2.2	0.2	2.0

Estimates are based on the baseline Cox PHR analysis; HR = Hazard Ratio; *: p-values considered significant.

3.3.2 Late genitourinary toxicity

When comparing both randomization arms for late RTOG/EORTC GU toxicity, no significant differences were seen for the overall toxicity scores, although the incidence of late GU toxicity was slightly higher in the 78 Gy-arm (Fig. 4A). With regard to the GU indicators (Fig. 5), only the incidence of 'Nocturia' was significantly higher in the high-dose treatment arm (p=0.05) (Fig. 5). Figure 5 shows that the overall late RTOG/EORTC GU toxicity is mainly due to 'Nocturia', and to a lesser extent to 'Dysuria requiring drugs'. The 3-year cumulative risks for RTOG/EORTC GU grade ≥ 2 were 28.5% and 30.2% for the 68 Gy- and the 78 Gy-arm, respectively. For GU grade ≥ 3, these risks were 5.1% and 6.9%, respectively. Grade 4 RTOG/EORTC GU toxicity occurred in 1 patient,

randomized to receive 68 Gy. This patient had a Bricker urinary diversion because of a severely reduced bladder capacity.
The time course of toxicity in figure 4 suggests a further increase of toxicity after 3 years. More mature analysis with a longer follow-up is necessary to confirm this trend, as the number of patients at risk after 3 years becomes small.

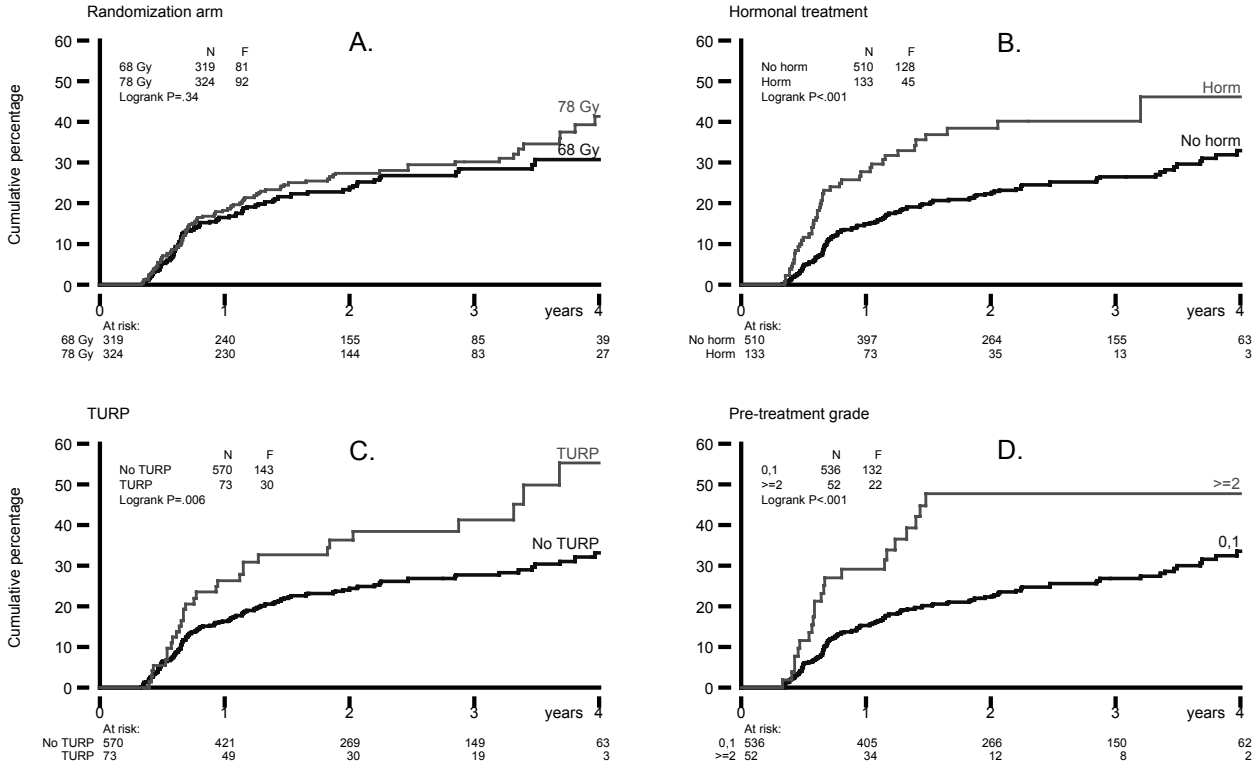

Figure 4: Kaplan-Meier plots of late GU toxicity. Comparison of both randomization arms (A), of hormonal status (B), of TURP before radiotherapy (C) and of the pretreatment RTOG GU score (D) for RTOG/EORTC grade ≥ 2. The numbers of patients at risk are mentioned at the foot of each graph. N = total number of patients; F = number of events.

Testing all potential prognostic factors in a Cox PHR baseline model with the defined GU toxicity endpoints, several significant associations were found. Prognostic factors for late RTOG/EORTC GU toxicity grade ≥ 2 were: hormonal therapy (HT), prior TURP and pretreatment GU score (Table 4). HT and prior TURP also affected late GU grade ≥ 3. The use of HT resulted in higher RTOG/EORTC GU scores (Fig. 4B). This toxicity was mainly due to a significantly higher incidence of 'Nocturia' ($p<0.001$) in patients treated with HT. Patients who had a TURP before radiotherapy also experienced more late GU symptoms (Fig. 4C), and more specifically, a significantly higher incidence of 'Urinary obstruction' ($p<0.001$) and 'Dysuria requiring drugs' ($p=0.05$). A pretreatment GU score ≥ 2 was significantly associated with late GU toxicity (Fig. 4D). These patients had a significantly higher incidence of three indicators: 'Nocturia' ($p<0.001$), 'Urinary frequency during the day' ($p=0.02$) and 'Urinary obstruction requiring treatment' ($p=0.02$). Finally patients with diabetes mellitus had significantly more 'Nocturia' ($p=0.01$). Surprisingly, smoking was associated with more 'Dysuria requiring drugs' ($p=0.02$). In the multivariate Cox PHR analysis, all the covariates associated with GU endpoints remained significant. Age, dose-volume group, history of abdominal surgery, a cardiovascular history and use of acetyl salicylic acids were not associated with late GU toxicity.

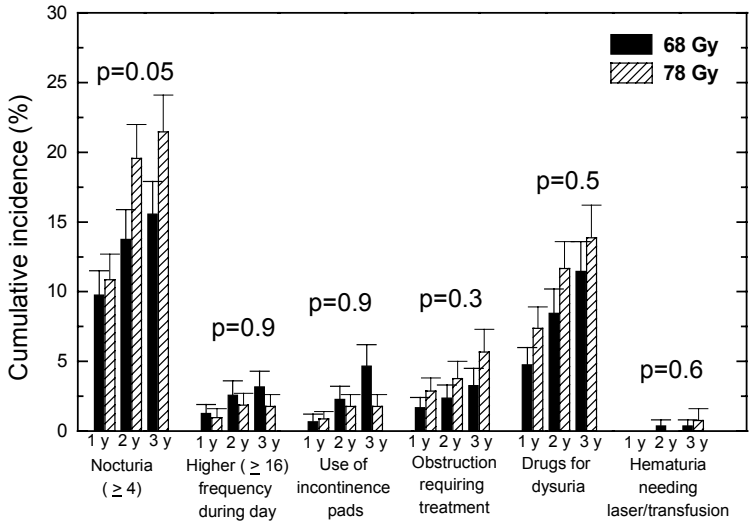

Figure 5: Late GU toxicity: cumulative incidences of the indicators at 1, 2 and 3 years from start of radiotherapy, in both randomization arms. The error bars indicate the standard error. The p-values compare both randomization arms and are obtained from the Cox PHR analysis using the baseline model.

4. DISCUSSION

This multi-institutional phase III-trial, randomizing prostate cancer patients between 68 Gy and 78 Gy, showed a significantly higher incidence of late rectal bleeding and late nocturia in patients included in the high-dose treatment arm. For the other endpoints incidences of acute and late toxicity were generally slightly higher in the 78 Gy-arm, but these differences were not significant. Before discussing the toxicity results we briefly want to make some considerations about scoring of toxicity.

4.1 Scoring of toxicity

Comparison of late toxicity between different trials is complicated, since the variety of adapted toxicity scales is large. The toxicity scoring systems widely used for rectal and bladder radiation complications are the RTOG/EORTC and SOMA/LENT scoring systems, often modified in one way or another (33). We recorded the toxicity according to both (adapted) scoring scales in order to compare them, but in this analysis we focused on the RTOG/EORTC results. Briefly, the GI toxicity scored by RTOG/EORTC or SOMA/LENT gave almost identical results. Actually, this means that the applied adaptations made them equivalent. However, for the SOMA/LENT GU toxicity, the score was shifted towards more severe complications compared to the RTOG/EORTC score due to the higher weight of urinary frequency in the SOMA/LENT score, as previously shown by Boersma et al (23).
In our study, late toxicity scores were based on both the physician's report and the patient's self-assessment questionnaire through the use of extensive checklists. And as showed by Goldner *et al.*, this is a more consistent and reliable way to record toxicity, than based on the physician's report only (34). Especially for GU toxicity Goldner *et al.* found an underestimation of the GU symptoms by the physician. Thus, the use of both self-assessment questionnaires and the physician's notes, but also our adapted scoring system with numerical details can explain the relatively high rate of late grade ≥ 2 complications.

4.2 Acute toxicity & prognostic factors

No significant differences were seen in acute GI and GU toxicity when comparing both dose-levels. This corresponds to the results found in the MDACC trial, randomizing patients between 70 Gy and 78

Gy (35), and the French trial, randomizing patients between 70 Gy and 80 Gy (24), where also no significant differences were seen between the low-dose and high-dose treatment arms. Our crude incidences of maximal acute GI and GU toxicity are comparable with those two trials, although slightly higher for both randomization arms, especially when comparing with the MDACC trial. This difference can partially be due to the somewhat different and less severe RTOG toxicity scales used in the MDACC trial compared to our scales (e.g. mild rectal bleeding, infrequent gross hematuria or the need for sanitary pads for mucous discharge were scored as a grades 2, while we score these items as grades 3).

The use of hormonal treatment (HT) was a prognostic factor for acute GI toxicity and resulted in an improved GI tolerance. Reduction of the prostate volume by HT with subsequently smaller field sizes can explain this finding, but further investigation with dose volume parameters will be performed to clear up this point. Other studies reported no impact of neo-adjuvant and concomitant HT on acute GI toxicity (36,37). Acute GU toxicity on the other hand, was increased in our patients who received a hormonal treatment. In the RTOG 9406 dose-escalation trial a significantly increased acute GU toxicity was seen in patients receiving HT compared to RT alone (38), but a further analysis showed this was only true in men with a poor pretreatment urinary function (37).

In our study, the presence of pretreatment GI and GU symptoms (grade ≥ 2) was associated with more acute GI and GU toxicity respectively, but the patient group with pretreatment GI symptoms was very small, accounting for only 14 patients, and significance level was only borderline. Therefore no conclusions can be drawn out of this result about pretreatment GI toxicity. For GU toxicity on the other hand, our results clearly showed that having GU symptoms before starting radiotherapy is a strong predictor for acute GU toxicity, as 94% of the patients with a grade ≥ 2 before radiotherapy also scored a grade ≥ 2 as maximal acute GU score. We can however not deduce from this RTOG scale whether these symptoms before and during treatment were of the same kind or not.

The dose-volume group was also a significant prognostic factor for acute GI toxicity, but not for acute GU toxicity. Patients of dose-volume groups III and IV had more GI symptoms compared to group I. These were the patients receiving a higher dose on the seminal vesicles, resulting in more rectum volume irradiated to high doses. Further analysis of toxicity with dose-volume parameters will have to confirm this explanation.

As previously reported by Schultheiss *et al*., a TURP prior to radiotherapy was associated with significantly less acute GU complications (39). This is probably due to the fact that patients have already been relieved from some GU symptoms and are also less subject to for example radiation-induced edema.

4.3 Late toxicity & prognostic factors

Increasing the dose to the prostate from 68 Gy to 78 Gy resulted in significantly more rectal bleeding requiring a laser treatment or transfusion, and in more nocturia. A significantly higher incidence of late *rectal bleeding* in the high-dose treatment arm was not unexpected, as in the dose-escalation study, performed previously in one of the participating hospitals (23), a trend was found that a total radiation dose of $\geq$ 74 Gy resulted in a higher incidence of severe rectal bleeding. Others also reported a significant association of late rectal bleeding and a higher treatment dose (40,41,42). Patients with a history of *abdominal surgery* in particular were prone to develop late rectal bleeding, and this resulted in a significantly higher overall late RTOG/EORTC score. These patients, with previous surgery, also needed significantly more incontinence pads, probably because of rectal blood loss, and experienced more proctitis. Abdominal surgery included not only lymph node dissection, but also disease-unrelated abdominal surgery, such as appendectomy or surgical repair of an inguinal hernia. The incidence of late GI complications in patients with a history of abdominal surgery excluding iliac lymph node dissection was also significantly higher, although this correlation was slightly less pronounced (results not shown). Smit *et al.* previously described a significantly higher risk of late GI toxicity in patients

with previous bowel disease or surgery compared to those with no preexistent disease (43). Liu et al, conversely, did not find a correlation between abdominal surgery and late toxicity (44).
To the best of our knowledge, the association of frequent *nocturia* with a higher treatment *dose* has not been described earlier. Not only the treatment dose, but also diabetes mellitus, a higher pretreatment GU score and HT were found to be predictive for developing frequent nocturia. This difference for nocturia between the two randomization arms was only borderline significant and so the question rises if this result could be a fortuitous finding resulting from the multiple comparisons. The same remark can be made about the surprising association of smoking and dysuria requiring drugs.
The presence of *pretreatment GI and GU symptoms* was associated with more late GI and GU toxicity, respectively. This is consistent with previous findings (45). For GI toxicity, only 14 patients reported GI symptoms grade ≥ 2 before starting radiotherapy, and this number of patients is too small to rely on. The presence of pretreatment GU symptoms was associated with late GI toxicity grade ≥ 2, but not with grade ≥ 3. This indicates that these patients are indeed more likely to complain about late toxicity, but not about severe late toxicity.
Overall, *hormonal treatment* did not significantly influence late GI toxicity in our study, while late GU toxicity was significantly higher in patients who received HT. In this study 22% of the patients were treated with HT. Roughly half of these received neo-adjuvant and concomitant HT for a total duration of 6 months, while the other half had neo-adjuvant and concomitant HT, followed by adjuvant HT during 3 years. We analyzed them as one group although in the literature the use of neo-adjuvant HT seem to have a different impact on late GI treatment toxicity compared to those receiving (also) adjuvant HT. Long-term adjuvant HT seemed to result in more late GI toxicity compared to neo-adjuvant HT alone (46,47). The reason for this difference between short-term and long-term HT is still unclear, but a plausible explanation is that the LHRH-agonists may have an influence on the reparative process of the irradiated normal tissue, maybe through an inhibitory effect on EGFR on these normal tissues (48). But even when we compare the impact of neo-adjuvant HT between different studies, the results are conflicting. The RTOG 94-06 trial reported no effect of neo-adjuvant HT on late GI or GU toxicity (37), while Schultheiss *et al.* described an increased late GI and GU toxicity (39). Liu *et al.* also found a higher incidence of late GI toxicity, but only in patients who received ≤ 2 months of neo-adjuvant HT (44). How can we explain all these conflicting results? HT causes shrinkage of the prostate (49), resulting in reduced radiation field sizes. If this shrinkage is not taken into account in the treatment planning, this can result in a higher incidence of complications (39). On the other hand, the results of Lilleby *et al*. suggested a further volume decrease till 9 months of HT, although the largest changes occurred during the first 3 months of HT (50). This finding demonstrates the impact of the duration of neo-adjuvant HT on toxicity. We plan to analyze the effect on toxicity of the two treatment modalities (short-term versus long-term HT) separately, taking into account the dose volume parameters and the exact interval between start of HT and planning CT scan.
In this study a *TURP before radiotherapy* was associated with significantly more late GU complications compared to patients who never underwent this procedure. More specifically, urinary incontinence and urethral strictures were more frequently seen in patients with a prior TURP. This is consistent with the findings of Sandhu *et al.*, where in addition no significant difference in late GU toxicity was found between TURP patients treated with high-dose (≥ 75.6 Gy) conformal radiotherapy compared to lower doses (51).
Patients with *diabetes mellitus* were also found to have an increased risk of needing incontinence pads for rectal discharge and of having more nocturia, but this did not result in a significantly higher RTOG/EORTC GI or GU score, contrary to the results of Herold *et al.* (52). But only 38 (6%) patients had diabetes mellitus, and this is a small group for statistical analysis. *Age* had no influence on late toxicity. Contrary to acute GI toxicity, the different *dose-volume groups* did not show a differential effect on overall late GI and GU toxicity, except for the stool frequency, where a higher cumulative incidence was seen in groups III and IV. An analysis with dose-volume parameters will be performed

to study the differences in dose-volume parameters of the exposed normal tissues between the different dose-volume groups.

4.4 Other considerations

Despite the higher radiation doses, our results show an acceptable complication rate. Probably the small margins used for the boost, especially towards the rectum where no margin was taken, contributed to this result. But we are aware that a longer follow-up is needed to confirm these data, especially because prostate cancer patients have a potentially long survival. Boersma *et al.* also described that the more severe complications often occurred later (23). Furthermore the incidences of toxicity are globally higher in the high-dose treatment arm. In the MDACC trial, for example, a first report did not show significant differences in toxicity, while with an extended follow-up the grade 2-3 rectal complication rate was twice as high in the high-dose treatment arm compared to the conventional treatment arm (15). The difference in bladder complications on the contrary was still not significant in their study, but there we have to be cautious too, since bladder complications may develop later than rectal toxicity. On the other hand, comparison with the MDACC trial is not completely fair, as they used conventional treatment till 46 Gy, followed by 3D-conformal technique for the rest of the treatment, while we used 3D-conformal during the whole treatment. Furthermore HT was an exclusion criterion in their study, while we found that HT significantly improved acute GI tolerance and reduced acute and late GU tolerance.

In general, besides the treatment techniques used, and the in- or exclusion of HT, we have to keep in mind that several other factors may hamper comparisons between different studies concerning this topic, such as different definitions of CTV margins, adapted toxicity scales, way of collecting toxicity data (based on physician's report and/or patients' self-assessment questionnaires), dose specification or variable dose constraints.

Finally we want to mention that IMRT allows for greater sparing of the surrounding normal tissue and it may therefore play a role in further reducing toxicity. In our study, a small group of 41 patients in the high-dose treatment arm (12%) were treated with simultaneous integrated boost technique using IMRT (26). But because this technique was introduced during the trial, these patients have a shorter follow-up and we did not analyze them separately yet.

5. CONCLUSIONS

Although the incidences of toxicity were slightly higher in the high-dose treatment arm, no significant differences in toxicity were seen between 68 Gy and 78 Gy, except for late rectal bleeding and nocturia. Thus, radiotherapy of the prostate to 78 Gy resulted in an acceptable complication rate, but a longer follow-up is needed to confirm these data. In addition, this study shows that other factors than the radiation dose may be important in predicting toxicity from radiotherapy. A history of abdominal surgery was a poor prognostic factor for late GI toxicity. A TURP prior to radiotherapy resulted in less acute GU, but more late GU toxicity. Higher doses to the SV leaded to more acute GI toxicity. Patients receiving a hormonal treatment experienced less acute GI symptoms, but more acute and late GU toxicity. The presence of pretreatment symptoms was associated with more acute and late toxicity.

The use of indicators, which score more specific symptoms, is of paramount importance, since it allows us to trace the reason for a higher overall GI or GU toxicity score. In addition, a significantly higher incidence of such an indicator did not always result in a significantly higher score on the global GI or GU toxicity scale, and by omitting scoring these separate symptoms, differences in toxicity can be missed.

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APPENDIX

Table A1: Acute GI complications according to the RTOG morbidity scale (adaptations with regard to the original RTOG scale in italics)

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

Table A2: Late GI and GU complications according to the RTOG/EORTC morbidity scale (adaptations with regard to the original RTOG/EORTC scale in italics)

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

* The difference between grade 1 and grade 2 GI pain, mucosal loss or bleeding is most easily made, when grade 2 is defined as morbidity requiring specific medication: Grade 1 = stool softener, diet modification, occasional (≤2/week) non-narcotic drug, occasional antidiarrheal agent (= 2/week), occasional use of incontinence pads (1-2 days / week); grade 2 = regular (> 2/week) use of (non)-narcotic drugs for pain, regular (> 2/week) antidiarrheals, steroid suppositories, 1 laser; † with the exception of antibiotics.

Table A3: Some indicators for RTOG/EORTC and/or SOMA/LENT grade ≥ 2 (infrequently encountered symptoms were not included in this list)

GI Indicators
1. Pain/cramps/ tenesmus requiring medication 2. Proctitis requiring use of steroids 3. Rectal bleeding requiring laser treatment or transfusion 4. Use of incontinence pads for rectal discharge of blood/mucus/stools (pads > 2 days a week) 5. Higher stool frequency (≥ 6)
GU Indicators
1. Nocturia (≥ 4) 2. Higher urinary frequency during the day (≥ 16) 3. Higher urinary frequency during 24 h (≥ 9) 4. Use of incontinence pads for urinary incontinence (pads >2 days a week) 5. Dysuria requiring medication 6. Urinary obstruction requiring treatment (at least catheterisation) 7. Hematuria requiring laser treatment or transfusion

Technical aspects

Three-dimensional conformal radiotherapy (3DCRT) is more than placing customized two-dimensional blocks in the treatment fields. Three dimensional treatment planning, margin control through positioning control (mega voltage imaging) and Beams-Eye-View (BEV) blocking with a multileaf collimator (MLC) are major components of such a treatment.
With the introduction of 3DCRT for the treatment of prostate carcinoma the treatment fields became bigger than before. Especially the developed algorithm for the 3-dimensional (3D) GTV-to-PTV expansion was responsible for this. This 3D expansion resulted in a theoretical tumor control probability increase of up to 15 % compared to the conventional 2D expansion. The more conformal the 95% isodose volume encloses the PTV, the larger the errors will be when an (erroneous) 2D PTV is used instead of the 3D PTV (Chapter 1).
Initially, another reason for more generous treatment fields was the use of large cranial and caudal penumbra block margins to avoid tumor under dosage due to the overlapping penumbrae of the treatment fields. A relatively simple static intensity modulation technique using two small additional cranial and caudal treatment fields enabled us to reduce the cranial/caudal field dimensions. This 1.6 cm field length reduction resulted in a significant reduction in rectum and bladder volumes receiving a high dose (Chapter 2).
Controlling the daily patient positioning and prostate mobility can result in a further reduction of the field dimensions. Megavoltage imaging (MVI) and correction protocols play a major role in reducing the set-up uncertainties and thereby the margins. In the repeat CT scan study (DDHK 96/11; Chapter 3) GTV mobility and (supine and prone) positioning were studied. In supine position, there were obvious time trends in rectum diameter, translations in AP and SI direction and rotation around the LR-axis of the prostate. Due to the radiation induced acute proctitis, the average rectum diameter and prostate (AP and CC) position returned to the planning CT situation by week 6. The time trends in supine position result in a significant random variation. In prone position, there was no time trend; the systematic variations are significantly larger than the corresponding random variations
The systematic set-up variations were smaller than the systematic internal organ movements, which is partly due to the applied correction protocol. Due to larger random errors for the patients in prone position a larger number of corrections were needed. Compared to patients in supine position, patients in prone position had smaller random but somewhat larger systematic variations in the most important coordinates of the internal CTV position. The estimated planning margins to account for the geometrical uncertainties were therefore similar for the two treatment positions. For practical reasons, concerning MVI, the supine position was preferred. The observed variations were translated into a CTV-PTV margin of 10 mm, which was used in the CKVO dose escalation study.
In this (dose escalation) study the time trend, observed in the repeat CT scan study, was used as well to reduce the boost margins in the rectal direction. The observed rotation will enable us to reduce the margins with the implementation of an anisotropic margin. This will further reduce the exposure of the most caudal part of the rectum or anus and as such reduce the chances of compliance related symptoms.

The implementation of in vivo dosimetry, using an EPID (electronic portal imaging device) based MVI, could reveal problems like incorrect performance of the treatment unit, erroneous design, production or application of compensators and deviations of the patient anatomy during the daily treatment fractions. The observation of MVI distortion and prostate displacement through gaseous bowel content is interesting though not very practical (Chapter 4) Displacement by gas could be visualized, but given the practical workload and the limited prevalence (23%) will be unpractical.
On the other hand displacement by fecal bowel content, probably more important than bowel gas, will not be visualized. On line EPID automated dose verification in IMRT will however give dose changes

due to gaseous displacement of the prostate. Random (and maybe systematic) dose variation will be the consequence.
Prostate markers or direct visualization by means of for example a cone beam CT scan will give us the opportunity to study or adjust for prostate mobility (individually).
Reduction of the CTV to PTV or PTV to field edge margins has proven to be a major factor to reduce the normal tissue exposure. The use of IMRT techniques by itself, and/or using more than 3 (5) 3DCRT fields, is not very effective when using generous margins. The inverse concomitant calculation of elective and boost treatment fields will, however, result in a DVH reduction in these normal tissues.

Clinical aspects

Three Dimensional Conformal RadioTherapy aims at the (physical) reduction of exposure of normal tissues as illustrated in so called Dose Volume Histograms (DVH).
A DVH reduction will however not always directly translate in a reduction of toxicity.
Despite a highly significant reduction in exposed bladder volume (DVH) acute and late toxicity was not reduced in the DDHK 9414 toxicity study (17-18% acute grade >1 and
9-11% late grade >1, chapter 5 and 6). For bladder toxicity, the relations of dose/volume parameters and toxicity were not clear at all. Late bladder toxicity was mainly influenced by the urological symptoms and frequency at the start of treatment. The origin of these urological symptoms might be trigonal or urethral. Due to the close relationship of these regions and the prostate +/- seminal vesicles, these symptoms will not be easily preventable.
Rectal and intestinal toxicity was studied extensively. Because of a large variation in rectal and anal exposure due to anatomical variations, there is a wide overlap of volumes in the conformal and conventional treatment arms. This overlap decreased the impact of the 3DCRT treatment technique on toxicity. Although there was a statistically significant intestinal volume reduction exposed, this difference was small.
Comparing radiotherapy techniques, 32% and 19% acute grade 2 gastrointestinal toxicity was observed for conventional and conformal radiotherapy, respectively. It appeared that the reduction in acute gastrointestinal toxicity could be explained mainly by a reduction in anal toxicity and not in rectum/sigmoid toxicity. A non-significant reduction of grade 2 acute toxicity for rectal symptoms (18% and 14%, respectively) was observed and a statistically significant reduction of acute anal grade 2 toxicity (16% and 8% for conventional and conformal radiotherapy, respectively) was found (Chapter 5).
Comparing conventional and conformal radiotherapy for late rectal toxicity there was only a trend in favor of the conformal radiotherapy (grade >1, 10% and 7% respectively). In univariate analysis both the DVH volume ≥ 90% tumordose (TD) of the rectum and anus were significantly related to grade ≥ 1 rectal toxicity. A highly significant relation was observed between acute rectal / anus toxicity and late rectal toxicity (Chapter 6).
According to the patient self-assessment questionnaire, 85% of the patients report no or slight overall intestinal symptoms and 2% severe intestinal symptoms. Compliance related symptoms bothered the patients the most. Proctitis related symptoms were less dominant.

Another important observation of the clinical studies was the major influence of patient related factors. Twenty five percent of patients started with intestinal symptoms before treatment. Especially the pre-treatment defeacation frequency and urological symptoms / frequency had a significant relationship with late toxicity. Late grade 2 toxicity was increased two-fourfold in patients with pre-existing symptoms. Therefore, studies without a base line registration of symptoms could overrate the acute and late toxicity of radiotherapy. In a multivariate analysis all other variables failed to have a significant

influence when the anal volume exposed to ≥ 90% of the tumor dose and pre-treatment defecation frequency was accounted for.

Based on the same patient questionnaires data, DVH (Chapter 7) and dose map studies (Chapter 8) were performed in close collaboration with colleagues of the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam.
At 3 years of follow-up, 19 % of the patients experienced some form of rectal blood loss. For the rectum with and without the anal region, the average DVH of bleeders was significantly higher compared to the average DVH of the non-bleeders. For the anal region this difference was not significant.
The analysis of relative DVHs of the rectal wall (with and without the anal region), showed significant relations between the irradiated volume and the probability of rectal blood loss within 3 years, for dose levels between 25 Gy and 60 Gy.
The most significant volume-effect relationship was found at 60 Gy for the rectum wall, excluding the anal region, especially at 70 % of the volume. Patients with DVH's below this point had an incidence 21 % of rectal bleeding compared to a 52 % incidence above this cut-off point. When the irradiated (60 Gy) rectum volume increased from 25 % to 100% in the proportional hazard model, the probability for rectal bleeding increased from 10 % to 63 %. Although one cut off point seems to be most significant, we should keep the whole volume range in mind. We should realize that this toxicity study was performed with conservative doses and treatment volumes. Relations (e.g. bowel volume cut off point) might change, when studied at higher tumor dose. The future CKVO analysis will most likely answer this question.

As mentioned before, bleeding is not the main late rectal / intestinal symptom. Details from the patient questionnaires (Chapter 8) showed us cumulative incidences of 5 % for diarrhea, 19 % for rectal bleeding, 31 % for increased stool frequency, 34 % for soiling, 26 % for faecal incontinence, 15 % for painful cramps, 23 % for mucus loss and 16 % for urge. The prevalence of moderate/severe complaints was however only 2-5 %.
Using dose maps (area's exposed) for analysis again the area receiving a dose ≥ 60 Gy was related with bleeding in the multivariable analysis. In the same multivariable testing soiling, as late toxicity symptom, was related to smoking and acute soiling complaints. Increased stool frequency was related to acute intestinal complaints and age.
Dose maps sub-areas, receiving a dose ≥ 60 Gy, were tested (univariable) in the PHR (proportional hazard rate) model. For bleeding (and mucus loss) the superior 80 % of the map was important. For soiling (and faecal incontinence) the inferior 40 % and for urgency the most superior 10 % and 20 % were the most significant dose map sub-area.
In a multivariable (MV) analyses for soiling "acute complaints" remained significant and the tested sub-area (% area receiving > 60 Gy,) became less or not significant.
For mucus loss, the MV results showed that the acute complaints became non significant, while the tested sub-area remained at the same significance level. When the dose map was cut into 4 regions from superior to inferior, and into 4 regions from posterior to anterior (left, anterior, right, posterior) no additional significant information was found.

Other important aspects of the treatment of prostate carcinoma are the consequences of treatment for sexual activity. Both radiotherapy and prostatectomy will to some extent cause some degree of erectile dysfunction. Combination with androgen ablation for longer periods will further enhance these side effects.
Patients were selected on the basis of prognostic factors (e.g. age, condition and/or unfavorable tumor related factors) for surgery or radiotherapy. This same selection resulted in a difference in the sexual

quality of life in favor of those patients waiting for prostatectomy (Chapter 9). Comparative studies without a base line description and/or correction for the pre-treatment sexual functioning will therefore overestimate the side effects of radiotherapy. Another important observation of this study was the psychological consequence of the diagnosis and preparation for therapy. Fifteen to 20% of the patients reported a decrease in sexual interest, activity and pleasure. It was not clear what the influence of psychological aspects was on sexual functioning after treatment.
The exact reasons for erectile dysfunction after prostatectomy and radiotherapy are not fully understood. Apart from psychological factors, smoking, arteriosclerosis, diabetes, a diversity of medication, direct damage or secondary to a fibrotic reaction play a role in the development of sexual dysfunction. It is suggested that erectile dysfunction after radiotherapy is associated with an arteriogenic origin. Sildenafil induces relaxation in the corpora cavernosa smooth muscles and subsequently causes an inflow of blood.
In chapter 10 a (cross over) randomized study was reported for patients with complaints of erectile dysfunction who completed radiation (3D-CRT, mean dose 68 Gy) at least 6 months before the study. Sixty patients out of 406 (15%) were interested and eligible. Forty five percent of patients on Sildenafil reported an improvement and 55% reported a successful intercourse. All side effects were mild or moderate, transient, and did not result in drug discontinuation. A potential limitation of our study was the absence of data on erectile functioning before treatment. Eight percent of patients treated with a placebo reported an improvement, while 18% was successful at intercourse. The different aspects of these observations should be studied in future; medication was not the only factor.

CKVO study

In collaboration with the colleagues of the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam the data from the DDHK 94/14 toxicity study were used for preparative analysis for the NKB analysis. The conclusions of this analysis, as described in chapter 7 and 8, will be tested at the CKVO dose levels.
Other aspects of the CKVO study were quality control of treatment and data-management. The quality control of the contoured organs and target volumes and the comparison of the different planning systems were published by Rasch et al.
The different expansion routines in the planning systems lead to significantly different PTVs and were corrected. The differences in technique caused a 10% difference in treated volume. A further refinement of the treatment technique (Intensity Modulated RadioTherapy, IMRT) and a so-called concomitant boost technique was realized in the last 41 patients treated in the AVL-NKI.
Differences in delineation of the rectum greatly influenced the calculated risk of rectal complications. Applying a stricter definition for delineation of organs at risk was described to improve the reliability of the trial results. Data-management was evaluated and corrected to guarantee a uniform scoring. To reduce differences in interpretation of toxicity data, patient questionnaires were used combined with the remarks and actions of the physician to create a modified (acute and late) EORTC/RTOG and SOMA/LENT score.
In chapter 11, the first analysis of acute and late toxicity is presented with a median follow up of 31 months. No significant differences were seen between the two dose levels when comparing for maximum acute GI and GU toxicity. The pre-treatment score and dose-volume groups were significantly related to acute GI symptoms grade ≥ 2. Patients having hormonal therapy (HT) experienced less acute GI toxicity. A higher pre-treatment GU score and use of HT were associated with more acute GU side effects, while a TURP prior to radiotherapy was associated with less acute toxicity.
The incidences of late GI symptoms were higher in the high-dose treatment arm (not significant, except for the indicator ‘Rectal bleeding requiring laser/transfusion’ 2% versus 9% at 3 years follow

up). Gastro Intestinal toxicity (RTOG/EORTC) grade ≥ 2 at 3 years were 23.2% and 29.7%, for grade ≥ 3 these figures were 2.3% and 4.7%, for the 68 Gy- and the 78 Gy-arm respectively. Prognostic factors for late GI toxicity were the history of abdominal surgery, the pre-treatment GI score and the dose-volume group.
For late (RTOG/EORTC) GU toxicity, no significant differences were seen for the overall toxicity scores, although the incidence of late GU toxicity was slightly higher in the 78 Gy-arm. The 3-year cumulative risks for GU grade ≥ 2 were 28.5% and 30.2% and for GU grade ≥ 3 5.1% and 6.9%, for the 68 Gy- and the 78 Gy-arm, respectively.
Prognostic factors for late GU toxicity grade ≥ 2 were: hormonal therapy, prior TURP and pre-treatment GU score.

The patient perception, as scored in the patient questionnaires, was a major component of this toxicity score. The toxicity scores seem therefore slightly higher than published. We believe however that the patient is the golden standard. In a number of publications the underscore of the physician compared to the patient perception has been demonstrated.
Future research will focus on the relation of EORTC/RTOG and SOMA/Lent score and patient perception. Especially the incongruent relation of patient urological perception and the Soma /Lent score will be an important issue. The weight of the urinary frequency in the Soma/Lent score seems to be overrated.

Future analyses will be performed using the clinical and physical data of the CKVO study. Toxicity studies with and without relations of dose volume parameters, so called dose maps and rectum modeling will be performed. When tumor control data (planned for the end of 2004) have matured. Combining the CKVO study data with the other international randomized studies from the MD Anderson Hospital, Houston USA, and the Medical Research Council (MRC study RT01),UK, will hopefully give us more accurate dose / tumor effect relationships at the different dose levels (internationally) studied.
With more accurate models we hope to be able to predict late toxicity. Using these models we can optimize treatment plans for the individual patient. Further treatment refinement, like image guided IMRT or guidance by biological marker studies seems to be feasible.
Many questions are still to be answered. Apart from those mentioned before other practical questions remain: i.e. what is the role of brachytherapy? What is the role of radiotherapy compared to surgery? Especially the last question is fascinating. The design and implementation of such a study will probably wait for a number of years as both modalities continue to progress.

Technische aspecten

Drie dimensionale conformatie radiotherapie (3DCRT) is meer dan het plaatsen van (twee dimensionale) blokken in de bestralingsvelden. Drie dimensionale planning, “Beams Eye View” blokken met hulp van de “multileaf collimator” (MLC) en controle over de positie op de behandeltafel door middel van MegaVolt Afbeelding (MVA) zijn belangrijke componenten van een dergelijke behandeling. Met de introductie van 3DCRT voor de behandeling van prostaat kanker werden de bestralingsvelden initieel groter dan in de periode daarvoor. Met name de programmatuur, welke een drie dimensionale marge rond het prostaat doelvolume moest genereren, bleek verantwoordelijk voor deze veldgrootte. De theoretische tumorcontrole zou door gebruik van een twee dimensionale benadering 15% lager uitkomen ten opzichte van een drie dimensionale marge. Als de 95% isodose meer conform en krapper rond het doelvolume wordt gekozen zal de theoretische tumorcontrole bij gebruik van 2 diemnsionale blokken verder afnemen. (hoofdstuk 1)
Een andere reden voor de grotere bestralingsvelden bleek de onderdosering in craniocaudale richting als gevolg van de penumbra van de bestralingsbundels. Een relatief simpele oplossing in de vorm van twee kleine aanvulveldjes craniaal en caudaal stelde ons in staat de veldlengte te beperken. Deze 1,6 cm veldlengte reductie zorgde voor een significante beperking van het volume van blaas en rectum blootgesteld aan de hoge doses. (hoofdstuk 2)
Een verdere reductie van de afmetingen van de bestralingsveld kan verkregen worden door de behandelpositie en beweeglijkheid van het doelvolume (prostaat met/zonder vesiculae seminalis) te controleren. Megavolt afbeelding en daaraan gekoppelde correctie protocollen zijn hiervoor van groot belang. In een prospectieve studie (DDHK 96/11; hoofdstuk 3), werden, door middel van herhaalde CT scan, de beweeglijkheid van de prostaat en de positie onnauwkeurigheid in rug en buikligging onderzocht. In rugligging wordt in het verloop van de behandeling een verplaatsing (anterior/posterior en craniocaudaal) en rotatie (over een links-rechts as) van de prostaat waargenomen als gevolg van een wisselende rectumvulling. Als gevolg van de bestralingsreacties van het rectum neemt de gemiddelde rectum vulling, en als gevolg prostaat positie, na 6 weken dezelfde positie in als bij de planning CT scan voor de start van behandeling. Deze verplaatsing veroorzaakt een “random”variatie welke groter is dan de systematische variatie in positie. In buikligging wordt geen tijdverloop gezien; de systematische variatie is in deze positie groter dan de “random” variatie.
De positionering van de patiënt bleek door het gebruik van zgn. MVA correctie protocollen nauwkeurig. Deze positie onnauwkeurigheid is kleiner dan die van de prostaatbeweging. Een groot aantal positie correcties moest plaatsvinden in buikligging. Ten opzchte van de patienten in rugligging hadden patienten in buikligging kleinere random variaties, maar iets grotere systematische variaties van de prostaat positie. De planning marge , welke de behandel en prostaat positie in rekening brengt is voor beide behandelposities gelijk. Om praktische overwegingen (beperking van het aantal MVA correcties) is gekozen voor de buikligging als behandelpositie. Wanneer de waargenomen variaties in rekening worden gebracht bleek een marge van 10 mm voldoende. Deze werd dan ook gebruikt in de CKVO studie. Binnen deze zelfde studie werd het vastgestelde verloop in positie in de loop van de tijd gebruikt om de booster marge richting rectum (na 7 weken behandeling) tot een minimum te reduceren.
De gevonden beweeglijkheid van de prostaat (rotatie) stelt ons in staat gebruik te maken van een zgn. “anisotrope” marge, welke met name de belasting van het meest distale deel van het rectum cq anus zal doen afnemen. Hierdoor zal de kans op klachten van dit gebied, met name met betrekking tot de opvang capaciteit van ontlasting, kunnen afnemen.

Het gebruik van MVA als mogelijkheid om de dosis in vivo te meten, kan gebreken van de behandeling zichtbaar maken. Te denken valt aan een bestraling apparaat dat niet goed functioneert,

onnauwkeurigheid in de aanmaak en toepassing van compensatoren en veranderingen van de anatomie van de patiënt. De vaststelling van de dosis afwijking en prostaatverplaatsing door darmgas met behulp van deze techniek is interessant. (hoofdstuk 4).
Het beperkt voorkomen (23%) en de effecten op de werkbelasting maken deze bevinding niet goed praktisch toepasbaar. Ook worden hiermee de effecten van een wisselende vullinggraad door ontlasting, waarschijnlijk van groter belang dan darmgas, niet afgebeeld. Indien deze techniek wordt toegepast bij de implementatie van intensiteit gemoduleerde radiotherapie (IMRT) zal dit fenomeen leiden tot random dosisafwijkingen.
Het gebruik van prostaatmarkers of een directe afbeelding, met behulp van een zgn. Coned Beam CT scan, bied ons de mogelijkheid de prostaat beweeglijkheid te bestuderen en (individueel) te corrigeren. De reductie van de marges is gebleken een van de belangrijkste factoren te zijn om de gezonde organen minder te belasten. De toepassing van meer ingewikkelde bestralingsplannen, zoals IMRT en/of meer dan 3(5) bestralingsvelden, hebben weinig opgeleverd bij gebruik van relatief grote marges. Enkel de toepassing van IMRT in het kader van een zgn. concomitant planning van electief en boost deel van de behandeling, leid op zich tot een reductie van het bestraald volume.

Klinische aspecten

Dire dimensionale conformatie radiotherapie beoogt een beperking van de bestraling van de normale weefsels te bereiken. Dit kan (fysisch) worden geillustreerd door een zogenaamd dosis volume histogram (DVH). Een reductie van het bestraald volume (uitgedrukt in een DVH) vertaald zich echter niet direct in een verminderde toxiciteit. Ondanks een hoog significante reductie van het bestraald blaasvolume zijn de acute en late toxiciteit in de DDHK 94/14 toxiciteit studie niet afgenomen met 17-18% acute toxiciteit graad >1 en 9-11% late toxiciteit graad >1 (hoofdstuk 5 en 6). De dosis/volume relaties voor blaas toxiciteit zijn niet duidelijk. Late blaas complicaties worden hoofdzakelijk beïnvloed door urologische symptomen en frequentie voor de start van de behandeling. De oorzaak van de bestralingsreactie zou gezocht kunnen worden in de bestralingsreacties van het trigonum of van de urethra. Door de nauwe relatie van de prostaat en vesiculae seminalis met deze structuren zullen deze symptomen lastig te voorkomen zijn.

Rectum en darm toxiciteit werden uitgebreid onderzocht. Door een grote anatomische variatie in rectum en anus is er een grote overlap van bestraalde volumina, waardoor de effecten van 3DCRT worden gemaskeerd. Door de conformatie techniek onstaat een klein, maar significant, verschil in de DVH. Een reductie van <u>acute</u> toxiciteit (graad 2) van 32% naar 19% werd waargenomen. Deze toxiciteit reductie lijkt vooral verklaard door een afname van anale toxiciteit en niet zozeer door afname van rectum/sigmoid toxiciteit. Voor rectum toxiciteit (graad 2) werd een niet significante reductie waargenomen van 18% naar 14%; voor anale toxiciteit een significante afname van 16% naar 8%. (hoofdstuk 5)
Met betrekking tot <u>late</u> rectale toxiciteit is er slechts een trend in het voordeel van de conformatie radiotherapie (graad >1 respectievelijk 10% en 7%). In een univariate analyse bleken zowel het volume van het rectum als de anus blootgesteld aan een dosis van ≥ 90% van de tumordosis (TD) gerelateerd aan de late rectum toxiciteit. Ook werd een significante relatie gevonden tussen acute rectum en acute anus toxiciteit en late rectum complicaties (hoofdstuk 6)
In de analyse gebaseerd op de door de patiënten ingevulde vragenformulieren, gaf 85% van de patiënten aan geen of lichte symptomen te hebben van de behandeling. Ernstige klachten werden slechts door 2% van de patiënten aangegeven. Klachten gerelateerd aan de opvangcapaciteit van het rectum (compliance) lijken de overhand te hebben. Proctitis gerelateerde klachten lijken minder dominant.

Een andere opvallende conclusie uit deze analyse bleek de grote invloed van patiënt gerelateerde op de late toxiciteit. Vijf en twintig procent van de patiënten start al met darmklachten voor de behandeling. Met name de defaecatie frequentie, maar ook de aanwezigheid van urologische klachten en/of hoge mictie frequentie, voor de start van behandeling zijn gerelateerd aan late symptomen. Matig ernstige complicaties (graad 2) doen zich 2.5 tot 4 maal vaker voor indien patiënten starten met defaecatie / urologische klachten. Studies, zonder informatie over deze klachten voor de behandeling, zullen de toxiciteit van de bestralingsbehandeling overschatten. In de multivariate analyse bleken andere factoren geen aanvullende informatie te verschaffen als het anus DVH volume (90%TD) en de defaecatie frequentie voor de behandeling in rekening werden gebracht.

Gebaseerd op dezelfde patiënten vragenlijsten werden aanvullende DVH (hoofdstuk 7) en zogenaamde dose map (hoofdstuk 8) analyses verricht in nauwe samenwerking met de collegae van het Antoni van Leeuwenhoek ziekenhuis / Nederlands Kanker Instituut uit Amsterdam.
Na drie jaar follow-up werd in 19% van de patiënten (licht tot ernstig) rectaal bloedverlies gemeld. De gemiddelde DVH van het rectum (met of zonder anus) voor de zogenaamde “bloeders” bleek statistisch ongunstiger ten opzichte van de “niet-bloeders”. Deze relatie was niet aanwezig voor het anus volume.
De analyse van de (relatieve) DVH van de rectum wand (met of zonder de anale regio) liet een relatie zien tussen het volume bestraald met een dosis van 25 tot 60 Gy en rectaal bloedverlies na drie jaar follow-up. De grootste significantie werd gevonden op het dosis niveau van 60 Gy voor de rectum wand (zonder het anale gebied) met een breekpunt op 70% van het volume. Bij een DVH onder dit niveau werd in 21% bloedverlies gezien; boven dit niveau 52%. In het (probability) model op basis van de klinische data, werd een toename van de kans op rectaal bloedverlies voorspelt van 10% naar 63% als het bestraald (60 Gy) volume toeneemt van 25% naar 100%. Hoewel één breekpunt als meest significant wordt aangegeven moeten wij niet de andere dosis punten vergeten. Men moet niet vergeten dat deze toxiciteit studie werd verricht met conservatieve doses en behandelvolumina. De gevonden relaties zullen op hogere bestralingsdoses nader onderzocht moeten worden. De toekomstige CKVO/NKB analyse zal hierop een antwoord geven.

Zoals eerder vermeld bleek rectaal bloedverlies niet de meest belangrijke klacht als uiting van late toxiciteit. Details uit de patiënten vragenlijsten leren ons dat 5% van de patiënten last heeft van diarree, 19% bloedverlies, 31% een verhoogde defaecatie frequentie, 34% vlekken in de onderkleding, 26% slijm of faeces verlies, 15% pijnlijke krampen, 23% slijm verlies en 16% loze aandrang (hoofdstuk 8).Matig ernstige of ernstige klachten worden slechts door 2-5% van de patiënten gemeld.
Met behulp van de zogenaamde dose maps werd wederom een relatie gevonden tussen rectaal bloedverlies en het oppervlak blootgesteld aan doses $\geq$ 60 Gy. In dezelfde multivariabele analyse bleken vlekken in het ondergoed gerelateerd aan roken en acute klachten van dezelfde aard. Een verhoogde defaecatie frequentie is gerelateerd aan acute darmklachten en de leeftijd.
Verschillende delen van het rectum oppervlak (dose map) blootgesteld aan doses $\geq$ 60 Gy werden getest in een zogenaamd proportional hazard rate model. Bloed en slijmverlies (proctitis klachten) bleken gerelateerd aan de craniale 80% van het rectum/anus oppervlak. Voor vlekken en incontinentie bleek de caudale 40% het meest voorspellend. Voor loze aandrang bleek dit in de craniale 10-20% gelegen.
In een multivariabel model bleven de acute klachten voor vlekken in de onderkleding significant, terwijl het blootgestelde oppervlak zijn significantie verloor.
Voor slijmverlies bleek deze relatie precies anders. Het blootgestelde oppervlak bleef significant voorspellend en de acute klachten niet.

Bij de onderverdeling van het rectum/anus oppervlak in meerdere delen (voor, achter, links, rechts en cranial en caudaal) werd geen aanvullende significante relatie ontdekt.

Andere belangrijke aspecten van de behandeling van prostaat kanker zijn de gevolgen voor de seksualiteit. Zowel radiotherapie als chirurgie zullen beiden, in zekere mate, met name de kwaliteit van de erectie beïnvloeden (erectiele disfunctie). De combinatie met hormonale therapie (androgene onderdrukking), voor een langere periode, zal de negatieve seksuele gevolgen verder versterken.
Door selectie van de patiënten op basis van prognostische factoren (zoals leeftijd, conditie en/of ongunstige tumor gerelateerde factoren) blijkt de seksuele kwaliteit van patiënten, welke wachten op een prostatectomie, gunstiger (hoofdstuk 9). Vergelijkende studies, zonder uitgangswaarden of correctie voor de seksuele kwaliteit bij het starten van de behandeling, zullen de complicaties van de bestraling overschatten.
Een andere interessante observatie van deze studie zijn de psychologische gevolgen van de diagnose en voorbereidingen van de daadwerkelijke behandeling. In deze periode rapporteren
15-20% van de patiënten een verminderde seksuele interesse, activiteit en bevrediging. De invloed van deze psychologische aspecten op de kwaliteit van de seksualiteit na de behandeling is niet duidelijk.

De oorzaken voor het verlies van erectie kwaliteit na prostatectomie en radiotherapie worden niet volledig begrepen. Naast psychologische factoren, roken, arteriosclerose, diabetes, vele medicamenten, directe schade of secundair aan een litteken reactie spelen allen een rol in het ontstaan van erectiele disfunctie. Er wordt gesuggereerd dat de effecten van bestraling plaatsvinden op het niveau van de arterioles. Sildenafil veroorzaakt een relaxatie van de gladde spieren in de corpora cavernosa waardoor bloed zich in deze organen verzameld. In hoofdstuk 10 wordt een (cross over) gerandomiseerde studie beschreven. In deze studie wordt de werking van sildenafil bestudeerd bij patiënten die tenminste 6 maanden tevoren bestraald werden met een dosis van tenminste 68 Gy. Vierhonderd zes patiënten werden aangeschreven. Zestig (15%) hadden interesse en waren geschikt voor deze studie. Bij gebruik van sildenafil geeft 45% van de patiënten een verbetering aan en meld 55% een succesvolle coitus. Alle bijwerkingen waren mild of matig, van voorbijgaande aard en resulteerde niet in het staken van de medicatie. Een potentiële tekortkoming van deze studie betreft het ontbreken van seksuele informatie voor de behandeling. Bij gebruik van een placebo geeft 8% van de patiënten een verbetering aan en zegt 18% in staat te zijn tot een succesvolle coïtus. De verschillende aspecten van deze waarneming zullen in de toekomst bestudeerd worden. De medicatie is niet de enige factor.

CKVO studie

In samenwerking met de collegae van het Antoni van Leeuwenhoek ziekenhuis / Nederlands Kanker Instituut werden de gegevens van de DDHK 94/14 toxiciteit studie gebruikt als voorbereiding op de analyse van de CKVO 96/10 dosis escalatie studie. De conclusies van deze analyse, zoals beschreven in hoofdstuk 7 en 8, zullen getest worden op de dosis niveaus van de CKVO studie.

De kwaliteit van de behandeling en het datamanagement van de CKVO studie werden onderzocht. De controle van de het intekenen van de risico organen en doelvolumina en de vergelijking van de planning procedure werd beschreven door Rasch (literatuur lijst). De 3 dimensionale expansie routine van de verschillende planning systemen leidde tot significante verschillen in de creatie van het PTV. Deze routine werd aangepast. De verschillen in planning veroorzaakte een (blijvend) verschil in behandeld volume. Een verdere verfijning van de bestralingstechniek in de vorm van IMRT en de zgn. concomitant boost technique (gelijktijdige boost techniek) werd gerealiseerd bij de behandeling van de laatste 41 patiënten in Amsterdam.

De verschillen in de intekening van het rectum veroorzaakte verschillen in de (theoretische) risico berekeningen van mn rectum complicaties. Door meer strikte afspraken over de inteken procedure werd getracht de onnauwkeurigheid mbt dit aspect te verkleinen.
Het datamanagement werd geëvalueerd en gecorrigeerd om tot een uniforme score te kunnen komen. Om de verschillen in interpretatie van de toxiciteit te verkleinen werden de gegevens van de patiënten vragenlijsten gebruikt naast de aantekeningen en acties van de behandelend radiotherapeut om tot een gemodificeerde (acute en late) EORTC/RTOG en SOMA/LENT score te komen.
In hoofdstuk 11 wordt de eerste toxiciteit analyse gepresenteerd met een mediane controle tijd van 31 maanden. Er werd geen significant verschil vastgesteld voor beide dosis niveaus wat betreft de acute rectum en blaas toxiciteit. De klachten, voorafgaande aan de behandeling, en de verschillende dosis/volume groepen bleken gerelateerd aan de acute rectum toxiciteit (graad $\geq$ 2). Patiënten met hormonale therapie bleken minder acute rectum toxiciteit te ontwikkelen.
Meer urologische klachten voorafgaande aan de behandeling en hormonale therapie bleken gerelateerd aan meer acute urologische toxiciteit (graad $\geq$ 2), terwijl een transurethrale resectie (TURp) voorafgaande aan de radiotherapie aanleiding gaf tot minder acute urologische klachten.

Hoewel het percentage late gastro intestinale klachten licht hoger is voor de patiënten behandeld met een dosis van 78 Gy is dit verschil niet significant met uitzondering van de indicator: rectaal bloedverlies waarvoor laser behandeling of transfusie (2 en 9% na drie jaar, respectievelijk). Gastro intestinale toxiciteit (EORTC/RTOG) graad $\geq$ 2 wordt in respectievelijk 23,2 en 29,7% waargenomen; graad $\geq$ 3 in 2,3 en 4,7% voor respectievelijk 68 Gy en 78 Gy. Prognostische factoren voor het ontstaan van deze late darm toxiciteit bleken abdominale chirurgie in de voorgeschiedenis, de klachten voorafgaande aan de behandeling en de dosis/volume groep.
Ook voor late urologische toxiciteit wordt een licht verschil te nadele van de hoge bestralingsdosis gezien. Wederom is dit verschil niet significant. Na 3 jaar wordt respectievelijk 28,5% en 30,2% urologische toxiciteit (graad $\geq$ 2) vastgesteld. Graad $\geq$ 3 wordt waargenomen bij 5,1 en 6,9% van de patiënten bestraald op de respectievelijke dosis niveaus van 68 en 78Gy. Risicofactoren voor late urologische toxiciteit zijn: hormonale therapie, TURp voorafgaande aan de behandeling en urologische klachten voorafgaande aan de behandeling.

De invloed van de waarneming van de patiënten zelf, zoals vertaald in de patiënten vragenlijst, op de uiteindelijke toxiciteit score is groot. Als gevolg lijken de toxiciteit percentages van deze studie hoger dan die vermeld worden in de literatuur. Wij zijn van mening dat de patiënt de “gouden standaard” zou moeten zijn. In een aantal publicaties wordt het verschil in toxiciteit ervaring van de patiënt en de behandelend dokter onderschreven. Toekomstig onderzoek zal oa gericht zij op het verschil tussen de officiële toxiciteit score systemen (EORTC/RTOG en SOMA/LENT) ten opzichte van de beleving van de patiënt. Met name het verschil in beleving van de patiënt en de urologische SOMA/LENT score behoeft aandacht. Het gewicht wat in de SOMA/LENT score wordt gegeven aan de mictie frequentie lijkt te groot.

Toekomstige analyses zullen plaatsvinden met gebruik van de klinische en fysische data van de CKVO studie. Toxiciteit studies met en zonder dosis volume relaties, dose maps en rectum modellen zullen worden ondernomen. Als de gegevens, met betrekking tot de tumorcontrole, rijp genoeg blijken, zal ook voor tumorcontrole een dergelijke analyse plaatsvinden. Het ligt in de bedoeling de gegevens van de CKVO studie te koppelen aan de andere internationale studies (MD Anderson Hospital, Houston en het Royal Marsden Hospital, London) op dit gebied. Deze meta-analyse zal ons inzicht kunnen geven over de dosis effect relatie voor de tumorcontrole op de verschillende dosis niveaus van deze studies.

Wij hopen dat de gegevens van de toxiciteit studie en de CKVO studie ons een gedetailleerd idee gaan geven over de toxiciteit gerelateerd aan de 3DCRT bestraling van prostaat kanker. Met meer nauwkeurige modellen zal een voorspelling van de bijwerkingen en complicaties mogelijk zijn. Met deze modellen kunnen wij de behandeling individualiseren. Een verdere verfijning door middel van (image guided) IMRT of het gebruik van tumor biologische markers lijken in de nabije toekomst te realiseren.
Vele vragen zijn echter nog onbeantwoord. Naast de vragen zoals hierboven weergegeven zijn er andere praktische en interessante vragen:
Wat is de rol van de brachytherapie? Hoe ligt de verhouding tussen een prostatectomie en radiotherapie (uitwendig en door middel van brachytherapie)?
Met name de laatste vraag is fascinerend. Maar daar waar beide behandelmodaliteiten nog steeds een verdere verbetering in techniek laten zien, zal een vergelijkende studie helaas nog (enige) jaren op zich laten wachten.

Dankwoord

Eindelijk is het dan zover. Het boek(je), dat de onderzoeksresultaten bundelt van de prostaat conformatie werkgroep, is voltooid. De effecten van de introductie van 3D Conformatie radiotherapie, voor wat betreft de toxiciteit, zijn hiermee beschreven. De resultaten van de prostaat werkgroep zijn redelijk succesvol te noemen. Twee gerandomiseerde studies en een technische studie zijn voltooid. Door het Revolving Fund van het Erasmus MC, CKTO en NKB is dit project financieel ondersteund, waarvoor hartelijk dank. Helaas vereist een klinische studie van enige omvang, tijd, voordat data rijp zijn voor publicatie. Soms zijn de studie uitkomsten anders dan verwacht. Zoals uit de inhoud blijkt is dit niet het werk van een persoon, maar een samenwerking van meerdere personen en disciplines binnen het Erasmus MC en daarbuiten.

Mijn dank gaat in eerste instantie uit naar de promotie commissie. Ik wil hen danken voor de tijd om dit verzamelde werk te beoordelen. In het bijzonder dank ik mijn promotoren Peter Levendag en Joos Lebesque. Peter, jij hebt soms getwijfeld aan de goede afloop. Jouw kritisch commentaar heeft mij diverse malen aan het denken gezet. Joos, vanuit een “Ajax-Feijenoord” situatie, zijn wij (met anderen) tot een goede samenwerking gekomen. De voltooing van de CKVO studie, de eerste resultaten van de NKB studie en in het bijzonder de “recycling” van het materiaal van de DDHK 94/14 studie, zijn wat mij betreft een duidelijk positief resultaat. Jouw steun in de laatste fase was voor mij erg belangrijk.

De keuze van de paranimfen (Marjolein en Mischa) is niet toevallig. In hen zijn de groepen vertegenwoordigd, die een belangrijke bijdrage aan de voltooing hebben geleverd.
Marjolein, jij bent vanaf het begin, enthousiast, betrokken bij het conformatie project. Door jou (Gert, Conny, Theresia en Petra) is veel werk verricht, waarvoor zelfs internationaal belangstelling bestond. De laboranten groep, in het bijzonder, heeft een belangrijke bijdrage geleverd aan de realisatie van de 3DCRT. Niet alleen de mensen van de MM50 en later de Neptunus, maar ook de mensen van de voorbereiding en planning. Hans en Eric bedankt voor de technische ondersteuning.
Mischa, jij bent samen met Wilma, onderdeel van de nauwe, plezierige samenwerking met het Antoni van Leeuwenhoek ziekenhuis. In de voorbereiding voor de CKVO analyse is door jullie belangwekkende informatie verkregen uit de DDHK 94/14 studie. Ook wil ik de Amsterdamse collegae, Stephanie, Coen en Guus voor hun bijdrage bedanken.
Ik hoop (Marjolen en Mischa) dat ik samen met jullie na de voltooing van dit promotie project, met dezelfde positieve instelling, nieuw onderzoek kan opzetten.

Uiteraard bedank ik de collegae radiotherapeuten en (oud) assistenten, die door hun bereidwilligheid patienten in de studies hebben geincludeerd, ondanks het extra werk voor uitleg, uitvoer en follw-up. Ook wil ik hen danken voor de waarneming tijdens mijn afwezigheid. Hierbij dank ik uiteraard ook de collegae buiten de “Daniel”, in het bijzonder Hans en Annerie, maar ook diegene die Rotterdam verlaten hebben voor een ander instituut.

Wim van Putten wil ik bedanken voor zijn geduld, kritische bijdrage en (bereidwillige) medewerking aan de Amsterdamse onderzoeksactiviteiten.

Ook ben ik dank verschuldigd aan de afdeling fysica (oa. Maarten en Ben), maar Joep in het bijzonder, voor hun Rotterdamse bijdrage. Ik vind het jammer, dat door andere prioriteiten, een grotere betrokkenheid de laatste jaren niet mogelijk was.

Luca en Marie Louise dank ik voor de samenwerking voor wat betreft de sexuele consequenties van de behandeling van prostaat kanker. Meerdere aspecten zouden wij nader moeten uitwerken.

Ik dank Manouk en Elly voor hun mentale steun in moeilijke momenten. De verpleging en andere medewerkers van de verpleegafdeling A0 voor hun positieve instelling en enthousiasme.

Wendy en Jeanette (Joyce en Marlies) dank ik voor de positieve werksfeer en secretariele ondersteuning.

Niet in de laatste plaats ben ik dank verschuldigd aan de medewerkers van het trial bureau, met name Paula, Gerda en Marjolein. Door hun inzet (en die van de Amsterdamse collegae) is gedetaileerd onderzoek mogelijk.

Ik dank de patienten voor hun vertrouwen en bereidheid tot deelname aan de klinische studies .
Zonder hun medewerking, en trouw invullen van de vragenformulieren, zijn deze studies onmogelijk.

De regionale urologen worden bedankt voor de verwijzing en het vertrouwen.
Nieuw onderzoek is noodzakelijk om de radiotherapie resultaten verder te verbeteren en de positie van dosis escalatie, concommittant boost technieken en brachytherapie duidelijk te maken.
De samenwerking met de afdeling urologie van het Erasmus MC (prof. Schröder, prof. Bangma en Kirkels) wordt hierbij zeer gewaardeerd.

Met de mensen, waarmee ik de afgelopen jaren op een plezierige wijze heb samengewerkt, hoop ik dat de komende jaren te blijven doen.

Last but not least dank ik Fieneke, Marieke en Bart voor het geduld en mentale steun. Zonder steun van het thuisfront wordt niet veel bereikt. Er zijn belangrijke lessen geleerd. Een beter evenwicht tussen werk en gezin is het streven.

Peter Koper werd op 21 december 1955 te Leiden geboren. In 1974 werd het VWO-Atheneum diploma behaald aan het Thomas More College te ‘s Gravenhage. In dat zelfde jaar kon de studie Geneeskunde gestart worden aan de Erasmus Universiteit te Rotterdam. Deze studie werd op 24 april 1981 afgerond door het behalen van het Artsexamen. Na de militaire diensttijd verkreeg hij de positie arts-assistent (niet in opleiding) op 1 november 1982 in de Dr.Daniel den Hoed Kliniek. Van 1 april 1984 tot 1 januari 1988 volgde de opleiding tot radiotherapeut met als opleider mevrouw Prof. Dr. B.H.P. van der Werf Messing. Sindsdien is hij werkzaam op de afdeling radiotherapie van het Erasmus MC, locatie Daniel den Hoed Kliniek. Sinds 1 januari 1991 vervuld hij de positie van chef de clinique (later medisch coördinator) en plaatsvervangend hoofd van de afdeling radiotherapie onder leiding van Prof. Dr. P.C.Levendag.

Sindsdien is hij de voortrekker van de gynaecologische werkgroep. Na retrospectief onderzoek is samen met collega Meerwaldt en Creutzberg de PORTEC I studie geïnitieerd en gecoördineerd met de medewerking van diverse collegae van de betrokken specialismen. Collega Creutzberg heeft, als assistent in opleiding en later radiotherapeut, met succes deze studie afgerond.
Op het gebied van de behandeling van het gevorderd cervix carcinoom werd door hem, als lid van de hyperthermie werkgroep, een bijdrage geleverd aan de realisatie van de gerandomiseerde hyperthermie studie in het kader van een Ontwikkeling Geneeskunde project.
Als locaal coördinator is hij betrokken bij de vervolgstudies nl PORTEC II en RADCHOC.

Op verzoek van Prof. Dr. P. C. Levendag is in 1994 de introductie van drie dimensionale radiotherapie voor het prostaatcarcinoom, na een stage bij Prof. C. Perez, St. Louis, en S. Leibel, New York, ter hand genomen. Een gerandomiseerde toxiciteit studie (DDHK 94/14) werd afgerond. De gegevens van deze studie vormen een belangrijk deel van dit proefschrift.
In 1996 werd een zogenaamde pilotstudy (DDHK 96/11) gestart, welke de technische verbeteringen van deze bestralingstechniek onderzocht. Het materiaal van deze studie vormde de basis van de Revolving Fund subsidie. Met deze subsidie is J. Stroom als research fysicus aan het project toegevoegd. Het onderzoeksresultaat was/is onderdeel van zijn en deze promotie.
Sinds 1995 is in samenwerking met collega dr.J. Lebesque, radiotherapeut in het NKI/Antoni van Leeuwenhoek ziekenhuis te Amsterdam, een gerandomiseerde dosis escalatie studie geschreven. Deze studie (CKVO 96/10) en de daaraan verbonden NKB studie (NKB 98-1813) zijn door het NKB financieel ondersteund. Het klinisch deel van de studie is, na inclusie van 669 patiënten, in februari 2003 afgesloten.
Onderzoek naar seksuele toxiciteit in relatie met de radiotherapeutische behandeling is opgestart in samenwerking met L. Incrocci. Dit werd door collega Incrocci met succes afgerond en vormde een onderdeel van zijn promotie.
Sinds 2001 is in nauwe samenwerking met de afdeling urologie van het Erasmus MC (Prof. Dr. Schröder, Prof. Dr. Bangma en Dr. Kirkels) en collega Jansen, High Dose Rate Brachytherapie geïntroduceerd in het Erasmus MC voor het vroege stadium prostaat carcinoom. Deze werkgroep organiseert om het jaar een symposium (“behandelopties gelokaliseerd prostaatcarcinoom”) waarbij de (Rotterdamse) ervaringen van de diverse disciplines worden gepresenteerd.

Al meer dan 23 jaar heeft Peter een relatie met Fieneke Ruoff, is 17 jaar met haar getrouwd en heeft een dochter, Marieke, 16 jaar oud, en een zoon, Bart, 15 jaar oud.

Prostate cancer

Multiple two-dimensional versus three-dimensional PTV definition in treatment planning for conformal radiotherapy
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Field margin reduction using intensity-modulated x-ray beams formed with a multileaf collimator
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Acute morbidity reduction using 3dcrt for prostate carcinoma: a randomized study
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Sexual functioning in patients with localized prostate cancer awaiting treatment
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