External beam radiotherapy for prostate cancer: the potential for dose escalation

Irene M. Lips

Cover: Foto van onbekende fotograaf, bewerkt door Roy Sanders.
Ofschoon iedere poging is ondernomen om de volgens de auteurswet rechthebbende van de foto te traceren, is dit niet mogelijk gebleken. De auteur biedt graag bij voorbaat excuses aan voor eventuele onvrijwillige inbreuk op het auteursrecht en verzoekt rechthebbende contact op te nemen.

ISBN: 978-90-393-5621-0
Lay out: Roy Sanders
Printed by: PrintSupport4U, Meppel, The Netherlands

External beam radiotherapy for prostate cancer: the potential for dose escalation

"Uitwendige radiotherapie voor prostaatkanker: mogelijkheden voor dosis escalatie"
(*met een samenvatting in het Nederlands*)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr.G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op vrijdag 21 oktober 2011 des ochtends te 10.30 uur

door

Irene Marina Lips
geboren op 14 februari 1982
te Amsterdam

Promotor:	Prof. dr. ir. J.J.W. Lagendijk
Co-promotoren:	Dr. M. van Vulpen Dr. U.A. van der Heide

Het beschreven werk werd mede mogelijk gemaakt door een subsidie van KWF kankerbestrijding (UU 2006-3638). Deze uitgave is tot stand gekomen met financiële steun van KWF kankerbestrijding, Stichting Contactgroep Prostaatkanker, Röntgen Stichting Utrecht, Nucletron B.V., Abbott B.V. en Ipsen Farmaceutica B.V.

Contents

Chapter 1

Introduction

Prostate Cancer

Prostate cancer is a major health problem worldwide, with 217730 newly diagnosed prostate cancer patients in the Unites States in 2010 and 10166 men with newly diagnosed prostate cancer in the Netherlands in 2009 (Dutch Comprehensive Cancer Centres; Jemal *et al.*, 2010). Despite improved treatment outcome and the advances in early detection of prostate cancer, prostate cancer still is a common cause of cancer death in the western world. In 2010, 32050 men died from prostate cancer in the United States and 2421 men in the Netherlands died from prostate cancer in 2008 (Dutch Comprehensive Cancer Centres; Jemal *et al.*, 2010). Prostate cancer most often affects elderly men with most cases occurring in men between 65 and 74 year old (Crawford *et al.*, 2009).

The clinical behavior of prostate cancer differs between biologically indolent microscopic tumors to highly aggressive cancer with a poor prognosis. Based on the initial prostate-specific antigen level (iPSA), Gleason score and tumor stage patients can be classified as having low-risk, intermediate-risk or high-risk disease (Heidenreich *et al.*, 2011). The currently internationally accepted criteria from Ash *et al.* (2000) stated low-risk as patients having T1c-T2a, Gleason score <7 and iPSA <10ng/mL. Intermediate-risk is defined as having one factor of T2b-c, or Gleason score = 7, or iPSA 10-20 ng/mL; in case of two of these factors a patient is classified as high-risk. Furthermore, high-risk includes patients with one or more factors of T3, or Gleason score >7, or iPSA> 20 ng/mL.
Different treatment strategies are available for prostate cancer. Common treatment options include watchful waiting, radical prostatectomy, external beam radiotherapy and brachytherapy. For low-risk tumors the results of external beam radiotherapy are comparable to radical prostatectomy and brachytherapy with freedom from biochemical failure rates approximating 95% after 5- to 10-year follow-up (Lu-Yao *et al.*, 1997). For high-risk patients external beam radiotherapy is preferred in combination with hormonal therapy (D'Amico *et al.*, 2008). The outcome for intermediate- and high- risk patients is worse with freedom from biochemical failure ranging between 60% and 75% after 5- to 10 years follow-up (Peeters *et al.*, 2006; Pollack *et al.*, 2002; Widmark *et al.*, 2009).

Toxicity

Because the outcome after different treatment methods, concerning freedom from biochemical failure, shows only small variation, the toxicity patterns and the quality of life (QoL) after each treatment have a great influence on the treatment choice. In general, irritative and obstructive urinary symptoms are more common after brachytherapy, urinary incontinence and erectile impotence is more frequent after

radical prostatectomy and external beam radiotherapy is associated with bowel symptoms.

For external beam radiotherapy the entire toxicity pattern consists of gastrointestinal, genitourinary side effects and erectile dysfunction. The acute gastrointestinal symptoms caused by radiation proctitis include abdominal cramping, flatulence, urgency, increased stool frequency, flatulence and proctalgia. Late gastrointestinal toxicity compromises persistent diarrhea, rectal urgency, rectal bleeding, rectal or anal stricture, ulcers and perforation.

Urinary toxicity during external beam radiotherapy is due to cystitis or urethritis. Possible adverse events include dysuria, urgency, urinary incontinence, increased frequency, hematuria, urinary retention and bladder spasms. Long-term genitourinary complaints manifest as urinary incontinence, urethral strictures, hemorrhage and bladder contracture (Hamilton *et al.*, 2001). Another side effect after external beam radiotherapy is erectile dysfunction. The reported percentage of patients that preserve their erectile ability is approximately 70% (Pinkawa *et al.*, 2009; van der Wielen *et al.*, 2007). The incidence of erectile dysfunction progressively increases during follow-up time after radiotherapy. Radiotherapy associated erectile dysfunction is influenced by the use of neoadjuvant androgen deprivation therapy, patient age and comorbidities such as cardiovascular diseases and diabetes (Pinkawa *et al.*, 2009; van der Wielen *et al.*, 2007).

Acute and late toxicity after external beam radiotherapy can be influenced by several factors. The severity of complaints is related to the irradiation dose to the organ at risk and the volume of the organ included (Gulliford *et al.*, 2010; Vargas *et al.*, 2005; Karlsdottir *et al.*, 2008; Heemsbergen *et al.*, 2010). A transurethral resection of the prostate (TURP) prior to radiotherapy is associated with significantly more late genitourinary toxicity (Heemsbergen *et al.*, 2010; Peeters *et al.*, 2005a; Sandhu *et al.*, 2000). The likely mechanism of increased late toxicity is related to the relative devascularisation of the urethra after TURP and the decreased capability of the mucosa to repair sublethal damage after radiotherapy (Sandhu *et al.*, 2000). Hormonal treatment is a prognostic unfavorable factor for late genitourinary side effects (Peeters *et al.*, 2005a; Schultheiss *et al.*, 1997), for acute genitourinary toxicity (Valicenti *et al.*, 2003) and for erectile impotence (van der Wielen *et al.*, 2007; Zelefsky *et al.*, 1999; Turner *et al.*, 1999). Furthermore, a protective effect for hormonal treatment is reported for acute gastrointestinal side effects (Peeters *et al.*, 2005a; Christie *et al.*, 2005; Vavassori *et al.*, 2007). Both gastrointestinal and genitourinary adverse events are increased in patients with diabetes (Schultheiss *et al.*, 1997; Vavassori *et al.*, 2007; Giordano *et al.*, 2006). The likely mechanism of an increase in toxicity is related to impaired repair of radiation-damaged tissue (Herold *et al.*, 1999). Furthermore, late toxicity seems to be correlated with acute toxicity (Karlsdottir *et al.*, 2008; Schultheiss *et al.*, 1997; Heemsbergen *et al.*, 2006) which is referred to as consequential late effect.

Acute radiation response causes tissue damage, which eventually leads to late effects after a latent symptom-free interval.
The acute gastrointestinal and genitourinary symptoms usually resolve within several weeks after treatment. Acute toxicity is defined as symptoms occurring within 90 days after the start of treatment (Trotti *et al.*, 2000). The majority of long-term gastrointestinal toxicity after external beam radiotherapy manifests itself within three years of follow-up time (Pollack *et al.*, 2002; Karlsdottir *et al.*, 2008; Schultheiss *et al.*, 1997; Zietman *et al.*, 2005). Late genitourinary complaints have been reported to develop even after three years (Karlsdottir *et al.*, 2008; Schultheiss *et al.*, 1997). For measurement of both acute and late toxicity after treatment the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Trotti *et al.*, 2003) can be used. This grading system is generally organized by organ system categories and defines grade 1 as minimal, usually asymptomatic and not interfering with functional endpoints. Grade 2 adverse effects are considered moderate, usually symptomatic and interventions such as local treatment or medications may be indicated. Grade 3 effects are considered severe and very undesirable and include more serious interventions such as surgery or hospitalization. Grade 4 effects are potentially life threatening, catastrophic or disabling. There are no guidelines to define an acceptable toxicity profile after a certain treatment, but in general the most important adverse events, that needed to be limited, are the serious and life-threatening adverse events (grade 3 and 4).

Quality of life

For evaluation of treatment not only toxicity is important but also impact on QoL (Litwin *et al.*, 1999). The satisfaction with treatment outcomes among patients and their spouses or partners is influenced by the treatment-related change in QoL (Sanda *et al.*, 2008). Especially for patients with prostate cancer, who may live for years after the initial diagnosis, QoL after treatment is of major importance. Health-related QoL involves patient's own perceptions of their health and ability to function in life. Quality of life represents not only physical function as a representation of treatment-related side effects, but also domains like role function, vitality, mental health and social interactions to evaluate the impact on normal functions or social roles (Litwin *et al.*, 1999). To measure health-related QoL, validated QoL questionnaires should be used including a disease-specific and organ-specific module. General QoL domains address the components of overall well being, while the disease-specific domains focus on the impact of particular organs dysfunctions that affect QoL. Quality of life measurements should be patient assessed because it is know that the assessment of patient's symptoms by the physician underestimates the morbidity reported by patients (Litwin *et al.*, 1998; Goldner *et al.*, 2003). Especially for the older prostate cancer patients a longitudinal study design including baseline scores is essential (Osoba *et al.*,

2005; Chen *et al.*, 2009). For the interpretation of QoL results, a statistically significant difference is only interesting if it is also clinically relevant for the patients. A change of 10% (or in general, 0.5 standard deviation) of the scale width is perceptible to patients as a meaningful change (Osoba *et al.*, 2005).

Dose escalation

Several trials have proven that dose escalation in external beam radiotherapy improves the biochemical free survival (Peeters *et al.*, 2006; Pollack *et al.*, 2002; Zietman *et al.*, 2005; Kupelian *et al.*, 2005; Dearnaley *et al.*, 2007) . Pollack *et al.* (2002) compared the efficacy of 70 Gy versus 78 Gy on 305 patients with stage T1-3 prostate cancer in a randomized controlled trial. For patients with a pre-treatment PSA > 10 ng/mL the freedom from biochemical failure rate at five year was 43% versus 62% respectively, in favor of the higher dose group. The randomized controlled trial from Peeters *et al.* (2006) compared 68 Gy versus 78 Gy on 669 patients with stage T1-4 prostate cancer. Five-year freedom from failure rate was significantly improved from 54% to 64%.
To improve the poor treatment results in intermediate- and high-risk prostate cancer patient, further increase in dose is considered to be needed (Peeters *et al.*, 2006; Pollack *et al.*, 2002; Zelefsky *et al.*, 2002; Morgan *et al.*, 2007). The tumor control probability (TCP) volume effect implies that a higher dose is needed at the primary tumor (Goitein *et al.*, 1985). Furthermore, dose response models suggest that the overall cure rate in high-risk prostate cancer patients is limited due to radioresistent hypoxic tumors and that the areas with severe hypoxia will need very high (ablative) doses (Nahum *et al.*, 2003). This hypothesis is strengthened by the finding that local recurrences often originate in the primary tumor rather than in focal prostatic intraepithelial neoplasia (Pucar *et al.*, 2007; Cellini *et al.*, 2002). Dose escalation to the entire prostate is not considered achievable by reason of unacceptable toxicity risks. This problem can be overcome by partial boosting strategies. Planning studies showed that an ablative microboost to the macroscopic intraprostatic tumor area while the dose constraints to the rectum and bladder can be maintained is theoretically feasible (van Lin *et al.*, 2006; Pickett *et al.*, 1999; Xia *et al.*, 2001). The macroscopic tumor area within the prostate can be defined using a combination of anatomical and functional imaging. In addition to anatomic T2 weighted sequence, a combination of different functional imaging modalities can be used (Groenendaal *et al.*, 2010; van der Heide *et al.*, 2011). Dynamic contrast-enhanced (DCE)-magnetic resonance imaging (MRI) gives a characterization of the tissue vasculature (Padhani *et al.*, 2002). With this technique it is possible to detect the tumor, because tumors tend to contain higher density of leaky blood vessels. With diffusion weighted imaging (DWI)-MRI the mobility of water molecules is measured (Hosseinzadeh *et al.*, 2004). Tumor tissue can be identified on DWI-MRI, because in tumor the extracellular volume is reduced, leading to reduced

water diffusion in tumor tissue. MR spectroscopic imaging (MRS) provides metabolic information in which regions of cancer show higher choline and lower citrate levels (Scheidler *et al.*, 1999).
Boosting the radiation dose within the primary tumor might increase the local control. By reducing local failure, a reduction of distant metastases and improvement in survival can be expected, due to the relationship between these treatment outcomes (Coen *et al.*, 2002; Kupelian *et al.*, 2008; Jacob *et al.*, 2004). However, before a randomized clinical trial can be performed to investigate whether an ablative microboost to the macroscopic tumor within the prostate, is indeed effective in improving treatment outcome, one needs to be sure that this approach is feasible and safe.

Developments in external beam radiotherapy

To be able to deliver an ablative microboost while severe toxicity remains limited all treatment uncertainties need to be minimized. Several developments in external beam radiotherapy have increased the accuracy of the treatment and created the ability to minimize the dose to the normal tissue. The conformal radiotherapy planning techniques consisting of large irradiation fields are replaced by intensity-modulated radiotherapy (IMRT) in which the fluency profiles of the radiation beams are no longer homogenous (*Figure 1*). With the use of IMRT sharp dose gradients and very inhomogeneous dose distributions can be obtained, leading to less irradiation to the organs at risk while the dose to the prostate can be escalated. Intensity-modulated radiotherapy provides the possibility for dose painting, in which the delivered dose distribution is being adapted based on functional and biological imaging information (Bentzen *et al.*, 2005; Ling *et al.*, 2000).

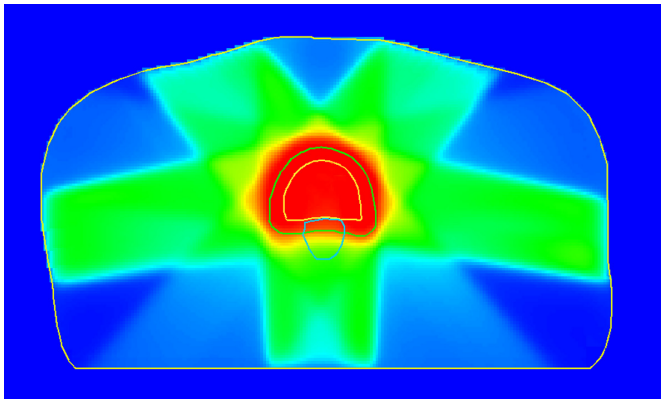

Figure 1. Transversal image of a dose distribution of an IMRT radiotherapy plan.

To ensure accurate target coverage with the prescribed dose, a margin is created expanding the clinical target volume (CTV) to the planning target volume (PTV), to account for geometric uncertainties (*Figure 2*).

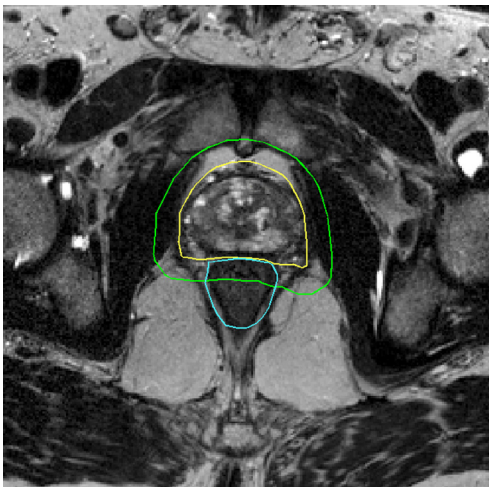

Figure 2. Delineation of the clinical target volume (yellow), planning target volume (green) and the rectum (blue) on a transversal T2-weighted magnetic resonance image.

These uncertainties include systematic and random errors (van Herk *et al.*, 2004). By minimizing these errors, the margin to account for these errors can be reduced. A smaller margin decreases the dose that is delivered to the organs at risk adjacent to the target volume. To localize the prostate during treatment and secure its position relative to the irradiation beam, image guided radiotherapy has been introduced (Smitsmans *et al.*, 2004; Nederveen *et al.*, 2003). At first alignment of the patient to markers on the skin was replaced by position verification based on internal bony structures (Hurkmans *et al.*, 2001). However, variation in bladder and rectal filling causes internal motion of the prostate relative to the bony anatomy (Nederveen *et al.*, 2003; Schallenkamp *et al.*, 2005), which can only be corrected for when the prostate itself is being located during treatment. The location of the prostate can be identified with the use of conebeam imaging (Smitsmans *et al.*, 2004) or by visualizing fiducial gold markers implanted in the prostate as a surrogate for the prostate itself (Moman *et al.*, 2010) (*Figure 3*).

The positioning uncertainties between treatment fractions are called interfraction motion. To correct for the interfraction prostate motion, various position verification correction protocols can be used. The prostate location can be identified during each fraction or less frequent during the treatment period. The correction of the variation can be done on-line by determining the location of the prostate before each fraction

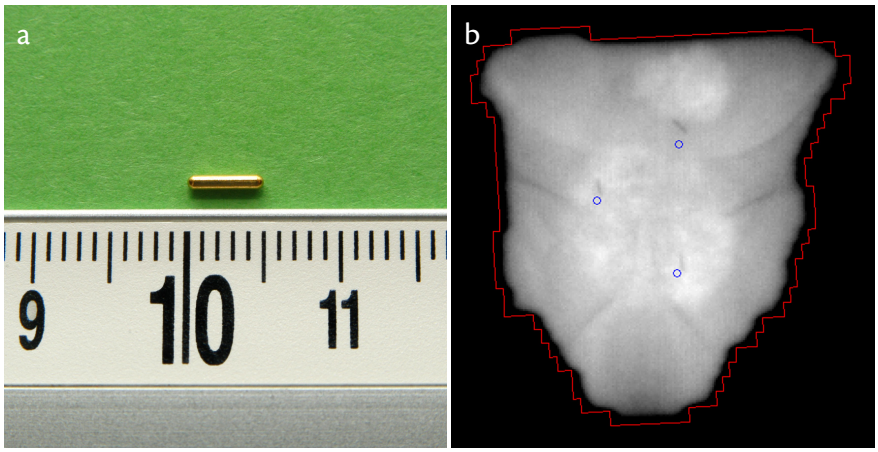

Figure 3. (**a**) Example of a fiducial gold marker. (**b**) Electronic portal image taken from the first segment of the irradiation beam. The actual location of the three fiducial markers can be seen as three dark spots and the location of the three markers based on the planning CT-scan are projected by blue circles.

and perform corrections directly after imaging before irradiation takes place. Because systematic errors have the largest influence on the position uncertainty during treatment compared to the random errors, also an off-line protocol can be used. Off-line protocols aim to reduce the average position deviation during treatment (van Herk *et al.*, 2004; van der Heide *et al.*, 2007). The conventional off-line protocols estimate the systematic deviation in the first fractions of the treatment, making the assumption that this estimate is representative for the entire treatment. With a no-action-level protocol, the average position deviation after the first fractions is used as a correction for the set-up in all following fractions. A shrinking-action-level (SAL) protocol, immediately corrects large deviations, because they are considered clinically relevant and smaller deviations are only corrected if they persist over some fractions. Such an approach attempts to estimate the systematic positioning error early in treatment. A regular SAL protocol stops when no correction is needed for the average position deviations over a predefined number of fractions. An adapted SAL protocol continues the measurements after the regular procedure, which can be done weekly of daily during the rest of the treatment. A running average is determined over the past predefined number of fractions and compared to the action level.

The intrafraction prostate motion is the movement of the prostate during the actual irradiation on any given day. An important cause of intrafraction motion is thought to be moving gas pockets inside the rectum (Nichol *et al.*, 2010; Nederveen *et al.*, 2002). By minimizing the interfraction position uncertainties, the intrafraction motions will have greater impact. In an attempt to tackle the problem of prostate motion, several methods have been introduced such as dietary guidelines, medicines like laxatives

(magnesium oxide), deflatulences (simethicon) and antiperistaltics (glucagon), fixed treatment times (after 10 AM), rectal gas removal by insertion of a finger or the use of a rectal balloon (Wu *et al.*, 2001; Smitsmans *et al.*, 2008; Madsen *et al.*, 2003; Ogino *et al.*, 2008; Padhani *et al.*, 1999; van Lin *et al.*, 2005).

Outline of this thesis

The question is whether the improvements in external beam radiotherapy for prostate cancer provide the possibility to accurately deliver an ablative microboost to the intraprostatic tumor while avoiding an increase in treatment-related toxicity and a clinically relevant deterioration in QoL. Therefore, the uncertainties in delivery and the expected clinical outcome have to be looked at.

The influence of the interfraction position uncertainties for inhomogeneous IMRT dose distributions with an integrated microboost to the tumor is unknown. At the UMC Utrecht a daily off-line position verification protocol in combination with implanted fiducial gold markers is used in clinical practice, which supplies the daily location of the prostate. This information provides the possibility to investigate the effect of translation and rotational interfraction errors for complex dose distributions with estimated individual position data. The influence of two different position verification strategies on IMRT dose distributions with a microboost to the intraprostatic tumor areas could therefore be studied and the required margins to account for the remaining setup errors considered (chapter 2).

Chapter 3 and 4 address the problem of intrafraction prostate motion. Several groups prescribe magnesium oxide and a diet during the course of radiotherapy, in an attempt to reduce this geometric uncertainty. However, there is no clear evidence that these interventions are indeed effective in reducing the amount of intrafraction motion during radiotherapy. For all patients treated at our department between 2002 and 2009, the intrafraction prostate motion is determined. The influence of an antiflatulent diet, which was introduced at our department in 2008, on the intrafraction motion is evaluated (chapter 3). The effect of magnesium oxide on intrafraction motion is investigated in a double-blind placebo-controlled randomized clinical trial (chapter 4).

Previous dose escalation trials reported statistically significant higher incidences of acute and late gastrointestinal and genitourinary toxicity for patients treated with higher dose levels (Peeters *et al.*, 2005a, Zietman *et al.*, 2005; Dearnaley *et al.*, 2007; Kuban *et al.*, 2008; Syndikus *et al.*, 2010; Al-Mamgani *et al.*, 2008; Beckendorf *et al.*, 2010; Beckendorf *et al.*, 2004). The hypothesis is that with the use of more accurate position verification and improved planning techniques, the organs at risk will be better spared leading to less treatment-related toxicity. However, whether the use of advanced radiotherapy techniques indeed provides the possibility to treat the prostate with a high dose while the organs at risk can be spared, needs to be confirmed. At our institute the use of IMRT in combination with marker-based position verification was

already introduction in 2001, which offers the possibility to evaluate the treatment-related toxicity with a long follow-up period. Chapter 5 describes the acute and late toxicity after high dose IMRT with fiducial marker-based position verification. In chapter 6 a comparison is made between the short-term QoL after 70 Gy conformal radiotherapy with position verification based on bony anatomy and 76 Gy IMRT in combination with fiducial markers for position verification. The evaluation of the late QoL after high-dose external beam radiotherapy is the topic of chapter 7.

To investigate whether an ablative microboost to the macroscopic tumor within the prostate is indeed beneficial, a randomized clinical trail needs to be performed. The study design for such a trial is presented in chapter 8.

Finally, chapter 9 gives a summary of the most important results and discusses whether it is feasible and safe to deliver an ablative microboost to the macroscopic tumor within the prostate.

Chapter 2

Interfraction motion

This chapter has been published as:

I.M. Lips, U.A. van der Heide, A.N.T.J. Kotte, M. van Vulpen and A. Bel.

Effect of translational and rotational errors on complex dose distributions with off-line and on-line position verification.

International Journal of Radiation Oncology, Biology, and Physics 2009; 74: 1600-8.

Abstract

Purpose

To investigate the influence of translational and rotational errors on prostate intensity-modulated radiotherapy (IMRT) with an integrated boost to the tumor and to evaluate the effect of the use of an on-line correction protocol.

Methods and Materials

For 19 patients, who had been treated with prostate IMRT and fiducial marker-based position verification, highly inhomogeneous IMRT plans, including an integrated tumor boost, were made using varying margins (2, 4, 6, and 8 mm). The measured translational and rotational errors were used to calculate the dose using two positioning strategies: an off-line and an on-line protocol to correct the translational shifts. The estimated dose to the targets and the organs at risk was compared with the intended dose.

Results

Residual deviations after off-line correction led to statistically significant, but very small, reductions in dose coverage. Even when a 2-mm margin was used, the average reduction in dose to 99% of the volume was 1.4 ± 1.9 Gy for the tumor, 1.5 ± 1.5 Gy for the prostate without seminal vesicles (boost volume), and 4.3 ± 4.6 Gy, including the seminal vesicles (clinical target volume). Patients with large systematic rotational errors demonstrated a substantial decrease in dose, especially for the clinical target volume. If an on-line correction protocol was used, the average mean dose and dose to 99% of the volume of the targets improved. However, the extensive dose reduction for patients with large rotational errors barely recovered with on-line correction.

Conclusion

For complex prostate IMRT with an integrated tumor boost, the use of an on-line correction protocol yields little improvement without the correction of rotational errors.

Introduction

Escalation of the radiation dose for prostate cancer from 68 Gy to 78 Gy resulted in a significant improvement in biochemical relapse-free treatment outcome (Peeters *et al*., 2006; Pollack *et al*., 2002; Zietman *et al*., 2005). An additional increase in radiation dose is suggested to improve the treatment outcome (Eade *et al*., 2007). However, the bladder and rectum are dose-limiting organs, and additional dose escalation will increase the risk of developing complications. To improve local control while keeping the toxicity risk acceptable, conventional homogeneous dose distributions have been replaced by integrated partial boost strategies (Nedervan *et al*., 2001; Bos *et al*., 2005). Most local recurrence seems to originate in the primary tumor location (Cellini *et al*., 2002; Pucar *et al*., 2007); therefore, irradiation of a dominant intraprostatic lesion (DIL) might improve the local control rates. These high-dose intraprostatic boosting strategies have been proved to be feasible (Pickett *et al*., 1999; De Meerleer *et al*., 2005; van Lin *et al*., 2006; Singh *et al*., 2007).

To ensure accurate target coverage with the prescribed dose, a margin is created, expanding the clinical target volume (CTV) to the planning target volume (PTV), to account for geometric uncertainties. These uncertainties include systematic and random errors. Van Herk *et al*. (2000) and Stroom *et al*. (1999) developed margin recipes to account for the translational deviations during treatment. These margin rules were derived for homogeneous, three-dimensional conformal radiotherapy (RT). The use of intensity-modulated RT (IMRT) leads to inhomogeneous dose distributions, nonspherical and small target shapes, and less steep penumbras. Therefore, the effect of geometric deviations for IMRT is different from those predicted using the margin recipe (Gordon *et al*., 2008; Siebers *et al*., 2005). Several investigators have investigated the consequences of on-line and off-line correction strategies for prostate IMRT (Bos *et al*., 2005; Beaulieu *et al*., 2004; Cheung *et al*., 2005; Meijer *et al*., 2008). However, in those studies, the effect of different setup strategies on an IMRT plan with a high dose to a DIL was not studied.

At our institute, the daily prostate position is determined using gold fiducial markers. The fiducial marker configuration serves as a surrogate for the position and orientation of the prostate itself. Combined with our off-line shrinking-action-level (SAL) positioning protocol, we were able to reduce the systematic error in clinical practice to < 0.8mm in all directions (van der Heide *et al*., 2007). Kotte *et al*. (2007) evaluated the intrafraction motion of our patient group and concluded that a 2-mm margin is sufficient to account for intrafraction motion. In the present study, we wanted to determine the effect of the rotational and residual translational errors, obtained with our off-line adapted SAL correction protocol (van der Heide *et al*., 2007), for highly inhomogeneous IMRT plans including a boost to the DIL. We also investigated the benefit of removing the random translational errors using an on-line correction

protocol.
Therefore, we investigated the influence of two different position verification strategies on the IMRT dose distributions with a boost to the DIL, when the margins were being reduced. We created IMRT plans with an integrated boost to the DIL using various margins for patients, who had previously undergone IMRT with daily portal imaging of fiducial markers. Subsequently, we recalculated the new dose distributions with inclusion of the setup errors for the two positioning strategies, using the estimated individual position data. For the 'estimated off-line' dose distribution, we simulated the rotations and residual translations after off-line position correction. For the 'estimated on-line' dose distribution, we simulated the rotational errors and correction of all translational errors to assess the sole influence of the rotational errors. We evaluated these 'estimated' dose distributions and considered the required margins to account for the remaining setup errors for prostate IMRT with an integrated boost to the DIL.

Methods and materials

Patients

Nineteen patients with Stage T1-T3N0M0 prostate cancer were used for this planning study. All patients had undergone five-field IMRT of 76 Gy in 35 fractions combined with fiducial marker-based position verification. Portal images of the three implanted gold markers were made of the first segments of all beam directions using an iView-GT amorphous silicon flat-panel detector (Elekta, Crawley, UK) (Kotte *et al*., 2007). The daily registration of the fiducial gold markers resulted in deviations, which were fed into our adapted SAL correction protocol (van der Heide *et al*., 2007). The adapted SAL protocol was applied, and the necessary table shifts were executed the next treatment fraction. For this planning study, the clinical positioning data were used to reconstruct the remaining setup errors after applying different correction protocols. The rotations were determined using the method of Horn *et al*. (1988).
During treatment, the patients had not received any instruction for emptying the rectum before the RT session, and no specific diet was prescribed. Fifteen minutes before computed tomography (CT)/ magnetic resonance imaging (MRI) and the RT sessions, the patients were instructed to void the bladder. The patients were treated in the supine position, and a knee cushion for alignment of the legs was used to prevent any rotation of the hip.

Imaging and delineation

The prostate, seminal vesicles and organs at risk were delineated using a CT scan with 3-mm slices combined with registered MRI scans. The MRI scans were made with a 3 Tesla MRI system (Gyroscan NT Intera, Philips Medical Systems, Best, The Netherlands).

Axial T1-weighted (repetition time, 570 ms; excitation time, 30 ms; 25 slices of 4 mm; field of view, 20 x 20 cm; reconstruction matrix, 256 x 256) and T2-weighted (repetition time, 8,400; excitation time, 120 ms; 25 slices of 4 mm; field of view, 20 x 20 cm; reconstruction matrix, 256 x 256) were obtained using a spin echo sequence. A three-dimensional balanced steady-state free precession image (repetition time, 5.2 ms; excitation time, 2.5 ms; flip angle, 21º; 90 slices of 1 mm, field of view, 25 x 25 cm; reconstruction matrix, 512 x 512) was particularly useful for delineation of the prostate gland.

The CTV included the entire prostate and the seminal vesicles. The PTV was created by expanding the CTV with a margin in all directions. The boost volume (BV) was defined as the CTV without the mobile, cranial parts of the seminal vesicles (*Figure 1 a,b*). A DIL, within the prostate, was identified on diffusion-weighted MRI and defined as the gross tumor volume (GTV). The median volume of the 19 GTVs was 2.1 cm^3 (interquartile range, 1.1–2.6). *Table 1* lists the locations of the DIL inside the prostate. The rectum was contoured from the anus or ischial tuberosities to the rectosigmoid flexure or sacroiliac joints. The bladder was completely outlined from the bladder neck to the dome.

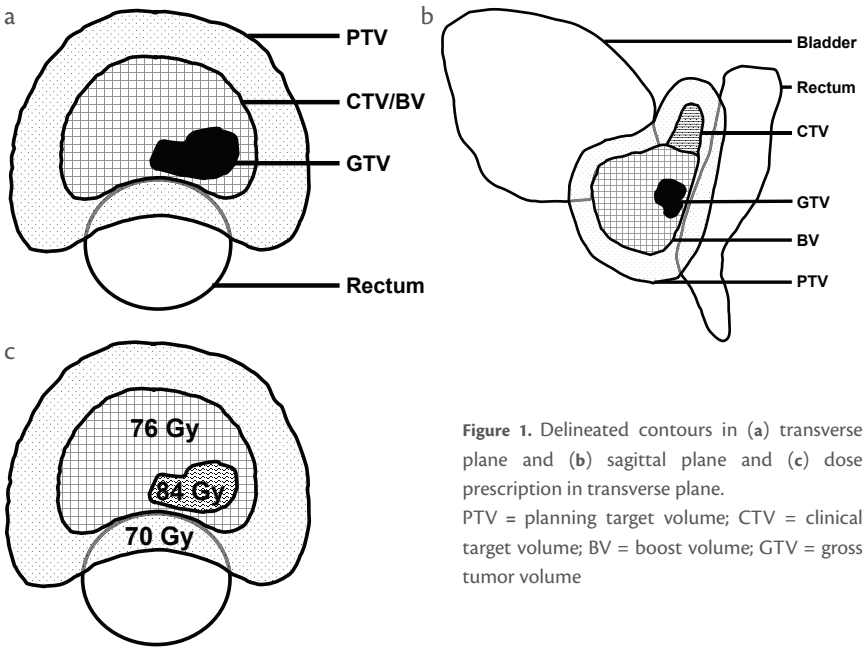

Figure 1. Delineated contours in (**a**) transverse plane and (**b**) sagittal plane and (**c**) dose prescription in transverse plane.
PTV = planning target volume; CTV = clinical target volume; BV = boost volume; GTV = gross tumor volume

Table 1. Locations of 19 dominant intraprostatic lesions by zone.

Location	*n* (%)
Zone	
Peripheral zone	14 (74)
Central zone	5 (26)
Craniocaudal direction	
Cranial	3 (16)
Middle	12 (63)
Caudal	4 (21)
Left-right direction	
Left	4 (21)
Medial	5 (26)
Right	10 (53)
Ventrodorsal direction	
Dorsal	11 (58)
Middle	8 (42)
Ventral	0 (0)

Dose prescription

The CT images of these patients were transferred to our planning system (PLATO, Nucletron BV, Veenendaal, The Netherlands). For each patient, seven-beam step-and-shoot IMRT plans were made using the inverse treatment planning module. To investigate the effect of geometric uncertainties on the highly inhomogeneous dose distributions and the coverage of a boost to the DIL, the dose prescription was 70 Gy to the PTV, 76 Gy to BV, and 84 Gy to the GTV (*Figure 1c*). The dose to the BV was prescribed to the part of the PTV where dose escalation was possible without exceeding the dose constraints for the organs at risk (Nederveen *et al*., 2001). The maximal dose to the GTV was limited to 107% of the prescribed dose (90 Gy). For each patient, four plans were created using varying PTV margins (2, 4, and 6 mm and the clinically used 8 mm). A margin of 2 mm was not sufficient to account for all other uncertainties during treatment.

The rectum dose-limiting constraints were < 5% of the rectal volume could receive a dose > 72 Gy; < 25% could receive > 70 Gy; and < 60% could receive > 50 Gy. For the bladder, the constraint was that < 10% of the volume could receive a dose > 72 Gy. The defined constraints for the organs at risk were achieved in all plans.

The planning goal was to give a mean dose, equivalent to 100% of the prescription dose, and that ≥ 99% of the volume should receive > 95% of the prescription dose (D99% > 95%). Thus, the planning goals were a mean dose of 70 Gy to the PTV, 76 Gy to the BV, and 84 Gy to the GTV; a D99% of 66.5 Gy to the PTV, 72.2 Gy to the BV, and 80 Gy to the GTV. Dependent on the position of the GTV and the anatomy of the

prostate in relation to the rectum, the dose to the bladder and rectum was limiting for dose escalation to the GTV or the BV. Because of the overlap of the target volumes, the mean dose for the PTV and BV was greater than prescribed.

Table 2. Rotations errors and residual translation errors with off-line correction protocol.

Variable	Left-right	Ventrodorsal	Craniocaudal
Rotation axis			
M (°)	0.2	0.02	- 0.6
Σ (°)	6.3	2.0	2.8
σ (°)	4.9	1.0	1.4
Range (°)	- 12.1 to 9.1	- 2.6 to 5.2	- 6.9 to 7.1
Translation axis			
M (°)	0.2	0.2	0.04
Σ (°)	0.8	0.8	0.5
σ (°)	2.5	3.8	2.5

M = mean systematic errors; **Σ** = standard deviation of systematic rotation errors; and **σ** = random rotation error. Range numbers indicate the range of the systemic errors.

Dose calculation

For each patient, four plans were created. These plans represented the 'intended' dose distributions. To investigate the influence of the positioning errors on the dose distributions, we simulated the effect of the daily setup errors established with two different position correction strategies. *Table 2* lists the magnitudes of the translations for the off-line data set for the 19 patients. For the daily off-line adapted SAL protocol, the setup rotations and residual translations were simulated using the individual displacements/rotations in all three directions. For simulation of the on-line strategy, the rotational errors remained, and all translational errors were corrected. It was assumed that no intrafractional movements of the prostate, delineation errors, or deformation of the prostate or the organs at risk had occurred. A research module of PLATO recalculated the dose for each setup deviation and summed the dose distribution of the 35 fractions (van Herten *et al*., 2008), resulting in the 'estimated off-line' and 'estimated on-line' dose distribution (*Figure 2*). The translational errors were included by shifting the isocenter, and for simulation of the rotations, we rotated the whole patient (van Herten *et al*., 2008). These dose calculations are more accurate than a dose matrix blurring method because the changes in the equivalent path length for beams were taken into account in the calculations. Nevertheless, this recalculation method neglected the possible effect of anatomic changes outside the prostate. The order of including the rotations was craniocaudal axis, ventrodorsal axis, and, finally, the left–right axis.

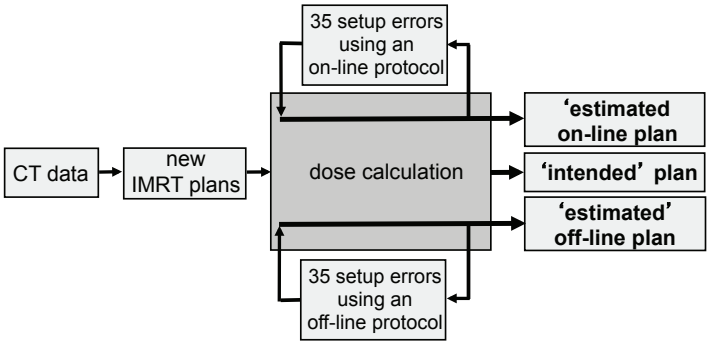

Figure 2. Flowchart of simulation process.
CT = computed tomography; IMRT = intensity-modulated radiotherapy.

Evaluation

For evaluation of the 'estimated' plans, we focused on the dose to the targets (CTV, BV, and GTV). The rectum and bladder constraints concerning the V72Gy was most often the limiting factor; therefore, we chose to evaluate the effect of the position deviations to the organs at risk by comparing the V72Gy of the 'estimated' and 'intended' plans. The 'intended,' 'estimated off-line', and 'estimated on-line' dose distributions were compared using paired *t* tests performed with the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL). A *p* value of <.05 was considered statistically significant. To analyze the difference between the four margins in the 'intended' dose distributions, one-way analysis of variance was performed, for which the independent variable was margins and the dependent variable was the intended dose. A Bonferonni post-hoc analysis was performed when an effect with p <.05 was seen.

Results

'Intended' dose distributions

For all plans, the dose to the PTV achieved the prescribed 70 Gy (data not shown). The rectum and bladder constraints limited the dose escalation to the BV when a margin of 8 mm was applied. Three patients had a D99% for the BV of 71 Gy, instead of the prescribed 72 Gy (95% of the prescription dose of 76 Gy) for plans with an 8-mm margin. The mean dose to the GTV increased significantly (p = .03) as the BV and CTV margins decreased (*Table 3* and *Figure 3*). For 3 patients, the prescribed mean dose of 84 Gy for the GTV was not reached when an 8-mm margin was used. The use of a 6-mm margin led to an underdosage of the GTV for 1 patient. *Figure 4a* shows that for 2 of these patients, the location of the GTV was close to the rectum, which could explain the difficulties in tumor coverage. *Figure* 5 shows that the rectum and bladder volume receiving a dose >72 Gy decreased when smaller margins were used ($p \leq .0001$ and p = .002, respectively).

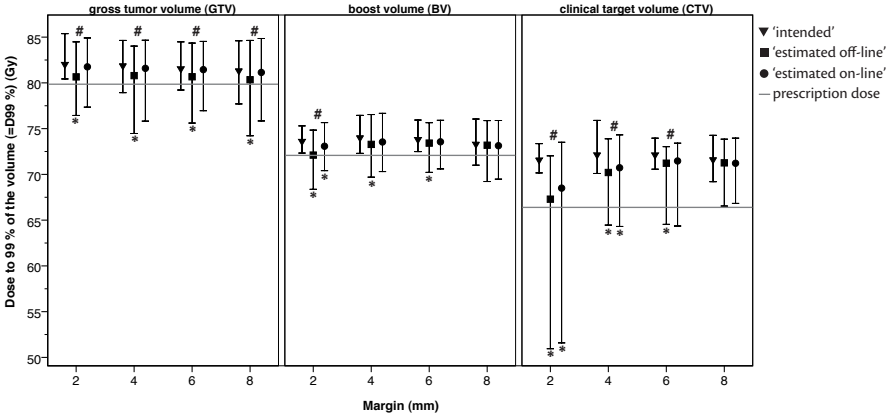

Figure 3. Average and range of ≥ 99% of volume receiving dose to gross tumor volume (GTV), boost volume (BV), and clinical target volume (CTV) without ('intended') and with ('estimated off-line' and 'estimated on-line') inclusion of position uncertainties.

* statistically significant difference between 'intended' and 'estimated' dose (p <.05);

statistically significant difference between 'estimated off-line' and 'estimated on-line' dose (p <0.05).

Table 3. Average mean dose to clinical target volume, boost volume, and gross tumor volume without ('intended') and with ('estimated off-line' and 'estimated on-line') inclusion of position uncertainties.

		Mean dose (Gy)		
Target	**Margin (mm)**	**'intended'**	**'estimated off-line'**	**'estimated on-line'**
CTV	2	78.3 (76.2-80.4)	77.9 (76.2-79.8) *	78.2 (76.2-80.3) #
	4	78.3 (75.9-80.9)	78.1 (76.3-80.2)	78.1 (76.0-80.0)
	6	78.1 (76.5-80.5)	78.0 (76.6-80.4)	78.1 (76.3-80.4)
	8	77.7 (75.4-79.3)	77.6 (75.9-79.7)	77.6 (75.7-79.2)
BV	2	79.4 (77.4-82.3)	79.1 (76.6-81.9) *	79.4 (76.6-82.3) #
	4	79.2 (77.5-82.0)	79.1 (77.7-81.6)	79.2 (77.2-81.6)
	6	79.0 (77.1-82.0)	78.9 (77.0-82.0)	79.0 (76.6-82.0)
	8	78.5 (76.7-81.2)	78.5 (76.7-81.3)	78.5 (76.4-81.2)
GTV	2	85.5 (83.8-87.0)	84.5 (81.4-86.8) *	85.4 (82.0-87.0) #
	4	85.2 (83.8-87.3)	84.3 (80.4-87.8) *	85.0 (81.8-87.9) #
	6	84.9 (82.7-86.6)	84.1 (81.4-87.6) *	84.8 (81.4-87.2) #
	8	84.5 (82.5-87.8)	83.7 (80.3-87.7) *	84.4 (81.1-87.7) #

CTV = clinical target volume; BV = boost volume; GTV = gross tumor volume. Data in parentheses are ranges. * Statistically significant difference between 'estimated off-line' and 'intended' mean dose (p <.05); # Statistically significant difference between 'estimated off-line' and 'estimated on-line' mean dose (p <.05).

'Estimated off-line' dose distributions

The 'estimated off-line' mean dose to the CTV exhibited a small, but statistically significant, decrease compared with the 'intended' mean dose when a 2-mm margin was used (p = .001). All plans demonstrated adequate 'estimated off-line' mean doses of > 70 Gy to the CTV, even when a 2-mm margin was used. The maximal decrease in the mean dose to the CTV using a 2-, 4-, 6-, and 8-mm margin was 1.4, 1.5, 1.2, and 1.0 Gy, respectively. The 'estimated off-line' D99% of the CTV was significantly reduced compared with the 'intended' D99% for plans with a 2-, 4-, or 6-mm margin, leading to an underdosage for 3 patients when a 2-mm margin was used. Of these 3 patients, 1 had a systematic rotational error described by a backward tilt of 12.1°. This patient demonstrated an 'estimated off-line' D99% of 51.0 Gy when a 2-mm margin was used, and greater margins led to a D99% > 66.5Gy. With the use of 4- and 6-mm margins, only 1 patient had an 'estimated off-line' D99% less than the prescription dose (both 64.5 Gy). This patient had a systematic rotational error of 9.1° around the left–right axis (*Table 3* and *Figure 3*).

The 2-mm margin plans demonstrated, after inclusion of the off-line setup errors, a small, but statistically significant, dose decrease to the BV. Leading to a D99% of < 95% of the prescription dose to the BV for 5 patients, however, the minimal D99% was still 68.4 Gy. With the use of a 2-, 4-, 6-, and 8-mm margin, the average reduction in D99% for the BV was 1.5, 0.7, 0.4, and 0.1 Gy, respectively.

Inclusion of the off-line setup uncertainties caused a significant dose decrease to the GTV. *Table 4* lists the average and maximal decrease in the mean dose and D99% for each margin. No difference was found between the use of a 2-, 4-, 6-, or 8-mm margin in the dose reduction between the 'intended' and 'estimated off-line' plans for the GTV. The maximal decrease from the 'intended' to 'estimated off-line' mean GTV dose for a 2-, 4-, 6-, and 8-mm margin was 4.8, 4.1, 2.7, and 4.4 Gy, respectively. These large decreases were all seen in 1 patient. The GTV of this patient was located at the apex of the prostate (*Figure 4b*).

Table 4. Average dose decrease in mean dose and D99% between 'intended' and 'estimated' dose distributions for dominant intraprostatic lesion.

	'estimated off-line'		'estimated on-line'	
Margin (mm)	**Mean (Gy)**	**D99% (Gy)**	**Mean (Gy)**	**D99% (Gy)**
2	1.0 (4.8)	1.4 (6.6)	0.1 (2.7)	0.3 (3.9)
4	0.9 (4.1)	1.1 (4.5)	0.2 (2.7)	0.3 (3.1)
6	0.8 (2.7)	0.9 (3.6)	0.1 (1.5)	0.1 (2.3)
8	0.8 (4.4)	1.0 (5.1)	0.2 (2.9)	0.2 (3.4)

D99% = ≥ 99% of volume receiving dose. Data in parentheses are maximal dose decrease.

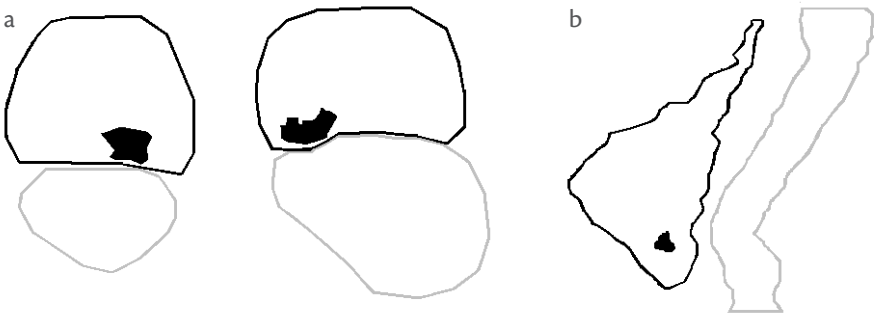

Figure 4. Location of dominant intraprostatic lesion (DIL) (black area) inside prostate (black line). The gray line indicates the location of the rectum. (**a**) Two patients with DIL location close to rectum (transverse plane). (**b**) One patient with DIL located at apex (sagittal plane).

'Estimated on-line' dose distributions

If on-line correction were performed, all setup translations would be corrected. Thus, for the 'estimated on-line' dose distributions, only the effect of rotational errors remained. *Table 3* and *Figure 3* show that the 'estimated on-line' coverage of the GTV differed significantly from the 'estimated off-line' coverage, with no significant difference present between the 'estimated on-line' and 'intended' GTV coverage. With the use of a 2-, 4-, 6-, or 8-mm margin, the number of patients for whom the prescribed dose to the GTV was not reached decreased from 5, 5, 6, and 8 for the 'estimated off-line' dose distribution to 2, 3, 3, and 4 patients for the 'estimated on-line' dose distribution, respectively. The maximal decrease from the 'intended' to 'estimated on-line' mean GTV dose for a 2-, 4-, 6-, and 8-mm margin was 2.7, 2.7, 1.5, and 2.9 Gy, respectively (*Table 4*). The patient with these large decreases in GTV dose with both the off-line and the on-line protocol had a GTV located at the apex. This location, combined with a systematic backward tilt of 7.2°, caused the reduction in GTV coverage after inclusion of the remaining setup errors. No significant reduction in the mean dose to the BV or CTV was seen after inclusion of the on-line setup uncertainties. The D99% of the BV showed a decrease in the 'estimated on-line' D99% compared with the 'intended' D99% when a 2-mm margin was used, and the CTV demonstrated a significant reduction in the D99% for the plans with a 2- and 4-mm margin.

Thus, the inclusion of setup errors using the on-line protocol resulted in less dose decrease compared with the off-line protocol. However, although the average dose reductions for these 19 patients between the 'estimated on-line,' 'estimated off-line', and 'intended' dose distributions were statistically significant, the magnitude of these average reductions were very small (*Table 3* and *Figure 3*). This average dose decrease

probably would not be clinically relevant. Although the average D99% of the 19 patients changed little after including the setup uncertainties, some of the patients had a large reduction in D99% with the use of the off-line protocol. The use of the on-line protocol hardly influenced the clinically relevant dose reduction for these patients. In particular, the D99% of the CTV decreased considerably for patients with large systematic rotational errors around the left–right axis, independent of the two correction strategies.

Organs at risk

Figure 5 shows the rectum and bladder V72Gy resulting from simulation of the off-line and on-line setup uncertainties. The V72Gy established with the on-line protocol was significantly greater statistically than the V72Gy resulting from the off-line correction because of blurring. The use of the off-line protocol led to violation of the dose constraints for the bladder for 2 patients when an 8-mm margin was used, and for 1 of these patients, the violation also occurred with a 4- and 6-mm margin. A 2-, 4-, 6-, and 8-mm margin resulted in overdosage to the rectum in 1, 2, 3, and 2 plans, respectively. The on-line protocol resulted in an even greater increase in the rectum V72Gy for these patients. All patients with the V72Gy constraints greatly exceeded after the inclusion of the setup uncertainties demonstrated systematic rotational errors around the left–right axis of 8° – 12 °.

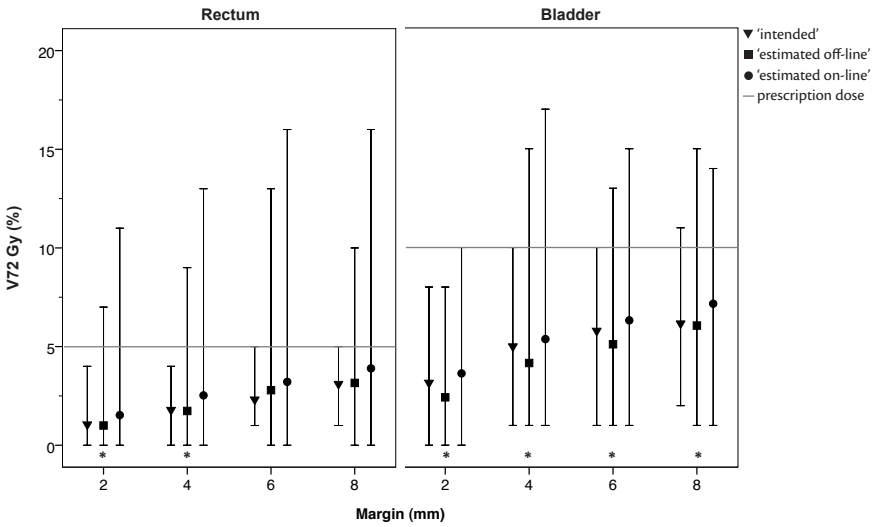

Figure 5. Average and range of percentage of volume receiving dose >72 Gy (V72Gy) for rectum and bladder without ('intended') and with ('estimated off-line' and 'estimated on-line') inclusion of position uncertainties.

* = statistically significant difference between 'estimated off-line' and 'estimated on-line' V72Gy (p <.05)

Discussion

The purpose of the present study was to investigate the effect of off-line and on-line correction protocols for highly inhomogeneous prostate IMRT plans with an integrated boost to a DIL, when the margins are being reduced.

'Estimated off-line' dose distribution

The effect of the geometric errors with the off-line adapted SAL protocol was simulated to investigate the effect of these uncertainties for an individual patient. The 'estimated off-line' dose delivered to the targets was less than the dose calculated for the 'intended' plan. However, the changes between the 'intended' and 'estimated' plans were very small, even when the margins were reduced to 2 mm. In the published data, the minimal margins using various off-line correction strategies have been greater (range, 5–12 mm) (Bos *et al*., 2005; Craig *et al*., 2005; Gordon *et al*., 2007; Nuver *et al*., 2007).

The simplified recipe such as was proposed by van Herk *et al*. (2000) and Stroom *et al*. (1999) for a margin between the CTV and PTV is that 2.0–2.5 times the total standard deviation (SD) of systematic errors (Σ) plus 0.7 times the total SD of the random errors (σ') is required to ensure that for 90% of the patients, 99% of the CTV receives 95% of the prescribed dose. Applying that to our clinical IMRT cases (Σ = 0.7 and σ' = 4.0 (Beaulieu *et al*., 2007)) implies that a margin of 4 mm would be inadequate. However, our results indicated that for the BV and CTV, a 4-mm margin was sufficient to account for the positioning errors.

The margin recipe, developed for homogeneous RT plans, does not take into account multiple target volumes. Also, the variable position of the target inside an inhomogeneous dose distribution can result in under- and overdosage of the target. Over 35 fractions, the overdosage will compensate the underdosage, leading to little influence of the random errors on the dose to the target. The dose to the GTV was more sensitive for random errors, because no overdosage for this target could occur.

Gordon *et al*. (2008) proposed that the relative shallow dose gradient of the IMRT technique at the rectum–prostate interface compared with the steep dose gradients at this site established with the three-dimensional conformal technique is another explanation for why most plans had an adequate dose distribution after including the setup deviations. The simplified margin recipe, 2.5 times Σ plus 0.7 times the combined SD of random variation, excluding the penumbra (σ'), overestimated the required PTV margin in the present study. However, the precise margin recipe reads: 2.5 Σ + 1.64 ($\sigma - \sigma_p$), where s is the quadratic sum of the SD of all random variations, including the SD describing the penumbra (σ_p). The simplified recipe for random variations is only valid for a σ_p of 3.2 mm, and for our complex IMRT, the dose gradients at the border of the volumes were much broader than 3.2 mm. When a very shallow dose gradient is used

in the formula, this leads to a smaller required margin. In conclusion, dose gradients have a large influence on the margin calculation and should not be excluded in the margin recipe for complex IMRT.

'Estimated on-line' dose distribution

The random errors remaining after application of the off-line protocol can be reduced with daily on-line correction of the prostate position (Beaulieu *et al*., 2004; Alonso-Arrizabalaga *et al*., 2007). Our study has demonstrated that the benefit of an on-line strategy for complex inhomogeneous prostate IMRT plans is small. The on-line protocol corrected the detected translational errors, but the rotational errors were ignored. In our study, patients with large rotational errors had a substantial change in the dose. The effect of rotation was largest for the CTV, which can be explained by the elongated shape of the seminal vesicles and because the seminal vesicles have a greater distance to the rotation point. The rotation data of the 19 patients are listed in *Table* 2 and agree well with previously published findings (Aubry *et al*., 2004; van der Heide *et al*., 2007). Important dosimetric implications, due to rotations, have also been described by Cranmer-Sargison (2008) for three-dimensional conformal RT and by van Herten *et al*. (2008) for IMRT plans. The small estimated dose difference between the use of the off-line adapted SAL and the on-line correction protocol was less important than the dose changes caused by the rotational errors. Therefore, the benefit of on-line correction relative to the use of off-line correction was very small.
For correction of the rotational errors, the possibilities are several. First, the tabletop can be rotated in three directions using robotic couches. For patient safety, most robotic couches have a restricted rotation angle of ≤ 3°. Therefore, problematic large rotations cannot be corrected for, and the target coverage will only slightly improve using a robotic couch (van Herten *et al*., 2008). Second, in published reports, a correction strategy has been proposed that applies gantry and collimator angle adjustments, making it possible to correct almost every prostate rotation (Yue *et al*., 2006; Rijkhorst *et al*., 2007; van der Heide *et al*., 2005). Rotations can also be corrected using adaptive RT techniques (Court *et al*., 2005). Another solution would be to create a new treatment plan by performing a new CT scan. A new treatment plan could be useful for patients with large systematic rotational errors or if the seminal vesicles were systematically located at a different position relative to the planning CT scan.

Dominant intraprostatic lesion

New imaging modalities, such as magnetic resonance spectroscopy, dynamic contrast-enhanced MRI, and diffusion-weighted MRI, provide the possibility of determining a DIL inside the prostate. By increasing the radiation dose only to this region, tumor control can be improved, while still sparing the surrounding tissues. The present

planning study showed that smaller margins around the prostate resulted in greater 'intended' radiation doses to the DIL. Thus, a reduction of margin sizes through accurate position verification results in the possibility of boosting the DIL further.
No margin was applied around the DIL, because the DIL was located inside the CTV, to which a dose of 76 Gy was applied. Thus, the dose gradients around the DIL started at 76 Gy instead of 0 Gy. This dose gradient from 76 Gy to 84 Gy, instead of from 0 Gy to 84 Gy, justifies the absence of a margin. De Meerleer *et al*. (2005) created no margin around the DIL as well, because they reported that the DIL does not move independently of the CTV. The effect of the setup errors on DIL coverage was independent of the various margins used for the CTV and BV. This implies that the dose gradients close to the DIL did not differ much among the four margins used, probably because the dose build-up for the DIL was similar for the plans with different margins. The largest decrease in DIL coverage was seen in 1 patient with a DIL located close to the apex and a systematic rotational error of 7.2° around the left–right axis. This implies that when the DIL is located far from the rotation point (e.g., at the apex) correction of rotational errors is important to ensure coverage of the DIL.

Study limitations

In the present study, we approximated the rectum as though it moved rigidly with the prostate, ignoring that the shape and size vary throughout treatment (Hoogeman *et al*., 2004). However, the high dose to the rectum was located close to the prostate in the anterior part of the rectum. The motion of this important side of the rectum correlates with the motion and volume changes of the prostate (Padhan *et al*., 1999; Frank *et al*., 2008); thus, it was reasonable to assume that the rectal motion and variation in shape and size during treatment would have little influence on the dose to the anterior part of the rectum. Furthermore, we neglected possible prostate movement resulting from gas in the rectum. Gas pockets cause a changed scatter contribution from the rectum, which can lead to a small dose reduction inside the peripheral zone of the prostate.
The prostate was also approximated as a rigid body, ignoring possible deformations. However, the deformation of the prostate during the treatment course is small, relative to the organ motion, and most of the shape variations occur for the seminal vesicles (Deurloo *et al*., 2005).
Another limitation was that the setup errors were assessed only by the position of the fiducial markers. Thus, the movement of the prostate relative to the bony anatomy was not taken into account, ignoring the potential effect of differences in the external contours. However, this effect on the dose distribution is within 2% (Chen *et al*., 2004) and was minimized because the beam directions were chosen such that they were not passing through the femoral heads. In the present study, we simulated the translational and rotational errors using an off-line and on-line correction protocol. For clinical practice, our results represent the minimal required margins, because the

margins should also account for other uncertainties, such as intrafraction prostate motion, prostate deformations, reliability of the repositioning systems, inaccuracy of marker detection, uncertainty in determination of the center of gravity of the seeds within the CT scan, and uncertainty in the delineation of the target volumes. The magnitudes of these uncertainties are different for each institute; therefore, general recommendations for the required margin in clinical practice could not be given. The results of the present study have demonstrated that a 2- mm margin would be sufficient to account for the geometric errors if the rotational errors were corrected during treatment. The required margin should be extended by approximately a few millimeters to account for the remaining uncertainties. When such small margins are introduced in clinical practice, one should consider adding an extra margin around the DIL to account for possible extracapsular extension, especially in patients with a high prostate-specific antigen level and biopsy Gleason score (Chao *et al*., 2006).

Conclusion

For complex prostate IMRT with an integrated boost to the DIL, the influence of the geometric errors, not corrected for by our off-line adapted SAL correction protocol, was small. The residual setup motion caused only modest changes in dose, even when the clinically used 8-mm margins were reduced to 6, 4, or 2 mm. Patients with large systematic rotational errors did have a substantial decrease in dose, particularly for the seminal vesicles. Also, the coverage of the DIL when the location was close to the apex diminished owing to large systematic rotational errors. This dose decrease did not recover when an on-line correction protocol for translations only was used. Therefore, for complex prostate IMRT with an integrated boost, solving the rotations off-line is expected to improve the treatment more than it would using an on-line protocol without rotation correction.

Chapter 3

Intrafraction motion: magnesium oxide

This chapter is accepted for publication as:

I.M. Lips, C.H. van Gils, A.N.T.J. Kotte, M.E. van Leerdam, S.P.G.Franken, U.A. van der Heide and M. van Vulpen.

A double-blind placebo-controlled randomized clinical trial with magnesium oxide to reduce intrafraction prostate motion for prostate cancer radiotherapy.

International Journal of Radiation Oncology, Biology, and Physics. 2011

Abstract

Purpose

To investigate whether magnesium oxide during external beam radiotherapy for prostate cancer reduces intrafraction prostate motion in a double-blind, placebo-controlled randomized trial.

Methods and Materials

At the Department of Radiotherapy, prostate cancer patients scheduled for intensity-modulated radiotherapy (77 Gy in 35 fractions) using fiducial marker-based position verification were randomly assigned to receive magnesium oxide (500 mg twice a day) or placebo during radiotherapy. The primary outcome was the proportion of patients with clinically relevant intrafraction prostate motion, defined as the proportion of patients who demonstrated in ≥ 50% of the fractions an intrafraction motion outside a range of 2 mm. Secondary outcome measures included quality of life and acute toxicity.

Results

In total, 46 patients per treatment arm were enrolled. The primary endpoint did not show a statistically significant difference between the treatment arms with a percentage of patients with clinically relevant intrafraction motion of 83% in the magnesium oxide arm as compared with 80% in the placebo arm (p = 1.00). Concerning the secondary endpoints, exploratory analyses demonstrated a trend towards worsened QoL and slightly more toxicity in the magnesium oxide arm compared to the placebo arm, however these differences were not statistically significant.

Conclusions

Magnesium oxide is not effective in reducing the intrafraction prostate motion during external beam radiotherapy and therefore there is no indication to use it in clinical practice for this purpose.

Introduction

Because the external beam radiotherapy treatment of prostate cancer typically is delivered in up to 40 treatment fractions, the reproducible positioning of the target for irradiation is a major source of concern. Image-guided radiotherapy (IGRT) uses imaging in the radiotherapy treatment room to localize the prostate and secure its correct position relative to the irradiation beams (Smitsmans *et al*., 2004; Nederveen *et al*., 2003). As a result, the exposure of normal tissues is minimized. This increased accuracy has been exploited to escalate the radiation dose to the prostate for improving tumor control, without increasing the toxicity of the treatment (Lips *et al*., 2008).

While the positioning uncertainties between treatment fractions are minimized, the movement of the prostate during the actual irradiation on any given day (intrafraction motion) still is a problem. For prostate, as for other organs in the pelvic region, an important cause of intrafraction motion is thought to be moving gas pockets inside the rectum (Nichol *et al*., 2010; Nederveen *et al*., 2002).

In an attempt to reduce the intrafraction motion of the prostate, several groups started to prescribe a daily use of magnesium oxide laxative during the course of radiotherapy (Nichol *et al*., 2010; Wu *et al*., 2001; Smitsmans *et al*., 2008). The rationale behind this approach lies in the hypothesis that magnesium oxide diminishes the amount of gas pockets and causes a more stable rectal filling. Currently this medication is also being used in the clinical practice of cervical cancer irradiation (Chan *et al*., 2008). Surprisingly, however, no clear evidence exists that magnesium oxide is effective in reducing the amount of intrafraction motion during treatment. In addition, it has not been established whether a potential advantage of magnesium oxide in reducing prostate motion would counterbalance the negative aspect of magnesium oxide such as physical discomfort consisting of diarrhea and the burden of daily intake of medication (Xing *et al*., 2001).

The purpose of this study is to investigate whether the ubiquitous use of magnesium oxide during external beam radiotherapy has indeed the intended effect of reducing organ motion during treatment. To this end, we carried out a double-blind, placebo-controlled randomized trial in patients treated with intensity-modulated radiotherapy (IMRT) for prostate cancer. The patients were randomized between the intake of magnesium oxide and placebo. We evaluated not only the effect on intrafraction prostate motion, but also on the toxicity and quality of life (QoL).

Methods and materials

The study population consisted of patients with prostate cancer scheduled for IMRT using fiducial markers for position verification at the Department of Radiotherapy at the University Medical Center (UMC) Utrecht. Contraindications to participation in

the study included severe constipation; kidney stones; heart block; abdominal diseases (M. Crohn, colitis ulcerosa, diverticulitis); severe renal failure or creatinine clearance of < 50 ml/min/1.73 m^2; or a history of extensive abdominal surgery. Furthermore, patients were not eligible for this study if they used laxatives, tetracyclines, digoxine, iron of ciprofloxacine. Patients were recruited during the intake consultation at the Department of Radiotherapy. Written informed consent was obtained from all patients and the study protocol was approved by the Medical Ethical Committee of the UMC Utrecht.

All patients received IMRT with a dose of 77 Gy in 35 fraction of 2.2 Gy to the prostate (Lips *et al*., 2008; Nederveen *et al*., 2001). For daily off-line position verification, three fiducial gold markers were implanted transperineally into the prostate (Moman *et al*., 2010; Lips *et al*., 2009a; van der Heide *et al*., 2007). During treatment, patients did not receive any instruction for emptying the rectum before the radiotherapy session. One hour before the pre-treatment planning scans and the radiotherapy sessions, the patients were instructed to drink 500 ml to create a full bladder. An antiflatulent diet during treatment was prescribed to all patients (Smitsmans *et al*., 2008). The patients were treated in supine position. A knee cushion for alignment of the legs was used to prevent any rotation of the hip.

Patients were randomized to receive two capsules of 250mg magnesium oxide twice a day (a total dose of 1000mg per day (Smitsmans *et al*., 2008)) or to receive two placebo capsules twice a day during treatment. All capsules were prepared, tested and packaged in individual boxes by the Department of Pharmacy of the UMC Utrecht. The placebo capsules were visually identical to the capsules of magnesium oxide and were filled with microcrystalline cellulose. The boxes with capsules were randomized using the DESIGN computer program (Dallal *et al*., 1988) after which the Department of Pharmacy delivered the boxes blinded to the Department of Radiotherapy. So the patient, the attending physician and the investigator were blinded to the patient's treatment. Patients received the box from their attending physician during the gold marker implantation. Patients started taking the capsules two days before the pre-treatment planning scans after which intake was stopped. Two days before the first radiotherapy fraction, patients restarted and continued until the last fraction, including weekend days when no irradiation fractions were given. After treatment, patients were asked to return their boxes with the remaining capsules, to evaluate drug compliance.

The main study parameter was the intrafraction prostate motion. The treatment time during one fraction varied between 5 and 7 minutes. For position verification, three fiducial gold markers were implanted inside the prostate (Moman *et al*., 2010). Daily imaging of the fiducial markers was used for off-line position verification, using an adapted 'shrinking action level' protocol (van der Heide *et al*., 2007; Lips *et al*., 2009a). During treatment, the fiducial gold markers were visualized using portal images of the largest segment of all five beams (beam directions are 260º, 320º, 40º, 100º and

180°), using the iView-GT amorphous silicon flat-panel detector (Elekta Ltd, Crawley, UK). Analysis of images took place using in-house developed software, which allowed automatic detection of the fiducial gold markers (Nederveen *et al*., 2000). Each daily registration was visually inspected by two radiographers, and was manually adjusted as required. Within every treatment beam, the location of the gold markers could be established under the assumption of minimal marker movement during a fraction. With this method, described by Kotte *et al*. (2007; Adamson *et al*., 2009), the range of motion during each fraction is determined and used as the intrafraction motion. The range of motion is defined as the vector length of the (maximal – minimal) position in all three dimensions. A patient with clinically relevant intrafraction motion was defined as a patient who demonstrated in ≥ 50% of the fractions an intrafraction motion outside a range of 2 mm.

Secondary study parameters were acute toxicity and QoL. Toxicity was measured by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Trotti *et al*., 2003). The physician in attendance scored the complaints before treatment (defined as pre-treatment complaints) and the acute toxicity weekly during treatment and four weeks after treatment (defined as acute toxicity). All symptoms were registered even if they occurred only on one single occasion. The highest toxicity score for each patient was used, to calculate an overall genitourinary (GU) and gastrointestinal (GI) score of the CTC items. Furthermore, the start of medicines during treatment, such as loperamide to treat diarrhea, was scored. General health-related QoL was measured using the RAND-36 generic health survey (Hornbrook *et al*., 1995), cancer-specific QoL using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) (Aaronson *et al*., 1993), and the prostate tumor specific QoL using the EORTC prostate cancer module (QLQ-PR25) (Borghede *et al*., 1996). The RAND-36 assesses physical and social functioning, physical and emotional role restriction, mental health, vitality, pain, general health and change in health. The EORTC QLQ-C30 contains five functional scales, three symptoms scales, a global QoL scale and six single-items. The EORTC QLQ-PR25 assesses urinary, bowel and sexual symptoms and functioning, and the side effects of hormonal treatment. The first questionnaire was handed over to the patient one week before treatment at the Department of Radiotherapy and the second one was sent to the patient one month after the completion of the treatment. Scales and items of these questionnaires range in score from 0 to 100. For RAND-36 and for the 'global' QoL and functional scales of the EORTC questionnaires, a high score represents a high level of QoL and better functioning. For the symptom/problem items of the EORTC questionnaires, higher scores represent a higher level of symptoms and consequently a worse QoL. A change of 10% (or in general, 0.5 standard deviation) of the scale width is perceptible to patients as a meaningful change, and a change in QoL of 10 points is therefore considered clinically relevant (Osoba *et al*., 2005).

The analysis of 427 patients treated at our department between August 2001 and December 2005 revealed a percentage of patients with clinically relevant intrafraction motion of approximately 80% (Kotte *et al*., 2007). To determine the sample size for this study, we used an expected difference in patients with clinically relevant intrafraction motion of 30% when radiotherapy treatment is given with daily magnesium oxide compared with no laxative medication. To detect a reduction in the proportion from 80% to 56% with 80% power with a one-sided test at a 5% significance level, a total of 46 patients in each group were sufficient.

Patients were analyzed according to the intention-to-treat principle. The baseline characteristics included: age, tumor stage, tumor grade, current smoker (defined as at least 1 cigarette per day), current alcohol drinker (defined as at least 1 unit per week), pre-treatment use of medication (defined as the intake of at least one medicine at start of the RT), hormonal treatment (defined as the use of hormonal therapy at the start of RT), history of transurethral resection of the prostate (TURP) and time interval between TURP and start of the RT, initial prostate-specific antigen (iPSA) level and drug compliance of study medication (determined by the difference between the expected remaining capsules, based on the prescribed amount, and the actual returned amount of capsules). An insufficient intake was defined as an intake of at least 1 week short. The intrafraction motion per fraction was used to calculate the average and standard deviation (SD) of the intrafraction motion per patient. Because the average intrafraction motion was not normally distributed within the two groups, differences between the two groups were tested with the non-parametric Mann-Whitney U test. To determine the effect of magnesium oxide on the intrafraction motion, the percentage of patients in the placebo group and the magnesium oxide group with clinically relevant intrafraction motion were compared using the Fisher's exact test. If the prescription of antidiarrheal medicines, such as loperamide, during radiotherapy shows large differences between the magnesium oxide and the placebo group, the potential impact on the intrafraction motion will be estimated by comparing the results with and without adjustment for the use of antidiarrheal medicines by using the Mantel-Haenszel method.

Secondary analyses included Fisher's exact tests for examination of differences in pre-treatment complaints and acute toxicity. To handle low cell count problems, the toxicity results were dichotomized in grade <2 and grade ≥ 2. To examine differences in QoL between the two groups, the proportion of patients with clinically meaningful changes in QoL between baseline and one month after treatment were calculated. Differences between the two treatment groups in the three categories of responses (worsened, stable or improved QoL) were tested with the Chi square test. In case of low cell count problems, the Fisher's exact test using two categories (worsened versus stable/improved QoL) was used. Because of the multiple comparisons for the QoL items, the *p* value was set at a conservative .01 for determining statistical significance

(Movsas *et al*., 2009). For all other analyses, which did not include the QoL measures, a *p* value of <.05 was considered statistically significant. All analyses were performed using Statistical Package for Social Sciences, version 16.0 (SPSS, Chigaco, IL).

Results

Between December 2008 and February 2010, 92 patients were enrolled and randomly assigned on this trial. Patient participation and flow is depicted in a CONSORT diagram (*Figure 1*). The most common reasons for exclusion were; the use of digoxine or laxatives; or kidney stones.

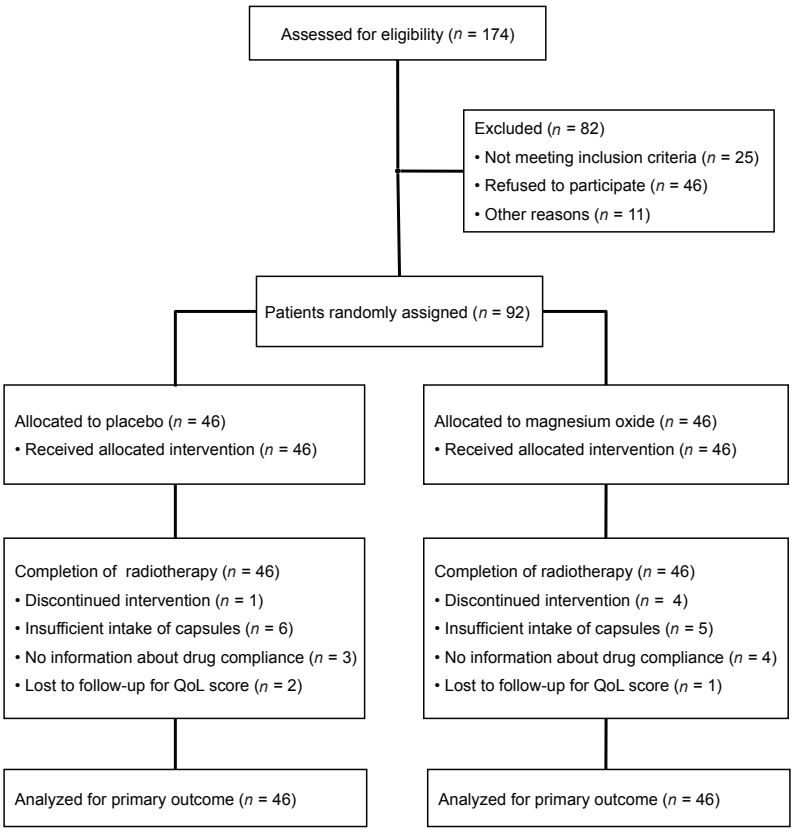

Figure 1. CONSORT patient flow diagram

Eleven patients were scheduled for additional lymph node irradiation which would result in more irradiation to the bowel and consequently affects the amount of side effects and were therefore excluded ('excluded for other reasons'). Five patients discontinued the intake of capsules during treatment because of side effects consisting of diarrhea. One of these patients was randomized to the placebo arm en stopped 2 weeks after start of radiotherapy. The other patients were randomized to the magnesium oxide arm and stopped 1, 2, 2.5 and 3 weeks after start of the radiotherapy. Evaluation of the drug compliance revealed that the intake of 11 patients was insufficient. Baseline patient characteristics are provided in *Table 1*.

Table 1. Patient baseline characteristics.

Characteristic	Magnesium oxide Arm (*n* = 46)		Placebo Arm (*n* = 46)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	70.5		71.0	
Upper and lower quartile	65.0 – 73.3		67.8 – 75.0	
Tumor stage				
T1/2	6	13	13	28
T3	40	87	33	72
Tumor grade				
Gleason 4-6	12	26	12	26
Gleason 7	20	44	20	44
Gleason 8-10	14	30	14	30
Current smoker	5	11	6	13
Current alcohol drinker	23	50	18	39
Pre-treatment use of medication	37	80	42	91
Hormonal treatment	24	52	23	50
History of TURP	10	22	14	30
Time between TURP and start of RT, months				
Median	31.0		12.5	
Upper and lower quartile	3.8 – 138.5		4.0 – 128.0	
iPSA, ng/mL				
Median	12.2		12.2	
Upper and lower quartile	8.0 – 24.2		7.7 – 25.3	
Drug compliance of study medication*				
Median	0		0	
Upper and lower quartile	-7 – 17		-8 – 8	
Prescription of antidiarrheal medicine during radiotherapy	7	15	4	9

TURP = transurethral resection of the prostate; RT = radiotherapy; iPSA = initial prostate-specific antigen.
* Drug compliance of study medication is defined as the difference between the expected remaining capsules, based on the prescribed amount, and the actual returned amount of capsules.

The pre-treatment use of medication included mainly cardiovascular medicines such as statins, antihypertensive drugs and anticoagulants; medicines for treatment of benign prostatic hyperplasia; anti-diabetic drugs; and hormonal treatment. The median time interval between TURP and start of radiotherapy was longer in the magnesium oxide group, however the distribution was very large in both groups and the minimum interval was 2 months in both groups. An interval of at least 6 weeks is required by the clinical radiotherapy protocol to keep the risk of increased genitourinary toxicity after a TURP acceptable. No statistically significant difference between the two study arms was seen in drug compliance.

The primary endpoint of clinically relevant intrafraction prostate motion did not show a statistically significant difference between the magnesium oxide and the placebo arm (p = 1.00; *Table 2*). The magnesium oxide treatment arm demonstrated a percentage of 83% of patients with clinically relevant intrafraction motion compared to 80% for the placebo arm. The average and SD intrafraction motion per patient was not statistically significant different between the two groups either (p = .94 and .80, respectively).

Table 2. Descriptive statistics for the intrafraction prostate motion.

	Magnesium oxide Arm (n = 46)	Placebo Arm (n = 46)	*P*	Risk ratio (95% CI)	Risk difference (95% CI)
Average intrafraction motion per patient, mm					
Median	2.7	2.7			
Upper and lower quartile	2.2 - 3.5	2.2 - 3.4	.94*		
SD intrafraction motion per patient, mm					
Median	1.0	0.9			
Upper and lower quartile	0.7 - 1.3	0.7 - 1.3	.80*		
Patients with clinically relevant intrafraction motion†					
No.	38	37		1.03	2.2
%	83	80	1.00‡	(0.85 to 1.25))	(-13.7 to 18.0)

SD = standard deviation.

* Mann-Whitney U test; † Clinically relevant intrafraction motion was defined as patients who demonstrated in ≥ 50% of the fractions an intrafraction motion outside a range of 2 mm; ‡ Fischer's exact test.

During radiotherapy, antidiarrheal medicines were more often prescribed in the magnesium oxide group compared to the placebo group. The adjusted Mantel-Haenszel relative risk for intrafraction motion was 1.02 (95% CI: 0.83 to 1.23) and did not differ more than 10% from the crude relative risk, so no adjustment for this factor was indicated.

Figure 2 shows the overall GU and GI pre-treatment complaints and acute toxicity for the magnesium oxide and the placebo group. Adverse events relatively common in both groups included proctitis, diarrhea, rectal or perirectal pain, flatulence, dysuria and urinary frequency/urgency. The magnesium oxide treatment arm demonstrated more grade ≥ 2 overall GI toxicity (21.7% for placebo arm versus 37.0% for the magnesium oxide arm), which was not significantly different between the two arms (p = .17). The overall GU toxicity incidence demonstrated no statistically significant difference between the two study arms either.

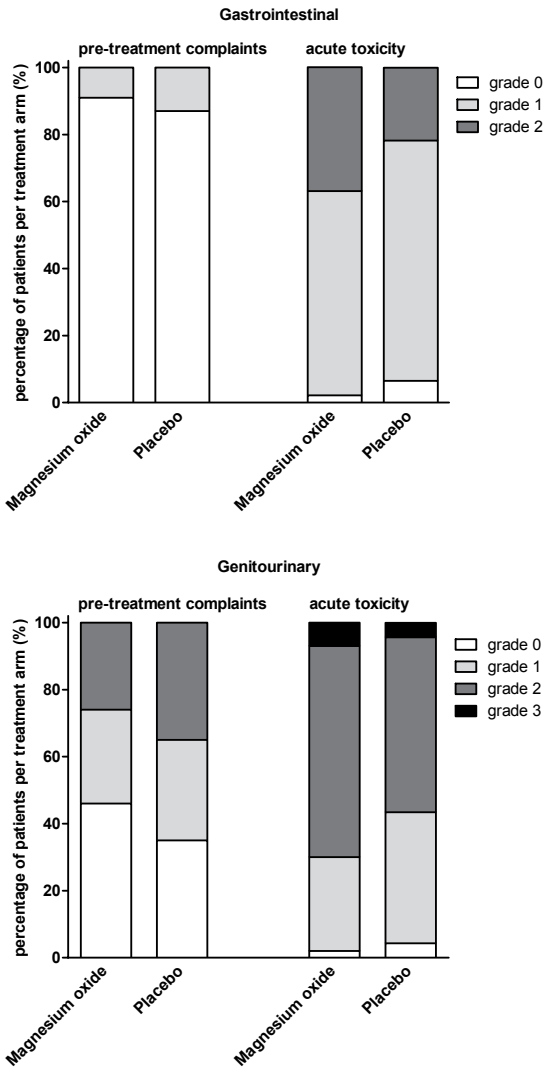

Figure 2. Pre-treatment complaints and acute toxicity, as measured by Common Toxicity Criteria for adverse events version 3.0 (CTCAE v.3).

The comparison of the magnesium oxide and placebo arm for the QoL items assessed in this study demonstrated no significant differences between the two groups in the change in any of the QoL items between baseline and one month. *Figure 3* shows the proportions of patients per treatment groups with clinically meaningful changes in QoL scores between baseline and 1 month after treatment of six QoL items. These six QoL items revealed the largest differences in worsened QoL between the magnesium oxide and the placebo arm. Most QoL items demonstrated the highest proportion of patients with worsened QoL in the magnesium oxide arm, however, as mentioned above, these differences were not statistically significant.

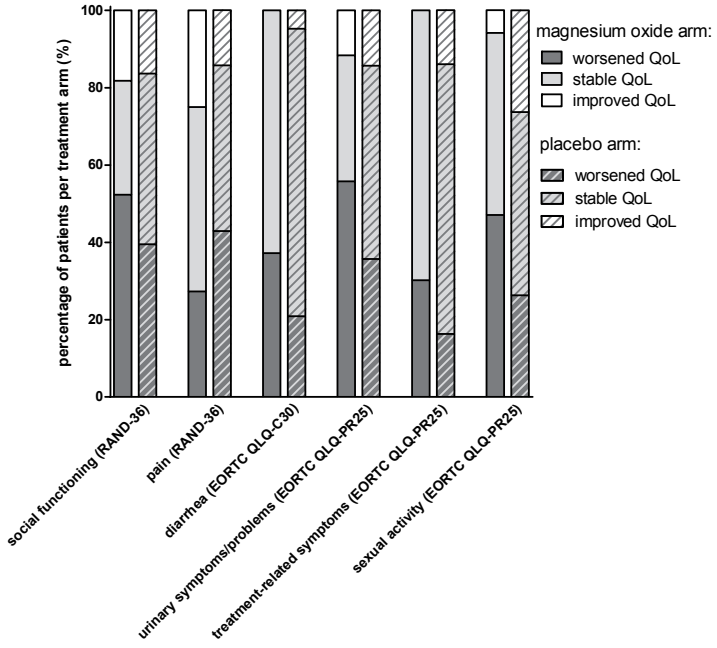

Figure 3. Proportions of patients per treatment group showing clinically meaningful changes in quality of life (QoL) scores between baseline and 1 month after treatment. Patients are classified as worsened QoL (>10% worsening in QoL scores), stable QoL (<10% change in QoL scores) or improved QoL (>10% improvement in QoL scores). Only the six QoL items with the largest differences in worsened QoL between the magnesium oxide and the placebo arm are shown.

Discussion

The results of this trial did not show any benefit of magnesium oxide laxative compared with placebo for reducing the intrafraction prostate motion during radiotherapy. Concerning the secondary endpoints, exploratory analyses demonstrated a trend towards worsened QoL and slightly more toxicity in the magnesium oxide arm compared to the placebo arm, however these differences were not statistically significant.

To improve the accuracy of the radiation field placement, several attempts have been made to tackle the problem of intrafraction motion during radiotherapy. To manage prostate motion, certain methods have been investigated aiming at the reduction of the amount of gas pockets inside the rectum, with varying success: dietary guidelines, medicines like laxatives (magnesium oxide), deflatulences (simethicon) and antiperistaltics (glucagon), fixed treatment times (after 10 AM), rectal gas removal by insertion of a finger or the use of a rectal balloon (Wu *et al*., 2001; Smitsmans *et al*., 2008; Madsen *et al*., 2003; Ogino *et al*., 2008; Padhani *et al*., 1999; van Lin *et al*., 2005). Laxative use during radiotherapy was first described in literature by Wu *et al*. (2001), who reported small standard deviations for interfraction prostate motion in patients instructed regarding dietary management, fluid intake and laxative use in comparison to the interfraction prostate motion reported in other studies. Smitsmans *et al.* (2008) reported a significantly increased cone-beam computed tomography image quality, which was suggested as an indirect indicator for intrafraction motion, after introduction of a dietary protocol consisting of dietary guidelines, magnesium oxide tablets (1000 mg per day) and treatment time after 10 AM The effect of a dietary protocol, including milk of magnesia laxative, on the intrafraction motion was only directly investigated by Nichol *et al.* (2010) who reported no significantly reduced intrafraction prostate motion. Magnesium oxide promotes bowel evacuation by causing osmotic retention of fluid which distends the colon. Distention of the colon increases the peristaltic activity. Excess motility causes less absorption of water in the colon resulting in diarrhea or loose feces. This will result in more mass movements transporting feces from the colon to the rectum and therefore more rectal activity. This might explain the failure to reduce the prostate motion with magnesium oxide.

The side effects due to the radiotherapy usually start 2 weeks after the initiation of treatment (Peeters *et al*., 2005b). This makes it difficult to distinguish whether they are the result of radiation alone or due to the combination with laxative use. This trial was not powered to reveal statistically significant differences in QoL and toxicity. Nevertheless, exploratory analyses did show a trend towards worsened QoL and the magnesium oxide arm demonstrated more GI adverse events, more loperamide was prescribed for severe diarrhea and more patients decided to stop de study medication because of side effects compared to the placebo group. Therefore, the use of magnesium oxide may be harmful for patients.

A limitation of the study is that no information was obtained about the compliance to the antiflatulent diet in both treatment arms. The influence of the study medication on the bowel motion might have prompted the patients to change their food pattern. As a result, the compliance to the antiflatulent diet might be different between the two treatment arms, which could have influenced the intrafraction motion. Intrafraction motion could also have been influenced by a difference in drug compliance between both groups. An attempt was made to measure drug compliance by counting the remaining capsules. However, handing in the expected amount of remaining capsules is no guarantee for a correct intake of the capsules during treatment. Finally, the exact physiological mechanism causing the intrafraction prostate motion in both groups was not determined. Therefore, it was not possible to further explore the influence of magnesium oxide on for example rectal gas bubbles or peristaltic activity.

Conclusion

The results of this trial demonstrate that magnesium oxide is not effective in reducing the intrafraction motion during external beam radiotherapy. Therefore, there is no indication to use it in clinical practice for this purpose.

Chapter 4

Intrafraction motion: diet

This chapter is accepted for publication as:

I.M. Lips, A.N.T.J. Kotte, C.H. van Gils, M.E. van Leerdam, U.A. van der Heide and M. van Vulpen.

Influence of antiflatulent dietary advice on intrafraction motion for prostate cancer radiotherapy.

International Journal of Radiation Oncology, Biology, and Physics. 2011

Abstract

Purpose

To evaluate the effect of an antiflatulent dietary advice on the intrafraction prostate motion in patients treated with intensity-modulated radiotherapy (IMRT) for prostate cancer.

Methods and Materials

Between February 2002 and December 2009, 977 patients received five-beam IMRT for prostate cancer to a dose of 76 Gy in 35 fractions combined with fiducial markers for position verification. In July 2008, the diet, consisting of dietary guidelines to obtain regular bowel movements and to reduce intestinal gas by avoiding certain foods and air swallowing, was introduced to reduce the prostate motion. The intrafraction prostate movement was determined from the portal images of the first segment of all five beams. Clinically relevant intrafraction motion was defined as ≥ 50% of the fractions with an intrafraction motion outside a range of 3 mm.

Results

A total of 739 patients were treated without the diet and 105 patients were treated with radiotherapy after introduction of the diet. The median and interquartile range of the average intrafraction motion per patient was 2.53 mm (interquartile range, 2.2–3.0) without the diet and 3.00 mm (interquartile range, 2.4–3.5) with the diet ($p < .0001$). The percentage of patients with clinically relevant intrafraction motion increased statistically significant from 19.1% without diet to 42.9% with a diet (odds ratio, 3.18; 95% confidence interval, 2.07–4.88; $p < .0001$).

Conclusions

The results of the present study suggest that antiflatulent dietary advice for patients undergoing IMRT for prostate cancer does not reduce the intrafraction movement of the prostate. Therefore, antiflatulent dietary advice is not recommended in clinical practice for this purpose.

Introduction

The biochemical relapse-free treatment outcome for prostate cancer is improved by escalation of the radiation dose to the prostate (Peeters *et al.*, 2006; Zietman *et al.*, 2005; Pollack *et al.*, 2002). Additional dose escalation is expected to lead to further improvement (Eade *et al.*, 2007). However, by escalating the radiation dose, the risk of developing toxicity increases. To ensure adequate target coverage, the clinical target volume is expanded with a margin to the planning target volume (PTV). To keep the dose to the rectum and bladder within acceptable limits, this margin must be minimized as much as possible. In the past decades, several technical improvements have enabled a reduction of the treatment margin. The delineation of the prostate has become more precise, because the imaging quality improved and multimodality imaging began to be used (Villeirs *et al.*, 2005). Furthermore, the accuracy of the position verification of the prostate during treatment has improved with the introduction of gold fiducial markers (Nederveen *et al.*, 2003), cone-beam imaging (Smitsmans *et al.*, 2004) and daily on-line or off-line positioning protocols (van der Heide *et al.*, 2007). By minimizing the interfraction movement of the prostate and the delineation error, the remaining uncertainties, such as the intrafraction motion, will have a greater impact. According to the current data, the intrafraction motion is caused by rectum filling and, to a lesser degree, by bladder filling (Adamson *et al.*, 2009). Moving rectal gas was demonstrated to be the most important factor (Nichol *et al.*, 2010). Several methods have been investigated to minimize prostate motion due to bowel distension, including dietary guidelines, medicines such as laxatives (magnesium oxide), deflatulences (simethicon), and antiperistaltics (glucagon), fixed treatment times (after 10 AM), rectal gas removal by insertion of a finger, and the use of a rectal balloon (Smitsmans *et al.*, 2008; Nijkamp *et al.*, 2008; Wu *et al.*, 2001; Madsen *et al.*, 2003; Ogino *et al.*, 2008; Padhani *et al.*, 1999; van Lin *et al.*, 2005).

At our department, an antiflatulent diet was introduced to reduce the prostate motion for patients undergoing intensity-modulated radiotherapy (IMRT) for prostate cancer. To our knowledge, no investigation has been performed about the solitary effect of an antiflatulent diet on the intrafraction prostate motion. Therefore, the present study evaluated the influence of an antiflatulent diet on the intrafraction motion in patients undergoing IMRT for prostate cancer.

Methods and materials

Between February 2002 and December 2009, 977 consecutive prostate cancer patients were treated at our department to a dose of 76 Gy to the prostate (Lips *et al.*, 2008). The prostate was initially delineated using computed tomography only and, since 2004, using computed tomography combined with 3-T magnetic resonance imaging. A margin of 8 mm was applied to the prostate and seminal vesicles to create the PTV.

Patients underwent IMRT with a five-beam step-and-shoot technique and 10-MV photons. A mean dose of 76 Gy in 35 fractions of 2.17 Gy was prescribed to the PTV and 95% of the prescribed dose (72 Gy) was prescribed to 99% of the PTV. The dose in the part of the PTV overlapping the rectum and bladder was limited such that ≤ 5% of the rectum and ≤ 10% of the bladder would receive a dose of ≥ 72 Gy (Nederveen *et al.*, 2001).

For position verification, three fiducial gold markers were implanted inside the prostate (Moman *et al.*, 2010). Daily imaging of the fiducial markers was used for off-line position verification, using an adapted "shrinking action level" protocol (van der Heide *et al.*, 2007; Lips *et al.*, 2009a). The main study parameter was the movement of the prostate during one radiation fraction. The irradiation time of the technique varied from 5 to 7 min. During treatment, the fiducial gold markers were visualized using portal images of the largest segment of all five beams (beam directions, 260°, 320°, 40°, 100°, and 180°), using the iView-GT amorphous silicon flat-panel detector (Elekta, Crawley, UK). Image analysis occurred using in-house developed software, which allowed automatic detection of the fiducial gold markers (Nederveen *et al.*, 2000). For every treatment beam, the largest segment was used to take a portal image. On these portal images, the gold markers were detected and manually adjusted, if required, after visual inspection by 2 radiographers. Using the center of gravity of the two-dimensional marker locations on the five portal images, a three-dimensional path consisting of five points was derived that had a minimal overall length. The error in assuming the shortest path to localize the prostate was less than ~ 1.5 mm for 95% of localizations (Adamson *et al.*, 2009). With this method, described by Kotte *et al.* (2007), the range of motion during each fraction is determined and used as the intrafraction motion. The range of motion is defined as the vector length between the extreme positions in all three dimensions. Clinically relevant intrafraction motion was defined as ≥ 50% of the fractions with an intrafraction motion outside a range of 3 mm. Because in the published data, a margin of 2 mm has been suggested to account for intrafraction motion, we also studied the intrafraction motion outside a range of 2 mm (Nichol *et al.*, 2010; Kotte *et al.*, 2007).

In July 2008, an antiflatulent diet was introduced to reduce the prostate motion. The antiflatulent diet was based on the dietary guidelines described by Smitsmans *et al.* (2008) that are used nationwide. The diet aimed to minimize the rectal gas, because rectal gas is suggested to be the most important predictor for prostate movement (Nichol *et al.*, 2010). Most rectal gas is caused by bacterial digestion of the oligosacharides, raffinose, stachyose, and verbascose in legumes and fruit (Di Stefano *et al.*, 2007). The diet consisted of dietary guidelines to obtain regular bowel movements and to reduce intestinal gas by avoiding certain foods and air swallowing (*Table 1*).

Table 1. Contents of the diet.

Dietary advice
Start 5 days before planning CT/MRI scan and continue until the last radiotherapy fraction.
Suggestions for regular bowel motion:
Eat regularly by using three meals a day
Drink 2 liters of liquid per day and vary the type of liquids (tea, coffee, water, noncarbonated juice, milk, soup, broth)
Chew food well or cut your food into small pieces
Get sufficient physical exercise, if possible
Suggestions to avoid rectal gas and intestinal stimulation:
Avoid the following foods:
wholemeal bread with coarse seeds, rye bread, muesli, cruesli
citrus fruits, like orange/lemon/grapefruit(juice)
pineapple, dried fruits
leek, onions, garlic, cabbage, sprouts, peppers, mushrooms, corn, rhubarb
raw vegetables like tomato, lettuce, cucumber
dried pies and beans (kidney beans, navy beans, lentils, split peas)
hot en spicy foods
nuts and peanuts, coconut
carbonated beverages including beer and soda pop
Coffee: avoid > 4 cups a day
Suggestions to reduce the amount of swallowing air:
Eat slowly
Don't talk while eating
Avoid smoking
Avoid chewing gum

The patients received the dietary guidelines in a brochure during the intake consultation, together with an explanation from the attending physician concerning the diet.

During treatment, the patients did not receive any instruction for emptying the rectum before the RT session. Concerning bladder filling, the patients were advised to empty their bladder before computed tomography/magnetic resonance imaging and the RT sessions. No laxatives or other medicines were prescribed during treatment. The patients were treated in the supine position, and a knee cushion was used to prevent any rotation of the hip.

The baseline characteristics of the two groups were examined using the chi-square test for categorical variables and the independent two-sample *t* test for qualitative data. The range in intrafraction motion per fraction was used to calculate the average and standard deviation of the range in intrafraction motion for each patient. Because the average intrafraction motion was not normally distributed within the two groups, the data were examined using the nonparametric Mann-Whitney U test.

To determine the effect of the diet on the intrafraction motion, the percentage of patients with clinically relevant intrafraction motion within the two groups were compared using Fisher's exact test. The clinically relevant intrafraction motion was defined as the percentage of fractions and not as a number of fractions. Thus, if a patient were missing some intrafraction motions, this patient did not have to be excluded.

To adjust for possible confounding factors, a logistic regression model was created with clinically relevant intrafraction motion as the dichotomous dependent variable. The confounding effect of the following variables was studied one by one: age, tumor stage, and tumor grade. The variables that changed the crude effect estimated by >10% were included in the final model. All analyses were performed using the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL). A p value of < .05 was considered statistically significant.

Results

Of the 977 patients, 51 were excluded, because these patients had already been included in a different study that might have influenced the intrafraction motion. An additional 35 patients were excluded because they were treated in the transitional phase in which the diet was introduced. During these 3 months, we had no complete confidence whether the patients were treated with or without the use of the diet; therefore we decided to exclude these patients from the analysis. Finally, 47 patients were excluded because the intrafraction motion of fewer than one-half of the total 35 fractions was available for these patients (for the no-diet and diet group, 5.0 % and 7.1 %, respectively). The method of Kotte *et al.* (2007) to determine the intrafraction motion requires the location of the gold markers within all five treatment beams. Therefore, no intrafraction motion could be calculated when the marker position of one of the five beams was not available. In clinical practice, the detection of the marker position cannot be performed for a beam direction in the case of technical problems leading to poor image quality or failure to acquire images. For a total of 24,776 treatment fractions, all five images were available. The missing fraction data were equally distributed between the two groups (average available fractions, 29 fractions/patient for the no-diet group and 30/patient for the diet group).

Of the final 844 patients included in the analysis, 739 were treated before the introduction of the diet and 105 used the diet during their RT. The baseline characteristics of both groups are listed in *Table 2*. No significant differences between the two groups were found in terms of age (p = .7) or tumor grade (p = .1). A small, statistically significant, difference was found for the tumor stage, with relatively fewer patients with Stage T3 disease in the diet group than in the no-diet group (p = .02). This could be explained by changes in the treatment indications during the study period and the development in diagnostic methods. In both groups, most patients had locally advanced prostate cancer (Stage T3).

Table 2. Patient characteristics.

	No diet (n = 739)	Diet (n = 105)	p value
Age, years			
mean (range)	68 (46-82)	69 (55-81)	0.7
Tumor stage			
T1	79 (10.7)	18 (17.1)	0.02
T2	83 (11.2)	18 (17.1)	
T3	575 (77.8)	69 (65.7)	
T4	2 (0.3)	0 (0.0)	
Tumor grade			
Gleason 4-6	195 (26.4)	29 (27.6)	0.1
Gleason 7	377 (51.0)	45 (42.9)	
Gleason 8-10	166 (22.5)	30 (28.6)	
not available	1 (0.1)	1 (1.0)	

Values are number (percentage), unless otherwise noted.

The intrafraction motion in both groups is listed in *Table 3*. The median and interquartile range of the average intrafraction motion for each patient was 2.53 mm (interquartile range, 2.2–3.0) without the diet and 3.00 mm (interquartile range, 2.4–3.5) with the diet (p < .0001). We calculated the percentage of patients who demonstrated a clinically relevant intrafraction motion (defined as ≥ 50% of the fractions with an intrafraction motion outside a range of 3 mm). This percentage showed a statistically significant increase from 19.1% to 42.9% after introduction of the diet (p < .0001). The percentage of patients with ≥ 50% of the fractions with an intrafraction motion outside a range of 2 mm also increased after the introduction of the diet: from 77.5% without the diet to 86.7% with the diet (p = .031).

Table 3. Descriptive statistics of the range in intrafraction motion for patients treated without and with the use of the antiflatulent diet.

	No diet (n = 739)	Diet (n = 105)	p value
Mean intrafraction motion per patient (mm)			
Median (IQR)	2.53 (2.2-3.0)	3.00 (2.4-3.5)	<0.0001
Standard deviation of the intrafraction motion per patient (mm)			
Median (IQR)	0.90 (0.6-1.3)	0.82 (0.7-1.2)	0.363
Patients with an intrafraction motion in ≥ 50% of the fractions of			
> 2 mm	573 (77.5)	91 (86.7)	0.031
> 3 mm	141 (19.1)	45 (42.9)	<0.0001

IQR = interquartile range. Values are number (percentage), unless otherwise noted.

Figure 1 presents a scatter plot showing the individual percentage of fractions during treatment with an intrafraction motion outside a range of 2 mm (*Figure 1a*) or outside a range of 3 mm (*Figure 1b*) as the percentage of patients per group (diet vs. no diet).

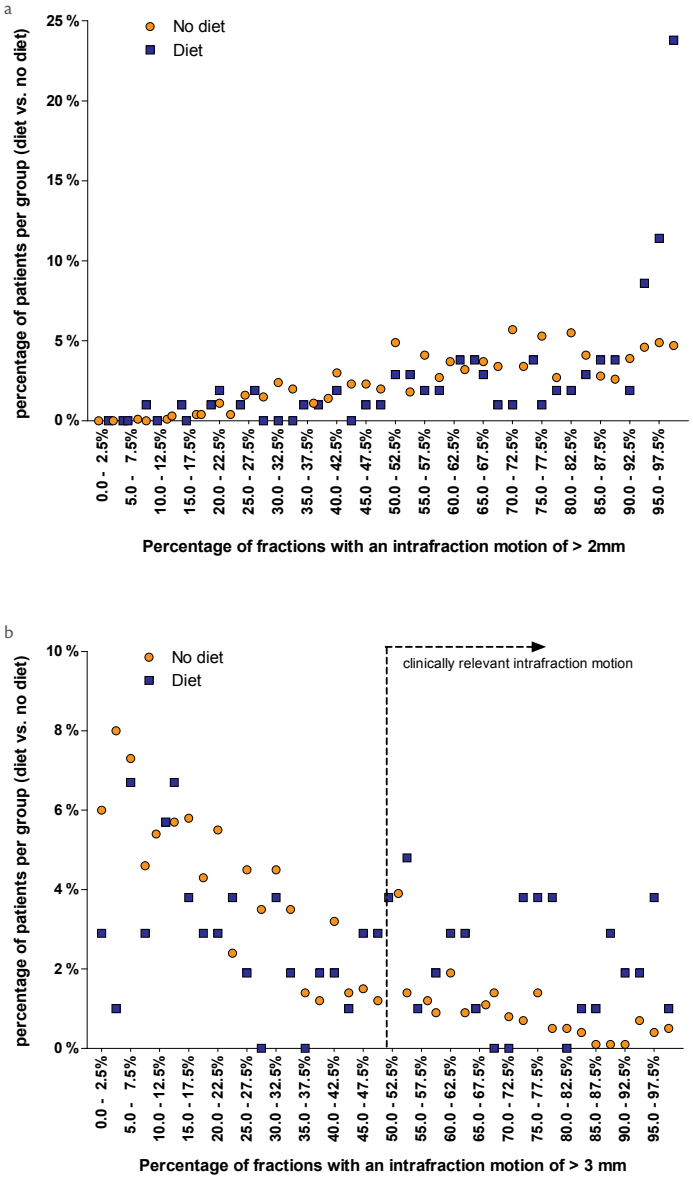

Figure 1. Scatter plot showing the individual percentages of fractions with an intrafraction motion outside a range of more than 2 mm (**a**) and more than 3 mm (**b**) as the percentage of patients per group (diet versus no diet).

The crude odds ratio for diet vs. no diet for clinically relevant intrafraction motion (intrafraction motion of >3 mm in ≥ 50% of all fractions) was 3.18 (95% confidence interval, 2.07–4.88). The variables of age, tumor stage, and tumor grade did not affect this relationship by >10%; thus, no inclusion of these variables in a multivariate model was required to adjust for possible confounding.

Discussion

To reduce the prostate motion during RT, an antiflatulent diet has been introduced in clinical practice. The evaluation of this intervention at our department has shown that after the start of the diet, the intrafraction motion did not decrease. In contrast, the amount of intrafraction motion was significantly larger in the patient group using the diet than in the group not using the diet. The percentage of patients with clinically relevant intrafraction motion increased from 19.1% without the diet to 42.9% with the diet ($p < .0001$).

Several nonrandomized studies have described the effect of a diet combined with other interventions, such as medicines and fixed treatment times. In combination with daily deflatulence medication (simethicon), an antiflatulance diet was suggested to provide a reduction of 30% of the interfraction prostate motion (Hentschel *et al.*, 2006). Wu *et al.* (2001) observed small standard deviations for interfraction prostate motion in a group of patients instructed regarding dietary management, fluid intake, and laxative use. The Antoni van Leeuwenhoek Hospital, Amsterdam, evaluated the influence of a dietary protocol (consisting of dietary guidelines, magnesium oxide tablets, and fixed treatment times) on the cone-beam computed tomography image quality, as an indirect indicator of intrafraction motion. A significant decrease in the incidence of feces and moving gas was seen, resulting in an increase in the image quality and therefore less intrafraction motion was inferred (Smitsmans *et al.*, 2008). However, this conclusion of reduced intrafraction motion was not supported by Nichol *et al.* (2010), who investigated the effect from a bowel regimen, comprising an antiflatulent diet and daily magnesium hydroxide (Milk of Magnesia), on intrafraction motion directly. They concluded that no reduction of intrafraction prostate motion occurred with their bowel regimen. The inconsistency between our results and some of the other studies might have been because we investigated the solitary effect of the diet and others combined the diet with a laxative and/or fixed treatment times.

An explanation for the increased intrafraction motion with the use of an antiflatulent diet found in our study might be that a change in food pattern influences stool frequency and thereby abdominal gas production. Epidemiologic studies have demonstrated a high prevalence of constipation and laxative use in the elderly. Prevalence for constipation as great as 50% has been suggested (Higgins *et al.*, 2004). Advancing age is associated with altered mechanical properties, altered macroscopic

structural changes, and altered control of the pelvic floor, which could affect bowel structure and function. However, the exact biologic basis of constipation in the elderly is not clear (Bouras *et al.*, 2009). Because many elderly already have some difficulty with keeping a regular bowel movement, they often use a laxative or certain special food intake to keep the stool acceptable (Bouras *et al.*, 2009). By altering their specific food pattern, their bowel movement might be stimulated, leading to the opposite effect of increased intrafraction motion instead of the intended decrease. Another possible explanation for the enlarged intrafraction motion with the diet might be increased bladder filling during RT. All patients were told to empty their bladder before treatment. However, patients using the diet might have faster bladder filling during RT because of the intake of 2 L of liquid daily.

No information is available about the compliance of our patients with the diet; thus, it is possible that our patients did not follow the dietary guidelines precisely. The specific dietary guidelines are difficult to manage and difficult to check. Patients received the dietary guidelines in a brochure without a diet-teaching session, which might have lessened the compliance to the diet. An abstract from Pettersson *et al.* (2007) suggested significantly reduced intake of certain foods after dietary counseling; however, no final results or conclusion has been presented in the published data. The insufficient compliance to the diet can explain the failure to result in a decrease in intrafraction motion; however, this cannot explain the increased intrafraction motion seen in our diet group.

The underlying mechanism of intestinal gas is a complex process and remains incompletely understood. Gas production results from swallowing, chemical reactions, and diffusion from the blood and bacterial fermentation. Gas disposal occurs through belching, diffusion into blood, bacterial consumption, and passage of flatus (Suarez *et al.*, 2002). Colonic bacteria, both gas-producing and gas-consuming microorganisms, play a major role in gas metabolism. Gas-producing bacteria ferment various unabsorbed substrates, releasing hydrogen and carbon dioxide. The volume of gas evacuated is determined by the action of colonic microflora on unabsorbed fermentable food residues entering the colon. Excessive anal gas evacuation depends on both the composition of the colonic flora and the diet. The composition of intraluminal flora is highly individual, which explains the variation in gas production in different subjects (Furne *et al.*, 1996). The intraluminal flora is difficult to modify, and no evidence exists that gas production can be reduced by manipulating the colonic flora. An antiflatulent diet is trying to reduce the arrival of undigested residues into the colon, where they serve as gas-producing substrates to colonic flora.

The amount of intrafraction motion described in our study underlines the importance of a margin of ≥ 2 mm to account for intrafraction motion suggested in the published data (Nichol *et al.*, 2010; Kotte *et al.*, 2007). It is difficult to determine whether the statistically significant increase of 0.47 mm in the median intrafraction motion caused

by the dietary advice is also clinically meaningful. During the treatment course of 35 fractions, the intrafraction shifts tend to wash out (Li *et al.*, 2008). In contrast, larger intrafraction motion might become of more importance in hypofractionated treatment regimens and with the minimization of other treatment-related inaccuracies, the margin accounting for the intrafraction motion becomes more critical. For the estimation of the clinical consequence of the increase in intrafraction motion by the use of a diet in our study, an evaluation of the treatment outcome should be performed. To investigate a difference between the two groups in treatment-related toxicity, quality of life, and tumor control, longer follow-up is needed.

Our study had an observational retrospective design, in which the extent of information concerning confounders, outcome, and determinant was limited. Because of the comparison, we made before and after the introduction of the diet, the treatment changes over time could have influenced our results. No adjustments in treatment, such as changes in the duration of the irradiation time or changes in the rectum and bladder instructions, were performed between 2002 and 2009. However, no information was available about other potential confounders, such as the use of laxatives on the patients' own initiative, the interval from the last bowel movement, or comorbidities such as abdominal disease (Crohn's disease, diverticulitis, lactose intolerance). Thus, possible confounding due to changes in time could not be excluded and whether the apparent worsening is a time era effect related to measurement is hard to rule out. Therefore, a randomized controlled trial would be appropriate to study the effect of the diet in further detail.

The problem of intrafraction motion can also be handled by improvement of the position verification. Real-time on-line position verification, correcting the intrafraction motion, can be established with the use of a Calypso monitoring system (Liu *et al.*, 2010), with a intrafraction stereographic targeting method (van Os *et al.*, 2009) or using a magnetic resonance imaging accelerator, which is currently being developed (Lagendijk *et al.*, 2008; Raaymakers *et al.*, 2009).

Conclusion

The results of the present study suggest that antiflatulent dietary advice for patients undergoing IMRT for prostate cancer does not reduce the intrafraction movement of the prostate. Therefore, it is not recommended to provide antiflatulent dietary advice in the clinical practice for this purpose. Additional research should be performed to clear up the exact mechanism of intrafraction prostate motion and how this mechanism can be influenced to minimize the intrafraction positioning error.

Chapter 5

Acute and late toxicity

This chapter has been published as:

I.M. Lips, H. Dehnad, C.H. van Gils,
A.E. Boeken Kruger, U.A. van der Heide and M. van Vulpen.

High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients.

Radiation Oncology. 2008 21; 3: 15.

Abstract

Purpose

We evaluated the acute and late toxicity after high-dose intensity-modulated radiotherapy (IMRT) with fiducial marker-based position verification for prostate cancer.

Methods and Materials

Between 2001 and 2004, 331 patients with prostate cancer received 76 Gy in 35 fractions using IMRT combined with fiducial marker-based position verification. The symptoms before treatment (pre-treatment) and weekly during treatment (acute toxicity) were scored using the Common Toxicity Criteria (CTC). The goal was to score late toxicity according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scale with a follow-up time of at least three years. Twenty-two percent of the patients experienced pre-treatment grade ≥ 2 genitourinary (GU) complaints and 2% experienced grade 2 gastrointestinal (GI) complaints.

Results

Acute grade 2 GU and GI toxicity occurred in 47% and 30%, respectively. Only 3% of the patients developed acute grade 3 GU and no grade ≥ 3 GI toxicity occurred. After a mean follow-up time of 47 months with a minimum of 31 months for all patients, the incidence of late grade 2 GU and GI toxicity was 21% and 9%, respectively. Grade ≥ 3 GU and GI toxicity rates were 4% and 1%, respectively, including one patient with a rectal fistula and one patient with a severe hemorrhagic cystitis (both grade 4).

Conclusion

High-dose intensity-modulated radiotherapy with fiducial marker-based position verification is well tolerated. The low grade ≥ 3 toxicity allows further dose escalation if the same dose constraints for the organs at risk will be used.

Introduction

Several randomized trials have demonstrated a significant benefit of an increased radiation dose for the treatment of prostate cancer (Peeters *et al*., 2006; Pollack *et al*., 2002; Zietman *et al*., 2005). Further dose escalation is expected to lead to further improvement (Eade *et al*., 2007). However, dose escalation is associated with an increased risk of acute and late toxicity (Peeters *et al*., 2006; Pollack *et al*., 2002; Zietman *et al*., 2005).

Prostate tumor cells are predominantly located in the peripheral zone of the prostate situated at the dorsal site (Chen *et al*., 2000). Therefore, the challenge is to achieve a sufficiently high-dose to the peripheral zone of the prostate, while providing an adequate sparing of the rectum. Intensity-modulated radiotherapy (IMRT) is able to deliver such dose distributions and has therefore become the preferred treatment technique (Cahlon *et al*., 2008; De Meerleer *et al*., 2004; Zelefsky *et al*., 2002; Skala *et al*., 2007; De Meerleer *et al*., 2007; Zelefsky *et al*., 2006).

Sharp dose gradients between the target volume and the organ at risk require reliable and accurate position verification to prevent decreased biochemical control and increased rectal toxicity (De Crevoisier *et al*., 2005). Fiducial gold markers implanted in the prostate have proved to be reliable markers of prostate position over the course of radiation treatment (Dehnad *et al*., 2003). Their position can be easily and automatically detected with electronic portal imaging devices, allowing for fast and accurate determination of the prostate position. Daily correction of the position of the prostate using fiducial markers minimizes the setup uncertainties (van der Heide *et al*., 2007).

Several prospective and randomized trials have accurately presented the incidences of their acute and late toxicity (Zietman *et al*., 2005; De Meerleer *et al*., 2004; Zelefsky *et al*., 2002; Skala *et al*., 2007; Beckendorf *et al*., 2004; Michalski *et al*., 2005; Peeters *et al*., 2005a; Storey *et al*., 2000). Only Skala *et al*. (2007) reported toxicity rates after prostate cancer treatment with three-dimensional (3D) conformal/IMRT using fiducial marker-based position verification. They collected patient-reported questionnaires of 365 patients to determine the incidence of late toxicity. Until now, no longitudinal study of physician-reported toxicity including baseline measurements has been published for patients treated with IMRT using fiducial markers. Therefore, we describe in this study the complete pre-treatment symptoms and the acute and late toxicity of a large number of patients treated with high-dose IMRT using daily fiducial marker-based position verification.

Methods and materials

According to literature, a follow-up of three years is sufficient for the majority of late rectal morbidity to manifest itself (Pollack *et al*., 2002; Zietman *et al*., 2005). Therefore, we evaluated toxicity in the entire population of patients (n = 331) treated at our department from August 2001 until December 2004, which resulted in a minimum follow-up time of 31 months for all patients. The prostate was delineated on a CT-scan and a margin of 8 mm was applied to the prostate and seminal vesicles to create a planning target volume (PTV). Patients received an IMRT treatment using a five-beam step-and-shoot technique (van der Heide *et al*., 2007; Kotte *et al*., 2007). A mean dose of 76 Gy in 35 fractions was prescribed to the PTV and 95% of the prescription dose (= 72 Gy) was prescribed to 99% of the PTV. The dose to the overlapping region with rectum and bladder was limited so that no more than 5% of the rectum and 10% of the bladder would receive a dose of ≥ 72 Gy (Nederveen *et al*., 2001). No elective pelvic node irradiation was performed.

Fiducial markers for position verification were transrectally implanted with the use of antibiotic prophylaxis (Dehnad *et al*., 2003). Daily portal images of the fiducial markers were taken to determine the position variations during treatment. With the use of an off-line adapted shrinking action level (SAL) protocol the systematic errors were less than 0.8 mm in all directions (van der Heide *et al*., 2007).

Pre-treatment symptoms and acute toxicity were scored using the Common Toxicity Criteria (CTC) version 2.0 (Trotti *et al*., 2000). Acute toxicity was present when one of the symptoms occurred within 90 days after the start of treatment (Trotti *et al*., 2000). Late toxicity was scored according to the Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer (RTOG/EORTC) morbidity scale version 9 (Cox *et al*., 1995), because the CTC version 2.0 only focuses on acute effects (Trotti *et al*., 2000). Follow-up took place 4 weeks after treatment, every 3 months in the first year and every 6 months thereafter at the Department of Radiotherapy. Every symptom was counted even if it occurred only on one single occasion.

Results

The patient characteristics of the 331 patients are presented in *Table 1*. The mean follow-up time was 47 months (range: 31–71 months). At the time of study entry, no national guidelines for hormonal treatment were available. Therefore, only 95 patients received adjuvant hormonal treatment. Bone scan and/or pelvic lymph node dissection was performed in all patients with prostate-specific antigen levels above 20 ng/ml to rule out M+ disease. Late side effects with a minimum follow-up time of 31 months were available for 320 patients, because three patients died and eight patients were lost to follow-up during the first three years.

Table 1. Patient characteristics of the 331 patients.

Characteristic	
Age at baseline, years	
Mean (range)	68 (46 - 80)
Initial PSA value, ng/mL	
Mean (range)	20 (0.5 - 175)
Biopsy Gleason score	
≤ 4	39 (12)
5 - 7	228 (69)
≥ 8	64 (19)
Tumor stage	
T1	37 (11)
T2	31 (9)
T3	262 (79)
T4	1 (1)
Hormonal treatment	
None	236 (71)
Short-term	70 (21)
Long-term	25 (8)
TURP	40 (12)

TURP = transurethral resection of the prostate; PSA = prostate-specific antigen. Values are number (percentage), unless otherwise noted.

In *Table 2*, the grades of pre-treatment symptoms and acute and late toxicity are shown. The highest toxicity score for each patient was used, to calculate an overall GU and GI score of the CTC items. Seventy-three patients (22%) showed pre-treatment GU symptoms of grade ≥ 2 and six patients (2%) experienced grade 2 proctitis complaints before radiotherapy.

Acute grade 2 GU and GI toxicity was found in 47% and 30% of our patient group. Ten patients (3%) developed grade 3 acute GU side effects with two patients having a urinary catheter before treatment (grade 3) and six patients having pre-treatment grade 2 GU symptoms. Acute grade 3 infections were seen in three patients: respectively a urinary tract infection, a pneumonitis and a prostatitis after marker implantation, that all needed intravenous antibiotic. No grade 4 acute toxicity was seen for both GU and GI. Ninety-nine percent of the patients with pre-treatment grade ≥ 2 GU symptoms demonstrated acute grade ≥ 2 toxicity, compared to 36% of the patients with pre-treatment GU complaints of < grade 2. As grade 3 toxicity seldom occurred, most patients with pre-treatment grade 2 complaints mainly continued having grade 2 toxicity during treatment.

Eighty-two and 33 patients demonstrated late grade ≥ 2 GU and GI toxicity, respectively. Two patients experienced late grade 4 morbidities: one patient experienced a severe haemorrhagic cystitis and required a suprapubic catheter. Three months before the start of the radiotherapy, he underwent a transurethral resection of the prostate

Table 2. Pre-treatment complaints and acute toxicity according to the Common Toxicity Criteria (CTC) and late toxicity according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scale.

Item	Toxicity				
	Grade 0	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Pre-treatment (n = 331)					
Genitourinary					
Urinary frequency/urgency	161 (49)	99 (30)	69 (21)	2 (1)	0 (0)
Urinary retention	317 (96)	13 (4)	1 (0.3)	0 (0)	0 (0)
Bladder spasms	328 (99)	3 (1)	0 (0)	0 (0)	0 (0)
Urinary incontinence	318 (96)	13 (4)	0 (0)	0 (0)	0 (0)
Hematuria	324 (98)	6 (2)	1 (0.3)	0 (0)	0 (0)
Dysuria	318 (96)	13 (4)	0 (0)	0 (0)	0 (0)
Overall	150 (45)	108 (33)	71 (22)	2 (1)	0 (0)
Gastrointestinal					
Proctitis	306 (92)	19 (6)	6 (2)	0 (0)	0 (0)
Rectal or perirectal pain	328 (99)	3 (1)	0 (0)	0 (0)	0 (0)
Overall	305 (92)	20 (6)	6 (2)	0 (0)	0 (0)
Acute toxicity (n = 331)					
Genitourinary					
Urinary frequency/urgency	25 (8)	154 (47)	144 (44)	8 (2)	0 (0)
Urinary retention	271 (82)	52 (16)	3 (1)	5 (2)	0 (0)
Bladder spasms	309 (94)	18 (5)	4 (1)	0 (0)	0 (0)
Urinary incontinence	305 (92)	23 (7)	3 (1)	0 (0)	0 (0)
Hematuria	317 (96)	7 (2)	6 (2)	1 (0.3)	0 (0)
Dysuria	165 (50)	139 (42)	26 (8)	1 (0.3)	0 (0)
Overall	19 (6)	147 (44)	155 (47)	10 (3)	0 (0)
Gastrointestinal					
Proctitis	71 (22)	168 (51)	92 (28)	0 (0)	0 (0)
Rectal or perirectal pain	275 (83)	32 (10)	24 (7)	0 (0)	0 (0)
Overall	63 (19)	169 (51)	99 (30)	0 (0)	0 (0)
Infection	313 (95)	3 (1)	12 (4)	3 (1)	0 (0)
Late toxicity (n = 320)					
Genitourinary	152 (48)	86 (27)	68 (21)	13 (4)	1 (0.3)
Gastrointestinal	193 (60)	94 (29)	30 (9)	2 (1)	1 (0.3)

Values are number (percentage).

(TURP) and he had pre-treatment grade 1 urinary frequency/urgency complaints and acute grade 1 dysuria and grade 2 hematuria and urinary frequency/urgency toxicity. Furthermore, this patient suffered from late grade 2 GI toxicity with frequent bleeding that required steroid enemas. The other patient developed a rectal fistula requiring surgery 18 months after radiotherapy. This patient had no pre-treatment GI complaints, but during radiotherapy he developed grade 2 perirectal pain and proctitis. For both patients the technical and dosimetric details of their radiotherapy treatment were evaluated and no abnormalities were found.

The incidence of late grade ≥ 2 GU toxicity for patients with pre-treatment grade ≥ 2 GU complaints was 58%, compared to 17% for patients with grade < 2 GU symptoms before radiotherapy. Calculation of relative risks (RR) accompanying 95% confidence intervals (95%-CI) demonstrated for patients with acute grade ≥ 2 GU complaints a 5.2 fold (95%-CI: 3.0–9.1) increased risk for late grade ≥ 2 GU compared to those who had acute grade < 2 GU complaints. Additionally, the risk of late grade ≥ 2 GI toxicity was increased for patients with acute grade ≥ 2 GI complaints (RR: 2.2; 95%-CI: 1.1–4.1).

Discussion

This data demonstrates that a dose of 76 Gy in 35 fractions, using IMRT and daily fiducial marker-based position verification, is well tolerated. Acute and late toxicity from different studies, when available, are presented in *Table 3*. The acute toxicity established in our patient group, in particular grade ≥ 3, was lower than reported in literature for 3D conformal radiotherapy (Zietman *et al*., 2005; Beckendorf *et al*., 2004; Michalski *et al*., 2005; Peeters *et al*., 2005a; Storey *et al*., 2000). Although different toxicity scales and radiotherapy techniques make a comparison difficult. De Meerleer *et al*. (2004) treated 114 patients with high-dose IMRT with position verification by visualizing the bony anatomy and reported comparable acute GI toxicity rates and somewhat lower grade 2 and higher grade 3 acute GU toxicity rates. Zelefsky *et al*. (2002) reported lower acute toxicity rates after high-dose IMRT with lower fraction doses of only 1.8 Gy. As in most other toxicity reports acute GU toxicity was more pronounced than GI toxicity (De Meerleer *et al*., 2004; Zelefsky *et al*., 2002; Beckendorf *et al*., 2004; Peeters *et al*., 2005a; Storey *et al*., 2000).

The randomized dose-escalation trials reported more late GI and comparable late GU morbidities (Pollack *et al*., 2002; Zietman *et al*., 2005; Peeters *et al*., 2005a). One hundred sixteen patients, treated with IMRT using a rectal balloon for position verification, demonstrated comparable late GI toxicity (Teh *et al*., 2005). De Meerleer *et al*. (2007) reported slightly higher late GI toxicity and comparable GU toxicity rates for 133 patients treated with IMRT. Zelefsky *et al*. (2006) described lower incidences of late toxicity for IMRT after a median follow-up time of only 24 months. Skala *et al*. (2007) reported somewhat lower late GU and GI toxicity rates, however the cross-sectional toxicity data was collected from patient-reported questionnaires.

Patients with pre-treatment grade 2 complaints mainly remained acute and late grade 2 toxicity. The predictive value of pre-treatment symptoms has also been reported by others (Peeters *et al*., 2005a; Heemsbergen *et al*., 2006; Koper *et al*., 2004; Peeters *et al*., 2005b).

Table 3. Acute and late toxicity from different studies.

	Acute toxicity						Late toxicity					
	GU (%) Grade			*GI (%) Grade*			*GU (%) Grade*			*GI (%) Grade*		
Authors	*2*	*3*	*4*	*2*	*3*	*4*	*2*	*3*	*4*	*2*	*3*	*4*
3D-conformal radiotherapy												
Storey, 2000, Pollack 2002	24	4	1	43	0	0	10	3	-	19	7	-
Beckendorf, 2004	30	7	-	28	2	-	-	-	-	-	-	-
Michalski, 2005	41	3	0	41	3	0	17	4	0	18	2	1
Zietman, 2005	49	1	1	57	0	0	20	1	0	17	1	0
Peeters, 2005a/2006	42	13	0	47	4	0	26	13	-	27	5	-
Intensity-modulated radiotherapy												
Zelefsky, 2002/2006	28	0.1	0	5	0	0	9	3	0	2	0.1	0
De Meerleer, 2004/2007	36	7	0	29	0	0	19	3	0	17	1	0
Teh, 2005	35	0	0	6	0	0	-	-	-	7	2	0
Skala, 2007	-	-	-	-	-	-	9	1	-	3	1	-
Current study	47	3	0	30	0	0	21	4	0.3	9	1	0.3

GU = genitourinary; GI = gastrointestinal; - = toxicity rate not available.

Although our patients had a median follow-up time of 47 months and all patients had a follow-up time of at least 31 months, continuing scoring of toxicity is needed, because an increase in GU complications has been reported after three years (Schultheiss *et al.*, 1997).

Conclusion

In conclusion, a dose of 76 Gy in 35 fractions using IMRT and fiducial marker-based position verifications is well tolerated, because the low incidences of grade ≥ 3 acute and late GU and GI side effects. These results provide possibilities for further dose escalation, because acceptable toxicity is expected when the same dose constraints for the organs at risk and good quality external beam radiotherapy are being used.

Chapter 6

Short-term quality of life

This chapter has been published as:

I.M. Lips, H. Dehnad, A.E. Boeken Kruger, R.J.A. van Moorselaar, U.A. van der Heide, J.J. Battermann and M. van Vulpen.

Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study.

International Journal of Radiation Oncology, Biology, and Physics. 2007; 69: 656-61.

Abstract

Purpose

To compare quality of life (QoL) after 70 Gy conformal radiotherapy with QoL after 76 Gy intensity-modulated radiotherapy (IMRT) in patients with locally advanced prostate carcinoma.

Methods and Materials

Seventy-eight patients with locally advanced prostate cancer were treated with 70 Gy three-field conformal radiotherapy, and 92 patients received 76 Gy IMRT with fiducial markers for position verification. Quality of life was measured by RAND-36, the European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30(+3)), and the prostate-specific EORTC QLQ-PR25, before radiotherapy (baseline) and 1 month and 6 months after treatment. Quality of life changes in time (baseline vs. 1 month and baseline vs. 6 months) of ≥ 10 points were considered clinically relevant.

Results

Differences between the treatment groups for QoL changes over time occurred in several QoL domains. The 76-Gy group revealed no significant deterioration in QoL compared with the 70-Gy group. The IMRT 76-Gy group even demonstrated a significantly better change in QoL from baseline to 1 month in several domains. The conformal 70-Gy group revealed temporary deterioration in 'pain', 'role functioning', and 'urinary symptoms'; for the IMRT 76-Gy group a better QoL in terms of 'change in health' existed after 1 month, which persisted after 6 months. For both treatment groups temporary deterioration in 'physical role restriction' occurred after 1 month, and an improvement in 'emotional role restriction' occurred after 6 months. 'Sexual activity' was reduced after treatment for both groups and remained decreased after 6 months.

Conclusion

Intensity-modulated radiotherapy and accurate position verification seem to provide a possibility to increase the radiation dose for prostate cancer without deterioration in QoL.

Introduction

Several randomized trials showed a significant improvement in biochemical relapse-free treatment outcome in prostate cancer with escalation of the radiation dose from 68 Gy to 78 Gy (Peeters *et al*., 2006; Pollack *et al*., 2002; Zietman *et al*., 2005). Further dose increase is expected to lead to further improvement (Zelefsky *et al*., 2002). By increasing the radiation dose the risk of developing complications also increases, and therefore a decrease in quality of life (QoL) should be expected. Raising the dose from 68 Gy to 78 Gy using conformal radiotherapy resulted in more late gastrointestinal and genitourinary toxicity (≥ 5% Grade 3) (Peeters *et al*., 2005a). However, advances in technology like intensity-modulated radiotherapy (IMRT) (Zelefsky *et al*., 2001) and improved position verification of the prostate (van der Heide *et al*., 2007; Dehnad *et al*., 2003) have enabled dose escalation while treatment-related complications are minimized. For evaluation of treatment, not only toxicity but also impact on QoL is increasingly important (Litwin *et al*., 1999).

At our department several QoL studies in patients with prostate cancer have been performed. For instance, QoL after permanent prostate brachytherapy in relation to dosimetry (van Gellekom *et al*., 2005) and the influence of adding hyperthermia to radiotherapy on QoL (van Vulpen *et al*., 2003) have been described. The purpose of this study was to investigate the QoL changes after dose-escalated radiotherapy. The few studies available concerning QoL after dose-escalated radiotherapy suggest that an increased radiation dose does not result in deterioration in QoL (Namiki *et al*., 2006; Little *et al*., 2003; Kupelian *et al*., 2001). However, in these studies either a cross-sectional design (rather than a more solid longitudinal design) was used, patient groups were small, or no baseline measurement of QoL was performed, which is essential in this older patient group. Validated QoL questionnaires, including a prostate-specific module, were occasionally missing. The vast majority of publications on health-related QoL in prostate cancer focus on men with localized disease. However, patients with an unfavorable prognosis (T >2a, prostate-specific antigen >10 ng/mL, or Gleason score >6) are expected to need an increased radiation dose as well as adjuvant hormonal treatment, resulting in higher incidences of toxicity and subsequently a decreased QoL (Pollack *et al*., 2002; Zelefsky *et al*., 2002).

In this study we used a prospective, longitudinal design, including baseline measurements and well-validated QoL questionnaires to investigate QoL changes in patients with locally advanced prostate cancer after conformal radiotherapy with a dose of 70 Gy, compared with IMRT with a dose of 76 Gy.

Methods and materials

From December 1997 to October 2001, 99 patients with mostly locally advanced prostate cancer received three-field conformal external beam radiotherapy (70 Gy). From October 2003 to November 2004, 116 patients with mostly locally advanced prostate cancer were treated with IMRT (76 Gy). Toxicity of all patients was measured using the Common Toxicity Criteria (version 2.0) (Trotti *et al*., 2002).

For the first group, a CT-planned three-dimensional conformal external beam technique was used to deliver a dose of 70 Gy at 2-Gy fractions (5 fractions per week). A conformal three-field isocentric technique was applied using 6- and 18-MV photons and a multileaf collimator (van Vulpen *et al*., 2003). Position verification was performed by visualizing the bony anatomy using portal imaging with electronic portal imaging devices. The accuracy of this method is limited because of the possible variation of the position of the prostate relative to the bony anatomy.

All patients in the IMRT group received dose escalation to the prostate corpus, delineated on CT, of 76 Gy in 35 fractions of 2.17 Gy with a multileaf collimator and 10-MV photons (van der Heide *et al*., 2007). In this group transrectally implanted gold markers were used for daily position verification, which provides more accurate positioning of the prostate, resulting in more precise delivery of the radiation dose to the prostate and the organs at risk (van der Heide *et al*., 2007; Dehnad *et al*., 2003).

General health-related QoL was measured by the RAND-36 generic health survey (16), cancer-specific QoL by the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30(+3)) (Aaronson *et al*., 1993), and prostate tumor–specific QoL by the EORTC prostate cancer module (QLQ-PR25) (Borghede *et al*., 1996).All questionnaires are well validated and are widely used in oncology trials (Henderson *et al*., 2004). Scales and items of these questionnaires range in score from 0 to 100. For RAND-36 and for the global QoL and functional scales of the EORTC questionnaires, a high score value indicates better functioning and a high level of QoL. For the symptom/problem items of the EORTC questionnaires, higher scores represent a higher level of symptomatology and consequently a worse QoL.

For the EORTC questionnaires, changes in time of 10 points or more are considered clinically relevant (Osoba *et al*., 1998). Because RAND-36 applied the same score range, the same interpretation of a clinically relevant change has been used (van Vulpen *et al*., 2003).

The first questionnaire was presented to the patient at the Department of Radiation Oncology before treatment. One and 6 months after the completion of treatment, the measurements were repeated. Seventy-eight patients of the conformal treatment group and 92 patients of the IMRT group completed all questionnaires at the three measurement points and were, therefore, included for this study. All questionnaires demonstrated a high response rate except for the questions regarding sexual activity.

Differences between the baseline characteristics of the two treatment groups were examined with the Chi-square or the Mann- Whitney U test. General linear model repeated-measures analyses of variance were performed with SPSS 10.0 (SPSS, Chicago, IL) to analyze the effect of radiotherapy treatment and time over all three time points. For the QoL changes without a significant difference between the two treatment groups, both treatment groups were analyzed together for QoL changes within time. Separately, two changes in QoL over time were analyzed (baseline vs. 1 month and baseline vs. 6 months) to evaluate the QoL changes between these measurement points. Test results with a p value of <.01 were considered statistically significant with Bonferroni correction. Cronbach's coefficient α was calculated to determine internal consistency reliability.

Results

The patient characteristics of the IMRT 76-Gy and conformal 70-Gy radiotherapy groups are shown in *Table 1*. No significant differences between groups were found in terms of age (p = .8), tumor stage (p = .5), tumor grade (p = .9), and prostate-specific antigen level (p= .5). Twenty patients of the conformal 70-Gy group received hyperthermia in addition to conformal radiotherapy. Because hyperthermia was shown not to affect QoL (van Vulpen *et al*., 2003), these patients were evaluated together with the patients who merely received conformal radiotherapy. At the time of study entry, no national guidelines for hormonal treatment were available. Therefore, only 9 patients of the conformal treatment group and 24 patients of the IMRT group received adjuvant androgen deprivation therapy (ADT). All patients had a World Health Organization performance score of <2.

For both treatment groups, no acute toxicities above Grade 2 were seen for any of the Common Toxicity Criteria categories (gastrointestinal, genitourinary, infection, and constitutional symptoms), except for one Grade 3 urinary tract infection with intravenous antibiotic indicated in the 76-Gy group.

In *Table 2*, the means and standard deviations of all variables of the QoL measures before treatment (baseline) and 1 month and 6 months after treatment are shown for the patient group receiving 70 Gy conformal radiotherapy (n = 78) and for the 76-Gy IMRT group (n = 92).

Repeated-measures analysis of QoL changes over all three time points between the patient groups resulted in statistically significant differences between the two treatment groups for several QoL items. For these QoL items the QoL changes over time were analyzed separately for the IMRT and the conformal groups (*Table 3*). The QoL items without significant differences between both treatment groups are presented in *Table 4*. To evaluate QoL changes over time for these items, the two treatment groups (n = 170) were described together to increase the number of patients in the analysis.

Table 1. Patient characteristics.

	Conformal (*n* = 78)	IMRT (*n* = 92)
Age at baseline, years		
mean (range)	67 (47-78)	67 (49-79)
Tumor stage		
T1	4 (5.1)	12 (13.0)
T2	13 (16.7)	5 (5.4)
T3	60 (76.9)	75 (81.5)
T4	1 (1.3)	-
Tumor grade		
G1	10 (12.8)	11 (12.0)
G2	54 (69.2)	62 (67.4)
G3	14 (17.9)	19 (20.7)
PSA, ng/mL		
mean (range)	28 (0.2-400)	19 (2-90)
0-20	50 (64.1)	65 (70.7)
21-80	24 (30.8)	25 (27.2)
> 81	4 (5.1)	2 (2.2)
Hyperthermia treatment		
number of patients	20	-
Hormonal treatment		
number of patients	9	24
Radiotherapy dose, Gy		
< 66	3	-
70	75	-
76	-	92

IMRT = intensity-modulated radiotherapy; PSA = prostate-specific antigen.
Values are number (percentage), unless otherwise noted.

Table 2. Means (± standard deviations) of scales and single items of each questionnaire for the conformal group and the IMRT group.

	Conformal 70Gy (*n* = 78)			IMRT 76Gy (*n* = 92)		
Item	*Baseline*	*1 month*	*6 months*	*Baseline*	*1 month*	*6 months*
RAND-36						
Physical functioning	85 ± 21	81 ± 20	84 ± 21	86 ± 17	84 ± 17	85 ± 18
Social functioning	80 ± 21	73 ± 28	84 ± 22	82 ± 18	86 ± 19	90 ± 16
Physical role restriction	78 ± 37	55 ± 44	76 ± 36	78 ± 35	72 ± 41	82 ± 33
Emotional role restriction	77 ± 36	75 ± 39	86 ± 30	78 ± 36	85 ± 31	91 ± 28
Mental health	75 ± 16	77 ± 14	79 ± 15	76 ± 16	78 ± 16	80 ± 16
Vitality	70 ± 19	64 ± 21	70 ± 18	69 ± 20	68 ± 19	69 ± 20
Pain	90 ± 18	79 ± 25	86 ± 19	88 ± 19	87 ± 19	91 ± 17
General health	68 ± 17	67 ± 17	70 ± 17	66 ± 16	66 ± 17	68 ± 19
Change in health	50 ± 21	42 ± 19	56 ± 25	44 ± 14	54 ± 26	63 ± 25
EORTC QLQ-C30(+3)						
Physical functioning	91 ± 15	85 ± 18	89 ± 17	89 ± 14	88 ± 13	88 ± 15
Role functioning	88 ± 20	75 ± 29	86 ± 22	87 ± 19	85 ± 20	89 ± 19
Emotional functioning	75 ± 19	81 ± 17	82 ± 20	78 ± 16	87 ± 18	88 ± 18
Cognitive functioning	86 ± 21	85 ± 21	84 ± 20	89 ± 16	86 ± 19	86 ± 20
Social functioning	90 ± 16	84 ± 22	90 ± 20	90 ± 16	92 ± 15	94 ± 12
Global health/QoL	79 ± 17	75 ± 18	79 ± 19	78 ± 15	78 ± 13	81 ± 13
Fatigue	21 ± 21	30 ± 25	21 ± 23	20 ± 19	24 ± 20	20 ± 19
Nausea and vomiting	1 ± 6	3 ± 11	3 ± 13	2 ± 8	2 ± 8	2 ± 5
Pain	11 ± 19	16 ± 23	14 ± 19	12 ± 20	13 ± 22	9 ± 17
Dyspnea	12 ± 25	12 ± 22	11 ± 21	9 ± 18	12 ± 21	15 ± 22
Insomnia	24 ± 32	30 ± 28	19 ± 30	23 ± 26	26 ± 26	16 ± 24
Appetite loss	2 ± 8	4 ± 15	3 ± 10	6 ± 14	2 ± 8	3 ± 10
Constipation	2 ± 8	8 ± 18	4 ± 15	3 ± 9	6 ± 15	7 ± 18
Diarrhea	6 ± 17	12 ± 20	8 ± 17	6 ± 16	13 ± 22	13 ± 24
Financial difficulties	1 ± 5	4 ± 14	4 ± 13	3 ± 10	3 ± 10	2 ± 8
EORTC QLQ-PR25						
Urinary symptoms/problems	18 ± 17	34 ± 23	14 ± 12	19 ± 15	22 ± 18	17 ± 15
Bowel symptoms/function	5 ± 12	11 ± 13	7 ± 11	5 ± 8	9 ± 11	8 ± 9
Treatment-related symptoms	6 ± 8	9 ± 10	10 ± 11	9 ± 12	13 ± 13	12 ± 12
Sexual functioning	26 ± 21	25 ± 20	28 ± 22	23 ± 20	24 ± 20	26 ± 22
Sexual activity	69 ± 22	56 ± 25	57 ± 23	66 ± 22	60 ± 29	51 ± 25

* EORTC QLQ-C30(+3) = European Organization for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module.

In RAND-36 a higher score reflects a better health. In EORTC QLQ-C30(+3) and QLQ-PR25 a high score reflects a high level of symptoms or functioning or quality of life.

Table 3 shows significant differences between the two treatment groups for QoL changes for baseline vs. 1 month. The IMRT 76-Gy treatment group demonstrated less deterioration in QoL for all scales and items compared with the conformal 70-Gy group. For baseline vs. 6 months, no significant differences between the treatment groups were seen. Analyzed separately, the conformal 70-Gy group revealed a temporary significant and clinically relevant deterioration in 'pain', 'role functioning', and 'urinary symptoms'. For the IMRT 76-Gy group only a clinically relevant improvement in the QoL item 'change in health' existed after 1 month, which was improved further at 6 months after treatment.

Table 3. Quality of life items with significant differences over time between treatment groups.

Item	QoL change over time		Difference between groups (*p* value)
	Conformal 70Gy without gold markers (*n* = 78)	IMRT 76Gy with gold markers (*n* = 92)	
Baseline versus 1 month			
RAND-36			
Social functioning	- 7.4 (ns)	3.5 (ns)	0.006
Pain	-10.3 (<0.0001)*	- 1.0 (ns)	0.01
Change in health	- 8.7 (0.01)	9.9 (0.002)*	<0.0001
EORTC QLQ-C30(+3)			
Physical functioning	- 5.7 (0.002)	- 0.3 (ns)	0.006
Role functioning	-12.2 (<0.0001)*	- 1.8 (ns)	0.006
EORTC QLQ-PR25			
Urinary symptoms/function	16.4 (<0.0001)*	2.5 (ns)	<0.0001
Baseline versus 6 months			
RAND-36			
Social functioning	4.3 (ns)	7.6 (<0.0001)	ns
Pain	- 4.2 (ns)	3.5 (ns)	ns
Change in health	6.0 (ns)	18.7 (<0.0001)*	ns
EORTC QLQ-C30(+3)			
Physical functioning	- 2.3 (ns)	- 0.7 (ns)	ns
Role functioning	- 2.2 (ns)	1.5 (ns)	ns
EORTC QLQ-PR25			
Urinary symptoms/function	- 4.0 (ns)	- 2.3 (ns)	ns

ns = not significant. Other abbreviations as in *Tables 1 and 2*.

Values are change over time (*p* value). $p \leq .01$ is considered significant. In RAND-36, a higher score eflects better health. In EORTC QLQ-C30(+3) and QLQ-PR25, a high score reflects a high level of symptoms or functioning or quality of life.

* Significant change in score of ≥ 10 points (clinically relevant).

For the QoL items without significant differences between the treatment groups, the QoL changes over time (baseline vs. 1 month and baseline vs. 6 months) for both treatment groups together are presented in *Table 4*. The comparison of health-related QoL at baseline with the measurement at 1 month revealed a significant decrease of ≥ 10 points in 'physical role restriction' and 'sexual activity'. The clinically relevant deteriorated 'sexual activity' remained after 6 months, and, furthermore, a clinically relevant improvement in QoL concerning 'emotional role restriction' was seen comparing QoL scores at baseline with scores after 6 months.

Table 4. Change in time in quality of life items without significant between-group differences over time, for the 170 patients in de IMRT and conformal groups combined.

Item	Baseline versus 1 month	Baseline versus 6 months
RAND-36		
Physical functioning	- 2.8 (ns)	- 1.0 (ns)
Physical role restriction	-15.0 (<0.0001)*	1.3 (ns)
Emotional role restriction	3.5 (ns)	10.6 (0.002)*
Mental health	1.9 (ns)	3.8 (0.002)
Vitality	- 3.7 (0.01)	0.2 (ns)
General health	- 0.3 (ns)	0.7 (ns)
EORTC QLQ-C30(+3)		
Emotional functioning	7.6 (<0.0001)	8.5 (<0.0001)
Cognitive functioning	- 2.4 (ns)	- 2.8 (ns)
Social functioning	- 2.3 (ns)	2.3 (ns)
Global health/QoL	- 1.7 (ns)	1.8 (ns)
Fatigue	6.0 (<0.0001)	- 0.4 (ns)
Nausea and vomiting	1.3 (ns)	1.2 (ns)
Pain	3.0 (ns)	-0.5 (ns)
Dyspnea	1.3 (ns)	2.5 (ns)
Insomnia	- 1.1 (ns)	- 6.2 (ns)
Appetite loss	- 0.8 (ns)	- 1.3 (ns)
Constipation	4.4 (0.002)	3.3 (ns)
Diarrhea	6.8 (0.002)	4.1 (ns)
Financial difficulties	2.1 (ns)	1.3 (ns)
EORTC QLQ-PR25		
Bowel symptoms/function	5.1 (<0.0001)	2.1 (ns)
Treatment-related symptoms	3.2 (<0.0001)	3.5 (<0.0001)
Sexual functioning	- 0.1 (ns)	2.7 (ns)
Sexual activity	- 9.8 (<0.0001)*	-13.9 (<0.0001)*

Abbreviations as in *Tables 1, 2, and 3*.

Values are change over time (*p* value). $p \leq 0.01$ is considered significant.

In EORTC QLQ-C30(+3) and QLQ-PR25, a high score reflects a high level of symptoms or functioning or quality of life. In RAND-36, a higher score reflects better health.

* Significant change in score of ≥ 10 points (clinically relevant).

With regard to the small number of patients (n = 33) treated with adjuvant ADT in our study, analysis of variance for repeated measures showed no significant difference between patients treated with ADT compared with patients without ADT, except for 'treatment-related symptoms' and 'change in health' (p = .003 and p = .004, respectively). Patients treated with ADT demonstrated more 'treatment-related symptoms' after 1 month and a better 'change in health' after 6 months.
For a sufficient internal consistency, a Cronbach's α coefficient of $\geq$ .70 is required. Reliability analysis resulted in a Cronbach's α value of $\geq$ .70 for all scales, except 'cognitive' and 'social functioning' in EORTC QLQ-C30(+3) (α between .58 and .76) and 'bowel' and 'treatment-related symptoms/problems', 'sexual functioning', and 'sexual activity' in QLQ-PR25 (α between .52 and .74).

Discussion

A comparison between patients treated with 70 Gy conformal radiotherapy without position verification by fiducial markers and patients receiving 76 Gy IMRT with the use of fiducial markers revealed no significant decrease in QoL changes over time with increased radiation dose. Our study even demonstrated significantly improved QoL changes for the high-dose radiotherapy group between baseline and 1 month in several domains compared with the 70-Gy treatment group.
In the conformal 70-Gy group, a temporary worsening of QoL occurred in terms of 'pain' and 'urinary symptoms'. The bladder and rectum of the 76-Gy treatment group might have received less radiation owing to the IMRT technique and improved position verification, resulting in less 'pain' and 'urinary symptoms' for the 76-Gy group compared with the conformal 70-Gy group. Because physical complaints limit the daily role activity, QoL concerning 'role functioning' showed a temporary decrease for the 70-Gy group as well. A significant decrease in QoL in terms of 'change in health' occurred for the 70-Gy group after 1 month, as opposed to a significant increase for the 76-Gy group. For the 70-Gy group the deterioration of this QoL item was restored after 6 months, and for the 76-Gy group the 'change in health' improved even further. Physical complaints explain the difference between the treatment groups. The "response shift" mechanism (referring to a changed internal standard on which patients base their perception, due to a life-threatening disease (Breetveld *et al*., 1991)) may be involved in the improvement of 'change in health' over time.
The cross-sectional study by Little *et al*. (2003), without validated QoL questionnaires and baseline measurements, revealed no significant differences in QoL between patients receiving 78 vs. 70 Gy. Kupelian *et al*. (2001) made a cross-sectional comparison between hypofractionated IMRT (70 Gy in 2.5-Gy fractions) and conformal radiotherapy (78 Gy in 2-Gy fractions) and also reported no significant difference in QoL. In accordance with our results, Namiki *et al*. (2006) demonstrated better QoL

for only 30 patients treated with 76 Gy IMRT compared with 70 Gy conventional and conformal radiotherapy. The relative increase in QoL might be an effect of less radiation damage due to improved radiation techniques. Intensity-modulated radiotherapy improves dose conformality of the target and reduces unnecessary radiation to surrounding normal tissue. Furthermore, position verification by fiducial markers in the prostate minimizes patient setup errors during treatment and leads to less rectal and bladder irradiation (van der Heide *et al*., 2007). Our report shows that improved technical possibilities, regarding IMRT and accurate position verification, provide the possibility of dose escalation with comparable and sometimes even improved QoL results. Therefore, to minimize the risk of QoL deterioration, an accurate radiotherapy technique should be used when further increasing the radiation dose to the prostate.
The evaluation of QoL changes over time for items without a group difference (*Table 4*) revealed a temporary worsening of QoL after 1 month in terms of 'physical role restriction', probably due to passing "mild" side effects. After 6 months, all patients showed a significant increase in 'emotional role restriction', which might be explained by (1) patients having time to adapt to the situation, (2) response shift mechanism, and (3) decreasing fear of recurrence and death over time (De Graeff *et al*., 2000).
For all patients a significantly worse QoL in terms of 'sexual activity' occurred after 1 month and persisted after 6 months. For both treatment groups the radiation damage causing erection or ejaculation dysfunction seems to be permanent. Scores of 'sexual activity' were only available for 30 patients in the IMRT 76-Gy group and 28 patients in the conformal 70-Gy group. The Dutch translation of the EORTC QLQ-PR25 requests an answer to the questions concerning 'sexual activity' only when patients had been sexually active in the last 4 weeks, thus causing a low response rate for this scale and perhaps leading to under or overestimated QoL in terms of 'sexual activity'. However, persistent reduction of 'sexual activity' after external beam radiotherapy has been extensively reported (Namiki *et al*., 2006; Little *et al*., 2003; Wahlgren *et al*., 2004; Korfage *et al*., 2005; Yoshimura *et al*., 2004; van Andel *et al*., 2004). The temporary significant worsening of QoL in terms of 'vitality', 'fatigue', 'constipation', 'diarrhea', and 'bowel symptoms' with a mean score difference of <10 points is the result of the acute side effects of external beam radiotherapy treatment (e.g., bowel complaints, pain, and fatigue) (Peeters *et al*., 2005a; Little *et al*., 2003; Wahlgren *et al*., 2004; Bacon *et al*., 2001).
Despite a prospective design including baseline measurements and using validated QoL questionnaires, the present study has some limitations. The study was not randomized, and patients were treated in a sequential fashion over different periods, which might have influenced the QoL changes over time. However, at baseline no significant differences between the two groups were present with regard to patient characteristics. Furthermore, at baseline the QoL measures did not differ significantly between groups. Late rectal and bladder toxicity usually occurs within 3 years of

completion of radiotherapy (2), and our short-term follow-up of 6 months may mask significant toxicity and consequently possible QoL changes. Longer follow-up is required to verify the comparable and perhaps even improved QoL after high dose vs. normal-dose external beam radiotherapy. In the future, it will be important for randomized studies of further dose escalation to measure QoL, as well as toxicity, with long-term follow-up.

Conclusion

Compared with 70 Gy conformal radiotherapy, no deterioration in QoL occurred when increasing the radiation dose for locally advanced prostate cancer, probably owing to such improved technical possibilities as IMRT and more accurate position verification. For several QoL items the dose escalated IMRT group even showed statistically significant and clinically relevant improved QoL changes over time compared with the conformal 70-Gy treatment group. Therefore, this study suggests that IMRT and accurate position verification provide the possibility of increasing the radiation dose for prostate cancer without deterioration in QoL. Longer follow-up is necessary to investigate long-term QoL after an increased radiation dose.

Chapter 7

Long-term quality of life

This chapter has been published as:

I.M. Lips, C.H. van Gils, U.A. van der Heide, A.E. Boeken Kruger and M. van Vulpen.

Health-related quality of life 3 years after high-dose intensity-modulated radiotherapy with gold fiducial marker-based position verification.

BJU International. 2009; 103: 762-7.

Abstract

Purpose

To evaluate the change in quality of life (QoL) 3 years after high-dose intensity-modulated radiotherapy (IMRT) using gold fiducial marker-based position verification in patients with locally advanced prostate cancer.

Methods and Materials

Between October 2003 and November 2004, 95 patients with locally advanced prostate cancer were treated with 76 Gy IMRT with gold-fiducial marker-based position verification. Before treatment (baseline) and 1, 6 and 36 months after RT the QoL was measured using the RAND-36, the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQC30(+ 3)) and the prostate tumor-specific module (EORTC QLQ-PR25). Changes in QoL with time of ≥ 10 points were considered clinically relevant.

Results

After 3 years there was a statistically significant improvement in QoL for 'emotional role restriction' and 'functioning', 'change in health', 'mental health' and 'insomnia', compared with baseline. 'Emotional role restriction' increased by > 10 points and was therefore clinically relevant, while all other differences were of < 10 points. There was a statistically significant deterioration of QoL after 3 years in 'physical' and 'cognitive functioning', 'bowel symptoms/function' and 'sexual activity'. Only the 'sexual activity' QoL score changed by 12 points and was therefore the only meaningful deterioration in QoL at 3 years after treatment.

Conclusion

IMRT and accurate position verification provide the possibility to deliver a high irradiation dose to the prostate without clinically relevant deterioration in long-term QoL, except for a persistent decrease in 'sexual activity' score.

Introduction

External beam radiotherapy is one of the treatment options for localized and locally advanced prostate cancer. Several randomized trials showed an improvement in biochemical relapse-free survival rate with an increase in irradiation dose (Peeters *et al*., 2006; Pollack *et al*., 2002; Zietman *et al*., 2005). Further increases in dose are expected to lead to further improvement (Eade *et al*., 2007). Especially patients with an unfavorable prognosis might benefit from an increased radiation dose (Pollack *et al*., 2002). By increasing the radiation dose, the risk of genitourinary and gastrointestinal toxicity also increases (Cheung *et al*., 2007). To evaluate treatment, not only toxicity but also the impact on quality of life (QoL) is important (Litwin *et al*., 1999).

Intensity-modulated radiotherapy (IMRT) can be used to increase the dose to the prostate while the dose to the organs at risk remains acceptable, because this technique provides better coverage of the target and sparing of the organs at risk. Furthermore, daily verification of the position of the prostate, using fiducial gold markers, improves the precision of the treatment, and therefore the organs at risk might receive less radiation dose (van Vulpen *et al*., 2008). The theoretical advantages of IMRT dose distributions and the reduction of the positioning errors with fiducial markers has been established. However, not many clinical results of IMRT in combination with accurate position verification have been published (Veldeman *et al*., 2008).

Previously, we reported that improved technical possibilities prevented a deterioration in QoL when the radiation dose was increased. Patients treated with 76 Gy IMRT with accurate position verification even had clinically relevant improvements in QoL over a period of 6 months, compared with a group treated with 70 Gy conformal RT (Lips *et al*., 2007). Yoshimura *et al.* (2007) described comparable QoL outcomes between IMRT and conformal RT. However, concerns have been raised about the short-term follow-up of both studies, because late bladder and rectal toxicity can develop several years after completing RT (Gardner *et al*., 2002). Late rectal toxicity usually occurs within 3 years of completing RT and bladder toxicity even continues to develop thereafter. Only one study reported the QoL scores at 3 years after IMRT, but this involved only six patients (Junius *et al*., 2007). A few studies described the QoL scores 2 years after IMRT (Namiki *et al*., 2006; Kupelian *et al*., 2001; Sanda *et al*., 2008).

Good-quality QoL research has to meet certain conditions; not only are large groups of patients important, but it is also important to measure the patients' perception of their health and ability to function in life, because physician assessment of treatment-induced complaints differs from morbidity reported by patients (Lilleby *et al*., 1999). Other conditions for good quality QoL research include validated QoL questionnaires including an organ-specific module, and a longitudinal study design including baseline scores, which is essential in this older patient group (Osoba *et al*., 2005).

In this prospective and longitudinal study, we measured long-term QoL, using a

prostate-specific module, of patients treated with IMRT of 76 Gy, using fiducial marker-based position verification. For this patient group we previously reported good QoL results at 1 and 6 months after RT, and in the present study we investigated the change in QoL between the measurement before RT (baseline) and 3 years afterward.

Methods and materials

Between October 2003 and November 2004, 116 patients with mainly locally advanced prostate cancer were treated with IMRT. The prostate was delineated on CT and a margin of 8 mm was applied to the prostate and seminal vesicles to create a planning target volume (PTV). Patients received IMRT with a five-beam 'step-and-shoot' technique and 10-MV photons. A mean dose of 76 Gy in 35 fractions of 2.17 Gy was prescribed to the PTV and 95% of the prescribed dose (= 72 Gy) was prescribed to 99% of the PTV. The dose in the part of the PTV overlapping the rectum and bladder was limited so that ≤ 5% of the rectum and 10% of the bladder would receive a dose of ≥ 72 Gy (Nederveen *et al*., 2001; van der Heide *et al*., 2007). For position verification, three fiducial gold markers were transrectally implanted inside the prostate, using antibiotic prophylaxis. During treatment the fiducial gold markers were visualized using portal images of the first fields of all five beam directions, using the iView-GT amorphous silicon flat-panel detector (Elekta Ltd, Crawley, UK). The position of the fiducial gold markers can be easily and reliable detected, allowing for fast and accurate determination of the position of the prostate. Daily imaging of the fiducial markers was used for off-line position verification, using an adapted 'shrinking-action-level' protocol (van der Heide *et al*., 2007).

General health-related QoL was measured using the RAND-36 generic health survey (Hornbrook *et al*., 1995), cancer-specific QoL using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQC30(+ 3)) (Aaronson *et al*., 1993), and the prostate tumor-specific QoL using the EORTC prostate cancer module (QLQ-PR25) (Borghede *et al*., 1996). All questionnaires are well validated and widely used in oncology trials (Henderson *et al*., 2004).

Scales and items of these questionnaires range in score from 0 to 100. For RAND-36 and for the 'global' QoL and functional scales of the EORTC questionnaires, a high score represents a high level of QoL and better functioning. For the symptom/problem items of the EORTC questionnaires, higher scores represent a higher level of symptoms and consequently a worse QoL. A change of 10% (or in general, 0.5 standard deviation (SD)) of the scale breadth is perceptible to patients as a meaningful change, and a change in QoL of ≥ 10 points is therefore considered clinically relevant (Osoba *et al*., 2005).

The first questionnaire was presented to the patient before treatment at the Department of Radiation Oncology; at 1, 6 and 36 months after completing the

treatment the measurements were repeated. For all patients treated between 2001 and 2004 at our department with 76 Gy IMRT and fiducial marker-based position verification, the pre-treatment, acute and late toxicity was scored (Lips *et al*., 2008). Ninety-five patients were included in the study, because 15 were lost to follow-up and six died within the 3 years of follow-up. All questionnaires had a high response rate, except for questions about sexual activity.

Because the data were normally distributed a paired sample *t*-test was used to examine differences in QoL scores between the time points (baseline vs. 3 years). The QoL changes between baseline, 1 and 6 months were analyzed previously (Lips *et al*., 2007). Test results with a $p \leq .01$ were considered statistically significant, to account for multiple comparisons. Cronbach's coefficient α was calculated to determine internal consistency and reliability of the questionnaires.

Results

The characteristics of the 95 patients included in the study are shown in *Table 1*; most had locally advanced prostate cancer (tumor stage T3).

Table 1. The characteristics of the 95 patients.

Characteristic	
Age at baseline, years	
Mean (range)	68 (46-79)
PSA level, ng/mL	
≤ 10	29 (31)
> 10-20	36 (38)
> 20	30 (32)
Gleason score	
2-6	48 (51)
7	28 (30)
8-10	19 (20)
Tumor stage	
T1	9 (10)
T2	4 (4)
T3	82 (86)
T4	0
Hormonal treatment	
None	59 (62)
Short-term(≈ 6 months)	26 (27)
Long-term(≤ 36 months)	10 (11)
TURP before radiotherapy	
Yes	8 (8)
No	87 (92)

TURP = transurethral resection of the prostate; PSA = prostate-specific antigen.
Values are number (percentage), unless otherwise noted

At the time of the study entry, no national guidelines for hormonal treatment were available, and therefore, only 36 patients received adjuvant androgen-deprivation therapy (ADT), which was divided into short-term (≈ 6 months) and long-term hormonal treatment (≤ 36 months). All patients had a World Health Organization performance score of ≤ 2.

During RT four patients developed grade 3 genitourinary toxicity, consisting of urinary frequency/urgency, urinary retention, haematuria and dysuria. One of these patients already had grade 3 complaints of urinary frequency before RT. There was no acute grade ≥ 3 gastrointestinal toxicity. Furthermore, one patient developed a urinary tract infection during RT that required intravenous antibiotic (grade 3).

Within 3 years after RT two patients developed grade 3 genitourinary toxicity and one developed severe radiation proctitis requiring several argon-plasma coagulations (grade 3).

Table 2 shows the mean (SD) of all QoL items before treatment (baseline), and 1, 6 and 36 months after treatment. Two-related samples tests between the QoL scores at baseline and after 3 years resulted in statistically significant differences between these time points for several QoL items. *Figure 1* shows the course in QoL of the QoL items with a significant difference after 3 years, vs. baseline scores. The RAND-36 questionnaire at 3 years showed a better QoL for 'emotional role restriction', 'mental health' and 'change in health', and worse 'physical functioning' than the baseline measurement. Only 'emotional role restriction' showed a change in QoL over time of > 10 points and was therefore considered as the only clinically meaningful change in QoL for this questionnaire (*Figure 1a*). The three statistically significant changes in QoL over time for the EORTC QLQ-C30 items were < 10 points and therefore not clinically relevant (*Figure 1b*). *Figure 1c* shows worse QoL for 'bowel symptoms/function' and 'sexual activity'. 'Sexual activity' showed a clinically relevant decrease of 12 points after 3 years; this QoL item was worse at 1 month after treatment and that persisted after 6 months and 3 years.

A subanalysis showed that there were no significant differences in QoL for 'sexual activity' between patients with and without ADT at baseline, with a mean (SD) QoL score of 54 (25) vs. 72 (22) at baseline and at 3 years after RT of 54 (32) vs. 56 (25). However, patients with no ADT had decreased 'sexual activity' scores between baseline and 3 years ($p = .004$), while patients with ADT had no deterioration in 'sexual activity' after 3 years compared with baseline. Unfortunately 'sexual activity' scores were only available for seven patients with ADT and 25 without.

We also compared the change in QoL for patients with and with no increase in toxicity between baseline and 3 years after RT. There were no clinically relevant and significant differences in the change in QoL for patients with an increase in gastrointestinal and genitourinary complaints compared with those with a decrease or no change in toxicity.

Table 2. The mean (SD) scores for scales and single items of each questionnaire.

Item	Baseline *n* = 95	1 month *n* = 85	6 months *n* = 85	3 years *n* = 95	*P* for difference, baseline vs. 3 years
RAND-36					
Physical functioning	87 ±14	85 ±17	86 ±16	83 ± 19	0.007
Social functioning	83 ±18	85 ±18	90 ±16	88 ± 18	ns
Physical role restriction	80 ±35	71 ±40	84 ±30	83 ± 32	ns
Emotional role restriction	79 ±35	87 ±30	92 ±25	90 ± 24	0.01*
Mental health	77 ±15	78 ±13	81 ±14	82 ± 15	0.001
Vitality	70 ±20	68 ±19	71 ±19	71 ± 22	ns
Pain	89 ±17	86 ±18	92 ±15	90 ± 19	ns
General health	68 ±16	67 ±16	70 ±18	66 ± 19	ns
Change in health	44 ±13	53 ±24	63 ±24	52 ± 16	0.002
EORTC QLQ-C30(+3)					
Physical functioning	89 ±13	88 ±13	89 ±14	87 ± 16	ns
Role functioning	88 ±18	86 ±20	90 ±18	88 ± 22	ns
Emotional functioning	80 ±15	88 ±16	89 ±16	88 ± 16	<0.0001
Cognitive functioning	91 ±14	87 ±18	87 ±18	85 ± 18	<0.0001
Social functioning	90 ±14	92 ±14	95 ±12	93 ± 17	ns
Global health/quality of life	79 ±14	79 ±12	82 ±13	80 ± 15	ns
Fatigue	19 ±19	23 ±21	18 ±18	21 ± 20	ns
Nausea and vomiting	2 ± 8	2 ± 7	1 ± 5	1 ± 6	ns
Pain	11 ±18	12 ±20	8 ±16	13 ± 21	ns
Dyspnea	8 ±18	11 ±21	13 ±21	13 ± 21	ns
Insomnia	21 ±25	24 ±25	15 ±24	14 ± 22	0.01
Appetite loss	5 ±13	2 ± 8	2 ± 7	3 ± 9	ns
Constipation	3 ±11	5 ±14	6 ±17	6 ± 14	ns
Diarrhea	5 ±16	13 ±21	11 ±22	8 ± 18	ns
Financial difficulties	3 ±11	4 ±10	2 ± 7	2 ± 9	ns
EORTC QLQ-PR25					
Urinary symptoms/problems	17 ±13	21 ±18	15 ±14	16 ± 13	ns
Bowel symptoms/function	5 ± 7	8 ±11	8 ±11	8 ± 12	0.004
Treatment-related symptoms	8 ±12	13 ±13	11 ±12	10 ± 10	ns
Sexual functioning	23 ±21	24 ±20	24 ±21	26 ± 21	ns
Sexual activity †	68 ±24	57 ±28	54 ±22	56 ± 26	0.01*

ns = not significant. EORTC QLQ-C30(+3) = European Organization for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module.

*Statistically significant and clinically relevant change in score between baseline and 3 years of ≥ 10 points. $P < .01$ is considered significant. †Sexual activity scores were available for only 32 patients.

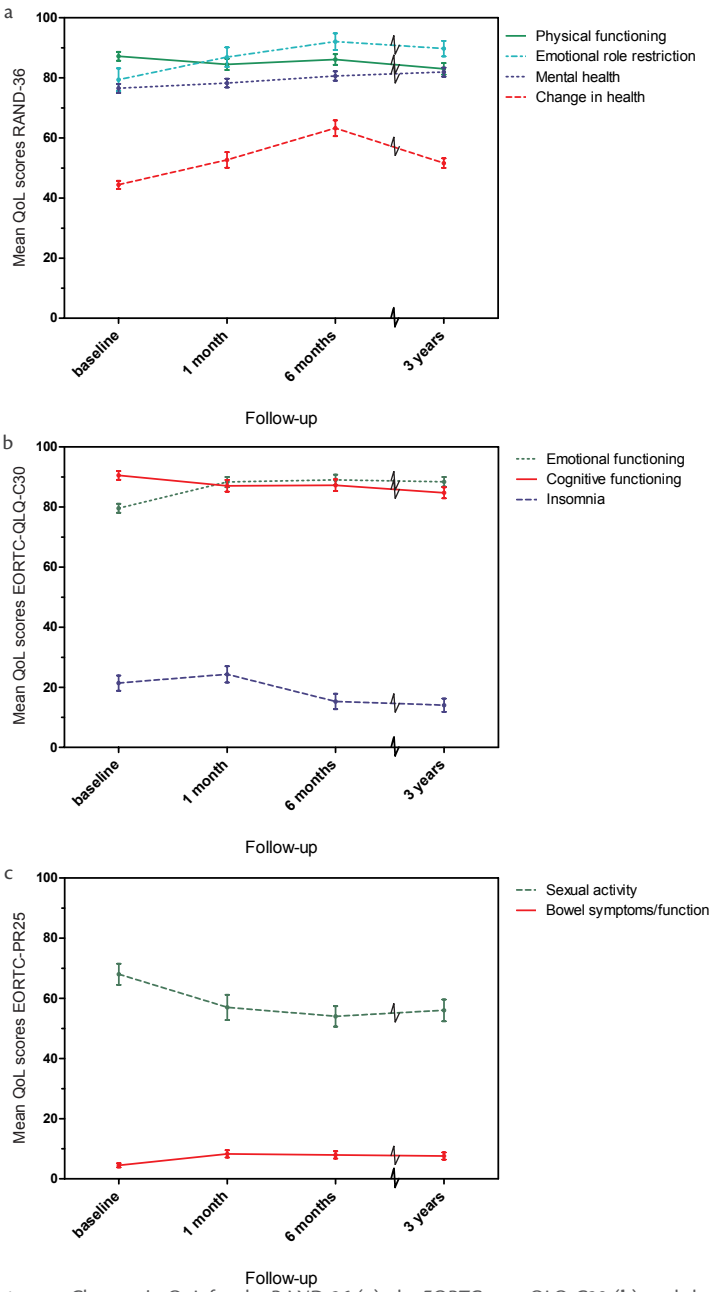

Figure 1. Changes in QoL for the RAND-36 (**a**), the EORTC core QLQ-C30 (**b**), and the EORTC-QLQ-PR25 (**c**) QoL items, with a significant difference between baseline and 3 years. Error bars represent the standard error. In the RAND-36, a higher score reflects better health. In EORTC QLQ-C30(+ 3) and QLQ-PR25, a higher score reflects a high level of symptoms or functioning or QoL.

For sufficient internal consistency, a Cronbach's α coefficient of $\geq .70$ is required. Reliability analysis gave a Cronbach's α of $\geq .70$ for all scales, except 'nausea' (.31–.73) and 'cognitive' and 'social functioning' (.52–.84) in the EORTC QLQ-C30(+ 3), and 'bowel function' (.33–.64), 'treatment-related symptoms/problems' (.50–.64) and 'sexual activity' (.58–.77) in the QLQ-PR25.

The present study, including 95 patients, was well powered to detect QoL differences of 10 points. In 95% of the scales the SD was 14–19 (*Table 2*). The power to detect a difference of 10 points between baseline and 3 years as statistically significant with 95 patients and a two-sided α of .01 is 100% (when using a SD of 14) and 99.7% (when using a SD of 19).

Discussion

To our knowledge, this is the first study to evaluate the change in QoL for a large group of patients 3 years after 76 Gy IMRT using gold-fiducial marker-based position verification. Previously, we reported that, compared with 70-Gy conformal RT, there was no deterioration in QoL after 6 months. In the present study, there was no meaningful deterioration of QoL 3 years after completing RT from the QoL before RT, except for the QoL item 'sexual activity'. Better planning of the target volumes and sparing of the organs at risk using IMRT and adequate position verification might have resulted in little radiation damage and consequently no clinically relevant effect of the side-effects on QoL.

The previous evaluation of the short-term QoL changes after 76 Gy IMRT (Lips *et al*., 2007) showed a significant and meaningful increase in 'emotional role restriction' after 6 months. This increase in QoL score remained after 3 years, with a difference of 11 points from baseline. A decreasing fear of recurrence and death, and having a long time to adapt to the situation, might be involved in the persistent increase of this QoL item.

The short-term analysis also showed that after 6 months there was an increase in 'change in health' score (Lips *et al*., 2007). The increase in QoL for 'change in health' between baseline and 3 years was significant ($p = .002$), but not clinically relevant (< 10 points). However, the change in QoL between 6 months and 3 years was significant, with a clinically relevant decrease of 11 points. The improvement in 'change in health' after 6 months was attributed to the 'response shift' mechanism (referring to a changed internal standard on which patients base their perception, due to a life-threatening disease (Breetvelt *et al*., 1991)). The worsening of 'change in health' thereafter might be due to ageing, as Aaronson *et al.* (1998) reported lower QoL scores for older respondents (> 70 years) than younger respondents in The Netherlands.

QoL for 'sexual activity' had already decreased by 1 month after RT. The persistent deterioration in QoL might be due to late radiation effects and has been reported previously (Namiki *et al*., 2006; Pinkawa *et al*., 2009; Little *et al*., 2003), but also the

patients' age and comorbities might have influenced sexual activity (Lue *et al*., 2000). Previous reports suggest an arteriogenic pathology as the main cause for erectile dysfunction after RT (Incrocci *et al*., 2002). The Dutch translation of the EORTC QLQ-PR25 requests patients to complete the questions about 'sexual activity' only when they were sexually active in the last 4 weeks. For that reason the 'sexual activity' scores were available for only 32 patients, which could have led to under- or overestimated QoL scores.

Sanda *et al.* (2008) reported long-lasting symptoms involving sexuality due to androgen suppression of limited duration. In the present study, patients treated with ADT had no deterioration in 'sexual activity' between baseline and 3 years, but they seemed to have worse 'sexual activity' scores before RT. At 3 years after RT there was no difference in 'sexual activity' between patients with and without ADT. This might be due to the few patients treated with ADT in our study. However, Yoshimura *et al.* (2007) even reported an improvement in sexual function during the follow-up, probably resulting from reduced sexual function before the start of RT, as a result of neoadjuvant hormone therapy.

In the present study, the increase in gastrointestinal and genitourinary toxicity did not significantly affect the change in QoL. This could be because the incidence of severe toxicity was very low, but the absence of a correlation between QoL and toxicity was reported previously (Lilleby *et al*., 1999; Staff *et al*., 2003). The increase in toxicity might be too small to be detected by the QoL questionnaires, but another explanation might be that patients had time to adapt to the RT-induced complaints and developed coping skills (Breetvelt *et al*., 1991).

After a follow-up of 6 months, there were no differences in QoL scores between IMRT and conformal RT, or improved QoL scores in patients treated with IMRT (Lips *et al*., 2007; Yoshimura *et al*., 2007). At ≈ 2 years after RT, Kupelian *et al.* (2001) reported no differences in QoL between a dose of 70 Gy in 2.5 Gy fractions using IMRT and conformal RT. However, a less solid cross-sectional design was used and only 24 patients were included. In accordance with our findings, Namiki *et al.* (2006) reported, for 12 patients at 2 years after monotherapy with 76 Gy IMRT, no significant difference in QoL from the baseline level. Recently Sanda *et al.* (2008) reported worse bowel and sexual QoL scores 2 years after external beam RT (either IMRT or conformal RT) than baseline scores. Unfortunately no technical specifications and treatment dose were described. Only Junius *et al.* (2007) measured the long-term QoL after IMRT; at 3 years after treatment with 66 Gy in 2.64 fractions there were no clinically relevant QoL changes for six patients, except an increase in 'emotional' and decrease in 'cognitive functioning', which was also seen in the present patients.

We used a high RT dose of 76 Gy because it is expected to lead to high biochemical control rates (Pollack *et al*., 2002; Peeters *et al*., 2006; Zietman *et al*., 2005). In the present study, we conclude that our treatment is well tolerated and causes no significant

clinical deterioration in QoL, but a longer follow-up is required to determine the biochemical or clinical failure in our patient group.

Conclusion

In conclusion, 3 years after IMRT with 76 Gy using fiducial gold marker-based position verification, all QoL items, except 'sexual activity', had no significant and clinically relevant deterioration compared with the QoL scores before the start of RT. The QoL for 'emotional role restriction' improved after 6 months and remained high 3 years after RT. The satisfactory QoL results 3 years after treatment might be a consequence of the few side-effects after treatment with IMRT and accurate position verification. IMRT is especially suitable for avoiding organs at risk, e.g. rectum and bladder, while a high dose of radiation is delivered to the prostate. In combination with daily position verification using fiducial markers, the organs at risk might have received little irradiation, leading to fewer complaints during and after treatment.

Chapter 8

FLAME-trial

This chapter has been submitted as:

I.M. Lips, U.A. van der Heide, K. Haustermans, F. Pos, E.N. van Lin, S.P.G. Franken, A.N.T.J. Kotte, C.H. van Gils and M. van Vulpen.

Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial).

Trials 2011

Abstract

Background

The treatment results of external beam radiotherapy for intermediate and high risk prostate cancer patients are poor with five-year biochemical relapse rates of approximately 35%. Several randomized trials have shown that dose escalation to the entire prostate improves biochemical disease free survival. However, further dose escalation to the whole gland is limited due to an unacceptable high risk of acute and late toxicity. Moreover, local recurrences often originate in the macroscopic tumor, so boosting the radiation dose at the macroscopic tumor within the prostate might increase local control. A reduction of distant metastases and improved survival can be expected by reducing local failure. The aim of this study is to investigate the benefit of an ablative microboost to the macroscopic tumor within the prostate in patients treated with external beam radiotherapy for prostate cancer.

Methods/Design

The FLAME-trial (**F**ocal **L**esion **A**blative **M**icroboost in prostat**E** cancer) is a single blind randomized controlled phase III trial. We aim to include 566 patients (283 per treatment arm) with intermediate or high risk adenocarcinoma of the prostate who are scheduled for external beam radiotherapy using fiducial markers for position verification. With this number of patients, the expected increase in five-year freedom from biochemical failure rate of 10% can be detected with a power of 80%. Patients allocated to the standard arm receive a dose of 77 Gy in 35 fractions to the entire prostate and patients in the experimental arm receive 77 Gy to the entire prostate and an additional integrated microboost to the macroscopic tumor of 95 Gy in 35 fractions. The secondary outcome measures include treatment-related toxicity, quality of life and disease-specific survival. Furthermore, by localizing the recurrent tumors within the prostate during follow-up and correlating this with the delivered dose, we can obtain accurate dose-effect information for both the macroscopic tumor and subclinical disease in prostate cancer. The rationale, study design and preliminary results of the first 50 patients included are described.

Trial registration

This study is registered at ClinicalTrials.gov: NCT01168479

Introduction

Localised prostate cancer can be treated by radical prostatectomy, brachytherapy or external beam radiotherapy. For low risk tumors the results of external beam radiotherapy are comparable to radical prostatectomy and brachytherapy with freedom from biochemical failure rates approximating 95% after 5- to 10-year follow-up (Lu-Yao *et al*., 1997). The outcome for intermediate and high risk patients is worse with freedom from biochemical failure ranging between 60% and 75% after 5- to 10-years follow-up (Widmark *et al*., 2009; Peeters *et al*., 2006; Pollack *et al*., 2002).

Several randomized trials have proven that dose escalation in external beam radiotherapy improves the biochemical disease free survival (Pollack *et al*., 2002; Peeters *et al*., 2006; Zietman *et al*., 2005; Dearnaley *et al*., 2007). Pollack *et al*. (2002) compared the efficacy of 70 Gy versus 78 Gy on 305 patients with stage T1-3 prostate cancer. For patients with a pre-treatment PSA > 10 ng/mL the freedom from biochemical failure rate at five year was 43% versus 62% respectively, in favor of the higher dose group. The randomized trial from Peeters *et al.* (2006) compared 68 Gy versus 78 Gy on 669 patients with stage T1-4 prostate cancer. Five-year freedom from failure rate was significantly improved from 54% to 64%. Further increase in dose is considered to improve the treatment results even further (Peeters *et al*., 2006; Pollack *et al*., 2002; Zelefsky *et al*., 2002). Moreover, local recurrences often occur at the site of the primary macroscopic tumor (Pucar *et al*., 2007; Cellini *et al*., 2002), so boosting the radiation dose to the macroscopic tumor might increase the local control. An improvement in distant metastases and survival can be expected by reducing local failure, due to the relationship between these treatment outcomes (Coen *et al*., 2002; Kupelian *et al*., 2008; Jacob *et al*., 2004).

Dose escalation to the entire prostate is not considered feasible by reason of unacceptable toxicity risks. This problem can be overcome by partial boosting strategies. In this way, the macroscopic tumor can be irradiated to a very high dose, while the dose constraints to the rectum and bladder can be maintained (Lips *et al*., 2009a; van Lin *et al*., 2006). This approach is being used to deliver a microboost to the dominant tumor region in a number of pilot studies (Miralbell *et al*., 2010; Gaudet *et al*., 2010; Fonteyne *et al*., 2008; De Meerleer *et al*., 2005). The dose to the macroscopic tumor is increasingly escalated. The highest dose was delivered in a feasibility study by Singh *et al.* (2007) who treated 3 patients with an ablative dose of 95 Gy to the macroscopic tumor within the prostate with no severe toxicity (≥ grade 3).

To investigate the benefit of an ablative microboost to the macroscopic tumor within the prostate, we started a randomized controlled trial (the FLAME-trial: **F**ocal **L**esion **A**blative **M**icroboost in prostat**E** cancer, clinical trials: study protocol number NCT01168479). The purpose of this trial is to assess whether a dose escalation to the macroscopic tumor increases the five-year freedom from biochemical failure rate. Furthermore, we will assess the influence of this dose escalation on treatment-related toxicity, quality of life (QoL) and disease-specific survival.

Methods / design

Study design

The FLAME-trial is a multicenter randomized controlled trial. Patients are recruited during the intake consultation at the Department of Radiation Oncology in one of the participating centers. After giving informed consent, patients are randomized to either the standard arm or to the experimental arm. Patients in the standard arm receive radiotherapy according to the current gold standard, namely 77 Gy in 35 fractions of 2.2 Gy to the whole prostate. Patients in the experimental arm receive an additional integrated microboost to the macroscopic tumor to a total dose of 95 Gy in 35 fractions.

To ensure unbiased assessment of QoL measurements, the patients are blinded for the actual treatment given (receiving an ablative microboost or not). The treating physician needs to be informed about the actual treatment, to be able to judge the treatment plans. This is unlikely to influence the assessment of the objective primary endpoint of the trial.

Patients

Men with histological proven intermediate or high risk adenocarcinoma of the prostate, who will receive external beam radiotherapy using optimal position verification with implanted fiducial gold markers, are eligible for the study. Intermediate or high risk is defined according to the currently internationally accepted criteria from Ash *et al.* (2000) as patients having one (intermediate risk) or more (high risk) factor of T2b-c, or Gleason score = 7, or initial prostate-specific antigen (iPSA) 10-20 ng/mL, or having one or more (high risk) factors of: T3, or Gleason score >7, or iPSA> 20 ng/mL. Patients with low risk tumors are not included in this study, because the treatment outcome for this group is already excellent with a 10-year prostate cancer-specific survival approximating 95% (3).

Exclusion criteria are: previous pelvic irradiation, previous prostatectomy, World Health Organization (WHO) score > 2, International Prostate Symptom Score (IPSS) ≥ 20, transurethral resection of the prostate (TURP) within 3 months from start of the treatment, general contraindications for MRI (i.e. cardiac pacemaker, metal implants or history of severe allergic reaction after administration of contrast agent) or the use of anti-coagulants that cannot be discontinued for the gold markers implantation.

The study protocol is approved by the Medical Ethical Committees of the participating hospitals. Written informed consent will be obtained from all patients.

Randomization

Randomization is performed by an independent trial center. If a patient meets the inclusion criteria and has provided informed consent, the physician contacts the trial center. To prevent randomly occurring differences in important prognostic factors across the two randomized groups, the randomization is stratified by TURP, hormonal treatment and by centre. A TURP prior to radiotherapy is associated with significantly more late genitourinary toxicity (Peeters *et al*., 2005a; Sandhu *et al*., 2000). The likely mechanism of increased late toxicity is related to the relative devascularisation of the urethra after TURP and the decreased capability of the mucosa to repair sublethal damage after radiotherapy (Sandhu *et al*., 2000). Hormonal treatment is a prognostic unfavorable factor for late genitourinary side effects (Peeters *et al*., 2005; Schultheiss *et al*., 1997) and erectile impotence (van der Wielen *et al*., 2007; Zelefsky *et al*., 1999; Turner *et al*., 1999). Furthermore, a protective effect for hormonal treatment is reported for acute gastrointestinal side effects (Peeters *et al*., 2005a; Christie *et al*., 2005; Vavassori *et al*., 2007). To prevent small numbers of patients in a particular hospital from all receiving, by chance, the same treatment, the hospital is chosen as one of the factors for stratified randomization as well.

Time schedule

Between October 2009 and October 2010, 50 patients were included at the Department of Radiation Oncology of the University Medical Center Utrecht. Based on this accrual and the fact that patients will also be recruited at other participating centers, we expect that the accrual will be completed within 5 years from start.

Radiotherapy

To minimize the positioning errors during treatment all patients are treated with an on-line position verification protocol using implanted fiducial gold markers (Lips *et al*., 2009a; Moman *et al*., 2010; van der Heide *et al*., 2007). Radiotherapy will be delivered with advanced radiotherapy techniques to be able to create adequate dose distributions.

A mean dose of 77 Gy in 35 fraction of 2.2 Gy is prescribed to the entire prostate gland (Nederveen *et al*., 2001; Lips *et al*., 2008). According to the current standard of care, the radiation margin around the prostate is 4 to 8 mm (van der Heide *et al*., 2007; Meijer *et al*., 2008). The dose in the part of the PTV overlapping the rectum and bladder is limited to keep the risk of severe gastrointestinal and genitourinary toxicity acceptable. To provide an accurate delineation of the prostate gland with respect to the surrounding tissues (Rasch *et al*., 1999; Usmani *et al*., 2010), the prostate is delineated on a computed tomography (CT) scan combined with a registered magnetic resonance

imaging (MRI) scan. The rectum is contoured from the anus or ischial tuberosities to the rectosigmoid flexure or sacroiliac joints. The bladder is completely outlined from the bladder neck to the dome.

Intervention

Patients randomized to the experimental arm are treated with the current gold standard of 77 Gy to the whole prostate and in addition receive an integrated microboost to the macroscopic tumor to reach a total dose of 95 Gy in 35 fractions of 2.7 Gy. To delineate the macroscopic tumor within the prostate, different MR imaging techniques are used. In addition to an anatomic T2 weighted sequence, a combination of the following functional imaging modalities can be used (Groenendaal *et al*., 2010; van der Heide *et al*., 2011). Dynamic contrast-enhanced (DCE)-MRI gives a characterization of the tissue vasculature (Padhani *et al*., 2002). With this technique it is possible to detect areas with macroscopic tumor, because tumors tend to contain higher density of leaky blood vessels. With diffusion-weighted imaging (DWI)-MRI the mobility of water molecules is measured (Hosseinzadeh *et al*., 2004). Tumor tissue can be identified on DWI-MRI, because in tumor the extracellular volume is reduced, leading to reduced water diffusion in tumor tissue. MR spectroscopic imaging (MRS) provides metabolic information with cancer regions showing higher choline and lower citrate levels (Scheidler *et al*., 1999).

Primary endpoint

To evaluate whether the addition of an ablative microboost to the macroscopic tumor within the prostate increases the five-year freedom from biochemical failure rate compared to the current standard of care. Biochemical failure is defined according to the Phoenix definition as a PSA rise of 2 ng/mL above the nadir PSA level (Roach *et al*., 2006). The PSA level is measured every six months until 10 years after treatment.

Secondary endpoints

Secondary endpoints are treatment-related toxicity, QoL and disease-specific survival. Treatment-related toxicity is measured by the Common Toxicity Criteria for adverse events version 3.0 (CTCAE) (Trotti *et al*., 2003). The following adverse events are scored: urinary frequency/urgency, urinary retention, bladder spasms, urinary incontinence, genitourinary hemorrhage, dysuria, rectal or perirectal pain, proctitis, diarrhea, flatulence hemorrhoids, anal incontinence, erectile dysfunction. The physician in

attendance scores the complaints before treatment, acute toxicity (weekly during treatment and 4 weeks after treatment) and late toxicity (every six months until 10 years after treatment). All symptoms are registered even if they occur only on one single occasion. Grade > 2 is considered severe toxicity.
General health-related QoL is measured using the RAND-36 generic health survey (Hornbrook *et al*., 1995), cancer-specific QoL using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30)(Aaronson *et al*., 1993), and the prostate tumor-specific QoL using the EORTC prostate cancer module (QLQ-PR25) (Borghede *et al*., 1996). The RAND-36 assesses physical and social functioning, physical and emotional role restriction, mental health, vitality, pain, general health and change in health. The EORTC QLQ-C30 contains five functional scales, three symptoms scales, a global QoL scale and six single-items. The EORTC QLQ-PR25 assesses urinary, bowel and sexual symptoms and functioning, and the side effects of hormonal treatment. The first questionnaire is handed over to the patient one week before treatment at the Department of Radiation Oncology and the next questionnaires are sent to the patient every six months until 10 years after the completion of the treatment.
For disease-specific survival, death with metastases is considered a death caused by the disease.

Safety

An independent data safety monitoring board (DSMB) will evaluate the toxicity and clinical outcome. The DSMB receives an update of the toxicity in total and per treatment arm every 3 months. Serious toxicity, defined as any acute or late toxicity requiring surgical intervention, any grade 4 toxicity, and any not-transient (duration >6 months) late toxicities grade 3, will immediately be reported to the DSMB. An overview of the percentage of biochemical recurrences per treatment arm together with the evaluated number of patients per arm will be sent to the DSMB yearly as well as a statistical comparison of the incidence of serious and less serious toxicities in the two arms. The DSMB decides on stopping or continuing the trial. Exact rules cannot be specified in advance, but an increase in the incidence of toxicity (grade 3-4) with 5% or a smaller, but statistically significant increase, are among the reasons to consider stopping the trial. The DSMB can decide to prematurely stop the trial in case the improvement in outcome in the experimental aim is higher than anticipated in the trial design.

Sample size considerations

The statistical power of the study was calculated for the primary endpoint (five-year freedom from biochemical failure). Based on data of two randomized clinical trials

(Peeters *et al*., 2006; Pollack *et al*., 2002) reporting the treatment results of patients treated with a radiation dose equal to the dose of the standard arm of our trial, we expect that the five-year freedom from biochemical failure of the standard arm will be approximately 64%. We expect that an additional ablative microboost to the macroscopic tumor will increase this number with at least 10%. With a statistical power of 80% to detect this increase from 64% to 74% (p <.05, one-sided), we require 283 patients in the standard arm and 283 patients in the experimental arm.

Data analysis

All analysis will be performed according to the intention-to-treat principle. Cox proportional hazards regression will be used to analyze differences in biochemical failure and disease-specific survival between the two treatment arms. Survival curves will be estimated by the Kaplan-Meier technique. Differences between both groups in the incidence of acute side-effects will be tested with the Chi square test. The incidence of late toxicity will be analyzed actuarially with the Kaplan-Meier method, the log rank test and Cox regression analysis. To examine differences in QoL between the two treatment groups, the proportion of patients with clinically meaningful changes in QoL (i.e. the proportions with improved, stable, and deteriorated scores) at the different time points will be calculated. A change of 10% (or in general, 0.5 standard deviation) of the scale width is perceptible to patients as a meaningful change (Osoba *et al*., 2005). Differences between the two treatment groups in the three categories of responses (improved, stable and deteriorated QoL) will be tested with the Chi square test. Because of the multiple comparisons for the QoL items, the p value is set at a conservative .01 for determining statistical significance (Movsas *et al*., 2009). For all other analyses, which do not include the QoL measures, a p value of <.05 is considered statistically significant.

Preliminary results

The first 50 patients included in the FLAME- trial, were treated between October 2009 and October 2010 at the Department of Radiation Oncology of the UMC Utrecht. All patients received seven-beam intensity-modulated radiotherapy (IMRT). A mean dose of 77 Gy in 35 fraction of 2.2 Gy was prescribed to the planning target volume (PTV) and at least 70 Gy was prescribed to 99% of the PTV (Nederveen *et al*., 2001; Lips *et al*., 2008). We aimed at limiting the dose to the rectum and bladder so that ≤ 5% of the rectum and ≤ 10% of the bladder receives a dose of ≥ 72 Gy. Furthermore, a volume of 1 cc of the bladder and rectum receives a maximum dose of 80 Gy and 77 Gy, respectively, and ≤ 50% of the rectum receives a dose of ≥ 50 Gy (Lips *et al*., 2008). All treatment plans were checked by two investigators (UAH and MV) before start of the treatment. The beam directions were 0º, 50º, 100º, 155º, 205º, 260º and 310º.

The location of the fiducial markers was determined by visualizing the markers using portal images of the first segment of the 0º beam and the 260º beam. A difference of more than 1 mm compared to the planning-CT was corrected on-line. After 5 fractions the average rotation of the prostate was calculated. A rotation of 3º around the anterior-posterior or the left-right axis and a rotation of 6º around the cranio-caudal axis was corrected by changing the gantry or table rotation or the collimator angle. The portal images of the first segment of the remaining beams were used to determine the average intrafraction prostate motion (Kotte *et al*., 2007). For each patient the individual intrafraction and remaining rotational errors were used to calculate the actual delivered doses to the target and the organs at risk.

The patients were treated in supine position. One hour before the pre-treatment planning scans and the radiotherapy sessions, patients were instructed to drink 500 ml to create a full bladder. A full bladder during radiotherapy results in a decreased amount of bladder volume in the high dose region and a lower dose to bowel loops compared to treatment with an empty bladder (Pinkawa *et al*., 2006). No antiflatulent diet or laxative was prescribed (Lips *et al*., 2011). When the rectum filling on CT and MRI differed considerably, a new CT or MRI scan was performed, to minimize the registration uncertainty between these two imaging modalities.

For delineation of the macroscopic tumor within the prostate, defined as the gross tumor volume (GTV), anatomical and functional imaging was performed on a 3 Tesla MRI scanner (Achieva Philips Medical Systems, Best, the Netherlands). The exam included 3 anatomical scans: a multislice T2 weighted turbo spin echo (TSE) sequence (TR/TE 8400/120 ms), a T1 weighted sequence and a balanced turbo field echo (TFE) sequence (TR/TE 2.8/1.4 ms, FOV = 25 cm, slice thickness = 1 mm). The DCE-MRI protocol consists of a 3D spoiled gradient echo sequence (TR/TE 4.0/1.0 ms, flip angle 6º). Scans were repeated 120 times at 2.4s interval. A single acquisition consisted of 20 axial slices of 2.5 mm. The field of view is 40 x 40 cm^2, the reconstruction matrix 160x160. For contrast enhancement, 0.1 mg/kg body weight gadobutrol (1.0M (Gadovist, Schering) was injected intraveneously. Trace-kinetics modeling was done using the Tofts model (Tofts *et al*., 1999) resulting in 3D maps of the transfer constant K^{trans}. Diffusion-weighted imaging scans were performed using a multislice single shot SE-EPI sequence (FOV = 38 cm, slice thickness = 3 mm, intersection gap = 1mm, TR/TE = 5000/54ms, acquisition matrix = 152 x 107, b values = 0, 300, 5000, 100 s/mm^2). The delineation of the GTV was done by the treating physician and checked by two investigators before start of the treatment. To account for possible extracapsular extension, the delineation of the macroscopic tumor was expanded with an extra margin of 4 mm (Chao *et al*., 2006). *Figure 1* shows an example of the delineation of the GTV and the dose distribution for a patient in the experimental arm. *Table 1* shows the patient characteristics of the first 50 patients. Twenty-three patients were randomized into the experimental arm and 27 into the standard arm.

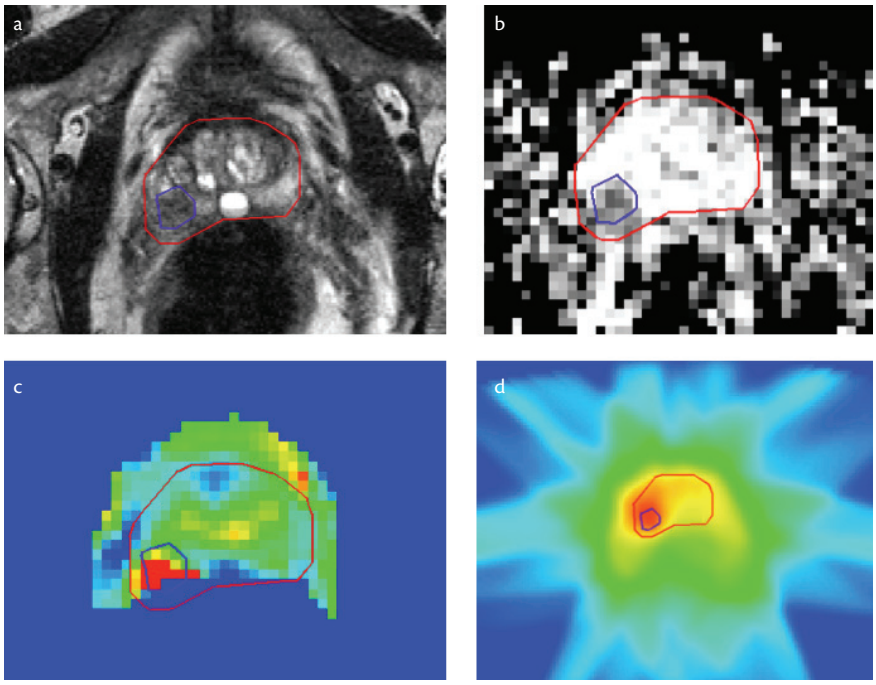

Figure 1. Example of the delineation of the macroscopic tumor area (GTV) on T2 weighted MRI (**a**), an apparent diffusion coefficient map derived from diffusion-weighted MRI (**b**) and a K^{trans} parameter map obtained from dynamic contrast-enhanced MRI (**c**) and the dose distribution (**d**).

Discussion

The FLAME-trial is designed to investigate the effect of an ablative microboost to the macroscopic tumor for patients treated with external beam radiotherapy for prostate cancer.

Previous studies demonstrated that the rate of toxicity after high dose external beam radiotherapy with the use of accurate position verification is low and consequently high QoL is reported (Lips *et al*., 2008; Lips *et al*., 2007; Lips *et al*., 2009b; Marchand *et al*., 2010; Zelefsky *et al*., 2006). Planning studies showed that an ablative microboost to the macroscopic tumor is theoretically feasible within the currently used dose constraints for rectum and bladder (Pickett *et al*., 1999; Xia *et al*., 2001; van Lin *et al*., 2006). Furthermore, a feasibility study of Singh *et al*. (2007) reported excellent early toxicity after simultaneous integrated IMRT boost of 95 Gy to the intraprostatic lesions As a result, with the use of optimal position verification combined with the currently used dose constraints, the toxicity in the experimental treatment arm with the ablative microboost of 95 Gy is expected to be acceptable.

Table 1. Patient characteristics.

	Patients included in the FLAME-trial (n = 50)	
Characteristic	**No.**	**%**
Age, years		
Median	70.5	
Upper and lower quartile	66.8 – 73.0	
Tumor stage		
T1	3	6
T2	8	16
T3	38	76
T4	1	2
Tumor grade		
Gleason score 4-6	14	28
Gleason score 7	17	34
Gleason score 8-10	19	38
iPSA, ng/mL		
Median	14.3	
Upper and lower quartile	9.9 – 21.0	
Cardiovascular disease	33	66
Diabetes mellitus	5	10
Prescription of long term hormonal therapy	26	52
History of TURP	10	20

TURP = transurethral resection of the prostate; iPSA = initial prostate-specific antigen.

Previous trials demonstrated a biochemical benefit of dose escalation. However, up to now none of the dose escalation trials were able to detect an improvement in disease specific or overall survival. However, all trials were designed for biochemical survival instead of overall or disease-specific survival due to the natural behavior of prostate cancer. For this reason the FLAME-trial is also powered for biochemical disease free survival. An improvement in local control without a proven benefit in overall survival is only acceptable when severe toxicity remains limited. Furthermore, to establish whether a benefit in biochemical failure free survival also counterbalances the negative aspects of dose escalation, such as a small increase in toxicity, it is important that QoL is taken into account. Therefore, repeated QoL measurements are performed in patients included in this trial.

The precise delineation of the macroscopic tumor within the prostate is a topic of ongoing research (Groenendaal *et al*., 2010; van der Heide *et al*., 2011; Langer *et al*., 2009). In the FLAME-trial the delineation of the macroscopic tumor is based on anatomical and functional imaging according to the current opinion. The different imaging techniques might show conflicting results about the boundaries of the

macroscopic tumor area, leading to difficult delineation decisions. Therefore, it is of major importance to investigate the precise location of a recurrence and to establish what dose was prescribed to that location. When a patient shows a rising PSA without distant metastases, DCE-MRI and MRS can be used to detect the location of recurrent prostate cancer (van Vulpen *et al*., 2009; De Visschere *et al*., 2010; Kim *et al*., 2010; Rouviere *et al*., 2007; Haider *et al*., 2008). By correlating the dose distribution of the initial radiotherapy with the location of a local recurrence, accurate dose-effect information can be obtained. The dose-effect data generated from this analysis will help us to evaluate the required dose for each cancer subunit and to provide a better understanding of the different imaging techniques. The dose distributions of the patients treated in the experimental arm, are inhomogeneous with very low and very high delivered doses, and for that reason provide important dose-effect information to create a reliable dose-effect curve.

A randomized study design is indicated to resolve the problem of confounding effects. To our knowledge, no other randomized controlled trials are being performed to investigate the benefit of an ablative microboost to the macroscopic tumor in prostate cancer patients. Beside Singh *et al.* (2007), three other groups performed a pilot study in which a microboost to the dominant tumor region was delivered. Miralbell, *et al.* (2010) treated 50 patients, after 64-64.4 Gy in 1.8-2 Gy fractions to the whole prostate, with a hypofractionated boost of 2 fractions of 5 to 8 Gy to the dominant tumor region, delineated by anatomical imaging. After a median follow up time of 63 months, a 5-year biochemical disease-free and disease-specific survival of 98% and 100%, respectively, were reported with acceptable long-term toxicity. Gaudet *et al*. (2010) selectively delivered a brachytherapy hyperdosage of ≥ 216 Gy (150% of the prescribed dose) to the macroscopic tumor, defined according to positive areas on sextant biopsy, in 70 patients with localized prostate cancer treated with permanent seed prostate implant. No difference in acute or late toxicities compared to 120 patients with a standard plan were seen. Fonteyne *et al*. (2008) and De Meerleer *et al.* (2005) performed the largest trial in which 230 patients were treated with a mean dose of 81-82 Gy to a dominant lesion, defined by T2 weighted MRI or MRI plus spectroscopy. With the use of IMRT and daily ultra-sound based prostate positioning, the acute toxicity remained low with no grade 3 or 4 acute gastrointestinal toxicity and 7% grade 3 genitourinary toxicity.

Analyses of the actual delivered dose in the first 50 patients included in the FLAME-trial, revealed that it is possible to deliver a high dose to the macroscopic tumor area without compromising the dose constraints for the nearby organs at risk. The influence of the remaining intrafraction and rotational errors using an on-line position verification protocol is minimal.

Conclusion

The aim of the FLAME-trial is to assess in patients treated with external beam radiotherapy for prostate cancer, the potential benefit of an additional ablative microboost to the macroscopic tumor on biochemical control. In addition, the subgroup of patients that will develop a local recurrence within the prostate after treatment can be used to obtain accurate dose-effect information for both the dominant lesion and subclinical disease in prostate cancer.

The study protocol was approved by the Medical Ethical Committee. The trial is registered at ClinicalTrials.gov (Registration identification number: NCT01168479; URL: http://clinicaltrials.gov/ct2/show/NCT01168479)

Chapter 9

Summary and general discussion

This thesis addressed the potential for dose escalation in patients treated with external beam radiotherapy for prostate cancer. For low risk prostate cancer patients the treatment outcome is already excellent (Lu-Yao *et al*., 1997), however for intermediate and high risk patients outcome is insufficient and improvement is desired (Peeters *et al*., 2006; Pollack *et al*., 2002; Widmark *et al*., 2009). Previous dose escalation trials found that an increase in dose to the prostate resulted in an improved biochemical free survival (Peeters *et al*., 2006; Pollack *et al*., 2002; Zietman *et al*., 2005; Kupelian *et al*., 2005; Dearnaley *et al*., 2007). Further dose escalation is expected to lead to further improvement (Morgan *et al*., 2007; Zelefsky *et al*., 2002; Nahum *et al*., 2003). However dose escalation to the whole prostate is not considered achievable by reason of unacceptable toxicity risks. Recurrences often occur in the primary tumor (Pucar *et al*., 2007; Cellini *et al*., 2002), so therefore an ablative microboost to the primary tumor might be beneficial. To establish whether this approach is feasible and safe, several questions were answered. Firstly, the position uncertainties during treatment were investigated by exploring the effect of interfraction errors (chapter 2) on complex dose distributions with an integrated microboost to the macroscopic tumor and by looking at the intrafraction prostate motion and whether the use of a laxative (chapter 3) or a diet (chapter 4) could reduce this error. Secondly, the expected toxicity (chapter 5) and quality of life (QoL) (chapter 6 and 7) after treatment with an escalated dose to the tumor was explored. Finally, the design of the FLAME-trial, a randomized clinical trial to investigate the benefit of an ablative microboost to the macroscopic tumor within the prostate, was presented (chapter 8).

Interfraction motion

To compensate for variations in treatment position and internal organ motion, a margin around the target is added. The treatment volume is thereby increased and an overlap with the organs at risk is created, which increases the risk of treatment-related toxicity. Thus for delivery of an ablative microboost within the prostate while the dose to the organs at risk remains acceptable, a small margin is desirable. The size of a margin is determined by the systematic and random errors and can be calculated with margin recipes (van Herk *et al*., 2000; Stroom *et al*., 1999). The margin rules were derived for homogenous, three-dimensional conformal radiotherapy, while the complex intensity-modulated radiotherapy (IMRT) dose distributions with an ablative microboost to the macroscopic tumor are inhomogeneous, nonspherical and have small target shapes and less steep penumbras. In chapter 2 the dose distributions for prostate IMRT with an integrated boost to the macroscopic tumors for 19 patients were recalculated with the use of their individual translational and rotational errors measured during treatment. The use of an on-line protocol to correct the translational errors led to an improvement of the dose coverage in comparison to the use of an off-line protocol. However patients with large systematic rotational errors demonstrated a substantial

decrease in dose, irrespective of the use of an off-line or on-line correction protocol. Especially when the macroscopic tumor is located far from the rotation point, a correction of the rotational errors is necessary to establish a sufficient coverage of this volume. Rotation corrections can be done in clinical practice by several ways, such as rotation of the tabletop using robotic couches (van Herten *et al*., 2008), collimator and gantry angle adjustments (Yue *et al*., 2008; Rijkhorst *et al*., 2007; Yue *et al*., 2006), or using adaptive radiotherapy techniques (Court *et al*., 2005). However, correction of the rotations determined by implanted markers assumes the prostate, including the seminal vesicles, to be a rigid body. The seminal vesicles are flexible and have been demonstrated to move independently of the prostate and the markers (van der Wielen *et al*., 2008; Smitsmans *et al*., 2011; Liang *et al*., 2009). Marker-based rotation correction might therefore lead to an incorrect dose delivery at the location of the seminal vesicles (Mutanga *et al*., 2010). Consequently prudence is called for correction of rotational errors, determined with marker-based image guidance, when the seminal vesicles are part of the target volume. On the other hand the dose coverage of the macroscopic tumor might be more important than the dose to the seminal vesicles, which gives good reason for correction of marker-based rotational errors for inhomogeneous dose distributions with an ablative microboost to the tumor.

The results described in chapter 2 revealed that the required margin to account for the geometric uncertainties was smaller than expected by the simple margin recipe. This can be explained by the very shallow dose gradients that are created in complex IMRT plans, which should not be excluded in the margin recipe for complex IMRT. Furthermore, the inhomogeneous dose distribution can cause a compensation of an underdosage by an overdosage of the target over the 35 fractions. So for complex IMRT dose distributions, the required margin to account for the random interfraction position errors becomes very small. Before the margins in clinical practice can be reduced, the magnitude of other uncertainties has to be determined. For example the intrafraction motion, prostate deformation, reliability of the repositioning systems, inaccuracy of marker detection, uncertainty on determination of the center of gravity of the seeds within the computer tomography (CT) scan and uncertainty in the delineation of the target, have to be taken into account.

Another uncertainty that will become relevant when the margins become very small is the extracapsular extension of the macroscopic tumor within the prostate. In prostatectomy specimens with extracapsular extension, the median distance of the microscopic extension was 2.4 mm and 5% of the patients demonstrate an extension of > 4 to 5 mm beyond the capsule. In patients with a prostate-specific antigen (PSA) level of ≥ 10 ng/ml and Gleason score ≥ 7, this risk may exceed even 20%. The extracapsular extension occurred primarily posterolaterally (Chao *et al*., 2006). A target with a large extracapsular extension could potentially be missed during highly accurate radiation delivery using small treatment margins. To compensate for this uncertainty, adding an extra margin around the macroscopic tumor should be considered.

Intrafraction motion

Because the interfraction position uncertainties can be minimized with on-line position verification, the minimization of intrafraction motion gains interest. The hypothesis is that gas pockets and changing rectal filling are the major causes of intrafraction motion. Therefore several groups started to prescribe daily laxative and a diet to reduce the amount of gas pockets and create a more stable rectal filling. Other studies investigating the possibilities to reduce the intrafraction motion (Smitsmans *et al*., 2008; Wu *et al*., 2001; Madsen *et al*., 2003; Ogino *et al*., 2008; Padhani *et al*., 1999) often used a combination of interventions (such as a laxative in combination with a diet and fixed treatment times), which makes it impossible to determine the solitary effect of each intervention. To be able to distinguish the effect of a diet from the use of a laxative, two studies were performed to investigate the effect of each intervention separately. In chapter 3 the results of a double-blind, placebo-controlled randomized trial showed that magnesium oxide did not reduce the intrafraction motion during external beam radiotherapy for prostate cancer. Chapter 4 describes that after the introduction of a diet during radiotherapy in clinical practice the intrafraction prostate motion increased.

The absent of a benefit from a diet or a laxative concerning the reduction of the intrafraction prostate motion might be explained by the age of our patient population. Epidemiologic studies demonstrated a high prevalence of constipation and laxative use in the elderly with a suggested prevalence for constipation as high as 50% (Higgins *et al*., 2004). The exact biologic mechanism is unclear, but advancing aged is associated with altered mechanical properties, structural changes and altered control of the pelvic floor (Bouras *et al*., 2009). To keep a regular bowel movement, many elderly have their specific food pattern (Bouras *et al*., 2009). A dietary advice or other interference with the rectal activity for example by a laxative, might disturb this precarious balance, leading to more variation in rectal filling instead of the intended stable rectal filling. This leads to the conclusion that manipulation of the rectal filling in the rather elder prostate cancer patients is problematic.

Another explanation for the failure in reducing the intrafraction prostate motion, could be that the hypothesis of intrafraction motion being caused by gas and rectal filling is not correct. Despite studies that suggest gas as a major source (Nederveen *et al*., 2002; Nichol *et al*., 2010; Ghilezan *et al*., 2005), the major source of intrafraction motion might be different, for example due to clenching of the pelvic muscle, bladder filling, leg motion or pelvic rotation (Padhani *et al*., 1999; Nederveen *et al*., 2002; O'Doherty *et al*., 2006; Mah *et al*., 2002). So therefore, the exact cause of intrafraction prostate movement needs to be investigated further. Once the mechanism is well understood, we might be able to come up with a theoretical new solution for the problem. Before such an attempt, to reduce the intrafraction motion, can be

introduced in clinical practice, the benefit should be proven first. The exploratory analyses in chapter 3 demonstrated a trend towards worsened QoL and slightly more toxicity in patients using magnesium oxide compared to the control group. So there can be harm in trying, due to the physical discomfort consisting of diarrhea and the burden of daily intake of medication. For that reason, the theoretical benefit of an intervention, without clinical evidence, is not sufficient for daily use in clinical practice. Furthermore, it has to be verified whether an advantage in reducing the intrafraction motion also counterbalances the negative aspect of a method.

Because a reduction of the intrafraction motion with a diet or a laxative is not possible, an improvement of the position verification would be a way to handle the problem. Correcting of the intrafraction motion can be established with real-time on-line position verification using for example a calypso monitoring system (Liu *et al*., 2010; van Os *et al*., 2009), an intrafraction stereographic targeting method (van Os *et al*., 2009) or a magnetic resonance imaging (MRI)-accelerator which is currently being developed (Raaymakers *et al*., 2009; Lagendijk *et al*., 2008). However, the question is whether these techniques are necessary and what the size of the problem is for radiotherapy treatments with an ablative microboost to the macroscopic lesion within the prostate? The effect of the random interfraction error was demonstrated to be small for inhomogeneous IMRT dose distributions with an integrated microboost to the tumor (chapter 2); therefore the influence of the random intrafraction motion is also expected to be minimal for these complex dose distributions. According to literature, the residual systematic and random error due to intrafraction prostate motion is small (Litzenberg *et al*., 2006; Su *et al*., 2010; Kotte *et al*., 2007) and a margin of at least 2 mm would be sufficient to account for the intrafraction prostate motion. In the future, when all other treatment uncertainties are being minimized and margins can therefore be reduced, the intrafraction motion might become a clinically relevant problem which should be dealt with.

Other treatment uncertainties

Besides the interfraction and intrafraction errors, another important treatment uncertainty to consider is the delineation error. The variation in target delineation is a systematic error and consequently has a large impact on the accuracy of the dose delivery. Several studies reported both intra- and interobserver variability for the delineation of the prostate volume (Rasch *et al*., 1999; Fiorino *et al*., 1998; Steenbakkers *et al*., 2003; Parker *et al*., 2003). With the introduction of multimodality imaging, the delineation of the prostate has become more precise. Addition of magnetic MRI to CT for delineation of the prostate and the organs at risk, decreased the interobserver delineation variation and reduced the delineated prostate volume (Rasch *et al*., 1999; Rasch *et al*., 2005; Villeirs *et al*., 2005; Usmani *et al*., 2010). The use of the lateral

projection in addition to the transversal planes has demonstrated to improve prostate contouring (McLaughlin *et al*., 2010) and the additional use of axial and coronal MR scans improves the localization accuracy of the prostatic apex and the anterior aspect of the rectum (Debois *et al*., 1999). The use of multiple image modalities does require adequate image registration. High quality image registration avoids loss of information and is able to keep high resolution in multiple planes, which makes it possible to delineate the target in three dimensions. Furthermore, the delineation of the prostate might further improve by, for example, teaching interventions (Szumacher *et al*., 2010), the use of an atlas (Gregoire *et al*., 2003) and modification of the input user interface device (MITDOG, 2010).

The geometric variability from delineation is mainly caused by the fact that target volumes are manually defined by human users. Therefore, further improvement in the quality of target volume delineation can be expected from (semi)automatic delineation tools (Mahr *et al*., 1999; Bellon *et al*., 1997). Semi-automated methods have being suggested to reduce the intraobserver and interobserver variability in comparison with totally manual delineation (Bellon *et al*., 1997). An automatic delineation method using non-rigid registration of a set of prelabeled atlas images demonstrated that an automatic delineation of the prostate was possible in three-dimensional MR scan with a variation close to the manual interobserver variation (Klein *et al*., 2008). The use of automatic delineation tools can reduce the variability, but the interpretation of the images remains uncertain. Therefore, even if the delineation inaccuracies can be minimized, adding a margin to incorporate the effect of the delineation error is required.

Beside a minimization of the delineation uncertainty of the whole prostate, a dose escalation to the macroscopic tumor within the prostate requests a precise delineation of the macroscopic tumor lesions. Many studies focused on the sensitivity and specificity to detect prostate cancer with the use of functional imaging. The combination of different imaging techniques led to high accuracy for detecting and staging prostate cancer with specificity and sensitivity values up to 96% (Fütterer *et al*., 2006a; Fütterer *et al*., 2006b; Seitz *et al*., 2009; Kim *et al*., 2005; Hara *et al*., 2005). The imaging techniques showed their ability to accurate diagnose prostate cancer, however the potential of these new techniques for tumor delineation in radiotherapy still needs further exploration (Groenendaal *et al*., 2010; Langer *et al*., 2009; van der Heide *et al*., 2011). For delineation purposes, it is important to identify the boundaries of the macroscopic tumor. When delineation is done manually, the conflicting findings on the different imaging modalities (Groenendaal *et al*., 2010) might give difficult delineation decisions and lead to very large intra- and interobserver variations. Up to now, no quantification of the uncertainty from manual delineation of the macroscopic tumor within the prostate has been reported in literature.

The observer variability can be removed and reproducible results can be obtained by automated analysis of the multiple images. Tumor prediction models can be created based on the combination of different imaging modalities by using for example voxel-wise analyses (Langer *et al*., 2009) or supervised support vector machine methods (Ozer *et al*., 2010). In this way, areas with high tumor risk can be identified and being incorporated in the dose painting concept (Haie-Meder *et al*., 2005).
In the FLAME-trial the delineation of the macroscopic tumor is based on anatomical and functional imaging according to the current opinion. Therefore, it is of major importance to investigate the precise location of a recurrence and to establish what dose was prescribed to that location. When a patient shows a rising PSA without distant metastases, DCE-MRI and MRS can be used to detect the location of a prostate cancer recurrence (van Vulpen *et al*., 2009; De Visschere *et al*., 2010; Kim *et al*., 2010; Rouviere *et al*., 2007; Haider *et al*., 2008). A suspected lesion needs to be histological proven by biopsy, which can be done with the use of MRI-guided biopsy techniques. By correlating the dose distribution of the initial radiotherapy with the location of a local recurrence, accurate dose-effect information can be obtained. The dose-effect data generated from this analysis will help us to evaluate the required dose for each cancer subunit and to provide a better understanding of the different imaging techniques. The dose distributions of the patients treated in the experimental arm of the FLAME-trial, are inhomogeneous with very low and very high delivered doses, and for that reason provide important dose-effect information to create a reliable dose-effect curve.

Toxicity

Especially for prostate cancer with in general good prognosis and small differences between the various treatment modalities, toxicity following treatment is of major importance. The previous dose escalation trials reported statistically significant higher incidences of acute and late gastrointestinal and genitourinary toxicity for patients treated with higher dose levels (Zietman *et al*., 2005; Dearnaley *et al*., 2007; Peeters *et al*., 2005a; Kuban *et al*., 2008; Syndikus *et al*., 2010; Al-Mamgani *et al*., 2008; Beckendorf *et al*., 2010; Beckendorf *et al*., 2004). Severe acute gastrointestinal complaints (grade ≥ 3) were reported in up to 5% of the patients and for genitourinary side effects this number was 13% (Peeters *et al*., 2005a; Beckendorf *et al*., 2004). Late grade ≥ 3 gastrointestinal toxicity occurred in approximately 6-8% of the patients treated in the high dose treatment arms and for genitourinary complaints percentages of grade ≥ 3 toxicity up to 13% were reported (Kuban *et al*., 2008; Syndikus *et al*., 2010; Al-Mamgani *et al*., 2008; Beckendorf *et al*., 2010).
Most patients included in these trials were treated using three-dimensional conformal radiotherapy and position verification based on the bony anatomy. Due to the influence of bladder and rectum changes, the prostate moves independently from the

bony anatomy. Therefore, alignment of the patient based on the bony anatomy, might lead to a deposition of the high irradiation dose to the organs at risk instead of the prostate. Furthermore, with three-dimensional technique less sharp dose gradients can be made, leading to less sparing of the surrounding normal tissue compared to more advanced IMRT technique. The hypothesis was that with the use of more accurate position verification and improved dose distributions using IMRT technique, the organs at risk will be better spared leading to less treatment-related toxicity.

Chapter 5 describes the acute and late toxicity for 331 patients treated at our department with a high dose of 76 Gy to the whole prostate using IMRT in combination with gold fiducial marker-based position verification. The use of these advanced radiotherapy technique led to only 3% grade 3 genitourinary acute toxicity and no grade ≥ 3 gastrointestinal acute toxicity. The severe grade ≥ 3 genitourinary and gastrointestinal toxicity rates were 4% and 1% respectively, including one patient with a rectal fistula and one patient with a severe hemorrhagic cystitis (both grade 4). There is no clear consensus of what is acceptable versus unacceptable toxicity (Swanson *et al*., 2011) and a comparison with literature is difficult due to the use of different toxicity scales. Often the general toxicity scoring systems such as the RTOG/EORTC are modified in one way or another (Swanson *et al*., 2011; Hanlon *et al*., 1997). To promote uniformly reporting of adverse events, the CTCAE version 3.0 have been developed (Trotti *et al*., 2003). This multimodality grading systems includes both acute and late effects and when using this grading system, a more reliable comparison of outcome between trails and institutions will become possible.

In general, the acute and late toxicity found in our study population was lower than described after conformal radiotherapy with position verification based on the bony anatomy (Zietman *et al*., 2005; Peeters *et al*., 2005a; Kuban *et al*., 2008; Syndikus *et al*., 2010; Al-Mamgani *et al*., 2008; Beckendorf *et al*., 2004; Peeters *et al*., 2005b; Michalski *et al*., 2010; Storey *et al*., 2000). The results of our study were confirmed by other articles reporting excellent toxicity results after IMRT with accurate position verification (Zelefsky *et al*., 2002; Guckenberger *et al*., 2010; Zelefsky *et al*., 2006; De Meerleer *et al*., 2004; De Meerleer *et al*., 2007; Skala *et al*., 2007; Marchand *et al*., 2010; Ghadjar *et al*., 2010; Ghadjar *et al*., 2008). Genitourinary side effects tend to accumulate and continue to emerge during the next 15 years after treatment (Schultheiss *et al*., 1997; Karlsdottir *et al*., 2008; Gardner *et al*., 2002); therefore a lengthened follow-up period might reveal an increase in the incidence of late toxicity. However with advancing age, urinary symptoms increase, so therefore it is difficult to determine whether late urinary symptoms are due to late radiation effects of result from the aging process. No unacceptable rates of severe toxicity after IMRT are expected, because the majority of severe side effects have been reported to occur within 3 years of treatment (Pollack *et al*., 2002; Zietman *et al*., 2005; Karlsdottir *et al*., 2008) and due to the consequently late damage effect (Heemsbergen *et al*., 2006), the low rates of acute toxicity reported after IMRT are prognostic for low incidences of late toxicity.

The ability to treat the whole prostate with a high dose while the organs at risk are adequately spared, demonstrated by acceptable treatment-related toxicity, provides the possibility to escalate the dose even further. When the dose to the macroscopic tumor area within the prostate is increased while the dose to the bladder and the rectum remains within the current used dose constraints, no unacceptable toxicity rates can be expected.

In our study, the two patients with highly severe late toxicity (grade 4) did not show abnormalities in the dose delivered to the bladder and the rectum, leading to the hypothesis that these patients were more sensitive for radiation-induced toxicity and that other factors than dose-related factors play a major role. In our patients, pre-treatment complaints seemed to be predictive for grade ≥ 2 toxicity, which has also been reported by others (Peeters *et al*., 2005b; Ghadjar *et al*., 2010; Ghadjar *et al*., 2008; Heemsbergen *et al*., 2006; Barnett *et al*., 2011; Koper *et al*., 2004). Other factors known to predispose patients to the development of toxicity include additional treatments, such as hormonal treatment and surgery (TURP, abdominal surgery), and patient characteristics such as age, smoking history, body mass index and comorbidities such as diabetes and hypertension. (Peeters *et al*., 2006; Schultheiss *et al*., 1997; Barnett *et al*., 2011; Huang *et al*., 2002; Cheung *et al*., 2004; Fiorino *et al*., 2008; Hanks *et al*., 2003; Herold *et al*., 1999; Al-Abany *et al*., 2005; Sanguineti *et al*., 2002; Skwarchuk *et al*., 2000).

Knowledge about the patient-related factors, influencing the development of radiation-induced toxicity, is increasingly important. The delivery of radiation has become more accurate, which makes it possible to control the dosimetric variables. When individual pre-treatment toxicity risks can be predicted, this might offer the possibility to use individual dose constraints and in this way avoid severe side effects after treatment. Therefore, further research should focus on understanding the mechanism behind the radiation-induced toxicity and investigate the patient-related factors that influence the normal tissue toxicity after radiotherapy (Swanson *et al*., 2011). In clinical practice, the pre-treatment toxicity risks could be incorporated in individual decision making using nomograms (Valdagni *et al*., 2011).

Quality of life

The use of IMRT and accurate position verification using fiducial markers showed excellent toxicity results. However even more important to establish whether a high dose can be delivered without severe toxicity, is to determine the influence on the patients QoL. It was unknown whether a patient can be treated with a high dose to the prostate without compromising the patient's QoL. Chapter 6 showed that patients treated with 76 Gy IMRT in combination with fiducial gold markers demonstrated no deterioration in QoL compared to a group of patients treated with 70 Gy conformal radiotherapy and position verification based on bony anatomy. The high dose group

even demonstrated clinically relevant improvements in QoL over a period of 6 months compared to the group treated with 70 Gy conformal radiotherapy. This suggests that less treatment-related toxicity was present in the 76 Gy group. So despite a high dose to the prostate, the dose to the organs at risk in this group might have been lower, owing to the IMRT technique and improved position verification.

Unfortunately the patients in chapter 6 were treated in a sequential fashion over different periods, which might have influenced the QoL changes over time and caused confounding. To minimize the effect of potential confounders, the benefit of IMRT could be investigated in a randomized clinical trail. No randomized trails have been performed to investigate the benefit of IMRT for prostate cancer, however two other prospective and longitudinal studies reported the advantage concerning better QoL with the use of IMRT compared to conventional radiotherapy (Yoshimura *et al*., 2007; Namiki *et al*., 2006). The benefit of IMRT compared to conventional radiotherapy for toxicity- related endpoints was proven in randomized controlled trials for head and neck and breast cancer (Staffurth *et al*., 2010). With this evidence and the excellent results after IMRT for prostate cancer, a randomized trial would not be ethical any more.

The QoL in chapter 6 was only measured 6 months after treatment and treatment-related toxicity continues to develop thereafter (Schultheiss *et al*., 1997; Karlsdottir *et al*., 2008; Gardner *et al*., 2002). So to determine whether the excellent QoL results 6 months after high dose IMRT in combination with fiducial marker-based position verification persisted when late toxicity occurred, the long-term QoL was measured and described in chapter 7. The comparison between baseline QoL and QoL 3 years after high dose 76 Gy IMRT revealed a clinically relevant increase in 'emotional role restriction' which was already present 6 months after treatment. This improvement in QoL after IMRT has been reported by others (Marchand *et al*., 2010; Junius *et al*., 2007) and might be explained by (1) patients having time to adapt to the situation, (2) response shift mechanism (referring to a changed internal standard on which patients base their perception, due to a life-threatening disease) and (3) decreasing fear of recurrence and death over time (de Graeff *et al*., 2000; Korfage *et al*., 2007). Furthermore the only clinically relevant deterioration after 3 years was seen for 'sexual activity'. This can be the results from radiation induced erectile dysfunction (van der Wielen *et al*., 2007), but also from the use of hormonal therapy, comorbidities and patients' age (Zelefsky *et al*., 1999; Pinkawa *et al*., 2009). The persistent reduction of 'sexual activity' after external beam radiotherapy has been extensively reported (Yoshimura *et al*., 2007; Namiki *et al*., 2011; Litwin *et al*., 1999; Little *et al*., 2003; Korfage *et al*., 2005). The returning of most QoL items to baseline level after delivery of high radiation dose to the prostate with IMRT is confirmed by others up to 5 years after treatment (Marchand *et al*., 2010; Namiki *et al*., 2009).

The satisfactory QoL results after high dose radiotherapy for prostate cancer using IMRT and accurate position verification, suggests that further dose escalation is possible without a clinically relevant deterioration in QoL when the combination of accurate delivery and compliance to current dosimetric constraints for the organs at risk will be used. However a dose escalation will certainly not lead to lower treatment-related toxicity. So, the toxicity risk will increase by delivering a higher dose to the target and the question is whether patients attach more weight to improving survival than to a reduced morbidity risk. For example older patients, patients with low risk localized prostate cancer, patients without hormone treatment and patients with a low anxiety or depression score are suggested to prefer a lower radiation dose (van Tol-Geerdink *et al*., 2006). So with high dose radiotherapy compliance to the dosimetric constraints for the organs at risk to assure a low complication rate is very important to maintain satisfactory QoL results. Furthermore the patient's preferences should be involved in radiotherapy decision making.

FLAME-trial

Chapter 8 presents the study design of the FLAME-trial. To our knowledge, no other randomized controlled trials are being performed to investigate the benefit of an ablative microboost to the macroscopic tumor area in prostate cancer patients. Beside Singh *et al.* (2007), three other groups performed a pilot study in which a microboost to the dominant tumor region was delivered. Miralbell *et al.* (2010) treated 50 patients, after 64-64.4 Gy in 1.8-2 Gy fractions to the whole prostate, with a hypofractionated boost of 2 fractions of 5 to 8 Gy to the dominant tumor region, delineated with the use of anatomical imaging. After a median follow-up time of 63 months, a 5-year biochemical disease-free and disease-specific survival of 98% and 100%, respectively, were reported with acceptable long-term toxicity. Gaudet *et al*. (2010) selectively delivered a brachytherapy hyperdosage of ≥ 216 Gy (150% of the prescribed dose) to the macroscopic tumor area, defined according to positive areas on sextant biopsy, in 70 patients with localized prostate cancer treated with permanent seed prostate implant. No difference in acute and late toxicities compared to 120 patients with a standard plan were seen. A group from Ghent University Hospital (Fonteyne *et al*., 2008; De Meerleer *et al*., 2005) performed the largest trial in which 230 patients were treated with a mean dose of 81-82 Gy to a dominant lesion, defined by T2 weighted MRI or MRI plus spectroscopy. With the use of IMRT and daily ultra-sound-based prostate positioning, the acute toxicity remained low with no grade 3 or 4 acute gastrointestinal toxicity and 7% grade 3 genitourinary toxicity.
This acceptable toxicity results from literature in combination with the findings presented in this thesis made it sensible to start the FLAME-trial. To prevent unacceptable toxicity rates in the experimental arm, the dose constraints for the

organs at risk may not be violated even if this results in a dose to the macroscopic tumor lower than the intended 95 Gy. For the FLAME-trial, it is of great importance to irradiate the part of the prostate, which is not included in the macroscopic tumor volume, with the current gold standard dose. Maybe in the future, the dose to the remaining parts of the prostate can be lowered and this can be used to redistribute the dose to increase the dose to the macroscopic tumor or achieve more sparing of the normal tissue. But with the current knowledge, the dose to the whole prostate can not be lowered to avoid the risk of lowering the doses in a part of the prostate were it is needed and hurt a patient by endangering a reduction in local tumor control. The complexity of IMRT and image guided radiotherapy in combination with the delivery of a very high radiation dose to the macroscopic tumor within the prostate, makes it important to evaluate the actual delivered dose distribution during treatment.

Conclusion

The results of this thesis provide possibilities for further dose escalation in external beam radiotherapy for prostate cancer. With the use of optimal position verification the influence of the geometric uncertainties for complex prostate IMRT with an integrated ablative boost to the macroscopic lesion appeared to be minimal and only small margins are necessary to account for the remaining inter- and intrafraction motion. The intrafraction prostate motion can not be reduced with the use of a laxative or diet during treatment. When a high irradiation dose is delivered using advanced radiotherapy techniques including accurate position verification and the currently used dose constraints for the organs at risk, no severe toxicity is expected when an ablative boost is administered to the macroscopic tumor within the prostate. Furthermore, no deterioration of the health-related QoL is expected due to the improved technical possibilities, such as IMRT and the use of gold-fiducial markers.
Because of the findings described in this thesis, it was safe and feasible to start the FLAME-trial. The study design of the FLAME-trial is presented in chapter 8. This single-blind multicenter randomized Phase III trial will investigate the benefit of an ablative microboost to the macroscopic tumor within the prostate. Hopefully, this will lead to an improved treatment outcome for patients with prostate cancer with regard to the tumor control and their QoL. By localizing the recurrent tumors within the prostate during follow-up and correlating this with the delivered dose, accurate dose-effect information for both the macroscopic tumor and subclinical disease in prostate cancer can be obtained.

Chapter 10

References

Nederlandse samenvatting

List of publications

Curriculum vitae

Dankwoord

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQC30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365–376.

Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51: 1055–1068.

Adamson J, Wu Q. Inferences about prostate intrafraction motion from pre- and post-treatment volumetric imaging. Int J Radiat Oncol Biol Phys 2009; 75: 260–267.

Al-Abany M, Helgason AR, Cronqvist AK, et al. Toward a definition of a threshold for harmless doses to the anal-sphincter region and the rectum. Int J Radiat Oncol Biol Phys 2005; 61: 1035-1044.

Al-Mamgani A, van Putten WL, Heemsbergen WD, et al. Update of dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008; 72: 980-988.

Alonso-Arrizabalaga S, BruallaGonza´lez L, Rosello´ Ferrando JV, et al. Prostate planning treatment volume margin calculation based on the ExacTrac X-ray 6D image-guided system: Margins for various clinical implementations. Int J Radiat Oncol Biol Phys 2007; 69: 936–943.

Ash D, Flynn A, Battermann J, et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000; 57: 315-321.

Aubry JF, Beaulieu L, Girouard LM, et al. Measurement of intrafraction motion and interfraction and intrafraction rotation of prostate by three-dimensional analysis of daily portal imaging with radiopaque markers. Int J Radiat Oncol Biol Phys 2004; 60: 30–39.

Bacon CG, Giovannucci E, Testa M, et al. The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer. J Urol 2001; 166: 1804–1810.

Barnett GC, De Meerleer G, Gulliford SL, et al. The impact of clinical factors on the development of late radiation toxicity: Results from the medical research council RT01 trial (ISRCTN47772397). Clin Oncol (R Coll Radiol) 2011 [Epub ahead of print].

Beaulieu L, Girouard LM, Aubin S, et al. Performing daily prostate targeting with a standard V-EPID and an automated radio-opaque marker detection algorithm. Radiother Oncol 2004; 73: 61–64.

Beckendorf V, Guerif S, Le Prise E, et al. 70 gy versus 80 gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2010; 80: 1056-1063.

Beckendorf V, Guerif S, Le Prise E, et al. The GETUG 70 gy vs. 80 gy randomized trial for localized prostate cancer: Feasibility and acute toxicity. Int J Radiat Oncol Biol Phys 2004; 60: 1056-1065.

Bellon E, Feron M, Maes F, et al. Evaluation of manual vs semi-automated delineation of liver lesions on CT images. Eur Radiol 1997; 7: 432-438.

Bentzen SM. Theragnostic imaging for radiation oncology: Dose-painting by numbers. Lancet Oncol 2005; 6: 112-117.

Borghede G, Sullivan M. Measurement of quality of life in localized prostatic cancer patients treated with radiotherapy. Development of a prostate cancer-specific module supplementing the EORTC QLQ-C30. Qual Life Res 1996; 5: 212–222.

Bos LJ, van der Geer J, van Herk M, et al. The sensitivity of dose distributions for organ motion and set-up uncertainties in prostate IMRT. Radiother Oncol 2005; 76: 18–26.

Bouras EP, Tangalos EG. Chronic constipation in the elderly. Gastroenterol Clin North Am 2009; 38: 463-480.

Breetvelt IS, Van Dam FS. Underreporting by cancer patients: the case of response-shift. Soc Sci Med 1991; 32: 981–987.

Cahlon O, Hunt M, Zelefsky MJ. Intensity-modulated radiation therapy: supportive data for prostate cancer. Semin Radiat Oncol 2008, 18: 48-57.

Cellini N, Morganti AG, Mattiucci GC, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: Implications for conformal therapy planning. Int J Radiat Oncol Biol Phys 2002; 53: 595–599.

Chan P, Dinniwell R, Haider MA, et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: A cinematic-MRI point-of-interest study. Int J Radiat Oncol Biol Phys 2008; 70: 1507-1515.

Chao KK, Goldstein NS, Yan D, et al. Clinicopathologic analysis of extracapsular extension in prostate cancer: Should the clinical target volume be expanded posterolaterally to account for microscopic extension? Int J Radiat Oncol Biol Phys 2006; 65: 999–1007.

Chen L, Price RA Jr., Wang L, et al. MRI-based treatment planning for radiotherapy: dosimetric verification for prostate IMRT. Int J Radiat Oncol Biol Phys 2004; 60: 636–647.

Chen ME, Johnston DA, Tang K, et al. Detailed mapping of prostate carcinoma foci: biopsy strategy implications. Cancer 2000, 89: 1800-1809.

Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: How localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. J Clin Oncol 2009; 27: 3916-3922.

Cheung MR, Tucker SL, Dong L, et al. Investigation of bladder dose and Volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2007; 67: 1059–1065.

Cheung P, Sixel K, Morton G, et al. Individualized planning target volumes for intrafraction motion during hypofractionated intensity-modulated radiotherapy boost for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 62: 418–425.

Cheung R, Tucker SL, Ye JS, et al. Characterization of rectal normal tissue complication probability after high-dose external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2004; 58: 1513-1519.

Christie D, Denham J, Steigler A, et al. Delayed rectal and urinary symptomatology in patients treated for prostate cancer by radiotherapy with or without short term neo-adjuvant androgen deprivation. Radiother Oncol 2005; 77: 117-125.

Coen JJ, Zietman AL, Thakral H, et al. Radical radiation for localized prostate cancer: Local persistence of disease results in a late wave of metastases. J Clin Oncol 2002; 20: 3199-3205.

Court LE, Dong L, Lee AK, et al. An automatic CT-guided adaptive radiation therapy technique by online modification of multileaf collimator leaf positions for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 62: 154–163.

Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995, 31: 1341-1346.

Craig T, Wong E, Bauman G, et al. Impact of geometric uncertainties on evaluation of treatment techniques for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 62: 426–436.

Cranmer-Sargison G. A treatment planning investigation into the dosimetric effects of systematic prostate patient rotational set-up errors. Med Dosim 2008; 33: 199–205.

Crawford ED. Understanding the epidemiology, natural history, and key pathways involved in prostate cancer. Urology 2009; 73: S4-10.

Dallal GE. DESIGN: A supplementary module for SYSTAT and SYGRAPH. 1988.

D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: A randomized trial. JAMA 2008; 299: 289-295.

De Crevoisier R, Tucker SL, Dong L, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2005, 62: 965-973.

De Graeff A, de Leeuw JR, Ros WJ, et al. Long-term quality of life of patients with head and neck cancer. Laryngoscope 2000; 110: 98–106.

De Meerleer G, Vakaet L, Meersschout S, et al. Intensity-modulated radiotherapy as primary treatment for prostate cancer: acute toxicity in 114 patients. Int J Radiat Oncol Biol Phys 2004, 60: 777-787.

De Meerleer G, Villeirs G, Bral S, et al. The magnetic resonance detected intraprostatic lesion in prostate cancer: Planning and delivery of intensity-modulated radiotherapy. Radiother Oncol 2005; 75: 325–333.

De Meerleer GO, Fonteyne VH, Vakaet L, et al. Intensity-modulated radiation therapy for prostate cancer: late morbidity and results on biochemical control. Radiother Oncol 2007, 82: 160-166.

De Visschere PJ, De Meerleer GO, Futterer JJ, et al. Role of MRI in follow-up after focal therapy for prostate carcinoma. AJR Am J Roentgenol 2010; 194: 1427-1433.

Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007; 8: 475-487.

Debois M, Oyen R, Maes F, et al. The contribution of magnetic resonance imaging to the three-dimensional treatment planning of localized prostate cancer. Int J Radiat Oncol Biol Phys 1999; 45: 857-865.

Dehnad H, Nederveen AJ, van der Heide UA, et al. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. Radiother Oncol 2003; 67: 295–302.

Deurloo KE, Steenbakkers RJ, Zijp LJ, et al. Quantification of shape variation of prostate and seminal vesicles during external beam radiotherapy. Int J Radiat Oncol Biol Phys 2005; 61: 228–238.

Di Stefano M, Miceli E, Gotti S, et al. The effect of oral alphagalactosidase on intestinal gas production and gas-related symptoms. Dig Dis Sci 2007; 52: 78–83.

Dutch Comprehensive Cancer Centres, www.ikcnet.nl/cijfers, visited 16 -05-2011.

Eade TN, Hanlon AL, Horwitz EM, et al. What dose of external beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007; 68: 682–689.

Fiorino C, Fellin G, Rancati T, et al. Clinical and dosimetric predictors of late rectal syndrome after 3D-CRT for localized prostate cancer: Preliminary results of a multicenter prospective study. Int J Radiat Oncol Biol Phys 2008; 70: 1130-1137.

Fiorino C, Reni M, Bolognesi A, et al. Intra- and inter-observer variability in contouring prostate and seminal vesicles: Implications for conformal treatment planning. Radiother Oncol 1998; 47: 285-292.

Fonteyne V, Villeirs G, Speleers B, et al. Intensity-modulated radiotherapy as primary therapy for prostate cancer: Report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. Int J Radiat Oncol Biol Phys 2008; 72: 799-807.

Frank SJ, Dong L, Kudchadker RJ, et al. Quantification of prostate and seminal vesicle interfraction variation during IMRT. Int J Radiat Oncol Biol Phys 2008; 71: 813–820.

Furne JK, Levitt MD. Factors influencing frequency of flatus emission by healthy subjects. Dig Dis Sci 1996; 41: 1631–1635.

Fütterer JJ, Heijmink SW, Scheenen TW, et al. Prostate cancer: Local staging at 3-T endorectal MR imaging--early experience. Radiology 2006a; 238: 184-191.

Fütterer JJ, Heijmink SW, Scheenen TW, et al. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. Radiology 2006b; 241: 449-458.

Gardner BG, Zietman AL, Shipley WU, et al. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. J Urol 2002; 167: 123–126.

Gaudet M, Vigneault E, Aubin S, et al. Dose escalation to the dominant intraprostatic lesion defined by sextant biopsy in a permanent prostate I-125 implant: A prospective comparative toxicity analysis. Int J Radiat Oncol Biol Phys 2010; 77: 153-159.

Ghadjar P, Gwerder N, Manser P, et al. High-dose (80 gy) intensity-modulated radiation therapy with daily image-guidance as primary treatment for localized prostate cancer. Strahlenther Onkol 2010; 186: 687-692.

Ghadjar P, Vock J, Vetterli D, et al. Acute and late toxicity in prostate cancer patients treated by dose escalated intensity modulated radiation therapy and organ tracking. Radiat Oncol 2008; 3: 35.

Ghilezan MJ, Jaffray DA, Siewerdsen JH, et al. Prostate gland motion assessed with cine-magnetic resonance imaging (cine-MRI). Int J Radiat Oncol Biol Phys 2005; 62: 406-417.

Giordano SH, Lee A, Kuo YF, et al. Late gastrointestinal toxicity after radiation for prostate cancer. Cancer 2006; 107: 423-432.

Goldner G, Wachter-Gerstner N, Wachter S, et al. Acute side effects during 3-D-planned conformal radiotherapy of prostate cancer. differences between patient's self-reported questionnaire and the corresponding doctor's report. Strahlenther Onkol 2003; 179: 320-327.

Gordon JJ, Crimaldi AJ, Hagan M, et al. Evaluation of clinical margins via simulation of patient setup errors in prostate IMRT treatment plans. Med Phys 2007; 34: 202–214.

Gordon JJ, Siebers JV. Evaluation of dosimetric margins in prostate IMRT treatment plans. Med Phys 2008; 35: 569–575.

Gregoire V, Levendag P, Ang KK, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. Radiother Oncol 2003; 69: 227-236.

Groenendaal G, van den Berg CA, Korporaal JG, et al. Simultaneous MRI diffusion and perfusion imaging for tumor delineation in prostate cancer patients. Radiother Oncol 2010; 95: 185-190.

Guckenberger M, Ok S, Polat B, et al. Toxicity after intensity-modulated, image-guided radiotherapy for prostate cancer. Strahlenther Onkol 2010; 186: 535-543.

Gulliford SL, Foo K, Morgan RC, et al. Dose-volume constraints to reduce rectal side effects from prostate radiotherapy: Evidence from MRC RT01 trial ISRCTN 47772397. Int J Radiat Oncol Biol Phys 2010; 76: 747-754.

Haider MA, Chung P, Sweet J, et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys 2008; 70: 425-430.

Haie-Meder C, Potter R, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005; 74: 235-245.

Hamilton AS, Stanford JL, Gilliland FD, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: Results from the prostate cancer outcomes study. J Clin Oncol 2001; 19: 2517-2526.

Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The radiation therapy oncology group protocol 92-02. J Clin Oncol 2003; 21: 3972-3978.

Hanlon AL, Schultheiss TE, Hunt MA, et al. Chronic rectal bleeding after high-dose conformal treatment of prostate cancer warrants modification of existing morbidity scales. Int J Radiat Oncol Biol Phys 1997; 38: 59-63.

Hara N, Okuizumi M, Koike H, et al. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. Prostate 2005; 62: 140-147.

Heemsbergen WD, Al-Mamgani A, Witte MG, et al. Urinary obstruction in prostate cancer patients from the dutch trial (68 gy vs. 78 gy): Relationships with local dose, acute effects, and baseline characteristics. Int J Radiat Oncol Biol Phys 2010; 78: 19-25.

Heemsbergen WD, Peeters ST, Koper PC, et al. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys 2006, 66: 3-10.

Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. part 1: Screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011; 59: 61-71.

Henderson A, Laing RW, Langley SE. Quality of life following treatment for early prostate cancer: Does low dose rate (LDR) brachytherapy offer a better outcome? A review. Eur Urol 2004; 45: 134–141.

Hentschel B, Lilienthal A, Oehler W. A simple method to reduce organ motion in prostate cancer—Use by quantification of interfraction motion of the gland. Radiother Oncol 2006; 81: 1061.

Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: A predictor for late radiation morbidity. Int J Radiat Oncol Biol Phys 1999; 43: 475-479.

Higgins PD, Johanson JF. Epidemiology of constipation in North America: A systematic review. Am J Gastroenterol 2004; 99: 750–759.

Hoogeman MS, van Herk M, de Bois J, et al. Quantification of local rectal wall displacements by virtual rectum unfolding. Radiother Oncol 2004; 70: 21–30.

Horn BKP, Hilden HM, Negahdaripour S. Closed-form solution of absolute orientation using orthonormal matrices. J Opt Soc Am 1988; 5: 1127–1135.

Hornbrook MC, Goodman MJ. Assessing relative health plan risk with the RAND-36 health survey. Inquiry 1995; 32: 56–74.

Hosseinzadeh K, Schwarz SD. Endorectal diffusion-weighted imaging in prostate cancer to differentiate malignant and benign peripheral zone tissue. J Magn Reson Imaging 2004; 20: 654-661.

Huang EH, Pollack A, Levy L, et al. Late rectal toxicity: Dose-volume effects of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2002; 54: 1314-1321.

Hurkmans CW, Remeijer P, Lebesque JV, et al. Set-up verification using portal imaging; review of current clinical practice. Radiother Oncol 2001; 58: 105-120.

Incrocci L, Slob AK, Levendag PC. Sexual (dys) function after radiotherapy for prostate cancer: a review. Int J Radiat Oncol Biol Phys 2002; 52: 681–693.

Jacob R, Hanlon AL, Horwitz EM, et al. The relationship of increasing radiotherapy dose to reduced distant metastases and mortality in men with prostate cancer. Cancer 2004; 100: 538-543.

Jemal A, Center MM, DeSantis C, et al. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010: 19: 1893-1907.

Junius S, Haustermans K, Bussels B, et al. Hypofractionated intensity modulated irradiation for localized prostate cancer, results from a phase I/II feasibility study. Radiat Oncol 2007; 2: 29.

Karlsdottir A, Muren LP, Wentzel-Larsen T, et al. Late gastrointestinal morbidity after three-dimensional conformal radiation therapy for prostate cancer fades with time in contrast to genitourinary morbidity. Int J Radiat Oncol Biol Phys 2008; 70: 1478-1486.

Kim CK, Park BK, Park W, et al. Prostate MR imaging at 3T using a phased-arrayed coil in predicting locally recurrent prostate cancer after radiation therapy: Preliminary experience. Abdom Imaging 2010; 35: 246-252.

Kim JK, Hong SS, Choi YJ, et al. Wash-in rate on the basis of dynamic contrast-enhanced MRI: Usefulness for prostate cancer detection and localization. J Magn Reson Imaging 2005; 22: 639-646.

Klein S, van der Heide UA, Lips IM, et al. Automatic segmentation of the prostate in 3D MR images by atlas matching using localized mutual information. Med Phys 2008; 35: 1407-1417.

Koper PC, Jansen P, van Putten W, et al. Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. Radiother Oncol 2004, 73: 1-9.

Korfage IJ, de Koning HJ, Essink-Bot ML. Response shift due to diagnosis and primary treatment of localized prostate cancer: A then-test and a vignette study. Qual Life Res 2007; 16: 1627-1634.

Korfage IJ, Essink-Bot ML, Borsboom GJ, et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005; 116: 291–296.

Kotte AN, Hofman P, Lagendijk JJ, et al. Intrafraction motion of the prostate during external-beam radiation therapy: Analysis of 427 patients with implanted fiducial markers. Int J Radiat Oncol Biol Phys 2007; 69: 419–425.

Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008; 70: 67-74.

Kupelian P, Kuban D, Thames H, et al. Improved biochemical relapse-free survival with increased external radiation doses in patients with localized prostate cancer: The combined experience of nine institutions in patients treated in 1994 and 1995. Int J Radiat Oncol Biol Phys 2005; 61: 415-419.

Kupelian PA, Ciezki J, Reddy CA, et al. Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. Int J Radiat Oncol Biol Phys 2008; 71: 16-22.

Kupelian PA, Reddy CA, Klein EA, et al. Short-course intensity-modulated radiotherapy (70 GY at 2.5 GY per fraction) for localized prostate cancer: Preliminary results on late toxicity and quality of life. Int J Radiat Oncol Biol Phys 2001; 51: 988–993.

Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/LINAC integration. Radiother Oncol 2008; 86: 25–29.

Langer DL, van der Kwast TH, Evans AJ, et al. Prostate cancer detection with multi-parametric MRI: Logistic regression analysis of quantitative T2, diffusion-weighted imaging, and dynamic contrast-enhanced MRI. J Magn Reson Imaging 2009; 30: 327-334.

Li HS, Chetty IJ, Enke CA, et al . Dosimetric consequences of intrafraction prostate motion. Int J Radiat Oncol Biol Phys 2008; 71: 801–812.

Liang J, Wu Q, Yan D. The role of seminal vesicle motion in target margin assessment for online image-guided radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2009; 73: 935-943.

Lilleby W, Fossa SD, Waehre HR, et al. Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. Int J Radiat Oncol Biol Phys 1999; 43: 735–43.

Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MD-CRT): Biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000; 47: 551-560.

Lips I, Dehnad H, Kruger AB, et al. Health-related quality of life in patients with locally advanced prostate cancer after 76 gy intensity-modulated radiotherapy vs. 70 gy conformal radiotherapy in a prospective and longitudinal study. Int J Radiat Oncol Biol Phys 2007; 69: 656-661.

Lips IM, Dehnad H, van Gils CH, et al . High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: Acute and late toxicity in 331 patients. Radiat Oncol 2008; 3: 15.

Lips IM, van der Heide UA, Kotte AN, et al . Effect of translational and rotational errors on complex dose distributions with off-line and on-line position verification. Int J Radiat Oncol Biol Phys 2009a; 74: 1600–1608.

Lips IM, van Gils CH, van der Heide UA, et al. Health-related quality of life 3 years after high-dose intensity-modulated radiotherapy with gold fiducial marker-based position verification. BJU Int. 2009b; 103: 762-767.

Lips IM, Kotte AN, van Gils CH, et al. Influence of antiflatulent dietary advice on intrafraction motion for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2011 [Epub ahead of print].

Little DJ, Kuban DA, Levy LB, et al. Quality-of-life questionnaire results 2 and 3 years after radiotherapy for prostate cancer in a randomized dose-escalation study. Urology 2003; 62: 707–713.

Litwin MS, Fitzpatrick JM, Fossa SD, et al. Defining an international research agenda for quality of life in men with prostate cancer. Prostate 1999; 41: 58–67.

Litwin MS, Lubeck DP, Henning JM, et al. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: Results of the CaPSURE database. J Urol 1998; 159: 1988-1992.

Litzenberg DW, Balter JM, Hadley SW, et al. Influence of intrafraction motion on margins for prostate radiotherapy. Int J Radiat Oncol Biol Phys 2006; 65: 548-553.

Liu W, Luxton G, Xing L. A failure detection strategy for intrafraction prostate motion monitoring with on-board imagers for fixed-gantry IMRT. Int J Radiat Oncol Biol Phys 2010; 78: 904-911.

Lue TF. Erectile dysfunction. N Engl J Med 2000; 342: 1802–1813.

Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. Lancet 1997; 349: 906-910.

Madsen BL, Hsi RA, Pham HT, et al. Intrafractional stability of the prostate using a stereotactic radiotherapy technique. Int J Radiat Oncol Biol Phys 2003; 57: 1285–1291.

Mah D, Freedman G, Milestone B, et al. Measurement of intrafractional prostate motion using magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2002; 54: 568-575.

Mahr A, Levegrun S, Bahner ML, et al. Usability of semiautomatic segmentation algorithms for tumor volume determination. Invest Radiol 1999; 34: 143-150.

Marchand V, Bourdin S, Charbonnel C, et al. No impairment of quality of life 18 months after high-dose intensity-modulated radiotherapy for localized prostate cancer: A prospective study. Int J Radiat Oncol Biol Phys 2010; 77: 1053-1059.

McLaughlin PW, Evans C, Feng M, et al. Radiographic and anatomic basis for prostate contouring errors and methods to improve prostate contouring accuracy. Int J Radiat Oncol Biol Phys 2010; 76: 369-378.

Meijer GJ, de Klerk J, Bzdusek K, et al. What CTV-to-PTV margins should be applied for prostate irradiation? Four-dimensional quantitative assessment using model-based deformable image registration techniques. Int J Radiat Oncol Biol Phys 2008; 72: 1416–1425.

Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys 2010; 76: 14-22.

Michalski JM, Winter K, Purdy JA, et al. Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose Level V. Int J Radiat Oncol Biol Phys 2005; 62: 706-713.

Miralbell R, Molla M, Rouzaud M, et al. Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: A sequential dose escalation pilot study. Int J Radiat Oncol Biol Phys 2010; 78: 50-57.

Moman MR, van der Heide UA, Kotte AN, et al . Long-term experience with transrectal and transperineal implantations of fiducial gold markers in the prostate for position verification in external beam radiotherapy: Feasibility, toxicity and quality of life. Radiother Oncol 2010; 96: 38–42.

Morgan PB, Hanlon AL, Horwitz EM, et al. Radiation dose and late failures in prostate cancer. Int J Radiat Oncol Biol Phys 2007; 67: 1074-1081.

Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: An analysis of RTOG 9801. J Clin Oncol 2009; 27: 5816-5822.

Multi-Institutional Target Delineation in Oncology Group. Human-computer interaction in radiotherapy target volume delineation: A prospective, multi-institutional comparison of user input devices. J Digit Imaging 2010 [Epub ahead of print].

Mutanga TF, de Boer HC, van der Wielen GJ, et al. Margin evaluation in the presence of deformation, rotation, and translation in prostate and entire seminal vesicle irradiation with daily marker-based setup corrections. Int J Radiat Oncol Biol Phys 2010 [Epub ahead of print].

Nahum AE, Movsas B, Horwitz EM, et al. Incorporating clinical measurements of hypoxia into tumor local control modeling of prostate cancer: Implications for the alpha/beta ratio. Int J Radiat Oncol Biol Phys 2003; 57: 391-401.

Namiki S, Ishidoya S, Ito A, et al. Five-year follow-up of health-related quality of life after intensity-modulated radiation therapy for prostate cancer. Jpn J Clin Oncol 2009; 39: 732-738.

Namiki S, Ishidoya S, Tochigi T, et al. Health-related quality of life after intensity modulated radiation therapy for localized prostate cancer: Comparison with conformal and conformal radiotherapy. Jpn J Clin Oncol 2006; 36: 224–230.

Namiki S, Tochigi T, Ishidoya S, et al. Long-term quality of life following primary treatment in men with clinical stage T3 prostate cancer. Qual Life Res 2011; 20: 111-118.

Nederveen A, Lagendijk J, Hofman P. Detection of fiducial gold markers for automatic on-line megavoltage position verification using a marker extraction kernel (MEK). Int J Radiat Oncol Biol Phys 2000; 47: 1435-1442.

Nederveen AJ, van der Heide UA, Hofman P, et al. Partial boosting of prostate tumours. Radiother Oncol 2001; 61: 117– 126.

Nederveen AJ, van der Heide UA, Dehnad H, et al. Measurements and clinical consequences of prostate motion during a radiotherapy fraction. Int J Radiat Oncol Biol Phys 2002; 53: 206-214.

Nederveen AJ, Dehnad H, van der Heide UA, et al . Comparison of megavoltage position verification for prostate irradiation based on bony anatomy and implanted fiducials. Radiother Oncol 2003; 68: 81–88.

Nichol AM, Warde PR, Lockwood GA, et al . A cinematic magnetic resonance imaging study of Milk of Magnesia laxative and an antiflatulent diet to reduce intrafraction prostate motion. Int J Radiat Oncol Biol Phys 2010; 77: 1072–1078.

Nijkamp J, Pos FJ, Nuver TT, et al. Adaptive radiotherapy for prostate cancer using kilovoltage cone-beam computed tomography: First clinical results. Int J Radiat Oncol Biol Phys 2008; 70: 75–82.

Nuver TT, Hoogeman MS, Remeijer P, et al. An adaptive offline procedure for radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys 2007;67:1559–1567.

O'Doherty UM, McNair HA, Norman AR, et al. Variability of bladder filling in patients receiving radical radiotherapy to the prostate. Radiother Oncol 2006; 79: 335-340.

Ogino I, Uemura H, Inoue T, et al. Reduction of prostate motion by removal of gas in rectum during radiotherapy. Int J Radiat Oncol Biol Phys 2008; 72: 456–466.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16: 139–144.

Osoba D, Bezjak A, Brundage M, et al. Analysis and interpretation of health-related quality-of-life data from clinical trials: Basic approach of the national cancer institute of canada clinical trials group. Eur J Cancer 2005; 41: 280-287.

Ozer S, Langer DL, Liu X, et al. Supervised and unsupervised methods for prostate cancer segmentation with multispectral MRI. Med Phys 2010; 37: 1873-1883.

Padhani AR, Khoo VS, Suckling J, et al. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. Int J Radiat Oncol Biol Phys 1999; 44: 525–533.

Padhani AR. Dynamic contrast-enhanced MRI in clinical oncology: Current status and future directions. J Magn Reson Imaging 2002; 16: 407-422.

Parker CC, Damyanovich A, Haycocks T, et al. Magnetic resonance imaging in the radiation treatment planning of localized prostate cancer using intra-prostatic fiducial markers for computed tomography co-registration. Radiother Oncol 2003; 66: 217-224.

Peeters ST, Heemsbergen WD, van Putten WL, et al. Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 2005a; 61: 1019–1034.

Peeters ST, Hoogeman MS, Heemsbergen WD, et al. Volume and hormonal effects for acute side effects of rectum and bladder during conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2005b; 63: 1142-1152.

Peeters ST, Heemsbergen WD, Koper PC, et al. Dose–response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006; 24: 1990–1996.

Pettersson A, Persson C, Johansson B, et al. Effects of dietary counseling on gastrointestinal complications and quality of life: A randomised controlled trial in prostate cancer patients undergoing radiotherapy. EJC Suppl 2007; 5: 1127.

Pickett B, Vigneault E, Kurhanewicz J, et al. Static field intensity modulation to treat a dominant intra-prostatic lesion to 90 Gy compared to seven field 3-dimensional radiotherapy. Int J Radiat Oncol Biol Phys 1999; 44: 921–929.

Pinkawa M, Asadpour B, Gagel B, et al. Prostate position variability and dose-volume histograms in radiotherapy for prostate cancer with full and empty bladder. Int J Radiat Oncol Biol Phys 2006; 64: 856-861.

Pinkawa M, Gagel B, Piroth MD, et al. Erectile dysfunction after external beam radiotherapy for prostate cancer. Eur Urol 2009; 55: 227-234.

Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose–response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002; 53: 1097–1105.

Pucar D, Hricak H, Shukla-Dave A, et al. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: Magnetic resonance imaging and step-section pathology evidence. Int J Radiat Oncol Biol Phys 2007; 69: 62–69.

Raaymakers BW, Lagendijk JJ, Overweg J, et al. Integrating a 1.5 T MRI scanner with a 6 MVaccelerator: Proof of concept. Phys Med Biol 2009; 54: N229–N237.

Rasch C, Barillot I, Remeijer P, et al. Definition of the prostate in CT and MRI: A multi-observer study. Int J Radiat Oncol Biol Phys 1999; 43: 57-66.

Rasch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. Semin Radiat Oncol 2005; 15: 136-145.

Rijkhorst EJ, van Herk M, Lebesque JV, et al. Strategy for online correction of rotational organ motion for intensity-modulated radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys 2007; 69: 1608–1617.

Roach M,3rd, Hanks G, Thames H,Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO phoenix consensus conference. Int J Radiat Oncol Biol Phys 2006; 65: 965-974.

Rouviere O. MR assessment of recurrent prostate cancer after radiation therapy. Radiology 2007; 242: 635,6; author reply 636-637.

Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008; 358: 1250–1261.

Sandhu AS, Zelefsky MJ, Lee HJ, et al. Long-term urinary toxicity after 3-dimensional conformal radiotherapy for prostate cancer in patients with prior history of transurethral resection. Int J Radiat Oncol Biol Phys 2000; 48: 643-647.

Sanguineti G, Agostinelli S, Foppiano F, et al. Adjuvant androgen deprivation impacts late rectal toxicity after conformal radiotherapy of prostate carcinoma. Br J Cancer 2002; 86: 1843-1847.

Schallenkamp JM, Herman MG, Kruse JJ, et al. Prostate position relative to pelvic bony anatomy based on intraprostatic gold markers and electronic portal imaging. Int J Radiat Oncol Biol Phys 2005; 63: 800-811.

Scheidler J, Hricak H, Vigneron DB, et al. Prostate cancer: Localization with three-dimensional proton MR spectroscopic imaging--clinicopathologic study. Radiology 1999; 213: 473-480.

Schultheiss TE, Lee WR, Hunt MA, et al. Late GI and GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37: 3-11.

Seitz M, Shukla-Dave A, Bjartell A, et al. Functional magnetic resonance imaging in prostate cancer. Eur Urol 2009; 55: 801-814.

Siebers JV, Keall PJ, Wu Q, et al. Effect of patient setup errors on simultaneously integrated boost head and neck IMRT treatment plans. Int J Radiat Oncol Biol Phys 2005; 63: 422–433.

Singh AK, Guion P, Sears-Crouse N, et al. Simultaneous integrated boost biopsy proven, MRI defined dominant intra-prostatic lesions to 95 Gray with IMRT: Early results of a phase 1 NCI study. Radiat Oncol 2007; 2: 36.

Skala M, Rosewall T, Dawson L, et al. Patient-assessed late toxicity rates and principal component analysis after image-guided radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2007; 68: 690-698.

Skwarchuk MW, Jackson A, Zelefsky MJ, et al. Late rectal toxicity after conformal radiotherapy of prostate cancer (I): Multivariate analysis and dose-response. Int J Radiat Oncol Biol Phys 2000; 47: 103-113.

Smitsmans MH, Wolthaus JW, Artignan X, et al. Automatic localization of the prostate for on-line or off-line image-guided radiotherapy. Int J Radiat Oncol Biol Phys 2004; 60: 623-635.

Smitsmans MH, Pos FJ, de Bois J, et al. The influence of a dietary protocol on cone beam CT-guided radiotherapy for prostate cancer patients. Int J Radiat Oncol Biol Phys 2008; 71: 1279–1286.

Smitsmans MH, de Bois J, Sonke JJ, et al. Residual seminal vesicle displacement in marker-based image-guided radiotherapy for prostate cancer and the impact on margin design. Int J Radiat Oncol Biol Phys 2011; 80: 590-596.

Staff I, Salner A, Bohannon R, et al. Disease-specific symptoms and general quality of life of patients with prostate carcinoma before and after primary three-dimensional conformal radiotherapy. Cancer 2003; 98: 2335–2343.

Staffurth J, Radiotherapy Development Board. A review of the clinical evidence for intensity-modulated radiotherapy. Clin Oncol (R Coll Radiol.) 2010; 22: 643-657.

Steenbakkers RJ, Deurloo KE, Nowak PJ, et al. Reduction of dose delivered to the rectum and bulb of the penis using MRI delineation for radiotherapy of the prostate. Int J Radiat Oncol Biol Phys 2003; 57: 1269-1279.

Storey MR, Pollack A, Zagars G, et al. Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 2000; 48: 635-642.

Stroom JC, de Boer HC, Huizenga H, et al. Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. Int J Radiat Oncol Biol Phys 1999; 43: 905–919.

Su Z, Zhang L, Murphy M, Williamson J. Analysis of prostate patient setup and tracking data: Potential intervention strategies. Int J Radiat Oncol Biol Phys 2010 [Epub ahead of print].

Suarez FL, Levitt MD. Intestinal gas. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger & Fordtran's gastrointestinal and liver disease pathophysiology/diagnosis/management. 7th ed. Philadelphia: WB Saunders; 2002. p. 155–163.

Swanson GP, Stathakis S. Rectal dose constraints for intensity modulated radiation therapy of the prostate. Am J Clin Oncol 2011; 34: 188-195.

Syndikus I, Morgan RC, Sydes MR, et al. Late gastrointestinal toxicity after dose-escalated conformal radiotherapy for early prostate cancer: Results from the UK medical research council RT01 trial (ISRCTN47772397). Int J Radiat Oncol Biol Phys 2010; 77: 773-783.

Szumacher E, Harnett N, Warner S, et al. Effectiveness of educational intervention on the congruence of prostate and rectal contouring as compared with a gold standard in three-dimensional radiotherapy for prostate. Int J Radiat Oncol Biol Phys 2010; 76: 379-385.

Teh BS, Dong L, McGary JE, et al. Rectal wall sparing by dosimetric effect of rectal balloon used during intensity-modulated radiation therapy (IMRT) for prostate cancer. Med Dosim 2005, 30: 25-30.

Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: Standardized quantities and symbols. J Magn Reson Imaging 1999; 10: 223-232.

Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: Version 2.0. an improved reference for grading the acute effects of cancer treatment: Impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 13-47.

Trotti A. The evolution and application of toxicity criteria. Semin Radiat Oncol 2002; 12: 1–3.

Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13: 176-181.

Turner SL, Adams K, Bull CA, et al. Sexual dysfunction after radical radiation therapy for prostate cancer: A prospective evaluation. Urology 1999; 54: 124-129.

Usmani N, Sloboda R, Kamal W, et al. Can images obtained with high field strength magnetic resonance imaging reduce contouring variability of the prostate? Int J Radiat Oncol Biol Phys 2011: 80: 728-734.

Valdagni R, Kattan MW, Rancati T, et al. Is it time to tailor the prediction of radio-induced toxicity in prostate cancer patients? building the first set of nomograms for late rectal syndrome. Int J Radiat Oncol Biol Phys 2011 [Epub ahead of print].

Valicenti RK, Winter K, Cox JD, et al. RTOG 94-06: Is the addition of neoadjuvant hormonal therapy to dose-escalated 3D conformal radiation therapy for prostate cancer associated with treatment toxicity? Int J Radiat Oncol Biol Phys 2003; 57: 614-620.

Van Andel G, Visser AP, Zwinderman AH, et al. A prospective longitudinal study comparing the impact of external radiation therapy with radical prostatectomy on health related quality of life (HRQOL) in prostate cancer patients. Prostate 2004; 58: 354–365.

Van der Heide UA, de Groot GM, Huisjes-Sluis A, et al. Adjustments to variation of the prostate orientation in de IMRT treatment using table, gantry and collimator rotations. Radiother Oncol 2005; 73: S343.

Van der Heide UA, Dehnad H, Hofman P, et al. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. Radiother Oncol 2007; 82: 38–45.

Van der Heide UA, Korporaal JG, Groenendaal G, et al. Functional MRI for tumor delineation in prostate radiation therapy. Imaging Med 2011; 3: 219-231.

Van der Wielen GJ, van Putten WL, Incrocci L. Sexual function after three-dimensional conformal radiotherapy for prostate cancer: Results from a dose-escalation trial. Int J Radiat Oncol Biol Phys 2007; 68: 479-484.

Van der Wielen GJ, Mutanga TF, Incrocci L, et al. Deformation of prostate and seminal vesicles relative to intraprostatic fiducial markers. Int J Radiat Oncol Biol Phys 2008; 72: 1604- 1611.

Van Gellekom MP, Moerland MA, van Vulpen M, et al. Quality of life of patients after permanent prostate brachytherapy in relation to dosimetry. Int J Radiat Oncol Biol Phys 2005; 63: 772–780.

Van Herk M, Remeijer P, Rasch C, et al. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 1121–1135.

Van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol. 2004; 14: 52-64.

Van Herten YR, van de Kamer JB, van Wieringen N, et al. Dosimetric evaluation of prostate rotations and their correction by couch rotations. Radiother Oncol 2008; 88: 156–162.

Van Lin EN, van der Vight LP, Witjes JA, et al . The effect of an endorectal balloon and off-line correction on the interfraction systematic and random prostate position variations: A comparative study. Int J Radiat Oncol Biol Phys 2005; 61: 278–288.

Van Lin EN, Fütterer JJ, Heijmink SWTPJ, et al. IMRT boost dose planning on dominant intraprostatic lesions: Gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H-spectroscopic MRI. Int J Radiat Oncol Biol Phys 2006; 65: 291–303.

Van Os M, Dirkx M, Rajan V, et al. On-line correction for intrafraction motion in prostate patients with fiducial markers. 10th biannual Estro meeting, Maastricht. 2009: abstract no 478.

Van Tol-Geerdink JJ, Stalmeier PF, van Lin EN, et al. Do patients with localized prostate cancer treatment really want more aggressive treatment? J Clin Oncol 2006; 24: 4581-4586.

Van Vulpen M, De Leeuw JR, Van Gellekom MP, et al. A prospective quality of life study in patients with locally advanced prostate cancer, treated with radiotherapy with or without regional or interstitial hyperthermia. Int J Hyperthermia 2003; 19: 402–413.

Van Vulpen M, van der Heide UA, van Moorselaar JR. How quality influences the clinical outcome of external beam radiotherapy for localized prostate cancer. BJU Int. 2008; 101: 944–7.

van Vulpen M, van den Berg CA, Moman MR, et al. Difficulties and potential of correlating local recurrences in prostate cancer with the delivered local dose. Radiother Oncol. 2009; 93: 180-184.

Vargas C, Martinez A, Kestin LL, et al. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. Int J Radiat Oncol Biol Phys 2005; 62: 1297-1308.

Vavassori V, Fiorino C, Rancati T, et al. Predictors for rectal and intestinal acute toxicities during prostate cancer high-dose 3D-CRT: Results of a prospective multicenter study. Int J Radiat Oncol Biol Phys 2007; 67: 1401-1410.

Veldeman L, Madani I, Hulstaert F, et al. Evidence behind use of intensity modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol 2008; 9: 367–375.

Villeirs GM, Van Vaerenbergh K, Vakaet L, et al. Interobserver delineation variation using CT versus combined CT + MRI in intensity-modulated radiotherapy for prostate cancer. Strahlenther Onkol 2005; 181: 424-430.

Wahlgren T, Brandberg Y, Haggarth L, et al. Health-related quality of life in men after treatment of localized prostate cancer with external beam radiotherapy combined with (192)ir brachytherapy: A prospective study of 93 cases using the EORTC questionnaires QLQ-C30 and QLQ-PR25. Int J Radiat Oncol Biol Phys 2004; 60: 51–59.

Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): An open randomised phase III trial. Lancet 2009; 373: 301-308.

Wu J, Haycocks T, Alasti H, et al. Positioning errors and prostate motion during conformal prostate radiotherapy using online isocentre set-up verification and implanted prostate markers. Radiother Oncol 2001; 61: 127–133.

Xia P, Pickett B, Vigneault E, et al. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intraprostatic lesions of prostate cancer to 90 gy. Int J Radiat Oncol Biol Phys 2001; 51: 244-254.

Xing JH, Soffer EE. Adverse effects of laxatives. Dis Colon Rectum 2001; 44: 1201-1209.

Yoshimura K, Arai Y, Ichioka K, et al. A 3-y prospective study of health-related and disease-specific quality of life in patients with nonmetastatic prostate cancer treated with radical prostatectomy or external beam radiotherapy. Prostate Cancer Prostatic Dis 2004; 7: 144–151.

Yoshimura K, Kamoto T, Nakamura E, et al. Health-related quality-of-life after external beam radiation therapy for localized prostate cancer: intensity modulated radiation therapy versus conformal radiation therapy. Prostate Cancer Prostatic Dis 2007; 10: 288–292.

Yue NJ, Knisely JP, Song H, et al. A method to implement full six-degree target shift corrections for rigid body in image-guided radiotherapy. Med Phys 2006; 33: 21–31.

Yue NJ, Kim S, Lewis BE, Jabbour S, Narra V, Goyal S, et al. Optimization of couch translational corrections to compensate for rotational and deformable target deviations in image guided radiotherapy. Med Phys 2008; 35: 4375-4385.

Zelefsky MJ, Cowen D, Fuks Z, et al. Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. Cancer 1999; 85: 2460-2468.

Zelefsky MJ, Fuks Z, Hunt M, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol 2001; 166: 876–881.

Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002; 53: 1111–1116.

Zelefsky MJ, Chan H, Hunt M, et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol 2006; 176: 1415-1419.

Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005; 294: 1233–1239.

Chapter 10

References

Nederlandse samenvatting

List of publications

Curriculum vitae

Dankwoord

Uitwendige radiotherapie voor prostaatkanker: mogelijkheden voor dosis escalatie.

Ondanks verbetering in de diagnostiek en de behandeling is prostaatkanker een veel voorkomende doodsoorzaak in de westerse wereld. Prostaatkanker komt het meest voor bij mannen tussen de 65 en 74 jaar oud. Een van de behandelopties voor prostaatkanker is uitwendige bestraling (= externe radiotherapie). Bij de radiotherapeutische behandeling wordt de totale voorgeschreven bestralingdosis (met als eenheid gray (Gy)) opgesplitst en gedurende een aantal aaneengesloten weken wordt de patiënt iedere dag met een kleine dosis (= fractie) bestraald. Tijdens iedere fractie wordt de patiënt met meerdere stralingsbundels vanuit verschillende richtingen bestraald. Prostaatkanker is een multifocale ziekte, wat betekent dat op meerdere plekken binnen de prostaat kankercellen gevonden worden. Voor de genezing van prostaatkanker is het essentieel dat alle kankercellen vernietigd worden. Daarom is de gehele prostaat doelgebied van de bestraling. De uitdaging is om de prostaat met een hoge dosis te bestralen, terwijl het omliggende weefsel zoveel mogelijk gespaard blijft. De prostaat is gelegen tussen de blaas en de endeldarm. Hoe minder dosis op deze omliggende organen (= risico organen) komt, des te minder bijwerkingen (= toxiciteit) een patiënt heeft. De plaats van de prostaat kan tijdens de behandeling variëren. Dit is het gevolg van enerzijds de beweging van de patiënt zelf en anderzijds de invloed van de omliggende organen zoals een wisselende blaas en endeldarm vulling. De beweging van de prostaat tussen de verschillende fracties wordt de interfractie beweging genoemd. De intrafractie beweging is de beweging van de prostaat tijdens de duur van een fractie (ongeveer 5 tot 7 minuten). Om te waarborgen dat de prostaat de voorgeschreven bestralingsdosis krijgt wordt de prostaat plus een extra onzekerheidsmarge rondom de prostaat bestraald. Hierdoor zal er een overlap zijn van het hoge dosis gebied met een gedeelte van de blaas en de endeldarm. De grootte van de marge wordt bepaald door de nauwkeurigheid waarmee de positie van de prostaat tijdens de behandeling bepaald kan worden. In het UMC Utrecht wordt sinds 2001 voor de plaatsbepaling van de prostaat tijdens de behandeling (= de positie verificatie) gebruikt gemaakt van goudmarkers. Hiervoor worden voor de start van de radiotherapie 3 gouden staafjes (= goudmarkers) in de prostaat geplaatst. Tijdens de bestraling wordt de stralingsbundel gebruikt om een röntgenfoto te maken van deze 3 goudmarkers. Hierdoor kan de exacte positie van de prostaat worden bepaald en de radiotherapie beter gericht worden gegeven.

Om het gezonde weefsel nog beter te kunnen sparen is de techniek om de bestraling te plannen de afgelopen decennia aanzienlijk verbeterd. De rechthoekige stralingsbundels zijn vervangen door bundels met een onregelmatige vorm, waarmee de bestralingvelden aangepast kunnen worden aan de driedimensionale vorm van het doelgebied. In het UMC Utrecht wordt gebruik gemaakt van een IMRT (intensity

modulated radiotherapy) techniek. IMRT is een geavanceerde techniek waarbij de vorm en de intensiteit van de stralingsbundel aangepast kan worden aan het doelgebied. Hiermee is het mogelijk om in het doelgebied een hoge bestralingsdosis te geven en direct rondom dit gebied de dosis te laag te houden (= scherpe dosis gradiënten) in tegenstelling tot conformale radiotherapie technieken waarbij grotere bestralingsvelden worden gebruikt.

Verschillende studies hebben aangetoond dat een verhoging van de bestralingsdosis (= dosis escalatie) ervoor zorgt dat de prostaatkanker na de behandeling langer wegblijft. Er zijn aanwijzingen dat als de tumor terug komt in de prostaat, dit vaak gebeurt in het gebied waar voor de behandeling de tumor zichtbaar was op beeldvorming, zoals op een MRI-scan (= het macroscopische tumorgebied). Uit theoretische modellen blijkt dat het verhogen van de bestralingsdosis in het zichtbare tumorgebied binnen de prostaat ervoor kan zorgen dat het risico dat de tumor daar terug komt kleiner wordt. Het is niet mogelijk om de bestralingsdosis in de gehele prostaat verder te verhogen omdat dit een onacceptabel hoog risico op ernstige toxiciteit tot gevolg zou hebben. Uit planningsstudies is gebleken dat het wel mogelijk is om in een gedeelte van de prostaat de dosis te verhogen, zonder dat de dosis in de blaas en de endeldarm onacceptabel hoog wordt.
Voordat onderzocht kan worden of het verhogen van de bestralingsdosis in het zichtbare tumorgebied binnen de prostaat betere behandelresultaten geeft, moet worden gekeken of deze behandelmethode haalbaar is en veilig uitgevoerd kan worden. In dit proefschrift worden daarom de bewegingsonzekerheden voor deze behandelmethode onderzocht en een inschatting gemaakt van de toxiciteit en kwaliteit van leven na de behandeling. Tot slot wordt de opzet van de FLAME-trial gepresenteerd, waarin onderzocht zal worden of een aanvullende hoge dosis op het zichtbare tumorgebied binnen de prostaat effectief is.

Interfractie beweging (= beweging van de prostaat tussen de fracties)

Na hoofdstuk 1, waarin een algemene inleiding voor dit proefschrift wordt gegeven, wordt in hoofdstuk 2 gekeken naar de invloed van de interfractie prostaatbeweging op dosisverdelingen met een geïntegreerde hoge dosis op het tumorgebied. Voor deze studie is gebruik gemaakt van de gegevens van 19 patiënten, die behandeld waren met uitwendige radiotherapie voor prostaatkanker. Tijdens de behandeling is gebruik gemaakt van positie verificatie door middel van het dagelijks afbeelden van de goudmarkers. Hierdoor zijn voor iedere patiënt op iedere behandeldag de exacte verplaatsingen en rotaties van de prostaat bekend. Voor iedere patiënt werden 4 nieuwe bestralingsplannen gemaakt waarbij 4 verschillende marges (2, 4, 6 en 8 mm) rondom de prostaat werden gebruikt. Bij alle plannen werd naast de standaard dosis

op de gehele prostaat een hoge dosis op het tumorgebied gepland. Om het effect van de prostaatbeweging op deze nieuwe dosisverdelingen te bekijken, werden voor ieder plan de individuele verplaatsingen en rotaties van de prostaat gesimuleerd (ook wel 'schudden' genoemd). Op deze manier kon beoordeeld worden welke marge voldoende is om de bewegingsonzekerheden op te kunnen vangen. Tevens werd gekeken wat het effect is van het corrigeren van de prostaatverplaatsingen op de dag waarop de verplaatsing gemeten is (on-line) en wanneer dit pas de volgende dag bij het geven van een volgende fractie plaats vindt (off-line). Rotaties van de prostaat werden niet gecorrigeerd, wat ertoe leidde dat bij patiënten met een grote rotatie van de prostaat de uiteindelijke dosis op de prostaat duidelijk minder was dan gepland. Voor het zichtbare tumorgebied was het effect van een rotatie op de uiteindelijk gegeven dosis het grootst wanneer het tumorgebied zich in de rand van de prostaat, dus ver bij het rotatiepunt vandaan, bevond. Bij patiënten met een tumorgebied in de rand van de prostaat zou dus overwogen kunnen worden om grote rotaties tijdens de behandeling wel te corrigeren.

Intrafractiebeweging (= beweging van de prostaat tijdens een fractie)

Door het gebruik van dagelijkse positie verificatie van de prostaat is de invloed van de interfractie beweging geminimaliseerd. Hierdoor gaan andere onzekerheden in de behandeling, zoals de beweging van de prostaat tijdens een fractie (= de intrafractie beweging), een belangrijkere rol spelen. De hypothese is dat de intrafractie beweging veroorzaakt wordt door passerende luchtbellen in de endeldarm of een verandering van de vorm van de endeldarm. Verschillende ziekenhuizen zijn daarom gestart met het voorschrijven een mild laxeermiddel, zoals magnesium oxide, of een dieet dat gasvorming tegengaat om hiermee een stabielere vulling van de endeldarm te bewerkstelligen en daardoor een vermindering van de intrafractie beweging.
In hoofdstuk 3 hebben wij onderzocht of magnesium oxide inderdaad effectief is in het verminderen van de intrafractie prostaatbeweging. Om deze vraag te beantwoorden werd een dubbel-blind gerandomiseerde studie uitgevoerd bij patiënten die behandeld werden met uitwendige radiotherapie voor prostaatkanker. De 92 patiënten die deelnamen aan deze studie werd op basis van loting (= randomisatie) in 2 groepen verdeeld. De ene groep kreeg tijdens de bestraling magnesium oxide voorgeschreven en de andere groep een placebo. De patiënt, de arts en de onderzoekers waren geblindeerd, dus zij wisten tijdens de behandeling niet tot welke groep een patiënt behoorde. Tijdens de behandeling werd bij alle patiënten tijdens alle 35 fracties de beweging van de prostaat gemeten. Bij iedere fractie wordt een patiënt achtereenvolgens vanuit 5 verschillende richtingen bestraald. Door bij iedere richting vanuit de stralingsbundel een afbeelding van de goudmarkers te maken, is op 5 momenten tijdens een fractie de positie van de prostaat bekend. Hiermee kan de minimale weg die de prostaat

tijdens de fractie heeft afgelegd bepaald worden. Er werd geen verschil gevonden in de hoeveelheid intrafractie prostaatbeweging tussen de patiënten die magnesium oxide gebruikten en de patiënten die een placebo gebruikten, dus magnesium oxide was niet effectief in het verminderen van de prostaatbeweging. Er werd wel een trend gezien dat patiënten die magnesium oxide gebruikten een slechtere kwaliteit van leven hadden en meer bijwerkingen tijdens en na de behandeling.
In 2008 werd op de afdeling Radiotherapie in het UMC Utrecht gestart met het voorschrijven van een dieet aan patiënten die voor prostaatkanker bestraald werden. Dit dieet bestond uit adviezen om gasbellen in de darmen te verminderen en om een stabiele darmvulling te creëren. Door het vermijden van bepaald voedsel en voorkomen van het inslikken van lucht, werd geprobeerd om de prostaatbeweging tijdens de behandeling te verminderen. In hoofdstuk 4 wordt het effect van dit dieet op de intrafractie prostaatbeweging geëvalueerd. Tussen 2002 en 2009 werden 739 patiënten zonder het dieet bestraald en 105 patiënten met het dieet. Voor alle patiënten werden voor iedere fractie de intrafractie beweging gemeten zoals hierboven beschreven. Na invoering van het dieet werd, onverwacht, een klinisch relevante en statistische significante toename van de intrafractie beweging gezien. Dit zou mogelijk verklaard kunnen worden door het vaak voorkomen van obstipatie en gebruik van laxeermiddelen in deze oudere patiënten groep (gemiddelde leeftijd 68-69 jaar). Veel ouderen hebben een specifiek eetpatroon ontwikkeld om een regelmatige stoelgang te realiseren. Door het verstoren van dit evenwicht door middel van een dieet zou juist meer variatie in de darmvulling veroorzaakt kunnen worden en daardoor dus meer intrafractie prostaatbeweging. Een andere verklaring zou kunnen zijn dat de intrafractie beweging niet het gevolg is van variatie in de endeldarm, maar een andere oorzaak heeft zoals rotatie van het bekken, spierspanning van de bekkenbodem of de blaasvulling.
Op basis van de resultaten van hoofdstuk 3 en 4 wordt geadviseerd om geen dieet of magnesium oxide voor te schrijven tijdens de bestraling van prostaatkanker.

Toxiciteit

De bijwerkingen (=toxiciteit) na de behandeling voor prostaatkanker zijn erg belangrijk, omdat de patiënten een goede levensverwachting hebben en het verschil in overleving met andere behandelingen, zoals chirurgische verwijdering van de prostaat of inwendige bestraling, klein is. Uit eerdere studies bleek dat het verhogen van de bestralingsdosis op de prostaat meer toxiciteit tot gevolg had. In deze studies werd gebruik gemaakt van conformale bestralingstechnieken en positie verificatie op basis van de botten. Voor het corrigeren van de positie van de patiënt tijdens de behandeling wordt hiervoor met de stralingsbundel een röntgenfoto gemaakt waarop de botten zichtbaar zijn. De prostaat beweegt echter onafhankelijk van de

botstructuren, omdat de plaats van de prostaat wordt beïnvloed door de vulling in de endeldarm en de blaas. Het corrigeren van de positie van de patiënt op basis van de botten kan er daardoor toe leiden dat de bestralingdosis in de blaas en de endeldarm terechtkomt in plaats van in de prostaat. Door een IMRT techniek te gebruiken in plaats van een conformale techniek, kan een hoge dosis in de prostaat worden gepland terwijl de dosis op de blaas en endeldarm laag wordt gehouden. In hoofdstuk 5 is onderzocht wat de toxiciteit is na een dosis van 76 Gy met een IMRT techniek in combinatie met positie verificatie op basis van goudmarkers. Hiervoor werd de acute en late toxiciteit gemeten voor 331 patiënten die met deze techniek zijn behandeld voor prostaatkanker. Het gebruik van de nieuwere technieken had tot gevolg dat tijdens en direct na de behandeling (gedefinieerd als de acute toxiciteit) slechts bij 3% van de patiënten ernstige plasklachten optraden en geen ernstige darmklachten. Het percentage ernstige plas- en darmklachten 3 jaar na de behandeling (gedefinieerd als de late toxiciteit) was respectievelijk 4% en 1%. Hieruit kan geconcludeerd worden dat met IMRT en de op goudmarkers gebaseerde positie verificatie, een dosis van 76 Gy op de prostaat goed getolereerd wordt. Door gebruik te maken van deze techniek kunnen de blaas en endeldarm adequaat gespaard blijven. Indien de dosis voorschrift op deze organen niet wordt overschreden is er geen onacceptabele toxiciteit te verwachten wanneer de dosis in de prostaat verder verhoogd wordt.

Kwaliteit van leven

Misschien nog wel belangrijker dan de toxiciteit, is de invloed van een behandeling op de kwaliteit van leven van de patiënt. Voor het meten van de kwaliteit van leven wordt naast de bijwerkingen ook gekeken naar het lichamelijk, psychische en sociaal functioneren en het algehele gevoel van welbevinden. In hoofdstuk 6 wordt het verschil in kwaliteit van leven onderzocht tussen patiënten die voor prostaatkanker bestraald zijn met 70 Gy en met 76 Gy. De 70-Gy groep is behandeld met een conformale techniek in combinatie met positie verificatie op basis van de botten. In de 76-Gy groep werd gebruik gemaakt van IMRT en positie verificatie op basis van goudmarkers. De kwaliteit van leven van patiënten die met 76 Gy werden behandeld was niet slechter dan de patiënten die behandeld werden met 70 Gy. De 76-Gy groep had zelfs een verbeterde kwaliteit van leven na 6 maanden in vergelijking met de kwaliteit van leven van de 70-Gy groep. Dit suggereert dat door de nieuwere bestralingstechniek de dosis op de blaas en de endeldarm lager is geweest ondanks dat de dosis in de prostaat zelf hoger was.

De late bijwerkingen na radiotherapie kunnen tot zeker 3 jaar na de behandeling optreden, daarom is in hoofdstuk 7 gekeken of bij de patiëntengroep die behandeld is met de hoge dosis (76 Gy) de kwaliteit van leven na 3 jaar nog steeds goed is. De kwaliteit van leven ten aanzien van de seksuele activiteit, die direct na de behandeling

verminderd was, is niet hersteld na 3 jaar. Dit werd ook in andere onderzoeken gezien. Alle andere kwaliteit van leven onderdelen waren 3 jaar na de behandeling weer op hetzelfde niveau als voor de behandeling. Het onderdeel 'emotionele rolbeperking' was na 3 jaar zelfs verbeterd ten opzichte van voor de behandeling, wat mogelijk verklaard kan worden doordat 1) patiënten tijd hebben gehad om aan de situatie te wennen, 2) hun interne maatstaf hebben veranderd door een levensbedreigende ziekte en 3) de angst voor een recidief of de dood is in de loop van de tijd minder geworden. De goede kwaliteit van leven resultaten die beschreven worden in hoofdstuk 6 en 7 suggereren dat, indien gebruik wordt gemaakt van nauwkeurige bestralingstechnieken en de dosisvoorschriften op de risico organen niet overschreden worden, een verdere dosis verhoging mogelijk is zonder een verslechtering van de kwaliteit van leven.

FLAME-trial

Op basis van de resultaten beschreven in dit proefschrift kan de dosis in het tumorgebied binnen de prostaat verhoogd worden zonder onacceptabele toxiciteit of een verslechtering van de kwaliteit van leven te verwachten. Hierdoor was het mogelijk om de FLAME (Focal Lesion Ablative Microboost for prostatE cancer)-trial te starten. Deze multicenter trial, waarvan de studieopzet in hoofdstuk 8 wordt beschreven, onderzoekt of een aanvullende bestralingsdosis in het tumorgebied binnen de prostaat betere behandelresultaten geeft. Voor dit onderzoek worden patiënten met prostaatkanker op basis van loting (= randomisatie) verdeeld over 2 groepen (= armen). De patiënten in de standaard arm worden behandeld volgens de huidige richtlijn met 77 Gy op de gehele prostaat. Patiënten die hebben geloot voor de experimentele arm worden naast de standaard dosis van 77 Gy op de gehele prostaat bestraald met een aanvullende dosis tot 95 Gy op het tumorgebied binnen de prostaat. Er moeten 566 patiënten deelnemen aan deze studie om 10% verlaging in het aantal patiënten waarbij de prostaatkanker terugkeert aan te kunnen tonen. De trial is in augustus 2009 gestart en de verwachting is dat binnen 5 jaar de benodigde 566 patiënten hebben meegedaan aan het onderzoek. Naast het terugkeren van prostaatkanker wordt tevens gekeken naar de toxiciteit, de kwaliteit van leven en de overleving na de behandeling. Indien patiënten na de behandeling een terugkeer van de tumor (= recidief) ontwikkelen, zal door middel van beeldvorming de locatie van het recidief in de prostaat bepaald worden. Door dit te combineren met de bestralingsdosis die op deze locatie gegeven is, zal het mogelijk zijn om een nauwkeurige dosis-effect curve te maken. Op deze manier kunnen we erachter komen hoeveel bestralingdosis precies nodig is in de verschillende gebieden van de prostaat.

Conclusie

Gezien de bevindingen in dit proefschrift kan geconcludeerd worden dat het haalbaar is om het zichtbare tumorgebied binnen de prostaat een aanvullende bestralingsdosis te geven. Indien deze aanvullende dosis op het tumorgebied wordt gegeven door middel van moderne planningstechnieken in combinatie met het nauwkeurige positioneren van de patiënt en als de dosis beperkingen voor de risico organen in acht worden genomen, zijn geen ernstige bijwerkingen of een verslechtering van de kwaliteit van leven van de patiënten te verwachten. Op basis van bovenstaande bevindingen was het mogelijk en veilig om de FLAME-trial te starten. In deze gerandomiseerde trial zal onderzocht wat het voordeel is van het geven van een aanvullende dosis op het zichtbare tumorgebied binnen de prostaat. Hopelijk zal dit leiden tot een verbeterde behandeling voor patiënten met prostaatkanker ten aanzien van de tumorcontrole en de kwaliteit van leven.

Chapter 10

References
Nederlandse samenvatting
List of publications
Curriculum vitae
Dankwoord

Lips I.M., Dehnad H., Boeken Kruger A.B., van Moorselaar R.J.A., van der Heide U.A., Battermann J.J., van Vulpen M. Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study. *Int J Radiat Oncol Biol Phys.* 2007;69:656-61.

Van den Bosch M.R., Lips I.M., Lagerburg V., van Vulpen M., Lagendijk J.J., Moerland M.A. Feasibility of adequate dose coverage in permanent prostate brachytherapy using divergent needle insertion methods. *Radiother Oncol*. 2008;86:120-5.

Klein S., van der Heide U.A., Lips I.M., van Vulpen M., Staring M., Pluim J.P. Automatic segmentation of the prostate in 3D MR images by atlas matching using localized mutual information. *Med Phys.* 2008;35:1407-17.

Lips I.M., Dehnad H., van Gils C.H., Boeken Kruger A.E., van der Heide U.A., van Vulpen M. High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. *Radiat Oncol.* 2008;3:15.

Lips I.M., van der Heide U.A., Kotte A.N., van Vulpen M., Bel A. Effect of translational and rotational errors on complex dose distributions with off-line and on-line position verification. *Int J Radiat Oncol Biol Phys.* 2009;74:1600-8.

Lips I.M., van Gils C.H., van der Heide U.A., Boeken Kruger A.E., van Vulpen M. Health-related quality of life 3 years after high-dose intensity-modulated radiotherapy with gold fiducial marker-based position verification. *BJU Int.* 2009;103:762-7.

Roeloffzen E.M.A., Lips I.M., van Gellekom M.P.R., van Roermund J., Frank S.J., Battermann J.J., van Vulpen M. Health-Related Quality of Life up to Six Years After 125I Brachytherapy for Early-Stage Prostate Cancer. *Int J Radiat Oncol Biol Phys.* 2010;76:1054-60.

Lips I.M., Kotte A.N.T.J., van Gils C.H., van Leerdam M.E., van der Heide U.A., van Vulpen M. The influence of an antiflatulent dietary advice on the intrafraction motion for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011 [epub ahead of print].

Lips I.M., Koster M.E.Y., Houwing R.H., Vonk E.J.A. Erlotinib-induced rash spares previously irradiated skin. *Strahlenther Onkol.* 2011;187:499-501.

Lips I.M., van Gils C.H., Kotte A.N.T.J., van Leerdam M.E., Franken S.P.G., van der Heide U.A., van Vulpen M. A double-blind placebo-controlled randomized clinical trial with magnesium oxide to reduce intrafraction prostate motion for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* [accepted for publication].

Lips I.M., van der Heide U.A., Haustermans K, Pos F., van Lin E.N., Franken S.P.G., Kotte A.N.T.J., van Gils C.H., van Vulpen M. Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial). *Trials* [submitted].

Chapter 10

References
Nederlandse samenvatting
List of publications
Curriculum vitae
Dankwoord

Irene Marina Lips is geboren op 14 februari 1982 te Amsterdam. Na het behalen van haar VWO diploma op het Sint-Oelbert gymnasium te Oosterhout begon zij in 2000 met de studie Geneeskunde aan de Universiteit van Utrecht. Na haar afstuderen in 2006 startte zij met promotieonderzoek op de afdeling Radiotherapie in het Universitair Medisch Centrum Utrecht onder supervisie van Dr. M. van Vulpen en Dr. U.A. van der Heide. Vanaf september 2008 volgde zij de opleiding tot Klinisch Epidemioloog aan de Universiteit van Utrecht, welke zij in de zomer van 2011 afrondde. In januari 2009 is zij gestart met de opleiding tot radiotherapeut-oncoloog in het Universitair Medisch Centrum Utrecht in clusterverband met het Radiotherapeutisch Instituut Stedendriehoek en Omstreken, onder supervisie van opleiders Dr. C.H.J. Terhaard en Drs. E.J.A. Vonk. Ze is getrouwd met Bas Snijders en sinds november 2010 hebben zij samen een zoon Boris.

Chapter 10

References
Nederlandse samenvatting
List of publications
Curriculum vitae
Dankwoord

Tot slot wil ik alle mensen bedanken die een bijdrage hebben geleverd aan dit proefschrift en daarbij in het bijzonder de volgende mensen hier noemen.
Allereerst wil ik alle patiënten bedanken voor hun deelname aan de studies, het innemen van de studiemedicatie en invullen van de vragenlijsten. Daarnaast wil ik de behandelende artsen en andere collega's voor hun medewerking bedanken in onder andere de inclusie van patiënten, het scoren van de toxiciteit en het verzamelen van data.
Mijn co-promotoren Dr. M. van Vulpen en Dr. U.A. van der Heide:
Marco, jouw enthousiasme en gedrevenheid waren voor mij een grote stimulans. Dank voor je zorg, je optimisme en je vertrouwen in mij.
Uulke, bedankt voor je heldere en leerzame feedback, je begrijpende woorden en dat we jaarlijks van jouw kookkunsten mochten genieten tijdens het prostaatetentje.
Prof. Battermann en prof. Lagendijk, door jullie visie op het wetenschappelijk onderzoek heb ik mij kunnen ontwikkelen. Dank voor de kansen die jullie mij hebben geboden.
De leescommissie: prof.dr. P.H.M. Peeters, prof.dr. I.H.M. Borel Rinkes, prof.dr. J.L.H.R. Bosch en prof.dr. M.A.A.J. van den Bosch, bedankt voor het beoordelen van mijn manuscript.
Alle mede-auteurs bedankt voor de plezierige samenwerking en jullie bijdrage.
Alexis, dank voor al je hulp, de gezelligheid en de ingewikkelde discussies waardoor ik uiteindelijk een beetje denk te begrijpen hoe je schudt.
Carla, dank voor de waardevolle input op het gebied van klinische epidemiologie en je zorgvuldige feedback op de manuscripten. Ik bewonder de manier waarop jij zo snel de vinger op de zere plek weet te leggen.
Alle naaste collega's met wie ik de afgelopen jaren heb gewerkt, dank voor jullie steun en het meedenken met het onderzoek en alles wat daarbij komt kijken. Dankzij alle leuke collega's op de afdeling ga ik iedere dag met veel plezier naar mijn werk. Radiotherapeuten, A(N)IOS, klinisch fysici, klifio's, onderzoekers, laboranten, doktersassistenten en secretaresses bedankt voor de gezelligheid en de goede werksfeer.
Mijn paranimfen, lieve Maaike en Sabine, bedankt voor jullie luisterend oor en het delen van onderzoekservaringen. Ik vind het een fijn gevoel om jullie naast mij te hebben op 21 oktober, zoals jullie ook in mijn leven dicht bij mij staan.
Lieve familie en vrienden, dank voor de ontspanning en alle vrolijkheid buiten mijn onderzoek. Lieve Adri en Corry, jullie hebben mij geleerd om mijn best te doen en me te ontwikkelen. Bedankt dat jullie zo met me meeleven en voor de oprechte interesse in mijn onderzoek. Lieve Boris, jouw bestaan relativeert alles op een mooie manier en dichter bij het hebben van een prostaat ben ik niet gekomen. Lieve Bas, ik voel me een bevoorrecht mens dat ik iedere dag van jou mag genieten. Dank voor al je wijze woorden en adviezen. Je maakt me een gelukkiger mens.