

**Erectile Dysfunction after External Beam
Radiotherapy for Prostate Cancer
Can it be prevented?**

Gerard Johan van der Wielen

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Cover: Nepalese stone Shiva Lingam (900-1000) on display at the Asian Art Museum in San Francisco, California. The Hindu god Shiva is the destroyer, without whom creation could not occur. Shiva's creative role is phallically symbolized by his representation as the frequently worshipped Shiva Lingam.

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Can it be prevented?

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**Erectile Dysfunction after External Beam Radiotherapy for Prostate Cancer
Can it be prevented?**

**Erectiele disfunctie na uitwendige radiotherapie voor prostaatkanker
Is preventie mogelijk?**

Proefschrift

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Chapter 1

Introduction

RADIOTHERAPY FOR PROSTATE CANCER

Around 8000 men are diagnosed with prostate cancer in the Netherlands every year (1). With the exception of skin cancer, it is the most common type of cancer in men. There are several ways to treat prostate cancer: hormonal therapy, radical prostatectomy, brachytherapy and external beam radiotherapy or a combination of these. A large part of the patients is treated with external beam radiotherapy. Three-dimensional conformal radiotherapy has been the standard technique for more than a decade.

In three-dimensional conformal radiotherapy a computed tomography (CT) scan, called a planning CT scan, is performed in order to image the prostate and the surrounding organs. The physician delineates the prostate and anatomical structures that may cause radiation-induced toxicity, the organs at risk. Using this planning CT scan a treatment plan is made with the goal to distribute a high radiation dose in the prostate and a minimal dose in organs at risk, like the rectum. To achieve this goal radiation beams incident from various directions are created conform to the contour of prostate, avoiding the organs at risk. However, there are several uncertainties regarding delineation of the planning CT scan, deformation and movement of the prostate and patient (2). Therefore a margin of commonly 1 cm around the prostate is added to account for these uncertainties. The actual radiotherapy treatment is then delivered during 7 or 8 weeks in up to 39 fractions of 2 Gray (Gy) in our institute.

ERECTILE DYSFUNCTION AFTER RADIOTHERAPY

All forms of treatment for prostate cancer, radiotherapy, prostatectomy and hormonal therapy, have an impact on sexual functioning and especially on erectile function (3-5). Because there is no clear evidence showing a survival benefit for one treatment above another (6), differences in quality of life after treatment, including sexual function, might influence the choice of treatment. A patient must be informed about the consequences of different treatments to enable the patient to make a rational choice.

Since the introduction of three-dimensional external beam radiotherapy, a large number of prospective studies analyzed what is called 'genito-urinary' toxicity after radiotherapy. Although erectile dysfunction is a common complication only a few prospective studies report on the 'genito' part of genito-urinary toxicity. However, most of these studies were hampered by the lack of questionnaires, inadequate follow-up, no exclusion of hormonal therapy or no information about the use of potency aids (7-13).

There are three essential anatomical structures in the vicinity of the prostate to achieve and maintain an erection. First of all, cavernous nerves, originating from the neurovascular bundles supply the penis with nitric oxide (NO) to start an erection (14). Secondly, the arterial flow through the internal pudendal arteries into the penis increases. The third structure is

formed by the corpora cavernosa, which ensure adequate trapping of blood to build up pressure (known as the veno-occlusive mechanism) (15).

Figure 1 shows a figure from McLaughlin et al. (16) displaying the basic anatomy in the vicinity of the prostate, including three nerve and vascular pathways. The posterior lateral pathway includes the neurovascular bundles, while the inferior lateral pathway includes the internal pudendal artery. (The anterior inferior pathway includes the dorsal venous complex).

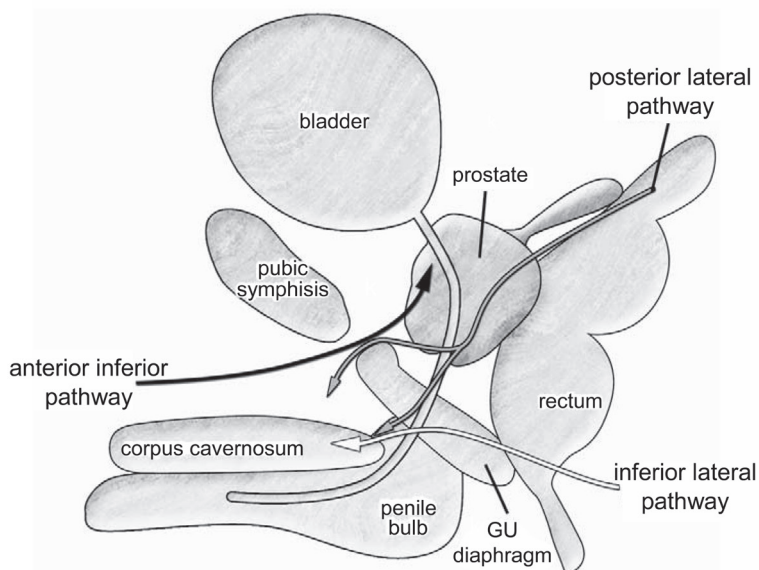


Figure 1. Basic anatomy in the vicinity of the prostate including nerve and vascular pathways.

GU diaphragm = genitourinary diaphragm.

(By the courtesy of Patrick W. McLaughlin).

PREVENTING ERECTILE DYSFUNCTION

There are two strategies to reduce the risk of erectile dysfunction after radiotherapy for prostate cancer. The first strategy is to find an anatomical structure that is responsible for erectile dysfunction. If such a structure is found treatment plans can be adjusted so that this structure is spared. The second strategy is to reduce the treatment margin, by minimizing one or more of the uncertainties for which the treatment margin is needed. If the treatment margin is reduced, all structures including those essential for a penile erection will receive a lower radiation dose.

The anatomical structure that is responsible for erectile dysfunction after radiotherapy might be found by analyzing the correlation between the radiation dose that is received by

that structure and whether or not erectile dysfunction has occurred. The corpora cavernosa and penile bulb can be easily seen on the planning CT scan and the radiation received by them can be analyzed. Although most studies have insufficient follow-up, are retrospective in nature or lack statistical power, some authors have already advised to spare the penile bulb (17-22). However, according to Dean and Lue the corpus spongiosum, which includes the penile bulb, is not essential during an erection. The corpus spongiosum only builds up one third to one half of the pressure of that in the corpora cavernosa, because it has minimal venous occlusion (15). If sparing of the penile bulb is achieved at the cost of reducing the margin around the apex, which often contains cancer cells, an oncological risk is taken (23-25). It is important to critically review all available literature on this topic and consider the alternatives, before one changes the clinical treatment.

Several studies have analyzed the neurovascular bundles and have not found any correlation between the radiation dose in the neurovascular bundles and erectile dysfunction after radiotherapy (26-30). The neurovascular bundles are in close proximity to the prostate. Therefore it would be difficult to completely spare the neurovascular bundles without losing target coverage. However, it is possible to reduce the volume of the neurovascular bundles that receives the full radiation dose.

So far only one study has analyzed the correlation between the radiation dose in the corpora cavernosa and erectile dysfunction after external beam radiotherapy (31). This retrospective study only analyzed 28 patients, making its conclusion disputable. The corpora cavernosa seem a likely structure to be responsible for erectile dysfunction after radiotherapy for prostate cancer. Several studies have concluded that the arterial blood flow in the cavernosal arteries is decreased in patients with erectile dysfunction after radiotherapy for prostate cancer (32-34).

Besides clinical studies, the structures potentially involved in erectile dysfunction after radiotherapy can also be investigated by animal experimental studies. The advantage of such an approach is that an actual histological analysis of the radiation damage to the different structures can be performed. So far, only two studies have used this approach with rats. Those two studies used one single fraction of radiation, while in the clinical treatment all patients are treated with multiple fractions. Development of a rat model treated with multiple fractions will also allow the evaluation of pharmacons that stimulate the arterial flow in the penis. Several studies, mostly animal experimental studies, have suggested that the use of such pharmacons might help in the recovery of erectile function after nerve-sparing prostatectomy (35). However, there are no reports available on the use of such pharmacons after radiotherapy for prostate cancer.

The second strategy to reduce the risk of erectile dysfunction is the reduction of the treatment margin around the prostate. If the treatment margin can be reduced, all structures around the prostate, including those responsible for erectile dysfunction, will receive a lower radiation dose. A treatment margin accounts for uncertainties regarding delineation,

deformation and movement. By reducing one or more of those uncertainties the treatment margin can be reduced without compromising target coverage.

The uncertainty of movement can be reduced by implanting gold cylinders, fiducial markers, into the prostate. Figure 2 shows an example of these fiducial gold markers. In the planning CT scan the positions of the fiducial markers can be correlated to the contours of the prostate. Before each treatment fraction the fiducial markers can be imaged from two orthogonal angles. This will give a precise location of the prostate. If the treatment couch is then shifted to accurately place the prostate at its intended position, there is a possibility to reduce the treatment margin.

Although this method allows improvement in positioning of the prostate, information about deformation of the prostate relative to the fiducial markers is required before a new, reduced treatment margin can be calculated. The deformation can be quantified by using repeat CT scans of prostate cancer patients with implanted fiducial markers. This information is then used to calculate a new smaller treatment margin, which reduces the radiation dose in all structures surrounding the prostate, including those responsible for erectile dysfunction.

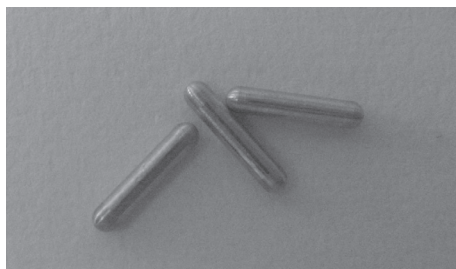


Figure 2 shows three fiducial gold markers used for implantation in the prostate. The markers are 1 mm in diameter and 5 mm in length.

SCOPE OF THIS THESIS

The general scope of this thesis is to find causes of radiation-induced erectile dysfunction and feasible methods to prevent erectile dysfunction after external beam radiotherapy for prostate cancer.

First it must be assessed whether prostate cancer patients are sexually active and to what extent external beam radiotherapy for prostate cancer causes erectile dysfunction (Chapter 2).

If the radiotherapy causes erectile dysfunction, certain anatomical structures must be involved in this process. A critical review of all studies on this topic is performed, to conclude whether or not treatment plans should already be adapted to avoid a specific structure (Chapter 3).

There are no prospective studies investigating the correlation between erectile dysfunction after external beam radiotherapy and the radiation dose to the corpora cavernosa, while

several studies found a decreased flow in the cavernosal arteries after radiotherapy (32-34). This thesis reports on the first prospective study published on this subject (Chapter 4).

Animal experimental studies allow a histological analysis of the effects of radiotherapy to the prostatic area. A pilot study is performed to analyze the impact of fractionated irradiation of the prostate on the penile arteries of the rat (Chapter 5).

Besides finding a specific structure that is responsible for erectile dysfunction, it is also possible to reduce the treatment margin. If the treatment margin is reduced, all structures including those essential for an erection will receive a lower radiation dose.

A method called stereographic targeting was developed in our institute. Stereographic targeting is a procedure for daily positioning corrections of the prostate based on implanted fiducial markers, which allows a reduction of the treatment margin without losing target coverage (Chapter 6).

However, before such a margin can be calculated, the deformation of the prostate relative to the fiducial markers must be quantified. A study was performed in which patients were implanted with fiducial markers, after which the deformation was analyzed with repeat CT scans using deformable registration (Chapter 7).

In the Discussion and Conclusion, the studies in this thesis and the ongoing studies are put in a broader perspective and a final conclusion is drawn (Chapter 8).

Chapter 2

Sexual function after three-dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial

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ABSTRACT

Purpose

The purpose of this study is to provide information about sexual function (SF) after three-dimensional conformal radiotherapy (3D-CRT) for prostate cancer while taking important factors into account that influence SF.

Methods and Materials

Between June 1997 and February 2003, a total of 268 patients from a randomized dose-escalation trial comparing 68 Gy and 78 Gy agreed to participate in an additional part of the trial that evaluated SF.

Results

At baseline 28% of patients had erectile dysfunction (ED). After 1 year, 27% of the pretreatment potent patients had developed ED. After 2 years this percentage had increased to 36%. After 3 years it almost stabilized at 38%. Satisfaction with sexual life was significantly correlated with ED. After 2 years one third of the pre-treatment potent patients still had considerable to very much sexual desire and found sex (very) important. No significant differences were found between the two dose-arms. Potency aids were used on a regular base by 14% of the patients.

Conclusion

By taking adjuvant hormonal therapy (HT), HT during follow-up and potency aids into account, we found a lower percentage of ED after 3D-CRT than reported in previous prospective studies. A large group of patients still had sexual desire, considered sex important and 14% used potency aids after 3D-CRT.

INTRODUCTION

Prostate cancer is the most common type of cancer in men in Western countries with the exception of basal and squamous cell skin cancers (36). There are several treatment modalities for prostate cancer: radical prostatectomy, external beam radiotherapy, brachytherapy, and hormonal therapy (HT). Because there is no clear evidence showing a survival benefit for any of these therapies above another (6), quality of life after treatment, including sexual function (SF), should influence the choice of treatment. Reliable information about the consequences of different types of treatment should be provided to all patients, to enable them to make a more rational choice of therapy. A decrease in SF is a common side effect in all forms of treatment for prostate cancer and is associated with impaired quality of life (37,38). Since the introduction of three-dimensional conformal radiotherapy (3D-CRT), several prospective studies have provided reliable information about health-related quality of life after such treatment for prostate cancer. Most studies have concentrated on gastro-intestinal and genitourinary toxicity. Less attention has been paid to SF. Studies reporting on SF after 3D-CRT have focused primarily on erectile dysfunction (ED), whereas sexual interest, pleasure, and activity are a significant part of SF as well. Limitations in prospective studies to the effect of 3D-CRT on ED have led to a large difference in reported ED rates, varying from 7% to 59% (7-11). Physician documented ED provides one of those limitations. Physicians tend to underestimate symptoms causing health related quality of life impairment (39). One study, using physician documented ED, reported a remarkably low percentage of post-irradiation ED of only 7% (8). On the other hand, patient documented ED by means of questionnaires provides more reliable results (39). Some studies were not designed with an objective to provide an accurate ED rate. These studies did not have an adequate follow-up period of at least 18 months with a sufficient number of patients (7,9). The time elapsed between 3D-CRT and ED evaluation is important as one should wait at least 18 to 24 months when ED occurrence reaches a maximum and remains stable further on (40). There are three more important factors that must be considered when evaluating SF. These factors are adjuvant HT, HT during follow-up because of biochemical or clinical relapse and the use of potency aids, like phosphodiesterase-5 (PDE5) inhibitors, intracavernosal injections (ICI), penis rings, and vacuum devices. So far, prospective studies reporting on SF after 3D-CRT did not take all of these factors into account (7-11).

The purpose of this present study is to report on the effect of 3D-CRT not only on erectile function but on other domains of SF as well, taking important factors into account that influence SF like adjuvant HT, HT during follow-up and potency aids.

METHODS AND MATERIALS

Our center coordinated a Dutch multicenter Phase III dose-escalation trial (trial code CKVO 96-10), in which patients with a localized adenocarcinoma of the prostate were randomized between prescribed dose levels of 68 Gy and 78 Gy. In our center 404 patients were included in this trial. All of them were asked to participate in an additional part of the trial in which quality of life and SF would also be evaluated. Between June 1997 and February 2003, 268 patients agreed to participate in the additional part of the trial in which SF would be evaluated. Forty-five patients were excluded because they did not fill out the questionnaire on SF within 30 days after trial registration. There is evidence that adjuvant HT (11), as well as HT as monotherapy (3), has a significant impact on SF. Because of treatment with adjuvant HT 29 patients were excluded from analysis, unless stated otherwise. Furthermore, patients who had a relapse were censored at the time of relapse. A relapse was defined as: biochemical relapse according to the ASTRO definition of 1996 (41), clinical relapse, or the start of therapy such as HT during follow-up or salvage therapy, whichever comes first.

Radiotherapy

The details of the dose-escalation trial have been described extensively before (42). Briefly, dose-volume groups were defined according to the risk of involvement of the seminal vesicles, according to Partin et al. (43). Patients with a T1b, T1c, and T2a prostate cancer with a risk of involvement of <10%, 10%–25%, and >25% were included in dose-volume Groups 1, 2, and 3, respectively. All patients with a T2b and T3a were treated in Group 3. Group 4 comprised all patients with a T3b or T4. For each dose-volume group, specific planning target volumes were defined. For dose-volume Groups 1 and 4, the clinical target volumes (CTVs) were defined as the prostate only and as the prostate with seminal vesicles, respectively. In dose-volume Groups 2 and 3, the seminal vesicles were excluded from the CTV after 50 Gy and 68 Gy, respectively. For all patients, a margin of 10 mm was added to the CTV to obtain the planning target volume for the first 68 Gy, and this margin was reduced to 5 mm (except toward the rectum where no margin was taken) for the last 10 Gy in the 78 Gy arm. In our center 3D-CRT was used with a 3-field technique using one anterior and two lateral wedged fields. In the high treatment arm a boost of 10 Gy was given with the same technique. The dose was specified to the ICRU reference point (2) and was delivered in fractions of 2 Gy. Treatment with adjuvant HT, duration and type of adjuvant HT was left to the discretion of the referring physician.

Sexual function

The SF was assessed with the Dutch module on sexual activity (SAC) consisting of 10 single items that do not add up to a scale (44). Sexual activity was defined as masturbation or intercourse. Each item contains three to five answer categories. A skip pattern enables differentiating in sexually active vs. inactive men. Sexually inactive men were asked why they were

inactive (no desire; no partner; partner had no desire; ED or other reasons), while sexually active men were asked whether ED (problems with achieving or maintaining erections) had occurred. Other items assessed spontaneous erections (not during sexual activity), desire, satisfaction with SF and importance of sex. Six retrospective questions were added to the SAc to assess the influence of the diagnosis of prostate cancer on SF. A copy of the complete questionnaire has been included in a previous article (45). ED was defined as (almost) always having problems in achieving or maintaining an erection if wished to, or not being sexually active because of erectile problems. The questionnaire was given to the patient at baseline and at 6 months, 1, 2, and 3 years after the start of 3D-CRT. The number of patients per item may fluctuate due to the fact that not all patients answered every question.

The study was designed before the introduction of oral PDE5-inhibitors, so no assessment of potency aids was done. Therefore a questionnaire was developed to retrospectively assess the use of potency aids: PDE5- inhibitors, ICI, intraurethral alprostadil, vacuum devices and/or a penisring. In June 2006 this questionnaire was sent to all patients, including those who used adjuvant HT, with at least 2 years of follow-up who did not have ED at baseline and who were alive at the moment the questionnaire was sent. The patients were asked 3 questions: Whether they had used potency aids on a regular base before 3D-CRT, during the first 2 years after 3D-CRT and/or after more then 2 years after 3D-CRT. Patients could answer "yes" or "no." When answering "yes" they were asked to make a choice between different kinds of potency aids.

Statistical Analysis

The statistical analysis was primarily descriptive. Differences between patient characteristics were tested with the Kruskal-Wallis and the Pearson Chi-square test. Correlation between ED and spontaneous erections was tested with the Pearson Chi-square test. Correlation between satisfaction with sexual life and ED was tested with the Kruskal-Wallis test. A separate analysis was performed to assess the correlation between being sexually active and adjuvant HT. Differences in being sexually active were tested with the Pearson Chi-square test.

RESULTS

Impact of the diagnosis of prostate cancer

Of the patients, 59% (114/192) recalled being sexually active before the diagnosis of prostate cancer. For the sexually active patients the diagnosis of cancer led to an important decrease in sexual activity in 33% (37/113), in sexual interest in 29% (33/113), in sexual pleasure in 18% (20/111); and there was an increase in problems achieving and/or maintaining an erection in 29% (32/111). In the 2 weeks before filling out the baseline questionnaire 52% (101/194) of the patients were sexually active.

Sexual function at baseline

Fifty-five out of 194 patients (28%) already had ED at baseline (Fig. 1). Of these 55 patients, 15 (27%) reported having always had problems with achieving and/or maintaining an erection but remained sexually active, either by masturbation or intercourse. All but one of these patients described their erection quality as semi rigid to flaccid. Of all patient characteristics only cardiovascular history was significantly correlated with ED at baseline ($p = 0.02$) (Table 1). Furthermore 38% (53/139) of the patients who did not have ED, were not sexually active. Patients were allowed to give more than one answer to the question why they were not sexually active. The most common reasons were: no desire in 55% (29/53) and no partner or a partner without desire in 26% (19/53).

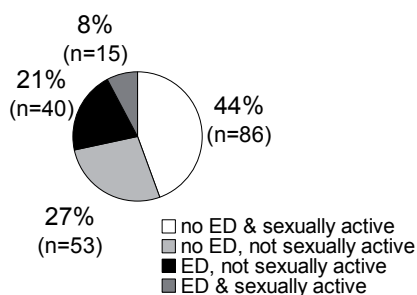


Figure 1. Erectile dysfunction (ED) and sexual activity at baseline

Characteristics	ED at baseline		No ED at baseline	
	both arms (%)	both arms (%)	68 Gy (%)	78 Gy (%)
Number of patients	55	139	66	73
Mean follow-up, months	31	27	27	28
Median age, years	70	68	68	68
Mean PSA, $\mu\text{g/L}$	14.5	13.0	12.7	13.2
T-stage \geq T3	13/53 (25)	44/137 (32)	21/64 (33)	23/73 (32)
Gleasonscore \geq 7	18/47 (38)	64/118 (54)	30/57 (53)	34/61 (56)
Diabetes Mellitus	4/55 (7)	4/139 (3)	2/66 (3)	2/73 (3)
Cardiovascular history	23/55 (42)*	35/139 (25)*	18/66 (27)	17/73 (23)

Table 1. Patient characteristics at baseline. The characteristics for patients with and without erectile dysfunction (ED) are shown separately. The characteristics for the standard arm (68 Gy) and the dose escalation arm (78 Gy) of the patients without ED are also shown separately.

PSA = prostate specific antigen

* $p=0.02$ Pearson chi-square test to compare patients with and without ED at baseline

Impact of radiotherapy

To assess the impact of 3D-CRT on SF, 55 patients of the 194 were excluded because they already had ED at baseline, leaving 139 patients for this analysis. After 1 year 27% of the patients

had developed ED (Fig. 2a). After 2 years this percentage had increased to 36%, after which the percentage of ED almost stabilized. After 3 years 38% of the patients had ED. Most of the patients suffering from ED after 2 years (20/35) were still sexually active. Despite the fact that they (almost) always had problems with achieving or maintaining an erection, they were still able to have intercourse or masturbate. All of these patients but one described the quality of erection as semi rigid to flaccid. There was a decline in sexual activity from 62% at baseline to 51% 2 years after 3D-CRT (Fig. 2b).

Of the patients, 29 were still sexually active and had not developed ED 2 years after 3D-CRT. Although they did not develop ED, 48% (13/27) of those patients did have a decline in erectile function. They had more problems with achieving (7/27) and/or maintaining (8/27) an erection and/or had a decline in the quality of erection (10/27) compared with their baseline.

There was a decrease in having spontaneous erections (not during sexual activity) from 70% (95/136) at baseline to 47% (46/97) after 2 years. Absence of spontaneous erections was significantly correlated with ED 2 years after 3D-CRT ($p < 0.01$). The percentage of patients indicating to have considerable to very much desire became slightly lower from 41% (56/136) at baseline to 32% (31/96) after 2 years. This was comparable for patients finding sex important or very important. At baseline 40% (55/137) of the patients found sex (very) important. After 2 years this percentage was 31% (30/97). At baseline 54% (73/134) of the patients were satisfied or very satisfied with their sexual lives, which was slightly lower after 2 years, 45% (42/94). Satisfaction with sexual life was significantly correlated to ED 2 years after 3D-CRT ($p < 0.01$). No statistically significant differences in ED, sexual activity, spontaneous erections, sexual desire, importance of sex or satisfaction with sexual life were found between the standard arm (68 Gy) and the dose-escalation arm (78 Gy) at 1, 2, and 3 years after 3D-CRT.

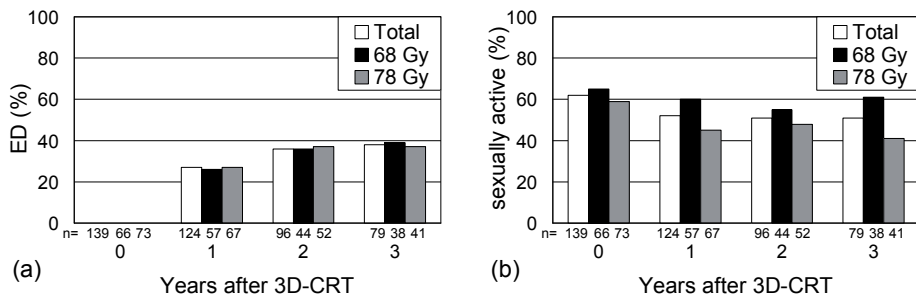


Figure 2. Percentage of patients with erectile dysfunction (ED) (A) and sexually active patients (B) at baseline and after three-dimensional conformal radiotherapy (3D-CRT). Patients with ED at baseline are excluded. The total number of patients (n) is shown under each bar. Differences in ED and sexual activity between the standard arm (68 Gy) and the dose escalation arm (78 Gy) were compared (Pearson Chi-square test). No significant differences were found.

Hormonal therapy

Twenty-nine patients were treated with adjuvant HT. This group of patients did not differ significantly from the group who did not receive adjuvant HT with respect to randomization arm ($p = 0.89$), Gleason score ($p = 0.17$), diabetes ($p = 0.27$), or cardiovascular history ($p = 0.16$). The mean age of patients treated with adjuvant HT was lower, 66 vs. 68 years, but this difference was not significant ($p = 0.10$). Patients treated with adjuvant HT had a significantly higher T-stage ($p < 0.01$) and a significantly higher mean PSA ($p < 0.01$). Significantly more patients treated with adjuvant HT were sexually active before diagnosis (Fig. 3). Adjuvant HT was started before the baseline questionnaire was filled out, and at baseline, the difference in sexual activity between the two groups was no longer significant. One year after 3D-CRT significantly less patients treated with adjuvant HT were sexually active. The difference between the 2 groups remained almost the same at 2 and 3 years after 3D-CRT, but the number of patients was less. So no statistically significant difference was found 2 and 3 years after 3D-CRT.

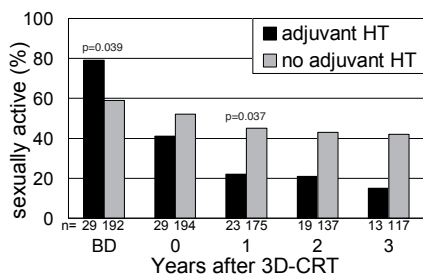


Figure 3. Percentages of sexually active patients treated with and without adjuvant hormonal therapy (HT) before diagnosis (BD) and at each year after three-dimensional conformal radiotherapy (3D-CRT). The total number of patients (n) is shown under each bar. Differences in sexual activity between patients treated with and without adjuvant HT were compared (Pearson Chi-square test). Values of $p < 0.05$ are shown.

Potency aids

The questionnaire assessing the use of potency aids was sent to all patients with at least 2 years of follow-up who did not have ED at baseline. In this case the questionnaire was also sent to patients who were treated with adjuvant HT. Seventeen patients were deceased and the addresses of three patients could not be retrieved. Questionnaires were sent to 91 patients of whom 81 patients responded (89%). Only one patient already used ICI before 3D-CRT and continued using it after 3D-CRT. Six patients started using oral PDE5-inhibitors within 2 years after 3D-CRT. Only one of these patients indicated not to have ED during follow-up in the SAC. He added the statement that he did have ED when not using a PDE5 inhibitor. None of the patients reported use of vacuum devices or urethral alprostadil. After more than 2 years after 3D-CRT 14% (11/81) of the patients used potency aids on a regular base.

DISCUSSION

Several studies, including one randomized controlled trial with HT as monotherapy, reported that HT has a significant impact on SF (3,11,46). Zelefsky et al. (11) reported that neoadjuvant HT increased the risk of ED even 5 years after 3D-CRT. Chen et al. (9) reported however that adjuvant HT did not appear to have an impact on SF after 3D-CRT. Our study showed a significant correlation with adjuvant HT and sexual activity. We believe that excluding patients treated with adjuvant HT will lead to a more precise assessment of the impact of 3D-CRT on SF. Potosky et al. (46) reported that HT as monotherapy not only has a significant impact on being sexually active, but also impacts libido and erectile function. In the present study the retrospective questions assessing sexual desire and erectile function before the start of adjuvant HT could not be compared with prospective questions during follow-up. Patients treated with HT during follow-up were censored at the start of HT. Therefore the effect of HT during follow-up on SF could not be analyzed in this study. A Kaplan-Meier plot in the study from Borghede et al. (8) did show that HT during follow-up after 3D-CRT has an impact on potency, although no statistical analysis was performed.

Most patients using potency aids reported ED in the SAC. Only one indicated no ED. Therefore the use of potency aids did not have an important influence on the percentage of ED in this study. Excluding patients, using potency aids, from this analysis would lead to a false low percentage of ED. Several validated questionnaires that assessed SF were available when this study was designed (47-51). However, no validated Dutch translations of those questionnaires were available at the moment of study design, but there was experience with the SAC in several studies (45,52,53). The SAC has been evaluated by Korfage et al. (44). The SAC has some advantages compared with the International Index of Erectile Function (IIEF) questionnaire (54). A large part of the IIEF questionnaire regards questions on sexual intercourse with penetration. Therefore the IIEF questionnaire is not suitable for homosexual men, patients without a sexually active partner or patients without a partner.

The diagnosis of prostate cancer resulted in a decrease in SF, although it must be considered that SF before diagnosis was assessed retrospectively. This agrees with a previous study from Incrocci et al. (45). Korfage et al. (55) reported the results of a prospective study on the impact of diagnosis on the patient's quality of life. Assessment of quality of life in a large group of patients who were about to be screened for prostate cancer was performed. In the men, who were diagnosed with prostate cancer, quality of life 2 months before diagnosis was compared with quality of life 1 month after diagnosis. diagnosis of prostate cancer led to a significant decline in quality of life (55).

So far the focus of studies on SF after 3D-CRT has been on ED. This study reports on sexual activity as well. A large percentage of the men with ED remained sexually active (20/35), even though almost all of the patients indicated to have a semirigid to flaccid penis during sexual activity. This raises the interesting question whether patients who have ED after 3D-CRT, might

remain sexually active by means of masturbation or oral sex, if their erection is insufficient for intercourse. To our knowledge this question has not been answered yet.

Zelevsky et al. (11) reported about a large group of 743 patients. Potency was defined as the ability to achieve an erection adequate for penetration. Of the patients, 27% were impotent before treatment, which is comparable to our 28%. The 5-year actuarial likelihood risk of potency loss was 60%. A significant difference was found between the 5-year actuarial likelihood risk of potency loss of 69% in patients treated with neoadjuvant HT and 56% in patients treated with 3D-CRT alone. The 5-year actuarial likelihood risk of 56% is higher than the ED rate in the present study of 38% after 3 years. Although a different definition for ED was used, there are other reasons as well that may explain why their rate of ED was higher. It is unclear whether patients treated with HT during follow-up were censored at the start of HT (11). Another difference is the longer follow-up period in their study. Although several studies that censored patients at the start of HT in follow-up, including the present study, report that the ED rate stabilizes after 2 years (8,10), a Kaplan-Meier plot in the study from Borghede et al. (8) clearly showed an increase in ED rates after 2 years only in patients treated with HT during follow-up.

Turner et al. (10) reported on a group of 290 patients. Total impotence was defined as the inability to achieve an erection at all or an inability to ever maintain an erection adequate for intercourse. Forty-seven patients with adjuvant HT were identified, but they were not excluded from analysis. Thirty-nine patients treated with HT during follow-up were censored at the start of HT. The baseline ED rate of 37% was higher than our 28%. Again, a different definition was used, but another explanation might be the fact that 16% of the patients were treated with adjuvant HT, but were not excluded from the analysis. The percentage of total impotence at 2 years after 3D-CRT was 59%. This percentage is higher than our 36% of ED at 2 years after 3D-CRT. Zelevsky et al. (11) reported that neoadjuvant HT leads to a significant higher percentage of ED. Furthermore only one third of the potent patients at baseline had a sufficient follow-up of 2 years. So compliance in follow-up was low. These two factors, next to the use of another definition, may contribute to the difference between the ED rate of 59% from the Turner study (10) and the 36% of the present study.

Zelevsky et al. (11) were the first to report that a higher radiation dose is significantly correlated with a higher incidence of ED after 3D-CRT. We did not find this correlation in our study. Although differences were seen in sexual activity between the standard arm and the dose-escalation arm, these differences were not statistically significant. Between our report and the report by Zelevsky et al. (11), there are two differences concerning the correlation between dose-escalation and ED. Zelevsky et al. (11) had a larger patient group. Furthermore, our report presents the results from a randomized dose-escalation trial, whereas the report of Zelevsky et al. (11) is based on a study in which the treatment with different dose levels was done sequentially during 7 years. Little et al. (56) did not find a difference in ED in their randomized dose escalation trial of 70 Gy vs. 78 Gy. Their group of 211 patients was smaller

than the patient group of Zelefsky et al. (11) and assessment of SF at baseline was done retrospectively. Furthermore the patients in the 70 Gy arm were treated with conventional radiotherapy, whereas the patients in the 78 Gy arm were treated with 3D-CRT for the last 16 fractions of 2 Gy. Given the contradictory data concerning the role of dose-escalation in ED after 3D-CRT, we believe that more research is needed to come to a final conclusion.

CONCLUSION

Previous prospective studies on the effect of 3D-CRT on SF may not have excluded all patients treated with adjuvant HT and censored patients treated with HT during follow-up at the start of HT. Therefore they might have given an overestimation of the rate of ED after 3D-CRT (10,11). We found an ED percentage of 36% 2 years after the start of 3D-CRT. We did not find a difference in ED between the two dose levels (68 Gy vs. 78 Gy). Two years after 3D-CRT almost half of the sexually active men who did not develop ED did have a decline in erectile function, about one third of the patients still had considerable to very much sexual desire and one third found sex (very) important. Potency aids were used regularly by 14% of the patients. Lower satisfaction with sexual life was significantly correlated with development of ED. Finding new techniques to lower the prevalence of ED after 3D-CRT for prostate cancer, has a great potential to improve the quality of life after treatment.

Chapter 3

Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review

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ABSTRACT

Erectile dysfunction (ED) is a common sequela after external beam radiotherapy and brachytherapy for prostate cancer. There are several structures in the vicinity of the prostate that are critical to erectile function and that receive a substantial radiation dose: neurovascular bundles (NVBs), internal pudendal arteries (IPAs), accessory pudendal arteries, corpora cavernosa and the penile bulb. Most reports analyzing the correlation between radiation dose to these structures and radiation-induced ED are limited by the small number of patients analyzed in each study. So far, there is no evidence for a role of the NVBs in radiation-induced ED. There are no reports on the IPAs, based on reduced arterial flow in the penis. Several studies show contradicting results on the corpora cavernosa, which house the erectile tissue required for erection. There are contradicting reports on the penile bulb, although studies with more patients tend not to find any correlation. Sparing of the penile bulb to improve potency-preservation is not sufficiently supported by the current literature. If sparing of the penile bulb is achieved by reducing the margin for the apex, an oncological risk is taken, while it is uncertain whether this will improve potency-preservation.

INTRODUCTION

There are three major requirements for adequate penile erection (i) functioning cavernous nerves which supply the penis with nitric oxide (NO) (14) (ii) arterial inflow through the internal pudendal or accessory pudendal arteries and (iii) healthy erectile tissue which ensures adequate trapping of blood in the penis to maintain erection (known as the venoocclusive mechanism) (15). The corpora cavernosa which house the erectile tissue (composed predominantly of smooth muscle, collagen and endothelium) are paired structures which are joined by a septum as they lie within the external penis. These structures diverge as the urethra passes cephalad into the bladder and each passes underneath its respective ischiopubic ramus (Fig. 1A). The corpus spongiosum, which is strictly speaking not an erectile body, surrounds the urethra. At the point of divergence of the corpora cavernosa the spongiosum is known as the bulb (Fig. 1B). Thus, the aforementioned anatomic structures are in close proximity to the prostate and the field of radiation. Erectile dysfunction (ED) is one of the most common sequelae of radiotherapy for prostate cancer, affecting 36–59% of patients after external beam radiotherapy (EBRT) (5,10,11) and 24–50% after brachytherapy (BT) (57-59) according to prospective studies.

Understanding the anatomic structures responsible for radiation-induced ED will enable radiation oncologists to avoid delivery of a high radiation dose to those structures. DiBiase et al. (26) were the first to investigate this area. Since then many reports on this subject have followed. The purpose of this review is to provide a critical overview of these reports.

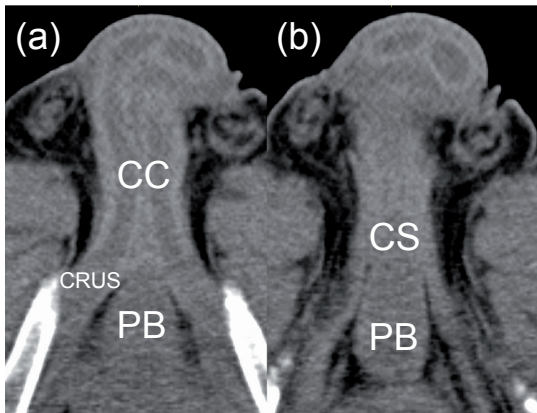


Figure 1. (a) The penile bulb (PB), the corpora cavernosa (CC) and the crura (crus) on a CT can. (b) The penile bulb is continuous with the rest of the corpus spongiosum (CS) in a more caudal CT slice.

MATERIALS AND METHODS

On June 18, 2007 a systematic search for published articles was performed using the electronic database PubMed. The following search terms were included erectile, penile, bulb, crura, crus, cavernosa, cavernous or neurovascular in combination with the search term prostate and the search terms radiation, radiotherapy, brachytherapy or implantation. There was no limit applied on publication year, language or study design. All articles providing data on the correlation between erectile dysfunction after radiotherapy and the radiation dose in specific structures, other than the prostate, were selected. Further articles were found by scanning reference lists or relevant articles. The selected articles were entered into a database, using reference software (Reference Manager).

RESULTS

A total of 526 items were found. Of these items 16 were found to be relevant to this review. These items consisted of 15 articles and 1 abstract. Only the articles were used for this review, because the abstract, by its nature, only provided limited information.

Penile bulb

Most studies have analyzed dose volume effects between radiation dose in the penile bulb and ED after BT or EBRT (Table 1) (17-22,27,30,31,57,60,61). However, it should be recognized that the penile bulb is not an essential structure in achieving and maintaining an erection (62). The penile bulb is the proximal enlargement of the corpus spongiosum. According to Dean and Lue (15) the pressure in the corpus spongiosum during erection is only one-third to one-half of the pressure in the corpora cavernosa, because there is minimal venous occlusion in the corpus spongiosum. Therefore the rigidity of the penis depends predominantly on the corpora cavernosa. While the role of the penile bulb can be questioned, the dose to the penile bulb is correlated with the dose in the proximalmost region of the corpora cavernosa, the crura, in both EBRT (18,63) and BT (20). It has been suggested that the dose to the penile bulb may be a surrogate for the dose in the crura (62). In addition, finding a significant correlation between the radiation dose received by the penile bulb and ED does not mean that lowering this dose would result in a decreased incidence of post-radiation ED. It is possible that the radiation dose in another structure in the vicinity of the penile bulb is responsible for radiation-induced ED, such as the crura, the IPAs, the NVBs or even other anatomic structures.

Several reports (17,19-21,27,60) have failed to give clear information how the penile bulb is contoured. Other reports (18,22,30,31,57,61) based the contouring of the penile bulb on the report from Wallner et al. (64). Wallner et al. (64) described the anatomic boundaries of the penile bulb based on pre- and post-BT CT scans and MRI scans and, transrectal ultrasound.

authors	year	other structures	prospective ED evaluation	n=	treatment technique	follow-up in month	significant correlation	findings
Fisch et al. (17)	2001	no	no	21	3D-CRT	24	yes	median D70 of the PB with a 70 Gy cutpoint
Merrick et al. (19)	2001	no	no	46	BT	mean 35	yes	minimum D25, D50, D70, D75, D90 and D95 of the PB
Merrick et al. (20)	2002	crura	no	60	BT	26-79	yes	minimum D50 of the PB
Merrick et al. (57)	2005	crura	yes	128	BT	13-42	no	minimum D50 of the proximal crura.
Kiteley et al. (27)	2002	NVB	yes	50	BT	24-45	no	no significant correlations
Wright et al. (30)	2004	NVB, crura	no	41	BT	12-41	yes	minimum D90 with a 10% cutpoint of the prescribed dose. Paradoxical result in NVB analysis
Selek et al. (31)	2004	corpora cavernosa	no	28	3D-CRT	≥ 24	no	paradoxical result: potent patients had a higher dose to penile base structures
Roach et al. (21)	2004	no	yes	158	3D-CRT	n.a.	yes	median dose to the penile bulb ≥ 52.5 Gy
Wernicke et al. (22)	2004	no	yes	29	3D-CRT	18-42	yes	median dose to D30, D45, D60 and D75
MacDonald et al. (61)	2005	no	yes	226	BT	≥ 24	no	no significant correlations
Mangar et al. (18)	2006	no	yes	51	3D-CRT	24	yes	mean D90 with a cutpoint of 50 Gy and 60 Gy
Brown et al. (60)	2007	no	yes	32	IMRT	24	no	no significant correlations

Table 1. Correlation between radiation dose to the penile bulb and radiation-induced erectile dysfunction: Summary of the published studies.

3D-CRT = three dimensional conformal radiotherapy

PB = penile bulb

BT = brachytherapy

D xx = dose delivered to xx % of an anatomic structure

NVB = neurovascular bundles

n.a. = not available

IMRT = intensity modulated radiotherapy

Because the penile bulb is continuous with the rest of the corpus spongiosum it is arbitrary where the boundary between the penile bulb and the rest of the corpus spongiosum is located (Fig. 1B). Two reports (18,31) used the level of the inferiormost aspect of the ischial tuberosities to define this boundary. However, this definition leads to a much larger volume, as pointed out by Buyyounouski et al. (65), because a part of the corpus spongiosum is included as well.

Several authors (17-22) have advised to spare the penile bulb. There are contradicting reports on the role of the penile bulb in radiation-induced ED. Several studies with small numbers of patients give results that may not be representative of the whole population, either in finding positive or negative correlations. For example, one study (31) with 28 patients found the following statistically significant correlation: patients who maintained potency seemed to have had more volume irradiated and the penile base structures received a higher radiation dose than the patients who had ED after radiotherapy. Two of the three larger studies, with more than 60 patients, did not find a correlation between post-radiation ED and the radiation dose to the penile bulb (57,61). Furthermore it has to be considered that often carcinoma is present in the apex of the prostate. In studies (23-25) analyzing prostatectomy specimen of patients after prostatectomy with T1 and T2 tumors, the apex of the prostate was involved in most of the cases. If sparing of the penile bulb is achieved by reducing the margin around the apex of the prostate, then an oncological risk will be taken, while it is still uncertain whether a lower percentage of patients would complain of post-radiation ED.

Neurovascular bundles

Radiation dose to the NVBs could be an important factor in understanding ED after radiotherapy. After radical prostatectomy the extent of the neurovascular bundle preservation is predictive of potency recovery (66). The NVBs are only a few millimeters apart from the prostate (67) and therefore they receive a high radiation dose (28). So far, only brachytherapy studies analyzed the dose in the NVBs (Table 2) (26-30). These studies based the position of the NVBs on a model, instead of the actual position, because the NVBs are not visualized on CT scans. In four of these studies (26-29) the model determining the position of the NVBs was based on an anatomical study of one single cadaver by Lepor et al. (67). More recent studies (68-70) showed that the NVBs are much more extensively spread (up to 3 cm anterior–posterior), than the model used to determine the position of the NVBs. Wright et al. (30) based their model of the NVBs on the average position of the NVBs of nine randomly selected prostate endorectal coil MRIs. However this model could not take into account inter-individual variation in topographic anatomy, which is especially pronounced near the apex of the prostate (70).

DiBiase et al. (26) were the first to report that three patients who had developed ED after BT had maximal NVB doses that far exceeded the average values. No statistical analysis was performed. The studies (27-30) following this initial report did perform a statistical analysis, but could not confirm that suggestion made by DiBiase et al. (26) that the radiation dose to

the neurovascular bundles might be correlated to ED after BT. In spite of this, it must be kept in mind that statistical power in these studies might not be sufficient. The number of patients in these studies was around 50 or less. Furthermore, there is room for improvements in the methods used, because none of the studies analyzed the radiation dose in the actual NVBs of each individual patient.

In patients who suffer from ED after radical prostatectomy the effectiveness of sildenafil is highly dependent on sparing of the NVBs. Zagaja et al. (71) report that sildenafil was ineffective after non-nerve sparing radical prostatectomy, whereas 33–80%, depending on age of the patient, responded to sildenafil after bilateral nerve sparing radical prostatectomy. So, if both NVBs are damaged during radical prostatectomy, sildenafil is ineffective. However, sildenafil is effective for ED after radiotherapy in half of the patients (72,73). Therefore it is unlikely that ED after radiotherapy can be fully explained by damage to the NVBs. Even if radiation to the NVBs is the main cause of ED after radiotherapy, it still would be questionable whether it is possible to spare the NVBs, because of their close proximity to the prostate.

authors	year	other structures	prospective ED evaluation	n=	treatment technique	follow-up in month	significant correlation	findings
DiBiase et al. (26)	2000	no	no	14	BT	n.a.	n.a.	Maximal NVB doses exceeded average values in 3 patients with postimplant impotence
Merrick et al. (28)	2000	no	yes	54	BT	median 37	no	no significant correlations
Merrick et al. (29)	2001	no	yes	34	BT	median 13	no	no significant correlations
Kiteley et al. (27)	2002	penile bulb	yes	50	BT	24-45	no	no significant correlations
Wright et al. (30)	2004	penile bulb, crura	no	41	BT	12-41	no	paradoxal result: decreased ED risk with a higher dose to the right NVB

Table 2. Correlation between radiation dose to the neurovascular bundle and radiation-induced erectile dysfunction: Summary of the published studies.

BT = brachytherapy

NVB = neurovascular bundle

ED = erectile dysfunction

Crura

In the penis the two corpora cavernosa lie side by side to each other. More posteriorly in the perineum the two corpora cavernosa separate and form the crura of the penis (64). The crura receive a substantial radiation dose during radiotherapy for prostate cancer, especially during

EBRT (63) and to a lesser extent during BT (20,30). Several studies have tried to elucidate the etiology of ED after radiotherapy by using Doppler ultrasound (32-34). These studies demonstrated a reduced flow in the cavernosal arteries and venous leakage of the corpora cavernosa in men with ED after radiotherapy. The study populations consisted mainly of EBRT patients. Carrier et al. (74) reported that rats irradiated at the prostatic area had a significant decrease in number of nitric oxide synthase-containing fibers in the corpora cavernosa. Nitric oxide is an important mediator of erection (14).

Two BT studies analyzed the proximal first and subsequent three centimeters of the crura (Table 3) (20,57). Another BT study analyzed the whole crura (30). While the only EBRT study contoured the corpora cavernosa until the most inferior aspect of the ischial tuberosities (31). Buyyounouski et al. (65) pointed out that contouring this larger part of the corpora cavernosa made it increasingly difficult to find statistical significance. Only the first centimeter received a high radiation dose (62). Contouring a larger part will lead to a large low dose volume. This will probably make the differences between the groups smaller. Although the corpora cavernosa seem a logical structure to be involved in radiation-induced ED, only one of the four studies (57) found a significant correlation between the dose in the crura and ED after radiotherapy. It should be considered, however, that the positive correlation study comprised a much larger number of patients than the studies that did not find a significant correlation. Lack of statisti-

authors	year	other structures	prospective ED evaluation	n=	treatment technique	follow-up in month	significant correlation	findings
Merrick et al. (20)	2002	penile bulb	no	60	BT	26-79	no	minimum D50 of the penile bulb
Merrick et al. (57)	2005	penile bulb	yes	128	BT	13-42	yes	minimum D50 of the proximal crura
Wright et al. (30)	2004	penile bulb, NVB	no	41	BT	12-41	no	no significant correlation
Selek et al. (31)	2004	corpora cavernosa	no	28	3D-CRT	24	no	potent patients more volume irradiated at a higher dose to penile base structures

Table 3. Correlation between radiation dose to the corpora cavernosa or crura and radiation-induced erectile dysfunction: Summary of the published studies.

BT = brachytherapy

D xx = dose delivered to xx % of an anatomic structure

NVB = neurovascular bundle

cal power might be the reason that these other studies (20,30,31) did not find a significant correlation.

Internal pudendal arteries

The reduced flow in the cavernosal arteries in patients with ED after radiotherapy for prostate cancer demonstrated by several studies (32-34) could also be caused by an obstruction of the arterial flow before it reaches the cavernosal arteries. This might be caused by radiation dose to IPAs. McLaughlin et al. (75) suggested this hypothesis. The IPAs can be visualized by means of MR imaging (75,76). The average distance from the CT-defined apex of the prostate to the IPAs is 0.9 cm (75). They receive a substantial radiation dose during EBRT (75). During BT the IPAs receive radiation as well, although this radiation dose is much lower than during EBRT (76).

Merlin et al. (77) conducted an experiment on rats that were irradiated at the pelvic region. The levels of endothelin-1, a potential vasoconstrictor (78), were increased in the irradiated rats compared to the control group. After induction of an erection by electrostimulation, the irradiated rats had significantly lower mean maximal intracavernous pressure. After injection of an endothelin-A receptor antagonist there was an improvement in intracavernous pressure (77).

Although there are several studies stressing the role of the IPAs in ED after radiotherapy, until now there are no reports analyzing the correlation between radiation dose received by the IPAs and ED after radiotherapy.

DISCUSSION

There are several important factors in studying ED after radiotherapy. First of all, to accurately quantify the negative impact of RT, the patients analyzed should be potent before the commencement of radiotherapy. This must be done preferably by means of a prospective study that documents ED by means of a validated questionnaire, filled out by the patient himself. Physicians tend to underestimate symptoms causing health related quality of life impairment (39). Furthermore the follow-up must be at least 24 months, after which the development of ED tends to stabilize (5,10). If follow-up is much longer, other factors than radiotherapy might become confounding in analyzing the effect of radiotherapy alone, for example, the accumulation or worsening of vascular comorbidities, which themselves will negatively affect erectile function outcomes. The Massachusetts Male Aging Study showed that the incidence rate of ED in the normal population for men between 60 and 69 years old is 4.6% per year (79). Moreover, a large proportion of the patients treated with radiotherapy for prostate cancer also receive adjuvant hormonal therapy, which has a large negative impact on sexual functioning, also years later (5,11). Therefore, neoadjuvant hormonal therapy and also hormonal therapy,

in case of relapse, influence the erectile function status of the patient. Furthermore, since the availability of phosphodiesterase 5 inhibitors the use of potency aids must also be taken into account when assessing ED. In addition, to find a significant correlation between ED and the dose in a certain anatomic structure, a sufficient number of patients is needed.

So far most studies that discuss the dose–effect correlation between radiation-induced ED and specific structures are based on a small number of patients (60 or less) (17-20,22,26-31,60). A small number of patients in combination with the analysis of multiple dose–volume histogram parameters in each study may have led to a publication bias. There are only 3 studies with more than 60 patients (21,57,61).

Roach et al. (21) have reported on the correlation between dose to the penile bulb and ED after EBRT. The analysis was performed on 158 patients from a non-randomized dose escalation study for localized prostate cancer who were potent at baseline. Neoadjuvant hormonal therapy was used in 24% of the patients. Potency criteria or method of assessment and duration of follow-up were not reported. Use of potency aids was not accounted for, but most patients were treated before the availability of sildenafil. Patients with median penile dose of ≥ 52.5 Gy had an association with a greater risk of ED after EBRT, compared with those receiving a dose of <52.5 Gy ($p = 0.039$).

MacDonald et al. (61) included 226 patients treated with BT in their study. The objective was to analyze the dose to the penile bulb in correlation with ED after BT. All patients had an erection sufficient for vaginal penetration before therapy and at least 24 months of follow-up. Assessment of ED was by both patient and physician. Lower ED rates were found in the physician-assessed ED. Adjuvant hormonal therapy, number of needles and the planning ultrasound target volume were significantly correlated with ED after BT. No significant correlation was found between the dose to the penile bulb and ED after BT.

Merrick et al. (57) analyzed 128 patients with respect to the correlation between the dose to the penile bulb and crura and ED after BT. Data from 2 prospective randomized brachytherapy trials were combined. Median follow-up was 29.1 months (range 13.1–42.8). Potency was defined as a score of ≥ 13 on the International Index of Erectile Function (IIEF) (54). Patients treated with hormonal therapy were not excluded. In univariate analysis, amongst other factors the penile bulb was significantly correlated to ED after radiotherapy. However, in multivariate analysis not the penile bulb but the dose delivered to 50% of the proximal first centimeter of the crura was significantly correlated to ED after radiotherapy. This was also the case for the pre-implant IIEF score.

This study illustrates that if other anatomic structures are taken into the analysis, they may be better correlated than the penile bulb with ED after radiotherapy. In this study that anatomic structure is the proximal centimeter of the crura. Though, there are other anatomic structures that should be taken into account as well. So far the NVBs have not been analyzed with a proper methodology. Furthermore, the radiation dose to the IPAs in correlation with ED after radiotherapy has not been analyzed yet, while they receive a substantial radiation

dose (75,76), provide arterial flow to corpora cavernosa (16) and arterial flow in the corpora cavernosa is decreased in patients with ED after radiotherapy (32-34).

CONCLUSION

Several authors (17-22) advised sparing of the penile bulb to preserve erectile function after radiotherapy for prostate cancer. However, the penile bulb seems to play little role in achieving an erection (62). Two of the three larger studies did not find a significant correlation between post-radiation ED and the radiation dose to the penile bulb (57,61). We believe that the rationale for sparing the penile bulb is not sufficiently supported by the current literature. If sparing of the penile bulb is achieved by reducing the margin around the apex, which often contains tumor in case of prostate cancer (23-25), an oncological risk is taken, and furthermore, it is uncertain whether this would improve potency-preservation.

Chapter 4

Dose-volume parameters of the corpora cavernosa do not correlate with erectile dysfunction after external beam radiotherapy for prostate cancer: results from a dose-escalation trial

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ABSTRACT

Purpose

To analyze the correlation between dose–volume parameters of the corpora cavernosa and erectile dysfunction (ED) after external beam radiotherapy (EBRT) for prostate cancer.

Methods and Materials

Between June 1997 and February 2003, a randomized dose–escalation trial comparing 68 Gy and 78 Gy was conducted. Patients at our institute were asked to participate in an additional part of the trial evaluating sexual function. After exclusion of patients with less than 2 years of follow-up, ED at baseline, or treatment with hormonal therapy, 96 patients were eligible. The proximal corpora cavernosa (crura), the superiormost 1-cm segment of the crura, and the penile bulb were contoured on the planning computed tomography scan and dose–volume parameters were calculated.

Results

Two years after EBRT, 35 of the 96 patients had developed ED. No statistically significant correlations between ED 2 years after EBRT and dose–volume parameters of the crura, the superiormost 1-cm segment of the crura, or the penile bulb were found. The few patients using potency aids typically indicated to have ED.

Conclusion

No correlation was found between ED after EBRT for prostate cancer and radiation dose to the crura or penile bulb. The present study is the largest study evaluating the correlation between ED and radiation dose to the corpora cavernosa after EBRT for prostate cancer. Until there is clear evidence that sparing the penile bulb or crura will reduce ED after EBRT, we advise to be careful in sparing these structures, especially when this involves reducing treatment margins.

INTRODUCTION

Erectile dysfunction (ED) is one of the most common sequelae after radiotherapy for prostate cancer, affecting 36–59% of patients after external beam radiotherapy (EBRT) (5,10-12). Finding an anatomic structure responsible for ED after EBRT or brachytherapy would enable physicians to avoid a high radiation dose in these structures and has the potential to reduce ED after radiotherapy. The correlation between the radiation dose in specific anatomic structures and ED after radiotherapy has been investigated in several studies (17-22,27-31,57,60,61). Most reports focused on the penile bulb (17-19,21,22,60,61). However, it should be recognized that the penile bulb is not an essential structure in achieving or maintaining an erection (62,63).

The penile bulb is actually the proximal enlargement of the corpus spongiosum. According to Dean and Lue (15), the pressure in the corpus spongiosum during erection is only one third to one half of the pressure in the corpora cavernosa. Furthermore, several studies demonstrated a reduced flow in the cavernosal arteries and venous leakage of the corpora cavernosa in men with ED after radiotherapy by using Doppler ultrasound (32-34). Therefore the corpora cavernosa and not the penile bulb seem to be a likely structure to be responsible for ED after radiotherapy.

Only Selek et al. (31) have investigated the correlation between ED after EBRT and the radiation dose to the corpora cavernosa. No correlation was found. Unfortunately, this study only analyzed 28 patients and several comments were made on its methodology (65). The purpose of the present prospective study is to analyze the correlation between ED and dose–volume parameters of the corpora cavernosa at 2 years after EBRT for prostate cancer with a larger number of patients. Furthermore, the comments on the study of Selek et al. (31) are taken into account.

PATIENTS AND METHODS

At our center, 404 patients were included in a Dutch multicenter dose–escalation trial (trial code CKVO 96-10), in which patients with a localized adenocarcinoma of the prostate were randomized to 68 Gy or 78 Gy radiation dose (80,81). The patients in our center were asked to participate in an additional part of the trial evaluating quality of life and sexual functioning. Of these patients, 268 agreed to participate in the additional part in which sexual functioning would be evaluated. Forty-five patients were excluded because of missing baseline data on sexual functioning. As there is evidence that (neo)adjuvant hormonal therapy (HT) has a significant impact on sexual function and erectile function (5,11,12), 29 patients treated with (neo)adjuvant HT were excluded. Another 55 patients already suffered from ED at baseline. Furthermore, patients who suffered from a relapse were censored at the time of relapse. A relapse was defined as: biochemical relapse according to the American Society for Therapeutic

Radiology and Oncology definition (41), a clinical relapse, or the start of therapy such as HT during follow-up or salvage therapy. Ninety-six patients, all potent before radiotherapy and with 2 years of follow-up, are the subject of this analysis.

Radiotherapy

The details of this trial have been described before (42). Briefly, four groups were defined based on the risk of involvement of the seminal vesicles, according to Partin et al. (43). The clinical target volume (CTV) of patients with T1b-T2a tumors with risk of involvement <10% consisted of the prostate only. In patients with T1b-T2a tumors with a risk of involvement between 10% and 25%, the CTV consisted of prostate plus seminal vesicles until 50 Gy, after which the seminal vesicles were excluded from the CTV. For T1b-2a tumors with a risk of involvement of more than 25%, T2b and T3a tumors the seminal vesicles were excluded from the CTV after 68 Gy. For T3b and T4 tumors the CTV consisted of the prostate plus seminal vesicles. For the first 68 Gy a CTV-planning target volume (PTV) margin of 10 mm was used. For the last 10 Gy in the 78 Gy arm a margin of 5mm was used, except toward the rectum where no margin was taken.

In our center, patients were treated at that time with threedimensional conformal radiotherapy with a three-field technique using one anterior and two lateral wedged fields. The prescribed dose was specified in the International Commission on Radiation Units and measurements reference point (2) and was delivered in daily fractions of 2 Gy. Treatment with (neo)adjuvant HT, duration, and type of (neo)adjuvant HT was left to the discretion of the referring physician.

Sexual function

The Dutch module on sexual activity (SAC) was used to assess sexual function (44,45). Sexual activity was defined as masturbation or intercourse. A skip pattern differentiates sexually active vs. inactive men. Sexually inactive men were asked why they were inactive (no desire, no partner, partner had no desire, ED, or other reasons). Sexually active men were asked whether they had experienced problems with achieving or maintaining erections. The definition of ED was (almost) always having problems in achieving or maintaining an erection, or not being sexually active because of erectile problems. The patients had to answer the SAC questionnaire at baseline and at 6 months, 1, 2, and 3 years after the start of EBRT.

Because the study was designed before the introduction of oral phosphodiesterase-5 (PDE5) inhibitors, no assessment of potency aids was done during the study protocol. Hence a questionnaire was developed to retrospectively assess the use of potency aids: PDE5-inhibitors, intracavernosal injections, intraurethral alprostadil, vacuum device, or a penile ring. The questionnaire contained the following items: the use of potency aids on a regular base before EBRT, during the first 2 years after EBRT, or after more than 2 years after EBRT. Patients could answer "yes" or "no." When answering yes, they were asked to make a choice between different

kinds of potency aids. This questionnaire was sent in June 2006 to all pretreatment potent patients with at least 2 years of follow-up and who were alive at the moment the questionnaire was sent.

Contouring

The proximal penis was contoured on the planning CT scan by one single observer (G.J.W.) blinded for the potency status of the patient. Contouring of the penile bulb was based on a report of Wallner et al. (64). The penile bulb was contoured until both corpora cavernosa do not join together anymore in the inferior axial slices. Contouring of the crura was continued in the inferior slices. Figure 1 shows a planning CT scan with contouring of the penile bulb and crura. Mulhall et al. (63) reported that the superiormost 1-cm segment receives the highest radiation dose after which there is a steep dose decline. Therefore the superiormost 1-cm segment of the crura was subtracted as a separate structure next to the structure of the whole crura and penile bulb.



Figure 1. Contoured structures on a planning computed tomography (CT) scan: penile bulb (white) with the crura left and right (black). The penile bulb was contoured (left) until the corpora cavernosa do not join together anymore in the inferior CT slices (right).

Statistics

The following dose–volume variables were analyzed for the crura, the superiormost 1-cm segment of the crura and penile bulb: mean dose, maximum dose, volume, relative volume receiving 5–80 Gy in intervals of 5 Gy (rV5, 10, 15–80), and absolute volume receiving 5–80 Gy in intervals of 5 Gy (aV5, 10, 15–80). Differences between patients with and without ED were tested with the Kruskal-Wallis and the Pearson chi-square test. Statistical analysis was

performed with SPSS, version 14.0, software. Level of statistical significance was adjusted for multiple parameters and set at $p < 0.01$.

RESULTS

The use of potency aids was retrospectively assessed using a mailed questionnaire. Fifteen patients were deceased and the addresses of three patients could not be retrieved. Therefore the questionnaires were sent to 78 patients, of whom 70 patients responded (90%). Of these 70 patients, only 1 patient used a potency aid before the start of EBRT and continued using intracavernosal injections after EBRT. Six patients started using oral PDE5 inhibitors within 2 years after EBRT. All of these 7 patients, except 1, also indicated to suffer from ED in the SAc 2 years after EBRT.

At 2 years after EBRT, 35 of the 96 patients (36%) suffered from ED. There were no statistically significant differences in patient characteristics between the patients with and without ED 2 years after EBRT (Table 1). No significant differences were found between mean dose, maximum dose, and volume of the different structures between patients with and without ED 2 years after EBRT (Table 2). Figure 2 shows the absolute dose–volume histogram (DVH) comparing the average DVHs for the different structures of patients with and without ED 2 years after EBRT. Figure 3 shows the relative DVH comparing the average DVHs for the different structures of patients with and without ED 2 years after EBRT. No statistically significant correlations were found between the different dose–volume variables and ED 2 years after EBRT.

Parameter	ED (n=35)	No ED (n=61)	<i>p</i> value
Treatment arm 78 Gy	19 / 35	33 / 61	0.99
Mean age, years	69	68	0.83
Mean PSA, $\mu\text{g/L}$	12.8	11.2	0.42
T-stage \geq T3	8/34	20/60	0.32
Gleasonscore \geq 7	15/30	28/52	0.74
Diabetes Mellitus	2/35	1/61	0.27
Cardiovascular history	10/35	16/61	0.80
Treatment arm 78 Gy	19 / 35	33 / 61	0.99

Table 1. Patient characteristics.

ED = erectile dysfunction

PSA = prostate specific antigen

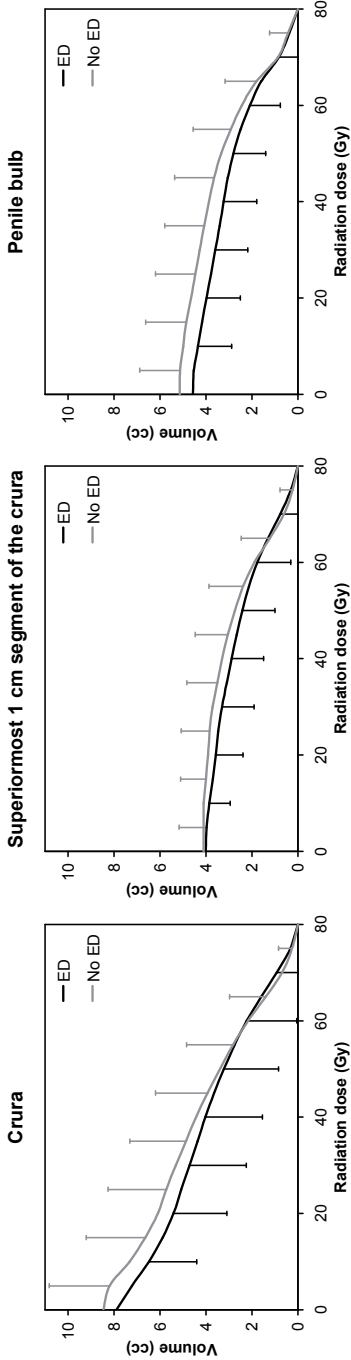


Figure 2. Average absolute dose-volume histograms (DVH) of the crura, the superiormost 1-cm segment of the crura and the penile bulb of patients with and without erectile dysfunction (ED) at 2 years after external beam radiotherapy. The error bars indicate 1 standard deviation. No statistically significant differences were found between the dose-volume parameters and ED (Kruskal-Wallis test).

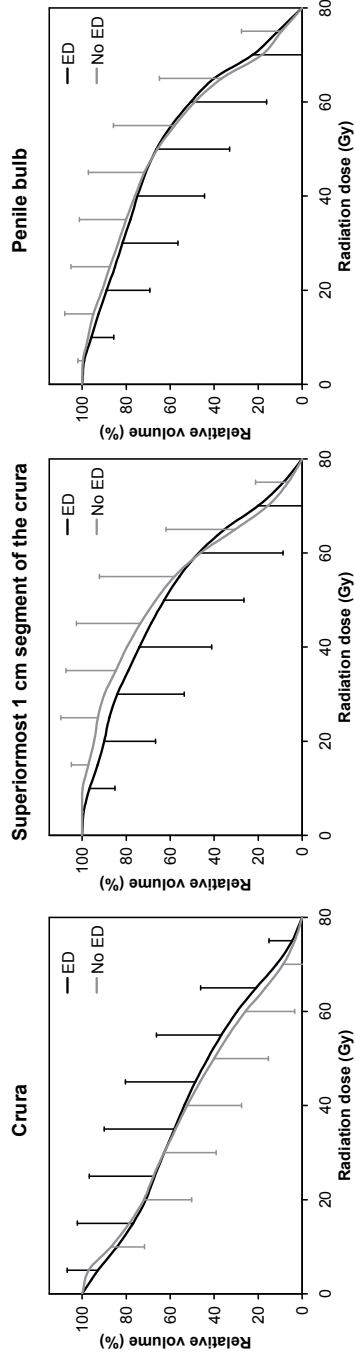


Figure 3. Average relative dose-volume histograms (DVH) of the crura, the superiormost 1-cm segment of the crura and the penile bulb of patients with and without erectile dysfunction (ED) at 2 years after external beam radiotherapy (EBRT). The error bars indicate 1 standard deviation. No statistically significant differences were found between the dose-volume parameters and ED (Kruskal-Wallis test).

Parameter	ED (n=35)	No ED (n=61)	p value
	mean (\pm SD)	mean (\pm SD)	
Crura mean dose	40.6 \pm 17.9	39.9 \pm 13.8	0.78
Crura max dose	67.7 \pm 11.7	69.6 \pm 5.9	0.78
Crura volume	7.9 \pm 2.3	8.5 \pm 2.6	0.16
Crura _{1cm} mean dose	52.6 \pm 17.8	54.2 \pm 13.4	0.90
Crura _{1cm} max dose	67.7 \pm 11.7	69.6 \pm 5.9	0.80
Crura _{1cm} volume	4.0 \pm 1.0	4.1 \pm 1.1	0.50
Penile bulb mean dose	53.4 \pm 16.8	53.3 \pm 13.1	0.71
Penile bulb max dose	70.1 \pm 9.2	71.3 \pm 5.4	0.87
Penile bulb volume	4.6 \pm 1.5	5.1 \pm 1.8	0.12

Table 2. Mean dose in Gy, maximum (max) dose in Gy and volume in mL of the crura, the superiormost 1-cm segment of the crura (Crura 1cm) and the penile bulb for patients with and without erectile dysfunction (ED) at 2 years after external beam radiotherapy.

DISCUSSION

Prostate cancer is the most common type of cancer for men in Western countries with the exception of skin cancer (82). A common treatment for prostate cancer is radiotherapy. Unfortunately, this leads to ED in 36–59% of the patients (5,10-12). Hence a large patient population would benefit from finding a new technique to reduce ED after radiotherapy for prostate cancer.

Radiation dose to the neurovascular bundles could be responsible for ED after radiotherapy. So far, only brachytherapy studies analyzed this possibility (26-30). None of these studies could find any statistically significant correlation between radiation dose to the neurovascular bundles and ED after brachytherapy for prostate cancer.

Many reports (17-19,21,22,60,61) that try to find a correlation between the radiation dose in a specific anatomic structure and ED after radiotherapy for prostate cancer focused on the penile bulb, but results are contradictory (17-22,27,30,31,57,60,61). Two of the three larger studies, with more than 60 patients, did not find a statistically significant correlation between the radiation dose to the penile bulb and ED after radiotherapy. In the present study, we were not able to find this correlation either.

Selek et al. (31) were the only ones who analyzed the correlation between ED and the radiation dose to the corpora cavernosa after EBRT for prostate cancer. They did not find any positive correlation. However, Buyyounouski et al. (65) argued that this correlation was not found for two reasons. First, the small number of patients might be the reason why no statistically significant correlation was found. Second, only the first centimeters of the crura receive a substantial radiation dose (63). Selek et al. (31) contoured the corpora cavernosa and penile bulb until the inferiormost aspect of the ischial tuberosities. As a consequence, the volumes of the analyzed structures were much larger than previously described. This shifts the DVH to lower doses for any given volume, making the differences between patients with and without

ED smaller. Statistical significance would be increasingly more difficult to achieve. However, this argument is only valid for the relative dose–volume parameters and has no influence on absolute dose–volume parameters in the higher dose region.

In the present article, we took the comments from Buyyounouski et al. (65) into account. To analyze the corpora cavernosa, only the crura were analyzed, including a separate analysis of the superiormost 1-cm segment of the crura. Mulhall et al. (63) demonstrated that the superiormost 1-cm segment of the crura comprehends the high radiation dose area, whereas there is a steep decline in radiation dose inferior of this segment. Nevertheless, even with a group of 96 patients, the present report still did not find any statistically significant correlation between ED and the radiation dose to the crura after EBRT for prostate cancer.

Next to the comments from Buyyounouski et al. (65), this study also took potency aids into account. The use of potency aids before the start of EBRT was low. Most patients using potency aids also indicated to suffer from ED in the SAc; therefore, the use of potency aids was not a large confounding factor in this study.

There was no validated Dutch questionnaire available to assess sexual function at the time of study design. However, there was experience with the SAc in several studies (45,52,53) and it has been evaluated by Korfage et al. (44). The SAc does have some advantages over the commonly used International Index of Erectile Function (54). A large part of this index is based on the assumption that patients have sexual intercourse with penetration. Therefore it is not suitable for homosexual men and patient without a (sexually active) partner.

Three studies have previously analyzed the correlation between ED and the radiation dose to the corpora cavernosa after brachytherapy for prostate cancer (20,30,57). One of these studies (57) (with the largest number of patients, $n = 128$) found a significant correlation, whereas the other two did not find a statistically significant correlation between the radiation dose to the corpora cavernosa and ED after brachytherapy for prostate cancer (20,30). There is a possibility that the present study still lacks statistical power. Another possibility might be that ED after brachytherapy has another etiology than ED after EBRT caused by the difference in dose distribution, but this does not seem logical.

It is certainly possible that the reduced flow in the cavernosal arteries demonstrated by several studies in men with ED after radiotherapy (32-34) is caused by radiation damage to the internal pudendal arteries and accessory pudendal arteries that supply the cavernosal arteries instead of the cavernosal arteries themselves. The internal pudendal arteries also receive substantial radiation dose (75,76), but so far there is no report analyzing the correlation between the radiation dose to the internal pudendal arteries and ED after radiotherapy. This correlation should certainly be analyzed in future studies.

CONCLUSION

Although it was suggested in previous publications (62,63) that the radiation dose to the corpora cavernosa might be correlated to ED after EBRT for prostate cancer, no evidence for this correlation was found in the present study as in the previous study. Unfortunately, there is no clear evidence yet that avoiding high radiation dose in a specific structure will decrease ED after EBRT (83). Therefore we believe that so far no adjustments should be made in the treatment plans to avoid high radiation dose in a specific structure - especially if sparing of such a structure involves reducing treatment margins, an oncologic risk is taken, whereas it is uncertain whether this will improve potency preservation.

Chapter 5

Changes in the penile arteries of the rat after fractionated irradiation of the prostate: a pilot study

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ABSTRACT

Introduction

External beam radiotherapy for prostate cancer leads to erectile dysfunction in 36%-43% of patients. The underlying mechanism is largely unknown, although some clinical studies suggest that the arterial supply to the corpora cavernosa is responsible. Two animal experimental studies reported on the effects of a single fraction of prostate irradiation on the penile structures. However, irradiation in multiple fractions is more representative of the actual clinical treatment.

Aim

The present prospective, controlled study was initiated to investigate the effect of fractionated prostate irradiation on the arteries of the corpora cavernosa.

Main Outcome Measures

Histological evaluation of the penile tissue in comparison with control rats at 2, 4 and 9 weeks after irradiation.

Methods

The prostate of twelve rats was treated with external beam radiation in 5 daily fractions of 7.4 gray. Three control rats were treated with sham irradiation. Prostatic and penile tissue was evaluated for general histology (hematoxylin-eosin). The penile tissue was further evaluated after combined staining for collagen (resorcin fuchsin) and α -smooth muscle actin (SMA) (Biogenex).

Results

The prostate showed adequate irradiation with fibrosis occurring at 9 weeks after irradiation. The corpora cavernosa showed arteries that had developed loss of smooth muscle cells expressing SMA, thickening of the intima and occlusions. All the control rats maintained normal anatomy.

Conclusion

This is the first animal experimental study that demonstrates changes in the arteries of the corpora cavernosa after fractionated irradiation to the prostatic area. The preliminary data suggests that erectile dysfunction after radiotherapy might be caused by radiation damage to the arterial supply of the corpora cavernosa.

INTRODUCTION

Prostate cancer is the most common type of cancer for men in Western countries with the exception of skin cancer (82). Both localized and locally advanced prostate cancer can be treated with external beam radiotherapy. However, 36% to 43% of the patients develop permanent erectile dysfunction during the first few years after external beam radiotherapy for prostate cancer (5,12).

Reducing erectile dysfunction after radiotherapy would help a large number of prostate cancer patients remain sexually active and improve their quality of life (37). Radiation treatment plans can be adapted to minimize the radiation dose to a specific anatomical structure, for instance by choosing specific angles for the radiation beams, as is usually done for the rectum. If the mechanism of erectile dysfunction after radiotherapy is fully understood, then it is possible to minimize the radiation dose to the anatomical structures that are involved.

Three anatomical structures are essential for an adequate penile erection: the neurovascular bundles / cavernous nerves supply the penis with nitric oxide to initiate an erection, after which the arterial inflow through the internal pudendal and cavernosal arteries increases and the corpora cavernosa build up pressure by adequate trapping of blood (the veno-occlusive mechanism) to achieve and maintain an erection (15). Although clinical studies investigated several anatomical structures, the cause of erectile dysfunction after radiotherapy is still largely unknown (83,84). There is some clinical evidence that damage to the arterial supply of the corpora cavernosa might be responsible (32-34,57).

Because clinical studies have not been able to elucidate the cause, animal experimental studies would seem to be a better model. Two rat studies reported defects in the vascular supply and loss of nerve and smooth muscle fibers. (74,77). However, these studies were performed with a single fraction of radiation, while clinical radiotherapy for prostate cancer is delivered in multiple fractions. Therefore the present study has been initiated to investigate the arteries in corpora cavernosa of the rat after fractionated irradiation of the prostatic area.

MATERIALS AND METHODS

Fifteen male Sprague-Dawley rats (Harlan, Zeist, The Netherlands), 2-3 months of age, were randomized into three groups of five rats. Rats were housed according to institutional guidelines, and procedures were carried out in compliance with the standards for the use of laboratory animals. For each group, 4 rats received external beam radiation and 1 rat was used as a control. All control rats were sham irradiated. The rats were anaesthetized with isoflurane/ N_2O/O_2 and immobilized in a supine position for approximately 7 minutes per radiation fraction. A lead shield (3 mm thick) was used to protect the testes and bowel, while an opening, measuring 30 mm wide and 40 mm long, allowed irradiation of the prostatic area (Figure

1). The lower border of the field was positioned 5 mm under the cartilage of the penis. The lateral borders were chosen 15 mm left and right of the median. The rats were irradiated with an anterior-posterior radiation field and a total dose of 37 gray, which was delivered during 5 daily fractions of 7.4 gray. This fractionation scheme is an equivalent of 19 fractions of 3.4 Gy, which is currently investigated in our institute. Moreover, Van den Aardweg et al. reported that five fractions of 7.6 Gy to the rectum caused no major toxicity.¹⁴ Radiation was delivered with a Philips RT250 Orthovolt X-ray machine (Philips, Eindhoven, The Netherlands) operating at 200 kV with a source-to-skin distance of 30 cm, a 4 x 6 cm² field and a dose rate of 1.50 Gy/min.

At 2, 4 and 9 weeks after irradiation a group of rats was sacrificed. This study was approved by the Dutch Animal Experiment Committee.

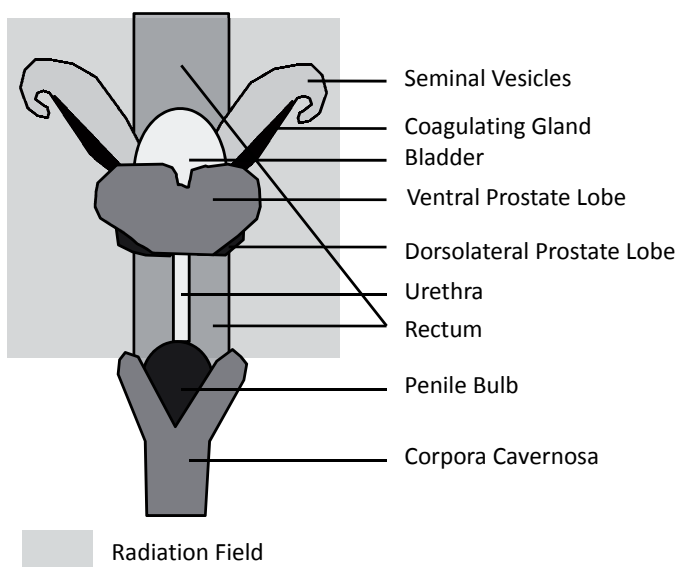


Figure 1 is a schematic picture of the anatomy of the prostate, rectum, bladder and penis of the rat and the radiation field.

Histology

The prostate and the penis were removed, fixed in 10 % formalin for a maximum of 48 hours and embedded in paraffin. Sections were cut at 4 μ m thick and attached to silane-coated slides. General histology staining was performed with hematoxylin-eosin (HE). The slides were then stained with both resorcin fuchsin to identify the collagen and elastin of the intima, and immunohistochemistry to identify the α -smooth muscle actin in smooth muscle cells. Immunohistochemical staining was performed with an antibody to α -smooth muscle actin (clone 1A4, 1:100, Biogenex, San Ramon, Ca, USA). The Envision HRP System (DAKO, Glostrup, Denmark) was used for visualization of the expression of antibodies. Pre-treatment

was performed with 0.1% protease from streptomyces griseus in phosphate buffered saline (SIGMA-ALDRICH, Zwijndrecht, Netherlands) at 37° Celsius for 10 minutes.

Two observers (GJW and MV) analyzed the slides blinded to whether the slides were control rats or irradiated rats.

RESULTS

Radiation-induced changes in the prostate

Histological samples of the rat prostate showed adequate irradiation damage (Figure 2). Two weeks after irradiation the prostate showed edema and atrophy in parts of the epithelium. Four weeks after irradiation the tissue recovered from the edema, but there was progression of the atrophic area of epithelium, fibrosis and the presence of macrophages and lymphocytes.

Two rats died at 8 weeks after irradiation. These two rats were not analyzed in this study. The remaining irradiated rats had to be sacrificed at 9 weeks, because they developed rectal bleeding in combination with loss of weight. Histological evaluation showed a swollen rectum, known as a megacolon. Furthermore, the rectal arteries showed extensive thickening

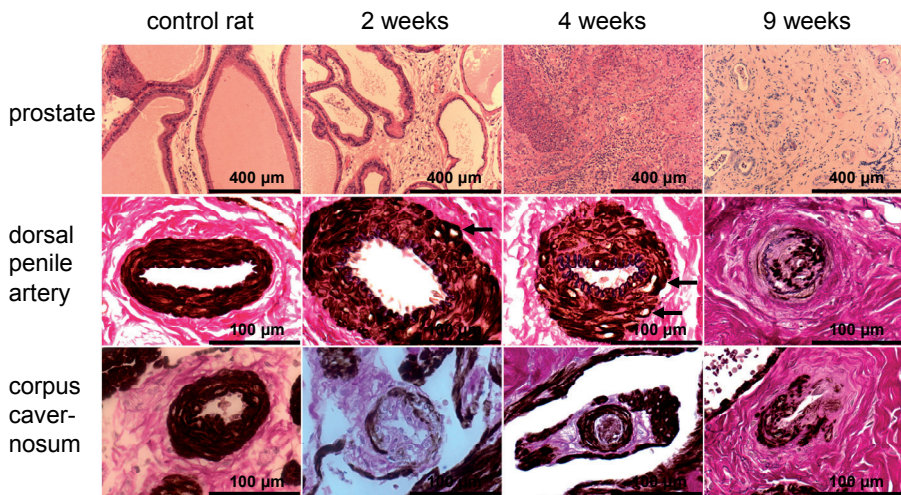


Figure 2 shows histology of prostatic and penile tissue of a control rat and rats sacrificed at 2, 4 and 9 weeks after irradiation.

The first row (prostate) shows the prostate stained with hematoxylin-eosin. Two weeks after irradiation edema is observed, followed by inflammation at 4 weeks and fibrosis at 9 weeks after irradiation.

The second row (dorsal penile artery) shows the dorsal penile artery with resorcin fuchsin and α -smooth muscle actin staining. The histology after irradiation shows smooth muscle cells in apoptosis (examples indicated with an arrow) and an increase in collagen in the arterial wall. At 9 weeks an artery is shown with severe thickening of the intima and loss of most smooth muscle cells expressing α -smooth muscle actin.

The third row (corpus cavernosum) shows arteries in the corpora cavernosa with resorcin fuchsin and α -smooth muscle actin staining. Again there is a decrease in smooth muscle expressing α -smooth muscle actin. The tissue sample at 4 weeks after irradiation shows an occlusion of an artery caused by a thrombus.

of the intima. The prostate tissue of these rats showed progression of the atrophic area of epithelium and fibrosis, while there was a clear reduction in the presence of macrophages and lymphocytes.

All control rats maintained normal anatomy.

Radiation-induced changes in the arteries of the penis

The proximal penis, which was on the edge of the radiation field in the scatter dose area, showed vascular changes in all irradiated rats (Figure 2). Arteries in the proximal penis showed apoptotic cells, as indicated by morphological signs, in the smooth muscle layer of the arterial wall 2 weeks after irradiation. An increase in collagen content in arterial walls and the first arterial occlusions by thrombosis were visible after 4 weeks. Nine weeks after irradiation there was a further increase in collagen content and a further loss of smooth muscle cells expressing α -smooth muscle actin. Furthermore, arteries were visible with extensive thickening of intima.

The distal penis, which did not receive radiation, did not show any histological changes (data not shown). The control rats also maintained normal anatomy.

DISCUSSION

The side-effects of radiotherapy can be reduced by adapting the treatment plan in such a manner that the responsible anatomical structure is spared during irradiation. However, clinical studies have not led to a clear understanding which structure should be spared to reduce the risk of erectile dysfunction after radiotherapy for prostate cancer. Therefore, there is an important role for animal experimental studies to find the mechanism that causes this form of erectile dysfunction.

To our knowledge, this is the first study demonstrating that fractionated external beam radiotherapy to the prostatic area of the rat induced changes in the penile arteries. Arteries in the proximal penis showed a reduction of smooth muscle cells expressing α -smooth muscle actin and an increase in collagen content in the arterial wall. Furthermore, arteries that showed thickening of the intima and occlusions were visible.

Our findings are supported by the two other studies, although these studies used a single fraction of irradiation. Merlin et al. performed an experiment in which rats were treated with a single fraction of 10 or 20 Gy to the prostatic area (77). Endothelin-1 (a potential vasoconstrictor (78)) was increased in rats treated with 20 Gy. Merlin et al. suggested that an increased endothelin 1 level could be involved in development of atherosclerotic lesions (77).

Carrier et al. conducted an experiment in which rats were treated at the prostatic area with a single fraction 10 or 20 Gy and found a decrease in nitric oxide synthase (NOS)-containing nerve fibers in the proximal shaft of the penis (74). Furthermore, they concluded that there

were defects in the vascular supply of the erectile tissue and a decrease in cavernous smooth muscle.

In the present study a radiation protocol with fractionated radiotherapy was chosen, because this is more representative of the actual clinical treatment. However, it is difficult to conclude if this leads to different effects by a comparison with these two studies, because their focus, endothelin-1 and NOS containing nerve fibers, has been different.

Three clinical studies reported a reduced flow in the cavernosal arteries, which are supplied by the internal pudendal arteries, in patients with erectile dysfunction after radiotherapy (32-34). The average distance from the computed tomography (CT)-defined apex of the prostate to the internal pudendal arteries is 0.9 cm (75). This means that the internal pudendal arteries will often be within the commonly used 1 cm margin where the full treatment dose is delivered. Although the arteries toward the corpora cavernosa were not investigated in our study, the rats developed changes in the arterial wall in the rectal arteries that received the full treatment dose and in the proximal penis itself. This is in agreement with the study of Goldstein et al. in which two patients with erectile dysfunction after radiotherapy showed bilateral narrowing of the internal iliac arteries and occlusions of the internal pudendal and penile arteries on selective pudendal arteriography (32). In future studies the arteries supplying the corpora cavernosa of the rat will need to be studied in detail.

However, one should not exclude the possibility that the changes in the arteries might be influenced by radiation damage to the neurovascular bundles. The animal cavernous nerve injury model, including intracavernosal pressure measurements, has been used in various studies to investigate methods to reduce erectile dysfunction after radical prostatectomy (85-88). Some of these studies reported a decrease in smooth muscle as well as an increase in fibrosis in the corpora cavernosa (89). Furthermore, androgen deprivation can induce similar changes (90).

Van den Aardweg et al. reported that no rats developed a megacolon after being treated with five daily fractions of 7.6 Gy to the rectum (91). This is in contrast with our findings that showed development of a megacolon in four rats. A likely explanation is that they used an opening in their lead shielding which is half the size of our opening (20mm x 15mm). Another experiment was performed with five fractions of 4.8 Gy and a 3 mm lead shielding with an opening of 20 mm long and 15 mm wide (unpublished data). However, the histological changes were very small compared to the control rats.

This pilot study, by its nature, included a limited number of rats. Future experiments, including intracavernosal pressure measurements, with a larger number of rats are needed to quantify and statistically confirm the preliminary data of this study. For future experiments, we advise to use a 3 mm lead shielding with a 20 mm x 15 mm wide opening and five daily fractions of more than 4.8 Gy and up to 7.4 Gy.

At present we are conducting a clinical study in which the internal pudendal arteries are imaged with magnetic resonance imaging with contrast in patients who will be treated with

external beam radiotherapy for prostate cancer. The correlation between the radiation dose received by the internal pudendal arteries and erectile dysfunction after radiotherapy can then be analyzed. On the other hand, new techniques are being developed to safely reduce the radiation dose to all structures surrounding the prostate, including those essential to a penile erection (92). Until the mechanism of erectile dysfunction after radiotherapy is fully understood, the sparing of all tissues surrounding the prostate, including those structures essential to a penile erection, is the most feasible way to reduce the risk of erectile dysfunction after radiotherapy for prostate cancer.

CONCLUSION

This is the first animal experimental study demonstrating changes in the arteries of the rat penis after fractionated irradiation of the prostatic area. Arteries developed loss of smooth muscle, intimal thickening and occlusions after five daily fractions of 7.4 Gy. The preliminary data suggest that erectile dysfunction after radiotherapy might be caused by radiation damage to the arterial supply of the corpora cavernosa. Further experimental studies are needed to support these preliminary data.

Chapter 6

Stereographic targeting in prostate radiotherapy: speed and precision by daily automatic positioning corrections based on kV/MV image pairs

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ABSTRACT

Purpose

A fully automated, fast, on-line prostate repositioning scheme using implanted markers, kilovoltage/megavoltage imaging, and remote couch movements has been developed and clinically applied. The initial clinical results of this stereographic targeting (SGT) method, as well as phantom evaluations, are presented.

Methods and Materials

Using the SGT method, portal megavoltage images are acquired with the first two to six monitor units of a treatment beam, immediately followed by acquisition of an orthogonal kilovoltage image without gantry motion. The image pair is automatically analyzed to obtain the marker positions and three-dimensional prostate displacement and rotation. Remote control couch shifts are applied to correct for the displacement. The SGT performance was measured using both phantom images and images from 10 prostate cancer patients treated using SGT.

Results

With phantom measurements, the accuracy of SGT was 0.5, 0.2, and 0.3mm (standard deviation [SD]) for the left–right, craniocaudal, and anteroposterior directions, respectively, for translations and 0.5° (SD) for the rotations around all axes. Clinically, the success rate for automatic marker detection was 99.5%, and the accuracy was 0.3, 0.5 and 0.8 mm (SD) in the left–right, craniocaudal, and anteroposterior axes. The SDs of the systematic center-of-mass positioning errors (Σ) were reduced from 4.0 mm to <0.5 mm for all axes. The corresponding SD of the random (σ) errors was reduced from 3.0 to <0.8 mm. These small residual errors were achieved with a treatment time extension of <1 min.

Conclusion

Stereographic targeting yields systematic and random prostate positioning errors of <1 mm with <1 min of added treatment time.

INTRODUCTION

Recent advances in electronic portal imaging devices (EPIDs) (93,94), as well as linear accelerator-integrated kilovoltage (kV) scanners (95,96), have enabled detailed investigation of the uncertainties in target position during external beam radiotherapy (EBRT). These uncertainties, stemming from deviations in patient anatomy during treatment relative to the anatomy during planning, lead to inaccuracies in the delivered dose distribution and possible loss of tumor control with an increased risk of complications. To account for the uncertainties, planning margins are added to the clinical target volume (CTV) to obtain the planning target volume (PTV) (2), while ensuring adequate CTV dose coverage. One of the goals of image-guided RT is to allow for the reduction of these margins through the reduction of the geometric errors during treatment, thereby potentially reducing toxicity.

Combined with kV and/or megavoltage (MV) daily imaging (on-line approach), implanted markers not only allow for elimination of large geographic misses, but also for the reduction of both random and systematic errors(97). Studies of the effect of systematic geometric misses due to a nonrepresentative rectal shape during acquisition of the planning computed tomography (CT) scan have indicated that such misses result in increased biochemical and clinical failure, even when margins of 1 cm have been applied (98,99). On-line corrections can eliminate such misses while simultaneously allowing for smaller CTV–PTV margins (100–103).

This report describes stereographic targeting (SGT), a method for fast and accurate on-line prostate positioning with implanted markers using orthogonal cross-fire kV/MV imaging. The clinical data obtained for the first 10 patients treated with SGT are presented.

METHODS AND MATERIALS

Preparation

Before CT scanning, cylindrical gold markers (1 mm x 5 mm; Heraeus GmbH, Engineered Materials Division, Hessen, Germany) were implanted in the prostate transperineally using 18-gauge needles under transrectal ultrasound guidance. Two markers were placed near the base and two near the apex. At least 1 week after implantation, the patients were scheduled for the planning CT scan (Somatom Sensation Open, Siemens Medical Solutions, Erlangen, Germany) with a reconstruction slice thickness of 2.5 mm. The interval between implantation and planning allowed for any edema to resolve so that the anatomy in the scan would be representative for treatment (101,104). The reference positions of the markers with respect to the isocenter were reconstructed with a tool (Define Marker 3D) in the EPID software program, which in the present study used digitally reconstructed radiographs (DRRs). The input for this tool was at least two DRRs with sufficient beam angle separation (minimally 60°). The marker positions were first manually identified in at least two DRRs by clicking on the two edges of

the marker. A rectangular contour was automatically drawn around the marker according to the two clicked points. Next, the tool automatically reconstructed the three-dimensional (3D) marker positions from the identified two-dimensional positions. For each marker identified on a DRR, the expected marker position in the other DRRs was indicated automatically to facilitate the process. The obtained reconstructed 3D marker reference positions were stored for later use in SGT.

Equipment

The cross-fire kV/MV imaging system (Fig. 1) used in SGT was developed on the Synergy linear accelerator (Elekta, Crawley UK). For MV imaging, either a charge-coupled device, camera-based EPID (TheraView NT [TNT], Cablon Medical, Leusden, The Netherlands) or an iView GT flat-panel EPID (Elekta, Crawley, UK) can be used. In the present study, the TNT EPID (Cablon Medical) was used. The gantry-mounted XVI system enables acquisition of a planar image from the kV beam orthogonal to the MV beam directly before MV acquisition. Hence, the XVI/EPID combination can be used for acquisition of an orthogonal pair of images without intermediate gantry rotation. The TNT software was extended to provide all necessary tools for image processing, marker detection, analysis, and application of the positioning corrections.

The Theraview Couch Set-up Assistant (TCSA) system applies patient positioning corrections by remotely steering the Elekta Precision couch. The prototype of the TCSA used in this study was developed in collaboration with Cablon Medical and Elekta. It consisted of an independent controller personal computer connected to the couch control cabinet and to the TNT workstation. Treatment plan information, as well as positioning corrections, were transferred from TNT software to the TCSA controller while safety checks were being performed. The checks included correspondence of the patient and treatment plan identification numbers with the record and verify system, TCSA and couch hardware status, and communication integrity. In the case of any inconsistency, the TCSA moves to a passive state and stops any motion being executed. In the "off-line mode," the relative couch position as read by the TCSA is first zeroed by pressing a dedicated button on the couch's manual controls. Any pretreatment corrections such as those generated by an off-line correction protocol are automatically executed by the TCSA while the motion enable bar is pressed. In the "on-line mode" used in SGT, zeroing the couch readout and execution of pretreatment corrections are the same but shifts of a maximum of 2 cm are also allowed under remote control of the TNT software. In the on-line mode, the radiographer in the control room must hold the keyboard spacebar of the TNT workstation to allow this couch motion.

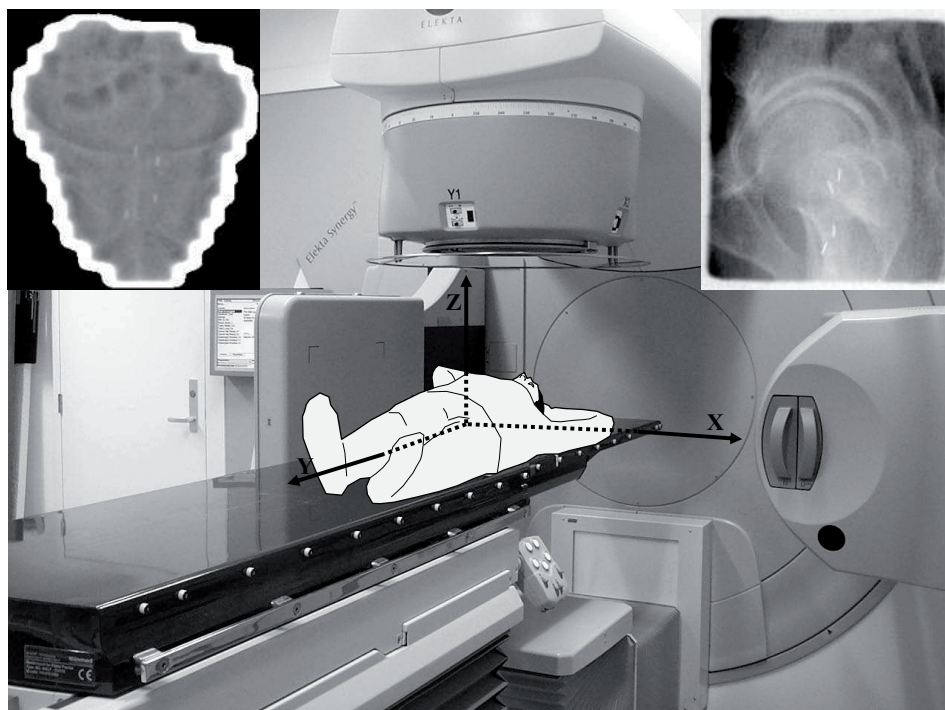


Figure 1. Coordinate system: anteroposterior (Z), craniocaudal (Y) and left–right (X), with orthogonal imagers and sample clinical images. (Top left) Megavoltage image. (Top right) Kilovoltage image.

SGT execution

At the start of each treatment fraction, the patient was positioned according to the alignment of the room lasers with the skin marks. If available, pretreatment (“off-line”) corrections were executed by the TCSA. Next, a lateral planar kV image (kVI) of 1024 x 1024 pixels was acquired with the XVI system using a dedicated collimator that projects a field size of 10 x 10 cm² at the isocenter. The clinical kVI acquisition settings (eight frames, 40 ms, 32 mA) resulted in a maximal skin dose of approximately 1.5 mGy. The acquired kVI was then automatically imported into the TNT workstation. The kVI acquisition was immediately followed by MV image (MVI) acquisition with the first part (2–6 monitor units [MU]) of the anteroposterior treatment beam. For IMRT, we apply the split IMRT field technique (105). In the split IMRT field technique, the IMRT field is divided into a static and a modulated field, and an MVI of the former field is used in SGT. Congruence of the isocenter positions of the two orthogonal imagers was checked daily as a part of our routine quality assurance program and was within 0.5 mm during the study period.

On the basis of the automatically extracted two-dimensional positions of the markers in the two orthogonal images, the 3D marker positions were reconstructed in the treatment coordinate system. The difference between the center of mass (COM) of the markers during

a treatment fraction and the corresponding COM from the planning CT is the translational correction. Prostate rotations about the COM with respect to the planning CT scan for all three axes were also calculated. The translational correction was remotely executed under TCSA guidance if the magnitude of the correction vector was >2 mm. After the correction has been applied, the SGT loop can be re-entered to acquire and analyze images for verification Fig. 2). If no further correction or verification is necessary, all treatment beams are delivered. In the present study, 3D verification using on a second kVI/MVI pair was always performed. In subsequent sections, we describe the procedure to automatically obtain the marker positions from the image pair in more detail.

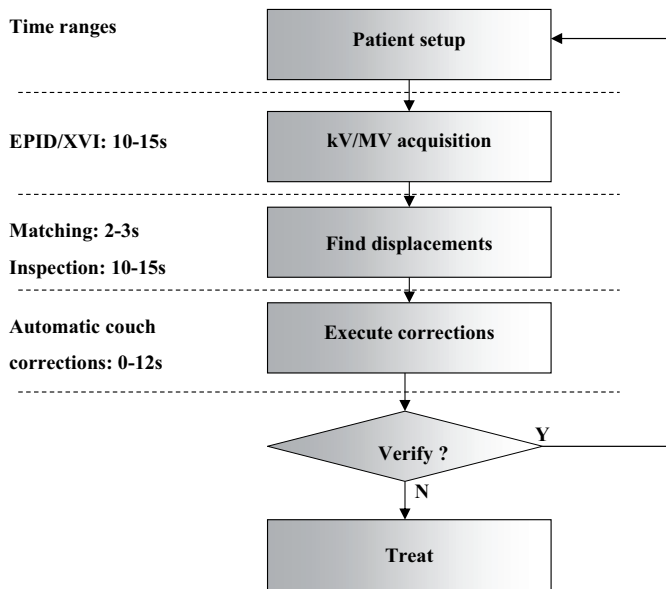


Figure 2. Stereographic targeting workflow with observed time ranges for various subprocesses.

Automatic marker detection and 3D position reconstruction

For the MVI, the image coordinate system was determined by registration of the detected field edge with the planned field edge (106). For the kVI, the image coordinate system was retrieved from the XVI database. For both images, fixed pattern noise was eliminated by dividing each image with a flat field image. Automatic marker detection in each image required a set of previously obtained reference marker positions for the corresponding view, as described in the section “Preparation”. The applied algorithm for automatic marker detection was based on a combination of template matching and marker extraction kernels (MEKs) (107), adapted for the rotations of individual markers. For each projected marker, the MEKs were calculated for a set of predetermined in-plane marker rotations. The range of these rotations was determined

by the initial marker orientation plus a maximal MEK rotation value (θ), which is set as an option in TNT. A θ value of 20° was sufficient for marker detection in the present study. The sum of the rotated MEKs formed the effective MEK, which was then convolved with the input image to form the marker response image (Fig. 3b,f). The image was binarized with adaptive thresholding to select only those features with sufficient marker response. Although the markers stand out in the binary image, some features with shapes similar to markers (e.g., because of bony edges, calcifications, or image noise) are also visible (Fig. 3c,g). To obtain the true marker positions from the spots in the binary image, Chamfer matching (108) was used. Because the Chamfer match was performed with all markers simultaneously, it was insensitive to the features in the binary image that did not represent the markers. After Chamfer matching, the centroid of the spot with greatest response in the neighborhood of a marker was chosen as the detected marker position. With the marker positions thus identified in two orthogonal images, the 3D rigid body transformation that best mapped the marker reference positions onto the positions during a treatment fraction was found analytically from the leastsquares minimization (109). The residue errors per marker directly yielded information about the rigidity of the template, as well as whether the markers were associated with the correct blobs. The quality of the match, both overall and for individual markers, could thus be assessed. In the visualization of the match results, the markers were presented with color coding to indicate this quality.

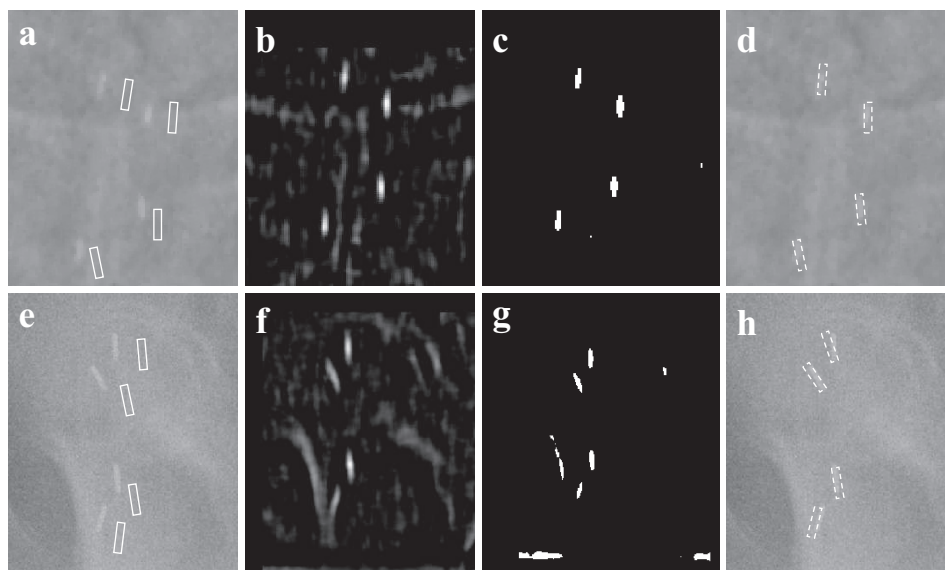


Figure 3. Marker matching on (a–d) megavoltage image and (e–h) kilovoltage image. Reference marker positions indicated by solid white rectangles and detected marker positions by dotted white rectangles. (a,e) Initial images, (b,f) images after convolution with marker extraction kernel, (c,g) images after binarization of convolution images, and (d,h) final images with detected marker positions.

Phantom measurements

The accuracy and success rate of SGT marker matching was studied for the clinically applied (kV/MV) image combination, as well as for another approach using two MVIs. Furthermore, the performance of SGT marker matching as a function of MV beam energy, as well as MV exposure, was investigated.

A phantom consisting of a stack of 10 square ($41 \times 41 \text{ cm}^2$) plates of RW3 (PTW, Germany) water-equivalent material was used. Each plate had a thickness of 1–2 cm so that the combined dimension of the phantom was $41 \times 41 \times 20 \text{ cm}^3$. Six gold markers were embedded in grooves on the two opposite faces of the central plate, with three markers on each face. The markers were placed such that the intermarker separation was 2, 4, and 1 cm in the left–right, craniocaudal, and anteroposterior directions, respectively. The phantom was placed on the treatment couch and shifts ranging from 0 to 20 mm in each direction with step sizes of 5 mm were executed using couch motion. Two orthogonal MVIs (MV “anteroposterior” and MV “lateral”) were acquired with varying exposures (1, 2, 4, 8 and 32 MU) after each shift, using the three available beam energies (6, 10, and 18 MV). A lateral kVI (kV “lateral”) was also acquired after each MVI acquisition at the clinically applied exposure for each phantom position.

The marker matching accuracy and success rate in the presence of combined phantom rotations and translations were also studied using a dedicated phantom consisting of a water-filled box ($30 \times 20 \times 30 \text{ cm}^3$) made of polymethyl metacrylate. Four gold markers were embedded in grooves on the two faces of a polymethyl metacrylate slab ($30 \times 20 \times 2 \text{ cm}^3$), with two markers on each face. This slab was immersed in the water-filled box. Predefined rotations about the three principal directions (range, 0–20°; with a step size of 5°) were applied to the phantom with markers. Both kVI/MVI and MVI/MVI orthogonal images were acquired after each rotation step. Phantom translations were applied using couch shifts, and MVI exposures of 6 MU and 32 MU at 6 MV were studied.

Ground truth values for marker matches

A tool developed in MATLAB was used to obtain the “ground truth” transformation (three translations and three rotations) that the SGT matching software should ideally yield. With this tool, markers are manually identified in an orthogonal pair of images by clicking on the centers of the markers in each image. Given two pairs of orthogonal images and the corresponding manually identified marker positions, the tool calculates the rigid body transformation between the pairs of images. For each pair of images used, the procedure was repeated three times, and the mean transformation was calculated and used as the ground truth.

TCSA precision

The precision of the TCSA was measured using the slab phantom with embedded gold markers. Initially, the phantom was placed on the couch, and the absolute 3D position of the couch was obtained. Next, two orthogonal kVIs were acquired with the phantom in the

initial position. Predetermined displacements ranging from - 2 cm to 2 cm were applied to the phantom using couch shifts. After each execution of three random displacements along the three orthogonal axes, the absolute position of the couch in the room coordinate system was determined. Next, two orthogonal kVIs of the phantom were acquired, and the couch was moved back to the initial position. All images were imported into TNT, and the automatic SGT marker-matching tool was used to measure the applied displacements by comparing the marker positions in each image set with those in the initial reference images. For these measurements, the clinically applied TCSA tolerance of 0.3 mm was used. The TCSA will not attempt to improve a deviation between the couch position readout and a prescribed position of <0.3 mm. This tolerance setting enables fast convergence toward the prescribed position, without oscillations around the optimal position.

Clinical study

The positioning accuracy obtained with SGT was investigated for 10 patients treated with SGT during EBRT with three or four implanted markers. The treatment plan beam angle was $360^\circ \pm 1^\circ$, $90\text{--}93^\circ$, and $264\text{--}270^\circ$ for the anteroposterior, left-lateral, and right-lateral directions, respectively. The dose prescription for 8 of the 10 patients was 72 Gy in 36 fractions at 2 Gy / fraction. Of the 10 patients, 2, who had previously undergone high-dose-rate brachytherapy, were treated with 1.8 Gy in 25 EBRT fractions, and the markers (three or four platinum cylinders; 3 mm x 1 mm) implanted during the brachytherapy procedure were used. For all patients, pre- and postcorrection kVI/MVI pairs were obtained, and the duration of all involved steps was logged. From the outcome of the automatic match in the SGT for these patients, the pre- and postcorrection systematic and random errors were calculated. In addition, for each fraction, the automatic match results found in the SGT procedure were compared with the ground truth values obtained with the tool described in the previous two sections to assess the accuracy of SGT positioning during clinical operation.

RESULTS

Phantom verification: translations

The kV/MV combination yielded greater marker detection rates than did the MV/MV approach because of the greater marker visibility in the lateral kV images (Fig. 4). The success rate was calculated as the fraction of automatic matches with a 3D deviation from ground truth of <2 mm. Because our goal with SGT was to obtain accuracy better than 2 mm for positioning errors, this was a conservative cutoff level. The mean and SD values expressing differences between the automated SGT result and ground truth per translation direction are reported in Table 1 for each exposure, beam energy, and combination of orthogonal images. In Table 1, slightly greater magnitudes of deviations from ground truth values were observed for the low

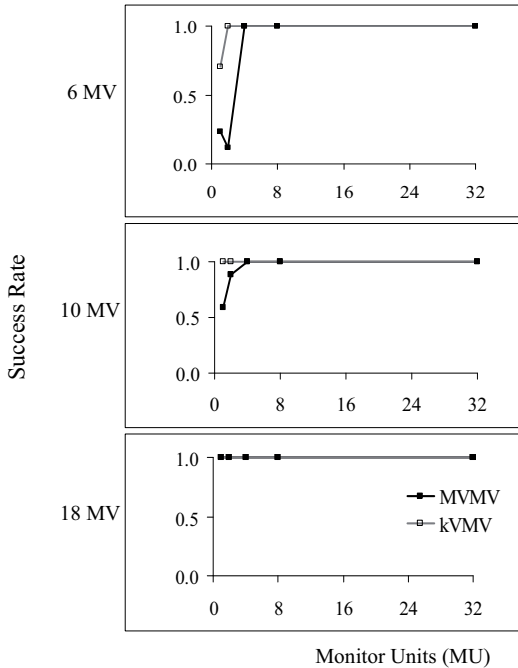


Figure 4. Image matching success rates (for marker translations) vs. monitor units at three beam energies for a phantom. kV/MV = initial stereographic targeting procedure using orthogonal kilovoltage image and megavoltage image combination. MV/MV = procedure using two orthogonal megavoltage images.

MVI exposures (1–2 MU); this was more so for the MVI/MVI pairs because of the lower image quality of the MVI compared with the kVI. This was also reflected in the lower success rate for MVI/MVI at the lowest exposures (Fig. 4).

The cumulative frequency distributions per beam energy of all the observed 3D deviations between the automated match and ground truth are shown in Fig. 5. From the regular behavior of these distributions, it was apparent that although a cutoff level of 2 mm for success was applied, in the small fraction of failure cases, the errors were always <3 mm. The best results (steepest descent in cumulative distribution) were obtained for the 18-MV beam.

Phantom verification: combined translations and rotations

Table 2 shows that even for the large combined rotations of $\leq 20^\circ$, the kVI/MVI image pairs yielded a success rate of 100% for both studied MVI exposures. The success rate was scored as the match results for which the 3D magnitude of the difference with ground truth was <2 mm for translations and <2° for rotations. For the MVI/MVI image pairs, a 30% decrease in the success rate occurred with the lower MVI exposures. The reason for using a low exposure is

		1 MU			2 MU			4 MU			8 MU			32 MU		
		x	y	z	x	y	z	x	y	z	x	y	z	x	y	z
MV/MV		(mm)			(mm)			(mm)			(mm)			(mm)		
6 MV	Mean	0.7	0.6	0.6	-0.1	0.9	0.8	0.3	0.6	0.1	-0.1	0.7	-0.1	-0.1	0.6	0.4
	SD	0.4	0.9	1.1	0.6	0.7	1.5	0.4	0.3	0.8	0.5	0.2	0.4	0.2	0.3	0.2
10 MV	Mean	-0.1	0.5	0.0	0.2	0.4	0.2	-0.1	0.6	-0.1	-0.1	0.6	0.5	-0.1	0.5	0.5
	SD	0.7	0.4	1.0	0.6	0.3	0.6	0.5	0.3	0.6	0.5	0.2	0.5	0.2	0.2	0.1
18 MV	Mean	-0.2	0.2	0.2	-0.2	0.3	0.5	-0.1	0.4	0.7	-0.1	0.4	0.6	-0.1	0.5	0.4
	SD	0.4	0.4	0.6	0.3	0.3	0.4	0.3	0.3	0.2	0.2	0.3	0.3	0.2	0.3	0.2
kV/MV																
6 MV	Mean	-0.1	0.1	0.6	0.1	0.1	0.6	0.4	0.1	0.5	0.1	0.1	0.6	0.0	0.1	0.6
	SD	0.9	0.4	0.2	0.5	0.3	0.2	0.4	0.3	0.1	0.5	0.2	0.1	0.2	0.2	0.1
10 MV	Mean	0.0	-0.1	0.5	0.1	-0.1	0.5	-0.1	-0.1	0.5	-0.2	-0.1	0.6	-0.2	-0.1	0.6
	SD	0.7	0.3	0.2	0.7	0.3	0.2	0.4	0.2	0.2	0.4	0.2	0.2	0.2	0.2	0.2
18 MV	Mean	-0.2	-0.1	0.3	-0.3	0.0	0.4	-0.2	0.0	0.3	-0.2	0.0	0.3	-0.1	0.1	0.3
	SD	0.3	0.2	0.1	0.3	0.2	0.1	0.3	0.2	0.1	0.2	0.2	0.1	0.2	0.2	0.1

Table 1. Means and standard deviations (SD) of differences with ground truth for phantom translations at different exposures and beam energies in 3 directions (x, y, z). The data is shown for two cases; using both MV/MV and kV/MV image pairs. In the case of MV/MV image pairs, the exposure pertains to both images.

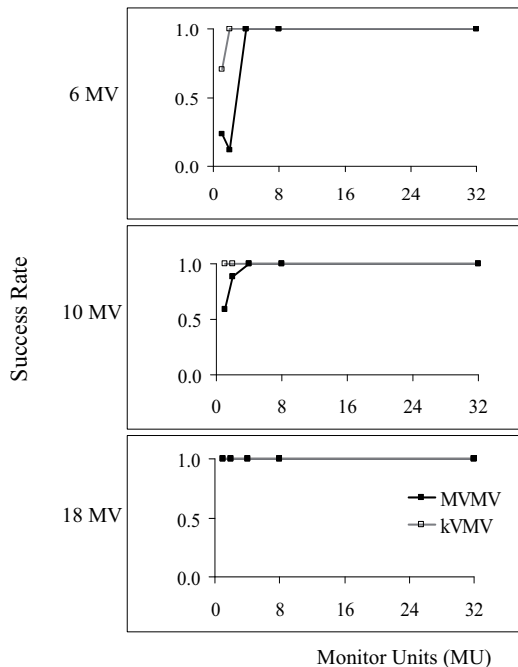


Figure 5. Cumulative frequency distributions of magnitudes of observed three-dimensional position deviations from ground truth as observed in experiments with phantom translations. For each energy, curves were constructed from data for all translations and megavoltage image exposures.

evident; we wanted to deliver no more than a few MUs before correctly positioning the target volume. Hence, the combination of kVI and MVI used in SGT is superior to using EPIDs only.

		6 MU						32 MU					
		x	y	z	Rx	Ry	Rz	x	y	z	Rx	Ry	Rz
		(mm)			(°)			(mm)			(°)		
MV/MV	Mean	-0.1	0.6	0.1	-0.3	0.2	0.3	0.2	0.5	-0.2	-0.3	0.1	0.3
	SD	0.4	0.4	0.7	0.8	0.7	0.6	0.4	0.2	0.3	0.4	0.5	0.4
	Success Rate	70 %						100 %					
kV/MV	Mean	0.0	0.0	0.3	-0.4	0.1	0.1	0.3	-0.1	0.2	-0.4	0.1	0.2
	SD	0.4	0.2	0.3	0.6	0.5	0.4	0.3	0.2	0.3	0.4	0.5	0.3
	Success Rate	100 %						100 %					

Table 2. Differences between SGT and ground truth for two exposures in experiments with combined translations (x, y, z) and rotations (R_x, R_y, R_z) using both MV/MV and kV/MV combinations. Success rates are also shown for both image combinations.

TCSA accuracy

As can be seen in Table 3, the precision of the positioning achieved with TCSA was better than 0.3 ± 0.3 mm (mean \pm SD) along all directions. This couch positioning precision was mainly limited by the TCSA tolerance setting of 0.3 mm, as well as the couch read-out accuracy.

	LR	CC	AP
	(mm)	(mm)	(mm)
Mean	0.29	0.03	0.23
SD	0.27	0.21	0.28

Table 3. Mean and standard deviations (SD) expressing differences between prescribed and measured couch shifts obtained with the TCSA.

Clinical results

Scatter plots of the deviations between the results obtained in the clinical application of SGT and ground truth are shown in Fig. 6. The marker detection success rate for the clinical images was 99.6%, with most of the deviations from ground truth <1 mm. The inaccuracy (mean \pm SD) of the SGT match with respect to the ground truth was 0.2 ± 0.4 mm for the left–right, 0.1 ± 0.5 mm for craniocaudal, and 0.0 ± 0.4 mm for the anteroposterior direction. Table 4 summarizes the results of the measured patient translational and rotational positioning (COM) errors before and after SGT positioning, accumulated for all treatment fractions. The small residual positioning errors obtained with SGT included the inaccuracies in the remotely controlled couch shifts, inaccuracies in the COM translation obtained from the SGT match, and the intrafraction motion during the period between pre- and postcorrection images. Considering only the errors resulting from setup (translation of the COM of the markers), the common equation of CTV-PTV margin = $2\Sigma + 0.7\sigma$ (110) resulted in margins >12 mm without SGT and margins of

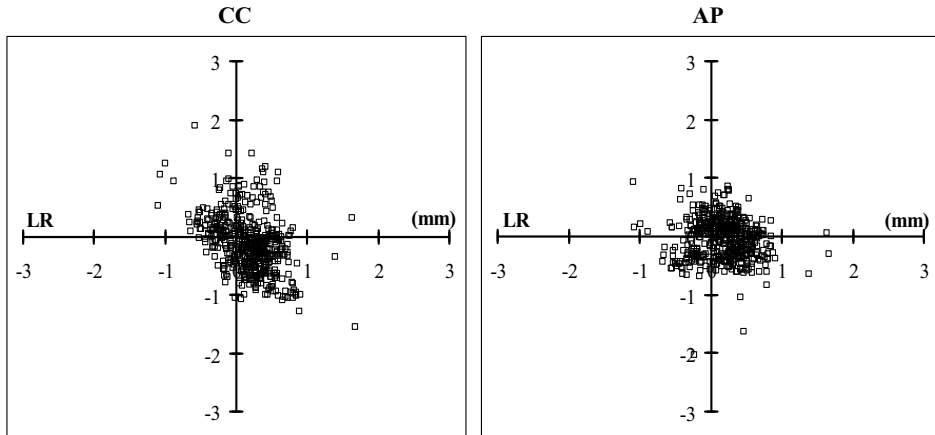


Figure 6. Scatterplots with deviations of prostate setup errors (translational) measured in clinic with stereographic targeting and ground truth values obtained in manual off-line analysis. AP = anteroposterior; CC = craniocaudal; LR = left-right.

	Translations (mm)						Rotations (°)					
	Σ_x	Σ_y	Σ_z	σ_x	σ_y	σ_z	Σ_{Rx}	Σ_{Ry}	Σ_{Rz}	σ_{Rx}	σ_{Ry}	σ_{Rz}
Pre SGT	1.7	4.1	2.9	1.6	2.7	3.2	4.9	1.3	1.7	4.2	1.6	1.3
Post SGT	0.2	0.5	0.4	0.6	0.7	0.8	5.0	1.4	1.9	3.9	1.6	1.3

Table 4. Measured translational and rotational prostate positioning errors (systematic (Σ) and random (σ)) before and after SGT repositioning.

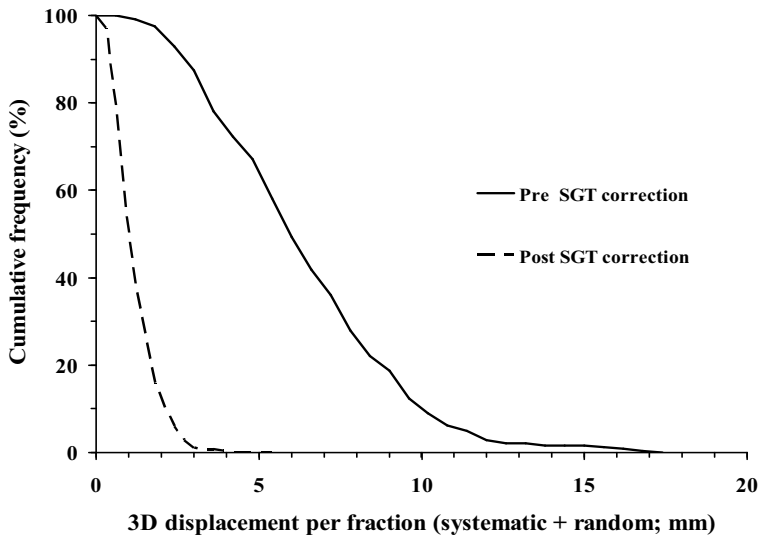


Figure 7. Cumulative frequency distribution of three-dimensional center-of-mass displacements of markers for all patients and fractions, before and after stereographic targeting (SGT).

about 2 mm after applying the SGT corrections. A cumulative histogram of 3D translational errors (3D vector length) of the COM of the prostate markers for all patients and fractions is shown in Fig. 7, in which each 3D error represented the sum of the systematic and random error. Before SGT, the observed errors could exceed 10 mm in all directions but were reduced to <3 mm after SGT. Furthermore, the procedure was fast. Considering the upper limits of the time ranges in Fig. 2 revealed that SGT positioning was performed within 45 s/fraction.

DISCUSSION

Using SGT, the systematic and random errors were reduced to 0.5 mm and 0.8 mm (SD), respectively, within 1 min/treatment fraction. The crossfire imaging, accurate automatic match with a high success rate (>99%), precise remote couch control system, and integration into one software environment are the ingredients that allow for this combination of speed and accuracy. Although in this study, the anteroposterior MV beam was used because it is a part of our treatment plan, the SGT can be started at any gantry angle.

Apart from the combined kV/MV imaging, our approach to on-line prostate positioning might seem similar to other stereoscopic imaging systems such as the ExacTraC X-ray 6D system (BrainLab AG, Heimstetten, Germany) (111-113). The published data on the final accuracy and timing achieved for prostate markers are limited, but the findings indicate that SGT is at least as accurate as the ExacTraC system (112). A relevant difference is that SGT uses two imaging devices that have a use in their own right. The XVI system is also used for cone-beam CT acquisition to visualize soft tissues insufficiently visible on planar images (e.g., the seminal vesicles and rectum in the case of the prostate). Such information can be used in adaptive radiotherapy strategies (114,115). Furthermore, the EPID can be used for position verification without an additional kV dose (third to last paragraph before “Conclusion” section), as well as for EPID dosimetry (116). Such flexibility is not offered by a dedicated planar imaging system such as the ExacTraC.

The combination of speed and accuracy for prostate positioning with implanted markers is hard to match with techniques relying on volumetric imaging alone (117). Cone-beam strategies for the prostate will likely involve offline correction schemes (114,115), partly because of the workload, speed, and registration success rate, but also because the kV dose is not negligible. Off-line corrections might be less effective for the hypofractionation schemes currently under study for prostate RT (118,119).

Although the importance of time trends for prostate targeting has not been fully established, a recent fiducial markerbased study indicated that the time trends must be taken into account for accurate prostate positioning ($\Sigma < 1$ mm) with off-line corrections (120). We have recently proposed an off-line scheme to deal with the time trends (121). The reduction of systematic and random positioning errors could be partially achieved with an adaptive strategy in

which CT scans acquired during the initial week of treatment are used to estimate patient-specific PTVs in an off-line manner (115). Nevertheless, systematic and random positioning errors of <1 mm (SD), regardless of the time trends, can only be achieved with an on-line approach.

The potential for planning margins as small as 2 mm when SGT is applied is hampered by various factors such as prostate rotation, intrafraction motion, target volume deformation, marker migration, and delineation (or generally, target definition) inaccuracies.

The measured prostate rotations (Table 4) are similar to the values reported in earlier studies (93,101,122,123). Various studies have shown that the prostate rotates mostly about the left–right axis, with the rotation center at the apex (101,124). If the prostate position is corrected according to the COM of the markers, inadequate coverage could occur, especially near the base (“undercorrection”) and apex (“overcorrection”), dependent on the chosen planning margin (101). The measured COM displacements contain a contribution from the rotations, and the COM translation corrections are exact only at the COM position. The residual deviations at the prostate boundary depend on the prostate shape and size. For a perfectly spherical prostate with the marker COM at its center, the COM translation corrections will yield 0 residual errors along the entire prostate boundary (i.e., each point within the boundary will be covered by the boundary after correction), regardless of the rotations. We calculated the required margins for SGT in the case of the rotations (Table 1) for various prostate shapes, ranging from circular to flattened at the base and sharpened at the apex. We added in quadrature post-SGT translational errors and local distances between prostate hulls induced by rotations, as given in Table 4, to obtain the effective Σ and σ . Assuming a prostate base–apex length of 4 cm, application of a margin equation of $2\Sigma + 0.7\sigma$ yielded a maximal CTV-PTV margin of 4 mm. However, larger displacements can occur at the seminal vesicles, owing to rotations, as well as deformations (122,125). We are currently conducting a multiple CT study to investigate the motion of the seminal vesicles and prostate boundary (deformations) with respect to fiducial markers. In that study, we have included the residual errors resulting from prostate and seminal vesicle deformation into a population-based margin calculation to obtain well-defined margins for SGT. Furthermore, we are presently developing a strategy to correct for the rotational positioning errors using on-line selection of an optimal plan matching the observed rotation) from a library of plans created for various prostate rotations. Because these plans could include seminal vesicle treatment, knowledge of the seminal vesicle motion in the presence of rotations is required to create optimally conformal plans.

Prostate intrafraction motion during EBRT has been well studied (93,102,126,127). We are conducting a study on intrafraction motion for prostate cancer patients treated with SGT by acquisition of extra kVIs and MVIs during treatment. The initial results have indicated that the intrafraction motion is mainly random, with a SD of <1 mm in both the anteroposterior and the craniocaudal directions. Hence, the contribution to planning margins will be small compared with previously mentioned factors. Because of the speed of the SGT procedure, the intrafraction motion between the moment of prostate position measurement and treatment

will be minimized and the intrafraction motion could be reduced further by repetition of the SGT procedure within one fraction (e.g., before each treatment beam). We are extending SGT with a system for continuous automatic detection of intrafraction motion using MVIs of the treatment beams (i.e., without an additional kV dose).

Marker migration and prostate deformation also contribute to the required planning margins. Recent studies have shown that the effect of marker migration is quite minimal for the prostate, and the overall effect of prostate deformations is <1 mm (122,125). In our study, no substantial migration of the markers was observed.

Finally, to fully use the possibility of margin reduction as a result of the reduction of patient positioning errors presented by SGT, one should minimize the delineation errors (122,128,129). One can treat delineation errors as one of the sources of systematic errors (129), but care must be taken with this approach because delineation errors do not necessarily behave stochastically. For instance, the prostate volumes on CT tend to be systematically larger than those observed on MRI and ultrasonography in transversal slices. However, CT can systematically underestimate the volume near the superior and inferior boundaries (130,131). Apart from anatomic position, the magnitude of the intermodality and inter- and intraobserver differences is also dependent

on the exact acquisition and delineation protocols applied. The use of a margin to account for small random delineation inaccuracies (e.g., intraobserver delineation errors) is reasonable. However, for systematic intermodality and interobserver variations, it is a rather crude tool. More promising approaches are offered by multimodality imaging and registration, as well as flexible delineation tools that allow for contouring in multiple planes simultaneously.

CONCLUSION

We have developed and clinically evaluated a fast and accurate procedure for daily on-line repositioning of the prostate using rapid sequential imaging of implanted markers with orthogonal kV and MV beams. The procedure is based on fully automated extraction and 3D registration of the imaged markers followed by remote couch control translations under control within a single software environment. This approach achieved residual systematic and random errors of <0.8 mm (SD) in the three principal axes, with an addition of <1 min to the treatment time. Furthermore, the procedure limits the imaging-specific dose, because the MVI is obtained with the therapeutic dose and the planar kVIs are acquired for only one direction.

Chapter 7

Deformation of the prostate and seminal vesicles relative to intraprostatic fiducial markers

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ABSTRACT

Purpose

To quantify the residual geometric uncertainties after on-line corrections with intraprostatic fiducial markers, this study analyzed the deformation of the prostate and, in particular, the seminal vesicles relative to such markers.

Patients and Methods

A planning computed tomography (CT) scan and three repeat CT scans were obtained for 21 prostate cancer patients who had had three to four cylindrical gold markers placed. The prostate and whole seminal vesicles (clinical target volume [CTV]) were delineated on each scan at a slice thickness of 1.5 mm. Rigid body transformations (translation and rotation) mapping the markers onto the planning scan positions were obtained. The translation only (T_{only}) or both translation and rotation were applied to the delineated CTVs. Next, the residue CTV surface displacements were determined using nonrigid registration of the delineated contours. For translation and rotation of the CTV, the residues represented deformation; for T_{only} , the residues stemmed from deformation and rotation. T_{only} represented the residues for most currently applied on-line protocols. The patient and population statistics of the CTV surface displacements were calculated. The intraobserver delineation variation was similarly quantified using repeat delineations for all patients and corrected for.

Results

The largest CTV deformations were observed at the anterior and posterior side of the seminal vesicles (population average standard deviation ≤ 3 mm). Prostate deformation was small (standard deviation ≤ 1 mm). The increase in these deviations when neglecting rotation (T_{only}) was small.

Conclusion

Although prostate deformation with respect to implanted fiducial markers was small, the corresponding deformation of the seminal vesicles was considerable. Adding marker-based rotational corrections to on-line translation corrections provided a limited reduction in the estimated planning margins.

INTRODUCTION

Prostate cancer is the most common type of cancer for men in Western countries (82) and is often treated with external beam radiotherapy (EBRT). However, external beam radiotherapy leads to Grade 2 late gastrointestinal toxicity in 1.6–32% of patients, Grade 2 late urinary toxicity in 15–41%, and erectile dysfunction in 36–43% (5,12,81). Therefore, a large patient population would benefit from techniques able to reduce these common sequelae.

Apart from imperfect target delineation, several uncertainties exist regarding movement of the clinical target volume (CTV), CTV deformation, and variations in beam geometry characteristics. A margin is added to the CTV to account for these uncertainties. The planning target volume (PTV) is the CTV plus this margin (2). A reduction of the CTV-PTV margin can lead to lower toxicity (132). The CTV-PTV margin can be reduced to less than the commonly used 1 cm with image guided radiotherapy (IGRT) or adaptive radiotherapy (101,115,133).

In our clinic a fully automated method for fast and accurate daily on-line prostate positioning during external beam radiotherapy was developed for the Synergy system (Elekta, Crawley UK) and clinically implemented (133). This method, Stereographic Targeting (SGT), is based on intraprostatic fiducial markers that are imaged in a crossfire of megavoltage and kilovoltage beams, followed by fully automated image analysis and remotely controlled couch shifts. Despite a high positioning accuracy for the center of mass (COM) with SGT, the margin reduction must be based on knowledge of the residue displacements over the entire surface of the CTV.

In this study, the residue displacements were obtained from repeat computed tomography (CT) scans delineated at a high resolution after rigid registration of the fiducial markers by using non-rigid registration. Quantification of these residues allows for the assessment of margins for markerbased setup corrections. For instance, the marker registration method allowed us to quantify the residue displacements when only translation corrections were applied. The latter displacements depend not only on the CTV-shape but also on the behavior of the seminal vesicle deformation in the presence of prostate rotations. Knowledge of these displacements is clinically relevant because on-line corrections are often limited to translation corrections (112,133). To our knowledge, this is the first study to quantify these rotation deviations in detail.

The use of fiducial markers as a reference frame in this study had another major advantage: the markers are clearly distinguishable on the CT scans and their relative positions are very stable (101,120). In contrast to methods that use delineated CTVs for initial rigid body registration (134), the rigid body match with markers hardly depends on the sought deformations or on the delineation errors. Therefore, fiducial markers present a suitable frame of reference for quantifying the deformations.

PATIENTS AND METHODS

Patients

Patients scheduled for external beam radiotherapy for prostate cancer were asked to participate in this study (i.e., undergo multiple CT scan sessions). Between August 2006 and March 2007, 21 patients agreed to participate and gave written informed consent. The clinical T category was as follows: Stage T1, 9 patients; T2, 5 patients; and T3, 7 patients. Patients with T3 tumors were treated with adjuvant hormonal therapy. Although not all patients were treated to the seminal vesicles, the whole seminal vesicles were analyzed for each patient in this study.

In each patient three to four fiducial markers (gold cylinders, 1 mm × 5 mm) were implanted transperineally using 18 gauge needles under transrectal ultrasound guidance and local anesthetic. The Medical Ethical Committee of our hospital approved the study, which was conducted in accordance with the Declaration of Helsinki.

Data acquisition

For the planning CT scan, the patients followed our routine clinical protocol. The planning CT scan (Somatom Sensation Open with HiRes-option, Siemens Medical Solutions, Erlangen, Germany) was scheduled ≥ 1 week after marker implantation to allow any possible edema to resolve. Patients used a laxative and were instructed to empty their rectum before the planning CT scan. Furthermore, they were instructed to empty their bladder and drink 0.5 L of fluid 1 h before the planning CT scan. In treatment weeks 2, 4 and 6 a repeat CT scan was acquired directly before or after a treatment fraction. Patients followed the same instructions, except for the use of a laxative.

All four scans were performed with the patient set-up as during treatment (supine position, head rest, and knee support and feet support). The CT scans were reconstructed with a slice thickness of 1.5 mm and a transversal pixel size of 0.7×0.7 mm².

The prostate and the whole seminal vesicles (CTV) were delineated on each CT scan by a single observer (G.J.W.) at the same slice resolution (1.5 mm). The distance from the inferior-most fiducial marker to the apex of the prostate from the planning CT scan was used as a guide to identify the apex on the repeat CT scans.

Analysis

The analysis was performed using in-house developed software (C++ using the itk/vtk toolkits and Matlab). Surface meshes were created from the Digital Imaging and Communications in Medicine (DICOM) exported contours. Hereafter, the CTV surface is referred to as the CTV and any quantity obtained from the planning and repeat CT scan is termed “reference” and “repeat”, respectively.

The rigid body transformation between the repeat and reference scans was obtained with a dedicated tool. A single marker was defined by the two longitudinal end positions of each

marker. In each repeat scan, the markers were identified and a rigid body transformation solving for translation and rotation about the COM of all markers, was performed. This transformation was then applied to the repeat CTV.

Next, the residual deformation between the repeat and reference CTV was estimated by non-rigid registration, see Chui and Rangarajan and Vasquez Osorio et al. (135-137) for details. The nonrigid registration finds a transformation function between two point sets derived from the CTV meshes. Then, the transformation function generated vectors that connect the points on the repeat CTV to the reference CTV. These vectors are referred to as “residue displacements”.

For each patient, the residue displacements were used to create an average CTV shape and the standard deviations (SDs) of the vector field-projections on the local surface normals were derived. We restricted ourselves to reporting motion along these normals because such motion is the most relevant to determine CTV coverage and required margins. To calculate and visualize the population statistics, the same nonrigid transformation software was used to create the population average CTV and to map patient specific local SDs onto the population average CTV. The procedure, described in detail in the Appendix, is illustrated in Fig. 1.

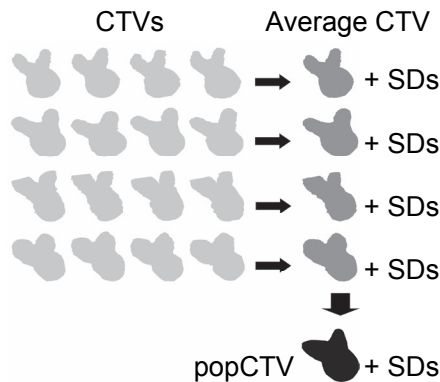


Figure 1. Light gray shapes represent rigidly registered clinical target volumes (CTVs). Subsequent nonrigid registration yielded average CTV for each patient (dark gray) and corresponding interfraction standard deviations of deformations. Patient-specific standard deviations are then projected on population average CTV (black).

Correction for delineation variation

The SDs described in the previous section might have been overestimated, owing to delineation inaccuracies. Because all scans were delineated by a single observer (G.J.W.) and because only variations from scan to scan determined the SDs, the overestimate resulted from intraobserver variation. Hence, two repeat scans in each patient were recontoured by the same observer (G.J.W.). The same non-rigid matching was applied to register Delineation 1 onto Delineation 2. The length of the subsequent deformation vectors was taken in quadrature

and averaged for both re-delineated scans to estimate the local SDs due to the delineations. Because these SDs comprise the inaccuracies in both delineations, they were divided by $\sqrt{2}$ to obtain the single delineation SD. The latter SDs were subtracted in quadrature from the deformation SDs to obtain the actual CTV shape variations.

Full correction vs. translation only correction

Large systematic and random rotations of the prostate about the left-right axis have been observed ($SD = 4\text{-}5^\circ$) when only translational corrections are applied (101,120,123).

To study the residue displacements due to rotations and deformations in the case of translational corrections determined from the markers' COM, we repeated the nonrigid registration analysis after only the translation part of the rigid body transformation (T_{only}) was applied to the CTVs. The effect of the rotations in a T_{only} correction protocol can increase if the COM of the markers is not coincident with the prostate COM (101). Because we used marker-based COM translations for registration, this effect was implicitly taken into account in our study.

Separation into systematic and random residue displacements

The SDs described in the previous section reflect the interfraction variation of residue displacements at the CTV surface. Interfraction variations are commonly referred to as random errors and are usually denoted by σ (138). If the displacements have no systematic time dependency during the treatment course (i.e., it is unimportant when the planning and repeat CT scans are obtained), then the SD of systematic errors, Σ , equals the SD of the random errors: $\Sigma = \sigma$ (115,138). The number of scans and patients in this study was too small to test this assumption in detail. Nevertheless, if Σ is locally significantly smaller or larger than σ , this should be taken into account in the margin calculations. We, therefore, investigated whether we could find large deviations from $\Sigma = \sigma$. The calculation of the Σ -maps is described in the Appendix.

RESULTS

Marker registration results and accuracy

The rigid body registration on fiducial markers determined the frame of reference in this study. We, therefore, determined the accuracy of this registration method. After registration, the match gives the remaining displacements for each marker. The SD of these displacements for all registrations was 0.4 mm in each direction. This SD included all deviations in the registration process, such as the accuracy of defining markers on the CT scans and the relative displacements of the markers. Consistent with the published data, these effects are small (101,120) and the assumption that the markers provide a proper frame of reference was thus confirmed. The SD for the COM position was 0.2 mm, equal to the accuracy of the translation part of the rigid body transformations we applied.

The SDs of the systematic (Σ) and random (σ) prostate rotation angles were approximately 4° about the left-right axis and $<2^\circ$ about the other axes. The average measurement inaccuracy of these rotations, calculated from the marker separations and the above-mentioned residue errors (0.4 mm SD) for each marker, was $<1^\circ$ (SD).

Residue interfraction displacements due to deformations and rotations

Figure 2 and Tables 1 and 2 summarize the residue displacements along the local surface normals, as obtained for the translation plus rotation (T+R) (residues due to deformation) and T_{only} (residues due to both deformation and rotation). Tables 1 and 2 list the average residue displacements of the different regions. Figure 2a shows the maps of the population averaged SDs (σ , see Appendix) of the residue displacements, uncorrected for delineation variation, along the CTV surface normals, projected onto the population average CTV shape in the case of T+R.

Tables 1 and 2 and Fig. 2b summarize the intraobserver delineation variation. This small variation was comparable for the prostate and seminal vesicles. Correcting the full variation for intraobserver variation, yielded the actual variation, as listed in Tables 1 and 2 and displayed in Fig. 2c, 2d. The effect of the intraobserver correction was small. The actual variation for case T+R reflects the interfraction motion of the CTV surface relative to the fiducial markers. Apparently, the prostate surface moves along with the fiducial markers as an almost fully rigid body (SDs ≤ 1 mm). In contrast, the seminal vesicles exhibited considerable relative motion. For the seminal vesicles, the SDs ranged ≤ 3 mm and was dependent on the position.

	Left	Right	Cranial	Caudal	Anterior	Posterior
Full variation, T + R	0.5	0.6	1.2	1.0	1.0	1.0
Intraobserver variation, T + R	0.4	0.5	0.3	0.4	0.7	0.5
Actual variation, T+ R	0.3	0.3	1.1	0.9	0.7	0.8
Actual variation, T_{only}	0.3	0.3	1.4	0.9	0.7	1.3

Table 1. Standard deviations (σ) for deviations along local surface normals in various regions of interest of prostate

Abbreviations: T + R = correction for rotation and translation; T_{only} = correction for translation only

Influence of rotations on residue displacements

When only the translation correction for the markers' COM was applied, we obtained the SD maps (Fig. 2d and the last rows of Tables 1 and 2). For the prostate, the residue displacements for T_{only} became slightly larger cranially and posteriorly with respect to T+R. These local increases were as expected, because the average prostate shape (Fig. 2) was most flattened in these regions (for a perfectly spherical prostate with the marker COM at its center, the increase would be zero).

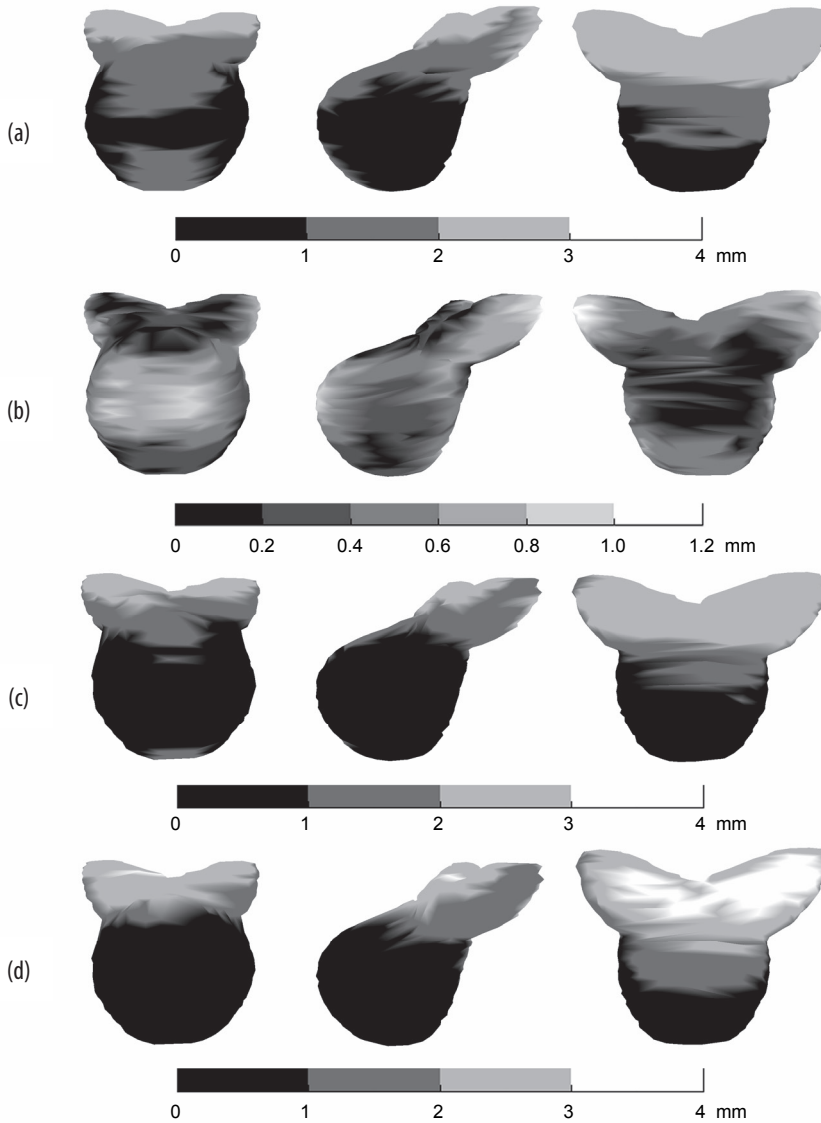


Figure 2. (a) Standard deviation of interfraction variation (σ) after marker-based rigid body registration (translation plus rotation [T+R]), as projected onto the population-averaged clinical target volume, uncorrected for intraobserver delineation variation. (b) Corresponding standard deviations of intraobserver delineation variation. (c) Same as in Fig. 2a, but now corrected for delineation variation in Fig. 2b (i.e., actual variation). (d) Same as Fig. 2c, but now for only rigid translation applied (T_{only}).

Similarly, the residue displacements for the seminal vesicles increased for T_{only} . Hence, the vesicles co-rotated with the prostate to a certain extent. Nevertheless, owing to the large deformation of the vesicles relative to the markers, the relative influence of the rotations on residue displacements was small (everywhere < 0.7 mm).

	Lateral left SV	Lateral right SV	Tip left SV	Tip right SV	Anterior left SV	Anterior right SV	Posterior left SV	Posterior right SV
Full variation, T+R	2.0	1.8	2.2	2.6	2.4	2.5	2.6	2.8
Intraobserver variation, T+R	0.8	0.9	0.7	0.7	0.3	0.3	0.4	0.6
Actual variation, T+R	1.7	1.6	2.1	2.5	2.3	2.5	2.5	2.7
Actual variation, T _{only}	1.7	1.7	2.2	2.7	2.8	2.9	3.1	3.4

Table 2. Standard deviations (σ) for deviations along local surface normals in various regions of interest of seminal vesicles
Abbreviations: SV = seminal vesicle; other abbreviations as in Table 1.

Systematic and random residue displacements

The residues in Fig. 2 were random interfraction displacements. Figure 3 shows the absolute values of the difference of the systematic (Σ) and random (σ) residue displacements as mapped onto the average CTV shape. The smallness of this difference (everywhere < 0.7 mm, and usually < 0.5 mm) was consistent with the assumption that $\Sigma = \sigma$. Hence, the CTV deformations with respect to the markers can be considered to be equal in the planning and repeat CT scans.

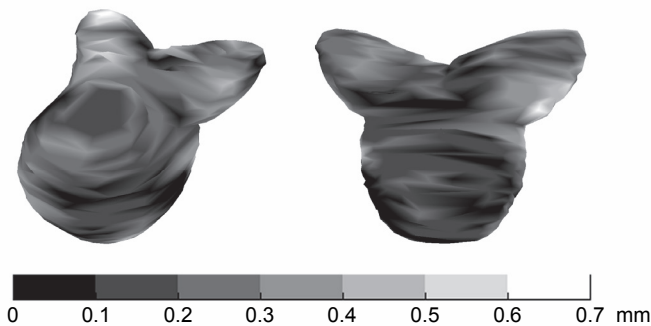


Figure 3. Absolute values of the difference of the systematic (Σ) and random (σ) residue displacements, projected onto the population-averaged clinical target volume.

DISCUSSION

The most detailed previous study on prostate and seminal vesicle deformation was by Deurloo et al. (134), who quantified the shape variations of the prostate and seminal vesicles by using repeat CT scans. Apart from the use of thicker CT slices than in the present study (3 mm vs. 1.5 mm), an important distinguishing feature was their initial rigid body transformation. This transformation was obtained from a chamfer match of the entire delineated gross tumor

volume (prostate and vesicles). Therefore, the deformation might have influenced their rigid body transformations. For Deurloo et al. this problem was not as relevant, because their study considered residue displacements in correction strategies based on prostate delineations from multiple CT scans. However, when using prostate markers for the rigid body registration, the actual shape variation near the seminal vesicles is expected to be greater than that derived in their approach. Indeed, Deurloo et al. obtained an average SD of 1.5 mm near the seminal vesicle tips. In contrast, we obtained 2.3 mm, and even larger SDs posteriorly (2.6 mm, Table 2). Consequently, for marker based correction strategies, the larger numbers for the seminal vesicles presented in this report might apply. The small prostate deformation reported by Deurloo et al. is very similar to the findings of the present study.

Meijer et al. (139) presented a repeat CT scan study with intraprostatic fiducial markers. The prostate and the first 2 cm of the seminal vesicles were included in the CTV. The results were reported in terms of the local planning margins for various correction strategies instead of local deformations. Consequently, these derived planning margins pertain to their specific dose distributions. Their result that perfect online set-up corrections based on markers allowed for margins of 3 mm for the prostate and 7 mm for the first 2 cm of the vesicles is consistent with the margins we derived in the next paragraph.

The planning margin calculation in the presence of deformations is a non-trivial subject. Margin recipes such as the CTV-PTV margin = $2\Sigma + 0.7\sigma$ (110) were derived for rigid body translation motions (110,140), in which the values of Σ and σ are constant along the surface of the CTV, together with assumptions on the dose distribution. Such recipes are already approximate and somewhat arbitrary for ideal cases (110,140). To discuss the full effect of non-rigid motion on planning margin estimates was beyond the scope of this study. For delineation errors, which can be considered to be small deformations, because they can be different at each point on the CTV surface, it has been suggested that a margin recipe such as given above is still approximately valid (140). Therefore, purely for illustrative purposes, we estimated the margins by applying local values of Σ and σ along the surface normals in a margin recipe. The thus-obtained margins in the case of on-line correction by SGT are shown in Fig. 4, for translation corrections (T_{only}) and translation plus rotation corrections (T+R). The corresponding residue displacements as reported in this study were added in quadrature to the Σ and σ values of COM displacements remaining after SGT correction (141). The latter contribution consisted of the small residue errors ($\Sigma \leq 0.5$ mm, $\sigma \leq 0.8$ mm in each direction) directly after on-line correction (133) as well as those caused by intrafraction motion. Kotte et al. (142) performed a markerbased study on prostate intrafraction motion in 427 patients. We took the values from their Table 2 ($\Sigma \leq 0.6$ mm, $\sigma \leq 0.9$ mm in each direction), consistent with the results we obtained in a smaller group. Furthermore, the presently unavoidable random intraobserver delineation errors (Fig. 2b) satisfied the criteria for inclusion in a CTV-PTV margin expansion, and were included in the margin calculation.

The decrease in margins when adding on-line (markerbased) rotation corrections was modest (Fig. 4b). For the prostate, this decrease was negligible, but for the vesicles it was approximately 1 mm. This small reduction was expected because the vesicles only partly co-rotated with the prostate.

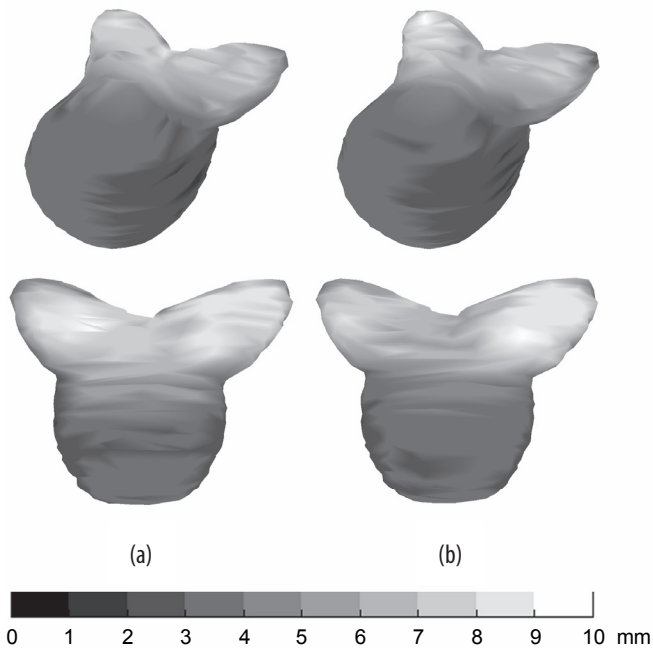


Figure 4. Local clinical target volume to planning target volume margins derived for on-line correction strategies, projected onto the population-averaged clinical target volume. (a) Only translation corrections (T_{only}). (b) Translation and prostate rotation corrections (T+R).

Despite the small residue errors near the prostate the margins for the seminal vesicles could not be reduced much <1 cm. However, Fig. 4 shows that when anisotropic margins would be used an additional reduction could be made at the lateral part of the seminal vesicles. The seminal vesicles seemed to deform mostly in the anterior-posterior and cranial-caudal direction because of variation in rectal and bladder filling. In this study, a mild laxative was only used before the planning CT scan. The use of a mild laxative to promote an empty rectum during treatment (if no diarrhea is present), might enable an additional reduction of the treatment margin, especially for the seminal vesicles.

Nonetheless, these results stemmed from the mainly geometrical considerations underlying the margin recipes. In particular for the seminal vesicles, it is unclear whether such relatively large margins need to be applied. Even a risk of seminal vesicle invasion is present, it might not be necessary to guarantee full-dose coverage for the entire seminal vesicle volume. However, only one study has provided quantitative information on seminal vesicle

involvement. Kestin et al. (143) analyzed 334 Stage T1 and T2 prostatectomy specimen. Of the 51 patients with seminal vesicle invasion, only 10% had tumor beyond the proximal 2.0 cm. They advised treating the seminal vesicles only in patients with sufficient expected risk and to include only the first 2.0 – 2.5 cm of the seminal vesicles in the CTV. However, no evidence has been provided to support the inclusion of only a part of the seminal vesicles in the CTV for Stage T3-T4 tumors.

Geometrical considerations alone are too limited to predict the clinical effect of margin and volume reductions at the seminal vesicles. Factors such as tumor clonogen density and characteristics, dose fractionation and the conformality of the dose distribution should be taken into account (144). We, therefore, are conducting a study, using the deformation data presented in the present study, to validate the planning margins for the prostate and in particular, the seminal vesicles in a full (radiobiologic) dose reconstruction.

CONCLUSION

The deformation of the prostate relative to the intraprostatic fiducial markers was small ($SD < 1$ mm). In contrast, the deformation of the seminal vesicles relative to these markers was significant ($SD \leq 3$ mm). Consequently, the effect on treatment planning margins of the corrections for prostate rotation was small. Future work, including actual dose distribution analyses, is required to conclude whether the CTV-PTV margin of the seminal vesicles can be reduced significantly less than the commonly used 1 cm for online set-up corrections based on fiducial markers.

APPENDIX: DERIVATION OF LOCAL SYSTEMATIC AND RANDOM RESIDUE DISPLACEMENTS AFTER RIGID BODY REGISTRATION

In each patient i ($1 \leq i \leq N_p$), prostate and seminal vesicles were delineated in each CT scan j ($1 \leq j \leq N_S$; $j = 1$ is a reference scan). The so obtained CTV surface meshes $S_{i,j}$ can be represented as a collection of $N_{i,j}$ 3D vectors $\vec{r}_{i,j}(k)$, each vector representing a surface point:

$$S_{i,j} = \{\vec{r}_{i,j}(1), \dots, \vec{r}_{i,j}(N_{i,j})\}; \vec{r}_{i,j}(\cdot) \in \mathfrak{R}^3. \quad (1)$$

Each repeat scan ($j > 1$) is rigidly registered with scan 1 using the fiducial markers. As mentioned in the manuscript, two cases were studied:

- a) apply only the translation

$$S_{i,j}^t = S_{i,j} + T$$

- b) apply both translation and rotation

$$S_{i,j}^t = RS_{i,j} + T$$

The analysis will continue with the rigidly transformed surfaces, $S_{i,j}^t$, which are now in the marker-based coordinate frame of the reference surface. We will henceforth drop the superscript "t" for readability.

Calculating patient average displacement vectors and average surface

For patient i and scan j , non-rigid transformations $f_{i,j}$ ($j > 1$) mapping the points of reference surface $S_{i,1}$ to points on repeat surface $S_{i,j}$ were obtained using the thin plate spline -robust point matching method. This method solves for both the transformation as well as the point-to-point correspondence between the surfaces (135,137). We assessed the accuracy of this method as follows. The inaccuracy in the non-rigid registration can be expressed as the distance between the target and deformed surfaces:

$e_{i,j} = f_{i,j}(S_{i,1}) - S_{i,j}$ on each surface point. The average value over all patients (i), scans ($j > 1$) and surface points of the 3D vector length of $e_{i,j}$ was 0.45 mm (SD 0.25mm). Hence, the surface mapping was very accurate for both prostate and seminal vesicles. Note however, that this mapping accuracy is not necessarily the same as the accuracy of the anatomical correspondence between mapped points. The latter cannot be derived from CT data alone.

With these transformations, we obtain the residue displacement vector fields

$$v_{i,j} = f_{i,j}(S_{i,1}) - S_{i,j} = \{\vec{v}_{i,j}(1), \vec{v}_{i,j}(2), \dots, \vec{v}_{i,j}(N_{i,1})\} \quad (2)$$

where the notation for $v_{i,j}$ is the same as for $S_{i,j}$ in Eq. (1). Note that, because $f_{i,1}(S_{i,1}) \equiv S_{i,1}$, we have $v_{i,1} \equiv 0$. Also, each matrix $v_{i,j}$ for patient i has the same number of columns $N_{i,j} = N_{i,1}$

The average surface $S_{i,a}$ of patient i is obtained from

$$S_{i,a} = S_{i,1} + \mathbf{v}_{i,avg} \quad \text{with} \quad \mathbf{v}_{i,avg} = \frac{1}{N_S} \sum_{j=1}^{N_S} \mathbf{v}_{i,j} \quad (3)$$

Construction of the population averaged CTV surface (popCTV)

A specific patient average shape is chosen ($S_{1,a}$) and non-rigid transformations $\{F_i\}$ from $S_{1,a}$ to $S_{i,a}$ are obtained. Similar to Eq. (2), the vector fields V_i that map the average surface of patient 1 onto that of patient i ($1 \leq i \leq N_P$) are

$$V_i = F_i(S_{i,a}) - S_{1,a} \quad (4)$$

Again, $V_1 \equiv 0$ by definition. The popCTV surface is obtained as

$$S_{AVG} = S_{1,a} + V_{avg} \quad (5)$$

where V_{avg} is the average over i of the fields $\{V_i\}$.

Patient specific systematic and random residue displacements

At each point k ($1 \leq k \leq N_{i,1}$) spanning the average surface $S_{i,a}$ of patient i , the systematic displacement $\varepsilon_i^n(k)$ along the surface normal $\hat{\mathbf{n}}_i(k)$, was obtained from

$$\varepsilon_i^n(k) = \frac{1}{N_S - 1} \sum_{j=1}^{N_S} \bar{\mathbf{n}}_i(k) \bullet \bar{\mathbf{v}}_{i,j}(k) \quad (6)$$

The corresponding SDs of random displacements along the surface normals, $\delta_i^n(k)$, were calculated using,

$$\delta_i^n(k) = \frac{1}{N_S - 1} \sqrt{\sum_{j=1}^{N_S} \left((\bar{\mathbf{v}}_{i,j}(k) - \bar{\mathbf{v}}_{i,avg}(k)) \bullet \bar{\mathbf{n}}_i(k) \right)^2} \quad (7)$$

Population systematic and random residue displacements

The systematic and random residue displacements defined in Eq. (6) resp. (7) are defined on the surface points of each patient specific average CTV surface $S_{i,a}$. We can map these points onto popCTV using the non-rigid transformation of Eq. (4). Thus, we obtain N_P values of ε_i^n and δ_i^n at each point spanning popCTV. The population random displacement σ is calculated by taking the root mean square average of the N_P patient specific random errors δ_n at each point on the popCTV surface.

Although ε_i^n is an unbiased estimator of the systematic displacement for patient i , its standard deviation, $SD(\varepsilon_i^n)$ slightly overestimates Σ due to a contribution by the random displacements for a finite number of scans (N_S): $SD(\varepsilon_i^n)^2 = \Sigma^2 + \sigma^2 / (N_S - 1)$ (see (145)). Using σ , this bias was corrected for. Thus obtained maps of Σ and σ were used in figures 2-4.

Chapter 8

Discussion & Conclusion

RADIOTHERAPY FOR PROSTATE CANCER

Prostate cancer is the most common type of cancer, with the exception of skin cancers, for men in Western countries (82) and is treated with external beam radiotherapy in a large number of patients. This leads to grade 2 late gastrointestinal toxicity in 11%-33% of the patients, grade 2 late urinary toxicity in 10%-39% and erectile dysfunction in 36%-56% (5,81,146,147). This makes erectile dysfunction one of the most common sequelae of external beam radiotherapy for prostate cancer. A decrease in sexual function is a common side effect in all forms of treatment for prostate cancer and is associated with impaired quality of life (37,38). A large number of patients would benefit from a technique that could reduce the risk of erectile dysfunction after external beam radiotherapy. Sparing a structure that is responsible for erectile dysfunction or reducing the treatment margin by using fiducial markers and on-line positioning corrections represent two possibilities to achieve this goal.

IMPORTANCE OF SEXUAL FUNCTIONING

Prostate cancer patients treated with external beam radiotherapy are approximately between 50 and 80 years of age (81). There is a decline in several aspects of sexual function during aging and one might wonder whether this population still has desire for sex and adequate erections.

In the Dutch Krimpen study (148) 88% of the 1605 men between the age of 50 and 78 years were sexually active and the prevalence of significant erectile dysfunction was no more than 26% in the highest age stratum of 70-78 years. Significant erectile dysfunction was defined as "severely reduced rigidity" or "no erections". In a Swedish study from Helgason et al. (149) sexual function was studied in 319 men between 50 and 80 years of age. Of those men, 68% reported erectile stiffness "sufficient for intercourse most of the time" and 88% reported to have at least some sexual desire.

Incrocci et al. (45) studied 158 patients with localized prostate cancer. Of those patients, 41% indicated to have (very) much sexual desire and sex was important to 78%.

This is in agreement with the results reported in Chapter 2, in which 28% of the patients suffered from erectile dysfunction in the two weeks before radiotherapy, 40% found sex (very) important, 41% had considerable to very much desire and 51% was sexually active. Two years after radiotherapy, 36% of the patients had developed erectile dysfunction. Other prospective studies reported percentages from 7% to 59% (7-12). Helgason et al. (37) found that most men were distressed when external beam radiotherapy for prostate cancer led to a decrease in sexual function.

In summary, most patients between 50 and 80 years of age are sexually active and have sexual desire. Unfortunately, radiotherapy for prostate cancer causes erectile dysfunction in

a considerable amount of patients. Therefore, a large group of patients would benefit from techniques that reduce the risk of erectile dysfunction after external beam radiotherapy.

SPARING STRUCTURES RESPONSIBLE FOR ERECTILE DYSFUNCTION

Erectile dysfunction after external beam radiotherapy for prostate cancer might be prevented by avoiding certain anatomical structures in the treatment plan. Then, a new question arises: what structure should be spared? Chapter 3 gives an overview of clinical studies that tried to find a correlation between erectile dysfunction and the radiation dose to the neurovascular bundles, the penile bulb and/or the corpora cavernosa (17-22,26-31,57,60,61,84). Most studies are hampered by a limited number of patients and have contradictory results. Therefore, there is no clear answer which structure is responsible for erectile dysfunction.

The majority of studies previously published did not take into account the use of hormonal therapy or potency aids and/or were retrospective in nature. Chapter 4 describes the largest study analyzing the correlation between the radiation dose to the corpora cavernosa and erectile dysfunction after external beam radiotherapy for prostate cancer. Even though this was a prospective study, taking into account hormonal therapy and the effects of potency aids, no significant correlation was found.

Erectile dysfunction after external beam radiotherapy for prostate cancer could be multifactorial instead of only based on the radiation damage to one single anatomical structure. If this is the case, it will be much harder to find a correlation between erectile dysfunction and the radiation dose to a specific structure. Furthermore, it is very well possible that the structure responsible for erectile dysfunction has not been investigated yet, like the internal pudendal arteries which supply the cavernosal arteries (75). Several studies have demonstrated a reduced flow in the cavernosal arteries in patients suffering from erectile dysfunction after radiotherapy for prostate cancer (32-34). Moreover, the current dose calculations of these studies are based on one (planning) CT scan. However, there can be differences in the dose distribution calculated on the base of one CT scan and the actual dose distribution that is delivered to the patient (129,150,151). Fortunately, new techniques, like the use of fiducial markers, reduce setup errors (133) and therefore will make dose distribution analysis in the future more precise.

Furthermore, because of the close proximity of several anatomical structures possibly involved, the radiation dose to one structure is often correlated to the structure adjacent to it, like the penile bulb and the corpora cavernosa (18,20,63). Therefore the evidence which structure is responsible for erectile dysfunction can not be purely based on a dose correlation. Before such a conclusion can be drawn, a randomized controlled trial must be undertaken in which the responsible structure is spared in one arm.

Another way to analyze this problem is by of animal experimental studies. Carrier et al. (74) conducted an experiment in which rats were treated at the prostatic area with one single fraction of 10 or 20 Gy and found a decrease in nitric oxide synthase-containing nerve fibres in the proximal shaft of the penis. Nitric oxide is believed to be the principal neurotransmitter mediating penile erection (152). Furthermore, the authors concluded that there were defects in the vascular supply of the erectile tissue and there was a decrease in cavernous smooth muscle. Merlin et al. (77) performed a similar experiment. The level of endothelin-1, a potential vasoconstrictor (78), was increased in rats treated with one single fraction of 20 Gy. Merlin et al. suggested that an increased endothelin-1 level could be involved in development of atherosclerotic lesions, because endothelin-1 acts as an autocrine growth factor for smooth muscle cells in the corpus cavernosum and pelvic vasculature (77).

However, in clinical practice not one single fraction, but multiple fractions are used to treat prostate cancer. Chapter 5 describes the changes in the penile arteries after fractionated irradiation of the prostatic area of the rat. Our pilot study shows that arterial changes, like thickening of the intima and occlusions, like suggested by Merlin et al. (77) and Carrier et al. (74) also develop after fractionated radiotherapy. However, future larger studies are needed to draw final conclusions and investigate the mechanism that caused these changes

MARGIN REDUCTION

By reducing the CTV-PTV margin, all structures surrounding the prostate receive a lower radiation dose, including the structures that are essential to a penile erection. The CTV-PTV margin accounts for uncertainties regarding movement, deformation and delineation. By reducing one or more of those uncertainties the treatment margin can be reduced without compromising target coverage.

The uncertainty regarding movement can be decreased by using stereographic targeting which is being described in Chapter 6. The prostate is implanted with 3 to 4 small golden cylinders, fiducial markers. These fiducial markers are identified in the planning CT scan, on which the prostate is delineated. Before each treatment fraction these fiducial markers are digitally imaged. The difference between the reference position and the current position of the fiducial markers is calculated and the treatment couch is shifted in order to correct the difference, within a threshold of 2 mm. Without marker-based correction protocols this difference could exceed 10 mm, while by using stereographic targeting this difference was reduced to <3 mm. Furthermore, the procedure is performed within 45 seconds per treatment fraction. A new development is the implantation of electromagnetic transponders that can be traced in real time without the use of X-ray beams (153).

Another possibility is the use of cone beam CT scans, in which a scan is made on the actual treatment couch right before a treatment fraction (128). However, Moseley et al. reported that

the accuracy of prostate localization with cone beam CT scans is inferior to fiducial markers (154). Moreover, the acquisition of a cone beam CT scan plus the localization of the prostate in the cone beam CT scan takes several minutes. Cone beam CT scans are therefore not very attractive for online positioning corrections. Although several attempts have been made to use ultrasound for accurate prostate localization, the results have not been very promising (155,156).

A treatment margin is not only needed for movement of prostate but also for deformation of the prostate. To calculate the extent of margin reduction that can be gained by stereographic targeting, one must quantify the deformation of the prostate relative to the fiducial markers. Chapter 7 describes a repeat CT study in which this deformation is quantified and a new margin is suggested. This new margin, 5 mm for the prostate and 9 mm for the seminal vesicles, is a large improvement on the previously used 1 cm margin for the prostate and vesicles. This new margin has also been clinically implemented.

In future the use of magnetic resonance imaging (MRI) may possibly reduce the uncertainty caused by delineation of the prostate. Because of better soft tissue visualization on MRI one might expect that delineation becomes more accurate, which can be analyzed with the inter- and intra-observer variation of the delineation. Rasch et al. found no significant differences in overall observer variation between axial CT and axial MRI scans (157). However, the observers outlined the CT scan while a hardcopy of the MRI scan was available to the observers at the same moment. Wachter et al. found no significant difference in interobserver variation in defining the apex in axial CT and axial MRI (158). They did find, not surprisingly, a significant difference between defining the apex in axial CT and sagittal MRI scans, in favour of the MRI. Unfortunately, no sagittal reconstructions of the CT scans were taken into the comparison. Villeirs et al. reported a significant decrease in interobserver variation, when the CT scan was recontoured with the addition of an axial, sagittal and coronal MRI scan and the help radiologist (159). Although, it is expected that better soft tissue visualization will lead to lower delineation variation, so far there is no good evidence to support this hypothesis.

Although there is no evidence that MRI will reduce the uncertainty of delineation, the volume of the prostate on MRI is a factor 1.1 to 1.4 smaller than on a CT scan (157-162). Several authors have suggested that on a CT scan the soft tissue structures surrounding the prostate might be included into the prostate volume (157,159-161). A MRI scan provides better soft tissue visualization making it easier to differentiate the prostate from the rectal wall, the neurovascular bundles, the venous plexus, the fibromuscular stroma, the levator ani muscles and the urogenital diaphragm. Furthermore, there is a good correlation between the volume of the prostate on MRI and radical prostatectomy specimens (163). Despite the controversy on the role of the penile bulb, one study already reported that prostate delineation on MRI reduces the dose to the penile bulb significantly (164).

Another way to reduce the irradiated volume and thereby healthy tissue surrounding the prostate, is not treating the entire seminal vesicles. If the risk of seminal vesicle invasion is low,

it is not necessary to include the seminal vesicles in the CTV. If there is a reasonable or high risk of seminal vesicle invasion, the whole vesicles will be irradiated. Some authors advise to include only a part of the seminal vesicles (143,165). This can reduce the radiation dose to the rectum, bladder and possibly the neurovascular bundles as well. However, there are only a few studies on this subject, using pathological examination of prostatectomy specimens (143,166-169). The study populations consisted mainly of clinical T1 and T2 tumors. Seminal vesicle invasion was found in 9%-19% of the patients. If seminal vesicle invasion was found, the tips of the vesicles were involved in 0%-56%. Kestin et al. (143) advised to treat the seminal vesicles only in patients with higher risk (PSA \geq 10 ng/ml, Gleason \geq 7 or clinical stage \geq T2b) and only to include the first 2.0 – 2.5 cm of the seminal vesicles in the CTV. They analyzed 334 prostatectomy specimen of which 51 had seminal vesicles invasion. Only 10% of those 51 patients with seminal vesicle invasion had tumor beyond the proximal 2.0 cm. However, it must be kept in mind that this study did not include any clinical T3 or T4 tumors.

The four other studies did not provide sufficient data on the depth of seminal vesicle invasion (166-169). Therefore these studies can not be used to define which part of the seminal vesicles should be included in the CTV. So, the inclusion of only a part of the seminal vesicles in the CTV for T1 and T2 tumors with a reasonable risk of seminal vesicle invasion is supported by limited data. Furthermore, there is no evidence supporting the inclusion of only a part of the seminal vesicles in the CTV for T3 (or T4) tumors.

MARKER IMPLANTATION

There are two ways of implanting the fiducial markers into the prostate, either transperineal or transrectal. Since these two options lead to the same result, it seems logical to select the safest one. There are no studies comparing the risk of complications of these implantation methods, but there are a few studies, which compare transperineal and transrectal biopsies. Because a foreign body is implanted in the prostate, the risk for infection is important.

Thompson et al. performed an experiment with 45 patients divided into three equal groups (170). Fifteen patients were given a placebo antibiotic prophylaxis and underwent a transrectal biopsy. All of them had a positive blood culture from blood taken 5 minutes after the biopsy. Four of them were symptomatic with temperature above 37.6 °C or rigors. The same was done with 15 other patients, but they received 1g cefamandole instead of the placebo. Only 8 (53%) patients had a positive blood culture. One of them was symptomatic. The other 15 patients had a transperineal biopsy without antibiotics. Only 6 (40%) had a positive blood culture. None of them was symptomatic.

Vis et al. compared sextant transrectal versus sextant transperineal biopsies (171). A group of 1,687 men who had a transrectal biopsy at the ERSPC (European Randomized Study of Screening for Prostate Cancer), section Rotterdam, were compared with 431 men from their

ERSPC partner in Florence who had a transperineal biopsy. The patients with transrectal biopsies were given antibiotic prophylaxis, while the patients with transperineal biopsies did not receive prophylaxis. The complication percentage for admittance to the hospital (0.4% versus 0.7%) and sepsis (0.18% versus 0.46%) were comparable, although more patients with transrectal biopsies needed antibiotic therapy, 3.1% versus 0.7%.

Langenhuijsen et al. were the only ones to describe the complications of transrectal marker implantation (172). They studied in a group of 209 patients. Fever was reported in 4% of these patients. However, this might be an underestimation, given the fact that 184 patients were analyzed retrospectively and received a questionnaire quite a long time, mean 90 weeks, after implantation.

There is only one small feasibility study on transperineal marker implantation by Henry et al. (173) with twelve patients. None of the patients reported any symptoms suggesting infection and the procedure was well tolerated by most patients.

Although there is no study comparing different ways of marker implantation the transperineal approach, seems to be the safest option. Furthermore, we have not only chosen to implant the markers transperineally, but also to give antibiotic prophylaxis.

Another issue that needs attention is swelling of the prostate because of edema by the implantation procedure. This is a well known problem in brachytherapy (101,104,174,175). The prostate volume can almost double because of this edema after brachytherapy (175). If this edema is not resolved before the planning CT is taken, the volume of the prostate will be too large in planning CT scan. If this is the case, the CTV will be too large and the gain of the fiducial markers might be lost. So far, there is no study analyzing this effect for fiducial marker implantation. In one brachytherapy study the half-life of this edema was 16 days after seed implantation with an average of 31 needles (174). Another brachytherapy study found a lower half life of 9 days after implantation with less needles, 18 needles on average (175). There is a significant correlation between the number of needles and the amount of swelling (174). In our institute only 2 needles are used to implant 3 to 4 fiducial markers and there is at least one week interval between the implantation and the planning CT scan. The fact that there are no big displacements of the markers after the planning CT scan as reported in Chapter 7, supports the idea that a week is sufficient time for most edema to resolve.

Gold is often used as it has a high specific gravity and it is commercially available. Other dense metals such as platinum, titanium and tungsten can also be used (176).

The markers have to be small to minimize morbidity and reduce the risk of marker overlap on the images. However, the markers must be large enough to be detected on MV images. Studies investigating marker size advise to use a marker size of 5.0 mm in length and 0.9 – 1.0 mm in diameter (176,177).

ONGOING STUDIES

At the moment four studies are being conducted. One study is being undertaken to expand the current stereographic targeting protocol. The goal of this study is to perform stereographic targeting to correct for shifts of the prostate during a treatment fraction. This might allow a further reduction of the treatment margin.

The DOFAR study (DOse volume effects and Fibrosis After Radiotherapy for prostate cancer) will investigate the possible role of the internal pudendal arteries, by using repeat MRI scans. The internal pudendal arteries will be imaged before radiotherapy to calculate the radiation dose. The correlation between radiation dose to the internal pudendal arteries and erectile dysfunction will be analyzed. Furthermore, the internal pudendal arteries will also be imaged one and two years after radiotherapy to visualize possible fibrosis, or occlusion.

The pilot study, described in Chapter 5, demonstrated changes in the penile arteries of the rat after fractionated irradiation of the prostate. The results of this study enable the start of the second part of the study, in which the use of an endothelin A receptor antagonist will be evaluated. An endothelin A receptor antagonist has the potential to improve the flow in the penile arteries and might prevent radiation damage that leads to erectile dysfunction.

The HYPRO study, HYpofractionated irradiation for PROstate cancer, is a multicenter study aiming to include 800 patients. The goal is to demonstrate the superiority of the hypofractionated schedule with respect to the relapse rate in combination with comparable toxicity.

All patients are treated with reduced treatment margins, by using fiducial markers or cone beam CT scans. Both the EORTC-PR25 prostate module and the International Index of Erectile Function (IIEF) will be filled out by all patients (54). This study will give the answer whether or not a reduced treatment margin will lead to lower risk of erectile dysfunction.

CONCLUSION

Before investigating ways to prevent erectile dysfunction after external beam radiotherapy for prostate cancer, one question must be answered: to what extent does external beam radiotherapy for prostate cancer cause erectile dysfunction?

Most men are sexually active before external beam radiotherapy for prostate cancer. Two years after radiotherapy 36% of the pre-treatment potent patient suffer from erectile dysfunction (this thesis). So, preventing erectile dysfunction has the potential to improve to quality of life in a large number of patients.

The radiotherapy treatment plan can be adapted to spare specific anatomical structures that may cause radiation-induced toxicity. Several authors advised sparing of the penile bulb to preserve erectile function. However, this is not sufficiently supported by the current literature and the penile bulb plays little role in achieving or maintaining an erection (this thesis).

Other structures essential for an erection have mainly been analyzed in studies with a limited number of patients or have not been analyzed at all.

Previous studies reported a reduced flow in the cavernosal arteries in patients with erectile dysfunction. This could be caused by radiation damage to the internal pudendal arteries or the cavernosal arteries themselves. In the study with the largest number of patients so far, no correlation was found between the radiation dose to the corpora cavernosa and erectile dysfunction after external beam radiotherapy for prostate cancer (this thesis). Although, little is known about the statistical power to prove such a correlation.

A pilot study shows that fractionated irradiation of the prostatic area of the rat leads to changes in the penile arteries, including thickening of the intima and occlusions (this thesis). This supports the hypothesis that arteries providing blood inflow in corpora cavernosa might be involved in erectile dysfunction after radiotherapy. The results of the clinical DOFAR study, investigating the internal pudendal arteries, hopes to shed some light on this topic.

Until it is clear which structure should be spared, the most feasible way to reduce erectile dysfunction is by minimizing the treatment margin and thereby lowering the radiation dose to all structures essential for a penile erection. A fast and accurate procedure to do daily on-line repositioning of the prostate based on imaging of implanted markers was developed and implemented at our institute (this thesis).

Stereographic targeting allows a large improvement in positioning of the prostate before each treatment fraction. The deformation of the prostate relative to these implanted markers was quantified, enabling the calculating of a new treatment margin (this thesis). Stereographic targeting and the analysis of deformations of the prostate have led to a large reduction in the clinical treatment margins.

The decrease in the radiation dose of all structures essential for an erection is likely to improve erectile function after external beam radiotherapy for prostate cancer.

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Summary

In this thesis the question is addressed whether there are possibilities to reduce or even prevent the incidence of erectile dysfunction after external beam radiotherapy for prostate cancer. Chapter 1 is a general introduction into external beam radiotherapy for prostate cancer, the most common side-effect, erectile dysfunction, and possibly ways to reduce or prevent erectile dysfunction. In chapter 2 to chapter 7 six studies are described which answer different sub-questions. Chapter 8 answers the main question of this thesis whether erectile dysfunction after external beam radiotherapy for prostate can be prevented.

CHAPTER 1

Prostate cancer is the most common type of cancer in men in Western countries apart from basal and squamous cell skin cancers. A large part of the prostate cancer patients are treated with external beam radiotherapy. Unfortunately, this treatment leads to gastro-intestinal and genito-urinary toxicity and also to erectile dysfunction in a considerable amount of patients. This thesis will focus specifically on the erectile dysfunction. Finding new techniques to decrease the incidence of erectile dysfunction after external beam radiotherapy for prostate cancer, has a great potential to improve the quality of life after treatment in a vast number of prostate cancer patients.

CHAPTER 2

Since the introduction of three-dimensional conformal radiotherapy, there are only a few prospective studies available that provide a rate of erectile dysfunction. Furthermore, most of those studies have insufficient follow-up and/or do not take into account important confounding factors that influence sexual function. Chapter 2 is based on a Dutch multicenter Phase III dose escalation trial (trial code CKVO 96-10), in which patients with a localized adenocarcinoma of the prostate were randomized between prescribed dose levels of 68 Gy and 78 Gy. Hormonal therapy, which has a large impact on sexual functioning, and potency aids were taken into account. There was no difference in erectile dysfunction between the different dose levels. However, there was a significant reduction in sexual activity in patients treated with adjuvant hormonal therapy. This supports the methodology to take hormonal therapy

into account, when assessing sexual function. One year after radiotherapy 27% of the pre-treatment potent patients had developed erectile dysfunction. Two years after radiotherapy 36% of 96 patients suffered from erectile dysfunction, after which the percentage stabilized.

CHAPTER 3

Finding an anatomic structure responsible for erectile dysfunction after radiotherapy will enable physicians to avoid a high radiation dose in this structure and has the potential to reduce erectile dysfunction after radiotherapy. In Chapter 3 we search for evidence in literature which anatomic structures should be spared. There are three major requirements for adequate penile erection: (i) functioning neurovascular bundles and cavernous nerves which supply the penis with nitric oxide, (ii) arterial inflow through the internal pudendal and cavernosal arteries and (iii) healthy erectile tissue in the corpora cavernosa which ensures adequate trapping of blood in the penis to maintain erection (known as the veno-occlusive mechanism). Most studies have analyzed the correlation between the radiation dose to the penile bulb and erectile dysfunction. Several authors have already advised to spare the penile bulb. However, the penile bulb is not an essential structure to achieve or maintain an erection and the studies show contradicting results. The neurovascular bundles have been analyzed in studies with a small number of patients and no correlation between the dose in the neurovascular bundles and erectile dysfunction has been found. The corpora cavernosa have only been analyzed in four studies, showing different results. To our knowledge there is no study investigating the role of the internal pudendal arteries in erectile dysfunction after radiotherapy.

CHAPTER 4

Chapter 3 shows that there is no clear evidence for sparing a certain anatomic structure to reduce the percentage of erectile dysfunction after radiotherapy for prostate cancer. Several studies have shown reduced flow in the cavernosal arteries and venous leakage of the corpora cavernosa after external beam radiotherapy. Unfortunately only one retrospective study, with only 28 patients, investigated the correlation between erectile dysfunction after external beam radiotherapy and the radiation dose to the corpora cavernosa. The study did not find any statistical correlation. Chapter 4 is also based on the CKVO 96-10 study. Ninety-six patients with 2 years of follow-up, who were not treated with hormonal therapy, were analyzed. No correlation was found between erectile dysfunction and the radiation dose to the corpora cavernosa or penile bulb.

CHAPTER 5

Although several clinical studies investigated different anatomical structures, the cause of erectile dysfunction after radiotherapy is still largely unknown. There is some clinical evidence that damage to the arterial supply of the corpora cavernosa might be responsible. Chapter 5 describes the first animal experimental study that analyzed the effect of fractionated irradiation of the prostate on the penile arteries of the rat. The penis showed arteries which had developed loss of smooth muscle cells, thickening of the intima and occlusions. This preliminary data suggests that erectile dysfunction after radiotherapy might be caused by radiation damage to the arterial supply of the corpora cavernosa.

CHAPTER 6

There are two possible ways to reduce erectile dysfunction after radiotherapy. One is to find a specific anatomic structure that is responsible for erectile dysfunction and spare this structure during treatment. The other is an aspecific way, in which all structures surrounding the prostate receive less radiation dose. The clinical target volume (CTV) is an anatomical volume that contains demonstrated and suspected tumor considered to need treatment. In case of prostate cancer the CTV is the prostate, with or without seminal vesicles. To account for uncertainties regarding delineation, deformation and movement of the CTV a margin is added to the CTV. The planning target volume (PTV) is the CTV plus this margin. The CTV-PTV margin can be reduced below the commonly used 1 cm by using techniques that reduce the uncertainty regarding movement of the CTV. Chapter 6 describes such a technique, called stereographic targeting. Stereographic targeting was developed in our clinic to allow fast and fully automated accurate daily on-line positioning of the prostate by using implanted fiducial markers, orthogonal imaging and a remote controlled treatment couch. This new technique led to a reduction in standard deviations of the systematic (Σ) and random errors (σ) from 4.0mm to <0.5mm and from 3.0mm to <0.8mm, respectively.

CHAPTER 7

Stereographic targeting allows a large improvement in positioning of the prostate. However, to safely reduce the CTV-PTV margin, information is required on the deformation of the prostate and seminal vesicles relative to the implanted fiducial markers. Twenty-one patients implanted with fiducial markers were analyzed by means of repeat CT scans. Intraobserver delineation errors were up to 0.7 mm standard deviation. Deformation of the prostate was small with a standard deviation of about ≤ 1 mm. However, for the seminal vesicles deformation the standard

deviations went up to 3 mm. Chapter 6 provides data on the residu errors of stereographic targeting and previous studies have provided information on intrafraction motion. Since we now have information on delineation, deformation and movement of the prostate and seminal vesicles, a new CTV-PTV margin can be calculated. Chapter 7 indicates that a CTV-PTV margin of 5 mm for the prostate and 9 mm for the seminal vesicles could be used.

CHAPTER 8

Chapter 8 provides a general discussion and conclusion. At present there is no clear evidence that sparing a certain anatomic structure will lead to a reduction of erectile dysfunction after external beam radiotherapy for prostate cancer. However, the use of implanted fiducial markers and daily online setup corrections by using stereographic targeting does allow for a large reduction in the treatment margin. Consequently all structures surrounding the prostate, including those essential for a penile erection, will receive less radiation. It is likely that this will also lead to a lower percentage of erectile dysfunction. The HYPRO study, which is now being conducted, will be able to confirm this hypothesis within a few years from now.

Samenvatting

In dit proefschrift wordt de vraag beantwoord of er de mogelijkheden zijn om erectiele disfunctie na uitwendige radiotherapie voor prostaatkanker te voorkomen. Hoofdstuk 1 geeft een algemene introductie over uitwendige radiotherapie voor prostaatkanker, de meest voorkomende bijwerking, namelijk erectiele disfunctie, en de mogelijkheden om erectiele disfunctie te verminderen dan wel te voorkomen. In hoofdstuk 2 tot en met hoofdstuk 7 worden zes studies beschreven, waarin diverse subvragen worden beantwoord. Hoofdstuk 8 beantwoordt de hoofdvraag van dit proefschrift: Is preventie van erectiele disfunctie na uitwendige radiotherapie voor prostaatkanker mogelijk?

HOOFDSTUK 1

Prostaatkanker is het meest voorkomende type kanker bij mannen in de westerse wereld met uitzondering van huidkanker. Een groot deel van de prostaatkanker patiënten wordt behandeld met uitwendige radiotherapie. Helaas geeft deze behandeling bijwerkingen in het maagdarmsstelsel, de urinewegen en ook erectiele disfunctie bij een aanzienlijk deel van de patiënten. Dit proefschrift richt zich specifiek op erectiele disfunctie. Het vinden van technieken om de kans op erectiele disfunctie te reduceren, heeft grote potentie om de kwaliteit van leven na behandeling te verbeteren voor een groot aantal prostaatkanker patiënten.

HOOFDSTUK 2

Sinds de introductie van drie-dimensionale conformele radiotherapie zijn er slechts enkele prospectieve studies die de kans op erectiele disfunctie beschrijven. Bovendien hebben de meeste van deze studies patiënten te kort gevolgd en/of houden zij geen rekening met andere factoren die seksueel functioneren beïnvloeden. Hoofdstuk 2 is gebaseerd op een Nederlandse multicentra fase 3 dosis escalatie studie (studie code CKVO 96-10), waarin patiënten met gelokaliseerd adenocarcinoom van de prostaat werden gerandomiseerd tussen de voorgeschreven dosisniveaus van 68 Gy en 78 Gy. Er werd rekening gehouden met hormonale therapie en middelen voor erectiestoornissen, aangezien deze een grote invloed hebben op het seksueel functioneren. Tussen beide dosisniveaus werd geen verschil in erectiele disfunctie gevonden. Adjuvante hormonale therapie bleek echter wel tot een significante daling van

seksuele activiteit te leiden. Dit steunt de methodologie om rekening te houden met hormonale therapie, indien seksueel functioneren geanalyseerd wordt. Eén jaar na radiotherapie had 27% van de patiënten die voor behandeling potent waren erectiele disfunctie ontwikkeld. Dit percentage steeg tot 36% na twee jaar, waarna dit percentage stabiliseerde.

HOOFDSTUK 3

Het vinden van een anatomische structuur die verantwoordelijk is voor erectiele disfunctie na radiotherapie maakt het mogelijk deze structuur te sparen. Deze methode heeft een goede potentie om de kans op erectiele disfunctie na radiotherapie te verminderen. In hoofdstuk 3 wordt gezocht naar bewijs in de literatuur welke structuur gespaard moet worden. Er zijn drie benodigdheden voor een adequate erectie: (i) functionerende neurovasculaire bundels en caverneuze zenuwen die stikstofmonoxide afgeven in de penis, (ii) arteriële instroom door de arteria pudenda interna en arteria cavernosa en (iii) gezond erectiel weefsel dat de veneuze uitstroom uit de corpora cavernosa voldoende belemmert om de erectie te behouden. De meeste studies hebben de correlatie tussen de bestralingsdosis in de peniele bulbus en erectiele disfunctie geanalyseerd. Verscheidene auteurs hebben zelfs al geadviseerd de peniele bulbus te sparen. Echter, de peniele bulbus is geen essentiële structuur om een erectie te krijgen of te behouden en de studies laten tegenstrijdige resultaten zien. De neurovasculaire bundels zijn alleen geanalyseerd in studies met een klein aantal patiënten, waarbij in geen enkel geval een correlatie is gevonden tussen de dosis in de neurovasculaire bundels en erectiele disfunctie. De corpora cavernosa zijn slechts geanalyseerd in vier studies, welke verschillende resultaten lieten zien. Er geen studie beschikbaar die de rol van de arteria pudenda interna bestudeert bij erectiele disfunctie na radiotherapie.

HOOFDSTUK 4

Hoofdstuk 3 laat zien dat er niet duidelijk bewezen is welke specifieke anatomische structuur gespaard moet worden om erectiele disfunctie na uitwendige radiotherapie voor prostaatanker te verminderen. Verschillende studies hebben wel aangetoond dat de arteriële bloedstroom in de arteria cavernosa verlaagd is en dat er veneuze lekkage is bij de corpora cavernosa na uitwendige radiotherapie. Helaas is er maar één retrospectieve studie, met slechts 28 patiënten, die de correlatie heeft bestudeerd tussen erectiele disfunctie en de bestralingsdosis in de corpora cavernosa. Deze studie vond geen correlatie. Hoofdstuk 4 is ook gebaseerd op de CKVO 96-10 studie. Zesennegentig patiënten met een follow-up van 2 jaar, die niet behandeld zijn met hormonale therapie, werden geanalyseerd. Er werd geen cor-

relatie gevonden tussen erectiele disfunctie en de bestralingsdosis in de corpora cavernosa of de peniele bulbus.

HOOFDSTUK 5

Alhoewel meerdere klinische studies verschillende anatomische structuren hebben onderzocht, is de oorzaak van erectiele disfunctie na radiotherapie nog steeds grotendeels onbekend. Er is enig klinisch bewijs dat de schade aan de arteriële toevoer van de corpora cavernosa verantwoordelijk zou zijn. Hoofdstuk 5 beschrijft de eerste dierexperimentele studie naar het effect van gefractioneerde bestraling van de prostaat op de vaten in de penis van de rat. De penis liet arteriën zien met verlies van gladde spiercellen, verdikking van de intima en occlusies. Deze voorlopige data suggereert dat erectiele disfunctie na radiotherapie voor prostaatkanker wellicht veroorzaakt wordt door schade aan de arteriële toevoer van de corpora cavernosa.

HOOFDSTUK 6

Er zijn twee mogelijkheden om de kans op erectiele disfunctie na radiotherapie te reduceren. De ene is het vinden van een specifieke anatomische structuur die verantwoordelijk is voor erectiele disfunctie en deze vervolgens te sparen tijdens de behandeling. De andere mogelijkheid is een aspecifieke manier, waarbij alle structuren rondom de prostaat een lagere bestralingsdosis krijgen. Het klinisch doelvolumen is een anatomisch volume dat de aangetoonde en verwachte tumor bevat die behandeld moet worden. In het geval van prostaatkanker is het klinisch doelvolumen de prostaat, met of zonder zaadblazen. Om rekening te houden met de onzekerheden van intekening, deformatie en beweging van het klinisch doelvolumen wordt er een marge toegevoegd aan het klinisch doelvolumen. Het planning doelvolumen is het klinisch doelvolumen plus deze marge. Deze behandelingsmarge kan gereduceerd worden beneden de veelgebruikte 1 cm door gebruik te maken van technieken die de onzekerheid van beweging verminderen. Hoofdstuk 6 beschrijft een dergelijke techniek, genaamd stereographic targeting. Stereographic targeting werd ontwikkeld in ons ziekenhuis om een snelle en volautomatische accurate dagelijkse positionering van de prostaat mogelijk te maken. Dit wordt bereikt met behulp van in de prostaat geïmplanteerde goudmarkers, orthogonale afbeeldingen en een op afstand bestuurbare behandelingstafel. Deze nieuwe techniek heeft geleid tot een reductie in de standaard deviaties van de systematische en willekeurige fouten van respectievelijk 4.0 mm tot <0.5 mm en 3.0 mm tot <0.8 mm.

HOOFDSTUK 7

Stereographic targeting maakt een grote verbetering van positionering van de prostaat mogelijk. Om echter op veilige wijze de behandelingsmarge te reduceren is informatie nodig over deformatie van de prostaat en zaadblazen ten op zichte van de geïmplanteerde goudmarkers. Eénentwintig patiënten werden geïmplanteerd met 3 tot 4 goudmarkers en vervolgens werden zij geanalyseerd met behulp van herhaalde CT scans. Intraobserver intekeningsfouten waren tot 0.7 mm standaard deviatie. Deformatie van de prostaat was klein met een standaard deviatie van ongeveer ≤ 1 mm. Echter, voor de zaadblazen ging de standaard deviatie van de deformatie tot 3 mm. Hoofdstuk 6 geeft data over de overblijvende afwijking na stereographic targeting en voorgaande studies hebben informatie gegeven over intrafractie beweging. Omdat we nu informatie hebben over intekening, deformatie en beweging van de prostaat en zaadblazen, kan een nieuwe behandelingsmarge berekend worden. Hoofdstuk 7 geeft aan dat een behandelingsmarge van 5 mm voor de prostaat en 9 mm voor de zaadblazen gebruikt kan worden.

HOOFDSTUK 8

Hoofdstuk 8 geeft een algemene discussie en conclusie. Op dit moment is er geen duidelijk bewijs dat het sparen van een bepaalde anatomische structuur zal leiden tot een reductie van erectiele disfunctie na uitwendige radiotherapie voor prostaatkanker. Echter, het gebruik van geïmplanteerde goudmarkers and dagelijkse positioneringscorrecties door middel van stereographic targeting maakt het mogelijk de behandelingsmarge sterk te reduceren. Hierdoor krijgen alle structuren rondom de prostaat, inclusief diegene essentieel voor een erectie, een lagere bestralingsdosis. Het is waarschijnlijk dat dit ook zal leiden tot een lager percentage erectiele disfunctie. The HYPRO studie, die nu wordt uitgevoerd, zal deze hypothese binnen enkele jaren kunnen bevestigen.

List of abbreviations

ASTRO	american society for therapeutic radiology and oncology
aV xx	absolute volume receiving xx gray
BT	brachytherapy
CC	corpora cavernosa
COM	center of mass
Crura 1cm	superiormost 1-cm segment of the crura
CS	corpus spongiosum
CT scan	computed tomography scan
CTV	clinical target volume
DOFAR study	dose volume effect and fibrosis after radiotherapy for prostate cancer study
DRR	digitally reconstructed radiographs
DVH	dose-volume histogram
D xx	dose delivered to xx % of an anatomical structure
EBRT	external beam radiotherapy
ED	erectile dysfunction
EPID	electronic portal imaging devices
ERSPC	european randomized study of screening for prostate cancer
GJW	Gerard Johan van der Wielen
Gy	gray
HE	hematoxylin-eosin
HT	hormonal therapy
HYPRO study	hypofractionated irradiation for prostate cancer study
ICI	intracavernosal injections
IGRT	image guided radiotherapy
IIEF	international index of erectile function
IMRT	intensity modulated radiotherapy
IPA	internal pudendal artery
kV(I)	kilovoltage (image)
MEK	marker extraction kernel
MR(I)	magnetic resonance (imaging)
MU	monitor units
MV(I)	megavoltage (image)
n.a.	not available

NO	nitric oxide
NVB	neurovascular bundles
PB	penile bulb
PDE5-inhibitors	phosphodiesterase-5 inhibitors
popCTV	population average CTV
PSA	prostate specific antigen
PTV	planning target volume
rV xx	relative volume receiving xx gray
SAc	Dutch module on sexual activity
SD	standard deviation
SF	sexual function
SGT	stereographic targeting
SMA	α -smooth muscle actin
TCSA	theraview couch set-up assistant
TNT	Theraview NT
T _{only}	translation only
T+R	translation plus rotation
3D	three-dimensional
3D-CRT	three-dimensional conformal radiotherapy
Σ	systematic error
σ	random error

Curriculum Vitae

Gerard van der Wielen werd op 5 januari 1979 geboren te Naarden. Het grootste deel van zijn jeugd groeide hij op in Leiden en behaalde zijn VWO diploma in 1997 aan het Stedelijk Gymnasium in Leiden. In datzelfde jaar begon hij aan zijn studie geneeskunde aan de Universiteit Leiden. In 2005 sloot hij zijn studie geneeskunde af met het keuze co-assistentschap urologie in het Leids Universitair Medisch Centrum. Dit werd gevolgd door zijn promotie onderzoek op de afdeling radiotherapie in samenwerking met de afdeling urologie in het Erasmus MC – Daniel den Hoed. In januari 2009 is hij begonnen aan de heelkundige vooropleiding in het ziekenhuis Bronovo (opleider dr. H.J. Smeets, chirurg) om deze in 2011 te vervolgen met zijn opleiding tot uroloog in het Hagaziekenhuis (opleider F.M.J.A. Froeling, uroloog) en het Leids Universitair Medisch Centrum (opleider prof.dr. R.C.M. Pelger, uroloog).

Dankwoord

Het werk als full-time arts-onderzoeker is een aparte baan. Je begint aan een traject van enkele jaren, waarbij er aanvankelijk maar weinig zekerheden zijn. Welke artikelen ga je schrijven? Gaat het überhaupt lukken om te promoveren? Zo ja, zal deze promotie dan bijdragen aan de zo gewilde opleidingsplek of had je toch beter in de kliniek kunnen blijven? Na de grote voldoening van de acceptatie van het eerste artikel begon langzamerhand het idee te groeien dat deze onzekerheden juist een grote vrijheid vormen. Als promovendus mocht ik mijn eigen tijd indelen, een grote stem hebben in de onderzoeksrichting en zelf een aantal artikelen schrijven.

Uiteraard is dit proefschrift niet het werk van mij alleen. In dit dankwoord wil ik iedereen bedanken zonder wie dit proefschrift niet mogelijk was geweest.

Luca Incrocci, jij hebt mij als copromotor vrijheid gegeven en altijd vertrouwen in mij gehad. Ik kon altijd bij je binnenlopen om even kort te overleggen, wat dan vervolgens meestal uitliep tot minstens een uur. Jij was altijd bereikbaar en ieder manuscript of studieprotocol was binnen enkele dagen van suggesties, commentaar en correcties voorzien. Dit heeft zeker bijgedragen tot het op tijd afronden van het proefschrift.

Hans de Boer, pas op een laat moment werd jij officieel mijn copromotor, maar al lang voor die tijd heb jij mij begeleid alsof je mijn copromotor al was. Wij hebben samen met Theodore vele discussies gevoerd die met name fysisch van aard waren. Jij hebt de tijd genomen mij deze zaken uit leggen en ik heb het enorm gewaardeerd dat de toevoegingen aan de discussies van een niet-fysicus serieus werden genomen.

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Beste professor Levendag, ik heb uw vertrouwen in mij altijd zeer gewaardeerd. Hoewel ik geen radiotherapeut ga worden, heb ik zeer nuttige radiotherapeutische kennis mogen opdoen op uw afdeling. Deze kennis zal zeker van pas komen in de urologie.

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PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student:	G.J. van der Wielen
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Promotors:	Prof.dr. P.C. Levendag Prof.dr. C.H. Bangma
Supervisors:	Dr. L. Incrocci Dr. J.C.J. de Boer

IN-DEPTH COURSES

ESTRO Teaching course on image-guided radiotherapy in clinical practice
2006, Brussels, Belgium

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