Towards focal salvage therapy for prostate cancer recurrences

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Op weg naar focale salvage therapie voor prostaatkanker recidieven
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General introduction

The prostate

The prostate gland is an accessory gland of the male reproductive system, with – in the non-diseased state – the size of a walnut. Its function is to produce fluid for semen. The cranial side (the base of the prostate) is closely situated against the neck of the bladder, surrounding the urethra that extends from the bladder neck through the prostate gland ('prostatic urethra') via an intermediate part to the penile bulb. The caudal side of the prostate (the apex) lies upon the external urethral sphincter and the posterior surface of the prostate rests against the rectum. At the anterior surface the prostate is separated from the pubic symphysis by retroperitoneal fat and muscle fibres (1).

Anatomically, the prostate gland is divided in several zones. Some variation exists in the literature in the nomenclature used. The transitional zone, central gland and peripheral zone are considered the most important zones from a pathological point of view (1-4). Three common pathologic conditions can arise in the prostate, namely: prostatitis, benign prostate hyperplasia (BPH) and prostate cancer. Prostatitis is an inflammation of the prostate gland, which can be acute or chronic. BPH is an enlargement of the centrally located transitional zone surrounding the urethra, causing symptoms of obstruction by compression of the urethra. It is so common (prevalence of 50% amongst 50-year old men, with or without symptoms) that it can almost be regarded as a normal aging process (5). A causal relation between BPH and prostate cancer has never been established, but both entities do share common etiologic factors and some kind of linkage has been suggested (6;7).

Cancer of the prostate; facts and figures

Approximately 70% of the prostate tumours arise in the peripheral zone of the prostate gland (8). As the peripheral zone is largely located at the posterior aspect of the gland, these tumours can be palpable by digital rectal examination. In contrast with BPH, cancer will not cause urinary symptoms, because of the anatomical position of the peripheral zone with respect to the urethra, unless the tumour becomes large. Most prostate cancer diagnoses are the consequence of incidental measurements of the prostate specific antigen (PSA) level in the blood. An elevated PSA level causes anxiety in men, and is commonly seen as a reason for further evaluation. In this case prostate biopsy is performed. Histopathological analysis of biopsy tissue can subsequently lead to the diagnosis of prostate cancer in a subgroup of the referred patients.

Prostate tumours are nearly always adenocarcinomas, originating from the tubulo-acinar glands. The tumours are classified histopathologically using the Gleason grading system, taking into account the glandular pattern and the degree of differentiation (9;10). The Gleason score is widely accepted to correlate more or less with the patient's

prognosis. Therefore, it is used in treatment decisions, in combination with the TNM-classification, which, as in other types of cancer, describes the extent of the cancer. In small tumours, with a low Gleason score, one could choose active surveillance ('watchful waiting') over immediate treatment. The reproducibility of the Gleason score is, however, considered poor (just 80% when assigned by Gleason himself!) (11). The limited reliability of the Gleason score based on biopsy material, together with the low specificity of elevated PSA levels, makes the decisions concerning prostate cancer screening programs (which are currently hot topics in the western world) very difficult.

The current public and scientific interest for prostate cancer screening is understandable, since prostate cancer is a major health problem worldwide. In the Netherlands, prostate cancer is the second most frequent cancer in men, next to lung cancer. In 2007, 9588 patients were newly diagnosed with prostate cancer (incidence rate of 102 per 100.000 men per year). In the same year 2425 men died from prostate cancer (incidence rate 26 per 100.000 per year) (12). New developments in the diagnosis and treatment of prostate cancer can therefore lead to major individual and societal gains.

Treatment of prostate cancer

The two generally accepted methods for the treatment of prostate cancer are surgical removal of the total prostate ('radical prostatectomy') and radiotherapy of the prostate, which can be external beam radiotherapy or brachytherapy. New treatment techniques are gradually being introduced, but not yet widely available and, more importantly, not proven to be equally effective as the current standard of care. Of these new techniques, cryosurgery (freezing) and high intensity focused ultrasound (HIFU) are the best known.

The choice for a specific treatment strategy depends on the disease extent and the tumour differentiation grade, but also on the patient's preferences. For locally confined tumours of any grade, without capsular extension (T1 or T2), prostatectomy or radiotherapy are considered appropriate treatment methods. If capsular extension is suspected (T3), external beam radiotherapy is preferred. In moderate and poorly differentiated tumours, external beam radiotherapy can be combined with adjuvant or neo-adjuvant hormonal therapy. Brachytherapy is considered an appropriate treatment option for patients with T1 or T2, moderate or well-differentiated tumours (13). In radiotherapy, ionising radiation is used to control malignant cells, by damaging the cell's DNA. A certain radiation dose (measured in Gray's) is prescribed to the tumour, in which the maximum dose is limited by the surrounding healthy tissue. Several radiotherapy techniques are used to deliver the radiation dose in prostate tumours: conventional or conformal external beam radiotherapy (EBRT), intensity

modulated radiotherapy (IMRT), iodine-125 (125-I) brachytherapy (also called low dose rate (LDR) brachytherapy), pulse dose rate (PDR) brachytherapy and high dose rate (HDR) brachytherapy. In Utrecht, brachytherapy is performed by 125-I implantation. Under transrectal ultrasound guidance, iodine seeds are implanted in the prostate through multiple transperineally inserted needles. In contrast to EBRT and IMRT, which are delivered in multiple fractions and therefore take several weeks, 125-I implantation takes only one treatment. The radiation dose from the iodine seeds after implantation is given off to the prostate tissue in months.

IMRT is an advanced form of EBRT, in which small radiation beams are used to treat the target volume more accurately, making it possible to escalate the dose to the prostate while the dose to the surrounding tissue is kept equal or even reduced. During IMRT of the prostate, position verification based on pre-treatment implanted fiducial markers in the prostate plays an important role in achieving optimal treatment accuracy. It has been shown that, using an offline shrinking-action-level (SAL) protocol, a mean systematic inter-fraction error of approximately 0.2 millimetre (standard deviation 0.8) (14) and a mean systematic and random intra-fraction error of less than one mm could be reached (15). With the use of IMRT, less treatment related toxicity (complications) is reported and quality of life after treatment is improved compared to conventional EBRT (16-18). Treatment results are expected to be even better in image guided radiotherapy (IGRT), which is the latest new development in the external beam radiotherapy scene. In IGRT, different imaging modalities (MRI in specific) are used to characterise the tumour within the prostate gland, and image guidance during treatment facilitates optimal treatment precision. This information is used to increase the treatment dose to the tumour locally (dose escalation). The results of IGRT are now investigated in a randomised controlled trial at the department of Radiation Oncology of the UMC Utrecht (Flame trial). Ultimately, the goal of IGRT is to adjust individual treatment plans according to the individual tissue properties, in which, for example, areas with the highest tumour load receive the highest treatment dose (so called 'dose painting').

Follow-up after radiotherapy

After radiotherapy, the patient is seen by both the urologist and radiation oncologist on a regular basis. Evaluation of the blood PSA level is an essential part of these check-ups. After radiotherapy, the PSA level gradually decreases until it reaches its lowest level ('nadir'). This process may take several years. Often, and sometimes after a stable phase, the PSA starts to rise again. This can be a benign temporarily PSA 'bounce' but it can also be a sign of local recurrent tumour or distant metastasis. If the PSA rises above a certain level, at which point a benign PSA bounce is less plausible, the situation is called 'biochemical failure' or 'biochemical recurrence'. Multiple definitions

exist to define this point. The Phoenix definition is described as a PSA rise of 2 ng/mL above the nadir PSA level (19;20). Biochemical failure following the ASTRO definition is described as 3 subsequent rises of the PSA level, with minimal intervals of 3 months between the measurements (21). Sometimes absolute PSA thresholds are used in the literature as well. No matter what definition is used, a rising PSA level always causes distress in patients, while the cause remains unknown until time gives the answer: the PSA level starts to decrease again (meaning the rise was actually a PSA bounce) or increases further (meaning distant metastasis). It can, however, also be possible that the prostate tumour is regrowing locally. In these cases, patients might benefit from another treatment (so called 'salvage' treatment, a last curative attempt). Therefore, patients with biochemical failure that would be eligible for salvage treatment, sometimes undergo prostate biopsy to detect local recurrent tumour. If a local recurrent tumour is pathologically proven, salvage treatment can be offered.
The exact numbers of patients that suffer from recurrent prostate cancer after radiotherapy are unknown. The risk of developing recurrent disease depends heavily on the tumour stage and tumour differentiation grade, and risks over 50% for the worst risk profiles are presented in literature (22-25).

Treatment of recurrent prostate cancer ('salvage' treatment)

As described, salvage treatment is the last curative treatment attempt in patients with recurrent prostate cancer. Several treatment methods are available that can be applied in the salvage setting, namely: salvage prostatectomy, salvage external beam radiotherapy, salvage brachytherapy, salvage cryosurgery or salvage HIFU. Hormonal therapy is often named in the list of salvage treatment modalities, but is actually a palliative treatment strategy and should not be referred to as such.
Survival and toxicity rates are described in the literature for each salvage method. However, there are no randomised trials and the differences in study populations and methods between the published articles strongly hamper comparison between the treatments. Despite this incomparability, the overall conclusions of these articles appear to be quite similar: the survival after treatment is limited, and the toxicity rates are high (26-29). Furthermore, there are no studies investigating whether salvage treatment even increases the chances of survival compared with the natural history. Therefore, it is not that strange that in clinical practice, physicians seem to be rather reticent in referring patients for salvage treatment. The only alternative for patients with biochemical failure is a wait and see policy, and generally, if the PSA level has risen above a certain level (±20 ng/ml), hormonal therapy is started with palliative intentions. This will limit disease progress for several years, but will not prevent the development of distant metastases and eventually death.

Detecting local recurrent prostate cancer

To detect recurrences in an early stage, a more efficient diagnostic process is essential for patients with biochemical failure. Therefore, alternative tests are needed in addition to the PSA measurements. Transrectal ultrasound (TRUS) is often used to visualize the prostate in the intervention setting, however, for the detection of primary or recurrent tumours its diagnostic value is found to be insufficient (30;31). In contrast, magnetic resonance imaging (MRI) is considered a promising diagnostic method, because of its excellent soft tissue contrast and broad possibilities regarding techniques on functional imaging (32).

MRI works by firing radiofrequency pulses that influence the spins of hydrogen atoms in the human body within a magnetic field. The energy that is released if these spins flip back to their original positions is used to create images. The settings of the MRI can be adjusted in such a way that specific tissue properties can be visualized, that can be helpful in identifying specific (pathologic) entities. Aside from conventional settings ('sequences') that visualize the anatomy, there are several functional sequences. One of these sequences is dynamic contrast enhanced (DCE)-MRI, or also called 'perfusion' MRI. DCE-MRI is an imaging method that visualizes the patterns of contrast enhancement in tissues, after injection of an intra-vascular contrast agent. A wide range of physiological factors, like vessel density and endothelial permeability, influences contrast enhancement patterns. Based thereon the change in vascularisation of pathological tissue can be reflected in an altered enhancement curve and changed signal MR signal intensities. The rough scan data are analysed by a pharmacokinetic model, like the Tofts model, and transformed in images of outcome parameters reflecting the differences in enhancement curves. The Tofts model, which is used in the UMC Utrecht, generates the following outcome parameters: the volume transfer coefficient (K^{trans}), the volume of the interstitial or extravascular-extracellular space (EES) per unit volume of tissue (v_e) and the flux rate constant between EES and plasma (k_{ep}) (33). The rate constant is the ratio of the transfer constant to the EES ($k_{ep} = K^{trans} / v_e$). In the prostate cancer literature, K^{trans} is commonly used for studies concerning DCE-MRI and is considered the most important parameter.

In the last decade, much research has been conducted on the value of DCE-MRI in the diagnosis of prostate cancer. It has been shown that DCE-MRI, especially in combination with other (functional) MRI techniques, can be used (1) to differentiate tumours from healthy prostate tissue, (2) to differentiate between low- and high-grade tumours, (3) to differentiate between various stromal densities and (4) to improve the overall detection rate of prostate tumours in a suspect population (34-38).

Based on this research, we can conclude that DCE-MRI might also be a potential candidate to detect recurrent prostate cancer after radiotherapy. There is, however, an important difference. After irradiation of the prostate gland, the tissue becomes

fibrotic. This is a biological process that can take months or even years, and does not develop equally in every patient. These tissue changes may influence the contrast enhancement of the tissue in DCE-MRI, and may therefore make the interpretation of the DCE-MRI different. Not much literature is available regarding this subject. Three articles present a diagnostic study on the use of DCE-MRI in patients treated with radiotherapy, and the sensitivity and specificity found by these groups ranged between 0.49 and 0.74, and 0.73 and 0.92 respectively (39-41). These studies did not take the time aspect after treatment into account. Only one study is published that describes the differences between pre- and post-radiotherapy DCE-MRI, however, this study only focuses on short term effects (within 1 year after treatment) (42).
In addition is must be noted that the potential use of DCE-MRI in the follow-up after radiotherapy goes beyond 'just' the diagnosis of recurrent cancer. With respect to further treatment, the localization of recurrent tumours within the prostate is also of major importance, as will be described further in this thesis.

Current problem and aims of this thesis

As pointed out, recurrent cancer is a significant problem for patients treated with radiotherapy for prostate cancer. The diagnosis is difficult due to a lack of reliable diagnostic tools, and therefore salvage treatment is often offered too late, if offered at all. The current practice, of referring patients in a late stage, at which time the chances of success do not weigh against the treatment related toxicity risk, should be improved. The hypothesis is that if recurrent tumours could be detected in an early phase, more patients would still harbour organ confined disease, and this would increase the success rate of salvage treatment. To make this happen, we must improve the current diagnostic work-up of patients suspect for recurrent prostate cancer, to facilitate the detection of recurrent cancer in an early phase. One of the aims of this thesis is to investigate whether DCE-MRI could play a role in the early diagnosis and localization of recurrences. Furthermore, the next goal is to investigate if, with the support of DCE-MRI, a focal treatment target can be defined: a localized area of tumour within the prostate gland. By fine-tuning the treatment - that means restricting the treatment target area - the toxicity rates might decrease, improving the general image of salvage treatment and the resulting referral behaviour of physicians. So, the general goal of this thesis is to investigate the feasibility of focal salvage treatment, supported by DCE-MRI, to improve the early diagnosis and focussed treatment of patients with recurrent prostate cancer.

MRI-guidance in focal salvage therapy

Currently in the UMC Utrecht, brachytherapy procedures are performed transperineally guided by TRUS. However, TRUS is not accurate for delineation of the prostate with regard to surrounding organs and not accurate for tumour detection and extent of disease evaluation. With better imaging of the prostate and surrounding organs, an improvement of treatment outcome can be expected. For example, in brachytherapy an increase of the accuracy of seed positioning and a better visualization of the prostate and surrounding structures, will increase local control and decrease toxicity. Therefore, an MRI-guided implant technique is considered a logical next step in optimising the prostate needle placement (43;44). This is especially the case for focal salvage treatment, because of the specifically defined focal target area and the importance of limiting the treatment dose in previously irradiated tissue. Next to MRI-guided brachytherapy, also MRI-guided biopsies can be valuable in patients suspect for recurrent cancer, because DCE-MRI and other MRI sequences can guide the biopsy towards the suspect focal lesion (45). Hence, MRI-guidance for diagnosis and treatment requires special attention in the development of focal salvage treatment techniques.

Outline of this thesis

Chapter 2 of this thesis describes the clinical outcome after conventional salvage brachytherapy of the total prostate gland is described. In Chapter 3, results are presented of a comparison between the DCE-MRI of patients with recurrent prostate cancer versus the DCE-MRI of control patients, free from recurrent cancer. The potential gain in toxicity rates, if DCE-MRI would be used to create a focal salvage treatment planning, is described in Chapter 4. Chapter 5 covers an outline of the long-term experience with TRUS-guided transrectal and transperineal implantation of fiducial gold markers, which serves as a baseline comparison for the MRI-guided robotic implantations described in Chapter 6. Finally, the first clinical results of focal salvage brachytherapy are presented in Chapter 7, and the clinical impact of the various studies of this thesis will be discussed in Chapter 8.

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2 | Chapter two

Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy

Abstract

Purpose

To evaluate the outcome and toxicity after salvage iodine-125 (125-I) implantation for patients with locally recurrent prostate cancer after primary 125-I implantation and external beam radiotherapy.

Methods and Materials

Retrospectively, 31 patients were analyzed with pathology proven local recurrent prostate cancer after primary external beam radiotherapy (n=20) or 125-I implantation (n=11), and who had undergone salvage 125-I implantation between 1994 and 2009. For recording biochemical failure rates, the Phoenix definition and the American Society for Therapeutic Radiology and Oncology (ASTRO) definition were applied. Toxicity was scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Results

The mean (±SD) follow-up was 9 years (±4). The Freedom From biochemical Failure after 1 and 5 years follow-up were 51% and 20%, respectively. 14 (45%) patients died of prostate cancer after a mean (±SD) follow-up of 73 (±39) months. Grade 1, 2 or 3 toxicity of the genitourinary tract was reported in 29%, 58% and 3% of the patients, respectively, in the acute phase, and in 16%, 39% and 19%, respectively, in the late phase. Grade 1, 2 or 3 toxicity of the gastro-intestinal tract was reported in 45%, 10% and 0%, respectively, of the patients in the acute phase, and in 48%, 3% and 6%, respectively, in the late phase. Grade 4 toxicity of any tract occurred in none of the patients in the acute or the late phase.

Conclusion

Freedom From biochemical Failure after salvage 125-I implantation for locally recurrent prostate cancer after radiotherapy is limited, and both genitourinary and gastrointestinal toxicity occur frequently.

Introduction

A considerable proportion of patients treated with radiotherapy (external beam or brachytherapy or a combination) as a primary treatment for clinically localized prostate cancer will eventually develop recurrent disease. The estimated recurrence risks presented in literature range from 22 to 63% after external beam radiotherapy (1;2) and from 8 to 72% after brachytherapy (2-4), depending on various risk factors like tumour stage, differentiation grade and Prostate Specific Antigen (PSA) levels. Although it is difficult to distinguish between locally recurrent disease and distant metastases when the PSA level increases after primary treatment, many of these patients will harbour organ confined disease (5). Hormonal deprivation therapy is frequently offered to these patients, however, this is a palliative treatment strategy, and patients with a strictly local recurrence might still be cured. Local salvage treatment is the last curative option at this stage, but it is associated with a high rate of complications and is, therefore, unpopular (6). Furthermore, there are no reports available that show an effect of salvage therapy on overall survival. Therefore, the role of salvage treatment in clinical practice is still a subject of debate. Different salvage treatment modalities are currently in practice, such as radical prostatectomy, external beam radiotherapy and 125-I implantation. Also, cryosurgery and high-intensity focused ultrasound (HIFU) are increasingly gaining interest (7-10). Literature is scarce, describes a variety of study populations and treatment methods, and shows discordant results in terms of treatment effect and toxicity. As a consequence, current treatment decisions still often depend on patients' and doctors' (subjective) preferences. To inform patients adequately in this stage of disease, more data regarding treatment results are required. Currently, a prospective Phase II trial (Radiation Therapy Oncology Group (RTOG) 0526) of salvage brachytherapy is ongoing, which will fulfill this need. However, the completion of this trial is expected to take several years, and the long-term follow-up even longer. In 2000, we have reported the feasibility of salvage 125-I implantation after previous radiotherapy in the pelvic area (11). This article describes the long-term outcome and toxicity in the acute and late phases of patients who received salvage 125-I implantation for localized prostate cancer recurrences after both primary external beam radiotherapy and primary 125-I implantation.

Methods and Materials

Since 1994, 31 patients have been treated with 125-I seed implantation for recurrent prostate cancer, at the University Medical Center Utrecht (UMCU). All men had PSA failures after primary external beam radiotherapy (n=20, median dose 66 Gy) or primary 125-I implantation (n=11) for clinically localized prostate cancer. All local recurrences were confirmed by biopsy. Patients with distant metastases and/

or lymph node metastases, confirmed by CT and bone scan, were excluded. Patients were selected for salvage treatment based on a life-expectancy of at least 10 years, and all were counselled with respect to expected toxicity and outcome based on the experience at the institute. Baseline patient characteristics are presented in *Table 2.1*.

Table 2.1 Baseline characteristics of the study population (n = 31).

Characteristic	
Mean (±SD) interval between primary and salvage treatment, years	5.0 (2.8)
Mean (±SD) age at salvage treatment, years	69.3 (5.2)
Primary treatment	
EBRT	20 (64.5%)
125-I implantation	11 (35.5%)
Primary tumour stage	
cT1	5 (16.1%)
cT2	20 (64.5%)
cT3	6 (19.4%)
Primary Gleason score	
Gleason 2 - 6	13 (41.9%)
Gleason 7	13 (41.9%)
Gleason 8 - 10	2 (6.5%)
Unknown	3 (9.7%)
Recurrence Gleason score	
Gleason 2 - 6	5 (16.1%)
Gleason 7	17 (54.8%)
Gleason 8 - 10	4 (12.9%)
Unknown	5 (16.1%)
Mean (±SD) initial PSA, ng/mL	24.3 (17.7)
Mean (±SD) PSA before salvage, ng/mL	11.4 (7.6)
Mean (±SD) PSADT before salvage, months	13 (9)
Mean (±SD) prostate volume before salvage, cm^3	24 (10)

Abbreviations: SD = standard deviation; EBRT = external beam radiotherapy; PSADT = PSA doubling time.

The implantation of 125-I seeds was performed via a transperineal route, under transrectal ultrasound guidance. The standard target dose for all 125-I implantation procedures was 145 Gy. This technique has been previously described elsewhere (12;13). Our criteria for prostate implants were as follows: the percentage prostate volume receiving the prescribed dose of 145 Gy ($V_{T,100}$) >95% and about 2/3 and 1/3

of the prostate volume receiving 150% and 200% of the prescribed dose; the urethra dose ≤ 200% and the rectum dose ≤ 100% of the prescribed dose. Only patients with a prostate volume <50cc were eligible for implantation. In total, five patients received a course of hormonal treatment to reduce prostate volume three months before salvage.

Dosimetric analysis changed in time. Until 1997, no post- implant dosimetry was performed. From 1997 to present, each patient received a CT scan for postoperative dosimetry the day after implant. Since 2004, each patient also received a pre-operative 1.5 or 3.0 Tesla MRI scan and a second MRI scan 4 weeks post-implant together with a CT scan, again for dosimetry. The CT and MR datasets were registered using the seeds as landmarks, after which the CT scan was used for seed localization and the MRI scans for prostate delineation (13). For the patients who received a salvage 125-I implant after external beam radiotherapy, post-implant treatment dosimetry could be performed in the standard manner. For the patients who received a second 125-I implant, dosimetry was complicated. In the post-operative CT and MRI it will be very difficult to localize the newly administered seeds between the older seeds. Especially owing to the increase in artifacts and scatter, simply registering the pre- and postoperative CT's would introduce several methodological flaws. Therefore, in these patients, we relied on the intraoperative plans and no further dosimetry has been performed. *Figures 2.1* and *2.2* present examples of typical dose distributions of 125-I implants after a previous implant (*Figure 2.1*) or after primary external beam treatment (*Figure 2.2*). The case visualized in *Figure 2.1* presents the dose distribution of a 73-year old patient with a recurrence (Gleason 6) 10 years after primary 125-I implantation.

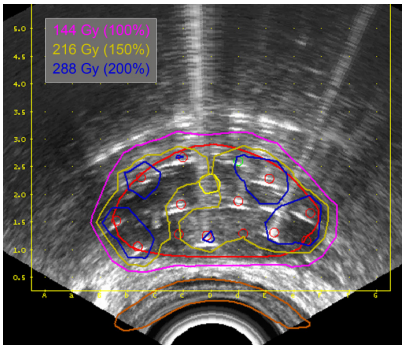

Figure 2.1 Typical dose distribution of 125-I implant after a previous implant; intra-operative plan based on transrectal ultrasound images.

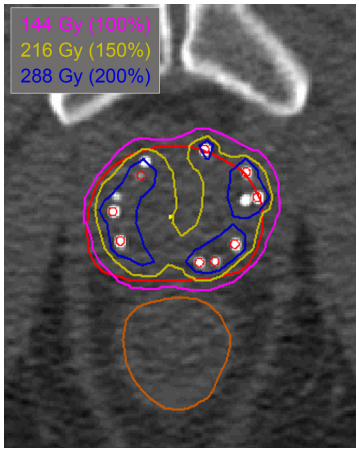

Figure 2.2 Typical dose distribution of 125-I implant after primary external beam treatment, 4 weeks post-treatment plan based on CT images.

The prostate volume was 11 cc, and with 14 needles, 37 seeds were implanted. As described earlier, a dose of 145 Gy was prescribed to 100% of the prostate volume. The resulting D90 in the intra-operative planning was 196 Gy. The V100, V150 and V200 values were 99%, 74% and 29%, respectively. The D2cc and D1cc in the rectum were 57 Gy and 105 Gy, respectively. The V150 in the urethra was 20% (0.05cc) and the peak dose in the urethra was 208 Gy (0.01cc). The case visualized in *Figure 2.2* presents the 4 weeks post-implant dose distribution of a 68-year old patient with a recurrence (Gleason 6) 6 years after primary external beam radiotherapy. The prostate volume was 28cc, and with 18 needles, 48 seeds were implanted. The D90 in the post-implant plan was 133 Gy, and the V100, V150 and V200 were respectively 87%, 59% and 24%, respectively. The D2cc and D1cc in the rectum were 71Gy and 124 Gy, respectively. The V150 in the urethra was 65% (0.02cc) and the peak dose was 260 Gy (0.01cc).

Treatment outcome and toxicity after salvage 125-I implantation were recorded retrospectively by chart review. Biochemical failure was defined as a rise of more than 2 ng/mL above nadir PSA level (the Phoenix definition) and as three consecutive rises in PSA without backdating (the ASTRO definition). For further statistical analysis of the biochemical failure data, the data derived from the Phoenix definition were used (14). The PSA doubling time (PSADT) was also calculated, using two observations for each patient (nadir PSA as first observation and last PSA measurement before salvage as last obervation). In addition, the disease specific survival of the population was evaluated. Prostate cancer-related death was defined as death from or in the presence of distant metastasis. Genitourinary (GU) and gastrointestinal (GI) complications were retrospectively converted to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (15). Toxicity before treatment and toxicity occurring in the acute (within 90 days after treatment) and late phases (more than 90 days after treatment) were separately documented for all patients (15).

Statistical analysis

Descriptive statistics and survival analysis were performed with Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA). Baseline characteristics are reported as means for continuous variables or as percentages for categorical or dichotomous variables. Kaplan-Meier survival analyses were performed for Freedom From biochemical Failure (FFF) and Disease Specific Survival (DSS). In addition, an explorative analysis was performed to identify potential predictors for further research. We applied multivariable Cox regression analysis to relate candidate predictors to FFF. The a priori list of candidate predictors for FFF included initial PSA, primary Gleason score (2-6, 7 or 8-10), PSA before salvage and PSADT before salvage. Gleason score of the recurrent tumour was not included as a factor owing to the limited value of this score because of the effect of radiation and the resultant risk of misinterpretation

(16).For the development of the predictive model, we started with all candidate predictors (full model). Subsequently, we eliminated the variables by backward selection with a p-value ≥ 0.15 (based on Wald test results). Toxicity before and after salvage is presented as the proportion of patients suffering from GU or GI toxicity with corresponding confidence intervals.

Results

Results from retrospective evaluation concerning biochemical failure and survival are presented in *Table 2.2*. After 125-I implantation, 25 (81%) of 31 patients suffered from biochemical failure, as defined by the Phoenix criteria, after a mean (±SD) follow up of 29 (±24) months. Up to now, 14 (45%) patients have died because of prostate cancer after salvage 125-I implantation, at a mean (±SD) follow up of 73 months (±39).

Table 2.2 Biochemical failure rates and survival after salvage (n=31).

Variable	
Mean (±SD) FU after salvage, years	9.2 (±3.8)
Mean (±SD) PSA nadir, ng/mL	4.9 (±6.5)
Mean (±SD) time to nadir, months	9 (±9)
Number of patients with biochemical failure	
Phoenix definition	25 (81%, CI 63-93%)
ASTRO definition	16 (52%, CI 33-70%)
Mean (±SD) time to failure, months	
Phoenix definition	29 (±24)
ASTRO definition	39 (±25)
Death	
Yes, of prostate cancer	14 (45%, CI 27-64%)
Yes, other cause	2 (6%, CI 1-21%)
Mean (±SD) time to death, months	
Prostate cancer deaths	73 (±39)
Other causes	61 (±78)

Abbreviations: SD = standard deviation; FU = follow-up; ASTRO = American Society for Therapeutic Radiology and Oncology; CI = 95% confidence interval.

Figure 2.3 represents the Kaplan-Meier curve for Freedom From biochemical Failure (FFF) following salvage 125-I implantation. The FFF after 1 and 5 years follow up were 51% and 20%, respectively. The Kaplan-Meier curve of Disease Specific Survival (DSS) after salvage is shown in *Figure 2.4*. The 5 and 10-years DSS are 74% and 46%, respectively. The overall survival after 5 and 10 years are 72% and 39%, respectively.

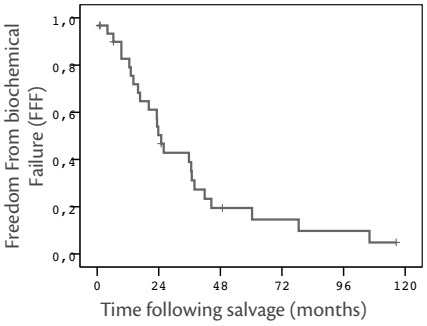

Figure 2.3 Kaplan-Meier prediction of Freedom From biochemical Failure following salvage 125-I implantation.

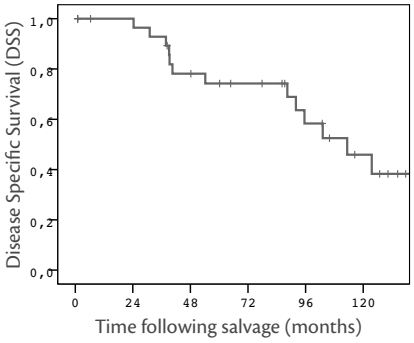

Figure 2.4 Kaplan Meier prediction of Disease Specific Survival following salvage 125-I implantation.

Significant predictors of FFF in the multivariate Cox regression model were primary Gleason score and PSADT before salvage. Neither initial PSA nor PSA before salvage were independent predictors for FFF. Compared with a Gleason score of 6 or lower (grade 1 tumours), a Gleason score of 7 (grade 2) has a hazard ratio of 2.2 (95% confidence interval (CI) 0.8 – 6.0). The hazard ratio of a Gleason score higher than 7 (grade 3), compared to low grade tumours, is 12.4 (95% CI 1.9 – 83.2). Regarding PSADT before salvage, an increase in PSADT corresponds to a decreased failure risk, with a hazard ratio of 0.9 (95% CI 0.9-1.0) for every additional month.
Figure 2.5 shows the Kaplan-Meier survival curves of FFF of all patients divided into two groups based on pre-salvage PSADT (*Figure 2.5a*), and divided into three groups based on primary Gleason score (*Figure 2.5b*). Log Rank tests were significant for both analyses, with p = 0.052 and p = 0.030, respectively, for PSADT and Gleason score.

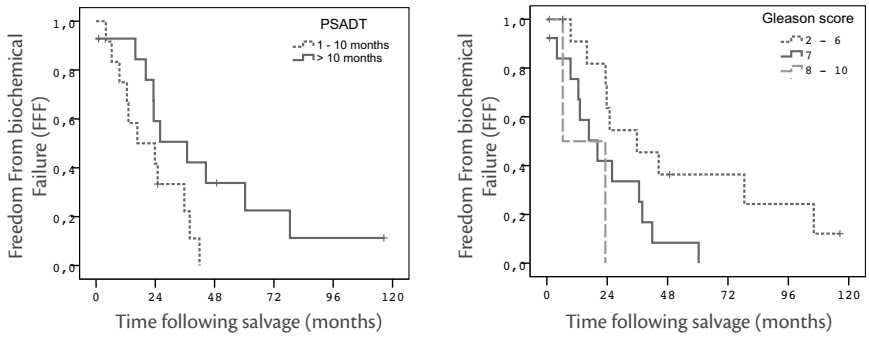

Figure 2.5 Kaplan-Meier prediction of Freedom From biochemical Failure, risk stratification based on pre-salvage PSADT (categorized) (5a) and primary Gleason score (5b).

The incidence of GU and GI toxicity before treatment, and in the acute and late phase is presented in *Table 2.3*. Data are presented separately for patients primarily treated with 125-I or external beam radiotherapy.

Table 2.3 Incidence of acute and late toxicity after salvage 125-I implantation, patients treated primarily with external beam radiotherapy (n = 20) and 125-I implantation (n=11).

	Before salvage		Acute phase		Late phase	
	EBRT	125-I	EBRT	125-I	EBRT	125-I
Genitourinary toxicity*						
Grade 1	5 (25%)	1 (9%)	5 (25%)	4 (36%)	2 (10%)	3 (27%)
Grade 2	2 (10%)	0	13 (65%)	5 (45%)	9 (45%)	3 (27%)
Grade 3	0	0	0	1 (9%)	4 (20%)	2 (18%)
Grade 4	0	0	0	0	0	0
Gastrointestinal toxicity*						
Grade 1	6 (30%)	0	9 (45%)	5 (45%)	10 (50%)	5 (45%)
Grade 2	0	0	3 (15%)	0	1 (5%)	0
Grade 3	0	0	0	0	1 (5%)	1 (9%)
Grade 4	0	0	0	0	0	0

Abbreviations: EBRT = external beam radiotherapy; 125-I implantation.

* According to the Common Terminology Criteria for Adverse Events version 3.0.

For all patients treated primarily with either 125-I implantation or EBRT together (summed data not presented in *Table 2.3*), minor toxicity (grade 1 or 2) in the GU tract was present before treatment in 25% of the patients, occurred in 87% of the patients in the acute phase and in 55% in the late phase. The far most frequent complaint was urethral obstruction because of swelling of the prostate. Severe GU toxicity (grade 3) occurred in 3% in the acute phase and 19% in the late phase, and this comprised urethral strictures and fistula. In 3 out of 7 patients suffering from grade 3 toxicity after salvage, grade 1 toxicity had been present before salvage.

For all patients together, minor toxicity of the GI tract was presented by 19% of the patients before treatment, by 55% of the patients in the acute phase and by 51% in the late phase. The presented complaints were rectal discomfort and pain with occasional bleeding, with minor findings at endoscopy. Severe GI toxicity (grade 3) occurred in 6%, solely in the late phase. In both cases the patient suffered from a fistula. None of the two patients had suffered from GI toxicity before salvage. Grade 4 toxicity occurred in neither the GU nor the GI tract.

Discussion

The objective of this study was to evaluate the treatment results of salvage 125-I implantation for patients with recurrent prostate cancer after previous external beam radiotherapy or 125-I implantation. Our results show 5-year FFF rates of 23% following 125-I implantation (Phoenix definition). FFF declines rapidly after salvage therapy. This could be because of incomplete salvage procedures, but it is more likely that dissemination of cancer cells had already started before salvage was performed, particularly because a number of patients in this study showed high-risk disease features. Patients with short PSADT before salvage and patients with primary high grade tumours have a high risk of dissemination at the time of salvage, and the resulting high failure rates of these patients can be seen in the Kaplan-Meier survival plots (*Figure* 2.5). Toxicity, in particular GU toxicity, occurs frequently in the current treatment group. Although the prevalence of toxicity before salvage treatment is already considerable, a large increase is seen in the acute phase after treatment (within 90 days). In the late phase (after 90 days and further), the incidence of both GU and GI toxicity still exceeds the incidence before treatment. However, most of the reported symptoms can be categorized as minor toxicity. Severe toxicity occurred in only 1 patient in the acute phase but in 8 patients in the late phase.

Several articles describe treatment outcome and toxicity after salvage brachytherapy, most often preceded by external beam radiotherapy as primary treatment. Studies presenting the results of salvage 125-I or 103-Pd implantation in patients treated with primary 125-I implantation are scarce, and population sizes are generally small (17-20). Comparison is hampered by differences in study populations, treatment methods, and the different definitions for failure. Nguyen et al. (2007) present comparable endpoints, evaluated in patients treated with both primary external beam radiotherapy and brachytherapy (17). FFF (Phoenix definition) after 4 years was 70%, which is considerably better than our FFF (20%). This is most likely caused by the selection of solely low risk patient by Nguyen et al. The incidence of major toxicity in the GU and GI tract, presented by Nguyen et al, was similar to our study (30% vs. 29%). In addition, most of the serious complications occurred in the late phase, which is similar in our study. Other studies in the literature focus mainly on patients initially treated with external beam radiotherapy (9;21;22). Beyer et al. (1999) studied 17 patients and report an FFF rate (ASTRO definition) of 83% after 5 years for patients with low-to moderate-grade tumours, and 30% for patients with high-grade tumours. Overall survival was 93% after 5 years (21). Lee et al. (2008) report an FFF rate (ASTRO definition, without backdating) after 5 years of 38% in 21 patients, with a 5-years overall survival rate of 81% (9). Considering the relative small study groups, we should be careful comparing the existing literature to our data, but the FFF and survival rates seem to be following the same trends after 5 years follow-up.

This study is a retrospective analysis, and has several limitations. The assessment of failure rates is subjected to the different definitions that are available to define biochemical failure. During retrospective chart evaluation, the ASTRO definition seemed more prone to bias due to variable follow-up intervals. Therefore, the Phoenix definition was used for further analysis. This also explains the difference between the numbers of patients with biochemical failure depending on the failure definition, presented in *Table* 2.2. But, it is unlikely that the application of an alternative failure definition would alter the outcome of the presented limited FFF. Next, regression analysis of risk factors is influenced by the relatively small subgroups. Therefore, we chose an explorative approach for regression analysis. Pre-salvage PSADT and primary Gleason score showed to be predictors for FFF. However, for more reliable subgroup analysis the study population should be larger than the current population. For example, the primary T stage is likely to be a predictor of FFF; however T stage was not included in the model because nearly all patients were Stage 2. For clinical practice, our results suggest that patients with high PSADT and a low primary Gleason score are in particular candidates for local salvage treatment, but this should be further investigated in a larger study. It is important that the selected patients are counseled for the high incidence of GU and GI toxicity. It should, however, be noted that the presented toxicity rates might be an underestimation of the real incidence due to the retrospective nature of this study; thus the real incidence might be even larger than presented here. No large differences are seen between patients treated primarily with EBRT or 125-I implantation, however, again these subgroups are too small to base conclusions on.

Currently, an RTOG trial (no. 0526) is ongoing for the prospective evaluation of salvage brachytherapy after external beam radiotherapy. The results from this trial may give more insight in the risk profiles of patients suitable for salvage brachytherapy. Because our study population includes patients who have been treated since 1994, the patient selection has not been in agreement with current brachytherapy guidelines for all patients. Consequently, several patients showing high-risk disease characteristics have been treated with salvage 125-I implantation. It is most likely that this has negatively influenced our results. Methods of patient selection should be an important subject for future research, in particular methods to distinguish between local and distant disease at the time of biochemical failure. PSA is widely used in each of the diagnostic, treatment and follow-up phases of prostate cancer management; however, using the PSA level alone as a guide can be misleading. The origin of a rising PSA level after primary radiotherapy is often uncertain, and an ongoing debate exists about which definition should be used to define biochemical failure (14). Therefore, better imaging methods are needed for patient follow-up, in particular to detect local recurrences at an early stage and to help exclude systemic disease before salvage therapy. In combination with PSA levels and biopsy results, this may provide a more reliable method for selecting patients for salvage treatment.

Some general recommendations can be given regarding the application of salvage in practice. A minimum interval of several years between primary treatment and salvage should be maintained to select only those patients with low risk of metastases. Further, patients with high-risk cancer as primary diagnoses are poor candidates for any salvage method. Last, in patients receiving a second 125-I implantation as salvage, the dose should not be additional to the first implant, but a full dose should be given to the gross tumour volume.
When a patient is selected for salvage treatment, the choice for a specific salvage method should be carefully deliberated upon for each individual case, taking into account specific indications and contra-indications for each method. Based on our results, compared with the current available literature, the superiority of one of the investigated salvage methods has not been proven.

Conclusions

After salvage 125-I implantation for prostate cancer recurrences, the 5-year FFF rate was 23%, and the DSS rate was 74%. The incidence of toxicity after salvage was considerable, however, most of it could be classified as minor toxicity. Severe toxicity of the GU and GI tract occurred in 29% of the patients, most often in the late phase. Because of the limited treatment outcome and the high toxicity rates, patients should be selected with great care, based on individual risk factors. More research is needed to improve current patient selection procedures in the work-up for salvage treatment.

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3 | Chapter three

Differences in DCE-MRI in patients with and without recurrent prostate cancer after radiotherapy; preliminary results of a matched case-control study

Abstract

Purpose

There is a need for more precise tumour localization in patients with recurrent prostate cancer after radiotherapy. Dynamic contrast enhanced (DCE-) MRI is a potential candidate, however, it is unknown how radiation induced tissue changes influence the pattern of contrast enhancement, and how DCE-MRI after radiotherapy must be interpret. The goal of this case-control study was to assess the differences in DCE-MRI between patients with and without local recurrent prostate cancer in the follow-up after radiotherapy.

Methods and Materials

30 patients with biopsy proven recurrent prostate cancer after radiotherapy ('cases') and 30 matched control patients ('controls') from the same follow-up population underwent an MRI exam, including DCE-MRI sequence and conventional T2-weighted MRI. The maps of the DCE parameter K^{trans} were compared between cases and controls, in a qualitative and quantitative manner.

Results

In both cases and controls, the central area directly surrounding the urethra shows elevated K^{trans} values. Outside this central area, cases show more areas with elevated K^{trans} compared to controls in the rest of the prostate. In the quantitative analysis there is a minimal shift towards higher K^{trans} values in cases compared to controls, demonstrated by a statistically significant difference for the mean highest 5% and 10% K^{trans} values in the total prostate between cases and controls ($p= 0.028$ and $p = 0.046$).

Conclusion

On a qualitative basis, there are important differences between patients with and without recurrent prostate cancer after radiotherapy. The presented qualitative results can be supportive in the evaluation and interpretation of DCE-MRI exams of prostate cancer patients in the follow-up after radiotherapy. Quantitatively, minimal differences between groups could be objectified. However, the quantitative analysis was complicated by the presence of substantial regions with elevated K^{trans} levels in the central area surrounding the urethra, in nearly all cases and controls. Extension of this study is required to facilitate further detailed analysis of these data.

Introduction

Patients treated with primary radiotherapy for prostate cancer are at risk of developing recurrent disease during follow-up. This risk depends on known risk factors like tumour stage and tumour differentiation grade, and can be over 50% for the highest risk categories (1-4). It is important to detect local recurrences in an early stage, because then curative 'salvage' treatment might still be possible. Prostate specific antigen (PSA) in the blood is widely used for the follow-up of prostate cancer patients after primary treatment, but using the PSA level alone as a guide can be misleading because the origin of a rising PSA level after primary radiotherapy is uncertain; it can be caused by local recurrent tumour, distant metastasis or prostate inflammation (5). Due to a lack of more specific diagnostic tools, a rising PSA in the follow-up after radiotherapy ('biochemical failure') is often assumed to be the first presentation of disseminated disease. Hormonal therapy, a palliative treatment, is commonly the next step. But, this treatment delays disease progression only temporarily and eventually the patient will die of disseminated disease. To prevent this from happening in patients that could have been treated curatively in an early stage, there is a need for new reliable diagnostic tools for the detection of local recurrent disease during follow-up.

Modern developments in Magnetic Resonance Imaging (MRI) offer superior possibilities in the early detection of primary prostate cancer and enable more precise tumour localization. Dynamic contrast enhanced (DCE-)MRI is a functional MRI technique based on tissue perfusion and vessel leakage. It has been subject of investigation in many studies on the diagnosis of primary prostate cancer, and the added diagnostic value has been shown extensively (6-10). Therefore, DCE-MRI could also be an attractive candidate to detect prostate cancer recurrences in irradiated tissue. The diagnostic value of DCE-MRI in combination with T2-weighted MRI for the detection of prostate cancer recurrences was investigated in a small number of studies. The combination was considered a useful diagnostic tool; with sensitivities and specificities ranging between 0.49 and 0.74, and 0.73 and 0.92, respectively (11-13). In these studies a conventional diagnostic study approach was applied; the MRI results were compared with biopsy tissue as a gold standard. This provides information regarding diagnostic reliability, but is does not show how to interpret DCE-MR images after radiotherapy. This is of importance because conventional MRI is difficult to interpret after irradiation, because of tissue changes in the prostate, like fibrosis (14). The development of fibrotic prostate tissue after radiotherapy may take months or even years and it is likely that this process will cause variation in DCE data over time. The goal of this study was to assess the differences in DCE-MR images and parameters between patients with and without local recurrent prostate cancer in the follow-up after radiotherapy. This is a first step to a reliable study of the diagnostic value of DCE-MRI to detect local recurrences in the follow-up after radiotherapy.

We chose to perform a matched case-control study. The advantage of this efficient study design is that the MRI of patients with recurrent cancer ('cases') are compared with patients without a recurrence ('controls'), and therefore 'natural' changes in contrast enhancement due to tissue fibrosis can be differentiated from changes due to recurrent disease. Our primary objective was to evaluate the qualitative differences in DCE-MR images between cases and controls, in a descriptive manner. Secondly, an objectification of the resulting differences between groups was initiated using quantitative DCE-MRI data.

Methods and Materials

Subjects

The study was conducted between January 2009 and May 2010 and was approved by our institutional committee on clinical research and ethics. Informed consent was obtained from all patients.

All consecutive patients with biochemical failure after primary treatment with external beam radiotherapy or brachytherapy for prostate cancer were asked to participate in the study prospectively. Biochemical failure was defined by the Phoenix definition (nadir PSA level plus 2 ng/mL (5)) or the ASTRO definition (3 consecutive rises in PSA level (15)). A minimal follow-up of two years after primary treatment was maintained, because of the uncertain reliability of pathologic evaluation of prostate biopsy material early after radiotherapy (16). In addition, hormonal therapy in the past year (17) and contra-indications for 3 Tesla MRI were considered exclusion criterion. Included patients underwent systematic prostate biopsy after the MRI exam. Patients with negative biopsy results were excluded from further analysis in this study, and patients with positive biopsy results were called 'cases'. All cases were counselled for further therapy. This was beyond the scope of this study and is therefore not further described.

For every case, a matched control patient was invited from the follow-up population of the Radiation Oncology department of our institute. Matches were made based on primary treatment modality (conformal external beam radiotherapy (EBRT), intensity modulated radiotherapy (IMRT) or Iodine 125 (125-I) brachytherapy), follow-up time since treatment (in months), primary clinical tumour stage and primary tumour differentiation grade (grade 1, 2 or 3). For potential controls, biochemical failure, as reported in the medical chart, was considered a reason for exclusion, in addition to the above described exclusion criteria for cases. Because of the high negative predictive value of the PSA test, 99% (18), prostate biopsy was not performed in this group and routine follow-up was continued after the exam. Controls were not informed on the results of their individual studies.

MRI technique and data extraction

Both study groups, cases and controls, underwent the same MRI exam. MRI examinations were performed on a 3 Tesla MRI scanner (Achieva Philips Medical Systems, Best, the Netherlands). Besides the DCE-MRI, the exam included 2 anatomical scans: a multislice T2-weighted turbo spin echo (TSE) sequence (TR/TE 8400/120 ms) and a balanced turbo field echo (TFE) sequence (TR/TE 2.8/1.4 ms). The DCE-MRI protocol consisted of a 3D spoiled gradient echo sequence (TR/TE 4.0/1.0 ms, flip angle 6°). Scans were repeated 120 times at 2.4s interval. A single acquisition consisted of 20 axial slices of 2.5 mm. The field of view was 40x40 cm^2, the reconstruction matrix 160x160. For contrast enhancement, 0.1 ml/kg body weight gadobutrol (1.0 M) (Gadovist, Schering) was injected intravenously. Tracer-kinetics modelling was done using the Tofts model resulting in 3D maps of the transfer constant K^{trans}, the extravascular extracellular space (EES) fractional volume v_e and the rate constant k_{ep} (19).

Based on the anatomical scans the prostate gland, the peripheral zone of the prostate gland and the central gland were delineated. The seminal vesicles were not included in the delineation. The images of the DCE parameter K^{trans} were analyzed in both cases and controls, in a qualitative and a quantitative method.

Qualitative analysis

The qualitative analysis entailed a methodical evaluation and clinical description of the K^{trans} map. To begin with, thresholds for K^{trans} were set between 0 and 0.4 min^{-1}, in every patient. Because of the normal variance in K^{trans} levels between patients, the upper threshold could then be adjusted manually if considered necessary, to reveal areas with relatively elevated K^{trans} levels compared to the rest of the prostate gland. The applied upper thresholds ranged between 0.3 and 0.8 min^{-1}. The number and location of the areas with elevated K^{trans} levels were described for every patient. After evaluation of the K^{trans} map itself, the K^{trans} images were again evaluated in combination with the registered T2-weighted images. Correspondence between elevated K^{trans} levels and hypo-intense T2 signal was assessed, as this might raise suspicion for recurrent tumour.

Quantitative (histogram) analysis

The K^{trans} data within the delineated volumes were extracted for further quantitative analysis, to objectify the results from the qualitative analysis. In our process of data extraction, all voxels with an unreasonable deviation from the model fit, caused by rectal air (at the level of the prostate) or implanted seeds or markers in the prostate, were excluded from further analysis. Per patient, and for each of the three delineated volumes, a series of statistical measures were calculated from the K^{trans} data, namely: mean, median, 90^{th}, 95^{th} and 98^{th} percentile, and the mean highest 2%, 5% and 10% K^{trans}. To compare the K^{trans} of cases and controls, a histogram analysis was performed for every measure in every volume.

Statistical analysis

Statistics were performed with Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA). Baseline characteristics are reported as means for continuous variables or as percentages for categorical variables. Differences in proportions between groups were tested using the Chi-square test. Differences in distributions of the various statistical outcome measures between the case and control group were tested using an unpaired T test. For all testing, a p-value <0.05 was considered statistically significant.

Results

The baseline characteristics of both study groups are presented in *Table 3.1*. The mean time between primary treatment and inclusion in this study was more than 5 years for both groups, and patients were around 70 years of age. Overall, approximately half of the patients had primarily been treated with brachytherapy, and half of the patients with external beam radiotherapy. Patients were distributed equally over the different tumour stages, and two third of the patients had primarily been diagnosed with a low grade tumour.

Table 3.1 Baseline characteristics of the study population*.

	Cases		**Controls**	
N	30		30	
Mean (±SD) follow-up, months	66,3	± 23.7	64,8	± 24.3
Mean (±SD) age at MRI, years	68,1	± 6.0	70,4	± 4.6
Primary treatment				
EBRT (70 Gy)	5	16,7%	4	13,3%
IMRT (76 Gy)	9	30,0%	10	33,3%
125-I (144 Gy)	16	53,3%	16	53,3%
Primary tumour stage				
T1	6	20,0%	9	30,0%
T2	11	36,7%	10	33,3%
T3	13	43,3%	11	36,7%
Primary tumour grade				
Gleason 4 – 6	20	66,7%	18	60,0%
Gleason 7	8	26,7%	10	33,3%
Gleason 8 –10	2	6,7%	2	6,7%

Abbreviations: EBRT = external beam radiotherapy; IMRT = intensity modulated radiotherapy; 125-I = Iodine 125 brachytherapy; Gy = Gray; SD = standard deviation.

* Values are numbers (percentages) unless otherwise stated.

Qualitative analysis

In 30 of the 30 cases (100%) and also in 28 of the 30 controls (93%) one or more areas with elevated K^{trans} were present in the K^{trans} map. The number of areas differed significantly between groups: 0, 1, 2 or 3 areas were present in respectively 0, 10, 15, and 5 cases and in 2, 21, 7 and 0 controls (p = 0.003) (*Figure 3.1*).

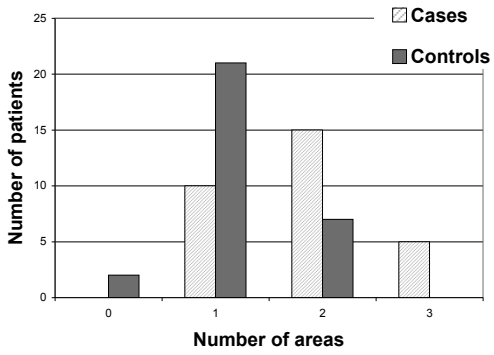

Figure 3.1 Number of areas with elevated K^{trans}, for cases and controls.

In nearly all patients, an area with elevated K^{trans} was situated around the urethra, in a pattern resembling the anatomical shape and position of the central gland (28 of 28 controls and 28 of 30 cases with at least one area of elevated K^{trans}.)
A typical example is shown in *Figure 3.2*. The central elevated K^{trans} area was symmetrically centred around the urethra in most patients (20 of 28 cases and 20 of 28 controls). However, in some subjects asymmetry of this area was present, which seemed to be caused by a connection between an area outside this central area and the central area itself (5 of 28 cases and 1 of 28 controls).

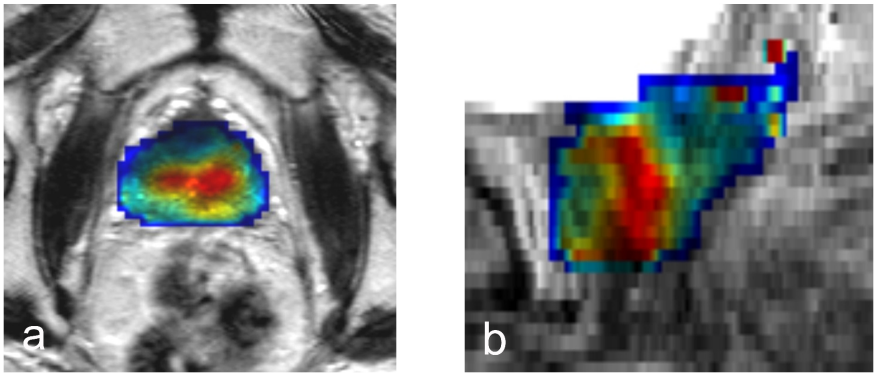

Figure 3.2 Typical example of a control patient with elevated K^{trans} levels in the central area surrounding the urethra. Tranverse (a) and sagittal (b) T2-weighted images with the K^{trans} colour map as an overlay.

Outside the enhancing central area, in cases, more areas of evevated K^{trans} were present in the prostate compared with controls. (In 7 controls, one area of elevated K^{trans} was present outside the central area and in 22 cases, one or more areas were present outside the central area.) A typical example of a case is shown in *Figure* 3.3. In comparison with the control shown in *Figure* 3.2, there is an additional area of elevated K^{trans} present in the peripheral zone of this case.

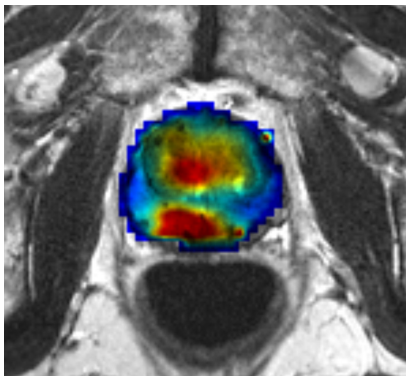

Figure 3.3 Typical example of a case, with elevated K^{trans} levels in the central area surrounding the urethra and an area in the peripheral zone.

Elevated K^{trans} areas outside the central area were compared with the corresponding T2-weighted MR images. A decreased T2 signal intensity was seen at the same location as the elevated K^{trans} areas in cases more often than in controls (22 out of 25 elevated K^{trans}-areas in cases, and 2 out of 7 elevated K^{trans}-areas in controls.)
In most cases and in some controls, an area suspect of tumour could be indicated. This was defined as an area with elevated K^{trans} levels outside or adjacent to the central area, in combination with lowered T2-weighted signal (24 cases and 11 controls). For cases, this location was situated in the peripheral zone in 15 patients, and in the central gland in 9 patients. For controls this was respectively 7 and 4 patients (*Figure 3.4*).

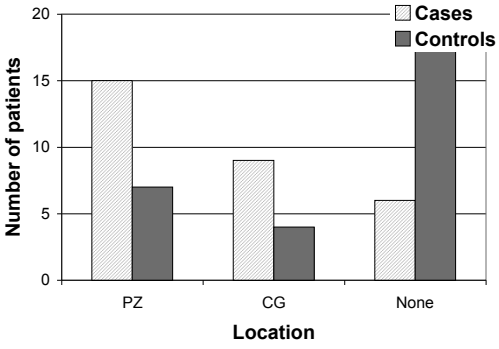

Figure 3.4 Location of the tumour suspect area, for cases and controls. PZ = peripheral zone; CG = central gland; None = no tumour suspect area allocated.

Quantitative (histogram) analysis

The results from the statistical analysis of the MRI data and the comparison between both groups is presented in *Table 3.2*. For both groups, the K^{trans} measures are presented for each volume (prostate gland, peripheral zone and central gland) separately. For the total prostate gland, the mean highest 2%, 5% and 10% and the 98th percentile were significantly higher in cases compared to controls (p = 0.020, 0.028, 0.046 and 0.027). For the central gland, the mean highest 2%, 5% and 10% and the 95th and 98th percentile were significantly higher in cases compared to controls (p= 0.007, 0.015, 0.027, 0.045 and 0.020) as well. There was no significant difference between the two groups for any of the given measures in the peripheral zone. Further subgroup analysis could not be performed because of the limited number of patients per subgroup.

Table 3.2 Results from the quantitative analysis: mean (± SD) values of various statistical measures calculated from extracted K^{trans} (min^{-1}) data, within each volume for cases and controls.

Delineated volume	Group	Volume (cc)	Mean	Median	Mean highest 2%	Mean highest 5%	Mean highest 10%	Mean 90th percentile	Mean 95th percentile	Mean 98th percentile
Prostate	Cases	27.7 ± 14.7	0.24 ± 0.09	0.21 ± 0.08	0.72 ± 0.27*	0.62 ± 0.23*	0.54 ± 0.20*	0.42 ± 0.16	0.50 ± 0.20	0.61 ± 0.23*
	Controls	29.4 ± 10.3	0.22 ± 0.07	0.20 ± 0.06	0.57 ± 0.19*	0.50 ± 0.16*	0.44 ± 0.14*	0.36 ± 0.12	0.42 ± 0.14	0.49 ± 0.17*
Peripheral zone	Cases	12.0 ± 6.3	0.20 ± 0.07	0.18 ± 0.06	0.54 ± 0.24	0.48 ± 0.19	0.42 ± 0.16	0.34 ± 0.12	0.40 ± 0.16	0.47 ± 0.19
	Controls	10.4 ± 4.1	0.19 ± 0.07	0.17 ± 0.06	0.50 ± 0.22	0.43 ± 0.18	0.37 ± 0.15	0.29 ± 0.11	0.35 ± 0.14	0.41 ± 0.18
Central gland	Cases	14.9 ± 10.1	0.27 ± 0.11	0.24 ± 0.09	0.75 ± 0.31*	0.65 ± 0.27*	0.58 ± 0.24*	0.47 ± 0.20	0.54 ± 0.23*	0.64 ± 0.26*
	Controls	18.5 ± 8.4	0.24 ± 0.07	0.21 ± 0.06	0.56 ± 0.19*	0.51 ± 0.17*	0.46 ± 0.15*	0.39 ± 0.13	0.44 ± 0.15*	0.50 ± 0.17*

* Differs statistically significant between cases and controls, with a p-value < 0.05.

Abbreviations: SD = standard deviation.

Discussion

In this study DCE-MRI was compared between patients with and without local recurrent prostate cancer after primary radiotherapy, in a matched case-control study. The data were evaluated in a qualitative, descriptive manner, in connection to clinical practice. To initiate an objectification of the observed differences between cases and controls, a quantitative histogram analysis was performed using the extracted K^{trans} data.
The qualitative evaluation of the maps of the DCE-MRI parameter K^{trans} demonstrates that the central area surrounding the urethra shows elevated K^{trans} values in nearly all patients, both cases and controls. In cases, areas with elevated K^{trans} levels outside the central region are more often seen than in controls, and this corresponds more often with decreased T2-weighted signal intensity. The quantitative analysis of the extracted K^{trans} data shows a very small shift towards higher K^{trans} values in cases, which resulted in significant differences between cases and controls when comparing the distributions of the K^{trans} data.

The consistent elevated K^{trans} in the central area of the prostate in both cases and controls is an important finding, because it could potentially be misinterpreted for tumour. The pattern of the elevated K^{trans} areas within the central gland, directs our hypothesis towards the presence of benign prostate hyperplasia. However, the patients in this study have all been treated with high radiation doses on the prostate, and were included after at least 24 months follow-up. Based on radiobiological effects, we had expected that fibrosis of the tissue would have taken place in the first years of follow-up, and that not only tumour but also regions of benign prostate hyperplasia would be eradicated by radiation. The central gland, that commonly contains benign prostate hyperplasia in the elderly population, is known to be associated with increased contrast enhancement in the non-irradiated prostate (9;10). Apparently, this effect continues to exists in the irradiated prostate. Based on our results we cannot explain this effect, but a pathology study of salvage prostatectomy specimens with specific attention on vessel status and organization could perhaps clarify the underlying physiological process.

Derived from the results from the qualitative analysis, some general recommendations can be made for the evaluation of DCE-MRI of the irradiated prostate in clinical practice. Because of the observed effects in the central area surrounding the urethra, interpretation of K^{trans} must be done with caution, in particular within the central gland. This result corresponds with one of the previous studies that compared DCE-MRI with biopsy results in patients suspect for recurrent cancer. Rouviere et al. (2004) found that the enhancement patterns within the prostate transitional zone largely

overlaps with tumour; both areas show early enhancement after contrast injection, different from the late contrast enhancement seen in normal tissue (note, in our study the transitional zone was not distinguished from the central gland.) The small number of biopsy cores obtained from this region however precluded a meaningful conclusion regarding diagnostic reliability (12). The remaining two studies of DCE-MRI after radiotherapy restricted their analysis to only the peripheral zone of the prostate (11;13). Also in a population of primary prostate cancer patients, Padhani et al. (2000) found no differences between central gland and tumour enhancement values (10).
So, elevated K^{trans} levels in the central area surrounding the urethra should not be mistaken for tumour, especially not if symmetry is present. Further, the presence of additional areas with elevated K^{trans} leads into the direction of recurrent tumour. The combination with matched T2-weighted images can be helpful in the interpretation, as this corresponds often with areas with elevated K^{trans} seen in cases. Lastly, it is important to note that in 6 cases, no clear tumour suspect area could be identified, but contrary, in 11 controls a tumour suspect area could be identified. This could be caused by intrinsic tissue properties. Hypothetically, tumours are heterogeneous in composition and not every tumour may have the vascular properties to enable elevated K^{trans} levels. Further, for controls, as a result of the lack of pathological feedback in this study, we cannot rule out that tumour suspect areas in fact present very early recurrences that did not lead to biochemical failure yet, or alternatively, primary tumour locations that are still in a process of regression. Thus, despite the differences between the two groups, the heterogeneous presentation of the K^{trans} patterns in both cases and control teaches us to interpret these images with care.

Next to the qualitative evaluation of the DCE-MR images, we also performed a quantitative analysis of the extracted K^{trans} data, in an attempt to objectify the results. This method of image analysis might be a solution in the specific category of patients presented in the current study; because patients without recurrent cancer apparently also present increased K^{trans} levels, like cases with recurrent cancer. Theoretically, quantitative differences could then be used for differentiation purposes, if the quantitative differences would be large enough.
For a better understanding of the results in this study, we delineated tumour suspect regions in cases, and calculated the volumes of these regions of interest (ROI). The mean ± SD volume of the ROI's was 2.1 ± 1.7 cc, compared with a mean volume of 27.7 ± 14.7 cc of the total prostate. The average tumour, therefore, makes up 7.6% of the volume of the average prostate. Assuming that tumour areas are associated with higher K^{trans} values, this explains the difference in mean 2, 5 and 10% highest K^{trans} between cases and controls.
We showed that patients with recurrent cancer have a significantly higher mean 2, 5 and 10% highest K^{trans} level within the total prostate. However, despite the significant

differences that were found between the two groups, the absolute differences appeared to be quite small and the variety within both groups is large. Further, differences were found in the central gland between groups, but not in the peripheral zone. It is very likely that these statistics are influenced to large extend by the elevated K^{trans} levels in the central area found in both cases and controls, especially since these areas were relatively large compared to other areas with elevated K^{trans} (sporadically covering the total central gland.) For a more robust analysis without the disturbing effect of the central gland, patients without peripheral zone tumours could be excluded from the analysis, and the analysis could then be limited to the peripheral zone only. However, to make this analysis possible in a reliable manner, more patients need to be included in this study, because at this point, only 15 cases and 7 controls present tumour suspect areas in the peripheral zone. If more patients were to be included, an analysis per treatment category and analysis per tumour differentiation grade would be interesting.

As stated, an important limitation of this study is its sample size. Although two groups of 30 patients is a fair amount compared to the other studies of DCE-MRI for the detection of recurrences, the small differences in the quantitative results and the heterogeneous findings in the qualitative results of this study, express the need for further analysis, in specific the subgroup analyses described above. Therefore, we will continue including control patients for every patient that presents with recurrent disease at our clinic, and we hope to be able to present more robust data regarding this subject in the future.

What could be seen as another limitation of this study, is that this research approach is not based on pathological tumour localization by a comparison with biopsy material or prostatectomy specimens. Therefore no investigation can be performed of the specific qualitative and quantitative characteristics of pathologically proven tumour lesions versus suspect areas on MRI that are not pathologically proven. But, because of the case-control design, this study does provide new information regarding the normal appearance on DCE-MRI of prostate tissue after radiotherapy, especially regarding the qualitative findings. This information can be used in a following diagnostic study and in clinical practice, to improve the current diagnostic reliability of DCE-MRI in the detection of prostate cancer recurrences.

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Int J Radiat Oncol Biol Phys 2010; 94(2):168-72.

4 | Chapter four

Focal salvage guided by T2-weighted and DCE-MRI for prostate cancer recurrences

Abstract

Purpose

Salvage treatment of the entire prostate for local recurrent cancer after primary radiotherapy is associated with high toxicity rates. Our goal was to show that, using dynamic contrast enhanced (DCE-)MRI for the visualization of recurrences, focal salvage treatment can be performed, with, potentially, a reduction in toxicity.

Methods and Materials

We performed MRI exams, including DCE sequence, in 7 patients with biopsy proven local recurrent prostate cancer. The specific regions of interest suspect for containing tumour were delineated, using DCE and T2-weighted MR images. Subsequently, focal salvage HDR brachytherapy treatment plans were created to illustrate the principle of focal salvage. Total salvage treatment plans were also created for comparison.

Results

The K^{trans} values from the DCE ranged from 0.33 to 0.67 min^{-1} for areas suspect for tumour and from 0.07 to 0.25 min^{-1} for normal tissue. In 4 cases, a focal salvage plan could be generated. Here, 93-100% of the Gross Tumour Volume (GTV) was covered with the prescribed dose, with relative sparing of the bladder, rectum and urethra. In the total salvage plans 24-53% of the GTV was covered, and the organs at risk received high doses. In 3 cases a focal salvage plan could not be created because of multifocal tumour, seminal vesicles extension or capsular extension.

Conclusion

Focal salvage treatment plans can be created in patients with local recurrent prostate cancer after radiotherapy. DCE-MRI supports the localization of the target area. This could lead to less toxicity in patients with local recurrent prostate cancer.

Introduction

Despite efforts to increase local control in prostate cancer patients with dose escalation, a significant number of patients have treatment failure within five years after treatment (1-3). In the case of local recurrent disease, several possibilities for salvage therapy exist. The choice for a specific salvage treatment depends on the primary treatment modality, individual patient characteristics and doctors' and patient preferences. Because the exact location of the recurrent tumour within the prostate is generally unknown, the general practice of salvage treatment involves treatment of the entire prostate.

Several studies have shown that, for salvage therapy, the rate of treatment related toxicity is high (4;5). Multiple factors may contribute to the fact that toxicity rates are higher after salvage therapy than after primary treatment. For salvage radiotherapy, the accumulation of the biological radiation dose probably plays an important role. Furthermore, patients tend to be older and to have more comorbidities when salvage is performed. In a retrospective evaluation of treatment effect and toxicity after salvage prostatectomy or salvage Iodine-125 brachytherapy, we found that minor or moderate complications occurred in nearly all patients (unpublished data M.R. Moman, 2008). This is an important drawback of salvage treatment. The high toxicity, in combination with unsatisfactory procedures to differentiate between local and distant recurrences, frequently results in the choice of a palliative treatment strategy with hormonal therapy. Consequently, potentially curative treatment is withheld from many patients.

Evidence is emerging that local recurrences are located predominantly at the site of the primary lesion (6;7). Apparently, tumour progression is caused by a single aggressive group of cells that did not respond to the primary radiotherapy, with possible minor localizations remaining in regression. This creates the potential to reduce the target volume for salvage treatment to the recurrent tumour only. The reduction in target volume would be expected to allow a dose reduction to the surrounding healthy tissue. By reducing the toxicity compared with conventional salvage treatment, focal salvage might be a more acceptable treatment alternative for patients with locally recurring prostate cancer.

For the practical application of focal salvage treatment, the focal tumour must be visualized. T2-weighted magnetic resonance imaging (MRI) combined with techniques such as MR spectroscopy, dynamic contrast-enhanced (DCE-) MRI and diffusion-weighted MRI are widely used to visualize tumours before treatment (8-11). After irradiation, T2-weighted MRI can be difficult to interpret because of fibrosis of prostate tissue, which is hard to differentiate from malignancy (12). However, recently, two publications showed that DCE-MRI can also be used to visualize recurrent tumours after primary radiotherapy. Sensitivities and specificities of respectively 70-74% and 73-85% were found (13;14).

In this study, we used the diagnostic potential of DCE-MRI to visualize recurrent tumours to investigate the feasibility of focal salvage brachytherapy. On the basis of the location and number of lesions in the prostate we determined whether focal treatment would be viable. For patients with a solitary tumour confined to the prostate, we conducted a planning study to compare treatment of the tumour focus only with treatment of the entire prostate gland.

Methods and Materials

Subjects

We evaluated the disease course of 7 patients with biochemical failure after primary radiotherapy, positive biopsy findings and an MRI exam that was indicative of recurrent tumour. Baseline patient characteristics are listed in *Table 4.1*. These patients had been treated primarily with conformal external beam radiotherapy (EBRT, 1 patient), intensity modulated radiotherapy (IMRT, 1 patient) or iodine 125 (125-I, 5 patients) brachytherapy. The details on the treatment techniques and dose have been previously described (15;16). The planned treatment dose was 70 Gy for EBRT, 76 Gy for IMRT and 144 Gy for 125-I brachytherapy.
Biochemical failure was defined as an increased prostate specific antigen (PSA) level of more than 2 ng/mL above PSA nadir level (Phoenix criteria) (17). Ultrasound guided transrectal biopsy cores were taken from all segments of the prostate by various referring urologists, according to the guidelines of the European Association of Urology (18). Because of the specific study design, topographic correlation of biopsy tissue with the DCE-MRI was not possible.
Eventually, after excluding systemic disease with a bone scan and pelvic CT or pelvic lymfadenectomy, two patients were treated with salvage cryoablation of the whole prostate, two patients underwent salvage radical prostatectomy and one patient was treated with salvage EBRT. The choice among the different salvage options was determined from individual factors.

MRI technique and analysis

MRI examinations were performed using a 3 Tesla MRI scanner (Achieva Philips Medical Systems, Best, the Netherlands). The DCE-MRI protocol consisted of a 3D spoiled gradient echo sequence (TR/TE 4.0/1.0 ms, flip angle 8°). Scans were repeated 120 times at 2.4s interval. A single acquisition consisted of 20 axial slices of 2.5 mm. The field of view was 40x40 cm^2, the reconstruction matrix 160x160. For contrast enhancement, 0.1 ml/kg body weight gadolinium-DTPA (1.0 M) (Gadovist, Schering AG, Berlin, Germany) was injected intravenously. Tracer-kinetics modeling was

Table 4.1 Baseline characteristics of the study population: patients with biopsy proven local recurrent prostate cancer.

	Number of patients
Total group	7
Primary tumour stage	
T1	2
T2	3
T3	2
Gs primary tumour	
4 – 6	5
7	2
8 –10	0
Primary treatment	
EBRT (70 Gy)	1
IMRT (76 Gy)	1
125-I (144 Gy)	5
	Median (range)
Initial PSA level, ng/mL	8.2 (3.3 – 17.0)
Age at primary diagnosis, years	62 (52 – 71)
Nadir PSA level, ng/mL	0.4 (0.1 – 1.0)
Time to nadir PSA, months	14 (1 – 35)
Time from treatment to recurrence, months	48 (26 – 82)
PSA doubling time at recurrence, months	9 (5 – 18)

Abbreviations: Gs = Gleason score; EBRT = external beam radiotherapy; IMRT = intensity modulated radiotherapy; 125-I = Iodine-125 brachtherapy; PSA = prostate specific antigen.

done using the Tofts model resulting in 3D maps of the transfer constant K^{trans}, the extravascular extracellular space (EES) fractional volume v_e and the rate constant k_{ep} (19). In addition to the DCE-MRI, the exam included 2 anatomical scans: a multislice T2-weighted turbo spin echo (TSE) sequence (TR/TE 8400/120 ms) and a balanced turbo field echo (TFE) sequence (TR/TE 2.8/1.4 ms).

The DCE maps were assessed with the T2-weighted MR images and the clinical information for all patients. Specific regions of interest were delineated, that were suspect for tumour because of a low signal intensity on T2-weighted images and an increased enhancement of the transfer constant K^{trans}. Diffuse areas with increased enhancement surrounding the urethra, without any abnormalities on the corresponding T2-weighted images, were defined as being non-suspicious as this is frequently caused by benign prostate hyperplasia and/or by normal vasculature.

Brachytherapy treatment planning

For all cases, focal salvage and total salvage high-dose-rate (HDR) brachytherapy plans were created using the treatment planning system Oncentra® MasterPlan (Nucletron B.V., Veenendaal, The Netherlands). The dose distribution was optimized with the inverse planning simulated annealing (IPSA) algorithm (20). A dose of 15 Gy given in 1 fraction was prescribed to 100% of the delineated gross tumour volume (GTV) for the focal plans, and to 100% of the prostate for the total plans. The maximum dose to the bladder and rectum was set as 6 Gy, and, for the urethra, a maximum dose of 10 Gy was set, according to the GEC/ESTRO-EAU recommendations for fractionated HDR monotherapy (21). The planning results, in particular GTV coverage and dose to the organs at risk, of the focal and total plans were compared.

Results

In the study population, the nadir PSA level after radiotherapy ranged from 0.1 to 1.0 ng/mL and the median PSA doubling time at the moment of biochemical failure was 9 months (range 5 - 18). Biochemical failure occurred after a median period of 48 months (range 26 - 82) after completion of primary radiotherapy. The K^{trans} images obtained from the DCE-MRI exams showed areas of increased enhancement in all patients. Values ranged from 0.33 to 0.67 min^{-1} for areas suspect for tumour and from 0.07 to 0.25 min^{-1} for normal peripheral zone tissue. In four patients an area of increased perfusion without tumour suspicion was seen in the central gland. The K^{trans} values in these non-suspicious central gland areas ranged from 0.30 to 0.84 min^{-1}. An example of an image with suspect enhancement is shown in *Figure 4.1*.

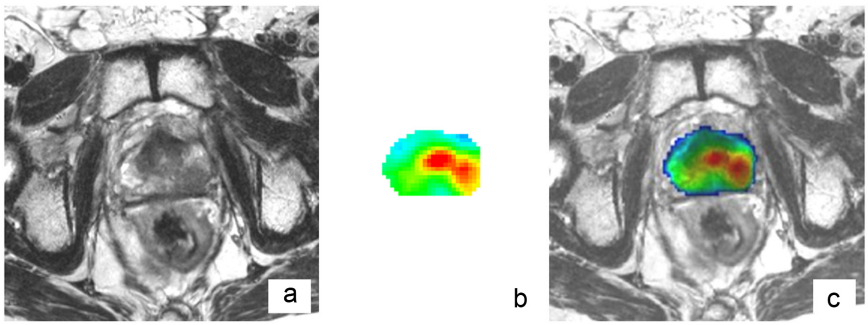

Figure 4.1 Transverse T2-weighted MR image of the prostate in a patient with biochemical failure after radiotherapy (1a). On the same level, the DCE map based on the parameter K^{trans} shows two areas of increased perfusion (1b). This DCE map is laid over the T2-weighted image for anatomical orientation (1c). The central area of increased perfusion most likely represents benign prostate hyperplasia, the area in the left peripheral zone is suspect for tumour.

The data from the DCE-MRI exams are summarized in *Table 4.2*.

Table 4.2 Results from DCE-MRI, values of K^{trans} per individual case.

Region	**Range in K^{trans}, min $^{-1}$**						
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Tumour suspect	0.35 - 0.44	0.36 - 0.41	0.33 - 0.67	0.37 - 0.69	0.36 - 0.51	0.36 - 0.57	0.36 - 0.46
Apparent normal tissue	0.09 - 0.25	0.07 - 0.25	0.16 - 0.24	0.13 - 0.23	0.11 - 0.24	0.13 - 0.28	0.11 - 0.23

In four patients a solitary tumour, confined to the prostate, was found. Of the remaining 3 patients, one had multifocal disease, one had extension of the tumour into the seminal vesicles and a third had extension in the seminal vesicles and through the prostate capsule. For multifocal disease, a focal treatment would not be suitable because it does not create an advantage compared with total salvage therapy. For brachytherapy, capsular extension and extension into the seminal vesicles is considered a contra-indication. For the remaining four patients, both a focal and a total salvage plan were generated. Results from all treatment plans, focal and total prostate treatment plans, are presented in *Table 4.3*.

Table 4.3 Results from focal HDR treatment planning compared with total prostate HDR treatment; percentage of GTV receiving the prescribed dose (15 Gy) and percentages of critical structures receiving a high dose (10 Gy for the urethra and 6 Gy for rectum and bladder).

		Volume			
Case	**Plan**	**GTV (% ≥ 15 Gy)**	**Urethra (% ≥ 10 Gy)**	**Rectum (% ≥ 6 Gy)**	**Bladder (% ≥ 6 Gy)**
1	Focal	99	1	3	3
	Total	38	90	21	17
2	Focal	93	2	3	<1
	Total	24	60	11	6
3	Focal	98	0	3	0
	Total	35	0	12	9
4	Focal	100	0	0	0
	Total	53	99	8	34

Abbreviations: HDR = high dose rate brachytherapy; GTV = gross tumour volume.

Figure 4.2 shows the focal HDR treatment planning for the patient presented in *Figure 4.1*. In this case, 99% of the GTV was covered with the prescribed dose of 15 Gy. The rectum and bladder received a dose > 6 Gy in < 3% of the volumes. The urethra

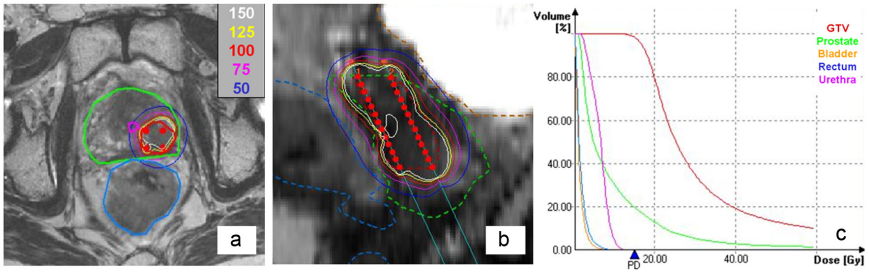

Figure 4.2 a-c. A transverse (2a) and sagittal (2b) T2-weighted MR image of the prostate with a HDR salvage treatment plan, applied to the same case as shown in Figure 4.1. Four HDR needles are needed to deliver a focal dose that covers the whole tumour within the prostate. The dose-volume histogram of the focal treatment plan is shown (2c). The GTV is covered with 100% of the prescribed dose, while critical organs are relatively spared.

received > 10 Gy in < 1% of the volume. When the total prostate was target in the treatment plan, the GTV, rectum, bladder and urethra received 15 Gy, 6 Gy, 6 Gy and 10 Gy to 38%, 21%, 17% and 90%, respectively. In the other three cases it was also possible to apply a high dose to the GTV when focal planning was performed, while the dose to the critical organs remained acceptable. In contrast, for the total treatment plans, adequate dose coverage of the GTV could not be reached in all cases; the volume of the GTV that was covered with the prescribed dose was maximum 53% (case 4). In addition, the dose to the organs at risk exceeded the defined constraints in all cases. The ranges in D2cc (the dose exceeded in 2cc of the volume) for the rectum and bladder volumes were 2.5 – 6.4 Gy and 1.4 – 4.3 Gy for the focal plans, and 5.0 – 7.2 Gy and 6.5 – 12 Gy for the total prostate salvage plans, respectively.

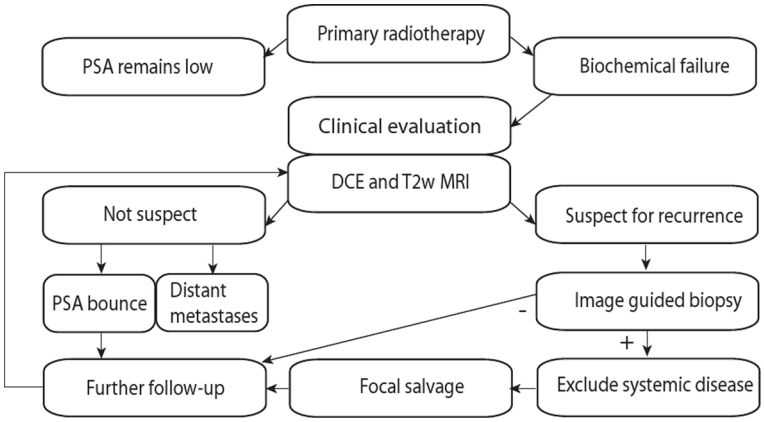

Figure 4.3 Flow chart showing the clinical incorporation of DCE-MRI in the follow-up of prostate cancer patients after radiotherapy. If the criteria for biochemical failure are met, a DCE-MRI can be performed, depending on the patients' perspectives (clinical evaluation). This procedure can be repeated during follow up if necessary.

Discussion

In this study, we investigated the possibility of focal salvage for patients with locally recurrent prostate cancer after radiotherapy. Using the data from DCE- and T2-weighted MRI focal salvage treatment plans were created. We showed the benefits of focal salvage, regarding target coverage and dose to the organs at risk compared with salvage of the total prostate gland.

For any salvage procedure to be successful, it is imperative that systemic disease has been excluded. Therefore a bone scan is required. Furthermore, the involvement of pelvic lymph nodes must be assessed with either an abdominal CT scan or a lymph-node dissection. In the future, newer nuclear imaging methods such as Positron Emission Tomography (PET) combined with ^{18}F-choline as a radiotracer might also be useful (22).

For focal salvage therapy additional requirements apply. Therefore patients should be selected with great care. First, a positive MRI exam must be confirmed by image-guided biopsy of the target area. Real-time MRI guided biopsy is not generally available, however, trans-rectal ultrasound (TRUS) could also serve as a biopsy guide (23;24). In both cases, the information of the DCE-exam containing the precise location of the suspected region should be available. The reliability of this technique has not yet been established, and more work is required in this area of research. Second, not every patient with biopsy proven local recurrent prostate cancer is a good candidate for focal therapy. Our results showed that for three of seven patients a focal treatment was not suitable. Multifocal disease limits the volume reduction of the treated volume that can be achieved compared with total salvage. We also believe that tumour extension outside the prostate capsule or into the seminal vesicles must be considered a contra-indication for focal salvage treatment. Thus, DCE-MRI can provide additional information for patient selection, enhancing the potential success of salvage treatment. Eggener et al. (25) proposed a set of criteria for primary focal therapy using multiple clinical, biopsy and imaging characteristics, that results in the exclusion of all high risk patients. For the primary treatment of prostate cancer this is a reasonable position, since many treatment alternatives are available. However, in the context of salvage therapy, this is less appropriate. High-risk patients are precisely the patients most likely to suffer from recurrent cancer. Therefore, rather than excluding these patients, we believe that we should select patients for salvage therapy using the criteria described in our study. Focal salvage therapy should be chosen according to the accurate determination of the target location. In this way, there is a possibility that patients with high-grade tumour recurrences qualify for focal salvage therapy, and be offered a chance of cure.

In principle, focal therapy cannot result in better local control than treatment of the total prostate gland. However, the therapeutic gain of focal salvage therapy would be a reduction in treatment-related toxicity. A focal salvage treatment implies that the dose is reduced to large parts of the prostate, as compared with total salvage therapy. The justification of this approach relies on the negative predictive value of the MRI exam. There is support for the reliability of DCE-MRI for the detection of recurrent prostate cancer. Haider et al. (2007) and Rouviere et al. (2004) reported negative predictive values of respectively 95% and 79% for DCE-MRI of the prostate peripheral zone, as determined from biopsy results (13;14). The specificity of DCE-MRI in the central gland is reduced by the presence of benign prostate hyperplasia (BPH) and peri-urethral vasculature. As we experienced in this study, areas showing increased perfusion in the prostate central gland (through benign prostate hyperplasia (BPH) or vasculature) can result in confusion in the visualization of recurrences. However, when DCE images are combined with T2-weighted and clinical information, differentiation between tumour and benign tissue seems to improve. An important factor influencing the sensitivity of DCE-MRI is the use of hormonal therapy and its effect on the tissue's vasculature (26). As a result, the negative predictive value of a DCE-MRI exam can be reduced in patients receiving hormonal therapy, and this must be taken into account in patients with biochemical failure.
Alternative MRI techniques such as Diffusion Weighted Imaging (DWI) or Magnetic Resonance Spectroscopic Imaging (MRSI) could also be supportive in the detection of local prostate recurrences after previous radiotherapy (27;28). Coakley et al. (29) have demonstrated that MRSI might be useful in the follow-up because radiation induced anatomic changes do not interfere with the metabolic information provided by MRSI.

We showed in this study that, because precise localization of the tumour might allow a reduction in treated volume, the dose to organs at risk can be reduced. Consequently, it is reasonable to expect that treatment related morbidity would diminish to an acceptable level. The high levels of toxicity of total salvage treatments are one of the main reasons why this option is not offered to many patients. With a substantial reduction in toxicity, focal salvage might become a more acceptable form of salvage therapy for a larger group of patients and thus lead to increased and earlier patient referral. We suggest the incorporation of DCE-MRI into clinical practice as visualized in *Figure 4.3*. When a patient develops biochemical failure, a clinical evaluation can be done in which the patient's wishes and perspectives are discussed. Known risk factors for treatment failure should be taken into account at this point. If additional local treatment is considered an option, MRI can be used to determine whether the disease is confined to the prostate and whether a substantial part of the prostate is free of disease. In such a case, focal salvage therapy could be offered to these patients with a chance of cure.

The interest in primary focal therapy is increasing (25;30-33). In contrast, partial salvage therapy has only recently been introduced in the literature, using cryosurgery (30). Alternative methods such as low dose rate brachytherapy (LDR), pulse dose rate (PDR) brachytherapy, HDR brachytherapy, high intensity focused ultrasound (HIFU), thermo-ablation and surgery could possibly be used as focal salvage techniques as well. In this study, we investigated the feasibility of HDR brachytherapy for focal salvage. HDR was considered a practical method for focal salvage because it is time efficient, especially when the dose is delivered in one fraction, and is an easy way to ensure the highly localized dose coverage of the target area while restricting the dose to the surrounding organs. To date, no guidelines are available for single fraction HDR monotherapy. The prescribed radiation dose of 15 Gy was chosen to demonstrate that a single high dose to the focal GTV is feasible, with sparing of the surrounding organs. A randomized controlled trial is needed to compare survival and toxicity of focal salvage versus salvage of the whole prostate gland.

Conclusion

We have demonstrated how a focal salvage treatment plan can be created for patients with local recurrent prostate cancer after radiotherapy. DCE-MRI can be supportive in the localization of the salvage target area. Focal salvage therapy can be performed in patients with a solitary, focal area of tumour within the prostate, without capsular extension, provided that the tumour is confirmed by image-guided biopsy. In this way, further development of current available imaging techniques may lead to less toxicity and better survival in patients with local recurrences through image guided focal salvage therapy.

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5 | Chapter five

Long-term experience with transrectal and transperineal implantation of fiducial gold markers in the prostate for position verification in external beam radiotherapy; feasibility, toxicity and quality of life

Abstract

Purpose

This study presents an overview of the experience with transrectal and transperineal implantations of fiducial markers for position verification in prostate radiotherapy, regarding the practical feasibility, procedure-related toxicity and influence on quality of life (QoL).

Methods and Materials

Since 2001, 914 patients scheduled for intensity modulated radiotherapy (IMRT) have received gold markers in the prostate. The incidence of severe toxicity, defined by the CTCAE v3.0. was evaluated retrospectively. The influence on QoL was measured prospectively in 36 patients using a combination of three validated questionnaires: the Rand-36, the EORTC QLQ-C30(+3) and the prostate cancer-specific EORTC QLQ-PR25. Next, the incidence of marker migration was assessed.

Results

From 2001 to 2005, 402 patients received markers via the transrectal route. Two of these patients developed urosepsis (grade 3 toxicity). Since 2005, 512 patients received markers via the transperineal route. No grade 3 or 4 toxicity occurred in this group. No significant and clinically relevant differences were found in QoL between pre- and post-implant measures. In 5 patients marker migration led to discontinuation of the marker-based IMRT.

Conclusion

Clinical use of transperineal implanted fiducial gold markers for position verification in external beam radiotherapy for prostate cancer is a feasible and safe procedure without influencing patients' QoL.

Introduction

Fiducial gold markers are commonly used for position verification in external beam radiotherapy for prostate cancer, and have proved to be a reliable tool to correct for inter-fraction motion of the prostate (1-3). In a previous paper on position accuracy, using an offline shrinking-action-level (SAL) protocol on 452 patients, we showed the mean systematic inter-fraction error to be approximately 0.2 mm (SD 0.8) (1) and the mean systematic and random intra-fraction error to be less than one mm (4). An improvement in health-related quality of life (QoL) after radiotherapy was found when using gold fiducial makers for position verification (5), and limited side effects were seen (6). Correcting the exact position of the prostate is important, considering the desire for further dose escalation in the prostate gland to improve the outcome after external beam radiotherapy (7).

Despite the fact that using fiducial gold markers is a generally accepted method for position verification, scarce literature exists on the toxicity and patients' experience of fiducial gold markers with regard to the implantation. Further, in order to safely use markers for position verification the percentage of marker migration (/loss) needs to be low. This has been subject of investigation in a few small studies in the literature (2;8;9).

In this study, we will give an overview of the experience and practical consequences of transrectal and transperineal marker implantation, based on a group of 914 patients. The practical feasibility, procedure related toxicity and influence on quality of life (QoL) will be discussed.

Methods and Materials

Implantation method

Since 2001, 914 patients scheduled for intensity modulated radiotherapy (IMRT) have received fiducial gold markers at random positions within the prostate. In this group, 219 patients have received two markers, in the beginning of the program. The next 695 patients received three markers. The gold markers are 5 mm in length, and 1 mm in diameter (Heraeus GmbH, Hanau, Germany) (*Figure 5.1*). Since August 2004, these gold markers contain a 0.3 mm diameter steel core, to improve the visualization on magnetic resonance imaging (MRI). The implant procedures were performed under antibiotics prophylaxis (ciprofloxacin 500 mg taken 2 times daily, for 3 days, according to our hospital protocol).

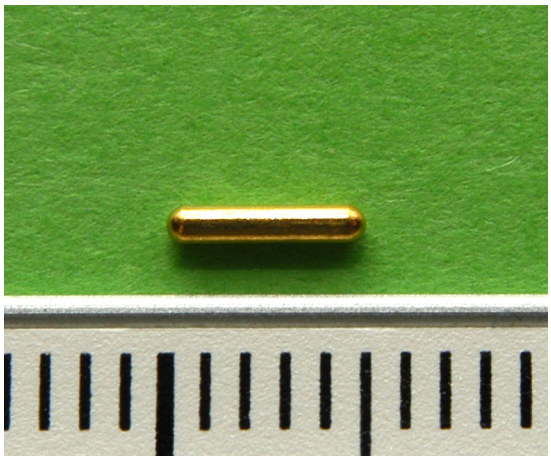

Figure 5.1 Fiducial gold marker.

Two different methods in gold fiducial marker implantation have been performed. In the first 402 patients, from 2001 until 2005, a transrectal insertion had been performed using three 18 G needles which were inserted through the biopsy needle channels in the transrectal ultrasound probe (10). From 2005 until now a transperineal approach has been performed on 512 patients by using a template (*Figure* 5.2). This change was made primarily because of practical reasons. To facilitate the transrectal ultrasound (TRUS)-guided implantation, the patient is placed in lithotomy position.

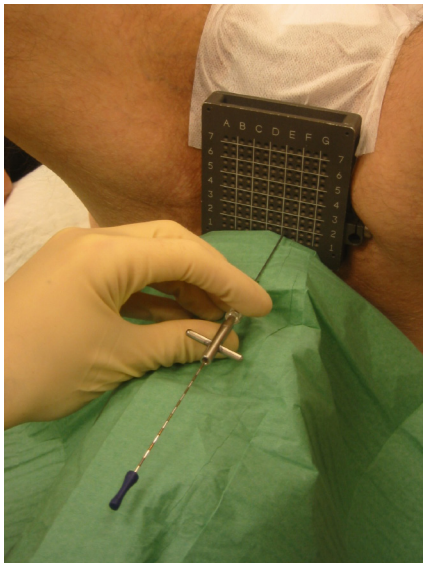

Figure 5.2 Implantation is facilitated by a template that is positioned against the perineum, placed on the transrectal ultrasound probe.

Two 18 G needles are inserted through the transperineal template, one in the left and one in the right lobe of the prostate. In both the transrectal and transperineal procedure two markers are left in one lobe via one needle, at least one centimeter distance from each other as visualized by ultrasound, and via the second needle one marker is left in the other lobe. The three markers are deliberately not put in the same transrectal plane to avoid the increase of scatter on CT. The total procedure takes approximately 15 minutes. The transrectal approach was performed without any anesthesia. Since the transperineal approach was started, subcutaneous anesthetics (Lidocaine 2%) was applied optionally, if preferred by the individual patient. The position of the markers is determined on a CT and MRI scan one week after marker implantation.

Toxicity assessment

Severe toxicity is recorded in a standard manner for all patients treated with radiotherapy in the UMC Utrecht, before radiotherapy, during treatment and in the follow-up. Direct marker implantation-related toxicity is not recorded specifically. Therefore, severe (grade 3 or grade 4) toxicity was obtained from the standardised toxicity charts and these were evaluated for a possible relation with the marker implantation procedure, with special interest to toxicity which occurred before the start of radiotherapy. Toxicity is reported as defined by the Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Quality of life assessment

To evaluate the influence of transperineal implantation on QoL, in 2008, 36 consecutive patients planned for IMRT were asked to participate in a prospective QoL study. A combination of three validated QoL questionnaires was used; the Rand-36 (11;12), the European Organization of Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30(+3)) and the prostate cancer-specific EORTC QLQ-PR25 (13;14). The patients were asked to fill in a questionnaire before (baseline) and 1 week after gold marker implantation. In the 1 week post-implant measure we added several specific questions concerning possible symptoms that could be expected as a results of implantation, based on the previous literature (15). The Visual Analogue Scale (VAS) was used to assess pain experience before, directly after the implantation and one week later. The collected data were analysed with Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA). A difference in test score of 10 points or more was considered clinically relevant (16). The difference in mean test scores for each QoL item between the two groups was tested on significance by the Wilcoxon signed-rank test. The sample size of 36 patients was calculated to have a power of 86% of detecting a 10-points difference in test scores between groups (one-tailed). A p value <0.01 was considered as being significant, to account for multiple comparisons.

Practical feasibility

To investigate how often implanted markers migrated during the treatment series, we analyzed the previous collected data of marker positioning on 881 patients. Our protocol (1) excluded all patients which showed significant marker migration during treatment (>2 mm migration, defined as an increase of >2 mm in distance between 2 markers). The charts of the patients that were taken out of the daily correction protocol prematurely were further investigated. The daily position verification data and the charts of these patients were evaluated to find out the cause of discontinuation of the marker-based position verification. The causes were listed and reported as frequencies.

Results

Toxicity assessment

From 2001 to 2005, 402 patients received fiducial gold markers via the transrectal route, performed by an urologist. In this period, two patients suffered from urosepsis following the marker implantation (grade 3 toxicity). No further grade 3 or grade 4 toxicity occurred.
Since 2005, 512 patients received fiducial gold markers via the transperineal route, performed by a radiation oncologist. No grade 3 of 4 toxicity has occurred until now.
The 36 patients that were asked to fill in the QoL questionnaire were also asked to report new symptoms in the genitourinary tract during the week after implantation. The results of this toxicity assessment are presented in *Table 5.1*. The most frequent symptoms were hematuria (40%), and hematospermia (25%).

Table 5.1 Symptoms in the week after marker implantation, n = 36.

Symptom	Frequency	(%)
Pain	3	(8.3)
Use of analgesics	0	(0.0)
Fever	1	(2.8)
Cold chills	3	(8.3)
Hematuria	14	(38.9)
Voiding complaints	2	(5.6)
Hematospermia	9	(25.0)
Rectal bleeding	0	(0.0)
Rectal discomfort	3	(8.3)

Quality of life assessment

The results from the QoL questionnaires and statistical analysis are presented in *Table 5.2*. For three QoL items ('Emotional functioning', 'Social functioning' and 'Insomnia') the mean test scores differed significantly between the two time points. However, the extent of these differences were considered not clinically relevant (difference less than 10 points for all three items (16).)

The mean ± SD VAS scores one week before implantation and one week after implantation were equal, to be exact 0.8 ± 1.3 points.

Independent from this assessment, the pain experience of the implant procedure itself was graded as a mean ± SD VAS score of 2.7 ± 2.1. Fear experience was described as 'none' in 22 patients, 'little' in 12 patients and 'quite some' in 2 patients. None of the patients experienced 'a lot' of fear. The question whether the patient would recommend this method to other patients, keeping in mind that the treatment is improved by using this position verification method (17), was answered 'yes' by 34 patients and 'don't know' by 2 patients. None of the patients answered this question with 'no'.

Practical feasibility

Data on daily marker positions were available 881 patients that were treated with IMRT since 2001. Ten patients had been taken out of the daily correction protocol prematurely. Medical chart evaluation revealed that in five of these ten patients marker migration had led to discontinuation of the marker-based position controlled IMRT because the maximum acceptable limit of 2 mm migration was reached. IMRT was replaced by conformal radiotherapy in all cases. In these patients, marker displacement ranged from 3 mm to 4 mm (three patients) and one marker was lost (one patient). For one patient the positioning data to calculate the exact migrated distance was not available. Four out of five patients with marker migration had received markers via the transrectal route.

In four other patients that had been taken out from the daily correction protocol the treatment was discontinued because of medical reasons (e.g. acute urinary retention treated with trans-urethral resection of the prostate), and in one patient extreme rectal filling had led to a transfer to conformal radiotherapy.

Table 5.2 Results from quality of life assessment before and after implantation.

Item	Baseline	Post-implant	Difference (p value)
RAND-36			
Physical functioning	86±20	84 ±24	NS
Social functioning	78 ±22	83 ±22	NS
Physical role restriction	74 ±38	76 ±38	NS
Emotional role restriction	81 ±34	80 ±35	NS
Mental health	75 ±22	80 ±17	NS
Vitality	73 ±18	76 ±19	NS
Pain	89 ±17	93 ±13	NS
General health	68 ±16	68 ±17	NS
Change in health	44 ±14	45 ±16	NS
EORTC QLQ-C30(+3)			
Physical functioning	89 ±16	88 ±13	NS
Role functioning	88 ±18	90 ±17	NS
Emotional functioning	79 ±19	85 ±14	0,003
Cognitive functioning	83 ±20	88 ±20	NS
Social functioning	86 ±22	92 ±15	0,008
Global health/quality of life	76 ±15	78 ±17	NS
Fatigue	17 ±21	17 ±19	NS
Nausea and vomiting	1 ±4	1 ±4	NS
Pain	8 ±16	7 ±12	NS
Dyspnea	15 ±22	11 ±20	NS
Insomnia	23 ±24	14 ±18	0,002
Appetite loss	3 ±9	1 ±6	NS
Constipation	5 ±18	6 ±21	NS
Diarrhea	6 ±15	8 ±22	NS
Financial difficulties	2 ±8	2 ±8	NS
EORTC QLQ-PR25			
Urinary symptoms/problems	13 ±14	12 ±11	NS
Bowel symptoms/function	3 ±7	4 ±9	NS
Treatment-related symptoms	6 ±8	6 ±8	NS
Sexual functioning	30 ±23	27 ±17	NS
Sexual activity *	69 ±22	65 ±22	NS

Abbreviations: EORTC QLQ-C30(+3) = European Organization for Research and Treatment of Cancer core quality-of-life questionnaire; EORTC QLQ-PR25 = EORTC prostate cancer module.
In RAND-36, a higher score reflects better health. In EORTC QLQ-C30(+3) and QLQ-PR25, a higher score reflects a high level of symptoms or functioning or quality of life; NS = not significant.
* Sexual activity scores were available for only 19 patients.

Discussion

In this study we evaluated the implant technique of fiducial gold markers from multiple perspectives; regarding procedure-related toxicity, influence on patient's QoL and practical feasibility specified as marker migration. We showed the feasibility of transperineal implantation of fiducial gold markers in the clinical practice of position verification. The procedure has no relevant influence on the patients' QoL and is not associated with major toxicity (no grade 3 or 4 toxicity). Regarding toxicity and the occurrence of marker migration, the transperineal implantation procedure is comparable with transrectal implantation, as presented in this study. Therefore transperineal implantation is a good and practical alternative for transrectal implantation, especially in clinics with experience in the field of transperineal procedures, for example, transperineal 125-I brachytherapy.

A literature search, concerning the use of fiducial markers in the prostate, was performed in PubMed. The majority of the resulting articles describe the effects of using fiducial markers for position verification on treatment accuracy, in prostate cancer external beam radiotherapy. Only one study, that includes results from 12 patients, describes the pain and toxicity of marker implantation via a transperineal route (17). Equal to the results from our study, transperineal implantation was found to be an acceptable intervention, associated with only minor complications. Two articles in literature describe the toxicity and feasibility of transrectal marker implantation (10;15). From our clinic, Dehnad et al. observed no grade 3 or 4 toxicity in 10 patients after transrectal implantation, and the amount of marker migration and prostate deformation was measured to be far below tumour delineation accuracy (10). This group of patients is included in our current study population. Langenhuijsen et al. evaluated toxicity in 209 patients receiving transrectal markers under prophylactic antibiotics. In this large population, 6.2% of the patients suffered from pain and fever (grade 2 toxicity), 1.9% of the patients suffered from minor voiding complaints and hematuria (> 3 days), hematospermia and rectal bleeding was presented by 3.8%, 18.5% and 9.1% of the patients, respectively (all grade 1 or grade 2 toxicity.) Advanced tumour stage, younger age and shorter duration of hormonal therapy were found to be risk factors for the observed complications (15). Comparison with our study populations is hampered by differences in study design, however, clinically relevant complications occurred in none of the patients evaluated by Langenhuijsen et al. and in none of the patients from our study treated with transperineal implantation. In our transrectal group, urosepsis (grade 3) occurred in two patients. Therefore, we can conclude that severe toxicity is very rare after fiducial marker implantation, for both the pure gold markers and the gold markers with a 0.3mm steel core. In the literature, the risk of infections is considered higher after transrectal implantation

compared to transperineal implantation, but there is a lack of evidence supporting this theory. There is, however, literature that compares the complications after transrectal prostate biopsy with the complications after transperineal biopsy. No difference in complications rate was found in a study by Hara et al., though, both groups had received prophylactic antibiotics (18). Because in our population no severe complications have occurred since transperineal implantation is performed, the routine prescription of prophylactic antibiotics has ended in our clinic since several months. And so far, no infections have occurred. Regarding anticoagulants use, we do not advise discontinuation of anticoagulant therapy to our patients because the risk of bleeding is considered inferior to the impact of possible blood clot formation. This is a justifiable point of view, since no severe bleedings have occurred in the past years.

At present, this study describes the largest population in the literature of patients receiving fiducial gold markers. The influence on QoL was never investigated before. A limitation is, however, that the QoL questionnaires that were used in this study are not designed to evaluate the short-term influence of particular interventions. Nevertheless, we considered it to be the best available method for this purpose. The results from the QoL analysis showed no clinically relevant changes in QoL due to marker implantation. This result corresponds with our hypothesis that marker implantations, both transrectal and transperineal, are minor interventions and acceptable methods in the patients work-up for radiotherapy. The QoL scores from our population, both before and after marker implantation, are similar compared to data we previously reported in the literature, measured in a comparable study population before the start of radiotherapy (5).

In the current study, loss of implanted markers or substantial migration occurred in only a minor proportion of our population. In these cases the IMRT plans were replaced by conformal treatment plans without marker-based position verification. Currently these kind of patients are treated with IMRT and position verification using cone beam CT (19). Multiple papers in the literature report the technical results of marker- based position verification, in particular data on intra- and inter-fraction motion and positioning accuracy (1;4). Migration of the implanted markers, however, is not often described. In five articles, which reported the incidence of marker migration (8-10;20;21), no substantial marker migration was found. One study found movements between markers of more than 2 mm in 10% of 30 patients (2). However, the study populations of these earlier studies were small (maximum 30 patients), and it is likely that the sample sizes were insufficient, taking into account the low incidence of migration that was found in our large population. Nonetheless, it is clear from the current study that marker migration is a rare incident during the treatment series. Last, we must add that next to marker migration, the practical feasibility of marker-based

position verification is also influenced by other factors, such as the visibility of markers on CT and MRI and inter-observer variability in marking the marker positions. These factors have been investigated and will be further discussed by Bol et al. (submitted for publication).

Conclusion

The clinical use of transperineal implanted fiducial gold markers for position verification in external beam radiotherapy for prostate cancer is a feasible and safe procedure without influencing patients' QoL. The use of fiducial markers can therefore be generally incorporated in radiotherapy practice, in order to facilitate marker-based position verification to improve the outcome from treatment in prostate cancer patients.

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Phys Med Biol 2010;55(5):N133-40.

6 | Chapter six

MRI-guided robotic system for transperineal prostate interventions: proof of principle

Abstract

Purpose

In this study, we demonstrate the proof of principle of the University Medical Center Utrecht (UMCU) robot dedicated for Magnetic Resonance Imaging (MRI)-guided interventions in patients.

Methods and Materials

The UMCU robot consists of polymers and non-ferromagnetic materials. For transperineal prostate interventions, it can be placed between patient's legs inside a closed bore 1.5T MR scanner. The robot can manually be translated and rotated resulting in five degrees of freedom. It contains a pneumatically driven tapping device to automatically insert a needle stepwise into the prostate using a controller unit outside the scanning room. To define the target positions and to verify the needle insertion point and the needle trajectory, a high resolution 3D balanced Steady State Free Precession (bSSFP) scan that provides a T2/T1-weighted contrast is acquired. During the needle insertion fast 2D bSSFP images are generated to track the needle on-line. When the target position is reached, the radiation oncologist manually places a fiducial gold marker (small seed) at this location. In total two needle trajectories are used to place all markers. Afterwards, a high resolution 3D bSSFP scan is acquired to visualize the fiducial gold markers.

Results

Four fiducial gold markers were placed transperineally into the prostate of a patient with a clinical stage T3 prostate cancer. In the generated scans, it was possible to discriminate the patient's anatomy, the needle and the markers. All markers were delivered inside the prostate. The procedure time was 1.5 hours.

Conclusion

This study proves that MRI-guided needle placement and seed delivery in the prostate with the UMCU robot are feasible.

Introduction

In the diagnostic and treatment procedures in prostate cancer as biopsies and brachytherapy, Magnetic Resonance Imaging (MRI) offers superior soft tissue contrast and consequently improved lesion detection (1). Therefore, MR-compatible robotic systems allowing real on-line MRI-guidance would be extremely valuable with these procedures (2-6).
Technical difficulties, like the restriction of using solely non-ferromagnetic materials, the limited space within the MR bore (2;7), the needle induced prostate rotation and deformation (8;9), the needle induced susceptibility imaging artefacts (10) and the RF heating of the needles and catheters (11;12) make robotic MRI guidance a hard task.
We worked for several years on the development of an MR-compatible robotic system which is able to solve the above mentioned problems and allows reliable on-line MRI-guidance (2;7-9;12). In this study we describe our first clinical experiences of this University Medical Center Utrecht (UMCU) robot dedicated for MRI-guided interventions in patients, as a proof of principle.

Methods and Materials

In this institutional review board approved study, we deliver fiducial gold markers (small seeds) inside prostates of patients eligible for external beam radiotherapy treatment (EBRT) using our MRI-guided robot. The markers will be used for the position verification of the prostate during EBRT (13).
Since the marker placement accuracy criteria are soft (target volume is the whole prostate gland), the MRI-guided implantation of these markers is ideal for in-vivo investigation of: the performance of the robot in a 1.5T magnetic field, the ability to track the needle during insertion with fast MR images, and the ability to place a small seed in the prostate.
Main characteristics of the first patient included in this study are: clinical tumour stage T3, age 76 years, body weight 84 kg, length 1.76 m, BMI 27 kg/m^2, prostate volume 75 cc.

Procedure

In accordance with the current manual ultrasound (US)-guided transperineal implantation technique, four gold markers (length 5 mm, outer diameter 1 mm) with an iron inner core (length 5 mm, diameter 0.1 mm) were placed with the UMCU robot transperineally inside the prostate using two parallel needle trajectories.
The patient was placed in supine position on the MR table with legs spread within the MR bore to provide space for the robot as shown in *Figure 6.1*.

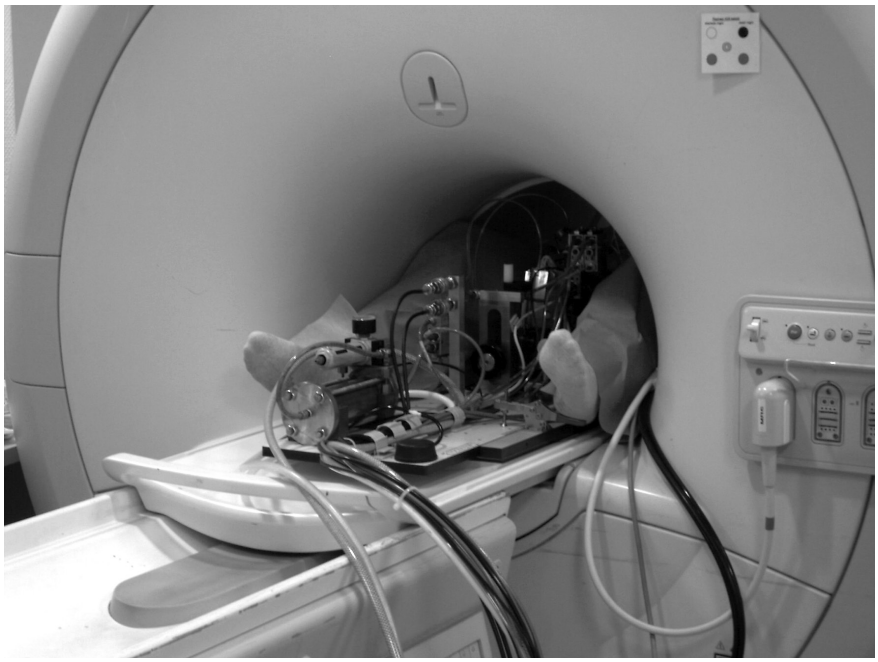

Figure 6.1 Illustration of experimental set-up. The robot was positioned between the legs of the patient.

For anaesthesia, lidocaine was injected in the perineal area prior to the procedure.
The needle insertion points at the perineum were determined by the radiation oncologist, each point about 1 cm lateral from the midplane. The needle was pushed manually just beneath the patient's skin through one of the insertion points. A high resolution 3D MR scan (see paragraph '*Imaging*' for more scan details) was acquired to check whether the prostate was freely accessible following the needle trajectory and to define a target position.
After image inspection, the robot tapped the needle stepwise towards this position while controlling the step size (typically 5 mm) and the needle depth. During the tapping fast 2D MR scans were acquired to track the needle trajectory on-line and to independently monitor the needle depth.
When the target position was reached the radiation oncologist manually placed a gold marker through the needle at this location. Then, the needle was tapped backwards to the second target position located on the same needle trajectory and the second marker was delivered. Next, the needle was tapped out of the patient and a second 3D MR scan generated to visualize the gold markers. This process was repeated for the second needle.

After the procedure, the patient was asked to define the pain score on the visual analogue scale (range 0-10, where 0 and 10 represent no pain and severe pain, respectively).

Robot

The robot consists of polymers and non-ferromagnetic materials as brass, copper, titanium and aluminium, and is pneumatically and hydraulically driven (*Figure 6.2*). The robot fits inside a closed 1.5T MR scanner (Achieva, Philips Healthcare, Best, the Netherlands) and can generally be placed between the legs of a patient with a body mass index (BMI) of <30 kg/m^2 (*Figure 6.1*). The robot is fixated on a wooden plateau that can be slid over the MR table. A clamp is used to hold this plateau at a chosen position (*see Figure 6.1*).

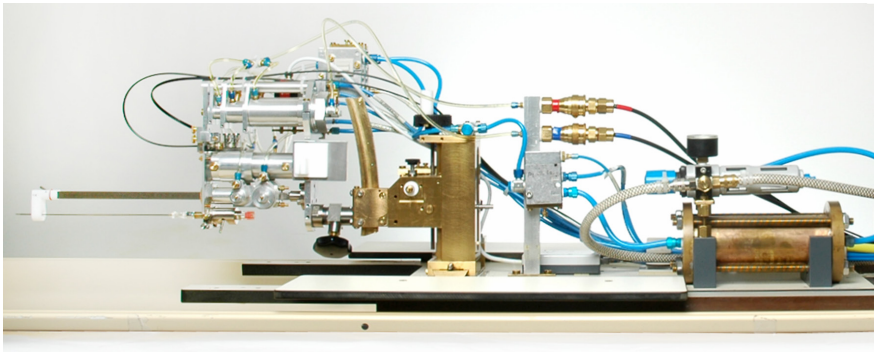

Figure 6.2 Picture of the UMCU robot that was used for the MRI-guided fiducial gold marker implantation.

The robot contains a tapping device to pneumatically tap a titanium needle including stylet (length 20 cm, outer diameter 1.65 mm) stepwise into the patient. Stepwise tapping has two major advantages: due to the high needle insertion speed tissue deformation will be reduced (8;9), and the needle trajectory can be controlled and modified in the time breaks between the steps. The tapping device produces a momentum of approximately 0.6 Ns. The maximum insertion depth of the needle per tap, the so-called stepsize, is adjustable using a buffer stop set by a hydraulic cylinder. Stepsize is measured by a potentiometer and the accuracy is <1 mm.
Both the tapping device and bufferstop can be controlled outside the scanning room using a controller unit, enabling the radiation oncologist to monitor the needle insertion on the MR scans in the operating room.

The tapping part can be manually rotated and translated offering five degrees of freedom. In this way, the entire prostate gland can be reached (2). In this study, however, only needle trajectories parallel to the MR bore were chosen.

Imaging

Since the needle should not penetrate critical structures as the rectum and pubic arch, and the markers have to be delivered inside the prostate gland, the MR images should not only visualize the needle and markers, but also patient's anatomy. For the implantation of the markers, a clear distinction of the prostatic border rather than the tumour is important. Furthermore the field of view (FOV) of the MR scans should be large to cover both the insertion point and prostate, while the acquisition time ought to be short to allow frequent image acquisitions. We applied balanced Steady State Free Precession (bSSFP) sequences to generate the desired images. These scans provide a T2/T1-weigthed contrast (14).
For the high resolution 3D bSSFP scan we used the following scan protocol: repetition time (TR)=6.4 ms, echo time (TE)=3.2 ms, acquisition time (T_{acq})=261 s, flip angle=50°, read-out bandwidth (BW_{read})=781.3 Hz/voxel, FOV(FH/AP/RL)=340x271x100 mm^3, acquisition voxel(FH/AP/RL)=1.3x1.0x2.0 mm^3, overcontiguous slices=yes, number of samples averages (NSA)=6.
The following scan protocol was applied to generate dynamic 2D bSSFP scans: TR=5.7 ms, TE=2.8 ms, T_{acq}=5.2 s, flip angle=45°, BW_{read}=256.6 Hz/voxel, FOV=300x300 mm^2, acquisition voxel=1.3x1.3x10.0 mm^3, number of slices=2 , NSA=2. These scans were planned in less than a minute to acquire images in two orthogonal planes (coronal and sagittal) with the insertion line of the planes on the needle trajectory. The position of the first 2D plane was set on the already acquired 3D bSSFP scan, while the location of the second orthogonal 2D plane was planned using the first generated 2D scan.

Results

Needle insertion was monitored on dynamic MR imaging in two planes. *Figure 6.3* shows several dynamic scans that were generated at different time points during needle insertion. Anatomical structures as prostate, rectum and bladder are clearly visible. Furthermore the needle can be distinguished due to a susceptibility artefact. The tip is better visible than the shaft. This figure also illustrates that some prostate deformation still occurs during the needle insertion. The displacement of the prostate base in *Figure 6.3e* (needle in prostate) with respect to *Figure 6.3a* (before prostate insertion) was 7 mm.

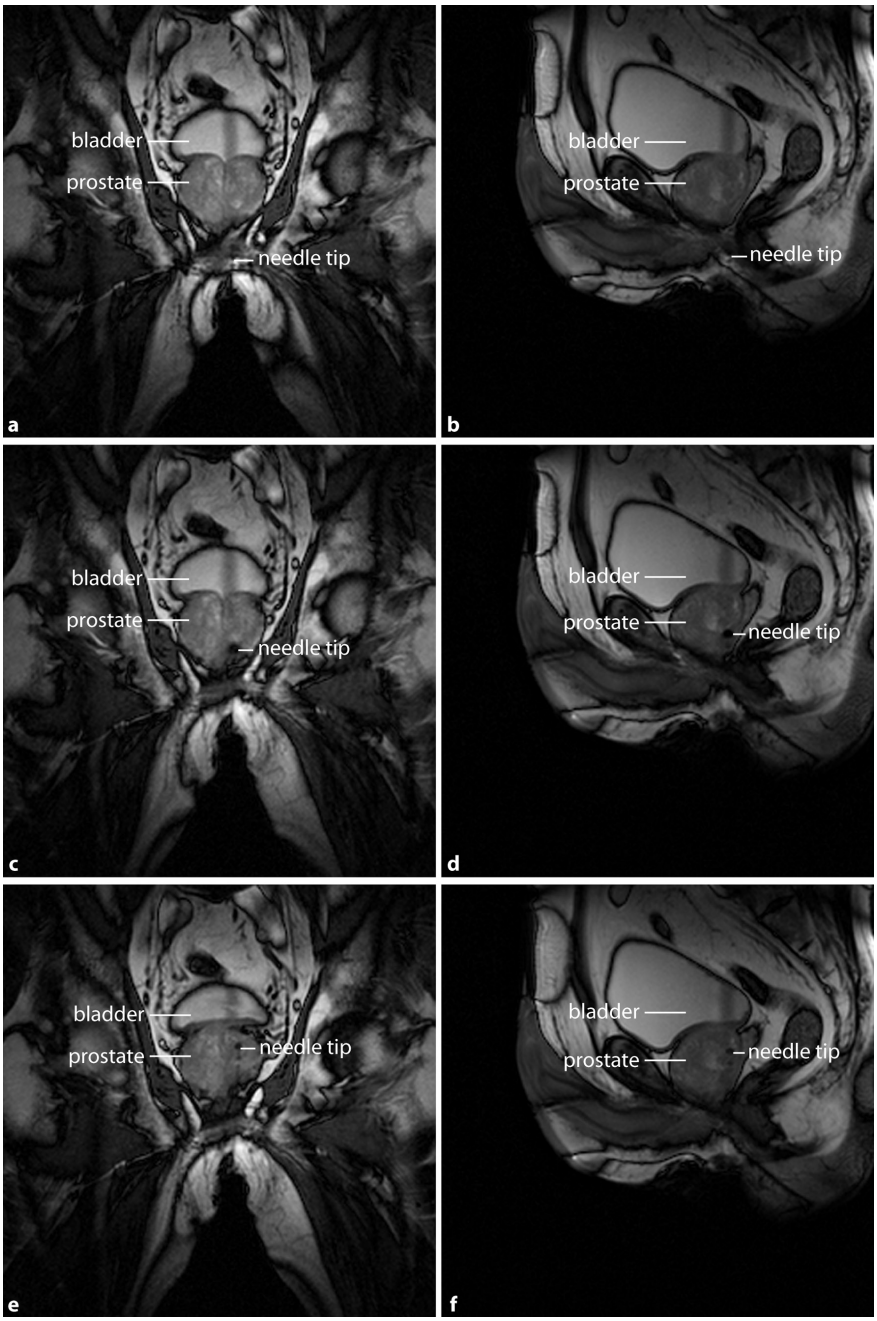

Figure 6.3 Coronal (a, c, e) and sagittal planes (b, d, f) of the needle and the prostate at three different time points.

In *Figure 6.4a* one of the acquired 3D bSFFP images is shown. This scan was generated after the insertion of the first needle just beneath the skin to control the intended needle trajectory. The needle artefact and patients anatomical structures are well definable. Small image artefacts due to the needle guide of the robot are visible. In *Figure 6.4b* another 3D bSFFP scan is shown, which was acquired at the end of the procedure. The gold markers induce a susceptibility artefact in the image, which makes it possible to localize them.
The robot was able to tap the needle stepwise into the prostate with a stepsize ranging from 2 to 8 mm. All markers were delivered inside the prostate. The procedure time was 1.5 hours. Pain score on the visual analogue scale was 2.5 points.

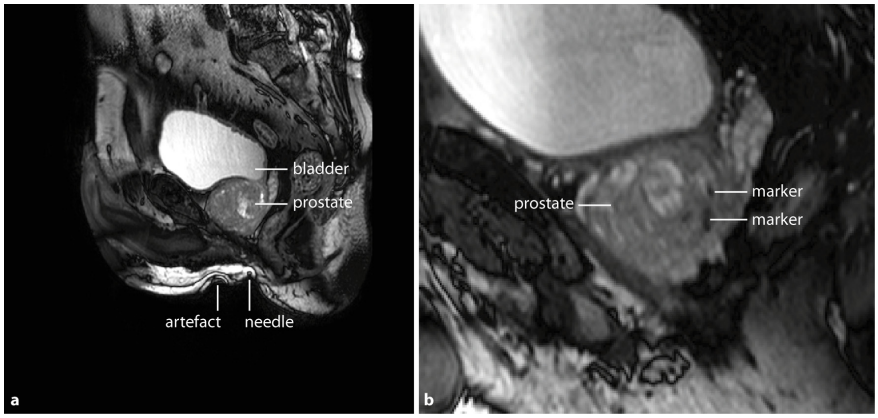

Figure 6.4 (a) 3D bSSFP scan after the insertion of the first needle to control intended needle trajectory, (b) 3D bSSFP at the end of the procedure.

Discussion

This study reveals that MRI-guided interventions are possible using the UMCU robot. The robot was able to tap the needle stepwise into the prostate during acquisition of fast dynamic 2D bSSFP scans to track the needle on-line. In only 5 seconds two images of orthogonal slices were obtained that visualized both the patient's anatomy and the needle, as shown in *Figure 6.3*.
Since the susceptibility artefact around a titanium needle parallel to the static magnetic field is confined to the tip, the needle tip is better visible than the shaft in *Figure 6.3*. From simulations and experiments we know that the real needle tip is approximately 5 mm proximal from the outer edge of the artefact using the bSSFP sequences of this study at 1.5T (10). The shaft of the needle can also be distinguished

in these images, mainly due to a signal void, and may become more prominent when the slice thickness is reduced. In the same figure a prostate deformation up to 7 mm was measured, which suggests to further increase the needle insertion speed (8;9).
The robot was MR-compatible, because no forces were measured when sliding the robot into the MR scanner. Nevertheless, the robot causes some image artefacts (see *Figure 6.4*). These artefacts are due to the susceptibility differences between the robot materials and human tissue and indicate the presence of local magnetic field distortions (10;14). These magnetic field distortions will lead to geometric image distortions (15), which are confined to the region around the robot and minimized by the use of large read-out gradients, so that they are negligible near the target position.
The patient was comfortable with the procedure. He was not deterred by the movements of the robot or the noise of the MR scanner.
For this first patient the procedure time was 1.5 hours. We aim to reduce the procedure time to about 45 minutes by speeding up the manual procedure steps as well as the imaging acquisitions. This might allow the acquisition of more (3D) MR images to investigate the marker placement accuracy under in-vivo conditions. Up until now we have concentrated on needle tracking and needle insertion accuracy.
In the future, we want to test the procedure for angular needle insertion and develop software to automatically track the tip of the needle and target position. This software may be used to further automate the procedure. Furthermore, we want to use the UMCU robot for MRI-guided diagnostic and treatment procedures such as biopsies and brachytherapy in the prostate. For these purposes, we would like to combine (or replace) our fast bSSFP scans with MR scans optimized for tumour visualisation.
Because of its unique way of needle insertion (tapping rather than pushing), which minimizes tissue deformation, the UMCU robot may also be useful for diagnostic and treatment procedures at other sites, where tissue deformation due to needle insertion is problematic, like breast.

Conclusion

This study shows that it is feasible to place fiducial gold markers in the prostate under MRI-guidance using the UMCU robot. The possibility to tap a needle and to deliver seeds in the prostate under MRI-guidance with our robot is a major step towards MRI-guided prostate brachytherapy and biopsies. It proves that in-vivo MRI-guided robotic interventions are possible.

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7 | Chapter seven

Acute toxicity of DCE-MRI based focal salvage in recurrent prostate cancer by 125-I brachytherapy

first results

Abstract

Purpose

Current salvage therapies consist of treating the entire prostate, as the exact location of the recurrent tumour is uncertain. Salvage is associated with high severe toxicity rates and is therefore not generally recommended. The use of Dynamic Contrast Enhanced (DCE-)MRI in patients with local recurrent prostate cancer provides the possibility of focal salvage as it shows the location of the tumour. This study presents the first acute toxicity data on focal salvage by iodine-125 (125-I) brachytherapy.

Methods and Materials

Seven patients with pathology proven local recurrent prostate cancer after radiotherapy were treated with focal salvage 125-I brachytherapy. The recurrent tumour (the gross tumour volume, GTV) was defined based on pre-operative T2-weighted and DCE-MRI in combination with results from systematic 10-core prostate biopsy. The goal was to deliver 145 Gy to the GTV while maintaining the dose limitations for organs at risk, as described by the ESTRO/EAU/EORTC guidelines. Acute toxicity was scored by the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). We consider the absence of any toxicity > grade 2 as clinically safe.

Results

In 5 patients, 100% of the GTV could be covered with the prescribed dose (145 Gy.) In 2 patients, 98% of the GTV was covered with the prescribed dose. The dose to the rectum was acceptable in all patients (median D2cc 56 Gy (range 18 – 84), D0.1cc 97 Gy (range 70 – 197).) The dose to the bladder was also acceptable (median D2cc 31 Gy (range 21 – 51) and D0.1cc 149 Gy (range 93 – 244)), except for the D0.1cc in one patient. Concerning the urethra, the median D10 was 126 Gy (range 99 – 239) and the D10 exceeded the defined limit in 2 patients. No severe toxicity (grade 3 of 4) occurred after treatment in any of the patients in the acute phase. Prostate specific antigen (PSA) declined after treatment in all patients.

Conclusion

Preliminary results show that focal salvage 125-I brachytherapy is not associated with acute severe toxicity.

Introduction

Patients that are treated with radiotherapy for primary prostate cancer are at risk of developing recurrent disease. There are no exact numbers available, but individual risks depend on well-known risk factors like tumour stage and tumour differentiation grade. For the highest risk groups, this risk can exceed 50% (1-4). The reason for not knowing the exact number is the relative absence of imaging modalities to determine the presence and location of a recurrent tumour. As a consequence, local recurrences are often missed when random prostate biopsies are performed in patients with biochemical failure after radiotherapy, or biopsies are not performed at all.
Current treatment possibilities for recurrent prostate cancer are local salvage therapies (of the whole prostate) with curative intent or the use of androgen deprivation therapy, a palliative treatment. The most common salvage techniques are salvage prostatectomy, cryosurgery and brachytherapy (high dose rate brachytherapy (HDR) or iodine-125 (125-I) brachytherapy) (5). Studies on the clinical outcome after salvage therapy show high failure rates and high toxicity rates, and the superiority of any of these salvage treatment modalities has not been shown (6;7). Moreover, to our knowledge, no literature exists that proves an increase in survival in patients with recurrent prostate cancer after radiotherapy with the use of salvage therapy.
In a retrospective evaluation of patients treated with salvage 125-I brachytherapy in our clinic, the freedom of biochemical failure was 20% after 5 years follow-up (8). From this perspective, it is open to discussion whether the benefits of this treatment weigh against the disadvantages, in terms of toxicity and subsequent impact on quality of life (8;9).

Currently, Dynamic Contrast Enhanced (DCE-)MRI provides the possibility to localize recurrent tumours after primary radiotherapy (10-12). DCE-MRI is a functional imaging technique based on tissue vascularisation and vessel leakage, which are both increased in tumour angiogenesis. With the introduction of DCE-MRI in the follow-up practice, patients could be diagnosed with recurrent cancer in an earlier phase, at which point the recurrent tumour is still confined to the prostate gland. The subsequent change in treatment population could improve the chances of success of salvage therapy in general.
However, in addition to early diagnosis, DCE-MRI can also be used in treatment planning. Following the availability of DCE-based tumour localisation, we previously presented an alternative approach to conventional salvage brachytherapy; so-called 'focal' salvage brachytherapy (13). In focal salvage brachytherapy, the target area for treatment is reduced to only that specific location within the prostate gland where the tumour is regrowing. This is in contrast to conventional salvage brachytherapy, in which the total prostate gland is considered target area. In the earlier study, we

showed that by performing focal salvage brachytherapy, treatment related toxicity is expected to be reduced significantly in comparison with conventional salvage brachytherapy, through a decrease in radiation dose to the organs at risk surrounding the prostate gland.
The ultimate goal of focal salvage brachytherapy in combination with DCE-MRI, is to be able to offer a treatment with a minimal risk of toxicity, and subsequent minimal influence on quality of life, and simultaniously an increase in survival. As a first step, the goal of this study is to investigate acute toxicity after focal salvage 125-I brachytherapy.

Methods and Materials

Subjects

From March 2009 until June 2010, seven patients with pathology proven local recurrent prostate cancer after radiotherapy were treated with focal salvage 125-I brachytherapy in the University Medical Center Utrecht (UMCU). Patients were considered eligible for focal salvage if they had a minimal of follow-up of two years after primary external beam radiotherapy or brachytherapy. Local recurrent cancer had to be confirmed by systematic 10-core prostate biopsy, in which every biopsy core was labeled after its location. The tumour had to be unilateral with a volume of less than one half of the total prostate and patients with evidence of capsular extension on digital rectal examination, transrectal ultrasound (TRUS) and MRI were excluded. The pre-treatment prostate specific antigen (PSA) level had to be less than 15 ng/mL, and bone scan and pelvic CT or lymfadenectomie had to be negative for bone and lymph node metastasis. Additionally, all patients were screened for contra-indications for 3 Tesla MRI.

Treatment planning and procedure

For all included patients, an individual treatment planning was made. A pre-operative MRI exam was performed in all patients, including a T2-weighted sequence and DCE-MRI. The area of recurrent tumour within the prostate, from now on denoted as gross tumour volume (GTV), was defined based on a combination of the systematic biopsy results and MR images. On MRI, an area was considered tumour if a hypo-intense signal on T2 was present in combination with increased contrast enhancement on DCE-MRI (*Figure 7.1*). To be defined as GTV, this area had to be confirmed by localized biopsy. If MRI did not show a suspect area while biopsy was positive in that specific location, that area was included in the GTV.

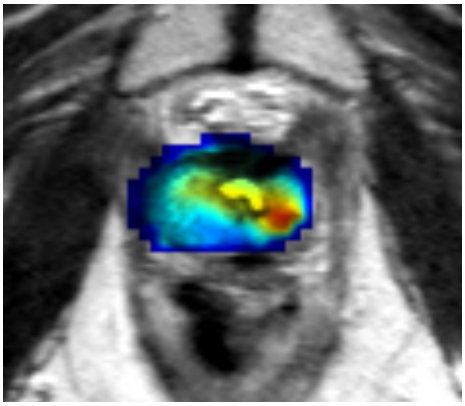

Figure 7.1 Transverse T2-weighted MR image of the prostate gland. A colourmap of the DCE-MRI parameter K^{trans} is laid over the anatomic image, and shows a focal area with increased contrast enhancement in the left peripheral zone.

The GTV, prostate gland, bladder and rectum were delineated on the T2-weighted MRI and subsequently copied to the brachytherapy planning software, Sonographic Planning of Oncology Treatment (SPOT, Nucletron BV, Veenendaal, the Netherlands). The pre-operative MRI and the delineations were intra-operatively matched with the real-time TRUS images obtained during the procedure. Contours were adapted to match the actual ultrasound image. During the procedures it was found that the prostate itself showed hardly any deformations, probably due to fibrosis after the primary treatment.

The implantation of 125-I seeds was performed via a transperineal approach, under TRUS guidance. All patients underwent general or spinal anesthesia. The brachytherapy needles were introduced into the prostate through a template that was situated on the TRUS probe, to cover the predefined GTV. This technique is principally equal to the conventional 125-I brachytherapy technique, that has previously been described (14). The number of needles and seeds for the patients in this study was adjusted to the volume of the GTV, as measured intra-operatively on the ultrasound images. Treatment margins where expanded up to a unilateral lobe, as far as such an expansion could be safely performed, to account for uncertainties in the definition and delineation of the GTV and the matching of the MRI and ultrasound images (*Figure 7.2*). The GTV was planned to receive 100% of the prescribed dose of 145 Gy. For the organs at risk (urethra, rectum and bladder) dosimetry was assessed according to the ESTRO/EAU/EORTC recommendations for 125-I brachytherapy (15). The goal, with respect to the organs at risk, was for the dose to be as low as possible. Following the ESTRO/EAU/EORTC recommendations, the D2cc of the rectum should be less than the prescribed dose to the GTV (145 Gy), and the D0.1cc (~D_{max}) less than 200 Gy (15). As no exact constraints are given for the bladder, the same constraints were applied as described for the rectum. For the urethra, the D10 should be less than 150% of the prescribed dose to the GTV (145 Gy) (15).

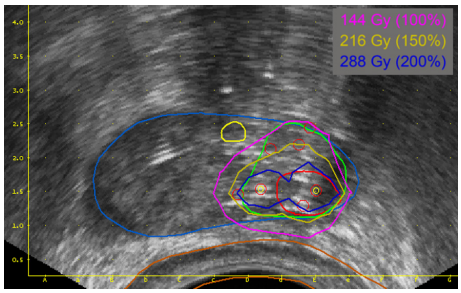

Figure 7.2 Transversal TRUS image of the prostate presented in Figure 7.1, showing the intra-operative dose distribution of the 125-I implantation.

Toxicity assessment

Genitourinary and gastrointestinal toxicity, including erectile dysfunction, was evaluated by means of the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) (16). Toxicity grading was performed by the treating physician, at 1, 6 and 12 months follow-up. The occurrence of any severe adverse events (grade 3 or higher as defined by the CTCAE) was considered undesirable. Furthermore, regular PSA measurements were performed during follow-up; at 1, 6 and 12 months. Patients were asked to fill in quality of life (QoL) questionnaires before and 1 and 6 months after salvage. The QoL questionnaire consisted of a combination of the Rand-36, the European Organization of Research and Treatment of Cancer core questionnaire (EORTC-C30 (+3)) and the prostate specific EORTC QLQ-PR25. However, because of the limited number of patients and limited follow-up, the QoL data will not be presented here.

Results

The age of the patients ranged between 66 and 75 years, and the time between primary and salvage treatment ranged between 4.0 and 8.3 years. The PSA before salvage ranged from 0.3 to 10.0 ng/mL. Further baseline characteristics of the study population are presented in *Table 7.1*.
Detailed dosimetric information for the GTV, prostate and organs at risk is presented in *Table 7.2*. In all patients, at least 98% of the GTV was covered with the prescribed dose. PSA levels declined from median (range) 3.7 (0.3 – 10.0) ng/mL before treatment to 2.1 (0.1 – 6.0 ng/mL) at the first follow-up visit, which took place approximately one month after treatment.

Table 7.1 Baseline characteristics of the study population (n=7).

Variable	
	Median (range)
Age, years	70 (66 – 75)
Time from primary treatment, months	75 (48 – 99)
Initial PSA, ng/mL	16.9 (5.4 – 39.5)
Nadir PSA, ng/ml	0.4 (0.2 – 2.2)
Pre-salvage PSA, ng/mL	3.7 (0.3 – 10.0)
PSADT pre-salvage, months	24 (8 – 90)
	n (%)
Initial tumour stage	
T1	0
T2	1 (14)
T3	6 (86)
Initial Gleason score	
Grade 4 - 6	4 (57)
Grade 7	1 (14)
Grade 8 – 10	2 (29)

Abbreviations: PSA = prostate specific antigen; PSADT = PSA doubling time.

Table 7.2 Dosimetry according to the intra-operative focal salvage brachytherapy plans.

Volume	**Variable**	**Median (range)**
Prostate	Volume, cc	24 (11 – 75)
	D90, Gy	25 (16 – 53)
	V100, %	41 (28 – 58)
GTV	Volume, cc	4 (1 – 13)
	D90, Gy	256 (181 – 185)
	V100, %	100 (98 – 100)
	V150, %	98 (78 – 100)
	V200, %	70 (47 – 90)
Urethra	D0.1cc, Gy	106 (89 – 201)
	D10, Gy	126 (99 – 239)
Bladder	D0.1cc, Gy	149 (93 – 244)
	D2cc, Gy	31 (21 – 51)
	D10, Gy	93 (77 – 121)
Rectum	D0.1cc, Gy	97 (70 – 197)
	D2cc, Gy	56 (18 – 84)
	D10, Gy	74 (57 – 100)

Abbreviations: GTV = gross tumour volume; Gy = Gray; D90 = dose in 90% of the volume; V100, 150 and 200 = volume receiving at least 100, 150 and 200% of the prescribed dose; D0.1 = dose in 0.1cc of the volume; D10 = dose in 10% of the volume; D2 = dose in 2cc of the volume.

Toxicity

The observed frequencies of genitourinary toxicity, gastrointestinal toxicity and erectile dysfunction are presented in *Table 7.3*. The median follow-up of the seven treated patients was 6 months, ranging from 2 to 16 months. Severe toxicity (grade 3 or 4) of the genitourinary and gastrointestinal tract was not observed in neither the acute nor the late phase. Grade 3 erectile dysfunction was observed in 3 patients, however, this had already been present before treatment. One of the patients died 9 months after treatment, which was not related to the prostate cancer or the given treatment.

Table 7.3 Observed frequencies of genitourinary and gastrointestinal toxicity and erectile dysfunction.

Toxicity	Pre-treatment (n = 7)	Acute phase* (n = 7)†	Late phase (n = 5)†
Genitourinary tract			
Grade 1	3	2	3
Grade 2	0	4	1
Grade 3	0	0	0
Grade 4	0	0	0
Gastrointestinal tract			
Grade 1	2	4	3
Grade 2	1	1	0
Grade 3	0	0	0
Grade 4	0	0	0
Erectile dysfunction			
Grade 1	0	1	1
Grade 2	2	2	0
Grade 3	3	3	2
Grade 4	0	0	0

* Acute phase is defined as <90 days post-treatment and late phase is >90 days post-treatment.
† For 1 patient, no information was available regarding erectile function after treatment.

Typical example

Figure 7.1 shows an example of an MRI image of one of the seven patients. The GTV in the left peripheral zone is clearly visible on this image, and the location within the prostate gland corresponded with the results of systematic prostate biopsy. *Figure 7.2* shows the intra-operative dose distribution of the 125-I implantation. The volume of the total prostate was 11 cc, and the volume of the GTV 1 cc. The D90 and V100 of

the GTV were 256 Gy and 100%, the D90 and V100 of the total prostate gland were 25 Gy and 41%. The D0.1cc and D10 of the urethra were 95 Gy and 111 Gy. The D0.1cc, D2cc and D10 of bladder and rectum were 146, 31 and 86 Gy, and 84, 56 and 74 Gy, respectively.

Discussion

This study describes the first results of focal salvage 125-I brachytherapy in patients with local recurrent prostate cancer after radiotherapy. The study focussed on patient safety, in terms of treatment related toxicity.
We showed that in these patients the GTV was covered completely with the prescribed dose of 145 Gy. The dose to the total prostate gland was considerably less than the dose to the GTV (D90 of median 25 Gy in the total prostate compared to 256 Gy for the GTV.) For the organs at risk, the dose to the rectum was within the earlier described limits. The D2cc of the bladder was within limits for all patients, however, the D0.1cc exceeded the limit of 200Gy in one patient (individual D0.1cc of 244 Gy.) In this particular patient the GTV was located close to the bladder base, which may have resulted in this peak dose, and GU toxicity grade 2 was seen in the acute and late phases. For the urethra, the D10 exceeded the defined limit (<150% of 145 Gy) in 2 patients (individual D10 of 160% and 165%.) This might be an indication that in focal salvage brachytherapy, the urethra is not an organ that can be spared easily.
Regarding the acute toxicity after treatment, no severe toxicity (grade 3) has occurred in the presented patients in the acute phase. Not all patients had sufficient follow-up for toxicity assessment in the late phase, however, in the patients that could be evaluated, no severe toxicity was present. The investigated population will be followed for the upcoming years, in which toxicity, clinical outcome (biochemical failure and survival) and QoL assessment will be continued.

Salvage is meant to improve survival after a prostate cancer recurrence, but in the absence of long term toxicity which can reduce QoL. As salvage to the entire prostate has a high chance of causing severe toxicity, it is not popular and large studies were not performed. The aim of focal salvage is to reduce the treatment area from the total prostate to only the focal area of recurrent tumour within the prostate. It can be expected that a focal treatment will reduce severe toxicity rates. No severe toxicity occurred in this study. If, after the inclusion of more patients, we can conclude that severe toxicity indeed seems to be significantly less in focal salvage, larger studies can be performed to investigate the influence on QoL and survival.

Focal salvage could, in theory, be performed by several treatment modalities. Salvage therapy aimed at a focal area within the prostate is only presented in one earlier study

in the literature. Eisenberg et al. (2008) performed partial salvage cryosurgery in 19 patients suffering from recurrent prostate cancer after radiotherapy. A biochemical recurrence-free survival rate of 50% after 3-years of follow-up was presented, with low treatment-related toxicity (17). Following the extensive experience of our institution, we chose to perform focal salvage therapy by 125-I implantation.

Multifocality of local recurrent prostate cancer might exist. For primary prostate cancer, it is known that 60 to 90% of the tumours grow multifocal within the prostate (18). For recurrent cancer after radiotherapy, exact numbers are unknown. It could be speculated that the frequency of multifocal cancer is far less than in primary prostate cancer, because the total prostate has been treated with a certain minimal treatment dose, and as not all tumours are equal in volume not all tumours will be equally likely to recur. Previous studies show that recurrent tumour tends to regrow at the site of the primary (largest) tumour (19;20). However, they do not show whether tumours also recur at other locations within the prostate.
If the recurrent focal tumour is treated curatively, it is possible that – in the case of multifocal primary cancer – a second recurrent tumour might occur in time. The advantage of focal salvage would then be, that the minimal treatment-related toxicity might allow a third, or maybe even a fourth focal treatment. However, this should be investigated in the future.

Compared to conventional salvage treatment, focal salvage is a less invasive treatment technique, as the number of needles, that is introduced into the prostate through the perineum, is only a fraction of the number of needles used in conventional salvage brachytherapy. The swelling that is caused by needle trauma is therefore expected to be less, which could favour the decrease in toxicity after focal salvage. A previous study from our clinic describes the toxicity and influence on QoL associated with TRUS-guided transperineal implantation of fiducial gold markers for position verification in external beam radiotherapy (21). No severe toxicity occurred in this population, and there was no influence on QoL. With some care, we could compare the focal salvage procedure with the implantation of fiducial markers, as both are TRUS-guided transperineal procedures using a limited number of needles. And, we might therefore argue that focal salvage could be performed under local anaesthesia in an outpatient setting, just as the implantation of fiducial markers. As the time of the focal salvage procedure is also less than in conventional salvage, focal salvage would then not only be less burden to patients but would also be more cost-effective. Of course, in the case of focal salvage, the effect of the radiation dose adds to the effects on the tissue caused by needle implantation.

Of course, an important limitation of the present study is the small number of patients and the limited follow-up time. In a study of 31 patients receiving conventional salvage

125-I brachytherapy (8), the frequency of grade 3 toxicity of the genitourinary and gastrointestinal tract was respectively 3.2% and 0% in the acute phase and 19.4% and 6.5% in the late phase. Thus far, the patients from the current study have not presented with severe toxicity. Focal salvage could be a promising new treatment approach in patients with recurrent prostate cancer after radiotherapy. It is, however, too early to draw a comparison between conventional and focal salvage, regarding toxicity rates, because more patients and longer follow-up are needed.

Further research must me conducted in this field. For the future, a randomized controlled trial would provide strong evidence of the benefits of focal salvage treatment versus no salvage at all, in terms of survival, treatment-related toxicity and quality of life.

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8 Chapter eight

General discussion

Prostate cancer is the most common type of cancer in men in the Western world (1;2). Next to surgery, radiotherapy (external beam radiotherapy or brachytherapy) is one of the main treatment options for prostate cancer patients. In the University Medical Center Utrecht alone, each year, approximately 400 prostate cancer patients are treated with curative intent. Patients treated for prostate cancer are at risk of developing recurrent disease. This risk depends on several risk factors like tumour stage and tumour differentiation grade, and can be more than 50% for the highest risk categories (3-5). If recurrent cancer is diagnosed, which can be quite difficult as described in the introduction, there are two main treatment options: conventional, total salvage therapy with curative intent or palliative hormonal treatment. The latter will control disease progression temporarily, but will eventually lead to disseminated disease and death from prostate cancer.

Commonly performed total salvage methods are salvage prostatectomy, salvage cryosurgery and salvage brachytherapy (HDR or 125-I brachytherapy). In *Chapter 2* of this thesis we showed that salvage 125-I brachytherapy is associated with high failure rates and the risk of serious toxicity. In a retrospective evaluation of this population in combination with a salvage cryosurgery population and a salvage prostatectomy population, we found similar results regarding failure rates and toxicity for the alternative treatment methods (unpublished data Moman MR, 2008). This corresponds with the literature, in which the superiority for one of the salvage techniques, with respect to failure rates and toxicity, has not been proven (6). Therefore, it can be concluded that improvement of the current salvage strategy is desirable.

In order to diminish the current toxicity rates after salvage, *'focal'* salvage therapy could be a possible solution. This treatment strategy is illustrated in a theoretical planning study in *Chapter 4* of this thesis, and the first clinical results are presented in *Chapter 7*. The hypothesis behind focal salvage is that, in contrast with primary prostate cancer, which is multifocal in 60 to 90% of the cases (7), recurrent prostate cancer may possibly be unifocal in many cases. To our knowledge there are no studies performed on the multifocality of recurrent prostate cancer. While the total prostate gland is primarily treated with a certain minimal high dose, it is not likely that all tumours will recur, let alone at the same time. Previous studies showed that tumours tend to regrow at the site of the primary tumour, which is considered to be the site with the highest tumour load (the index tumour) (8;9). However, they do not show whether tumours recur at other locations within the prostate.
In focal salvage therapy, a lower toxicity is expected because the treatment volume of the target is reduced, and consequently the dose to the surrounding organs at risk can be reduced (bladder, rectum and urethra). Focal salvage may therefore be a more acceptable treatment method compared to conventional total salvage. There

are, however, some important considerations to be made in the design of focal salvage, which are described in *Chapter 7*. The principal difficulty is that the exact pathologic mechanism behind salvage-related toxicity is unknown, and subsequently, it is unknown what dose constraints could be acceptable for the organs at risk, what treatment margins should be applied and what the minimum dose to the gross tumour volume (GTV) should be.

Early detection of recurrent prostate cancer in the follow-up after radiotherapy is essential for a chance on successful treatment. The current diagnosis begins with regularly performed PSA measurements. However, PSA has a high sensitivity, but a poor specificity for the diagnosis of local recurrences (10;11). In the case of biochemical failure, PSA measurements can therefore be followed by prostate biopsy. Depending on the biopsy technique, prostate biopsies do have a high specificity but, unfortunately, a limited sensitivity (12). Other diagnostic methods, like MRI and PET, are not, yet, generally used in this setting.

Literature has shown that DCE-MRI could be useful in the diagnosis of primary and recurrent prostate cancer (13;14). After irradiation, normal MRI is difficult to interpret because of tissue changes in the prostate, like fibrosis, which are not easily differentiated from malignant areas (15). The process of fibrosis after radiation could take months or even years. A possible hypothesis can be that the vascularisation of irradiated prostate tissue is decreased due to fibrosis. Local recurrent cancer will be characterized by increased vascularisation, and therefore the contrast between high and low perfused areas may be relatively high after irradiation in contrast to DCE-MRI in non-irradiated patients. The advantage of the design of the study presented in *Chapter 3* of this thesis is that the MRI of patients with recurrent cancer ('cases') are compared with patients without a recurrence ('controls'), and therefore 'natural' changes in contrast enhancement due to tissue fibrosis can be differentiated from changes due to recurrent disease.

The goal of the explorative study of *Chapter 3* was to investigate how DCE-MRI must be interpreted after radiotherapy. The results show that areas with elevated K^{trans} levels are present in both patients with and without prostate cancer. Almost without exception, the central area around the urethra shows elevated K^{trans} in cases and controls. Despite the similarities between patient with and without prostate cancer, *Chapter 3* describes some specific patterns that raise suspicion of recurrent cancer. The outcome of this study shows that DCE-MRI could be a promising tool for the detection of recurrences. However, the images and the data are not easy to read and DCE-MRI should for now be interpreted with care. The case-control study of *Chapter 3* will be extended in the future, to gather more information on this subject and to provide the possibility investigating specific subgroups, as is further described in detail in the discussion of *Chapter 3*. In addition, other diagnostic studies are needed to learn the

optimal way to handle DCE-MRI after radiotherapy and to define the real diagnostic value. A pathology study of salvage prostatectomy specimens after radiotherapy could for example provide more insight into the physiological mechanisms of irradiated prostate tissue, and its correlation with DCE-MRI. Furthermore, the combination of DCE-MRI with other functional MRI sequences may be valuable (16;17).
For now, if further treatment is desired, DCE-MRI could be used in the follow-up after radiotherapy in combination with PSA measurements and systematic prostate biopsy. In the subgroup of patients in whom the DCE-MRI shows a clear treatment target, DCE-MRI could be of use in the treatment planning of focal salvage, which is shown in *Chapter 4* and *Chapter 7*. Of course this should be combined with the results of systematic prostate biopsy, as this is still considered the ground truth for further treatment.

In order to achieve highly accurate focal salvage therapy and to be able to perform accurate biopsies of focal prostate lesions, it is recommendable to use MRI-guidance in the focal salvage treatment setting. To improve accuracy and efficiency even further, a robotic implant system in combination with MRI-guidance would give optimal results (18;19). This is as well required from a practical point of view, because of the limited space in the MRI bore. In the University Medical Center Utrecht an MRI compatible robotic implant system was developed for seed implantation into the prostate gland. The clinical introduction of this UMCU robot is described in *Chapter 6* of this thesis. For the first application, the implantation of fiducial markers was chosen instead of performing brachytherapy or biopsy because of practical reasons; most importantly, because the criteria for placement accuracy for markers are soft. Furthermore, the implantation of markers is a practical approach to test the clinical feasibility of MRI-guided robotic interventions in a relatively easy way in a large population.
The first MRI-guided robotic intervention was successful, with respect to technical and safety aspects, as presented in *Chapter 6*. However, several aspects require further attention. The total procedure of implanting 4 markers took approximately 1.5 hours. This needs to be shortened dramatically for the procedure to become clinically efficient and acceptable for the general patient, especially if the number of seeds is increased as is the case in brachytherapy. In addition, there are currently some manual steps in the total procedure, which are required to be automatic in an efficient procedure. Furthermore, for MRI-guided robotic brachytherapy and biopsy to become possible, more research must be performed regarding the accuracy of the UMCU robot. Thus, in the future more developments can be expected regarding the technical aspects of the robot and the total procedure.

In *Chapter* 5 of this thesis the results of manual TRUS-guided transperineal implantation of fiducial gold markers are described, which show that manual transperineal implantation is a feasible and safe procedure. This group can serve as a comparison for the feasibility and safety of MRI-guided robotic transperineal implantation of markers. Of course, actual comparison of robotic transperineal implantation of markers with this conventional method is not possible yet. We will continue to perform implantations using the UMCU robot, and the performance will be evaluated and compared when a sufficient number of patients have undergone the MRI-guided procedure.
The results from *Chapter* 5 are also important in the focal salvage setting because focal salvage is also a transperineal intervention using a limited number of needles, just like the manual transperineal implantation of markers. The conclusion regarding safety and influence on quality of life by the intervention itself might be, with some care, extrapolated to focal salvage brachytherapy.

Recently we have started to treat the first patients with focal salvage 125-I brachytherapy. The results from this small group are presented in *Chapter 7* of this thesis. The preliminary results regarding feasibility and safety are promising, but longer follow-up and more patients are needed to provide real evidence for focal salvage 125-I brachytherapy to become an acceptable treatment alternative for patients with recurrent cancer. For the future, a randomized controlled trial with three arms would provide the ultimate evidence for the clinical value of focal salvage treatment (the three arms being 'no treatment' versus 'total salvage' versus 'focal salvage') The endpoints of such a trial should include technical aspects, clinical outcome, treatment-related toxicity and the influence on quality of life.

Conclusion

This thesis describes a variety of explorative studies, which are the first steps towards a new approach in the diagnosis and treatment of patient with recurrent prostate cancer after radiotherapy. We demonstrated that focal salvage 125-I brachytherapy can be associated with less treatment-related toxicity compared to conventional salvage. Furthermore, we showed that DCE-MRI can be used to differentiate between patients with and without recurrent prostate cancer. Last, we also presented the first successful steps in MRI-guided robotic prostate interventions using the UMCU robot. These three major branches within the presented research will be continued to be investigated in the University Medical Center Utrecht in the future. More experience and further development will lead to better evidence to support the clinical implementation of these techniques and for better perspectives for prostate cancer patients.

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9 | Chapter nine

Summary

The diagnosis and treatment of patients with recurrent prostate cancer after radiotherapy is problematic in current clinical practice. Diagnostic possibilities for the detection of recurrences are limited. A rising PSA in the blood is not specific, there is not much literature available regarding imaging tools and also prostate biopsies have limited sensitivity. Further, conventional salvage techniques for the treatment of recurrences are known to have low chances of success and high toxicity rates. In order to improve the diagnosis and treatment of prostate cancer recurrences, research investments are needed. The various studies published in this thesis all serve the main research objective of improving the diagnosis and treatment of prostate cancer recurrences. It was investigated whether dynamic contrast enhanced (DCE-) MRI could serve as a diagnostic aid in the early detection of prostate cancer recurrences. Furthermore, we investigated the theoretical possibility of a new salvage treatment strategy, 'focal salvage', and tested the feasibility of this treatment in clinical practice.

In *Chapter 2* of this thesis, the clinical results are described of conventional salvage 125-I brachytherapy, of the whole prostate gland. In correspondence with the available literature, low rates of success and high toxicity rates were seen in this population. Only 20% of the treated patients were free from biochemical recurrence (rising PSA in the blood) five years after treatment. Furthermore, grade 1, 2 or 3 toxicity of the genitourinary tract was reported in respectively 29%, 58% and 3% of the patients in the acute phase, and in 16%, 39% and 19% in the late phase. Grade 1, 2 or 3 toxicity of the gastro-intestinal tract was reported in respectively 45%, 10% and 0% of the patients in the acute phase, and in 48%, 3% and 6% in the late phase.

Chapter 3 of this thesis describes the results of an explorative study of the use of DCE-MRI to detect recurrent prostate cancer after radiotherapy. The goal of the study was to learn how to interpret this specific functional MRI sequence in patients that primarily have been treated with radiotherapy for prostate cancer. For this purpose the MRI exams of two patient groups were compared: patients with and without pathology proven recurrent prostate cancer in the follow-up after radiotherapy. The study demonstrates that DCE-MRI shows abnormalities in patients with recurrent prostate cancer, but also in patients without recurrent cancer. An important finding in this study is that the central portion of the prostate surrounding the urethra shows increased contrast enhancement in nearly all patients with and without a recurrence. However, there are some clear patterns that can be recognized in patients with a recurrence compared to patients without a recurrence. Foci with increased contrast enhancement outside this central portion of the gland raise the suspicion of recurrent cancer, especially if these foci show an asymmetrical distribution and are located in the peripheral zone. The combination of increased enhancement on DCE-MRI and decreased signal intensity on the conventional T2 weighted sequence also raises the suspicion of recurrent cancer.

Chapter 4 describes the results of a treatment planning study, of which the goal was to investigate whether it is possible to create a focal salvage brachytherapy treatment plan, based on DCE-MRI and T2-weighted MRI. The results of this study show that it is indeed possible to create a focal salvage treatment plan based on MR images. From the dose calculations concerning the organs at risk surrounding the prostate gland, it can be concluded that with focal therapy the expected toxicity is indeed less when compared with conventional salvage therapy.

Chapter 6 of this thesis describes the proof of principle and the first clinical results of the 'UMCU' robot, which is specifically designed for MRI-guided prostate interventions. It was shown that is it possible to use the UMCU robot for the implantation of small seeds under MRI-guidance, and that it is an acceptable procedure from the patients' perspective. As a comparison, the feasibility, toxicity and influence on quality of life (QoL) was investigated in a cohort of patients that received fiducial gold markers in the conventional way; manually under transrectal ultrasound guidance. The results from this study are presented in *Chapter 5*. Here, 402 patients are described that received markers via the transrectal route. Two of these patients developed urosepsis (grade 3 toxicity). Another 512 patients received markers via the transperineal route. No grade 3 or 4 toxicity occurred in this group. No significant and clinically relevant differences were found in QoL between pre- and post-implant measures. In conclusion, this study shows that clinical use of transperineal implanted fiducial gold markers for position verification in external beam radiotherapy for prostate cancer is a feasible and safe procedure without influencing patients' QoL.

In *Chapter 7*, the first results are described of a feasibility study of focal salvage 125-I brachytherapy. Based on several inclusion criteria, 7 patients with pathology proven recurrent cancer were considered appropriate candidates for focal salvage therapy, and were treated with 125-I brachytherapy aimed at the localized area of recurrent tumour within the prostate gland. The results of the study show that it is clinically feasible and safe to perform focal I-125 brachytherapy in patients with local recurrent prostate cancer. A high dose can be given to the treatment target, while sparing the remaining of the prostate gland and the rectum and bladder. No serious toxicity occurred after treatment, in any of the patients.

10 | Chapter ten

Nederlandse samenvatting

Dankwoord

Curriculum vitae

List of publications

‘Op weg naar focale salvage therapie voor prostaatkanker recidieven’

Introductie

Met een incidentie van 102 per 100 000 per jaar is prostaatkanker de meest voorkomende vorm van kanker bij mannen in Nederland. Zowel ten gevolge van het toenemende gebruik van het prostaat specifiek antigen (PSA) als bloedmarker om prostaatkanker op te sporen en door de vergrijzing, volgt deze incidentie een stijgende lijn. Er zijn verschillende behandelmethoden beschikbaar, waarvan radiotherapie een van de meest toegepaste is. Echter, patiënten die behandeld zijn door middel van radiotherapie hebben toch kans dat de tumor in de prostaat opnieuw gaat groeien; men spreekt dan van een recidief. Op den duur leidt dit in veel gevallen tot uitzaaiingen (metastasen) met vaak overlijden als gevolg. De kans op een recidief is afhankelijk van verschillende risicofactoren, zoals het initiële tumorstadium en de agressiviteit (differentiatiegraad) van de tumor (Gleason score). Bij patiënten met een lokaal recidief, zonder uitzaaiingen op afstand, is er nog een laatste genezende (curatieve) behandeling mogelijk; de salvage behandeling. Er bestaan verschillende salvage behandelingen. De meest toegepaste zijn chirurgische verwijdering van de prostaat (prostatectomie), bevriezing (cryochirurgie) of radiotherapie (meestal inwendige radiotherapie, ofwel brachytherapie). Ook hormonale therapie wordt vaak in dit rijtje genoemd, echter, dit is niet correct gezien hormonale therapie geen curatieve maar een palliatieve behandeling is.

Salvage is niet populair, en wordt dan ook maar aan een beperkt aantal van de patiënten met een recidief aangeboden. De reden hiervoor is dat, ongeacht welke salvage methode wordt toegepast, de kansen op succes (genezing) klein zijn en ernstige en blijvende bijwerkingen (toxiciteit) veel voorkomen. Artsen zijn daarom vaak van mening dat de voordelen (kans op genezing) van salvage niet opwegen tegen de nadelen (toxiciteit), en zodoende wordt over het algemeen afgezien van verder onderzoek om een lokaal recidief op te sporen. Indien salvage wel wordt overwogen, wordt vaak lang gewacht met een eventuele behandelbeslissing. Daardoor heeft het recidief dan vaak de mogelijkheid gehad zich lokaal verder uit te breiden of toch te leiden tot metastasen op afstand. Hierdoor is de kans op een succesvolle salvage behandeling nog kleiner.

In dit proefschrift wordt een oplossing geboden voor bovenstaand probleem. Aan de ene kant dient de vroege detectie van recidieven gestimuleerd te worden door de inzet van nieuwe, of bestaande, diagnostische middelen, zoals dynamisch contrast

versterkte (DCE-)MRI. Aan de andere kant is het nodig dat de bijwerkingen (toxiciteit) van salvage verminderd worden. Dit laatste is mogelijk door bij een salvage behandeling het doelgebied (het gebied dat behandeld wordt) te verkleinen naar alleen het focale gebied van tumor binnen de prostaat. Dit in tegenstelling tot de hele prostaat als doelgebied, zoals in de huidige situatie bij de conventionele salvagemethoden het geval is. Hierdoor kunnen omliggende organen gespaard worden tijdens de behandeling, wat een vermindering in de toxiciteit tot gevolg kan hebben. Door deze veranderingen in de diagnostiek en behandeling van prostaatkanker recidieven, zou het mogelijk moeten zijn om patiënten met een recidief vroegtijdig te diagnosticeren en te behandelen, op het moment dat het recidief nog klein is. Dit kan leiden tot een hoger succespercentage van salvage behandelingen. In combinatie met de verminderde toxiciteit van de focale salvage behandeling kan dit bijdragen aan betere behandelresultaten.

Samenvatting

Na de introductie in Hoofdstuk 1, worden in *Hoofdstuk 2* de klinische resultaten beschreven van de conventionele salvage behandeling door middel van jodium-125 (I-125) brachytherapie. De resultaten van deze studie laten zien dat slechts 20% van de patiënten die behandeld zijn met salvage I-125 brachytherapie na 5 jaar nog vrij is van een biochemisch recidief (stijging van de PSA waarde in het bloed). Verder bleek dat graad 1, 2 en 3 toxiciteit van de urinewegen en geslachtsorganen voorkomt bij respectievelijk 29%, 58% en 3% van de patiënten in de acute fase, en in 16%, 39% en 19% van de patiënten in de late fase. Graad 1,2 en 3 toxiciteit van de darmen werd gezien bij respectievelijk 45%, 10% en 0% van de patiënten in de acute fase, en bij 48%, 3% en 6% in de late fase. (Graad 3 toxiciteit betekent ernstige bijwerkingen.) De resultaten van deze studie sluiten aan bij eerdere literatuur, waaruit blijkt dat, onafhankelijk van het type salvage, de succeskans klein is en de toxiciteit hoog. In combinatie met deze informatie laat de in *Hoofdstuk 2* beschreven studie zien dat er ruimte is voor verbetering in de huidige salvage strategie.

Voor een succesvolle salvage behandeling is een vroege detectie van prostaatkanker recidieven na radiotherapie noodzakelijk, omdat bij een vroege detectie de kans groot is dat het recidief nog een beperkt volume heeft en zich niet tot buiten de prostaat heeft uitgebreid. In *Hoofdstuk 3* staan de resultaten beschreven van een exploratieve studie naar het gebruik van DCE-MRI voor het diagnosticeren van prostaatkanker recidieven. Het doel van deze studie was om te leren hoe deze MRI sequentie geïnterpreteerd dient te worden in patiënten die door middel van uitwendige radiotherapie of brachytherapie behandeld zijn voor prostaatkanker. Voor dit doel werden de MRI's van twee groepen patiënten met elkaar vergeleken: patiënten mét en patiënten

zonder een recidief in de follow-up na radiotherapie. Enkele eerdere studies hebben reeds laten zien dat DCE-MRI een aanvullende diagnostische waarde kan hebben in de diagnostiek van primair prostaatkanker, maar ook van prostaatkanker recidieven.
Als gevolg van radiotherapie treden veranderingen op van het prostaatweefsel, zoals fibrose. Dit proces kan maanden tot jaren in beslag nemen. Een mogelijke hypothese kan zijn dat de bloedvoorziening van bestraald prostaatweefsel afneemt ten gevolge van fibrose. Een lokaal recidief tumor wordt door vaatnieuwvorming gekenmerkt. DCE-MRI is in staat om de bloedvoorziening van weefsel te meten en het zou dus mogelijk moeten zijn om onderscheid te maken tussen fibrotisch en recidief prostaatweefsel.
Ten opzichte van eerdere studies is het voordeel van de opzet van de in *Hoofdstuk 3* gepresenteerde studie, dat de MRI's van patiënten met en zonder een recidief met elkaar worden vergeleken. Daardoor kunnen natuurlijke veranderingen in contrast aankleuring als gevolg van weefsel veranderingen over de tijd, onderscheiden worden van contrast veranderingen door recidief tumor.
Uit de studie blijkt dat DCE-MRI afwijkingen laat zien bij patiënten met een recidief, maar ook bij patiënten zonder een recidief. Een nauwkeurige beoordeling van elke DCE-MRI in de follow-up na bestraling is noodzakelijk, maar er zijn duidelijk andere patronen van contrast aankleuring herkenbaar bij patiënten met een recidief in vergelijking met patiënten zonder een recidief. Een belangrijke bevinding is dat de centrale prostaat rondom de urethra versterkte contrast aankleuring laat zien in bijna alle patiënten, met of zonder een recidief. Foci met versterkte aankleuring buiten dit gebied komen vaker voor bij patiënten met een recidief, en ook asymmetrie en foci in de perifere zone van de prostaat zijn aanwijzingen voor een recidief. Ook de combinatie van versterkte aankleuring op DCE-MRI met afwijkingen ter plaatse zoals gezien op beelden van de conventionele MRI instelling, lijkt een aanwijzing te zijn voor de aanwezigheid van een recidief.
Deze studie zal in de toekomst uitgebreid worden, zodat we nog nauwkeuriger de verschillen kunnen bekijken binnen specifieke subgroepen van patiënten. Verder zijn meer studies nodig om beter te begrijpen wat DCE-MRI na radiotherapie ons precies laat zien. Een pathologische studie van salvage prostatectomie weefsel zou bijvoorbeeld meer inzicht kunnen geven in de normale mechanismen van doorbloeding in bestraald prostaatweefsel en de exacte correlatie met DCE-MRI. Verder zou de combinatie van DCE-MRI met andere MRI modaliteiten waardevol kunnen zijn voor het opsporen van recidieven.
Voor de huidige praktijk leert deze studie ons dat DCE-MRI een veelbelovend diagnostisch middel kan zijn voor de opsporing van prostaatkanker recidieven. Echter, de beelden zijn niet gemakkelijk te interpreteren en dit dient met grote voorzichtigheid te geschieden. Bij patiënten met een verhoogd PSA na radiotherapie die eventueel in aanmerking zouden komen voor salvage, kan DCE-MRI aangeboden worden. Indien DCE-MRI dan een duidelijke behandelfocus laat zien, kan het gebruikt worden bij de

therapie planning, zoals beschreven in *Hoofdstuk 4* en *Hoofdstuk 7*. Uiteraard dient de MRI gecombineerd te worden met de resultaten van systematische prostaatbiopten, omdat dit nog altijd de basis vormt van de behandelindicatie.

MRI, en in het bijzonder functionele MRI instellingen zoals DCE-MRI, kan niet alleen bijdragen aan de detectie en lokalisatie van prostaatkanker recidieven maar kan ook als leidraad dienen voor de salvage behandeling. *Hoofdstuk 4* beschrijft de resultaten van een planningsstudie waarin is onderzocht of MRI gebruikt kan worden om het exacte doelgebied voor behandeling van het recidief binnen de prostaat te definiëren. Dit doelgebied zou dan 'focaal' behandeld kunnen worden, de zogenaamde focale salvage behandeling. Een ander doel van deze studie was om te onderzoeken of focale salvage op basis van MRI in theorie tot een afname van de stralingsdosis in risico organen kan leiden, vergeleken met de conventionele salvage behandeling van de totale prostaat.
De hypothese achter focale salvage is dat prostaatkanker recidieven wellicht vaker unifocaal voorkomen, terwijl primaire prostaatkanker in 60-90% van de gevallen multifocaal is. Zover bij ons bekend, zijn er geen studies gedaan naar de multifocaliteit van prostaatkanker recidieven. Echter, aangezien de totale prostaat primair behandeld is met een minimale stralingsdosis is het niet waarschijnlijk dat alle tumoren, met verschillende volumina, allemaal en allemaal tegelijk recidiveren. Eerder onderzoek heeft wel laten zien dat prostaattumoren vaak terugkomen op de locatie van de primair dominante (grootste) tumor, maar laat niet zien hoe de situatie is in de rest van de prostaat.
De resultaten van de studie uit *Hoofdstuk 4* laten zien dat het inderdaad mogelijk is om op basis van MRI beelden een planning te maken voor focale salvage brachytherapie, en uit dosis berekeningen blijkt dat risico organen rondom de prostaat minder dosis krijgen dan bij conventionele salvage therapie. Op basis van deze gegevens verwachten we met focale salvage minder toxiciteit, gerelateerd aan de behandeling, dan bij de conventionele salvage therapie van de totale prostaat.

Om focale salvage op een nauwkeurige manier uit te kunnen voeren, is het aan te bevelen om bij de behandeling MRI te gebruiken als leidraad. Door middel van MRI is het mogelijk om het doelgebied, en de risico-organen rondom de prostaat, met meer detail in beeld te brengen dan met de huidig gebruikte transrectale echo (TRUS). Omdat de ruimte in een MRI beperkt is, en daardoor het tegelijkertijd sturen van de naald en kijken naar de beelden niet gemakkelijk is, zou een speciaal ontwikkelde robot voor prostaat interventies bij MRI geleide procedures uitkomst kunnen bieden. Het gebruik van een robot zou tevens kunnen bijdragen aan de nauwkeurigheid van de procedure. Een MRI geleide robot voor prostaat interventies kan niet alleen gebruikt worden voor de implantatie van brachytherapie bronnen, maar ook voor alternatieve procedures zoals het verrichten van prostaatbiopten. Dit laatste is tevens zeer

wenselijk in de setting van focale salvage. In het UMC Utrecht is een MRI compatibele implantatie robot ontwikkeld voor de implantatie van zaadjes in de prostaat. *Hoofdstuk 6* van dit proefschrift beschrijft de 'proof of principle' en de eerste klinische resultaten van deze UMCU robot. Voor de klinische introductie is de robot gebruikt voor de implantatie van goudmarkers, die gebruikt worden voor positie verificatie bij uitwendige radiotherapie. De resultaten van deze eerste procedure laten zien dat het mogelijk is om de UMCU robot, onder MRI geleide, te gebruiken voor de implantatie van goudmarkers in de prostaat, en dat het tevens een acceptabele procedure is vanuit het perspectief van de patiënt. Als vergelijking werd de toepasbaarheid, toxiciteit en invloed op kwaliteit van leven onderzocht in een groep patiënten die goudmarkers geïmplanteerd hebben gekregen op de normale, handmatige, manier, onder geleide van TRUS. Deze resultaten worden gepresenteerd in *Hoofdstuk 5*.
In deze studie worden 402 patiënten beschreven die transrectaal markers geimplanteerd hebben gekregen. Twee van deze patiënten ontwikkelden een urosepsis (graad 3 toxiciteit.) Verder kregen 512 patiënten transperineaal goudmarkers geïmplanteerd, en in deze groep trad geen graad 3 of 4 toxiciteit op. Er waren geen significante en klinisch relevante verschillen aantoonbaar in kwaliteit van leven tussen metingen voor en na de transperineale implantaties. In het kort laat deze studie zien dat de transperineale implantatie van goudmarkers een veilige procedure is zonder invloed op de kwaliteit van leven van de patiënt. Uiteraard is een echte vergelijking tussen de robot gestuurde transperineale implantatie van markers met de conventionele methode nog niet mogelijk. De implantaties met behulp van de UMCU robot zullen voortgezet worden, en de werking zal uiteindelijk geëvalueerd en vergeleken worden als een voldoende aantal patiënten de MRI geleide procedure heeft ondergaan.
De resultaten van de studie beschreven in *Hoofdstuk 5* zijn ook van belang voor focale salvage brachytherapie. De transperineale introductie van enkele naalden in de prostaat blijkt een veilige en een voor de patiënt acceptabele procedure te zijn. Met enige voorzichtigheid kan dit resultaat worden getransleerd naar focale salvage brachytherapie, omdat hier tevens sprake is van de transperineale introductie van enkele naalden in de prostaat. Salvage brachytherapie van de totale prostaat is tot nu toe een klinische procedure onder algehele of spinale anesthesie. Het is niet ondenkbaar dat we met de minder belastende focale salvage brachytherapie naar een poliklinische procedure kunnen toewerken, in overeenstemming met met de huidige goudmarker implantaties.

In *Hoofdstuk 7* worden de eerste resultaten beschreven van focale salvage in de praktijk. Het doel van deze studie was het evalueren van de veiligheid van focale salvage behandeling door middel van I-125 brachytherapie. Focale salvage kan in principe door middel van verschillende behandelingsmethoden uitgevoerd worden. Vanwege de uitgebreide ervaring in onze kliniek werd voor deze studie gekozen voor I-125 brachytherapie.

In deze studie werden 7 patiënten behandeld met I-125 brachytherapie, gericht op alleen de lokatie van het recidief binnen de prostaat. Het doelgebied werd afgekaderd op basis van DCE- en T2-gewogen MRI in combinatie met resultaten van systematische prostaatbiopten. De klinische veiligheid werd geëvalueerd aan de hand van de toxiciteit die optrad direct na de behandeling en op 1 en 6 maanden na de behandeling. De resultaten van deze studie laten zien dat het mogelijk is om focale salvage I-125 brachytherapie uit te voeren in patiënten met een lokaal prostaatkanker recidief. Er kan een hoge dosis worden gegeven aan het doelgebied, terwijl blaas, rectum en de rest van de prostaat relatief gespaard blijven. Bij geen van de patiënten kwam ernstige toxiciteit na de behandeling voor. Echter, het aantal patiënten in deze studie, en de gemiddelde follow-up, zijn beperkt waardoor directe vergelijking met de conventionele salvage behandeling nog lastig is.
Bij focale salvage wordt minder toxiciteit verwacht, vanwege een lagere stralingsdosis in de omliggende risico organen. Daardoor zou focale salvage een acceptabelere behandelmethode kunnen zijn dan conventionele salvage. Er zijn echter enkele belangrijke overwegingen die gemaakt dienen te worden bij de ontwikkeling van focale salvage methoden, zoals beschreven in *Hoofdstuk 7*. Moeilijke aspecten zijn onder andere dat niet volledig duidelijk is hoe salvage gerelateerde toxiciteit precies ontstaat. Daardoor is het niet bekend welke dosis beperkingen aangehouden moeten worden voor risico organen, welke marges rond de doelgebieden dienen te worden toegepast en wat de minimale dosis op het doelgebied zou moeten zijn.
In de toekomst zullen meer patiënten door middel van focale salvage brachytherapie behandeld gaan worden, en de lange termijn resultaten van zowel toxiciteit, kwaliteit van leven en klinische uitkomst zullen meer inzicht geven in de waarde van deze behandeling in vergelijking met de conventionele methode. Voor de toekomst zou een gerandomiseerde trial met 3 behandelarmen ('geen behandeling', 'conventionele salvage' en 'focale salvage') het ultieme bewijs kunnen leveren voor de klinische waarde van focale salvage brachytherapie. De eindpunten van deze trial zouden in ieder geval technische aspecten, klinische uitkomst, toxiciteit en invloed op kwaliteit van leven dienen te omvatten.

Concluderend laten de resultaten van de boven beschreven studies zien dat ondanks de teleurstellende resultaten van conventionele salvage brachytherapie, er een klinisch acceptabel behandelalternatief bestaat voor patiënten met een lokaal prostaatkanker recidief na radiotherapie: focale salvage therapie. In combinatie met verbeterde diagnostische mogelijkheden voor de vroege detectie en lokalisatie van prostaatkanker recidieven, en met behulp van robot gestuurde prostaatinterventies onder geleide van MRI, kan dit leiden tot betere vooruitzichten voor patiënten die behandeld zijn voor prostaatkanker.

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Maaike Renee Moman werd geboren op 16 maart 1983 te Meppel en groeide op in Amersfoort. In 2001 behaalde zij haar VWO diploma op Vallei College 't Atrium, en startte aansluitend de studie Geneeskunde aan de Universiteit Utrecht. Tijdens haar studie was zij lid van studentenvereniging C.S. Veritas. Na het afronden van de studie Geneeskunde in 2007 werkte zij gedurende korte tijd als arts-assistent Neurologie in het UMC Utrecht. Vanaf eind 2007 tot en met 2010 verrichte zij promotieonderzoek bij de afdeling Radiotherapie van het UMC Utrecht, in samenwerking met de afdeling Radiologie. In 2009 was zij verantwoordelijk voor de organisatie van de 2nd annual meeting van ISMRM Benelux Chapter, en in januari 2010 nam zij plaats als bestuurslid van de ISMRM Benelux Chapter. Vanaf september 2009 volgde zij tevens de master opleiding tot Klinisch Epidemioloog, welke zij zeer binnenkort zal afronden. In februari 2011 zal zij starten met de opleiding tot radioloog, binnen het opleidingscluster Utrecht. Maaike woont samen met Joris Bekkers, en in oktober verwachten zij hun eerste kindje.

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