MRI-GUIDED RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

CLINICAL EVALUATION AND DEVELOPMENT OF ERECTILE FUNCTION-PRESERVING TREATMENT

FREEK TEUNISSEN

MRI-guided radiotherapy for localized prostate cancer: clinical evaluation and development of erectile function-preserving treatment

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MRI-gestuurde radiotherapie voor gelokaliseerde prostaatkanker: klinische evaluatie en ontwikkeling van erectiele functiebehoudende behandeling

(met een samenvatting in het Nederlands)

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CHAPTER 1

Introduction

Localized prostate cancer incidence and treatment

Prostate cancer is the most diagnosed male cancer in the Netherlands, with approximately 13500 yearly new cases.[1] At diagnosis, approximately 60% of patients have localized disease, 20% locally advanced disease and 20% metastatic disease.[1] The definition of the spread of disease is based on the tumor-node-metastasis (TNM) stage.[2,3] The clinical T-stage ranges from 1 to 4 (Fig. 1). Stage T1 means the tumor is confined to the prostate and is not palpable during a digital rectal examination. Stage T2 tumors are confined to the prostate but are palpable during a digital rectal examination. Stage T3 tumors grow into the prostate capsule and/or into the seminal vesicles. Stage 4 tumors invade other organs. With N0 disease, there is no spread of cancer cells to the regional (i.e., pelvic) lymph nodes. When there is a spread of disease into the regional lymph nodes, this is called N1 disease. If cancer has spread to lymph nodes outside the pelvis or to other organs in the body, this is referred to as M1 or metastatic disease.

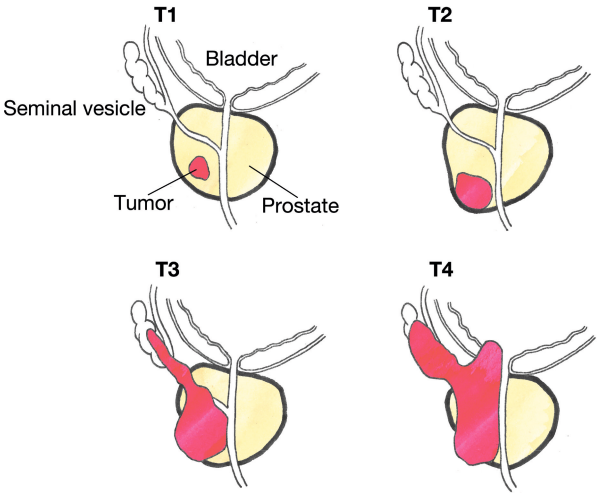

Figure 1: *Tumor (T) stage. T1: the tumor is confined to the prostate and not palpable during a digital rectal examination; T2: the tumor is confined to the prostate but palpable during a digital rectal examination; T3: the tumor grows into the prostate capsule and possibly also into the seminal vesicles; T4: the tumor grows into other organs.*

Localized prostate cancer can be categorized into three risk groups based on prostate-specific antigen (PSA) value, Gleason score, and clinical tumor (cT) stage. The two most commonly used classifications are the European Association of Urology (EAU)[2] and the National Comprehensive Cancer Network (NCCN)[3] (Table 1).

Table 1: *Prostate cancer risk stratification*

	Low risk	Intermediate risk	High risk
NCCN	T1-T2a and GS 2-6 and PSA ≤ 10 not very low-risk **very-low risk category**: T1c and GS ≤ 6 and PSA < 10 and fewer than 3 biopsy cores positive and ≤ 50% cancer in each core	T2b or T2c and/or GS = 7 and/or PSA > 10-20	T3a or PSA > 20 or GS 8-10 not very high risk **very high-risk category:** T3b-4
EAU	T1-T2a and GS ≤ 6 and PSA ≤ 10	T2b and/or GS = 7 and/or PSA > 10-20	≥ T2c or PSA > 20 or GS 8-10

Abbreviations: EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; T = T stage; GS = Gleason score; PSA = prostate-specific antigen.

For localized prostate cancer, several curative treatments are available. Four disease management options are considered standard of care.[2] The first is active surveillance, which means no immediate treatment, but a periodic monitoring of the tumor. No radical treatment is performed when the tumor remains low risk. Only when the tumor progresses, active treatment may be indicated. Within ten years after the start of active surveillance, approximately 50% of patients will undergo some form of treatment due to tumor progression or patient's choice.[4] For intermediate- and high-risk cases of localized prostate cancer, radical treatment with curative intent may be indicated. The standard radical treatment options are prostatectomy, external beam radiotherapy (EBRT), and low-dose-rate (LDR) brachytherapy.

During a prostatectomy, the prostate and seminal vesicles are surgically removed under general anesthesia. In the Netherlands, this is most often performed in a robot-assisted laparoscopic procedure.[5] After removal of the prostate, an anastomosis between the bladder and the urethra is made.

With conventional (i.e., computed tomography [CT]-guided) EBRT, three to four fiducial markers are placed within the prostate by needle insertion through the perineum. One week later, after prostatic edema has subsided, a magnetic resonance imaging (MRI) and CT scan are acquired prior to treatment. The MRI scan is used for delineation of the prostate and the surrounding healthy tissue, and the CT scan for the generation of a dosimetric pre-treatment plan. When making a treatment plan, the aim is to give optimal effective radiation dose to the prostate and a dose as low as reasonably possible to the surrounding healthy tissue, the "organs at risk" (OAR). Because of the close relation between some OAR and the prostate, the treatment plan can be a trade-off

between tumor control and toxicity. To guide this trade-off, dose prescriptions and dose constraints have been established, which represent a consensus of the minimal dose that the prostate and tumor should receive to ensure desired oncologic control and the maximal dose that the OAR may receive to keep toxicity within acceptable boundaries. Generally, for localized prostate cancer, 5 to 35 treatment fractions are delivered. Before each treatment fraction a cone-beam CT scan is made, and the fiducial gold markers visible within the prostate are matched with the fiducial markers on the pre-treatment plan to correct for daily translations that may occur. Depending on the risk group and treatment strategy, EBRT may be accompanied by androgen deprivation therapy (ADT).

With LDR brachytherapy, radioactive iodine-125 sources (seeds of 4.5 mm x 0.8 mm) are placed within the prostate using hollow needles through a transperineal route under spinal anesthesia. Approximately 60 sources are placed, depending on the tumor and prostate size. The sources will irradiate the prostate from the inside for approximately 6 months (clinically relevant dose half-life of I-125 is 59.5 days) and remain in the prostate for life.

Treatment-related toxicity

Tumor control for most localized prostate cancer patients after radical treatment is good, with a 10-year incidence of clinical progression of < 10% and a 10-year prostate-cancer-specific survival of > 99%.[1,4,6] However, all radical treatment options bear the considerable risk of treatment-related toxicity. The patterns of toxicity vary between treatment modalities.

With prostatectomy, there are risks of complications associated with surgical procedures, although the need for reoperation is very rare.[7] Frequently occurring toxicity after prostatectomy is urinary incontinence, which is caused by the anatomy-altering anastomosis that is made between the bladder and the urethra. After the operation, the pelvic floor has to adapt to the new situation, and the bladder sphincter must be trained. Many patients suffer from unwanted urine loss during the first months after the operation. Still, a year after surgery, approximately 60% of men experience unwanted urine leakage, and 54% use incontinence material.[8–10] About 4% of men are completely incontinent 1 year after surgery. Another major issue after prostatectomy is erectile dysfunction. During surgery, in selected cases effort is made to spare the neurovascular bundles that run on both dorsolateral sides of the prostate. Sparing these bundles while completely resecting the prostate can be a challenge and needs years of experience to master. Furthermore, the dominant intraprostatic lesion is most often located

dorsolaterally in the peripheral zone of the prostate, making it impossible to spare the ipsilateral neurovascular bundle and simultaneously achieve a pathological complete resection. Therefore, the neurovascular bundle is often sacrificed in favor of complete tumor resection. For cases where unilateral or bilateral neurovascular bundle sparing prostatectomy is achieved, 12- and 24-month erectile dysfunction ranges from 10% to 46% and from 6% to 37%, respectively.[11] Generally, erectile dysfunction is highest shortly after surgery and may show some improvement within 2 years. Overall, 76% of men have sustained surgery-induced erection problems 1 year after the procedure.

For EBRT, implantation of the fiducial gold markers is painful, but complications are rare. Toxicity that is reported after radiotherapy includes urinary and bowel symptoms, generally starting during treatment or shortly after the last fraction. For urinary symptoms, this is mainly includes urgency, frequency, and urinary tract pain. Most of these symptoms resolve after 3 months. However, about 48% of men still experience an increased urge to urinate 1 year after treatment.[8–10] Urinary incontinence after EBRT is rare. Bowel symptoms are most often transient, but about 15% of patients report symptoms of diarrhea 1 year after treatment. Two percent of patients develop severe late genitourinary symptoms, and 1.1% of patients have severe late gastrointestinal symptoms, such as severe cystitis or proctitis.[12,13] For patients receiving EBRT, EAU guidelines recommend short-term ADT of 4-6 months for intermediate-risk patients and long-term ADT of 2-3 years for high-risk prostate cancer patients.[2] ADT is associated with additional toxicity, including decreased bone mineral density; metabolic changes such as weight gain, decreased muscle mass, and increased insulin resistance; hot flashes; gynecomastia; reduced testicle size; anemia; and fatigue.[14] Prominent is the decrease of libido and sexual dysfunction in over 90% of patients. Because of the minimal survival benefit for intermediate-risk patients, in consultation with the patient, it can be decided to withhold ADT to prevent ADT-associated toxicity.[2]

With LDR brachytherapy, radioactive sources are implanted via several transperineal hollow needles, giving a small chance of infections and spinal anesthesia-associated complications.[15,16] LDR brachytherapy-related toxicity resembles EBRT-related toxicity. Patients experience mainly urinary and bowel symptoms. Although most symptoms resolve within 3 months, about 2% of men are completely incontinent 1 year after treatment, 65% of men experience an increased urge to urinate 1 year after treatment, and 24% of men suffer from diarrhea 1 year after treatment.[8–10] Acute urinary retention rates of 6% to 34% have been reported, and invasive treatment such as catheterization or transurethral resection of the prostate (TURP) may be indicated.[17,18] Late-onset severe toxicity such as severe proctitis and cystitis is reported to occur in < 3% for genitourinary toxicity and 1-3% of patients for gastrointestinal toxicity.[19]

Erectile dysfunction is an important problem after radiotherapy as well. In patients undergoing radical prostatectomy, erectile dysfunction typically peaks immediately after surgery. In contrast, erectile dysfunction following brachytherapy and EBRT tends to develop more gradually. One-, 2-, and 5-year erectile dysfunction rates have been reported to be 34%, 39%, and 57%, respectively, in a pooled analysis with brachytherapy, EBRT, and brachytherapy plus EBRT patients.[20] Brachytherapy and EBRT erectile dysfunction rates were not different.

During active surveillance, toxicity that develops over time is a result of aging. Within ten years after the start of active surveillance, approximately 50% of patients undergo radical treatment because of tumor progression or patient preference.[4] Those patients are then exposed to the risks of toxicity related to the respective radical treatment but may have postponed the onset of toxicity for several years.

Toxicity can have a detrimental effect on the patient's quality of life.[8,21,22] Urinary, bowel, sexual, and hormonal symptoms can impair normal daily activity and physical, social, and emotional functioning. Survival after localized prostate cancer treatment is high, urging the need for reducing toxicity and improving quality of life after treatment.

Treatment innovation

In the development of new treatments, the primary aim is to reduce toxicity and/or improve tumor control. Currently, focal therapies are being investigated.[23] With focal therapy, only the dominant intraprostatic lesion is treated instead of the whole prostate. Advantages of focal therapy are the reduction of toxicity, as less surgical or radiation damage is done to the prostate periphery where it borders the bladder, rectum, and neurovascular bundle and the urethra within the prostate. However, focal therapy may only be suitable for selected low- and intermediate-risk prostate cancer patients that received staging using MRI-guided biopsies to ensure sufficient tumor control. The most common types of focal therapy include irreversible electroporation, high-intensity focused ultrasound, and cryoablation.[2,24,25] All these treatments can be considered non-invasive or minimally invasive as treatment is performed by inserting one or multiple needles through the perineum into the prostate (irreversible electroporation and cryoablation) or a rectal probe (high-intensity focused ultrasound) and are performed in one session. After focal therapy, strict follow-up is warranted, and eventual re-treatment with focal or radical treatment may be indicated. Two studies that mainly included intermediate risk patients receiving focal therapy, showed that over 50% received additional focal or radical therapy within 5 years after initial focal therapy because of disease

progression.[26–28] Due to the lack of robust comparative data on medium- to long-term oncological outcomes, there remain significant uncertainties with regard to focal therapy as a proven alternative to either active surveillance or radical therapy. Therefore, current European guidelines recommend that focal therapy should be performed only within the context of a clinical trial setting or a well-designed prospective cohort study.[2]

Implementation of laparoscopic surgery and the surgical robot has led to radical resection of the prostate gland with minimal damage to the surrounding organs. The "neurosafe" method is an innovative technique that is currently being investigated.[29] During the neurosafe procedure, intraoperative fresh-frozen section analysis of the posterolateral aspect of the prostate margin is performed to assess whether cancer extends beyond the capsule to ensure negative but minimal surgical margins. The hypothesis is that it will decrease the chance of erectile and urinary dysfunction. However, at this moment, we are awaiting evidence of superiority.[30] Furthermore, several image-guided technologies such as augmented reality, fluorescence imaging, optical coherence tomography, confocal laser endomicroscopy and 3D printing can support the urologist during surgery, ensuring radical tumor resection with minimal healthy tissue damage.[31]

For radiotherapy, developments in the past decade have been focused on more precise dose delivery by evolving from three-dimensional conformal radiotherapy (3DCRT) to intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) to lower the dose to healthy surrounding tissue by delivering dose from multiple beam angles and with modulated intensity.[32,33] Improved precision of dose delivery facilitates hypofractionation. With hypofractionation a higher radiation dose is delivered in fewer fractions. Because dose per fraction is higher, it should be ensured that dose received by OAR remains within the predefined constraints. The dose constraints for OAR are established with the goal to keep toxicity within acceptable boundaries. The rationale behind hypofractionation is based on the α/β ratio, which is a measure of the sensitivity of a type of tissue to radiation dose per fraction in combination with total dose.[34] Tissues with a relatively low α/β ratio, such as prostate tumors, are more sensitive to a higher dose per fraction compared to tissues with a relatively higher α/β ratio, such as healthy rectum and bladder tissue. Studies have shown that hypofractionation for prostate cancer enhances biological effective dose to the tumor without increasing genitourinary and gastrointestinal toxicity.[35–40] High-dose-rate (HDR) brachytherapy, as an alternative to LDR brachytherapy, shares the rationale of hypofractionation with simultaneous dose escalation of improved tumor control without an increase of toxicity.[41] Another recent development is proton therapy. In contrast to photons, protons deposit the bulk of their radiation dose to a finite depth in tissue with minimal residual radiation beyond the target.[42] However, studies have not shown fewer side effects or better patient-reported

quality of life compared to IMRT.[43,44] Substantial treatment superiority of proton therapy over photon therapy for prostate cancer has to be proven to justify the high costs.[45]

Magnetic resonance-guided radiotherapy

One of the innovations in radiotherapy for localized prostate cancer is MRI-guided adaptive radiotherapy using an MR-Linac.[46] The MR-Linac is a linear accelerator with an integrated MRI scanner that enables daily dosimetric plan adaptation before and during EBRT dose delivery using online MRI.[47] The University Medical Center Utrecht (UMCU) conceptualized the device and is still one of the frontrunners in technical and clinical research involving the MR-Linac.[48] Currently, two commercial MR-Linac devices are available: the MRidian (ViewRay Inc., Mountain View, U.S.A.), which was clinically introduced in 2016, and the Unity MR-Linac (Elekta AB, Stockholm, Sweden), which was clinically introduced in 2018. The first combines a 0.35 T (i.e., low-field) MRI scanner with a 6 MV linear accelerator (a previous version used three Co-60 heads)[49], and the latter combines a 1.5 T (i.e., high-field) MRI scanner with a 7 MV linear accelerator.[46] With this technique, the dose can be adapted to the real-time anatomy of the patient, resulting in a smaller margin and a lower dose to the organs surrounding the target volume, such as the bladder and the rectum, as much as possible, ensuring optimal dose to the prostate gland and prostate tumor for optimal disease control. Theoretical advantages are lower toxicity and improved disease control.[47,50] Because of the MRI guidance, the implantation of fiducial markers in the prostate is no longer necessary, making the treatment noninvasive.[51] Currently, an “adapt to shape” (recontouring) and an “adapt to position” (similar to a couch shift correction on a CT-guided linac) procedure is performed before every daily fraction. The ultimate goal is to perform real-time adapt to shape plan adaptation during dose delivery. The hardware of the MR-Linac device is technically capable of real-time adapted dose delivery, but we are awaiting software that can adequately perform fast online auto-contouring and plan adaptation to be clinically utilizable before we can apply this treatment in clinical practice.[46,52,53] When fast online auto-contouring and plan adaptation can be performed, target volume margins can be further reduced, which theoretically will result in a lower dose to healthy tissue and, therefore, less toxicity.[50]

Research objectives and thesis outline

The research objective of this thesis is the evaluation of MRI-guided radiotherapy for localized prostate cancer and the comparison of MRI-guided radiotherapy with other

treatments for localized prostate cancer. Furthermore, the objective is to describe the development, implementation, and clinical evaluation of erectile function-preserving MRI-guided radiotherapy for localized prostate cancer.

Prospective registries and multi-trial platforms for the evaluation of MRI-guided adaptive radiotherapy

Many new treatment interventions for localized prostate cancer, such as MRI-guided radiotherapy, are promising and often rushed into clinical practice before solid evidence of efficacy and cost-effectiveness. The R-IDEAL recommendations (based on the IDEAL recommendations)[54] describe a framework for the clinical evaluation of technical innovations in radiation oncology.[55] Ideally, technical innovations should be evaluated against standard treatment before clinical implementation. However, due to the high pace of innovation, financial incentives, pressure from industry, and patients' demand for "high tech", this is often not feasible. R-IDEAL comprises six stages. Stage 0: radiotherapy predicate studies, stage 1: the idea, stage 2a: the development, stage 2b: the exploration, and stage 3: the assessment. The MR-linac has reached stage 4: the long-term evaluation. Large prospective patient cohorts and comparisons against conventional treatments are needed to evaluate the theoretical benefits.

Chapter 2 presents the first prostate cancer results of a large MRI-guided radiotherapy cohort: the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac (MOMENTUM) study. **Chapter 3** describes the development and first results of the Utrecht Prostate Cohort (UPC), a cohort serving as a multi-trial facility for localized prostate cancer patients treated with MRI-guided radiotherapy or conventional treatment. And in **chapter 4**, the patient preferences for MRI-guided radiotherapy and other conventional and innovative treatment options for localized prostate cancer are compared.

Erectile function-preserving MRI-guided radiotherapy

Reduction of erectile dysfunction after radical prostate cancer treatment remains a challenge. We propose a neurovascular-sparing approach during MRI-guided radiotherapy for the preservation of erectile function. The MR-Linac enables this treatment as the integrated high-field MRI scanner can visualize soft tissue to which the dosimetric plan can be adapted.[56] The hypothesis is that this treatment will reduce the rate of erectile dysfunction after radiotherapy for prostate cancer without substantially increasing the risk of tumor recurrence.

Chapter 5 presents the results of an interrater variability study for the contouring of the neurovascular bundle and internal pudendal artery. In **chapter 6**, the planning feasibility of neurovascular-sparing MRI-guided radiotherapy is elaborated on. **Chapter 7** presents the patient population that may be eligible for this treatment and to what extent the neurovascular bundle can be spared in those patients during MRI-guided radiotherapy. And in **chapter 8**, the advantage of MRI-guided radiotherapy over conventional EBRT for the delivery of neurovascular-sparing radiotherapy is discussed.

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CHAPTER 2

MRI-guided adaptive radiotherapy for prostate cancer: the first results from the MOMENTUM study—an international registry for the evidence-based introduction of MRI-guided adaptive radiotherapy

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Abstract

Background and purpose: Magnetic resonance imaging (MRI)-guided radiotherapy is a new technique for treatment of localized prostate cancer. We report the 12-month outcomes for the first prostate cancer patients treated within an international consortium (the MOMENTUM study) on a 1.5 T MR-Linac system with ultrahypofractionated radiotherapy.

Materials and methods: Patients treated with 5 × 7.25 Gy were identified. Prostate specific antigen (PSA) level, physician-reported toxicity (Common Terminology Criteria for Adverse Events [CTCAE]), and patient-reported outcomes (Quality of Life Questionnaire PR25 and Quality of Life Questionnaire C30 questionnaires) were recorded at baseline and at 3, 6, and 12 months of follow-up. Pairwise comparative statistics were conducted to compare outcomes between baseline and follow-up.

Results: The study included 425 patients with localized prostate cancer (11.4% low, 82.0% intermediate, and 6.6% high-risk), and 365, 313, and 186 patients reached 3, 6, and 12 months follow-up, respectively. Median PSA level declined significantly to 1.2 ng/mL and 0.1 ng/mL at 12 months follow-up for the non-androgen deprivation therapy (ADT) and ADT group, respectively. The peak of genitourinary and gastrointestinal CTCAE toxicity was reported at 3 months follow-up, with 18.7% and 1.7% grade ≥ 2, respectively. The QLQ-PR25 questionnaire outcomes showed significant deterioration in urinary domain score at all follow-up moments, from 8.3 (interquartile range [IQR]: 4.1-16.6) at baseline to 12.4 (IQR: 8.3-24.8, P = 0.005) at 3 months, 12.4 (IQR: 8.3-20.8, P = 0.018) at 6 months, and 12.4 (IQR: 8.3-20.8, P = 0.001) at 12 months. For the non-ADT group, physician- and patient-reported erectile function worsened significantly between baseline and 12 months follow-up.

Conclusion: Ultrahypofractionated MRI-guided radiotherapy for localized prostate cancer using a 1.5 T MR-Linac is effective and safe. The peak of CTCAE genitourinary and gastrointestinal toxicity was reported at 3 months follow-up. Furthermore, for patients without ADT, a significant increase in CTCAE erectile dysfunction was reported at 12 months follow-up. These data are useful for educating patients on expected outcomes and informing study design of future comparative-effectiveness studies.

Introduction

Prostate motion within the pelvis is common because of the presence or absence of gas within the rectum, bowel movement, and filling of the urinary bladder. To account for uncertainties during dose delivery with external beam radiotherapy (EBRT), such as intrafraction motion, the prostate is irradiated with an uncertainty margin, also known as the planning target volume (PTV). This margin is necessary for adequate dose delivery to the prostate. Unfortunately, the PTV margin also overlaps the healthy bladder, rectum, and neurovascular structures, which may lead to posttreatment genitourinary (GU), gastrointestinal (GI), or erectile toxicity.[1]

Magnetic resonance imaging (MRI)-guided radioherapy enables real-time visualization of target volume and organs-at-risk during EBRT.[2] Currently, MRI-guided radiotherapy enables correction for interfraction motion and deformation by applying daily contour adaptation and subsequent online replanning before dose delivery without the use of fiducials or beacons. Furthermore, it allows for visualization of intrafraction motion during dose delivery. Such imaging will enable beam pausing or treatment interruption in case there is substantial or unexpected intrafraction motion. This may reduce post-treatment toxicity while maintaining or improving tumor control.[3]

Currently, two commercial MRI-guided linear accelerator (MR-Linac) systems are available: the MRidian (ViewRay Inc., Mountain View, CA) and the Unity MR-Linac (Elekta AB, Stockholm, Sweden). The first combines a 0.35 T (i.e., low-field) MRI scanner with a 6 MV linear accelerator (a previous version used three Co-60 heads)[4] and the latter combines a 1.5 T (i.e., high-field) MRI scanner with a 7 MV linear accelerator.[5]

Although several radiotherapy departments have already implemented MRI-guided radiotherapy as a standard treatment for low- and intermediate-risk localized prostate cancer, the theoretical advantages of MRI-guided radiotherapy over conventional radiotherapy treatments such as computed tomography (CT)-guided EBRT have yet to be proven in clinical practice. Furthermore, clinical outcomes up to 12 months follow-up have been reported for low-field MRI-guided radiotherapy,[6,7] but not yet for high-field MRI-guided radiotherapy. This is essential, as high-field MRI-guided radiotherapy may induce different treatment-related challenges.[8] The Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac (MOMENTUM) study was initiated to facilitate evidence-based introduction of 1.5 T MRI-guided radiotherapy in daily practice.[9]

As a first step, we here report the 12-month toxicity, efficacy, and patient-reported outcomes (PROs) from the first prostate cancer patients enrolled in the MOMENTUM study, who were treated with 5 × 7.25 Gy on the Unity 1.5 T MR-Linac system.

Materials and methods

Patients

This study was conducted within the MOMENTUM study, an international collaboration of early adopters of the 1.5 T MR-Linac system, which received approval by local Institutional Review Boards of the participating institutions (Clinicaltrials.gov identifier NCT04075305).[10] In MOMENTUM, all patients treated with radiotherapy on an MR-Linac in one of the participating institutions are eligible for participation. For the current analysis, we included all MOMENTUM participants treated for localized prostate cancer with 5 × 7.25 Gy on a 1.5 T MR-Linac between May 1, 2019 and October 10, 2021. All intermediate-risk prostate cancer patients who are eligible for conventional 5 × 7.25 Gy and have no contraindication for MRI, can receive 5 × 7.25 Gy MRI-guided radiotherapy. Low- and high-risk patients can be treated off protocol, in accordance with the physician and patient.

Data acquisition

Within MOMENTUM, patient baseline characteristics, physician-reported toxicity, and PROs were prospectively collected at baseline (before start of radiotherapy treatment) and at 3, 6, 12, and 24 months after the last radiotherapy fraction. Biochemical treatment response was evaluated by prostate specific antigen (PSA) levels at baseline and during follow-up. Seventeen items of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[11] were prospectively obtained from medical records. In case CTCAEs were recorded at multiple time points between the follow-up moments, at 3 months follow-up the highest CTCAE grades between the end of the last fraction and 3 months, for the 6 months follow-up the highest CTCAE grades between 3 and 6 months, and for the 12 months follow-up the highest CTCAE grades between 6 and 12 months (i.e., cumulative incidence). All patients who signed informed consent for completing PRO questionnaires, received the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30[12] and a subset of patients also the EORTC QLQ-PR25.[13] For each follow-up time point, a separate case report form for PSA level, CTCAE, and PROs was filled out.

Treatment

All patients were treated in five fractions of 7.25 Gy with a 2-day interval between fractions. Before the first fraction, a pretreatment planning MRI scan was acquired on which the target volume and organs-at-risk were delineated. There is no need for a CT scan. Gross tumor volume, clinical target volume (CTV), and PTV delineations were at the discretion of the treating physician and varied across institutions (Supplementary material: Table 1). The Elekta Monaco treatment planning system (version 50.40.01, Elekta Inc., Stockholm, Sweden) was used to create intensity modulated radiotherapy treatment plans, prescribing a dose of 36.25 Gy to the PTV. During each fraction, after positioning the patient on the treatment table, a daily online T2-weighted MRI scan was acquired in treatment position. Bladder and rectal preparation before MRI-guided radiotherapy varied between the different institutes. In case a so-called "adapt to shape" (ATS) workflow was applied, the contours from the pretreatment planning MRI or online MRI from the first fraction (for fraction 2-5) were propagated onto the daily online MRI.[14] Afterward, contours were manually adjusted if necessary.[15] After approval of the daily contours, the treatment plan was recalculated and simultaneously a position verification MRI scan was obtained. Adapt to position (ATP) was applied in case of a substantial CTV shift, or regardless of the CTV shift (i.e., always ATP). Androgen deprivation therapy (ADT) prescription was at the discretion of the treating physician and ADT protocols varied across institutions.

Statistical analysis

Outcomes included PSA kinetics during follow-up, physician-reported toxicity (CTCAE) and PROs at baseline, 3, 6, and 12 months follow-up. Descriptive statistics were provided for patient characteristics. Normally distributed data was presented as mean with 95% confidence intervals (CI). Skewed data was presented as median with range or interquartile range (IQR). For PSA level, CTCAE grades, and PRO scores, paired comparisons between baseline and 3, 6, and 12 months follow-up were performed using the Wilcoxon signed-rank test. Minimal clinical important difference values are not yet available in literature or the PR25. Therefore, for each PRO score comparison, the effect size (ES) was calculated. The ES is calculated by dividing the standard score (z score) by the square root of the sample size (N). Analyses were performed for the total population and after stratification for ADT. A P-value < 0.05 was considered statistically significant. An ES of < 0.30 was considered small, 0.30 to 0.49 moderate, and ≥ 0.50 large.[16] All analyses were performed using R version 4.1.2.

Results

The study included 425 localized prostate cancer patients within MOMENTUM who had completed radiotherapy treatment. An ATS workflow was adopted in 310 (72.9%) patients and an ATP-only workflow in the remaining 115 (27.1%) patients. Three months follow-up was reached by 365 patients, 6 months follow-up by 313 patients, and 12 months follow-up by 186 patients. PSA values were available for 423 (99.5%) patients at baseline, 271 (74.2%) patients at 3 months follow-up, 223 (71.2%) patients at 6 months follow-up, and 117 (62.9%) at 12 months follow-up. Prospective CTCAE data was available for 227 (53.4%) patients at baseline, 177 (48.5%) patients at 3 months follow-up, 120 (38.3%) patients at 6 months follow-up, and 62 (33.3%) at 12 months follow-up. In total, 362 (85.2%) patients consented to fill out PRO questionnaires. The response rate of the PRO questionnaires was 85.4% at baseline, 80.2% at 3 months, 78.6% at 6 months, and 72.6% at 12 months follow-up.

The median (range) age was 70 (51-85) years. Most patients had intermediate risk prostate cancer (n = 337, 82,0%) followed by low-risk (n = 47, 11.4%) and high-risk (n = 27, 6.6%) according to the National Comprehensive Cancer Network risk groups (Table 1). Seventy-eight (18.4%) patients received ADT.

Table 1: *Baseline characteristics of patients with localized prostate cancer treated with 5 × 7.25 Gy on a 1.5 T MR-Linac*

Characteristic	No.
Age, median (range)	70 (51-85)
cT-stage, n (%)	
cT1	162 (39.2)
cT2	230 (55.7)
cT3	21 (5.1)
Missing, n	12
ISUP grade, n (%)	
1	90 (21.2)
2	261 (61.6)
3	69 (16.3)
4	4 (0.9)
Missing, n	14
PSA, n (%)	
< 10 ng/mL	291 (68.8)
10-20 ng/mL	120 (28.4)

Table 1: *Continued*

Characteristic	No.
> 20 ng/mL	12 (2.8)
Missing, n	2
Risk group (NCCN), n (%)	
Low	47 (11.4)
Intermediate	337 (82.0)
High	27 (6.6)
Missing, n	14
ADT, n (%)	
No	347 (81.6)
Yes	78 (18.4)
Missing, n	0

Abbreviations: ADT = androgen deprivation therapy; cT-stage = clinical tumor stage; IQR = interquartile range; ISUP = International Society of Urologic Pathology; NCCN = National Comprehensive Cancer Network; PSA = prostate specific antigen.

A significant decline in was observed in median (IQR) PSA level from baseline to 12 months follow-up of 7.8 (5.6-10.6) ng/mL to 1.2 (0.7- 2.0) ng/mL in the non-ADT group and from 8.7 (5.9-13.0) ng/mL to 0.1 (0.1-0.4) ng/mL in the ADT group (Fig. 1 and Supplementary material: Table 2).

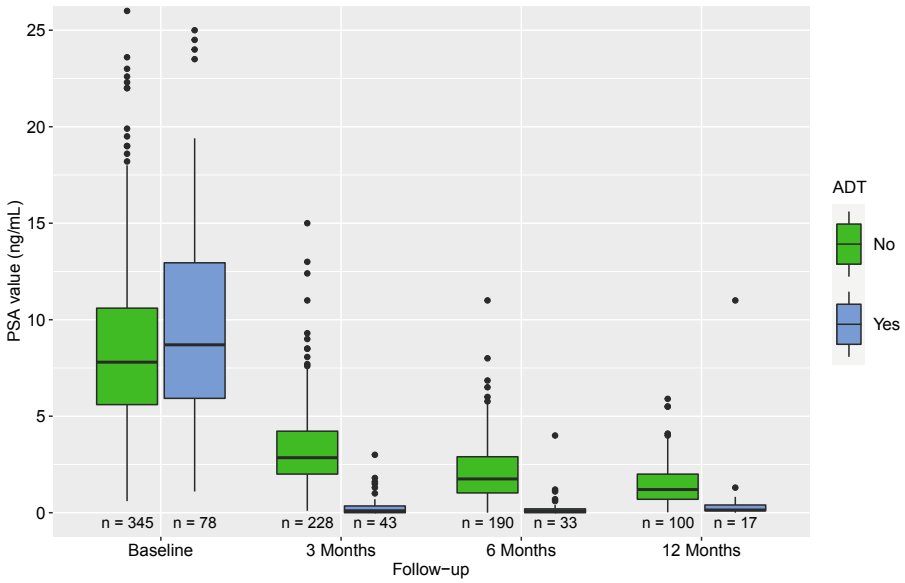

Figure 1: *Boxplots of prostate specific antigen level (PSA) level stratified by androgen deprivation therapy (ADT) treatment at baseline and follow-up.*

Physician-reported toxicity

Grades 1 and 2 GI toxicity was significantly higher at 3 months (17.5% and 1.7%, respectively) compared with baseline (6.2% and 0.9%, respectively, $P < 0.001$, Table 2). At 6 and 12 months follow-up, no significant difference with baseline GI toxicity was observed. GU toxicity increased significantly from 32.2% for grade 1 and 4.8% for grade 2 at baseline, to a rate of 38.6% grade 1, 18.7% grade 2 and 0.6% grade 3 toxicity at 3 months ($P < 0.001$). No statistically significant difference in GU toxicity at 6 and 12 months compared with baseline was observed (Table 2). For the non-ADT patients, a significant increase of ED toxicity from 24.3% grade 1, 13.5% grade 2, and 2.2% grade 3 ED at baseline to 28.8% grade 1, 21.2% grade 2, and 3.8% grade 3 ED at 12 months follow-up ($P = 0.034$) was observed.

Patient-reported outcomes

For the QLQ-PR25 urinary symptoms domain score, a significant increase in median score from 8.3 (IQR: 4.1-16.6) at baseline to 12.4 (IQR: 8.3-24.8, $P = 0.005$, ES = 0.28) at 3 months, 12.4 (IQR: 8.3-20.8, $P = 0.018$, ES = 0.28) at 6 months, and 12.4 (IQR: 8.3-20.8, $P = 0.001$, ES = 0.43) at 12 months follow-up was observed (Fig. 2 and Supplementary material: Table 3-5). Median bowel symptom domain scores did not change between baseline and all follow-up moments. After stratifying for ADT, no change was observed in the median sexual active domain score in the non-ADT group, but a significant decline in the median sexual function domain score from 83.5 (IQR: 64.7-91.8) at baseline to 75.3 (IQR: 58.5-83.5, $P = 0.002$, ES = 0.53) at 3 months follow-up and 75.0 (IQR: 58.3-83.4, $P = 0.015$, ES = 0.49) at 12 months follow-up.

The percentage of non-ADT patients who reported to be sexually active during the 4 weeks before filling out the QLQ-PR25 questionnaire was 70.4% at baseline, 67.7% at 3 months, 69.2% at 6 months, and 84.4% at 12 months. The percentage of patients reporting “quite a bit” to “very much” difficulty in getting or maintaining an erection (if sexually active) increased from 21.7% at baseline to 24.6% at 3 months, 25.5% at 6 months, and 31.6% at 12 months (Fig. 3).

Table 2: *Physician-reported toxicity using the CTCAE specified (summary of 17 items)*

	CTCAE grade				P-value*
	0	**1**	**2**	**3**	
GI toxicity					
Baseline n = 227	211 (93.0%)	14 (6.2%)	2 (0.9%)	-	
3 months n = 177	143 (80.8%)	31 (17.5%)	3 (1.7%)	-	< 0.001
6 months n = 120	105 (87.5%)	13 (10.8%)	2 (1.7%)	-	0.178
12 months n = 62	53 (85.5%)	8 (12.9%)	1 (1.6%)	-	0.072
GU toxicity					
Baseline n = 227	143 (63.0%)	73 (32.2%)	11 (4.8%)	-	
3 months n = 177	78 (44.1%)	66 (37.3%)	32 (18.1%)	1 (0.6%)	< 0.001
6 months n = 120	77 (64.2%)	34 (28.3%)	9 (7.5%)	-	0.503
12 months n = 62	38 (61.3%)	16 (25.8%)	8 (12.9%)	-	0.803
ED non-ADT patients					
Baseline n = 185	111 (60.0%)	45 (24.3%)	25 (13.5%)	4 (2.2%)	
3 months n = 145	98 (67.6%)	34 (23.4%)	11 (7.6%)	2 (1.4%)	0.118
6 months n = 102	56 (54.9%)	31 (30.4%)	13 (12.7%)	2 (2.0%)	0.052
12 months n = 52	24 (46.2%)	15 (28.8%)	11 (21.2%)	2 (3.8%)	0.034

**For comparison with baseline. The highest grade of a given toxicity that occurred in a timeframe (3 months = 0-3 months after treatment; 6 months = 3-6 months after treatment; 12 months = 6-12 months after treatment).*

Abbreviations: ADT = androgen deprivation therapy; CTCAE = Common Terminology Criteria for Adverse Events; ED = erectile dysfunction; GI = gastrointestinal; GU = genitourinary.

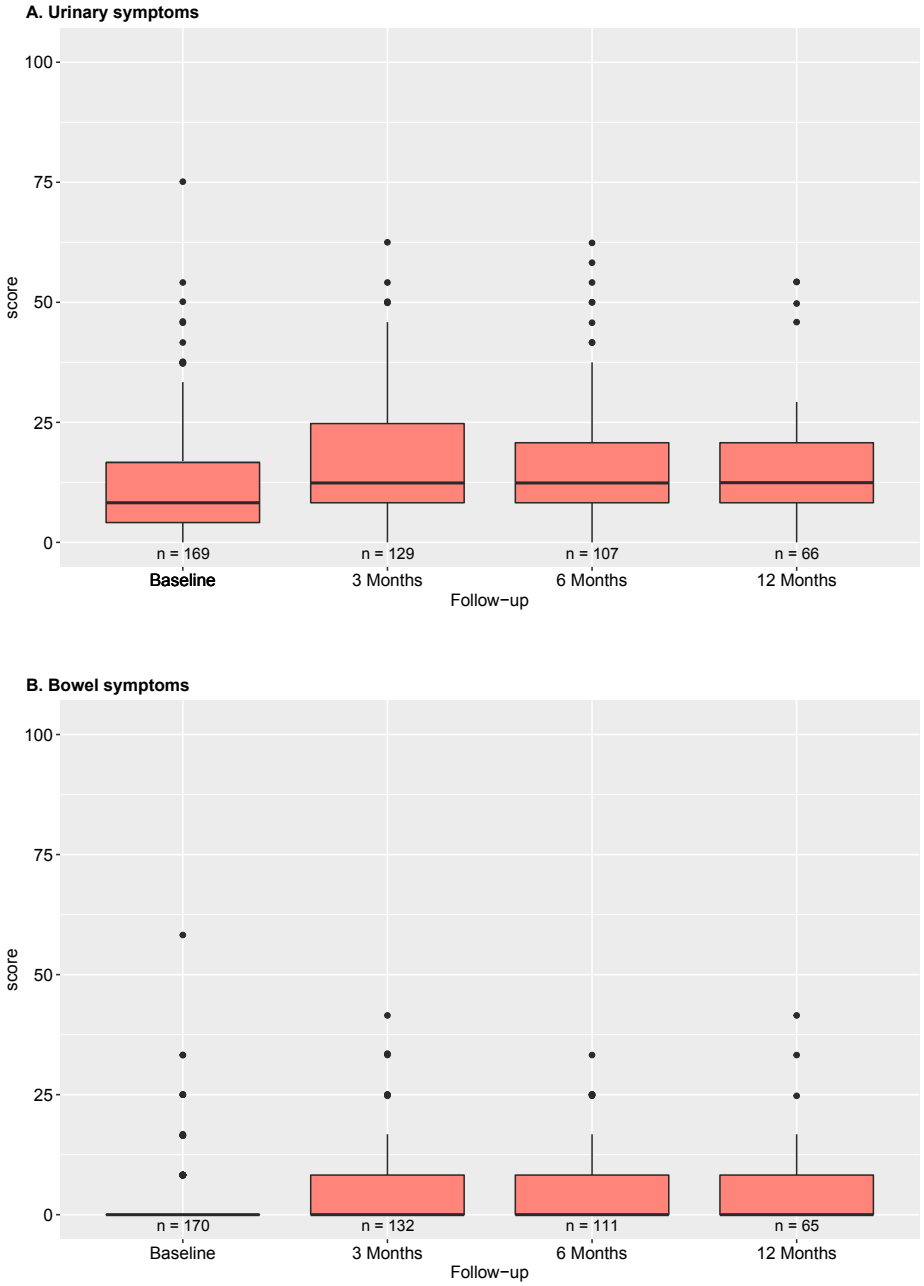

Figure 2: *Boxplots of Quality of Life Questionnaire PR25 domain scores at baseline and follow-up. A: urinary symptoms; B: bowel symptoms; C: sexual activity; D: sexual function. Sexual activity and function domain are stratified for androgen deprivation therapy treatment. Sexual function domain conditional on being sexually active.*

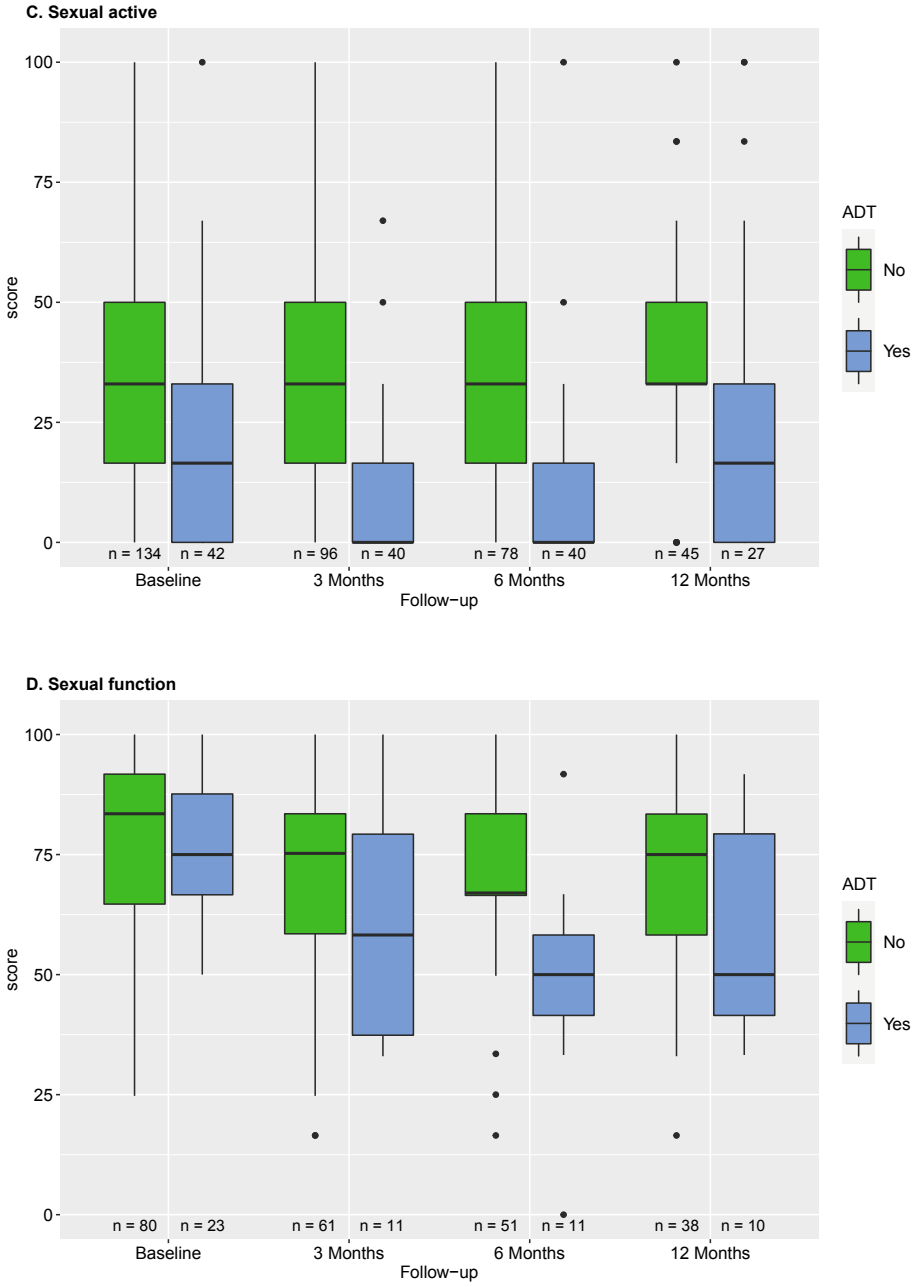

Figure 2: *Continued.*

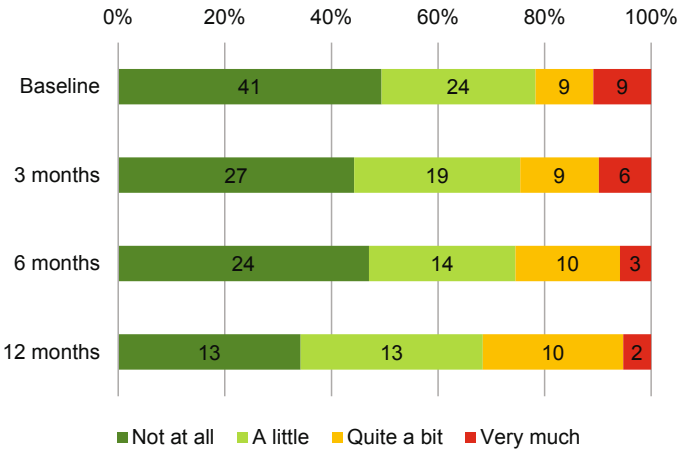

Figure 3: *Distribution of answers to Quality of Life Questionnaire PR25 question: "Did you have difficulty getting or maintaining an Erection?" Nonandrogen deprivation therapy patients only. Question should only be answered if recipient has been sexually active during the past 4 weeks (at moment of filling out the Quality of Life Questionnaire PR25 questionnaire).*

The QLQ-C30 function and symptom scales showed no significant deterioration between baseline and 3, 6, and 12 months follow-up. There was, however, a decline (improvement) in the fatigue domain score from 11.1 (IQR: 0.0-22.2) at baseline to 0.0 (IQR: 0.0-22.2, P = 0.025, ES = 0.20) at 12 months follow-up (Supplementary material: Table 3-5).

Discussion

In this article, we have reported the first 12-month follow-up results of 425 localized prostate cancer patients treated with 5 × 7.25 Gy on 1.5 T MR-Linac within the international, multicenter MOMENTUM study. These first results showed that treatment was effective and safe, with a significant and steep decline in PSA level up to 12 months follow-up and only one case of grade 3 GU toxicity and no grade ≥ 3 GI toxicity.

A transient but significant increase in cumulative GU and GI toxicity was reported at 3 months follow-up and a significant increase in ED toxicity for non-ADT patients was reported at 12 months follow-up to. Compared with baseline, no significant change in the QLQ-PR25 bowel and sexually active domains were observed at 3, 6, and 12 months follow-up. For the QLQ-PR25 urinary domain, a significant deterioration with a small ES was reported from baseline to 3, 6, and 12 months and a significant decline in the sexual function domain score at 6 and 12 months follow-up was observed, with a large and moderate ES, respectively.

Our findings are in line with the results of Bruynzeel et al, who reported the first early results in 101 localized prostate cancer patients who received 5 × 7.25 Gy on a low-field (0.35 T) MR-linac.[6] Their patient group consisted of a higher risk population (4.0% low, 36.6% intermediate, and 59.4% high-risk) and they used a urethra-sparing technique. The QLQ-PR25 urinary and bowel domain scores were comparable to those observed in our study. Also, the cumulative incidence of grade ≥ 2 GU and GI toxicity were 23.8% and 5.0% at 3 months follow-up, respectively, and were in the same range as the grade ≥ 2 GU toxicity of 18.7% and GI toxicity of 1.7% in our study. In a subsequent article by the same research group, the PROs in the same patient cohort up to 1 year of follow-up were reported.[7] Similar to the QLQ-PR25 results in our study, the effect sizes for the difference in PROs between baseline and 3, 6, and 12 months follow-up for both the urinary and bowel domain were small. The high rate of ADT use (83.2%), as a result of the predominantly high-risk patients included, caused a significant and clinically relevant negative effect on sexual activity. Because only 33% of patients completed the questions on sexual function, this domain was not analyzed in their article.

In a meta-analysis by Jackson et al, in which the results of 32 stereotactic body radiotherapy (SBRT) studies (median dose per fraction: 7.25 [range, 5-10] Gy and median fraction number: 5 [range, 4-9]) were summarized, a cumulative incidence of early grade ≥ 2 GU toxicity of 16.0% and GI toxicity of 6.2% were observed. Additionally, the cumulative incidence of late grade ≥ 2 GU and GI toxicity were 13.0% and 5.4%.[17] However, the results are not directly comparable to our results, as the timeframe of acute toxicity was not always ≤ 3 months in the studies included in the meta-analysis. Furthermore, late toxicity went beyond 12 months follow-up and toxicity was graded using both the CTCAE (19 studies) and Radiation Therapy Oncology Group (RTOG)/EORTC grading (13 studies) systems.

More detailed information on acute toxicity after SBRT on a CT-guided linac is available from the PACE B trial.[18] In the PACE B trial, the intervention arm consisted of patients with localized low- and intermediate-risk (National Comprehensive Cancer Network) prostate cancer, who received 5 × 7.25 Gy with an additional secondary CTV dose target of 40 Gy on a CT-guided linac (245 [59.0%] on a conventional linac and 170 [41.0%] on a CyberKnife system). Recommended CTV to PTV margins were 4 to 5 mm nonposterior and 3 to 5 mm posterior. None of the patients received ADT. The cumulative incidence of CTCAE grade ≥ 2 GU and GI toxicity was 30.8% and 15.7% at 3 months follow-up, respectively, which is higher compared with our results. The lower toxicity that is reported in our study may be a result of more accurate dose delivery due to the ability to perform online MRI-guided ATP and ATS.

Because ADT has a detrimental effect on sexual activity and function, we have limited our analysis of sexual activity and function to non-ADT patients only.[19] We observed a significant decline in sexual function from baseline to 3 and 12 months. The effect sizes indicated a large and moderate effect, respectively, which emphasizes the clinical relevance of the domain score decline. The significant increase in CTCAE erectile toxicity at 12 months follow-up supports this finding. To get a more detailed picture of sexual function of these patients, we looked at the individual questions of the QLQ-PR25. Of the non-ADT patients who reported to have been sexually active over the last 4 weeks at the time of filling out the QLQ-PR25 questionnaire, the percentage of patients who reported to have "quite a bit" to "very much" difficulty in getting or maintaining an erection increased significantly from 21.7% at baseline to 31.6% at 12 months. Previous reports on ED after SBRT treatment for prostate cancer showed a gradual decline in erectile function beyond 12 months follow-up up to 5 years after treatment. Therefore, longer follow-up and larger patient numbers are warranted to draw definitive conclusions regarding ED after MRI-guided radiotherapy.[20]

Theoretical advantages of MRI-guided radiotherapy include intrafraction motion monitoring and correction for interfraction prostate motion (translation and rotation) in case of applying an ATS procedure,[21] more accurate visualization of the dominant intraprostatic lesion for focal boosting,[22] visualization of neurovascular structures to allow sparing,[23] and the potential for MRI biomarker-based adaptive treatment.[24] However, for MRI-guided radiotherapy to become a cost-effective alternative to conventional CT-based EBRT, brachytherapy, or prostatectomy, a substantial reduction in toxicity is needed.[25] For this, comparative studies, preferably randomized controlled trials, are needed. The MIRAGE-trial is the first RCT comparing (low-field) MRI-guided radiotherapy with conventional CT-guided radiotherapy and is currently ongoing.[26] An interim analysis showed promising results, including a significantly lower acute grade ≥ 2 GU and GI toxicity in patients who received 5 × 8 Gy on an MR-Linac with 2 mm PTV margins compared with patients treated on a CT-guided linac with 4 mm PTV margins (incidence of grade 2 GU toxicity: 11 [22.4%] vs. 24 [47.1%], P = 0.01; incidence of grade ≥ 2 GI toxicity: 0 [0%] vs. 7 [13.7%], P = 0.01).[27] Furthermore, multiple prospective long-term registries are ongoing to collect follow-up data on toxicity and PROs in patients treated with MRI-guided radiotherapy as well as conventional EBRT, brachytherapy, prostatectomy, and active surveillance, which allow for comparison between the various treatments.[9,28] Also, fast intrafraction MRI scan acquisition, improved automatic contouring, and fast online and real-time adaptive replanning during beam-on need to be implemented to enable further margin reduction to reduce toxicity and to open up possibilities for extreme hypofractionation in two fractions feasible.[24,29,30,31]

We acknowledge that our study suffers from some limitations. First, the rate of missing CTCAE data was substantial, which should be considered when comparing our results to literature. CTCAE data was prospectively registered, but not all radiation oncologists systematically documented the toxicity using the 17 predefined CTCAE items. Furthermore, not all patients had an in-person appointment with their radiation oncologist at all follow-up moments and the COVID-19 pandemic even further reduced the number of in person appointments. Currently, efforts are being made to increase the CTCAE reporting rate, such as CTCAE registration using paper forms handed out to the physician as well as real-time remote symptom monitoring by a dedicated app.[32] We expect that this will improve CTCAE registration. The gradual decline of data availability rate toward later follow-up moments, which is also present for PSA values and PROs, may be caused by a delay in data registration in the study database.

Second, although the highest grade of CTCAE toxicity between 0 and 3 months was recorded for the 3 months follow-up time point, CTCAE registration was only standardized at 3 months follow-up. Therefore, toxicity which settles before 3 months, may have been missed if not documented in the medical records. This should be considered when comparing our toxicity outcomes at 3 months follow-up with other studies, such as the series reported by Bruynzeel et al (standardized CTCAE registration at last fraction, 6, and 12 weeks follow-up)[6] and the PACE B trial (standardized CTCAE registration at 2, 4, 8, and 12 weeks follow-up).[18] Both studies report a peak in toxicity between 0 and 3 months follow-up, which substantially decreased at 3 months follow-up. In our current report it remains unknown to what extent toxicity occurred and resolved between 0 and 3 months follow-up and whether this was reported at 3 months follow-up, but the cumulative incidence is likely an underestimation.

Third, the response rates for the PRO questionnaires were high during follow-up. However, a group of patients did not receive the QLQ-PR25 questionnaire, because they were simultaneously enrolled in another prostate-specific prospective registry (Clinicaltrials.gov identifier NCT04228211) for which the QLQ-PR25 was replaced with the Expanded Prostate Cancer Index Composite (EPIC)-26.[28,33] The QLQ-PR25 and EPIC-26 are similar in terms of questions and domains, but not directly comparable. So, for these patients, PRO data was not lost, but they were not eligible for the QLQ-PR25 analyses. Finally, no PRO data are available on follow-up moments between baseline and 3 months follow-up (e.g., directly after the final treatment fraction or at 1 month posttreatment). A transient deterioration of PRO scores during and shortly after radiotherapy may therefore have been missed.

Conclusion

The results presented in the current study show that the treatment of localized prostate cancer with SBRT on a 1.5 T MR-Linac is effective and safe. A transient but significant increase in the cumulative incidence of physician-reported GU and GI toxicity was reported at 3 months follow-up and a significant increase in physician-reported ED rates was reported at 12 months follow-up. Compared with baseline, no relevant deterioration in patient-reported bowel and sexual active domains was observed at 3, 6, and 12 months follow-up, however there was a significant decline in urinary domain scores at 3, 6, and 12 months and sexual function domain scores at 6 and 12 months follow-up. These data are useful for counseling patients on expected outcomes after MRI-guided radiotherapy and can be used to inform study designs of future comparative-effectiveness studies.

Supplementary material

Table 1-5:
https://ars.els-cdn.com/content/image/1-s2.0-S1879850022003630-mmc1.pdf

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CHAPTER 3

The first patient-reported outcomes from the Utrecht Prostate Cohort (UPC): the first platform facilitating “trials within cohorts” (TwiCs) for the evaluation of interventions for prostate cancer

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Abstract

Purpose: To describe the development and first outcomes of the Utrecht Prostate Cohort (UPC): the first "trials within cohorts" (TwiCs) platform for prostate cancer.

Materials and methods: All non-metastasized, histologically proven prostate cancer patients who are planned to receive standard of care are eligible for inclusion in the UPC. Patients provide informed consent for the collection of clinical and technical patient data, physician-reported outcomes, and patient-reported outcomes (PROs) up to 10 years post-treatment. Additionally, patients may provide broad consent for future randomization for experimental-intervention trials (TwiCs). Changes in PROs (EPIC-26 questionnaire domains) of the participants who received standard of care were analyzed using Wilcoxon signed-rank tests.

Results: In 2 years, 626 patients were enrolled, 503 (80.4%) of whom provided broad consent for future randomization. Among these, 293 (46.8%) patients underwent magnetic resonance imaging (MRI)-guided external beam radiation therapy (EBRT), 116 (18.5%) computed tomography (CT)-guided EBRT, 109 (17.4%) robot-assisted radical prostatectomy (RARP), and 65 (10.4%) patients opted for active surveillance. Patients treated with MRI-guided and CT-guided EBRT showed a transient but significant decline in urinary irritative/obstructive and bowel domain scores at 1-month follow-up. RARP patients showed a significant deterioration of urinary incontinence domain scores between baseline and all follow-up moments and significant improvement of urinary irritative/obstructive domain scores between baseline and 9- and 12-month follow-up. All radical treatment groups showed a significant decline in sexual domain scores during follow-up. Active surveillance patients showed no significant deterioration over time in all domains.

Conclusion: The first results from the UPC study show distinct differences in PROs between treatment options for prostate cancer.

Introduction

Prostate cancer is the most common cancer in men worldwide, with an estimated 1,414,259 new cases and 375,304 associated deaths in 2020.[1] Overall survival rates are high due to the non-aggressive nature of many localized prostate tumors and the availability of effective treatment options.[2]

Established curative (radical) treatment modalities for primary localized prostate cancer include external beam radiotherapy (EBRT), brachytherapy (BT), and robot-assisted radical prostatectomy (RARP). Radical treatments are associated with adverse events such as genitourinary (GU) and gastrointestinal (GI) problems, and erectile dysfunction (ED). Therefore, new treatment modalities, aimed at reducing adverse events and improving quality of life (QoL), are being developed. These include real-time magnetic resonance imaging (MRI)-guided EBRT and focal therapies such as high-intensity focused ultrasound (HIFU) or irreversible electroporation (IRE).[3-5] An alternative to active treatment for selected low- and intermediate-risk prostate cancer patients is active surveillance (AS).

Evaluation of new treatments is ideally performed using the randomized controlled trial (RCT) design. RCTs are often limited by slow recruitment, high rates of premature ending[6], limited generalizability due to strict patient inclusion criteria that may not represent the real-world patient population[7,8], fear for the experimental treatment, which can prevent patients from participating, or preference for the new intervention, leading to patient disappointment and even drop out as a result of allocation to the control arm.[9] To overcome some of these limitations, the trials within cohorts (TwiCs) design was developed.[10] In this TwiCs design, prospective cohorts or registries serve as facilities for simultaneous and randomized evaluation of multiple interventions for the same condition. The basis of TwiCs is a comprehensive prospective observational cohort of patients with the condition of interest (e.g., prostate cancer), who (in principle) undergo standard treatment and for whom relevant short- and long-term outcome measures are captured. For each experimental intervention that is compared to standard treatment in an RCT, a subcohort of eligible patients is identified within the cohort. From this subcohort of eligible patients, a random sample is offered the intervention. The outcomes of these randomly selected patients are then compared to the remaining eligible patients in the subcohort who received standard care. During the trial, the control group is not actively informed about the trial. The same process can be repeated (simultaneously) for other experimental interventions.[11,12]

Due to the high pace of technical innovations in prostate cancer treatment, we set up a comprehensive cohort of patients with non-metastasized, histologically proven prostate cancer, facilitating the TwiCs design: the "Utrecht Prostate Cohort for cancer treatment intervention studies and long-term evaluation" (UPC). With the UPC, we aim to: (1) create a real-life data infrastructure for the evaluation of short- and long-term clinical and patient-reported outcomes during and after treatment for prostate cancer. (2) Provide a facility for multiple interventional trials and observational studies for the evaluation of new treatment interventions for prostate cancer. This paper describes the infrastructural set up and presents the first data from all patients enrolled in the UPC study in the first 2 years of inclusion.

Materials and methods

Patients

The UPC study received approval from the Institutional Review and Ethics Board of the University Medical Center Utrecht (19-692/M), the Netherlands. All non-metastatic, histologically proven prostate cancer patients are eligible for participation in the UPC. After diagnosis, patients are informed by a researcher or research assistant about the study, after which written informed consent is obtained. Patients that are mentally incompetent or unable to understand the Dutch language are excluded from participation. Enrolment takes place at two urology clinics and one radiotherapy facility covering a large region within the Netherlands.

Staged-informed consent

In addition to signing informed consent for the collection, use, and sharing of clinical and technical data and receiving QoL questionnaires, patients may provide broad consent for random allocation to experimental interventional treatment(s) in the (near) future in case they are eligible for a trial within the cohort.[10,11] In this case, patients who are randomly allocated to the experimental arm are offered to undergo an experimental treatment, for which, in case they accept, additional written informed consent is obtained. Patients allocated to the control arm will receive standard treatment and are not informed while the study is ongoing. According to the TwiCs design, multiple trials can run within the UPC simultaneously. All patients are informed about the results after completion of a study within the UPC, irrespective of their participation in that specific study.

Clinical data

For the observational cohort, clinical data are prospectively collected and stored in a cloud-based database. Data are collected from the electronic patient records, referral letters, and annual data extraction from the Dutch cancer registry.

Sociodemographic data include: date of birth, family history of prostate cancer, educational level, Charlson Comorbidity Index (CCI), and Eastern Cooperative Oncology Group (ECOG) performance status. Disease characteristics include: date of diagnosis, PSA level, tumor nodes metastases (TNM) classification, pathological results, prostate volume, prostate imaging reporting and data system (PI-RADS) classification, prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) computed tomography (CT) results, and bone scintigraphy. Imaging data are stored in a Digital Imaging and Communications in Medicine (DICOM) repository. For patients undergoing RARP and/or pelvic lymph node dissection, additional pathologic information is collected, including pathologic tumor and lymph node status and surgical margins. Surgical complications are recorded using the Clavien Dindo classification. For radiotherapy patients, irradiated volume, prescribed dose, and documentation of androgen deprivation therapy prescription are collected. Acute and chronic toxicity is collected using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) version 5.

Recurrence- and progression-free survival are assessed following routine care by regular measurement of PSA level. Survival is assessed through follow-up questionnaires, the systematical assessment of the Municipal Personal Records Database, and the Dutch Cancer Registry.

Patient-reported outcomes (PROs)

Patients have the option to fill out paper QoL questionnaires or opt for online completion of the QoL questionnaires after secured login. Patients are invited to fill out questionnaires at baseline and at 1, 3, 6, 9, 12, 18, and 24 months post-treatment. Thereafter, questionnaires are filled out annually up to 10 years post-treatment. Annually, additional information is obtained on (serious) adverse events.

PRO questionnaires include: Expanded Prostate Cancer Index Composite Short Form (EPIC-26)[13], EORTC Quality of Life Questionnaire (QLQ-C30)[14], International Index of Erectile Function-5 (IIEF-5)[15], EuroQol questionnaire (EQ-5D-5L)[16], International Prostate Symptom Score (IPSS)[17], Hospital Anxiety and Depression Scale (HADS)[18], and Workability Index (WAI)[19] (the WAI questionnaire is not included at 1, 6, 9, and 18 months).

Statistical analysis

Descriptive statistics were reported for the questionnaire response rate, baseline characteristics, and the outcomes of the EPIC-26 questionnaire at baseline, 1, 3, 6, 9, and 12 months follow-up for each major treatment group. For the AS patient group, the first completed questionnaire was set as baseline questionnaire. Within each treatment group, follow-up EPIC-26 scores were compared to baseline using the difference in medians (Δ) and Wilcoxon signed-rank tests. A P-value < 0.05 was considered statistically significant. The minimal clinically relevant difference for the EPIC-26 domain scores was considered Δ = 5–7 for the urinary irritative/obstructive domain, Δ = 6–9 for the urinary incontinence domain, Δ = 4–6 for the bowel domain, Δ = 10–12 for the sexual domain, and Δ = 4–6 for the hormonal domain.[20] All analyses were performed using R version 4.1.2.

Results

Between February 5, 2020, and February 5, 2022, 626 patients were enrolled in the UPC. All participants signed informed consent for the use of their data for research purposes, 556 (88.8%) provided consent for filling out PRO questionnaires, and 503 (80.4%) provided broad consent for future randomization (TwiCs). Since the start of the study, two (0.3%) patients withdrew from participation, and nine (1.4%) patients deceased during follow-up.

On February 5, 2022, 293 (46.8%) patients had started or completed MRI-guided EBRT, 116 (18.5%) had started or completed CT-guided EBRT treatment, and 109 (17.4%) patients underwent RARP. An additional 65 (10.4%) patients opted for AS (Table 1). Patients who underwent RARP were youngest on average (mean: 68.2 years), followed by those who opted for AS (mean: 68.4 years), MRI-guided EBRT (mean 70.3 years), and CT-guided EBRT (mean 73.0 years). Most RARP and MRI-guided EBRT patients had intermediate-risk localized prostate cancer (53.2 and 74.1%, respectively), whereas most AS patients had low-risk localized prostate cancer (70.8%). In the CT-guided EBRT group, most patients had high-risk localized prostate cancer (72.4%).

Table 1: *Baseline characteristics of the four major patient groups within the UPC study*

Characteristic	Treatment group			
	MRI-guided EBRT	**CT-guided EBRT**	**RARP**	**AS**
n	293	116	109	65
Age, mean (SD)	70.3 (6.4)	73.0 (6.2)	68.2 (5.7)	68.4 (6.1)
Charlson comorbidity index, mean (SD)	0.6 (1.1)	0.8 (1.2)	0.3 (0.8)	0.4 (0.7)
Consent for receiving PRO questionnaires, n (%)	264 (90.1)	90 (77.6)	104 (95.4)	61 (93.8)
Fraction scheme, n (%)				
5 × 7.25 Gy	243 (82.9)	8 (6.9)	NA	NA
20 × 3.1 Gy	47 (16.0)	61 (52.6)	NA	NA
35 × 2.2 Gy	0 (0.0)	40 (34.5)	NA	NA
Other	3 (1.0)	7 (6.0)	NA	NA
ADT, n (%)	40 (13.7)	83 (72.8)	3 (2.8)	0 (0.0)
cT stage, n (%)				
cT1	150 (51.4)	36 (31.0)	57 (52.3)	53 (81.5)
cT2	128 (43.8)	39 (33.6)	39 (35.8)	11 (16.9)
cT3	13 (4.5)	40 (34.5)	13 (11.9)	1 (1.5)
cT4	1 (0.3)	1 (0.9)	0 (0.0)	0 (0.0)
Regional lymph node metastasis, n (%)	2 (0.1)	28 (24.1)	7 (6.4)	0 (0.0)
PSA, n (%)				
< 10 ng/ml	29 (9.9)	5 (4.3)	11 (10.1)	46 (70.8)
10–20 ng/ml	217 (74.1)	27 (23.3)	58 (53.2)	17 (26.2)
> 20 ng/ml	47 (16.0)	84 (72.4)	40 (36.7)	2 (3.1)
Gleason score, n (%)				
≤ 6	48 (16.4)	8 (6.9)	19 (17.4)	54 (83.1)
7	225 (76.8)	49 (42.3)	65 (59.7)	11 (16.9)
≥ 8	20 (6.8)	59 (50.9)	25 (23.0)	0 (0.0)
Risk classification (EAU), n (%)				
Low risk	29 (9.9)	5 (4.3)	11 (10.1)	46 (70.8)
Intermediate risk	217 (74.1)	27 (23.3)	58 (53.2)	17 (26.2)
High risk	47 (16.0)	84 (72.4)	40 (36.7)	2 (3.1)

Abbreviations: UPC = Utrecht prostate cohort; MRI = magnetic resonance imaging; CT = computed tomography; EBRT = external beam radiotherapy; RARP = robot assisted radical prostatectomy; AS = active surveillance; PRO = patient-reported outcome; ADT = androgen deprivation therapy; cT stage = clinical tumor stage; PSA = prostate-specific antigen; EAU = European association of urology.

The questionnaire response rate for the entire cohort was 78.8% at baseline, 76.7% at 6-month follow-up, and 71.0% at 12-month follow-up. For the EPIC-26 urinary irritative/obstructive domain, the MRI-guided and CT-guided EBRT patients reported significant and clinically relevant lower scores at 1-month follow-up compared to baseline (MRI-guided EBRT: Δ – 12.5, P < 0.001; CT-guided EBRT: Δ – 12.5, P < 0.001) (Fig. 1 and Supplementary material). RARP patients reported a significant and clinically relevant improvement in urinary irritative/obstructive domain scores at 9- (Δ + 6.2, p = 0.002) and 12-month (Δ + 6.2, P = 0.029) follow-up compared to baseline. In these patients, a significant and clinically relevant decline in the urinary incontinence domain scores at 1, 3, 6, 9, and 12-month follow-up compared to baseline was reported (Δ – 63.5, P < 0.001; Δ – 54.0, P < 0.001; Δ – 35.3, P < 0.001; Δ – 29.0, P = 0.001; Δ – 24.9, P = 0.045; respectively) and at 1-month follow-up by the CT-guided EBRT patients (Δ – 8.2, P = 0.031). For the bowel domain, the MRI-guided and CT-guided EBRT patients reported significant and clinically relevant lower scores at 1-month follow-up compared to baseline (MRI-guided EBRT: Δ – 8.3, P < 0.001; CT-guided EBRT: Δ – 8.3, P < 0.001). The median sexual domain score declined significantly from baseline up to 12-month follow-up from 43.0 to 21.5 (P < 0.001) for the CT-guided EBRT group, from 69.5 to 48.7 (P < 0.001) for the MRI-guided EBRT group, and from 75.0 to 25.0 (P < 0.001) for the RARP group. In the MRI-guided EBRT and CT-guided EBRT group, a significant and clinically relevant decline of the hormonal domain score from baseline was observed for all follow-up moments and for the RALP patients at 9-month follow-up. In the AS group, no significant difference in any of the domains at any follow-up point was observed.

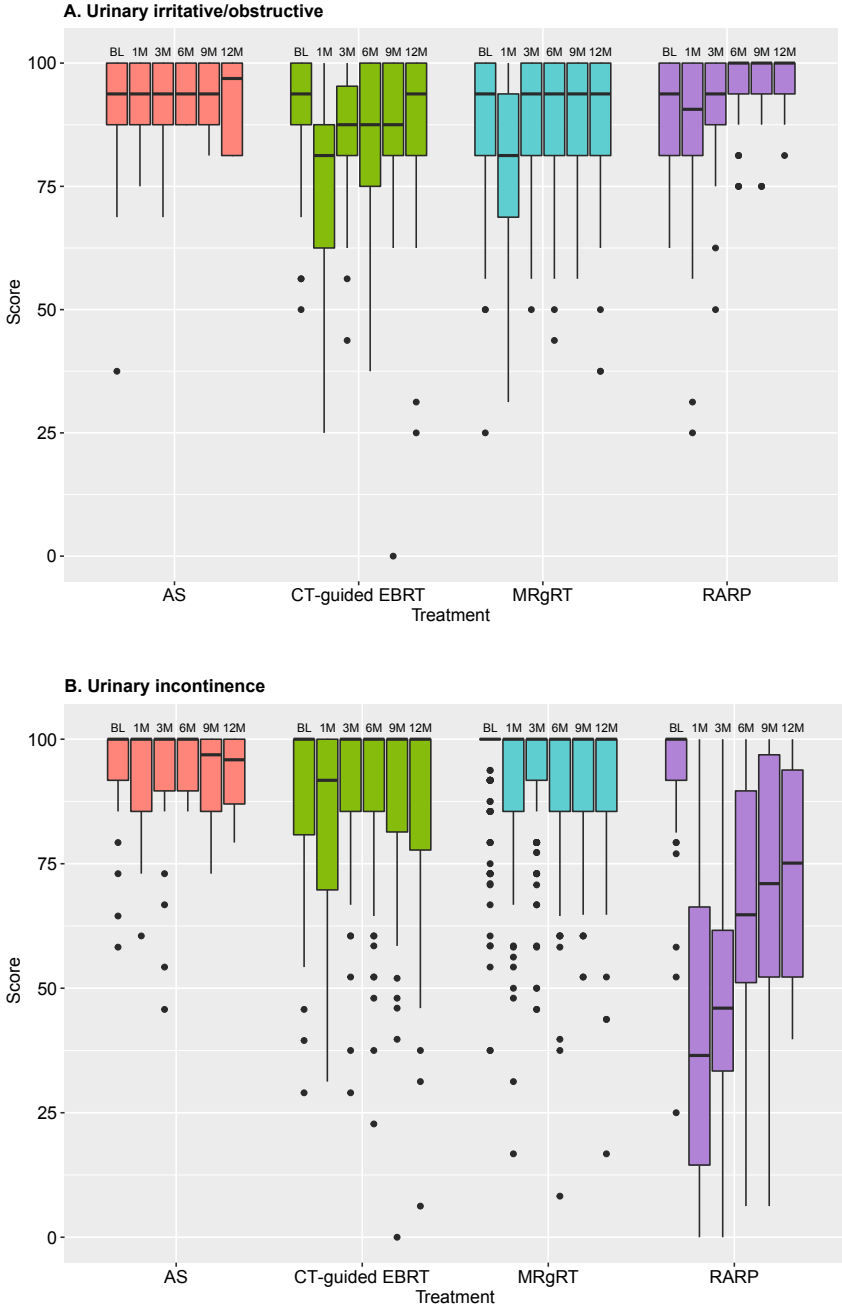
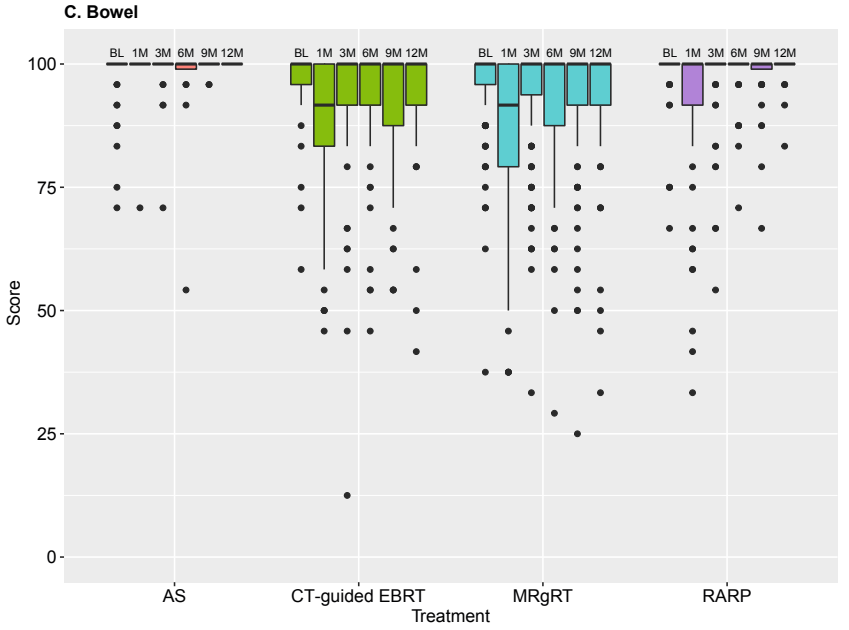


Figure 1: *EPIC-26 domain scores for the four largest patient groups at baseline and 1, 3, 6, 9, and 12 months follow-up (numbers at risk in Supplementary material).*

Abbreviations: BL = baseline; M = month; AS = active surveillance; EBRT = external beam radiotherapy; MRgRT = magnetic resonance imaging-guided radiotherapy; RARP = robot-assisted radical prostatectomy.



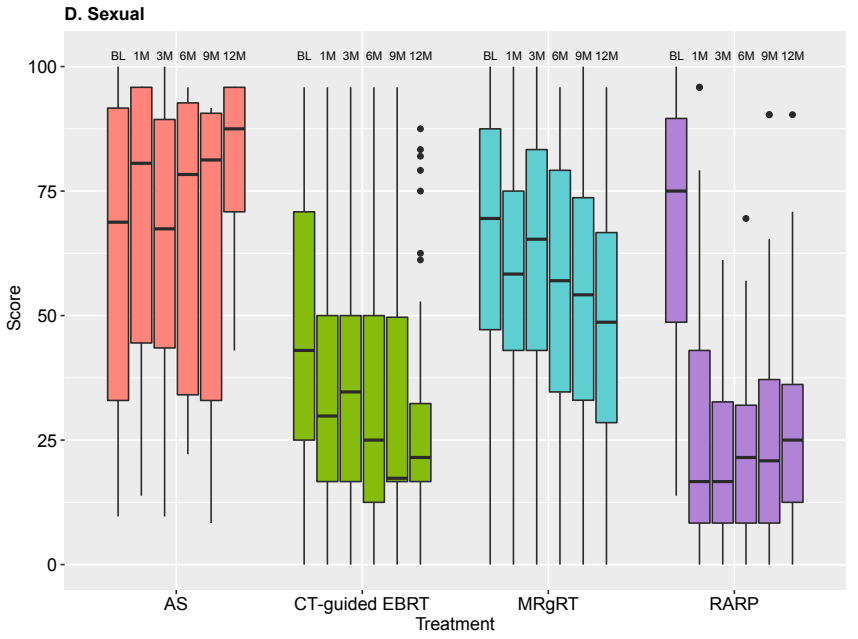


Figure 1: *Continued.*

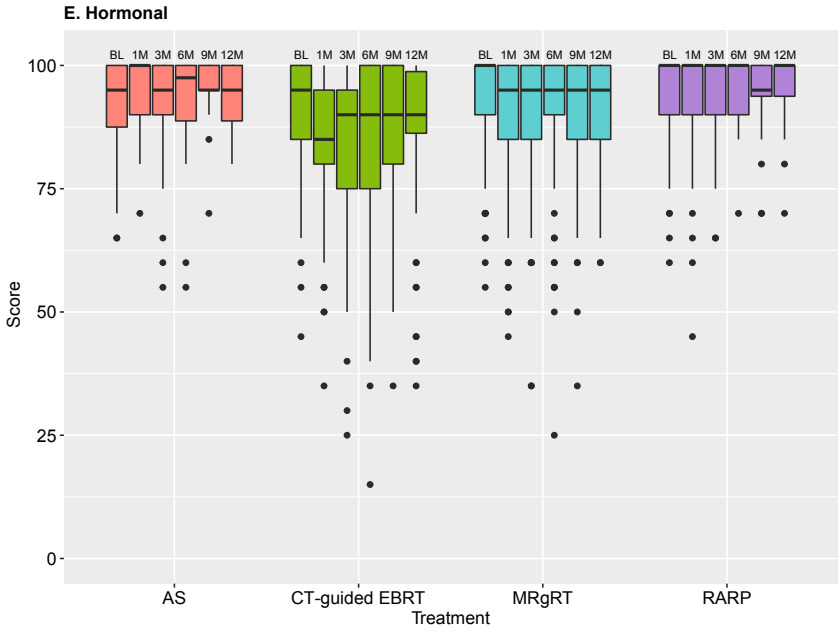


Figure 1: *Continued.*

Discussion

New treatments for prostate cancer patients are being developed at a rapid pace. Multiple (simultaneous) trials or other studies for new treatment interventions can be conducted within the UPC. We prospectively collect a predefined set of baseline and follow-up measurements for the cohort at regular time points. Using standardized PROs, we can effectively compare short- and long-term outcomes of treatment interventions to standard care, which will be important for the implementation of new treatment interventions in clinical practice. All future trials within the UPC will use the same predefined study population, and baseline and follow-up data will be collected at the same time points. This will enable direct comparison between standard-of-care and new treatment interventions and is in line with the International Consortium for Health Outcome Measures (ICHOM), which focuses on the standardization of outcome measures.[21] Next to TwiCs, the UPC study facilitates non-randomized comparison studies between the patient groups within the cohort, as well as with external cohorts. Because of the vast and detailed patient characteristics, treatment procedures, and outcomes collected within the UPC, the data can be used for post-marketing studies, technical development studies (following the R-IDEAL framework)[22], prediction studies, and imaging studies.

Across the different standard treatment groups within the UPC, different patterns in EPIC-26 domain scores are manifest. Initial analysis of the EPIC-26 domain scores showed no significant difference for any follow-up time points compared to baseline for all domains in the AS group. All radical treatment options showed significant and clinically relevant change in one or more domains at one or more follow-up moments, which is in line with large prospective cohorts in literature[23-26] and affirm the domains in which improvements can be made in terms of toxicity reduction. A limitation of this first UPC report is the relatively low number of included patients, especially towards longer follow-up, which lowers power for comparisons. Ongoing data collection and follow-up will increase these numbers for each treatment group and will enable us to conduct stratified or matched comparisons between groups within the cohort and with external cohorts, allowing the evaluation of differences in toxicity and efficacy between primary prostate cancer treatments.

The urge to prevent ED after radical treatment has led to the first trial that is currently running within the UPC. This single-arm phase II trial investigates the effect of neurovascular sparing MRI-guided radiotherapy on erectile function in a localized prostate cancer population (NCT04861194).[27,28] Because all study parameters for this trial are already prospectively recorded within the UPC (e.g., the IIEF-5 questionnaire for the measurement of erectile function), it can run very efficiently. Furthermore, UPC data are currently being used to analyze dose-toxicity relationships in MRI-guided radiotherapy patients to evaluate and possibly adjust existing or propose new dose constraints to further reduce toxicity after radiotherapy. Systematically recorded physician- and patient-reported toxicity (i.e., CTCAEs and PROs) and technical data (i.e., MRI-guided radiotherapy dose parameters) recorded within the UPC are used for this goal.

Currently, only non-metastatic prostate cancer patients that opt for AS or awaiting radical treatment are included. This can be extended to additionally include prostate cancer patients with metastatic or recurrent disease undergoing palliative or salvage treatments. Also, patients at risk of prostate cancer can be included to analyze diagnostic strategies before the diagnosis of prostate cancer. Furthermore, a biobank for genetic and (histo)pathologic studies will be added in the near future. The UPC study is designed in such a way that it can be expanded to other medical centers, and external institutions can apply to receive data for research purposes.

The TwiCs design overcomes some of the hurdles that are associated with running classic RCTs. Advantages of the TwiCs design over the classic RTC design include more efficient use of control patients, improved comparison between different trial interventions, enhanced generalizability, and reduced disappointment bias.[10,12] However, there

are some limitations of TwiCs design. First, the collected clinical data are generated from routine care and, therefore, may be considered pragmatic. Endpoints for trials within the UPC need to be part of the predefined outcomes measured for all patients. Second, the questionnaire return rates slowly decrease over time, which is also a concern in the UPC study and may influence data comparability and generalizability. Therefore, we are actively informing patients about the results of studies conducted within the cohort to keep participants actively involved and motivated to return the questionnaires. Third, in the TwiCs design, a patient allocated to the control arm is not informed about being a participant in a trial and is also not informed about the interventional treatment. The (conventional) control treatment can be considered the best treatment in terms of outcome based on the current, up-to-date guidelines. However, because a patient is withheld the information and possibly unaware of the existence of a specific experimental treatment, the patient does not have the opportunity to receive the experimental treatment off-protocol or outside a clinical trial. Although UPC participants sign informed consent for these procedures up-front, therapeutic misconception could remain an issue since optimism about potentially being randomized in the experimental arm when participating in the UPC could overshadow the equal chance of being randomized in the control arm and the even higher chance of not participating in a trial at all.[11,29] Therefore, researchers should extensively inform participants about this TwiCs procedure before participants sign consent.[30]

Conclusion

The UPC study is the first platform for prostate cancer according to the TwiCs design. It provides an ongoing prospective observational cohort and an infrastructure for multiple trials and other studies for the evaluation of new treatment interventions for prostate cancer. The initial results after 2 years of inclusion highlight the areas on which future research and new interventions should focus.

Supplementary material

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9427931/bin/345_2022_4092_MOESM1_ESM.docx

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CHAPTER 4

Patient preferences for treatment modalities for localized prostate cancer

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Abstract

Purpose: To assess the patient preferences and utility scores for the different conventional and innovative treatment modalities for localized prostate cancer.

Materials and methods: Patients treated for localized prostate cancer and healthy volunteers were invited to fill out a treatment-outcome scenario questionnaire. Participants ranked six different treatments for localized prostate cancer from most to least favorable, prior to information. In a next step, treatment procedures, toxicity, risk of biochemical recurrence and follow-up regimen were comprehensibly described for each of the six treatments (i.e., treatment-outcome scenarios), after which patients re-ranked the six treatments. Additionally, participants gave a visual analogue scale (VAS) and time trade-off (TTO) score for each scenario. Differences between utility scores were tested by Friedman tests with post hoc Wilcoxon signed-rank tests.

Results: Eighty patients and 29 healthy volunteers were included in the study. Before receiving treatment-outcome scenario information, participants ranked magnetic resonance-guided adaptive radiotherapy most often as their first choice (35%). After treatment information was received, active surveillance was most often ranked as the first choice (41%). Utility scores were significantly different between the six treatment-outcome scenarios, and active surveillance, non-invasive and minimally invasive treatments received higher scores.

Conclusion: Active surveillance and non-invasive treatment for localized prostate cancer were the most preferred options by prostate cancer patients and healthy volunteers and received among the highest utility scores. Treatment preferences change after treatment information is received.

Introduction

The majority of prostate cancer patients have localized disease at the time of diagnosis. Overall survival rates are high due to the nonaggressive nature of many localized prostate tumors and the effective treatment options.[1] Treatment modalities for localized prostate cancer include external beam radiotherapy (EBRT), low-dose-rate (LDR) brachytherapy, robot-assisted radical prostatectomy (RARP) and for low-risk prostate cancer, active surveillance.[2] Radical treatments bear a considerable risk of adverse effects such as erectile dysfunction, urinary problems and bowel problems. New treatment modalities that aim to reduce adverse events are being developed, such as magnetic resonance imaging (MRI)-guided adaptive radiotherapy and focal therapy, including irreversible electroporation, high-intensity focused ultrasound and cryoablation, but long-term functional and oncological outcomes are not yet available.[3-6]

Differences in risk for adverse events between the different treatment modalities are often poorly understood by patients.[7] It is reported that 65% of the patients do not know that they are at greater risk for incontinence after RARP than after radiotherapy (i.e., EBRT and brachytherapy) and that 61% have a comparable wrong perception about erectile dysfunction. On the other hand, 53% of the patients were unaware that after RARP, the risk for bowel problems is lower than after radiotherapy. Furthermore, 80% do not understand that mortality rates are comparable following active surveillance, RARP, EBRT and brachytherapy. Also, the risk of requiring definitive treatment after active surveillance is sometimes overestimated by patients. Often, a patient's decision to receive active treatment versus active surveillance is largely based on the urologist's recommendation.[8]

Besides treatment preference, cost-effectiveness is an important factor in the evaluation of conventional treatments and the implementation of new treatments. New, and often costly, innovative treatments are often rushed into clinical standard care before treatment superiority is proven against conventional treatments.[9] Early health technology assessment (HTA) aims to evaluate the cost-effectiveness of new treatments at an early stage. Utility scores, which are the measures of value that an individual gives under conditions of uncertainty that satisfy certain aspects, can guide in the early HTA of new treatment strategies for both conventional and new treatment modalities.[10]

It remains unclear what treatment modalities for localized prostate cancer are preferred by patients in case multiple treatment options are available, and what utility scores patients would give to those treatments. We aimed to assess the patient preferences and utility scores for treatment modalities for localized prostate cancer.

Materials and methods

Participants

The study was approved by our institutional ethics review board. Included were patients participating in the "Utrecht Prostate Cohort" (NCT04228211), who signed informed consent for receiving questionnaires and participating in future studies.[11] An unselected consecutive sample of equal numbers of patients who underwent active surveillance, RARP, conventional EBRT and MRI-guided radiotherapy were invited to participate in the present study. Patients who underwent treatment were approached at least 6 months after treatment.

Patients were invited by email and participating patients were asked to invite up to a maximum of five healthy male volunteers without prostate cancer, over 50 years of age, to anonymously fill out the same questionnaire. Questionnaires were filled out online through a secured link. Patients and volunteers were encouraged to fill out the questionnaires individually.

Treatment-outcome scenario questionnaire

A comprehensive treatment-outcome scenario questionnaire was developed based on the literature. The developed questionnaire was reviewed by an epidemiologist, a radiation oncologist and two urologists (Supplementary material: Treatment-outcome scenario questionnaire).

Firstly, participants were asked to fill out a general questionnaire including questions on patient characteristics and self-assessed health by the validated five-level version of the EuroQol 5-dimension (EQ-5D-5L) questionnaire.[12]

Secondly, participants were asked to hypothesize being newly diagnosed with localized prostate cancer and eligible for the following six treatment options: active surveillance (no active treatment), RARP, conventional EBRT receiving 5 × 7.25 Gy, LDR brachytherapy receiving radiation via interstitial iodide-125 sources, MRI-guided radiotherapy receiving 5 × 7.25 Gy on an MR-Linac and focal therapy by irreversible electroporation. Each treatment was described in one sentence, after which participants were asked to rank treatment options from most to least favorable.

Thirdly, treatment-outcome scenarios for all six treatment options were extensively described, including treatment procedures, and possible complications and adverse effects, along with their probability based on the European prostate cancer guidelines and recent literature (Supplementary material: Table 1).[1, 13-19] Prognosis was described

as the chance of biochemical recurrence and prostate cancer-specific mortality risk within 10 years after treatment. For the assessment of utility scores, participants were asked to rate each scenario on a visual analogue scale (VAS) from 0 to 100. A score of 0 represented the treatment-outcome scenario as the worst thinkable health condition and a score of 100 represented the treatment-outcome scenario as perfect health. Additionally, participants were asked to rate the scenarios according to the time trade-off (TTO) method. With the TTO method, participants indicate how many years (with a range of 0 to 10) of life in perfect health weigh up to 10 years of life in the health status after treatment as described in the specific scenario. A score of 0 indicated living with the outcomes of the treatment-outcome scenario to be unbearable and a score of 10 as equal to living in perfect health. To improve and estimate the participants' understanding of the scoring methods, the questionnaire contained two scenario examples and two exercise scenarios to start with.

Fourthly, the question to rank the six given treatment options from most favorable to least favorable was repeated, but now with the aforementioned background information from the six treatment-outcome scenarios. All four steps were on separate subsequent electronic form pages and participants were urged not to go back.

The treatment-outcome scenario questionnaire was tested in a pilot study with five prostate cancer patients. Their comments were used to improve the questionnaire.

Statistical analysis

The ranks of the six treatment options were presented as proportions. Proportions (discrete variables) and medians with interquartile range or means with SD (continuous variables) were calculated for baseline characteristics and VAS (0–100) and TTO (0–10) scores. The Spearman's rank correlation coefficient (ρ) was calculated to assess the correlation between VAS and TTO scores. We used the Friedman test to compare VAS and TTO scores between treatment scenarios. Stratified analyses were performed to evaluate whether utility scores differed for patients and volunteers, by age, previous prostate cancer treatment, education and baseline EQ-5D VAS score. When the Friedman test found a significant difference between the six ratings, the active surveillance scenario score was compared to all the other five scenario scores using post hoc Wilcoxon signed-rank tests. Bonferroni corrections for multiple testing were performed for all tests. The level of significance was set at $P < 0.05$. Statistical analysis was performed using R version 4.0.5.

Results

The questionnaire was sent out to 124 patients. Twenty-one (68%) active surveillance, 21 (68%) MRI-guided radiotherapy, 21 (68%) conventional EBRT and 17 (55%) RARP patients completed the questionnaire. The median time between treatment or start of active surveillance and filling out the questionnaire was 7.3 months (range: 6.0–10.0). At time of filling out the questionnaire, no patient had experienced tumor recurrence. Thirty-six volunteers completed the questionnaire, of which 29 met the inclusion criteria. Healthy volunteers were younger and reported a higher EQ-5D VAS score than the patient group (Table 1).

After receiving limited (one sentence) treatment-outcome scenario information, patients ranked MRI-guided radiotherapy most often as their first choice (33%), followed by active surveillance (23%) and RARP (21%) (Fig. 1). Active surveillance was most often ranked as the sixth choice (45%), followed by RARP (34%) and brachytherapy (9%). Patients ranked the treatment they had received themselves most often first, with 67% Active surveillance as first choice for active surveillance patients, 86% MRI-guided radiotherapy as first choice for MRI-guided radiotherapy patients, 38% of conventional EBRT as first choice for conventional EBRT patients and 65% of RARP as first choice for RARP patients. Fifty-five percent of patients that ranked active surveillance as first choice, ranked RARP as sixth choice and 67% of participants that ranked RARP as first choice also ranked active surveillance as sixth choice.

After receiving all the information from the different treatment-outcome scenarios, the number of first choices increased for active surveillance, remained the same for brachytherapy, and decreased for all other treatments (Fig. 2). Active surveillance was most often ranked as first choice (43%), followed by MRI-guided radiotherapy (28%) and RARP (14%). RARP was most often ranked as the sixth choice (42%), followed by active surveillance (30%) and brachytherapy (12%). Active surveillance, MRI-guided radiotherapy and RARP patients ranked the treatment they received themselves most often first with 86% active surveillance as first choice for active surveillance patients, 48% MRI-guided radiotherapy as first choice for MRI-guided radiotherapy patients and 41% RARP as first choice for RARP patients, which was an increase for active surveillance and a decrease for MRI-guided radiotherapy and RARP. Conventional EBRT patients most often ranked MRI-guided radiotherapy as first choice (33%). Patients that ranked active surveillance as first choice, most often ranked RARP as sixth choice (59%) and participants that ranked RARP as first choice most often ranked active surveillance as sixth choice (55%).

Table 1: *Baseline characteristics*

	MRI-guided radiotherapy	Conventional EBRT	RARP	Active surveillance	Healthy volunteers
n	21	21	17	21	29
Age, median (IQR)	69 (67–73)	73 (67–75)	69 (67–71)	69 (63–73)	67 (63–71)
BMI, median (IQR)	24.9 (22.6–29.2)	26.0 (24.4–27.8)	25.8 (24.3–27.2)	24.7 (24.4–26.2)	24.5 (22.8–26.2)
Marital status					
Single	1 (4.8)	2 (9.5)	1 (5.9)	0 (0.0)	0 (0.0)
Living together	2 (9.5)	1 (4.8)	1 (5.9)	2 (9.5)	3 (10.3)
Married	16 (76.2)	17 (81.0)	14 (82.4)	18 (85.7)	24 (82.8)
Divorced	0 (0.0)	0 (0.0)	1 (5.9)	1 (4.8)	2 (6.9)
Widow	2 (9.5)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Education, n (%)					
No school completed	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)
Primary school	1 (4.8)	0 (0.0)	1 (5.9)	1 (4.8)	0 (0.0)
High school	4 (19.0)	5 (23.8)	2 (11.8)	3 (14.3)	9 (31.0)
Vocational education	2 (9.5)	5 (23.8)	4 (23.5)	5 (23.8)	3 (10.3)
Higher education/university	14 (66.7)	11 (52.3)	10 (58.8)	11 (52.4)	17 (58.6)
Current employment, n (%)					
Full-time	3 (14.3)	1 (4.8)	1 (5.9)	6 (28.6)	12 (41.4)
Part-time	3 (14.3)	2 (9.5)	2 (11.8)	3 (14.3)	1 (3.4)
Unemployed/retired	15 (71.4)	18 (85.7)	14 (82.4)	12 (57.1)	16 (55.2)
Prostate cancer risk classification (EAU), n (%)					
Low	1 (4.8)	2 (9.5)	1 (5.9)	17 (81.0)	NA
Intermediate	18 (85.7)	2 (9.5)	10 (58.8)	3 (14.3)	NA
High	2 (9.5)	17 (81.0)	6 (35.3)	1 (4.8)	NA

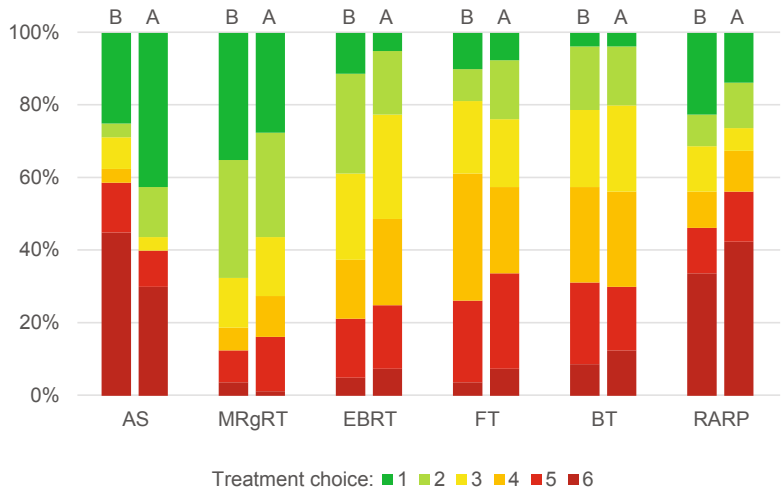
Table 1: *Continued*

	MRI-guided radiotherapy	Conventional EBRT	RARP	Active surveillance	Healthy volunteers
Androgen deprivation therapy, n (%)	3 (14.3)	15 (71.4)	0 (0.0)	0 (0.0)	NA
EQ-5D-5L dimensions, mean (SD)					
Mobility	1.6 (1.0)	1.5 (0.8)	1.3 (0.6)	1.2 (0.5)	1.1 (0.3)
Self-care	1.1 (0.4)	1.1 (0.2)	1.0 (0.0)	1.1 (0.5)	1.0 (0.0)
Daily activity	1.4 (0.7)	1.4 (0.9)	1.2 (0.4)	1.1 (0.4)	1.1 (0.4)
Pain/discomfort	1.6 (0.7)	2.0 (1.0)	1.9 (0.8)	1.6 (0.9)	1.6 (0.7)
Anxiety/depression	1.2 (0.4)	1.3 (0.7)	1.2 (0.5)	1.2 (0.4)	1.1 (0.4)
EQ-5D VAS, median (IQR)	89 (75–91)	81 (70–90)	85 (80–90)	81 (80–90)	90 (81–97)

Note: All data available.

Abbreviations: BMI = body mass index; EAU = European Association of Urology; EBRT = external beam radiotherapy; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; IQR = interquartile range; MRI = magnetic resonance imaging; NA = not applicable; SD = standard deviation; RARP = robot-assisted radical prostatectomy; VAS = visual analogue scale.

A. Patients



B. Healthy volunteers

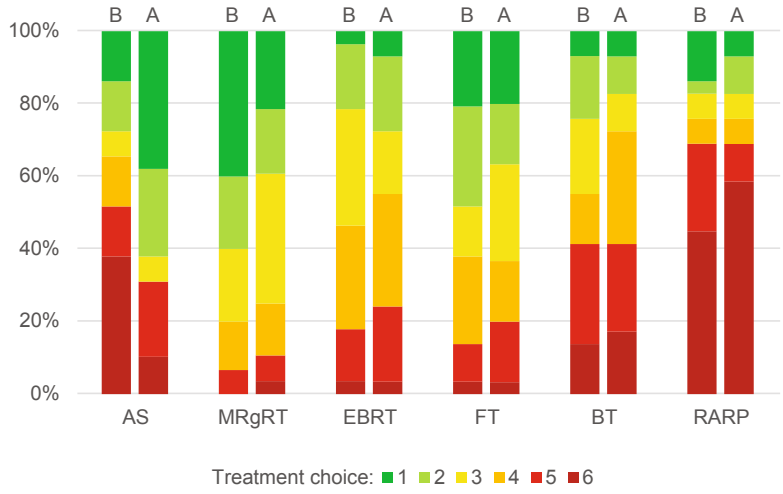


Figure 1: *Preferences for treatment of localized prostate cancer before and after treatment information was received (first choice to sixth choice) for (A) patients (n = 80) and (B) healthy volunteers (n = 29).*

Abbreviations: A = after information is received; B = before information is received; AS = active surveillance; BT = brachytherapy; EBRT = conventional external beam radiotherapy; FT = focal therapy; MRgRT = magnetic resonance imaging-guided radiotherapy; RARP = robot-assisted radical prostatectomy.

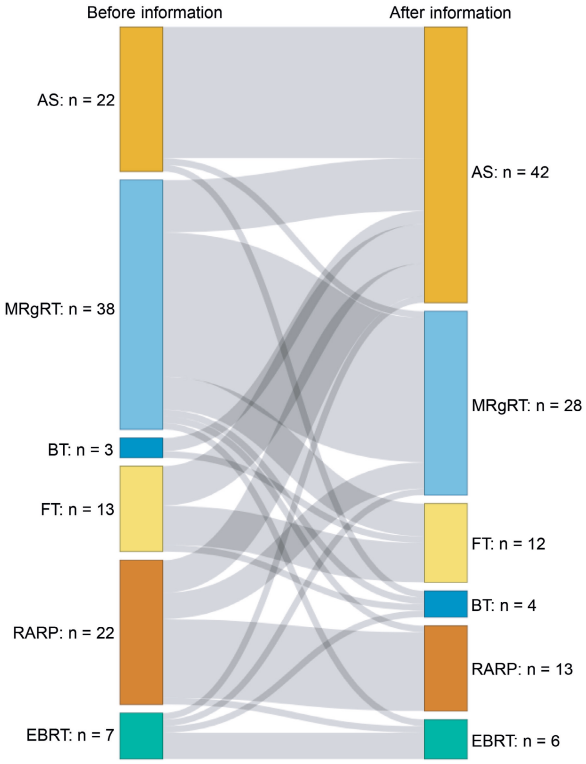


Figure 2: *Mitigation of first-choice treatment for localized prostate cancer after information was received of patients and healthy volunteers (n = 105). Four patients were excluded because multiple first choices were filled out.*

Abbreviations: AS = active surveillance; BT = brachytherapy; EBRT = conventional external beam radiotherapy; FT = focal therapy; MRgRT = magnetic resonance imaging-guided adaptive radiotherapy; RARP = robot-assisted radical prostatectomy.

Healthy volunteers ranked MRI-guided radiotherapy most often as first choice (41%), followed by focal therapy (21%), and both RARP and active surveillance (14%) before receiving information. RARP (43%), active surveillance (37%) and brachytherapy (13%) were most often ranked as sixth choice. After treatment information was received, active surveillance was most often ranked as first choice (38%), followed by both MRI-guided radiotherapy (21%) and focal therapy (21%). RARP (61%), brachytherapy (18%) and active surveillance (11%) were most often ranked as sixth choice.

VAS scores for the treatment-outcome scenarios correlated strongly with TTO scores for both the patient group ($\rho = 0.75$, $P < 0.001$) and the healthy volunteer group ($\rho = 0.73$, $P < 0.001$). VAS scores were significantly different between the six treatment-outcome scenarios and were highest for the active surveillance treatment scenario (Table 2). After stratification for treatment history, age, education level and EQ-5D VAS score, the

VAS scores between the six treatment-outcome scenarios remained significantly different, except for the treatment history group that was previously treated with RARP.

TTO scores between the treatment-outcome scenarios were significantly different for the total population and all strata except for the patients previously treated with RARP and patients of ≥ 70 years old (Supplementary material: Table 2).

Discussion

Preferences for treatment of localized prostate cancer vary substantially between men and depend on the level and content of information received about the treatment procedures and outcomes. Active surveillance was the most preferred treatment choice after treatment information was received, followed by MRI-guided radiotherapy, which suggests a preference towards no treatment or non-invasive treatment in our study population. A preference towards active surveillance and non-invasive and minimally invasive alternatives becomes apparent from the reported VAS scores for the treatment-outcome scenarios. Conventional EBRT, brachytherapy and RARP had significantly lower VAS scores as compared to active surveillance, while MRI-guided radiotherapy and focal therapy had similar scores.

The main advantage of active surveillance is that no radical treatment is used, so no treatment-induced toxicity occurs. However, active surveillance is generally only indicated for low-risk prostate cancer patients. Also, in the case of disease progression, radical treatment such as surgery or radiotherapy – with its sequelae – may be indicated.[20] The psychological burden of living with untreated prostate cancer may not be bearable for every patient, which may explain why active surveillance was also reported to be the least preferred treatment option, before and after treatment information was received.[21]

MRI-guided radiotherapy enables real-time MR imaging and plan adaptation during radiotherapy, and therefore no fiducial markers need to be implanted.[22] The treatment is completely non-invasive and potentially causes less toxicity than conventional EBRT making it an appealing alternative to conventional EBRT.[23] However, the reduction of toxicity is still hypothetical as clinical evidence is still lacking and long-term evaluation is ongoing.[24] Therefore, in the scenario descriptions, toxicity and survival outcomes for the MRI-guided radiotherapy treatment-outcome scenario were set to be identical to conventional EBRT. The current absence of evidence for lower toxicity may explain why several patients in our study preferred conventional EBRT over MRI-guided radiotherapy.

Table 2: *Visual analogue scale score for each treatment scenario of all participants and stratified by baseline characteristics*

Participants	**Active surveillance** Median (IQR)	**MRI-guided radiotherapy** Median (IQR)	**Conventional EBRT** Median (IQR)	**Focal therapy** Median (IQR)	**Brachytherapy** Median (IQR)	**RARP** Median (IQR)	**P**[a]
Total n = 109	85 (70–93)	80 (69–90)	75 (60–85)[b]	80 (70–90)	72 (60–80)[b]	65 (54–80)[b]	< 0.001
Patients n = 80	83 (70–92)	80 (69–90)	75 (60–83)[b]	80 (70–90)	72 (59–80)[b]	63 (50–80)[b]	< 0.001
Healthy volunteers n = 29	85 (75–93)	75 (70–85)	75 (61–89)	80 (78–90)	72 (70–80)	65 (59–80)[b]	< 0.001
Treatment							
Active surveillance n = 21	77 (75–90)	70 (61–80)b	61 (50–70)[b]	75 (66–85)	60 (50–80)[b]	50 (45–60)[b]	< 0.001
MRI-guided radiotherapy n = 21	81 (70–93)	90 (80–93)	75 (60–88)	72 (69–90)	80 (64–90)	60 (40–80)[b]	< 0.001
Conventional EBRT n = 21	90 (70–94)	80 (70–90)	80 (70–90)	90 (80–95)	73 (70–90)	70 (60–80)	0.001
RARP n = 17	80 (62–90)	75 (58–82)	75 (65–80)	80 (75–85)	75 (60–80)	80 (75–85)	0.999
Age							
< 70 n = 58	85 (75–93)	80 (70–90)	74 (60–81)[b]	85 (77–90)	75 (60–80)[b]	60 (51–80)[b]	< 0.001
≥ 70 n = 51	81 (70–91)	80 (68–90)	79 (61–89)	79 (66–85)	70 (60–80)	70 (60–80)[b]	0.020
Education level[c]							
Low n = 46	78 (63–90)	75 (66–81)	71 (60–81)	80 (70–85)	70 (50–80)[b]	60 (55–80)[b]	< 0.001

Table 2: *Continued*

Participants	**Active surveillance** Median (IQR)	**MRI-guided radiotherapy** Median (IQR)	**Conventional EBRT** Median (IQR)	**Focal therapy** Median (IQR)	**Brachytherapy** Median (IQR)	**RARP** Median (IQR)	**P**[a]
High n = 63	90 (75–94)	80 (70–90)	75 (64–89)[b]	85 (72–90)	76 (70–90)[b]	69 (53–80)[b]	< 0.001
EQ-5D VAS							
< 80 n = 31	80 (73–90)	80 (70–85)	70 (60–80)	80 (70–90)	73 (60–80)	65 (59–77)[b]	< 0.001
≥ 80 n = 78	85 (70–95)	79 (69–90)	75 (61–89)[b]	80 (71–90)	72 (60–84)[b]	63 (50–80)[b]	< 0.001

Note: Visual analogue scale score of 0 is worst and 100 is best. All data available.
Abbreviations: EBRT = external beam radiotherapy; IQR = interquartile range; MRI = magnetic resonance imaging; RARP = robot-assisted radical prostatectomy; VAS = visual analogue scale.
a: Based on a Friedman test for repeated measures for indicating a significant difference in VAS score between all treatment scenarios. b: Indicates a significant difference in VAS score between the active surveillance scenario and the indicated treatment scenario based on a Wilcoxon signed rank test. c: High education level includes higher education/university, and low education includes any other lower form of education.

Focal therapy is an experimental treatment. Literature reports low toxicity, but studies are limited by small samples and short follow-up.[25] Despite these uncertainties, the focal therapy treatment-outcome scenario VAS and TTO scores were among the highest. focal therapy was the fourth most often selected as first-choice treatment, before and after treatment information was received. This discrepancy may be influenced by the favorable toxicity outcomes on the one hand, but the uncertainties in terms of (biochemical-free) survival and the need for re-treatment on the other hand. Patients that consider focal therapy may therefore eventually prefer a completely expectative approach without any treatment-related toxicity, such as active surveillance or radical treatment, with more certainty of having biochemical free survival.

Brachytherapy was least often selected as the first choice, before and after treatment information was received. In the realm of radiotherapy, brachytherapy is the most invasive treatment. The risks of developing urinary and bowel symptoms are marginally higher compared to conventional EBRT and MRI-guided radiotherapy. Important advantages are the relatively short treatment in-hospital duration and the relatively low erectile dysfunction rate after treatment. However, from our results, we can conclude that for most participants, the advantages of brachytherapy do not weigh up against the disadvantages.

RARP was ranked third most often as first choice before and after treatment information was received, indicating RARP to be a relatively preferred treatment. Contradictory, in the total study population, utility scores for RARP were among the lowest, which can be explained by the invasive treatment procedure and the relatively high rate of urinary incontinence and erectile dysfunction after treatment. However, the group that was previously treated with RARP did not report lower but similar utility scores for the RARP outcome-scenario as for the other treatment scenarios, which suggests that there may be a distinct group that prefers RARP above the other less-invasive (i.e., no catheter, no hospitalization, and/or no incisions) treatment options.

Treatment preferences changed after information about the different treatment options was received. For example, active surveillance was the first choice for 21% of participants before information was received and for 41% after information was received. For RARP, this was 19% versus 12%. The idea of having to eradicate the cancer by removing it from the body can be a logical first thought, explaining a relatively high preference for RARP and a low preference for active surveillance in the first instance, as well as why patients that ranked RARP as first choice, most often ranked active surveillance as sixth choice. Fear may lead to less rational decision-making, especially when diagnosed with low-grade cancer.[26, 27] Our results suggest that active surveillance

is more accepted after extensive treatment information. Therefore, we advocate providing adequate information about treatment options, in particular for active surveillance as an option for lower-grade cancers.

Our study encourages future research and development into active surveillance and non-invasive and minimally invasive treatments such as MRI-guided radiotherapy and focal therapy. There is a demand for new technologies such as MRI-guided radiotherapy and focal therapy by patients and physicians, which also may have influenced the preference towards these treatments in this study.[28] New technologies often promise favorable outcomes but may be costly. Early HTA may provide insight into the requirements of these innovations, in terms of costs and toxicity reduction, to be a cost-effective alternative compared to standard treatments.[9] The utility scores from this study can be used for early HTA.[10, 29]

This study has some limitations. Firstly, the majority of the men that filled out the questionnaire had previously been treated for localized prostate cancer. In a previous paper, we described the first-year PRO of the patient groups where the patients from the current study are part of.[30] It indicates the toxicity that had been experienced by patients at the moment of filling out the current study›s questionnaire. Both good and bad experiences with a previously received treatment may influence treatment preferences and utility scores.[19] For example, most conventional EBRT and some MRI-guided radiotherapy patients that participated in this study, received neoadjuvant androgen deprivation therapy (ADT). Their own treatment experience may have been negatively impacted by the ADT, especially with regard to erection problems, whereas all radiotherapy treatment-outcome scenarios in our study were based on non-ADT treatment. To minimize the influence of the patients' own treatment experience, we invited equal numbers of active surveillance, MRI-guided radiotherapy, conventional EBRT and RARP patients and included them at least 6 months after treatment as a washout period. We were not able to invite brachytherapy and focal therapy patients as both treatments are not routinely performed at our institution. We also explicitly asked patients to assess the questionnaire not from their own prostate cancer scenario but from the hypothetical prostate cancer scenario that was described in the questionnaire. Furthermore, a reference group of healthy volunteers were invited by the participating patients who were asked to independently fill out the questionnaire. We found that the healthy volunteer group showed a similar pattern of preferences and utility scores compared to the patient group.

Secondly, for the healthy volunteer group that consisted of men older than 50 years, it should be noted that it is unknown what their initial knowledge of prostate cancer

treatment was at the moment of filling out the questionnaire. The initial level of understanding of the one-sentence treatment description for the six treatment options may vary between patients and even more so for the healthy volunteers participating in this study. This may have influenced their initial treatment ranking. However, prostate cancer patients that are confronted with several treatment options at the time of diagnosis may have the same level of (scarce) knowledge.

Thirdly, the outcomes were based on literature and reviewed by a multidisciplinary team, aiming to represent the treatment procedures and outcomes as objectively as possible. Treatment-outcome scenarios may, however, paint an optimistic or pessimistic picture of a certain treatment, which may differ from a patient's real-life experience. Furthermore, patient's prostate cancer risk classification and comorbidities, among other factors, may have an influence on treatment preferences and utility scores, and also treatment eligibility, which we did not account for in the present study. Moreover, for the toxicity profiles in the treatment-outcome scenarios, we focused on the 1-year outcomes as most toxicity for the different treatment options occurs during that time frame. However, some toxicities can occur after 1 year of follow-up. For example, a minor but significant increase in gastrointestinal toxicity, predominantly bloody stools, after 5 years of follow-up has been reported for radiotherapy treatment options (bloody stool about half the time or more frequently occurred in 1.3% for active surveillance, 1.1% for radical prostatectomy and 5.6% for radiotherapy after 5 years of follow-up [$P < 0.001$], as reported by Donovan et al.).[15] For the aforementioned reasons, the advantages and disadvantages of a certain treatment may have been overestimated or underestimated by the participants, which therefore influenced treatment preference. Currently, we prospectively collect outcome data of all localized prostate cancer patients treated in our region.[30] The aim is to use these outcome data to update the treatment-outcome scenario questionnaire for future studies on patient preferences for the treatment of localized prostate cancer.

Conclusion

Active surveillance and non-invasive treatment for localized prostate cancer were most preferred by patients treated for localized prostate and healthy volunteers and received among the highest utility scores. Preference for the different treatments strongly depended on the level of information received: with more information about the procedure and outcomes, patients moved towards a preference for active surveillance or non-invasive treatment.

Supplementary material

Treatment-outcome scenario questionnaire:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9931535/bin/BCO2-4-214-s001.pdf

Table 1:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9931535/bin/BCO2-4-214-s002.docx

Table 2:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9931535/bin/BCO2-4-214-s003.docx

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CHAPTER 5

Interrater agreement of contouring of the neurovascular bundles and internal pudendal arteries in neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer

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Abstract

Background and purpose: Radiation damage to neural and vascular tissue, such as the neurovascular bundles (NVBs) and internal pudendal arteries (IPAs), during radiotherapy for prostate cancer may cause erectile dysfunction. Neurovascular-sparing magnetic resonance imaging (MRI)-guided adaptive radiotherapy aims to preserve erectile function after treatment. However, the NVBs and IPAs are not routinely contoured in current radiotherapy practice. Before neurovascular-sparing MRI-guided radiotherapy for prostate cancer can be implemented, the interrater agreement of the contouring of the NVBs and IPAs on pre-treatment MRI needs to be assessed.

Materials and methods: Four radiation oncologists independently contoured the prostate, NVB, and IPA in an unselected consecutive series of 15 prostate cancer patients, on pre-treatment MRI. Dice similarity coefficients (DSCs) for pairwise interrater agreement of contours were calculated. Additionally, the DCS of a subset of the inferior half of the NVB contours (i.e., approximately prostate midgland to apex level) was calculated.

Results: Median overall interrater DSC for the left and right NVB was 0.60 (interquartile range [IQR]: 0.54–0.68) and 0.61 (IQR: 0.53–0.69) respectively and for the left and right IPA 0.59 (IQR: 0.53–0.64) and 0.59 (IQR: 0.52–0.64) respectively. Median overall interrater DSC for the inferior half of the left NVB was 0.67 (IQR: 0.58–0.74) and 0.67 (IQR: 0.61–0.71) for the right NVB.

Conclusion: We found that the interrater agreement for the contouring of the NVB and IPA improved with enhancement of the MRI sequence as well as further training of the raters. The agreement was best in the subset of the inferior half of the NVB, where a good agreement is clinically most relevant for neurovascular-sparing MRI-guided radiotherapy for prostate cancer.

Introduction

Erectile dysfunction is a common adverse effect of external beam radiotherapy (EBRT) for localized prostate cancer.[1] The prostate is located adjacent to neural structures and in close proximity to vascular structures responsible for erectile function such as the neurovascular bundles (NVBs), the internal pudendal arteries (IPAs), the corpora cavernosa (CCs), and the penile bulb (PB).[2] Radiation damage to these structures can lead to temporary or permanent decline of erectile function.[3, 4, 5]

Implementation of neurovascular-sparing radiotherapy treatments has been impeded by the routine use of computed tomography (CT) imaging in radiotherapy treatment planning. Using CT imaging, CCs and PB can be identified sufficiently, and PB is often included as organ at risk (OAR) in conventional EBRT.[6,7] However, other critical structures such as the NVBs and IPAs cannot be adequately identified on CT and are therefore not spared in conventional EBRT.[2,8]

The integration of Magnetic Resonance Imaging (MRI) has improved imaging and enables functional anatomy-based radiotherapy treatment planning.[2] Furthermore, the recent development of magnetic resonance imaging (MRI)-guided adaptive radiotherapy has enabled real-time high-resolution MRI imaging during dose delivery and facilitates correction for both inter- and intra-fraction movement and tissue deformations.[9] Planning target volumes (PTV) can therefore be smaller as safety margins are reduced.[10] These improvements in treatment conformity using MRI-guided radiotherapy facilitate neurovascular-sparing radiotherapy and could potentially improve sexual function outcomes in patients treated for localized prostate cancer. As the NVBs and IPAs are not routinely contoured in current clinical radiotherapy practice, we aimed to assess the interrater agreement in contouring the NVBs and IPAs on pre-treatment MRI.

Materials and methods

Patient selection and treatment

For this study the guidelines for reporting reliability and agreement studies (GRRAS) recommendations were followed.[11] Included were patients with localized prostate cancer (low to high risk according to the National Comprehensive Cancer Network [NCCN] risk classification) that received MRI-guided radiotherapy in five fractions of 7.25 Gy delivered during two and a half weeks on a 1.5 T MR-Linac system. All patients received a single 3.0 T planning MRI and 1.5 T pretreatment MRIs for daily plan adaptation prior to each fraction. Patients signed informed consent for sharing of their clinical data

within the MOMENTUM study (NCT04075305), which was approved by our institutional review board.[12]

Contouring instructions and pilot study

First, a consensus meeting was held with two radiologists and four radiation oncologists all dedicated in uro-oncology to determine the location and set the anatomical boundaries for NVB and IPA on MR imaging. After consensus was reached, a contouring atlas was developed (Supplementary material: Contouring atlas). Subsequently, a pilot study was initiated in which four senior dedicated prostate radiation oncologists (25, 15, 10, 10 years of experience respectively) independently contoured the prostate, NVBs, and IPAs in an unselected series of five consecutive patients on a single clinical pretreatment 3.0 T T2-weighted MRI scan. All raters contoured the structures individually and were blinded for the contours of the other raters. The in-house developed contouring software package Volumetool was used, which is also used for clinical contouring at our institution. All raters had access to the contouring atlas and were instructed to contour the NVB from at least the base of the seminal vesicles until the level of the urogenital diaphragm and the IPA from at least the level of the sacroiliac ligament until the level of the crus where it terminates into the common penile artery and the scrotal artery. Subsequently, per patient the four contours of the left and right NVB and left and right IPA were adjusted to run from the same superior to inferior level, based on the maximal superior to inferior distance overlap of the four contours, for every structure independently. Furthermore, a subset of the exact inferior half (i.e., approximately prostate midgland to apex level) of the NVB contours was generated, where the NVB generally is in closest proximity to the prostate and conflict between optimal dose coverage and sparing of neurovascular structures is greatest.

Main study

An evaluation of the pilot study was added to the contouring atlas (Supplementary material: Updated contouring atlas). Also, an optimized 3D turbo spin-echo MRI-sequence was developed to improve NVB and IPA visualization, which became our institution's standard for daily contouring and replaced the previous T2-weighted sequence (Supplementary material: Table 1). Four dedicated prostate radiation oncologists (15, 10, 5, 3 years of experience respectively), independently contoured the prostate, the left and right NVB and the left and right IPA in a new unselected series of 15 consecutive patients. Rater 1 and 2 also participated in the pilot study. All raters contoured the structures individually and were blinded for the contours of the other raters. Contouring was done on a single clinical pretreatment 1.5 T T2-weighted MRI scan of the pelvis that was acquired on an MR-Linac. The software package Volumetool was used for contouring.

All raters had access to the contouring atlas and evaluation of the pilot study, and were instructed to contour the NVB from at least the base of the seminal vesicles until the level of the urogenital diaphragm and the IPA from at least the level of the sacroiliac ligament until the level of the crus where it terminates into the common penile artery and the scrotal artery. Subsequently, per patient the four contours of the left and right NVB and left and right IPA were adjusted to run from the same superior to inferior level and a subset of the exact inferior half of the NVB contours was generated.

Statistical analysis

Interrater agreement was assessed by calculating the Dice similarity coefficient (DSC) of all possible rater pairs (i.e., four raters result in six rater pairs per patient).[13] DSC = 0 indicates no spatial overlap, 0 < DSC < 1 indicates partial spatial overlap and DSC = 1 indicates complete spatial overlap between two contours. Complementary average surface distance and maximum surface distance (i.e., Hausdorff distance) between the contours of all rater pairs were calculated.[14,15] Distances were calculated symmetrically and 3-dimensional. An average surface distance or Hausdorff distance of 0 indicates perfect overlap between two contours. Volume, DSC, average surface distance, and Hausdorff distance were calculated by analysis modules accompanying Volumetool. Distances are represented in mm and volumes in cc. Non-normally distributed data were presented as median with interquartile range (IQR).

Results

Pilot study

The pilot study included five patients which were each contoured by four raters. The mean age of the patients was 68 years old (range: 57 years–80 years), one had low-risk, and four had intermediate-risk prostate cancer. The median overall contoured volume was 3.54 cc (2.74 cc–4.16 cc) for the left and 3.74 cc (2.88 cc–4.87 cc) for the right NVB, and 2.83 cc (2.03 cc–4.32 cc) for the left and 2.96 cc (1.86 cc–3.96 cc) for the right IPA (Table 1).

Median overall interrater DSC (agreement) for the pilot study was 0.42 (IQR: 0.32–0.52) for the left NVB and 0.51 (IQR: 0.40–0.59) for the right NVB, and 0.57 (IQR: 0.47–0.63) for the left and 0.46 (IQR: 0.29–0.56) for the right IPA (Table 1). For the inferior half of the NVBs the median overall interrater DSC was 0.50 (IQR: 0.35–0.57) and 0.50 (IQR: 0.41–0.60) for the left and right side respectively.

Table 1: *Interrater agreement outcomes of contouring of the prostate, IPAs, and NVBs*

	Prostate Median (IQR)	IPA left Median (IQR)	IPA right Median (IQR)	NVB left Median (IQR)	NVB right Median (IQR)	NVB inferior half left Median (IQR)	NVB inferior half right Median (IQR)
Pilot study (5 patients)							
Overal volume (cc) n = 20	27.87 (23.80–31.93)	2.83 (2.03–4.32)	2.96 (1.86–3.96)	3.54 (2.74–4.16)	3.74 (2.88–4.87)	1.21 (0.93–1.39)	1.44 (1.11–1.72)
Overall distance between superior and inferior border (mm) n = 5	NA	42.00 (42.00–46.00)	44.00 (38.00–46.00)	34.00 (32.00–38.00)	32.00 (32.00–40.00)	18.00 (16.00–20.00)	16.00 (16.00–20.00)
Overall Dice similarity coefficent n = 30*	0.84 (0.82–0.87)	0.57 (0.47–0.63)	0.46 (0.29–0.56)	0.42 (0.32–0.52)	0.51 (0.40–0.59)	0.50 (0.35–0.57)	0.50 (0.41–0.60)
Overall average surface distance (mm) n = 30*	1.81 (1.38–2.02)	1.36 (1.12–2.38)	1.91 (1.28–3.39)	2.64 (1.77–3.36)	1.89 (1.59–2.38)	1.48 (1.16–1.97)	1.34 (1.20–1.84)
Overall Hausdorff distance (mm) n = 30*	7.17 (5.98–8.02)	8.60 (6.61–12.58)	11.98 (7.25–19.23)	11.89 (9.48–17.02)	9.16 (8.07–11.35)	6.67 (5.01–8.10)	6.44 (5.38–8.37)
Main study (15 patients)							
Overall volume (cc) n = 60	47.38 (34.45–56.84)	2.26 (1.77–2.95)	2.27 (1.66–2.97)	6.18 (5.22–8.31)	7.19 (5.83–9.08)	2.09 (1.51–2.85)	2.08 (1.54–2.77)
Overall distance between superior and inferior border (mm) n = 15	NA	42.00 (34.00–42.00)	38.00 (34.00–47.00)	46.00 (43.00–51.00)	48.00 (43.00–51.00)	24.00 (22.00–26.00)	24.00 (22.00–26.00)
Overall Dice similarity coefficient n = 90**	0.91 (0.89–0.92)	0.59 (0.53–0.64)	0.59 (0.52–0.64)	0.60 (0.54–0.68)	0.61 (0.53–0.69)	0.67 (0.58–0.74)	0.67 (0.61–0.71)
Overall average surface distance (mm) n = 90**	1.24 (1.09–1.55)	1.18 (1.05–1.63)	1.24 (1.01–1.49)	1.96 (1.59–2.31)	1.86 (1.53–2.52)	1.10 (0.89–1.42)	1.21 (1.04–1.51)

Table 1: *Continued*

	Prostate Median (IQR)	IPA left Median (IQR)	IPA right Median (IQR)	NVB left Median (IQR)	NVB right Median (IQR)	NVB inferior half left Median (IQR)	NVB inferior half right Median (IQR)
Overall Hausdorff distance (mm) n = 90**	5.99 (5.38–7.80)	8.24 (6.75–10.37)	7.84 (6.14–9.47)	12.13 (9.36–15.10)	11.78 (9.52–14.22)	6.39 (5.12–9.04)	7.84 (5.78–10.28)

**4 raters result in 6 rater comparisons (6 × 5 patients = 30).*

***4 raters result in 6 rater comparisons (6 × 15 patients = 90).*

Abbreviations: NVB = neurovascular bundle; IPA = internal pudendal artery; DSC = Dice similarity coefficient; IQR = interquartile range; NA = not applicable.

Median overall average surface distance was 2.64 mm (IQR: 1.77 mm–3.36 mm) and 1.89 mm (IQR: 1.59 mm–2.38 mm) for the left and right NVB respectively, and 1.36 mm (IQR: 1.12 mm–2.38 mm) and 1.91 mm (IQR: 1.28 mm–3.39 mm) for the left and right IPA respectively (Table 1).

Main study

For the main study, 15 patients were included which were each contoured by four raters. Mean age of the patients was 70 years old (range: 59 years–79 years), 1 had low-risk, 11 had intermediate-risk, and 2 had high-risk prostate cancer. The median overall contoured volume was 6.18 cc (5.22 cc–8.31 cc) for the left and 7.19 cc (5.83 cc–9.08 cc) for the right NVB, and 2.26 cc (1.77 cc–2.95 cc) for the left and 2.27 cc (1.66 cc–2.97 cc) for the right IPA (Table 1).

Median overall interrater DSC was 0.60 (IQR: 0.54–0.68) and 0.61 (IQR: 0.53–0.69) for the left and right NVBs respectively, and 0.59 (IQR: 0.53–0.64) and 0.59 (IQR: 0.52–0.64) for the left and right IPAs respectively (Table 1; Fig. 1, Fig. 2, Fig. 3). Assessment of the agreement of the inferior half of the NVBs resulted in a median overall interrater DSC of 0.67 (IQR: 0.58–0.74) for the left side and 0.67 (IQR: 0.61–0.71) for the right side.

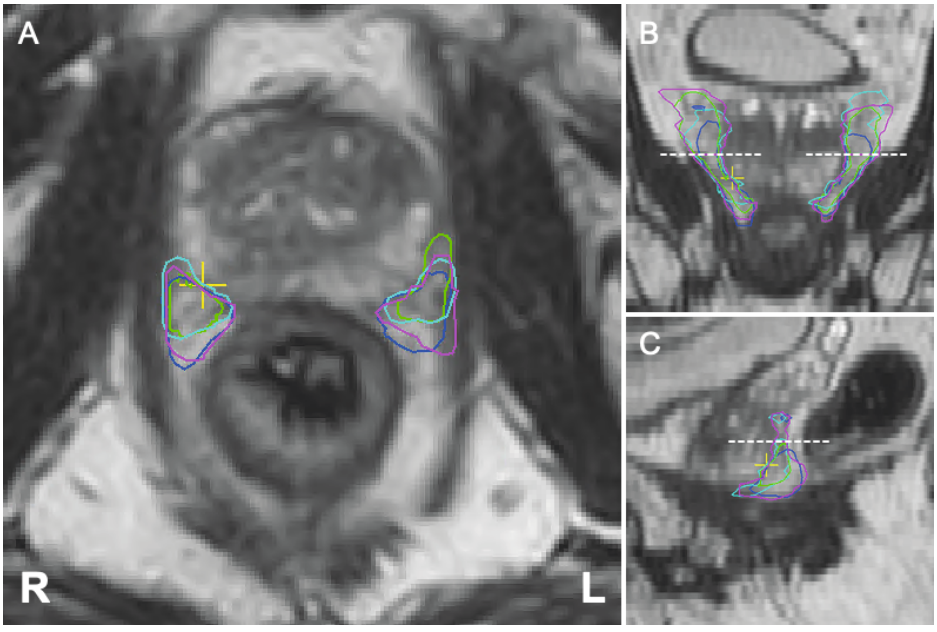

Figure 1: *Representative case of contours of the neurovascular bundles (prostate apex level) by four raters.*

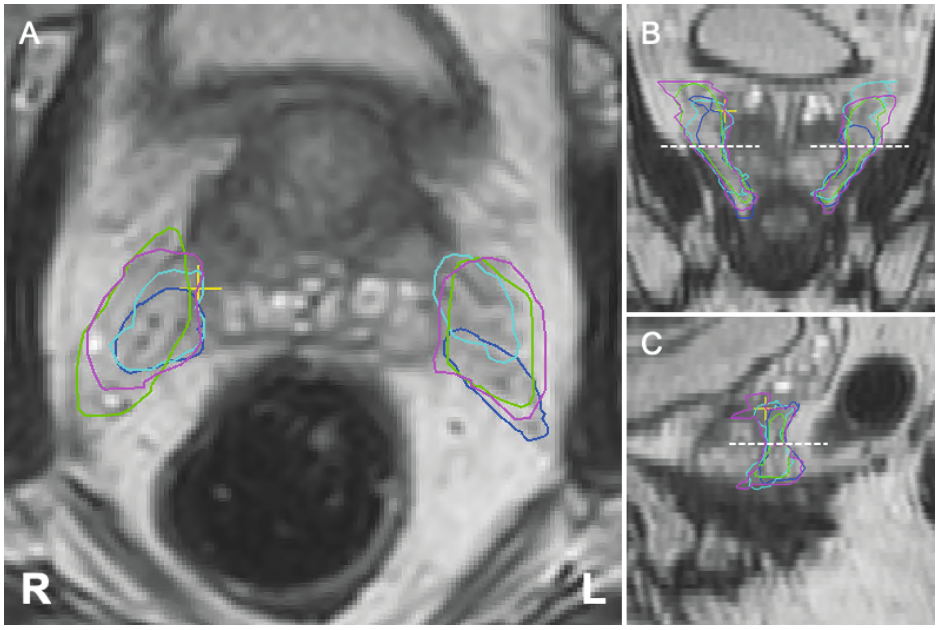

Figure 2: *Representative case of contours of the neurovascular bundles (prostate base level) by four raters.*

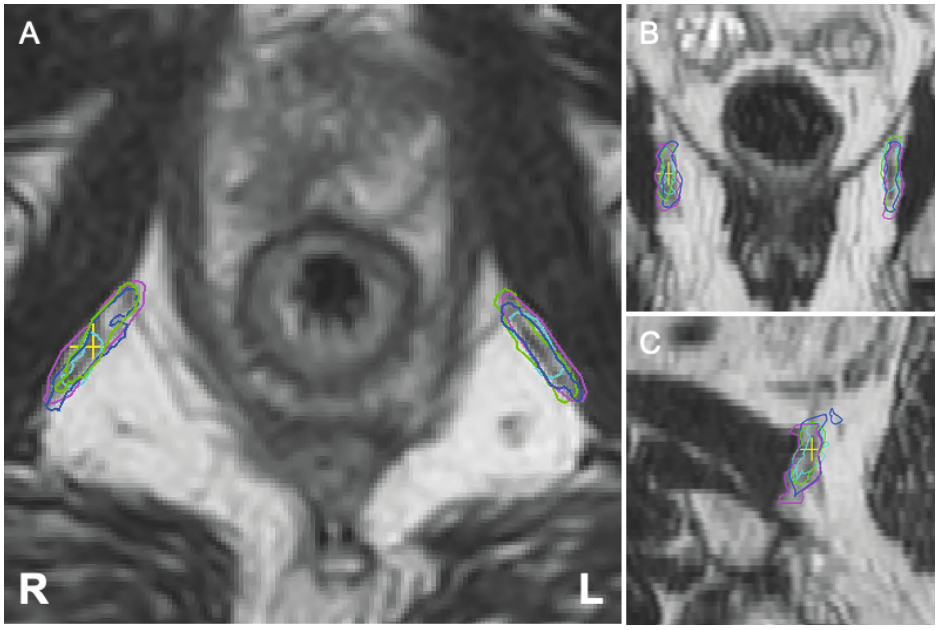

Figure 3: *Representative case of contours of the internal pudendal arteries by four raters.*

Median overall average surface distance was 1.18 mm (IQR: 1.05 mm–1.63 mm) and 1.24 mm (IQR:1.01 mm–1.49 mm) for the left and right IPA respectively, and 1.96 mm (IQR: 1.59 mm–2.31 mm) and 1.86 mm (IQR: 1.53 mm–2.52 mm) for the left and right NVB respectively (Table 1).

Discussion

This study is the first to assess the interrater agreement of both the NVB and IPA on MRI for MRI-guided radiotherapy. Assessment of the interrater agreement of the contours of the NVB and the IPA on pre-treatment MRI resulted in a median overall DSC of 0.60 (IQR: 0.54–0.68) and 0.61 (IQR: 0.53–0.69) for the left and right NVB respectively and 0.59 (IQR: 0.53–0.64) for the left and 0.59 (IQR: 0.52–0.64) for the right IPA.

In literature, a DSC of > 0.70 is often deemed as excellent agreement, referring to a study of Zijdenbos et al.[16] However, in that study the agreement between a semiautomatic multispectral segmentation technique and manually contoured white matter lesions in the brain was assessed. This is by no means directly comparable with the field of oncology. For example: a DSC of 0.70 between raters can be considered low for the contouring of a tumor, where all tumor tissue should be treated, but may be excellent for a structure-to-spare that conventionally is not spared at all, which should be taken into account when interpreting the DSC.

Although DSC is the most frequently used metric for contour agreement, it is advised to accompany the DSC with additional metrics such as the average surface distance and Hausdorff distance between contours, to put the DSC in perspective.[14,15] The DSC is comprehensible and works well as a crude measure of agreement, but has a lower sensitivity for fine details such as complex structure boundaries. Furthermore, a similar difference in terms of distance between two contours will result in a lower DSC between smaller volume contours as between larger volume contours. Therefore, volumetric overlap and distance metrics are generally not highly correlated and therefore should be used complementary. Taking the prostate in our study as a reference, the DSC of the IPAs and NVBs are substantially lower, however, average surface distances and Hausdorff distances are much more similar, especially for the inferior part of the NVB in comparison with the prostate (Table 1).

The few studies that have assessed the contouring agreement of the NVB, reported very different results. Cassidy et al. reported a mean DSC of 0.72 (standard deviation [SD]: 0.07) for the agreement of five radiation oncologists with a single “golden standard”

contour of a radiologist in 10 cases.[17] However, the 3 T T2-weighted MRI scans were pre-selected to only contain patients with a favorable and consistent NVB anatomy. Also, a better overall DSC is expected when all raters are compared with a single "golden standard" opposed to pairwise rater comparison. These factors may have led to an overestimation of the agreement. On the contrary, Roach et al. reported a mean DSC of 0.16 (SD: 0.17) for the left and 0.15 (SD: 0.15) for the right NVB for the interrater agreement of 13 raters contouring five cases, showing almost no agreement between raters.[18] They contoured nine different structures on small field-of-view T2-weighted MRI within the study, without specified training in contouring the NVBs, which could have led to a lower accuracy, resulting in a very low interrater DSC of the NVB contours.

To our knowledge, no studies on agreement of the contouring the IPA on MRI have been reported. However, a number of studies have shown the feasibility and potential of IPA sparing radiotherapy.[2, 8, 19] Spratt et al. conducted a single arm study sparing the CC and IPA during conventional EBRT for prostate cancer in 135 patients and showed that 88% of patients were still sexually active with or without the use of aids 5 years after treatment, while maintaining tumor control.[19] To date, this is the only study addressing the effect of sparing of the IPA on erectile function preservation.

We consider the agreement for the NVB and IPA in our study to be acceptable for the implementation of neurovascular-sparing MRI-guided radiotherapy, taking into account the DSC together with the average surface distance and Hausdorff distance. Moreover, subanalysis of the contours of the inferior part of the NVB showed a better DSC between raters (median overall DSC NVB left: 0.67 [IQR: 0.58–0.74], right: 0.67 [IQR: 0.61–0.71]) compared to the total contoured NVB and showed a relatively low median overall average surface distance of 1.10 mm (IQR: 0.89 mm–1.42 mm) for the left and 1.21 mm (IQR: 1.04 mm–1.51 mm) for the right side. This is important as the inferior (i.e., midgland to apex) part of the NVB is in closest approximation to the prostate (Fig. 1). At that level the conflict between dose coverage of the prostate and dose sparing of the NVBs is highest. Due to the steep dose gradient, further away from the target volume the delivered dose will be progressively lower. Therefore, a lower agreement is acceptable for structures-to-spare at further distance from the prostate such as the IPA and the superior part of the NVB, opposed to structures closer to the prostate such as the inferior part of the NVB. Furthermore, we showed that agreement improved in the main study after the contouring atlas was updated and the MRI sequence was improved with knowledge gained from the pilot study, even though the 1.5 T modality was used for the main study opposed to the 3 T modality for the pilot study. We used the 1.5 T modality in the main study as it is the actual MRI used for daily treatment adaptation during MRI-guided radiotherapy, which make the results better to translate

into clinical practice. The substantial improvement in the main study suggests that further enhancement of MRI as well as ongoing training will lead to a better agreement in future assessment, which is needed for clinical implementation of neurovascular-sparing MRI-guided radiotherapy.

In our experience the NVB is generally well identifiable at the prostate apex where it is delimited by the dorsolateral part of the prostate and the ventrolateral part of the rectum. Towards the base of the prostate, the NVB becomes more divergent and diffuse and therefore harder to distinguish (Fig. 2). Especially at the level of the vesicles identification and contouring is difficult and care should be taken that the NVBs are not confused with the seminal vesicles. In most cases the NVBs are located lateral to ventrolateral of the vesicles.[2] The IPAs were considered to be very well distinguishable on MRI throughout their entire trajectory. Starting from inferior up on the transverse plane, the artery makes a characteristic turn from lateral to ventral around the sacroiliac ligament entering the pelvis through the lesser sciatic foramen, then continuing and merging into the corpora cavernosa. Discordance of contours of the IPA in our study were mainly caused by the variance of width of the margin taken around the artery by the individual raters (Fig. 3).[2]

A limitation of this study is the limited non-random study sample. Anatomical variation of the NVB results in favorable and unfavorable variations for neurovascular-sparing radiotherapy.[2] The favorable variations are generally better to distinguish on MRI which could lead to a better agreement between raters. Although we contoured an unselected consecutive series of 15 patients in the main study, it remains unknown how these results compare to the general prostate cancer population anatomy and whether or not our series is relatively favorable or unfavorable, which might have caused an over- or underestimation of the interrater agreement. Furthermore, the contours of the NVB and IPA were adjusted to run from the same superior to inferior level. This was done because the NVB and IPA continue in superior direction far distant from the prostate and area of clinical relevance for neurovascular dose sparing. Large interrater variations of longitudinal contoured distance of the same structure can therefore skew results of measures of agreement. However, the adjusted superior to inferior distance varied between the contoured structures and patients, which explains the difference in volumes between the NVBs pilot and main study. Moreover, in the main study the contours were mainly extended towards the superior direction compared to the pilot study, where the NVB is more divergent and therefore generally contoured wider. The difference in contoured longitudinal distance of the NVB and IPA may induce a bias as contouring a longer distance results in more possibility of disagreement. Also, the superior part of the NVB is more difficult to contour, which became apparent from the results of our study. These factors may lead to a relatively lower DSC for greater longitudinal contoured distances

for the NVB and IPA, which should be kept in mind when interpreting the results. Nevertheless, despite the generally greater longitudinal contoured distance in the main study compared to the pilot study, the agreement remained better in the main study.

Conclusion

We found that the interrater agreement for the contouring of the NVB and IPA improved with enhancement of the MRI sequence as well as further training of the raters. The agreement was best in the subset of the inferior half of the NVB, where a good agreement is clinically most relevant for neurovascular-sparing MRI-guided radiotherapy for prostate cancer.

Supplementary material

Contouring atlas:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8605225/bin/mmc1.pdf

Updated contouring atlas:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8605225/bin/mmc2.pdf

Table 1:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8605225/bin/mmc3.docx

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CHAPTER 6

Adaptive MRI-guided neurovascular-sparing radiotherapy for preservation of erectile function in prostate cancer patients

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Abstract

Background and purpose: Erectile dysfunction is a common adverse effect of external beam radiotherapy for localized prostate cancer, likely as a result of damage to neural and vascular tissue. Magnetic resonance imaging (MRI)-guided online adaptive radiotherapy enables high-resolution MR imaging and paves the way for neurovascular-sparing approaches, potentially lowering erectile dysfunction after radiotherapy for prostate cancer. The aim of this study was to assess the planning feasibility of neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer.

Materials and methods: Twenty consecutive localized prostate cancer patients, treated with standard 5 × 7.25 Gy MRI-guided radiotherapy, were included. For these patients, neurovascular-sparing 5 × 7.25 Gy MRI-guided radiotherapy plans were generated. Dose constraints for the neurovascular bundle (NVB), the internal pudendal artery (IPA), the corpus cavernosum (CC), and the penile bulb (PB) were established. Doses to regions of interest were compared between the neurovascular-sparing plans and the standard clinical pre-treatment plans.

Results: Neurovascular-sparing constraints for the CC, and PB were met in all 20 patients. For the IPA, constraints were met in 19 (95%) patients bilaterally and 1 (5%) patient unilaterally. Constraints for the NVB were met in eight (40%) patients bilaterally, in eight (40%) patients unilaterally, and were not met in four (20%) patients. NVB constraints were not met when gross tumor volume (GTV) was located dorsolaterally in the prostate. Dose to the NVB, IPA, and CC was significantly lower in the neurovascular-sparing plans.

Conclusion: Neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer is feasible in the planning setting. The extent of NVB sparing largely depends on the patient's GTV location in relation to the NVB.

Introduction

Erectile dysfunction (ED) is a common adverse effect of external beam radiotherapy (EBRT) for localized prostate cancer. In patients treated with stereotactic body radiotherapy (SBRT), ED rates range from 26% to 55% at 60 months in previously sexually functioning patients.[1] The prostate is surrounded by structures responsible for the erectile function such as the neurovascular bundles (NVBs), the internal pudendal arteries (IPAs), the corpora cavernosa (CCs), and the penile bulb (PB). Radiation damage to these structures potentially leads to a decline of erectile function after treatment.[2]

Neurovascular-sparing radiotherapy for erectile function preservation has been proposed before.[2,3,4] Spratt et al. reported the first vessel-sparing treatment trial, delivering EBRT to the prostate while sparing the IPAs and CCs.[5] Their results were promising with a reported erectile function preservation rate of 67% (i.e., International Index of Erectile Function (IIEF)-5 ≥ 16) at 5 years after treatment.[6] Currently, the POTEN-C trial is ongoing, aiming to preserve erectile function in patients with localized prostate cancer by sparing the NVBs, IPAs, and PB using a conventional linac system to deliver SBRT in five fractions of 8–9 Gy.[7]

Due to the movement of the pelvic organs, daily plan optimization is desirable for neurovascular-sparing radiotherapy. However, NVBs and IPAs cannot be adequately identified on computed tomography (CT) due to lack of contrast. Magnetic resonance imaging (MRI) allows better visualization of these structures.[2,4] Therefore, MRI-guided online adaptive radiotherapy could pave the way for an optimized neurovascular-sparing approach. MR imaging prior to and during dose delivery facilitates correction for interfraction motion and tissue deformations. Within the near future fast auto-contouring and planning will provide a way to deal with intrafraction motion, thus allowing for further margin reduction and reduction of dose to organs at risk (OAR).[8,9]

To date, no study has examined the planning feasibility of neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer. Therefore, in this study we aimed to assess the feasibility of treatment planning for neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer and the potential dose reduction to neurovascular structures.

Materials and methods

Patient characteristics

For this planning study, 20 consecutive patients with localized low- to high-risk prostate cancer (National Comprehensive Cancer Network [NCCN] risk categories) without extracapsular extent were included, to account for the variation in tumor location and anatomy of the localized prostate cancer population. All patients were previously treated with standard 5 × 7.25 Gy MRI-guided radiotherapy on a Unity MR-Linac. In preparation for treatment on the MR-Linac patients received a pre-treatment multiparametric (mp) 3 T offline planning MRI (T2-weighted and diffusion weighted imaging (DWI) sequences; reconstructed resolution (mm3): 0.8/0.8/2.0) for optimal contouring of target volumes and OAR. Patients signed informed consent for sharing of their clinical data within the MOMENTUM study (NCT04075305), which was approved by our institutional review board.[10,11]

Neurovascular-sparing dose constraints and volume definitions

Dose constraints for the NVB, IPA, CC, and PB for a five-fraction scheme were established by consensus of a board of four expert prostate specialized radiation oncologists (25, 15, 10, and 10 years of clinical experience, respectively) and a radiation biologist (Supplementary material: Table 1). For neurovascular tissue an EQD2 α/β of 2.0 Gy and for vascular tissue an α/β of 3.0 Gy was applied.[12] The constraints for the IPA and CC were based on the five-fraction equivalent of the constraints as used in the study by Spratt et al. (IPA 100% < 36.0 Gy, CC 100% < 30.0 Gy in 42 fractions).[5] The PB constraint was based on the PACE-trial constraint (D50% < 29.5 Gy in five fractions).[13,14] For the NVB no constraints were described in literature. Therefore, the NVB dose constraint was based on literature for neural and vascular tissue and experience with radiation toxicity for both sacral and brachial plexus and was set to D0.1 cc ≤ 32.8 Gy.[5,14,15,16]

The GTV + 4 mm included the GTV (mpMRI visible tumor(s)) with a 4 mm isotropic margin excluding the rectum and bladder. The CTV included the GTV + 4 mm and prostate body with the base of the seminal vesicles and the PTV included the CTV with a 5 mm isotropic margin. Dose prescriptions for the PTV were adapted to allow neurovascular-sparing MRI-guided radiotherapy. The GTV + 4 mm should receive 34.4 Gy in ≥ 99% and the PTV 30.0 Gy in ≥ 99%; 32.6 Gy in ≥ 90% and 34.4 Gy in ≥ 80%. Because of the proximity of the NVB to the prostate and the priority of dose coverage of the GTV + 4 mm and PTV, we set the NVB dose constraint as “soft” constraint (i.e., not mandatory). The applied dose constraints for neurovascular-sparing 5 × 7.25 Gy MRI-guided radiotherapy are displayed in Table 1.

Table 1: *Target volume dose prescription and dose constraints for neurovascular-sparing 5 × 7.25 Gy MRI-guided radiotherapy*

Structure	Parameter	Dose constraint	
		Soft	Hard
PTV	V34.4 Gy (V95%)		≥ 80.0%
	V32.6 Gy (V90%)		≥ 90.0%
	V30.0 Gy (V83%)		≥ 99.0%
GTV + 4 mm	V34.4 Gy (V95%)		≥ 99.0%
Bladder	D0.5 cc		< 42.0 Gy
	D5 cc		< 37.0 Gy
	V32.0 Gy		< 15.0%
	V28.0 Gy		< 20.0%
Femur	D10 cc	< 30.0 Gy	
Rectum	D0.5 cc		≤ 40.0 Gy
	D1 cc	≤ 35.0 Gy	≤ 38.0 Gy
	V32.0 Gy		≤ 15.0%
	V28.0 Gy		≤ 20.0%
Sphincter (distal 3 cm of rectum)	D0.5 cc		≤ 40.0 Gy
	D1 cc	≤ 35.0 Gy	≤ 38.0 Gy
	Dmean		< 20.0 Gy
NVB	D0.1 cc	≤ 32.8 Gy	
IPA	D0.1 cc		≤ 20.0 Gy
CC	D0.01 cc		≤ 17.3 Gy
PB	D50%		< 29.5 Gy

Abbreviations: GTV = gross tumor volume; PTV = planning target volume; NVB = neurovascular bundle; IPA = internal pudendal artery; CC = corpus cavernosum; PB = penile bulb.

Neurovascular-sparing treatment planning

For each patient the left and right NVB, IPA, CC, and the PB were contoured on the pre-treatment offline 3 T T2-weighted planning MRI. Contouring was done by a single prostate specialized radiation oncologist (JVZ) with 10 years of clinical experience, using the in-house developed contouring software package Volumetool and contours were added to the standard planning contour set that was previously contoured by the treating radiation oncologist. The NVB was contoured from at least the base of the seminal vesicles until the level of the urogenital diaphragm (Fig. 1). On T2-weighted MRI the NVB is generally well identifiable at the level of the apex where it is delimited by the dorsolateral part of the prostate and the ventrolateral part of the rectum and can be followed towards the level of the seminal vesicles.[2,17] The IPA was contoured from

at least the level of the sacroiliac ligament until the crus where it terminates into the common penile artery and the scrotal artery.

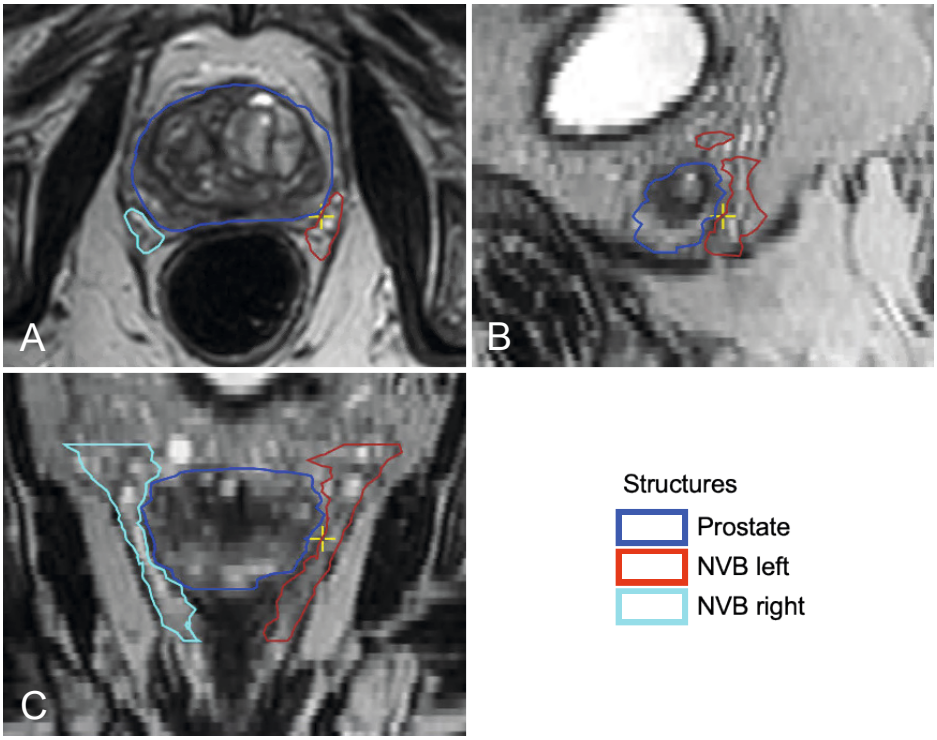

Figure 1: *Example of the contours of the neurovascular bundle of a single study patient. A: transverse plane; B: sagittal plane; C: coronal plane.*
Abbreviations: NVB = neurovascular bundle.

The planning MRI including contour set was imported into the treatment planning software Monaco 5.40.01 (Elekta AB, Stockholm, Sweden), to generate intensity modulated radiotherapy (IMRT) offline treatment plans for the Unity MR-Linac. Bulk relative electron density value of 1 was assigned to the body and values for the femoral heads and other bony structures were calculated using the average Hounsfield units of a matched CT scan. Seven-field IMRT technique was used (gantry angles: 0°, 50°, 100°, 155°, 205°, 260°, and 310°). The calculation grid spacing was 3 mm with a statistical uncertainty of 3% per control point and < 1% per voxel. The minimum segment width was 0.5 cm and area 1.5 cm2 and the minimum number of motor units was 5 with a maximum of 60 segments. No plan renormalization was used. During treatment the patient is supported by a soft pillow under the head and knee supporters under the feet. All settings were identical to the standard 5 × 7.25 Gy MRI-guided radiotherapy at our institution.

For neurovascular-sparing treatment planning, GTV + 4 mm and PTV coverage was the primary goal, secondary, meeting the conventional OAR (bladder, rectum, sphincter, and femurs) constraints, and tertiary, meeting the neurovascular structures constraints. In case the neurovascular-sparing constraints could not be met, a dose as low as reasonably achievable (ALARA) was pursued. The planning was done under supervision of a radiation therapist specialized in treatment planning (JH) with 10 years of clinical experience and all plans were evaluated by a prostate specialized radiation oncologists (JVZ).

Plan comparison

In a next step, we compared the neurovascular-sparing plans with the standard (i.e., non-neurovascular-sparing) pre-treatment plans. For all 20 patients, the matched neurovascular-sparing contour set including the NVBs, IPAs, CCs, and PB was registered to the actual clinical pre-treatment plan that was generated before to the MR-Linac treatment, using Monaco 5.40.01. Planned dose to the target volumes, conventional OAR, and neurovascular structures as would have been received in the standard planning setting were calculated in Monaco.

Statistical analysis

R version 4.0.5 was used for the statistical analysis. Pairwise Wilcoxon signed rank tests with Bonferroni correction for multiple testing were performed to compare the neurovascular-sparing planned dose with the standard planned dose. Furthermore, the NVBs were stratified between those that did and did not meet the dose constraint in the neurovascular-sparing plans. Population-median dose volume histogram (DVH) curves were generated using the R package “dvhmetrics”. Non-normally distributed data were presented as median with range and P-value of < 0.05 was considered statistically significant.

Results

All 20 patients’ treatment plans were considered clinically acceptable. Prescribed dose coverage of the GTV + 4 mm and PTV was achieved for neurovascular-sparing plans and the neurovascular-sparing dose constraints for the CC and PB were met in all patients (Table 2). The dose constraints for the IPA were met in 19 (95%) patients bilaterally and in 1 (5%) patients unilaterally. Constraints for the NVB were met in eight (40%) patients bilaterally, in eight (40%) patients unilaterally, and were not met in four (20%) patients (Fig. 2). In all cases where the GTV was located in the dorsolateral position, the NVB constraint could not be met.

Table 2: *Median prescribed dose for the neurovascular-sparing 5 × 7.25 Gy MRI-guided radiotherapy plans compared to the standard 5 × 7.25 Gy MRI-guided radiotherapy pre-treatment plans*

Structure	Volume (cc)		Planned dose					
			Parameter	Neurovascular-sparing plans		Standard plans*		P
	median	range		median	range	median	range	
PTV n = 20	105.8	68.3–185.2	V34.4 Gy (%)	88.3	81.1–97.4	98.9	97.0–99.9	< 0.01
			V32.6 Gy (%)	95.8	90.8–99.9	99.9	98.6–100	< 0.01
			V30.0 Gy (%)	99.9	99.5–100	100	99.2–100	0.03
GTV + 4 mm n = 20	14.1	1.6–57.9	V34.4 Gy (%)	100	99.8–100	100	100–100	< 0.01
Bladder n = 20	183.9	71.1–408.3	D0.5 cc (Gy)	37.2	36.5–37.9	37.1	35.1–38.3	0.03
			D5 cc (Gy)	35.7	34.3–36.8	35.7	33.1–36.8	0.71
			V32.0 Gy (%)	9.8	3.7–13.9	8.9	2.6–18.5	0.99
			V28.0 Gy (%)	15.3	5.9–20.0	13.8	4.4–27.5	0.99
Femur n = 40	217.5	146.7–290.6	D10 cc (Gy)	17.9	12.0–20.9	16.9	13.3–20.5	0.13
Rectum n = 20	79.9	50.6–190.8	D0.5 cc (Gy)	36.3	35.3–37.2	37.2	36.5–37.9	< 0.01
			D1 cc (Gy)	35.8	34.8–36.7	36.8	36.0–37.6	< 0.01
			V32.0 Gy (%)	6.1	3.3–9.2	7.7	4.9–13.1	< 0.01
			V28.0 Gy (%)	9.7	5.8–14.3	11.1	7.2–19.0	< 0.01
Sphincter n = 20	12.9	6.2–17.8	D0.5 cc (Gy)	24	2.9–34.9	24.5	4.7–36.1	0.27
			D1 cc (Gy)	18.8	2.6–33.2	19.6	3.9–34.9	0.46
			Dmean (Gy)	8.5	1.7–18.4	9	2.3–16.0	0.99

Table 2: *Continued*

Structure	Volume (cc)		Planned dose					
			Parameter	Neurovascular-sparing plans		Standard plans*		P
	median	range		median	range	median	range	
NVB n = 40	5.2	2.7–8.0	Dmean (Gy)	28.5	21.6–32.8	33.3	27.1–35.5	< 0.01
			D0.1 cc (Gy)	32.6	32.3–37.3	37.5	36.9–38.3	< 0.01
NVB constraint met in NS plan n = 24	4.9	2.7–8.0	Dmean (Gy)	27.6	21.6–30.2	33.2	27.1–35.5	< 0.01
			D0.1 cc (Gy)	32.6	32.3–32.7	37.3	36.9–38.2	< 0.01
NVB constraint not met in NS plan n = 16	5.7	3.7–7.3	Dmean (Gy)	30	25.0–32.8	33.7	29.2–35.3	< 0.01
			D0.1 cc (Gy)	36	34.8–37.3	37.6	36.9–38.3	< 0.01
IPA n = 40	2.1	1.2–4.0	Dmean (Gy)	11.9	7.1–15.4	19	9.1–28.3	< 0.01
			D0.1 cc (Gy)	19.4	10.2–22.9	29.5	11.6–35.2	< 0.01
CC n = 40	4.6	2.4–11.0	Dmean (Gy)	4.7	1.7–9.6	5.7	1.9–13.7	< 0.01
			D0.01 cc (Gy)	13.6	3.4–17.1	19.6	4.1–32.7	< 0.01
PB n = 20	6.2	3.8–11.8	Dmean (Gy)	7.9	2.2–17.4	8.4	2.1–27.0	0.08
			D50% (Gy)	4.6	2.1–17.0	3.8	1.5–28.3	0.74

**Standard 5 × 7.25 Gy MRI-guided radiotherapy dose prescription to PTV was 34.4 Gy in ≥ 99.0% (no separate clinical target volume or GTV + 4 mm prescription). Dose constraints for bladder, rectum, sphincter, and femur were identical for the neurovascular-sparing and standard plans.*

For the femur, NVB, IPA, and CC: left and right side are combined.

Abbreviations: PTV = planning target volume; GTV = gross tumor volume; NVB = neurovascular bundle; NS = neurovascular-sparing; IPA = internal pudendal artery; CC = corpus cavernosum; PB = penile bulb.

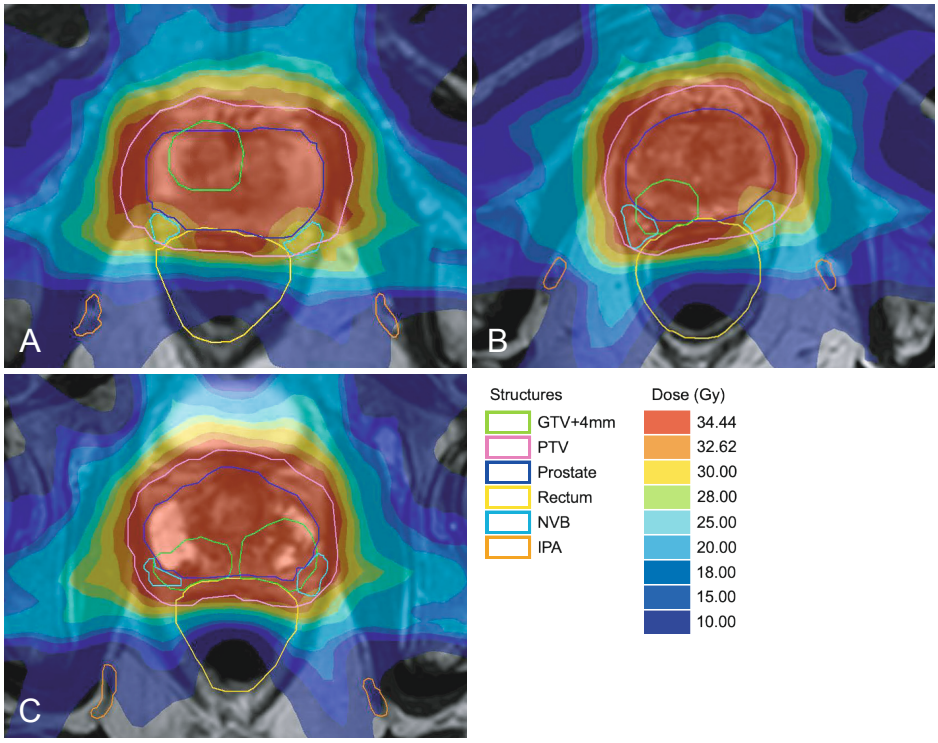

Figure 2: *Example of neurovascular-sparing 5 × 7.25 Gy MRI-guided radiotherapy plan dose distribution in three patients representing the three neurovascular bundle-sparing scenarios. A: NVB constraint met bilaterally (40% of patients); B: NVB constraint met unilaterally (40% of patients); C: NVB constraint not met (20% of patients).*

Abbreviations: GTV = gross target volume; PTV = planning target volume; NVB = neurovascular bundle; IPA = internal pudendal artery.

The comparison of the neurovascular-sparing plans with the standard plans is presented in Table 2, Fig. 3, and Supplementary material: Fig. 1. The median planned dose to the NVB, IPA, and CC was significantly lower in the neurovascular-sparing plans compared with the standard plans (NVB D0.1 cc: 32.6 Gy vs. 37.5 Gy, $P < 0.01$; IPA D0.1 cc 19.4 Gy vs. 29.5 Gy, $P < 0.01$; CC D0.01 cc: 13.6 Gy vs. 19.6 Gy, $P < 0.01$), also for the cases in which the NVB constraint was not met in the neurovascular-sparing plan (D0.1 cc 36.0 Gy vs. 37.6 Gy, $P < 0.01$). The median planned dose to the PB was not significantly different between the neurovascular-sparing plans and the standard plans. Median dose coverage of the PTV for the V34.4 Gy parameter was significantly higher in the standard plans compared with the neurovascular-sparing plans (98.9% vs. 88.3%, $P < 0.01$). The median planned dose to the bladder and sphincter was not significantly different between the two planning strategies except for the bladder D0.5 cc parameter, which was significantly lower in the standard plans compared with the neurovascular-

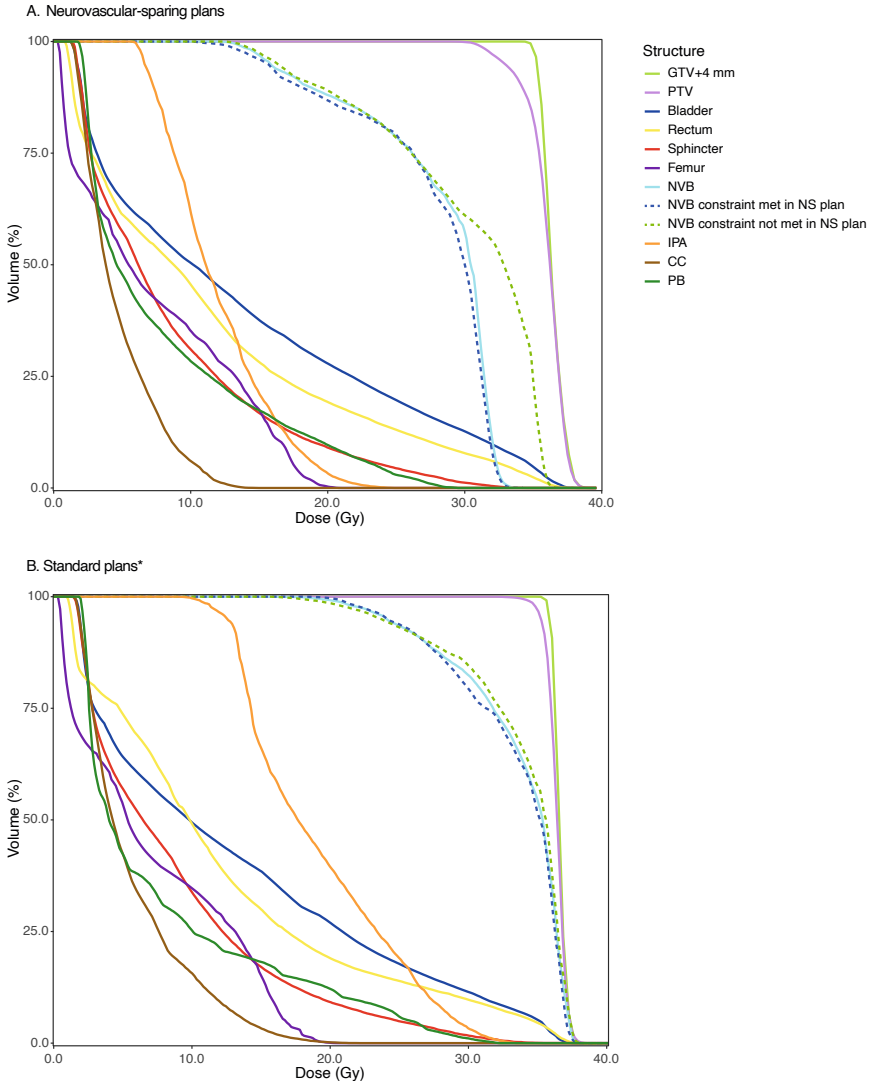

Figure 3: *Population-median DVH curves for (A) the neurovascular-sparing 5 × 7.25 Gy MRI-guided radiotherapy plans (n = 20) and (B) the standard 5 × 7.25 Gy MRI-guided radiotherapy plans (n = 20). Femur, NVB, IPA, and CC: n = 40 (left and right side are combined); NVB constraint met in NS plan: n = 24; NVB constraint not met in NS plan: n = 16.*

**Standard 5 × 7.25 Gy MRI-guided radiotherapy dose prescription to PTV was 34.4 Gy in ≥ 99.0% (no separate clinical target volume or GTV + 4 mm prescription). Dose constraints for bladder, rectum, sphincter, and femur were identical for the neurovascular-sparing and standard plans.*

Population-median DVH curves with 95% confidence intervals are displayed in Supplementary material: Fig. 1.

Abbreviations: PTV = planning target volume; GTV = gross tumor volume; NVB = neurovascular bundle; NS = neurovascular-sparing; IPA = internal pudendal artery; CC = corpus cavernosum; PB = penile bulb.

sparing plans (37.1 Gy vs. 37.2 Gy, P = 0.03). The median planned dose to the rectum was significantly lower in the neurovascular-sparing plans compared with the standard plans for all parameters (all P < 0.01).

Discussion

This study is the first to demonstrate that neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer is feasible in the planning setting. Predefined constraints for the CC and PB were met in all 20 patients, for the IPA in 19 (95%) patients bilaterally and 1 (5%) unilaterally, and for the NVB in 8 (40%) patients bilaterally and in 8 (40%) patients unilaterally. Dose to the NVB, IPA, and CC was reduced significantly, without substantially increasing dose to the bladder, rectum, and sphincter.

In all cases where the GTV was located in the dorsolateral position of the prostate and therefore the GTV + 4 mm directly bordering or partially overlapping the NVB, the NVB constraint could not be met (Fig. 2). Nevertheless, the median planned dose to the NVBs that did not meet the dose constraint in the neurovascular-sparing plans was still lower in the neurovascular-sparing plans compared to the standard plans. In the single case where the IPA dose constraint could only be met unilaterally, the IPA had an unfavorable anatomical location close to the prostate and was therefore partly located within the PTV. It should be noted that we used an isotropic PTV margin of 5 mm for this planning study, which generally includes part of the NVB and in some cases part of the IPA. In the near future fast-adaptive auto-contouring and online re-planning will enable further margin reduction, which should improve neurovascular-sparing capabilities of MR-Linac treatment, especially the sparing of the NVB.[22,23,24]

Although it is hypothesized that MRI-guided radiotherapy offers major advantages in terms of erectile function-preserving treatment because of the ability to adequately visualize the neurovascular structures and correct for interfraction and intrafraction motion and deformation, others have initiated studies on erectile function-preserving radiotherapy on conventional linacs. Spratt et al. conducted a single arm study in which 135 men with an IIEF-5 score of ≥ 16 at baseline underwent IPA and CC sparing radiotherapy and reported an erectile function preservation rate of 67% (i.e., IIEF-5 ≥ 16) at 5 years after treatment.[5] Their study population consisted of low-, intermediate-, and high-risk prostate cancer patients and treatment consisted of IMRT of 75.6 Gy in 1.8-Gy daily fractions or low-dose rate (LDR) brachytherapy to a prescription dose of 110 Gy, followed by IMRT of 45 Gy in 1.5-Gy fractions. For all high-risk patients, pelvic lymph nodes were treated to 45 Gy. Additionally, androgen deprivation therapy was

prescribed for a duration of 6 months at the discretion of the treating physician. Because of the heterogeneity of the study population and treatment strategies, the independent effect of the different study parameters on preservation of erectile function are difficult to deduct from this study.

The currently ongoing POTEN-C trial takes erectile function-preserving EBRT a step further by conducting a randomized controlled trial randomizing 120 low- to intermediate-risk patients between 5 fraction SBRT with or without sparing of the NVBs, IPAs and PB on a conventional linac.[7] The study is expected to complete in 2024. Still, to date the question remains to what extent the neurovascular structures, especially the NVB can be sufficiently and safely spared without adaptive MRI-guidance.

There are some considerations for our study. First, it is unknown to what extent radiation damage to each individual neural or vascular structure contributes to ED after radiotherapy. In literature the NVBs, IPAs, CCs, and PB are generally described as the most important structures contributing to radical prostate cancer treatment-induced ED.[2,18] It is hypothesized that ED after radiotherapy is predominantly a consequence of vascular damage to the IPAs, CCs, PB, and vascular part of the NVBs.[19] On the other hand, ED after prostatectomy is considered primarily a consequence of nerve damage and erectile function-preserving radical prostatectomy is focused on the sparing of the NVBs.[20] In literature it is widely reported that even unilateral sacrifice of the NVB will substantially increase the chance of developing ED after surgery.[21] For brachytherapy a high rate of ED after treatment is reported as well.[21] With brachytherapy, the NVBs will receive a higher radiation dose compared to the IPAs, CCs, and PB as these structures are better spared due to the typical steep dose gradient, suggesting that dose to NVBs plays an instrumental role in development of ED after brachytherapy.[22] Prospective dose-toxicity relationship studies need to be performed to adequately assess to what extent radiation damage to each individual neural or vascular structure contributes to ED after radiotherapy. Second, in this study the GTV + 4 mm was set to receive 34.4 Gy in ≥ 99.0% (EQD2 α/β = 1.5 Gy: 82.5 Gy) and the PTV 30.0 Gy in ≥ 99.0% (EQD2 α/β = 1.5 Gy: 64.3 Gy), 32.6 Gy in ≥ 90.0% (EQD2 α/β = 1.5 Gy: 74.8 Gy), and 34.4 Gy in ≥ 80.0%. These PTV constraints were lower compared to the standard 5 × 7.25 Gy MRI-guided radiotherapy PTV constraint (34.4 Gy in ≥ 99.0%) used in our institution, which resulted in a significantly lower PTV dose coverage compared to the standard plans. This dose reduction might influence biochemical control, but an increase of clinical failure and decrease of overall survival is not expected. A dose escalation study from 68 Gy to 78 Gy in mainly high-risk patients showed an improved freedom from failure from 47% to 54% after a median follow up of 70 months, but showed no difference in clinical failure and overall survival.[23] Moreover, the dose constraint of 30.0 Gy to ≥ 99% of the PTV

may radiobiologically have a greater impact on tumor control than the linear quadratic model suggests, especially since the validity of the linear quadratic model for extreme hypofractionation can be taken into doubt. There is substantial evidence that prostate cancer has a low α/β of around 1.5 Gy and may therefore be more susceptible for the impact of extreme hypofractionation on tumor control.[24] Furthermore, the recent Flame trial demonstrated an advantage of an integrated focal boost of the macroscopic visible tumor in a predominantly high-risk localized prostate cancer population in terms of biochemical recurrence free survival, without increasing toxicity.[25] It promotes the GTV as an important target for tumor control for which no concession on prescribed dose should be made, as was done in this study. Also, because of frequent tumor follow-up after treatment, recurrences will probably be diagnosed at an early stage with only localized disease. Patients then remain in the "window of curability" as several salvage treatment options are available.[26,27]

To assess the effect of neurovascular-sparing treatment, we initiated a single arm phase II trial (NCT04861194).[28] In this trial 70 men will receive neurovascular-sparing MRI-guided radiotherapy in five fractions of 7.25 Gy. Because of the slight reduction in PTV dose only low- and intermediate-risk patients with a satisfactory erectile function at baseline (IIEF-5 ≥ 17) and a wish for erectile function-preserving treatment are eligible. The primary endpoint is erectile function at 3 years after treatment. Secondary endpoints include biochemical recurrence free survival at 3 years after treatment and quality of life. Additionally, we will assess the dose-toxicity relationship for the individual neural and vascular structures potentially contributing to ED after radiotherapy.

The RATING guidelines for treatment planning were used for preparing the manuscript.[29] The authors concluded that the RATING score was 81%.

Conclusion

Neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer is feasible in the planning setting. Dose to the neurovascular structures can be reduced substantially. The extent of neurovascular-sparing largely depends on the patient's GTV location.

Supplementary material

Table 1:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8473534/bin/mmc1.docx

Figure 1:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8473534/bin/mmc2.pdf

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CHAPTER 7

Neurovascular-sparing MRI-guided adaptive radiotherapy in prostate cancer; defining the potential population for erectile function-preserving treatment

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Abstract

Background: Magnetic resonance imaging (MRI)-guided adaptive radiotherapy enables neurovascular-sparing treatment for localized prostate cancer. The aim of this treatment is preservation of erectile function by sparing the neurovascular bundles, the internal pudendal arteries, the corpora cavernosa, and the penile bulb. Internal pudendal arteries, corpora cavernosa, and penile bulb sparing can generally be achieved in all patients, but NVB sparing can be challenging due to its proximity to the prostate and is therefore dependent on tumor location. Prostate cancer patients that have sufficient erectile function at baseline and favorable tumor characteristics might benefit from this treatment. Currently, it is unclear what proportion of patients are eligible for neurovascular-sparing treatment and to what extent this is technically feasible.

Purpose: To define the eligibility and technical feasibility for neurovascular-sparing MRI-guided radiotherapy in intermediate-risk localized prostate cancer patients.

Materials and methods: A consecutive series of men that received 5 × 7.25 Gy MRI-guided radiotherapy for localized prostate cancer were included. Baseline erectile function was assessed using the International Index of Erectile Function (IIEF)-5 questionnaire. Additionally, the ability of sparing the neurovascular bundles was assessed in all patients. Per neurovascular-sparing protocol, the dominant intraprostatic lesion with a 4 mm isotropic margin should receive 34.44 Gy in ≥ 99% of the volume (i.e., high-dose area). When the high-dose area directly borders or overlaps the NVB because of a dorsolateral position of the dominant intraprostatic lesion, sparing of the NVB was considered not feasible on that side.

Outcomes: Patient-reported IIEF-5 baseline questionnaires and the technical feasibility of NVB sparing were assessed.

Results: Of the 102 men that completed the IIEF-5 questionnaire at baseline, 49.0% of patients reported to have an IIEF-5 score of ≥ 17. In those patients, the NVB could technically have been spared bilaterally in 20.0% and unilaterally in 68.0%.

Clinical implications: Our findings define the potential population for neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer and indicate the proportion in which the NVB can technically be spared.

Strength and limitations: The major strength of this study is the prospective collection of data. The limitations include that the neurovascular-sparing feasibility definition is based on pre-clinical planning data.

Conclusion: A substantial group of 49.0% of patients in our study had mild or no erectile dysfunction at baseline. Of these patients, the NVB could technically have been spared bilaterally in 20.0% and unilaterally in 68.0% during MRI-guided radiotherapy. Trials need to assess the effect of neurovascular-sparing MRI-guided radiotherapy on erectile function.

Introduction

Erectile dysfunction (ED) is a common adverse effect of radical treatments for localized prostate cancer such as radical prostatectomy, brachytherapy, and external beam radiotherapy (EBRT). ED has a negative effect on quality of life and should therefore be taken into consideration when deciding between treatment options.[1,2]

For radical prostatectomy, techniques for preservation of erectile function have been applied since the introduction of the nerve-sparing prostatectomy by Walsh and Donker in 1982.[3] However, even after bilateral nerve-sparing prostatectomy ED remains common with reported rates up to 37% at 2 years after surgery.[4]

For EBRT, innovations in treatment techniques have mainly been focused on reducing gastrointestinal and urinary toxicity by decreasing the dose to bowel and urinary bladder.[5,6] Structures relevant for erectile function, such as the neurovascular bundle (NVB) and internal pudendal artery (IPA), are currently not routinely spared during EBRT. This is mainly because these structures are generally not visible on CT imaging, which is conventionally used for daily treatment planning and adaption before treatment fractions.[7,8]

Our hospital has developed the MR-Linac, which has recently been introduced globally.[9] The MR-Linac combines a linear accelerator with a 1.5 T magnetic resonance imaging (MRI) scanner.[10] MRI-guided adaptive radiotherapy enables real-time high-field MR imaging of the prostate and surrounding (soft-)tissue during radiotherapy.[11] With this technique it is possible to adapt the radiotherapy plan to the movement and deformation of the prostate and surrounding (soft-)tissue during treatment in order to minimize radiation to healthy tissue.[12] MRI-guided radiotherapy is therefore very suitable for neurovascular-sparing (or erectile function-preserving) radiotherapy treatment.

During neurovascular-sparing MRI-guided radiotherapy the aim is to reduce the dose to the NVBs, IPAs, corpora cavernosa (CCs), and penile bulb (PB) as much as possible, while maintaining sufficient radiation dose to the prostate and tumor. We have previously demonstrated that adequate dose reduction to the IPAs, the CCs, and the PB can be accomplished without compromising the prostatic dose.[13] In contrast, reducing the dose to the NVBs can technically be more challenging as these structures are in closer proximity to the prostate. Sparing the NVBs might conflict with maintaining sufficient dose to the prostate, which is the main priority.

At our center, standard MRI-guided radiotherapy for intermediate-risk prostate cancer has been implemented in standard clinical practice, whereas MRI-guided radiotherapy

with neurovascular sparing has recently become available in clinical-trial setting. Ideally, neurovascular-sparing MRI-guided radiotherapy is applied in intermediate-risk prostate cancer patients with satisfactory to good erectile function at baseline and an anatomically favorable tumor location which enable bilateral sparing of the NVBs.

Currently, it is unclear to what extent characteristics of intermediate-risk prostate cancer patients that choose to undergo novel MRI-guided radiotherapy treatment are comparable to the standard radiotherapy and to what extent they have satisfactory to good erectile function at baseline. Furthermore, it is unknown in what proportion of patients neurovascular-sparing MRI-guided radiotherapy is technically feasible.

In this study, we aim to define the eligibility and technical feasibility of neurovascular-sparing MRI-guided radiotherapy. The results of this study should enable us to determine the relevance and potential of this novel treatment.

Materials and methods

Patients

We included all intermediate-risk (National Comprehensive Cancer Network category) prostate cancer patients within our institution's prospective registry (the "Utrecht Prostate Cohort," NCT04228211) treated between February 5, 2020 and November 1, 2021. All included patients received a total of 36.25 Gy to the prostate in 5 fractions using MRI-guided radiotherapy, which is is standard treatment for patients with intermediate-risk prostate cancer that opt for radiotherapy at our institution. Only patients that gave informed consent for filling out patient reported outcome questionnaires were included. In order to determine whether a shift in age of patients that undergo radiotherapy using MRI-guided radiotherapy is present, we compared the included patients with patients from the general Dutch population by extracting data from the Dutch national cancer registry in which all patients that are treated for prostate cancer in the Netherlands were recorded. For our analysis we extracted type of treatment (i.e., radical prostatectomy or EBRT), age, and risk group. We used the data from the year 2019, which was the last full non-COVID year.

Erectile function

For the assessment of erectile function, the International Index of Erectile Function (IIEF)-5 questionnaire was used.[14] The IIEF-5 addresses the erectile function over the past 6 months prior to filling out the questionnaire. IIEF-5 ≥ 17 was regarded as mild to no ED, IIEF-5 12–16 as mild to moderate ED, and IIEF-5 ≤ 11 as moderate to severe

ED. The IIEF-5 was accompanied by the Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire to assess sexual function. A sexual domain score of 0 was interpreted as worst and of 100 as best possible sexual function.[15] Only questionnaires that were filled out before first fraction were included.

Neurovascular bundle-sparing feasibility

Per protocol, all MRI-guided radiotherapy patients received a pre-treatment 3 T offline planning MRI (T2-weighted and diffusion weighted imaging [DWI] sequences) on which the dominant intraprostatic lesion (DIL) was contoured by the treating radiation oncologist and the radiotherapy pre-treatment planning was performed. The DIL indicated the MRI visible tumor within the prostate. A margin of 4 mm around the DIL was generated for potential microscopic disease. Per protocol the DIL + 4 mm isotropic margin should have received 34.44 Gy (95% of 36.25 Gy) in ≥ 99% of the volume [13] The clinical target volume (CTV) encompasses the prostate, the base of the seminal vesicles and DIL + 4 mm margin. To account for prostate motion during radiotherapy, a 5 mm isotropic margin was implemented around the CTV. The CTV + 5 mm, also known as the planning target volume (PTV) may receive a relatively lower dose coverage of 34.44 Gy in ≥ 80%, 32.62 Gy (90% of 36.25 Gy) in ≥ 90%, and 30.00 Gy (83% of 36.25 Gy) in ≥ 99% of the total volume *(*Fig. 1). The NVB dose constraint was set to ≤ 32.75 Gy in D0.1 cc (i.e., the 0.1 cc of the NVB that receives the highest dose, should receive no more than 32.75 Gy), which was based on literature for neural and vascular tissue and experience with radiation toxicity for sacral plexus and brachial plexus.[13]

Our group has previously demonstrated that in case the DIL + 4 mm margin (i.e., high radiation dose area) was located in the dorsolateral position, directly adjacent to or overlapping the NVB on the planning MRI, meeting the NVB dose constraint of ≤ 32.75 Gy in D0.1 cc, and thus NVB sparing, was not feasible on that side (Fig. 1).[13] Following that approach, DIL + 4 mm and PTV dose coverage (as per neurovascular-sparing protocol) could generally be met without compromising sparing of the bladder, rectum, IPAs, CCs, and PB. In this study we assessed whether the NVB could technically have been spared bilaterally or unilaterally based on the pre-treatment planning contours of the DIL + 4 mm margin in relation to the NVB for each patient with an IIEF-5 ≥ 17. The NVBs were contoured by one rater (FT) and systematically evaluated by another rater (JV) using a previously published contouring atlas[16] and the technical NVB-sparing feasibility (i.e., bilateral, unilateral, or no sparing) was assessed subsequently. Interrater agreement of NVB contouring was previously assessed in a pre-clinical interrater study, which showed a Dice similarity coefficient (DSC) of 0.67 of the NVB at prostate midgland to apex level where it is adjacent to the prostate.[16] Furthermore, DSC improved substantially after

MRI sequence optimization and rater training and therefore expected to further improve in the clinical setting.

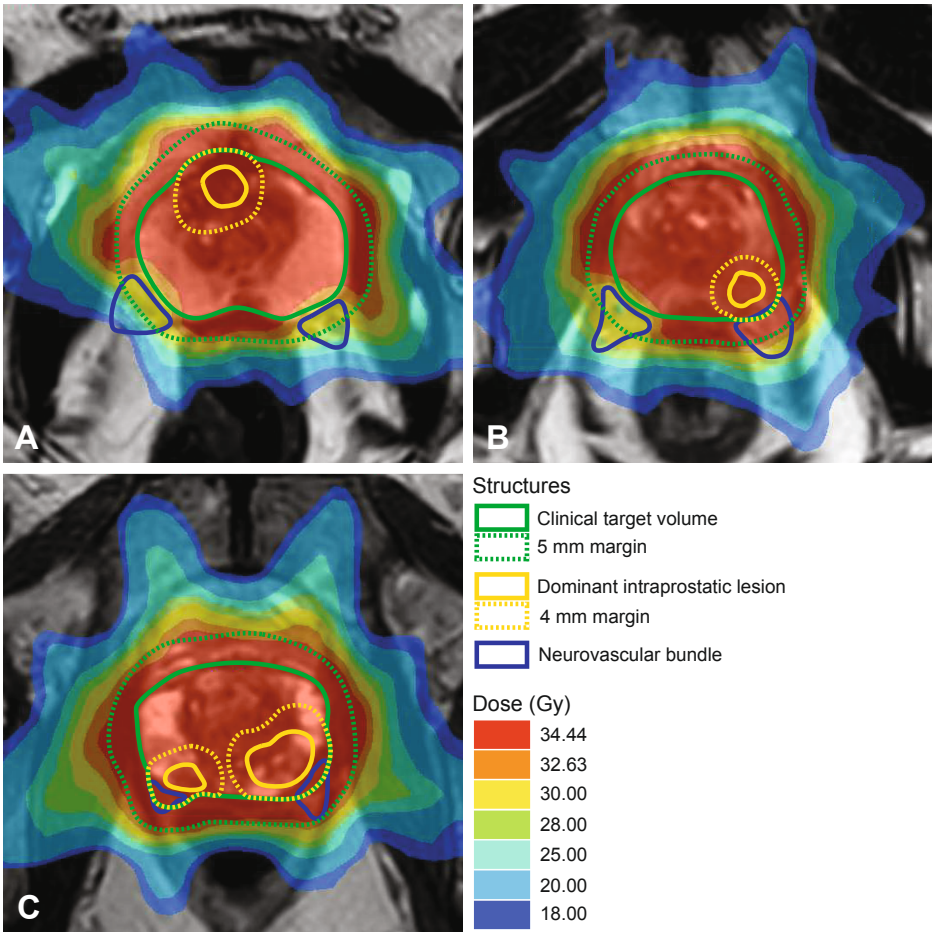

Figure 1: *Pre-treatment planning dose distribution, representing the variation in tumor location in relation to the neurovascular bundle (NVB) and ability of NVB sparing (axial plane). Yellow dashed line (i.e., high-dose area): represents the dominant intraprostatic lesion (DIL) with a 4 mm isotropic margin excluding the bladder and bowel. ≥ 99% of this area should receive 34.44 Gy. Green dashed line (i.e., low-dose area): represents the planning target volume (PTV). This includes the clinical target volume (CTV) with a 5 mm isotropic margin. The CTV consists of the whole prostate, base of the seminal vesicles, and the DIL + 4 mm. For the PTV ≥ 99% should receive 30.00 Gy, ≥ 90% 32.62 Gy, and ≥ 80% 34.44 Gy. The NVB dose constraint is set at D0.1 cc ≤ 32.75 Gy, meaning that the 0.1 cc of the NVB that receives the highest dose, should receive no more than 32.75 Gy to achieve NVB sparing. A: bilateral NVB sparing representing 20.0% of cases; B: unilateral NVB sparing representing 68.0% of cases; C: no NVB sparing representing 12.0% of cases.*

Descriptive statistics were presented as mean with standard deviation (SD) and were calculated using R 4.1.1.

Results

Patient characteristics

One hundred and fifty-four intermediate-risk localized prostate cancer patients were treated between February 5, 2020 and November 1, 2021 and were included in the study. One hundred and two (66.2%) patients filled out the IIEF-5 questionnaire at baseline. Mean age was 69 (SD: 6) years. In comparison, the mean age of the general Dutch intermediate-risk localized prostate cancer population that received EBRT in 2019 was 72 years (SD: 6; n = 1279) and patients that underwent prostatectomy in 2019 were on average 66 years (SD: 6; n = 1461).

Erectile function

Of the 102 patients that filled out the IIEF-5 at baseline, 50 (49.0%) had an IIEF-5 score of ≥ 17. Those patients were younger (mean age: 68 years, SD: 6 vs. 69 years, SD: 6) and had less comorbidities (mean CCI: 0.3, SD: 0.8 vs. 0.6, SD: 1.0). Patients with an IIEF-5 score of ≥ 17 reported a mean EPIC-26 sexual domain score of 78.3 (SD: 17.7) and patients with an IIEF-5 of < 17 reported a mean EPIC-26 sexual domain score of 58.5 (SD: 25.9). 4 (3.9%) patients that filled out the IIEF-5 indicated to not have had any sexual activity over the past 6 months.

Neurovascular bundle-sparing feasibility

Based on the predefined definitions, of the 50 patients that reported to have an IIEF-5 score of ≥ 17, the NVB could technically have been spared bilaterally in 10 (20.0%) patients and unilaterally in 34 (68.0%) patients.

Discussion

Neurovascular-sparing radiotherapy delivered with the MR-linac could become an important competitor of radical prostatectomy for patients that wish to preserve erectile function after definite prostate cancer treatment. This study is the first to estimate the potential patient population that will be eligible for erectile function-preserving treatment and to identify the proportion of patients in which the NVB can be spared during neurovascular-sparing MRI-guided radiotherapy.

Almost all patients that were treated for intermediate-risk localized prostate cancer with MRI-guided radiotherapy indicated to have been sexually active over the past 6 months before treatment (96.1%). We found that 49.0% of patients in our study had no or mild ED at baseline, which corresponded with a substantially higher EPIC-26 sexual domain score compared to the patients with moderate to severe ED (Δ = 19.8).[17] For the patients with no or mild ED, the NVB could have been spared bilaterally in 20.0% of the patients (n = 10) and unilaterally in 68.0% (n = 34) of the cases without significantly compromising tumor coverage. Previous data demonstrated that the IPA, CC, and PB can generally be spared in all cases.[13] These data demonstrate: (1) that efforts to preserve sexual function are extremely relevant within the MRI-guided radiotherapy patient population, and (2) that (partial) NVB sparing treatment is technically feasible in most patients.

In clinical practice, EBRT patients tend to be older and have more comorbidities compared to radical prostatectomy patients. Despite the fact that many studies have shown equality in terms of survival for both treatment modalities,[18] radical prostatectomy is often regarded as the first choice of radical treatment by many patients. However, after counseling patients (shared decision making) there is better understanding of the expected toxicities for each treatment modality, which subsequently leads to less decision regret after treatment.[19] Our study population is substantially younger than the general (conventional) EBRT population (on average 69 vs. 72 years old), but still older than the prostatectomy population (on average 69 vs. 66 years old). This might indicate that MRI-guided radiotherapy is already attracting a relatively younger group of patients. Neurovascular-sparing MRI-guided radiotherapy, which holds the promise to further reduce ED after radical prostate cancer treatment, may induce a further paradigm shift by drawing younger and healthier prostate cancer patients towards EBRT.

Neurovascular-sparing MRI-guided radiotherapy for prostate cancer for the preservation of erectile function is promising, but prospective studies must show efficacy before widespread clinical implementation. Erectile function preservation and tumor control need to be assessed, to be able to weigh the potential benefits against the risks. At our center we recently started the prospective phase II ERECT-trial (NCT04861194), which addresses the effectivity of neurovascular-sparing MRI-guided radiotherapy in 70 men with intermediate-risk prostate cancer with no or mild ED at baseline. Prior to every fraction, we utilize online contouring and re-planning and subsequent couch-shift registration of the prostate alone.[20] The primary endpoint of this study is erectile function at 3 years after neurovascular-sparing MRI-guided radiotherapy and biochemical recurrence at 3 years after treatment is among the secondary endpoints.

A limitation of this study is that the neurovascular-sparing feasibility is based on pre-clinical planning-study data.[13,16] Clinical studies, which are currently running (NCT03525262 and NCT04861194), must confirm the assumptions on which we based the feasibility of neurovascular sparing in this study.

Conclusion

At baseline 49.0% of patients receiving novel MRI-guided radiotherapy for intermediate-risk localized prostate cancer had good baseline erectile function with an IIEF-5 score of ≥ 17. Of patients with adequate erectile function at baseline, NVB sparing was technically feasible bilaterally in 20.0% and unilaterally in 68.0% of these patients. Trials need to assess the effect of neurovascular-sparing MRI-guided radiotherapy on erectile function.

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CHAPTER 8

Daily online contouring and re-planning versus translation-only correction in neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer

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Abstract

Neurovascular bundle (NVB) and internal pudendal artery (IPA) sparing during magnetic resonance imaging (MRI)-guided radiotherapy for prostate cancer aims for preservation of erectile function. Our present workflow involves daily online contouring and re-planning on a 1.5 T MR-linac, as alternative to conventional (rigid) translation-only corrections of the prostate. We compared planned dose for the NVB and IPA between strategies. Total planned dose was significantly lower with daily online contouring and re-planning for the NVB, but not for the IPA. For the NVB and IPA, the intrapatient difference between highest and lowest fraction dose was significantly smaller for the contouring and re-planning plans.

Introduction

Erectile dysfunction after stereotactic body radiotherapy for prostate cancer occurs in 26% to 55% of patients 5 years after treatment.[1] Literature suggests that radiation damage to predominantly the neurovascular bundle (NVB), internal pudendal artery (IPA), corpus cavernosum (CC), and penile bulb (PB) causes erectile dysfunction.[2]

Our group previously demonstrated that neurovascular-sparing magnetic resonance imaging (MRI)-guided adaptive radiotherapy, sparing the NVB, IPA, CC, and PB, is feasible. Currently, the first trial investigates this treatment's clinical outcomes in the single-arm phase-II ERECT trial (NCT04861194).[3,4] In the trial setting, patients with intermediate-risk prostate cancer and sufficient to good erectile function at baseline (i.e., IIEF-5 score of ≥ 17) are treated.[5]

MRI-guided radiotherapy enables online 1.5 T MR imaging before and during every fraction. Because soft tissue can be visualized with diagnostic quality, online contouring and re-planning can be performed, also called "adapt to shape" (ATS).[6] This procedure is a step further than online (rigid) translation-only correction in x, y, and z directions based on the prostate location, or "adapt to position" (ATP). Online translation-only correction is generally applied on conventional CT-guided radiotherapy devices using fiducial markers in the prostate. Because fiducial markers give information about the position of the prostate but not of the exact shape and due to the lack of soft tissue contrast on CT imaging, online contouring and re-planning for the NVBs may not be adequately applied on conventional external beam radiotherapy (EBRT).[2,7]

The position and shape of soft tissue structures may change under the influence of bladder and rectum filling between and during fractions. Therefore, daily online contouring and re-planning may have an advantage in both dose coverage of the target volumes and dose sparing of the OARs, including the neurovascular structures.[8]

The CC and PB are generally located more distant from the prostate than the NVB and IPA. The dose reduction of neurovascular-sparing MRI-guided radiotherapy is, therefore, predominantly accomplished in the NVB and IPA compared to standard MRI-guided radiotherapy and the hypothetical advantage of daily online contouring and re-planning over translation-only correction is most relevant in those structures.[3]

In this paper, we assess the dose/volume-based difference of daily online contouring and re-planning versus translation-only correction for the NVB and IPA in neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer.

Materials and methods

Patients and treatment

The first 20% (14/70) of patients treated within the ERECT trial were included. The ERECT trial received approval from the Institutional Review and Ethics Board of the University Medical Center Utrecht, the Netherlands. Patients signed informed consent for sharing of their data. All patients received neurovascular-sparing MRI-guided radiotherapy of 36.25 Gy in five fractions on a 1.5 T MR-Linac (Unity, Elekta AB, Stockholm, Sweden). Prior to radiotherapy, an offline 3 T MRI was made on which all structures were contoured (i.e., target volumes and OAR) using the in-house developed software tool "Volumetool". This planning MRI including contour set was imported into the treatment planning software to generate intensity modulated radiotherapy (IMRT) offline treatment plans. The gross tumor volume (GTV) + 4 mm consisted of the MRI-visible tumor with a 4 mm isotropic margin excluding the rectum and bladder. The clinical target volume (CTV) included the GTV + 4 mm and prostate body with the base of the seminal vesicles, and the planning target volume (PTV) included the CTV with a 5 mm isotropic margin. Depending on the position of the GTV, bilateral, unilateral, or no NVB sparing was utilized, which was determined prior to pre-treatment planning to ensure sufficient homogeneous GTV and PTV coverage during planning, and only allow a minor PTV dose reduction adjacent to the spared NVB. IPA, CC, and PB sparing was always utilized. Dose prescriptions were 34.4 Gy (95%) in ≥ 99% for the GTV + 4 mm isotropic margin (excluding rectum and bladder) and the 30.0 Gy in ≥ 99%; 32.6 (90%) Gy in ≥ 90% for the PTV. In the case of bilateral NVB sparing, the PTV 34.4 Gy dose prescription was set at ≥ 80%, in the case of unilateral NVB sparing ≥ 90%, and in the case of no NVB sparing ≥ 99%. This was done because for the unilateral and no NVB-sparing setting, the higher PTV 34.4 Gy dose prescription did not compromise the sparing of any of the other neurovascular structures or conventional OAR but resulted in a higher PTV coverage.[3] The dose constraint for the NVB was D0.1 cc ≤ 32.8 Gy, and for the IPA D0.1 cc ≤ 20.0 Gy. The IPA constraint was based on a previous vessel-sparing trial[9], and the NVB constraint on the literature on neural and vascular tissue and experience with radiation toxicity of the sacral plexus and brachial plexus (all dose prescriptions and constraints in Supplementary material: Table 1).[3] During treatment planning and online plan adaptation, we used a template in which target coverage was the primary goal, meeting the constraints of the conventional OAR the secondary goal, and meeting the neurovascular constraints the tertiary goal. Furthermore, the NVB constraint was a soft constraint.

During every fraction, an online 1.5 T T2w MRI scan was made on which the pre-treatment contours were registered using a semi-automated deformable registration method (sequence parameters in Supplementary material: Table 2). The contours of the target

volumes and OAR were automatically adapted to shape and if needed, adjusted manually (Fig. 1). This process was generally accurate for high-contrast structures on T2-weighted MRI, such as bladder, rectum, and IPA. Lower-contrast structures such as the prostate and especially the NVB generally had to be adjusted manually. In the next step, the treatment plan was adapted to the anatomy of the day. Dose to the NVB and IPA are controlled by cost functions. Isoconstraints of the cost functions were adjusted during online planning for plan optimization, but no cost functions were added or removed. During the treatment plan calculation, an online 3D T2w position verification MRI scan was made. The position verification scan was used to perform an additional ATP procedure directly before beam on to account for intratreatment patient motion during the ATS procedure.[10,11]

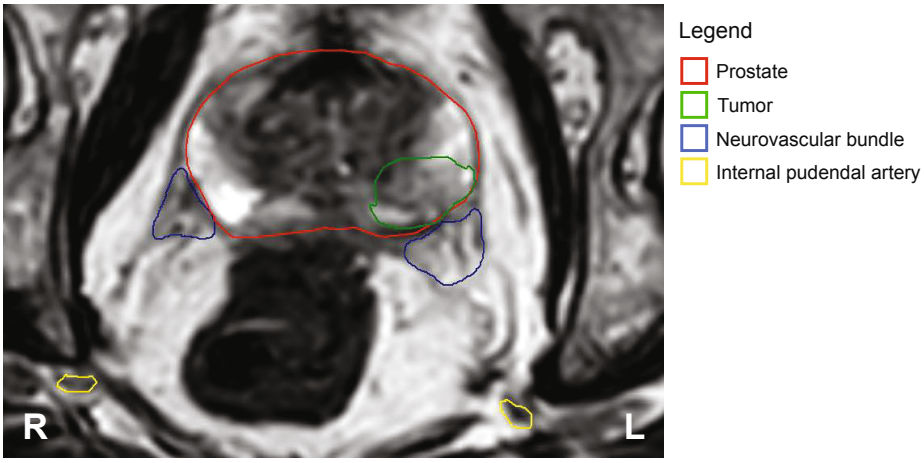

Figure 1: *Axial representation of the re-contoured prostate, tumor, neurovascular bundles, and internal pudendal arteries on an online 1.5 T T2w MRI scan (patient 14, fraction 1).*
Abbreviations: L = left; R = right.

Planned ATS and simulated ATP dose

All planning was done in Monaco 5.40.01. To compare the planned dose to the NVB and IPA in the ATS setting to the planned dose which would have been received in the ATP-only setting, the ATP dose was simulated. Therefore, the daily planning MRI scan of each fraction was matched (translations only) to the pre-treatment scan based on the prostate contour. The adapted daily contours of the NVB and IPA of each fraction were copied to the structure set on the pre-treatment scan using the rigid registration obtained from the prostate match. The planned dose that was received by the NVB and IPA of each fraction in case the pre-treatment plan would have been delivered for each fraction and only corrected for prostate translation as would have been done in an ATP-only workflow was calculated (i.e., simulated ATP planned dose).

The ATS planned dose to the NVB and IPA was calculated based on the plan that was calculated using the online pre-treatments scan after ATS was performed but before the position verification using ATP was performed. The used contours were identical to the simulated ATP contours. Planned ATS and simulated ATP dose-volume histograms for the NVB and IPA were exported.

Statistical analysis

R version 4.1.2 was used for the statistical analysis. The maximum dose to the 0.1 cc (D0.1 cc) of the NVB and IPA for each fraction of each patient was calculated using the R package "dvhmetrics". Per patient, estimated mean total dose and width of variance (difference in Gy between lowest and highest fraction multiplied by 5) for the planned ATS and simulated planned ATP setting were calculated. Pairwise comparisons of total dose and width of variance between the planned ATS and simulated planned ATP were analyzed using Wilcoxon signed-rank tests. Non-normally distributed data were presented as median with interquartile range (IQR). A P-value of < 0.05 was considered statistically significant.

Results

Fourteen patients with intermediate-risk prostate cancer completed treatment within the ERECT trial and were included. Bilateral NVB sparing was accomplished in three (21%) patients, unilateral NVB sparing in nine (64%), and no NVB sparing in two (14%) patients. IPA sparing was accomplished in all patients.

For the NVB D0.1 cc, the median (range) total planned dose for ATS was 32.7 Gy (32.6–33.2) and for simulated ATP 33.4 Gy (32.6–34.6) ($P = 0.002$) (Fig. 2). The median (range) width of variance was 0.5 Gy (0.1–1.2) and 1.6 Gy (0.7–2.7) ($P < 0.001$), respectively. For the planned IPA, the median (range) total planned D0.1 cc for ATS was 19.0 Gy (10.1–21.8) and for simulated ATP 18.0 Gy (10.1–26.5) ($P = 0.116$) (Fig. 2). The median (range) width of variance was 2.2 Gy (0.6–8.4) and 4.4 Gy (0.1–14.6) ($P = 0.004$), respectively.

The mean NVB dose exceeded the constraint in 4/15 (26.7%) NVBs in the ATS plans and 10/15 (66.7%) NVBs in the ATP plans. For the IPA constraint, that was 4/28 (14.3%) IPAs and 10/28 (35.7%) IPAs, respectively.

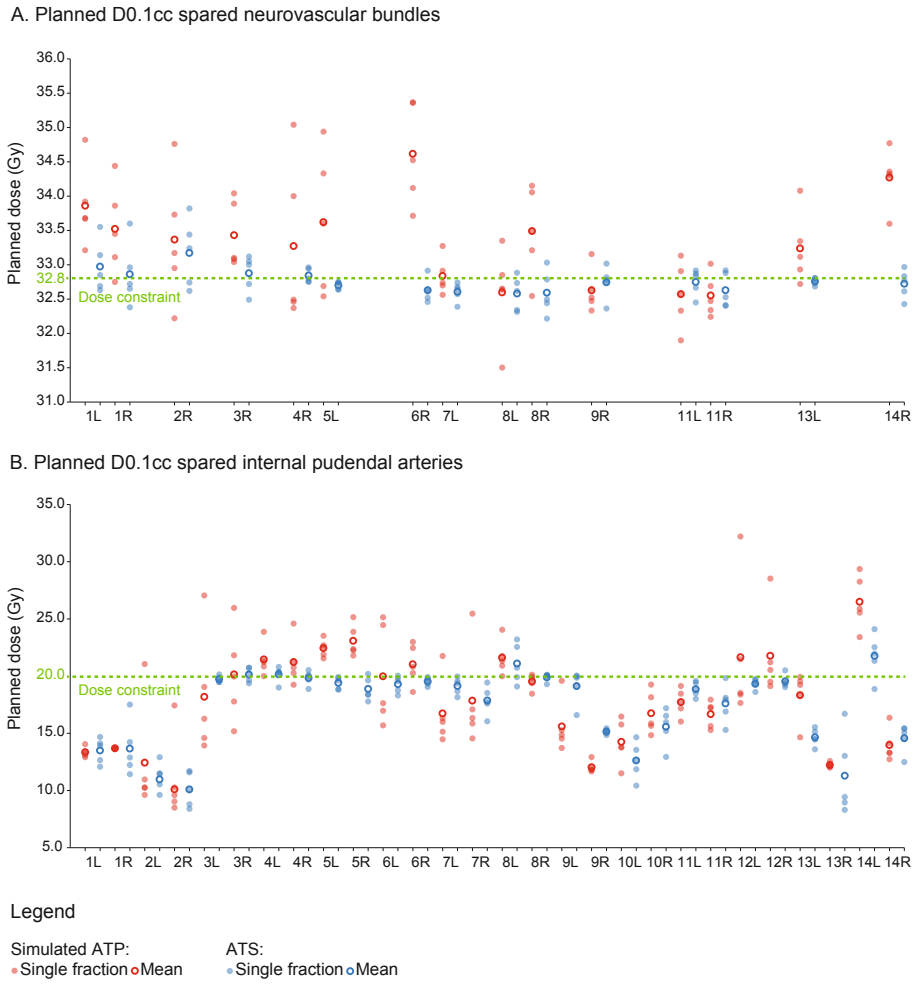

Figure 2: *Planned D0.1 cc for patients treated with neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer. A: spared neurovascular bundle; B: spared internal pudendal arteries. The single-fraction dose indicates the dose multiplied by 5.*

Abbreviations: L = left; R = right; ATP = adapt to position; ATS = adapt to shape.

Discussion

In this paper, we assessed the dose/volume-based difference between daily online contouring and re-planning versus translation-only correction for neurovascular-sparing MRI-guided radiotherapy. An advantage of daily MRI scanning is the re-evaluation of the pre-treatment contours. Factors such as scan quality and interrater variability can lead to suboptimal contours. Manual adjustment during daily online contouring and re-planning allows for re-evaluation of the pre-treatment contours, and in case of a

substantial difference, it can be decided to make a new optimized pre-treatment plan for the remaining fractions. In our series, this was done in one patient (patient 12), where we adjusted the IPA contours after re-evaluation based on the online MRI scan and made a new optimized pre-treatment plan upon after the second fraction.

The current drawback of online contouring and re-planning is that the contours need to be adjusted manually. This process takes time, during which there can be continuing motion and deformation. Therefore, a subsequent position verification MRI scan and translation-only correction is performed. When becoming available, fast online auto-contouring and plan adaptation before beam-on will make the manual adjustment of contours obsolete and reduce the need for subsequent position verification for intra-fraction motion.[12,13,14]

The question we wanted to answer in this study was: how does a daily "perfect" shift of a pre-determined reference dose distribution perform with respect to a daily dose re-optimization based on daily adapted contours regarding the sparing of neurovascular structures? Therefore, we chose the method described in section 2.2 (i.e., to evaluate the reference dose in the daily adapted contours after a shift based on the alignment of the prostate soft tissue). Executing such shifts depends on the specific hard- and software used in the adaptive radiotherapy setting. Whereas for conventional CT-guided radiotherapy, this is usually an actual couch shift, for the MR-Linac systems, it would be a virtual couch which may yield small deteriorations with respect to a perfect shift.[6] However, we considered such small template-dependent differences beyond the scope of this paper.

Another limitation is the inter- and intrarater variability of the contouring of the IPA and especially the NVB, which is a lower contrast soft-tissue structure with less pronounced boundaries at the level of the prostate base.[15,16,17] This may have led to an over- or underestimation of the difference between ATP and ATS in this study. However, our previous work showed that interrater variability is substantially lower at the mid prostate to apex level.[15] This is the level where the NVB is closest to the prostate, and any contour shifts will relatively have the largest effect on NVB dose, therefore making our ATP and ATS dose estimates more reliable. Also, in our clinical trial setting, the offline contouring is performed by a single specialized radiation oncologist and online by one of a team of four specialized radiation oncologist. One dedicated researcher supervises all contours, reducing the inter- and intrarater variability.

Conclusion

We showed that for the NVB, daily online contouring and re-planning resulted in lower median total dose compared to translation-only correction. Furthermore, the intrapatient width of variance of fraction dose for the NVB and IPA was lower with daily online contouring and re-planning. The high-field MR-Linac enables daily online contouring and re-planning for soft-tissue structures with low contrast. Our findings support the utilization of this treatment strategy and the further development of fast online auto-contouring and real-time plan adaptation for optimal neurovascular-sparing treatment for localized prostate cancer.

Supplementary material

Table 1 and 2:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9485897/bin/mmc1.docx

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CHAPTER 9

Summary

External beam radiotherapy (EBRT) is one of the three standard treatment options for localized prostate cancer, along with prostatectomy and low-dose-rate brachytherapy. These treatments are called “radical” treatments. Active surveillance is a fourth option for selected low- and intermediate-risk localized prostate cancers. Magnetic resonance imaging (MRI)-guided radiotherapy is a novel form of EBRT that utilizes an MR-Linac, a device that integrates an MRI scanner with a linear accelerator. This device enables MRI acquisition before and during radiation dose delivery to improve visualization of the target volume and surrounding tissue. This is especially important for organs prone to shape and position changes during and between the radiation fractions, such as the prostate under the influence of bowel movement and bladder filling. The hypothesis is that MRI-guided radiotherapy can deliver the radiation dose with greater accuracy and precision, resulting in less radiation to healthy tissue and better tumor coverage, causing less toxicity and better tumor control. Additionally, this technique makes it possible to increase the dose per fraction, enabling patients to receive treatment in fewer fractions.

The MOMENTUM study (short for: The Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac study) was initiated parallel to the clinical introduction of the MR-Linac to clinically evaluate MRI-guided radiotherapy. The MOMENTUM study includes and follows patients treated on a 1.5 T (Unity) MR-Linac at several early adopting centers worldwide. **Chapter 2** presents the outcomes in the first year after treatment of the patients within the MOMENTUM study who have been treated for localized prostate cancer with five fractions of 7.25 Gy. Five fractions of 7.25 Gy is the standard treatment for intermediate-risk prostate cancer at the University Medical Center Utrecht. Baseline and follow-up data at 3, 6, and 12 months were recorded, including prostate-specific antigen (PSA) levels, physician-reported toxicity, and patient-reported outcomes. We found that the median PSA level significantly declined up to 12 months after treatment. The peak of genitourinary and gastrointestinal physician-reported toxicity was observed at 3 months and settled at 6 and 12 months after treatment. Patient-reported outcomes showed a significant deterioration from baseline in urinary domain scores at all follow-up moments. Furthermore, both physician- and patient-reported erectile function worsened significantly in patients between baseline and the 12-month follow-up. This study shows that ultrahypofractionated MRI-guided radiotherapy for localized prostate cancer using a 1.5 T MR-Linac is effective and safe, but there is an increase in toxicity after treatment. Our reported outcomes are comparable to existing literature on MRI-guided radiotherapy outcomes. The MOMENTUM study continues to enroll patients and collect data, providing valuable real-world data on MRI-guided radiotherapy outcomes and enabling multiple comparative studies.

Chapter 3 describes the development and initial results of the Utrecht Prostate Cohort (UPC), which is the first "trials within cohorts" (TwiCs) platform for prostate cancer. The UPC is established to evaluate MRI-guided radiotherapy against the standard treatment options for localized prostate cancer. All patients with non-metastatic, histologically proven prostate cancer who are planned to receive standard of care are eligible for inclusion in the UPC. Patients provide informed consent for the collection of clinical and technical patient data, physician-reported outcomes, and patient-reported outcomes (PROs) for up to 10 years after treatment. Additionally, patients may provide broad consent for future randomization for experimental-intervention trials (TwiCs). If a TwiCs study is conducted, only the group that is randomized to receive the experimental treatment will be informed and may sign additional informed consent if willing to participate in the study. We analyzed the patient-reported outcomes up to 12 months after treatment of the patients included in the first 2 years of the cohort. Patients treated with MRI-guided radiotherapy and CT-guided radiotherapy showed a transient but significant decline in urinary irritative/obstructive and bowel domain scores at the 1-month follow-up. Prostatectomy patients showed a significant decline in urinary incontinence domain scores at all follow-up moments but significant improvement of urinary irritative/obstructive domain scores between baseline and 9 and 12 months of follow-up. All radical treatment groups showed a significant decline in sexual domain scores during follow-up. Active surveillance patients showed no significant deterioration over time in any domain. These initial results emphasize the outcome domains where treatments can be improved by reducing toxicity and provide insights into the toxicity profiles of the different treatments. The UPC is rapidly expanding with more participants, providing an ongoing prospective observational cohort and an infrastructure for multiple trials and comparative studies for the evaluation of new treatment interventions for prostate cancer, such as MRI-guided radiotherapy.

Patients with localized prostate cancer are often eligible for multiple treatment options, which can leave both the patient and physician faced with challenging decisions. **Chapter 4** assesses the preferences for the different treatment options for localized prostate cancer. Patients treated for localized prostate cancer participating in the UPC, along with healthy volunteers were invited to fill out a treatment-outcome scenario questionnaire. Prior to any information, participants ranked six different treatments for localized prostate cancer from most to least favorable (active surveillance, robot-assisted prostatectomy, conventional EBRT, low-dose-rate brachytherapy, MRI-guided radiotherapy, and focal therapy by irreversible electroporation). Next, detailed descriptions of the treatment procedures, toxicity, risk of biochemical recurrence, and follow-up regimen for each of the six treatments (i.e., treatment-outcome scenarios) were provided to the participants. They were then asked to re-rank the treatments based on this new

information. Additionally, participants provided a visual analog scale and time trade-off score for each scenario. The results showed that active surveillance and non-invasive treatments, such as MRI-guided radiotherapy, were the most preferred options by both patients and healthy volunteers and received among the highest visual analog scale and time trade-off scores.

Chapters 2 and 3 show that erectile function deterioration after radical prostate cancer treatment is a major issue and chapter 4 emphasizes patient preference for non-invasive treatments. These insights underscore the need for a non-invasive treatment for localized prostate cancer that can preserve erectile function. It has led to the development of neurovascular-sparing MRI-guided radiotherapy. The aim of this treatment is to preserve erectile function after radiotherapy by sparing structures such as the neurovascular bundle (NVB), the internal pudendal artery (IPA), the corpus cavernosum (CC), and the penile bulb (PB). The use of MRI during radiotherapy enables us to visualize these structures. Because this treatment approach had not been performed on an MR-Linac before, several steps had to be taken before clinical implementation. **Chapter 5** describes the first step, which involved a study to assess the interobserver agreement of contouring the neurovascular structures, as these structures are not regularly contoured during standard radiotherapy treatment. For this study, four radiation oncologists independently contoured the NVB and the IPA on the pre-treatment MRI scans of 20 patients. The agreement between the radiation oncologist was then calculated. We found that the interrater agreement for the contouring of the NVB and the IPA improved with the enhancement of the MRI sequence for better contrast and further training of the raters. The agreement was best for the inferior half of the NVB, which is clinically most relevant for neurovascular-sparing MRI-guided radiotherapy because it is closest to the prostate. These findings provide confidence that different radiation oncologists have sufficient agreement to perform the treatment consistently in the clinical setting.

Subsequently, a planning feasibility study was conducted, described in **chapter 6**. This study aimed to assess the planning feasibility of neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer. The study included 20 previously treated patients who had undergone standard MRI-guided radiotherapy, delivering 36.25 Gy in five fractions to the prostate. New neurovascular-sparing MRI-guided radiotherapy plans were generated for these patients. Dose constraints for the NVB, the IPA, the CC, and the PB were established based on the literature. The dose prescriptions to the prostate and visible tumor were adjusted with the aim of accommodating neurovascular sparing without compromising tumor control. Planned doses to regions of interest were compared between the new neurovascular-sparing plans and the actual standard

clinical pre-treatment plans of the 20 patients. In the neurovascular sparing plans, all 20 patients met the constraints for the CC and PB. For the IPA, constraints were met bilaterally in 19 (95%) patients and unilaterally in 1 (5%) patient. For the NVB, constraints were met bilaterally in eight (40%) patients and unilaterally in eight (40%) patients. In four (20%) patients, the NVB constraints were not met on both sides. However, in the cases where the neurovascular sparing constraints could not be met, a relative reduction in dose compared to the standard plans was achieved. In the cases where the NVB constraint could not be met, the gross tumor volume (GTV) was generally located dorsolaterally in the prostate near the bundle. In those cases, tumor coverage was prioritized over bundle sparing. The results of this study demonstrate that neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer is feasible in the planning setting and that the extent of IPA and NVB sparing depends on the patient's anatomy and tumor location.

Chapter 7 further elaborates on the eligibility and technical feasibility for neurovascular-sparing MRI-guided radiotherapy in intermediate-risk localized prostate cancer patients. This study included a consecutive series of men receiving standard 5 x 7.25 Gy MRI-guided radiotherapy for localized prostate cancer. For these patients, baseline erectile function was assessed using questionnaires. Additionally, the ability of sparing the NVBs was evaluated in all patients. Our findings revealed that half of the patients reported having good erectile function or only mild erectile dysfunction at baseline. In these patients, the NVB could technically have been spared bilaterally in 20.0% and unilaterally in 68.0% of cases. As observed previously in chapter 6, sparing of the IPA, CC and PB is possible in almost all cases. This study indicates that there is a substantial group of intermediate-risk prostate cancer patients who would be eligible for neurovascular-sparing MRI-guided radiotherapy. It emphasizes the potential of this treatment approach and the need for clinical evidence.

One of the current advantages of MRI-guided radiotherapy is the ability to perform "adapt to shape" (ATS) and subsequent "adapt to position" (ATP) instead of solely ATP prior to every fraction. During an ATP procedure, the rigid contour is adjusted in x, y, and z directions based on the prostate's location. During ATS, the contours of all relevant structures are adapted to the daily anatomical shape. The high-field MR-Linac enables ATS for soft-tissue structures with low contrast, such as neurovascular structures. In **chapter 8**, we describe a study that compared planned doses for the NVB and IPA between these strategies for patients receiving neurovascular sparing MRI-guided radiotherapy. The study showed that ATS has an advantage over ATP in terms of lower median total dose to the NVB and smaller dosimetric differences across the five fractions for both NVB and IPA per patient, resulting in more consistent

plans. Our findings support the utilization of ATS and the development of software for fast online auto-contouring and real-time plan adaptation with MRI-guided radiotherapy, enabling ATS during dose delivery for optimal neurovascular-sparing treatment for localized prostate cancer.

MRI-guided radiotherapy is continually evolving, with ongoing advancements in both technical and clinical innovations. The MOMENTUM study and the UPC are actively collecting data to evaluate MRI-guided radiotherapy for localized prostate cancer and to compare it to other treatments. Furthermore, neurovascular sparing MRI-guided radiotherapy is proven to be technically and clinically feasible and the first clinical trial to assess the effectiveness of neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer is currently underway.

CHAPTER 10

Discussion and future perspectives

Prospective registries and multi-trial platforms for the evaluation of MRI-guided adaptive radiotherapy

Many radiation oncology clinics worldwide have already implemented magnetic resonance imaging (MRI)-guided adaptive external beam radiotherapy even though clinical superiority over conventional computed tomography (CT)-guided external beam radiotherapy has not yet been proven.[1,2] As the number of treatment centers acquiring an MR-Linac continues to grow, effort should be made to evaluate MRI-guided radiotherapy against standard of care, and assess whether the theoretical promises hold in practice.[3]

Multiple treatment options are available for patients with localized prostate cancer. While there has historically been a lack of high-quality studies comparing different options such as surgery, radiotherapy, or active surveillance, the ProtecT trial has been a game changer. Recently, the 15-year outcomes of the ProtecT trial were published.[4] The study randomized patients with localized prostate cancer (66.3% low, 24.1% intermediate, and 9.6% high-risk disease, according to the EAU criteria[5]) between active surveillance, radiotherapy, and radical prostatectomy. In the active surveillance group, 61.1% eventually received radical treatment. This study demonstrated that survival outcomes were not significantly different. Death from prostate cancer occurred in 3.1% in the active surveillance group, 2.2% in the prostatectomy group, and 2.9% in the radiotherapy group. Although survival rates were very similar, toxicity profiles differed among the treatment modalities.[6]

Often, patients must make a choice between several treatment options. In chapter 4, we showed that treatment preferences varied across patients and are depend on information given for the different treatment modalities and their outcomes.[7] However, current outcome data, especially of long-term outcomes, are often based on outdated treatment techniques such as open radical prostatectomy and CT-guided radiotherapy, which is also the case for the ProtecT trial. As new techniques are being implemented with the aim to reduce toxicity, studies on outcomes should be continually evaluated to provide patients and physicians with the most up-to-date and accurate information about expected treatment outcomes.[8] The PACE-A trial made significant efforts in this regard.[9] In a randomized controlled trial, researchers compared prostatectomy (84% robot-assisted) with stereotactic body radiotherapy (SBRT) with a dose of 36.25 Gy in five fractions (76% Cyberknife) for localized prostate cancer. They found that at 2 years, a significantly lower number of SBRT patients reported using urinary pads. SBRT patients had a significantly worse EPIC[10] bowel subdomain score, but a significantly better EPIC sexual subdomain score. There was no difference in EPIC urinary subdomain score between the two treatment modalities.

Since the initiation of the PACE-A trial in 2012, radiotherapy techniques have continued to evolve, and techniques such as MRI-guided radiotherapy have become clinically available.[11] MRI-guided radiotherapy has the potential to further reduce toxicity because of more accurate dose delivery.[12] Due to the initial high costs, MRI-guided radiotherapy needs to be evaluated against standard of care.[3,13] Furthermore, the development and implementation of modern diagnostic tools such as multiparametric MRI, targeted biopsies, and PSMA-PET/CT have resulted in stage migration and changes in treatment strategies, which urge us to re-evaluate standard of care treatment outcomes.[14–16]

To compare MRI-guided radiotherapy with the current standard of care, the Utrecht Prostate Cohort (UPC) was initiated (chapter 3).[17] The UPC includes all localized prostate cancer patients treated with curative intent, regardless of the treatment modality, as well as patients undergoing active surveillance, and records their outcomes prospectively. It enables comparison between MRI-guided radiotherapy, CT-guided radiotherapy, radical prostatectomy, active surveillance, and other treatment modalities. The UPC has already demonstrated that patient-reported outcomes at 1-year follow-up are favorable for MRI-guided radiotherapy compared to conventional radiotherapy and prostatectomy. For MRI-guided radiotherapy patients, the peak in urinary and bowel symptoms occurs between the first radiotherapy fraction and 3 months after the last fraction, with scores returning to baseline level 3 months after the last treatment fraction. However, sexual and erectile function gradually deteriorate during the first year after treatment. The first results of the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac (MOMENTUM) study show similar toxicity after MRI-guided radiotherapy (chapter 2).[18] Nevertheless, longer follow-up is required to draw conclusions regarding late toxicity, such as radiation cystitis and proctitis. Additionally, it is essential to note that in the UPC, there is substantial heterogeneity between the treatment groups, and patient numbers are relatively low. Therefore, larger patient samples are needed to correct for confounders. Furthermore, selection bias by indication is inherent in such cohorts, which should be considered when translating the results to individual patients.[19]

During MRI-guided radiotherapy, the enhanced soft-tissue contrast provided by the integrated MRI system allows for more accurate target and organs at risk (OAR) delineation compared to CT-guided radiotherapy.[20] This improvement enables inter- and intrafraction shape and motion correction and plan adaptation, paving the way for new treatment applications.[21] These applications include (ultra)hypofractionation, boosting the radiotherapy dose to the tumor and sparing healthy tissue , which are currently under investigation.[22] To date, OAR sparing has primarily focused on reducing bladder and bowel toxicity.[23] Now, the improved soft-tissue visibility of MRI can facilitate neurovascular-sparing MRI-guided radiotherapy in order to preserve erectile function.

Erectile function-preserving MRI-guided radiotherapy

The ProtecT and PACE-A studies demonstrated favorable erectile-function outcomes following radiotherapy compared to prostatectomy.[9,24] However, the incidence of erectile dysfunction after radiotherapy remains high, and efforts should be made to reduce it.[25–27] We showed sufficient interrater agreement in contouring of the neurovascular structures on 1.5 T MRI (chapter 5), planning feasibility for neurovascular-sparing MRI-guided radiotherapy (chapter 6) and a substantial potential treatment population for neurovascular-sparing MRI-guided radiotherapy (chapter 7).[28–30] Based on these studies, we developed a clinical neurovascular-sparing MRI-guided radiotherapy protocol with the goal of preserving erectile function without compromising oncological outcomes or bowel and urinary toxicity. To evaluate the outcomes of this treatment approach, we initiated the ERECT trial, a single-arm trial delivering neurovascular-sparing radiotherapy using adaptive MRI-guided radiotherapy with a dose of 36.25 Gy in five fractions of 7.25 Gy delivered over the course of two and a half weeks.[31] To date, it is the only clinical study to perform neurovascular-sparing radiotherapy with MRI-guided plan adaptation. Accrual and radiotherapy treatment of all 70 patients have been completed, and we are currently awaiting the primary endpoint, which is erectile function 3 years after primary radiotherapy, expected in early 2026.

To our knowledge, one other prospective trial on erectile function-preserving radical radiotherapy is currently accruing patients: the POTEN-C trial, a trial randomizing between standard CT-guided SBRT and neurovascular-sparing CT-guided SBRT.[32] Both the ERECT and POTEN-C trials actively spare the neurovascular bundles (NVBs), internal pudendal arteries (IPAs), and penile bulb (PB). In the ERECT trial, the corpora cavernosa (CCs) are spared additionally. NVB sparing depends on tumor location, as the visible tumor within the prostate must receive a sufficient dose. Therefore, the POTEN-C trial excludes patients with a tumor < 5 mm from both NVBs and performs unilateral NVB sparing at contralateral side if this is the case. The ERECT trial has a similar approach but does not exclude patients with a tumor near both NVBs. In those patients, only IPA, CC, and PB sparing is performed. The advantage of the POTEN-C trial is the randomized controlled trial design, whereas the advantage of the ERECT trial is the utilization of adaptive EBRT with MRI guidance. MRI guidance may primarily be an advantage for sparing the NVBs, which are hard to distinguish on CT and are susceptible to movement in the pelvis.[33,34] The current studies need to establish the effect of neurovascular-sparing radiotherapy on short- and long-term erectile function and should provide essential information regarding the impact on (biochemical recurrence-free) survival.

MRI-guided radiotherapy utilizes MR imaging prior to and during each fraction, enabling a more accurate estimation of the actual dose received by each structure. These data, in combination with prospective registries of patient- and physician-reported toxicity and (biochemical recurrence-free) survival, will enable better dose/toxicity and dose/tumor response relationship analyses. Also, the influence on erectile dysfunction of other structures near the prostate can be investigated, such as the accessory pudendal artery.[35] In this manner, more accurate dose constraints for the individual neurovascular structures can be established.

The ERECT trial is a single-arm trial, making it susceptible to certain types of bias, such as selection bias. This should be considered when analyzing the data. Additionally, comparisons with literature should be approached with caution, as assessment of erectile function is performed heterogeneously throughout studies and the tools used to measure erectile function may have underestimated erectile dysfunction.[25,36,37] Because we conduct the ERECT trial within the UPC cohort, we will be able to match and select a control group of patients from the cohort that have been treated with standard MRI-guided radiotherapy of 36.25 Gy in five fractions.[17] These control patients underwent the same treatment procedures and follow-up as the ERECT trial patients, except for the sparing of the neurovascular structures during radiotherapy. Although we may be able to correct for many confounders, we will not be able to correct for bias and residual confounders. Therefore, an RCT for neurovascular-sparing MRI-guided radiotherapy remains the gold standard for evidence synthesis and will give the most definitive answer regarding the treatment's effect. Trials within cohorts (TwiCs) is a suitable design for such a trial, as neurovascular-sparing MRI-guided radiotherapy is a desired treatment for patients.[38] Because only the interventional group is informed in TwiCs, disappointment bias can be reduced.[39,40]

Sexual function is multifactorial. Besides erectile function, it encompasses sexual desire, sexual preferences, ejaculatory function, and multiple other organic and psychological factors.[41] Apart from erectile dysfunction, radiotherapy can adversely affect ejaculatory function, potentially leading to a reduced ejaculation volume or complete anejaculation. The etiology is unclear but may involve damage to the ejaculatory ducts. There are no validated medical or surgical approaches to prevent or reverse such damage.[42] Radiation-induced ejaculatory pain occurs in 5–10% of men following prostate radiotherapy. It has been hypothesized that ejaculatory pain may be caused by bladder neck or pelvic floor spasms. Utilization of alpha antagonists may relieve ejaculatory pain but can induce retrograde ejaculation. The question remains to what extent the decline of ejaculatory function bothers patients and whether efforts should be made to prevent the

decline. Until then, physicians should be aware of the adverse effects of radiotherapy and should inform their patients about it.

Advances in radiotherapy for prostate cancer aim to preserve some of the many factors associated with sexual function.[43] Adaptive MRI guidance is beneficial for neurovascular-sparing radiotherapy and this treatment may reduce the risk of erectile dysfunction. However, evidence from prospective trials such as ERECT and POTEN-C regarding short- and long-term outcomes is warranted before widespread clinical implementation. If neurovascular-sparing radiotherapy is proven effective, neurovascular-sparing dose constraints may be applied to radiotherapy for other malignancies involving the pelvic region, such as rectum and bladder cancers, as long as the tumor coverage is not compromised.[44] Moreover, techniques and strategies used to spare the neurovascular structures, can be adapted for urinary and bowel tissues.

Future perspectives: automated adaptive contouring, planning, and dose delivery—and individualized outcome prediction and treatment plans

There is still much room for improvement to fully realize the potential of MRI-guided radiotherapy. The aim of MRI-guided radiotherapy is to achieve real-time online auto-contouring, plan adaptation, and dose delivery to the target volume as accurately as possible, while minimizing dose to the OAR.[22] The recently published MIRAGE trial compared CT-guided radiotherapy utilizing 4 mm margins with MRI-guided radiotherapy utilizing 2 mm margins.[45] The MRI-guided radiotherapy was performed on a 0.35 T MR-Linac. Localized prostate cancer patients were randomly assigned to the intervention or control arm and received 40 Gy in five fractions. This is the first RCT comparing MRI-guided radiotherapy with CT-guided radiotherapy that studied the effect of margin reduction. The results are compelling in favor of MRI-guided radiotherapy utilizing 2 mm margins in terms of a significant reduction in acute grade ≥ 2 genitourinary toxicity (24.4% vs. 43.4%) and acute grade ≥ 2 gastrointestinal toxicity (0.0% vs. 10.5%).[46] These data encourage research into further margin reduction and its clinical implementation.

The hardware of the 1.5 T MR-Linac system is already capable of delivering online adaptive radiotherapy; however, the software to perform real-time online auto-contouring and plan adaptation is still in development.[47] Step by step, MRI-guided radiotherapy treatment innovations aimed at further reducing margins are being tested on the MR-Linac and implemented into the clinic. Recently, “JamTool” has been incorporated into the MRI-guided radiotherapy workflow at the University Medical Center Utrecht (UMCU).[48]

The JamTool workflow utilizes an additional fast MRI scan for position verification halfway through the treatment. Using this scan, a new plan adaptation is performed to correct for prostate movement due to changes in bladder and rectum anatomy, the so-called “adapt to position” (ATP). This is a semi-automated procedure that still requires manual contour alignment. It allows for a reduction of the clinical target volume (CTV) to the planning target volume (PTV) margin from an isotropic 5 mm to 2 mm in the cranial-caudal and lateral direction and 3 mm in the anterior-posterior direction. The JamTool procedure is a step towards continuous MRI-guided tissue tracking during beam-on and simultaneous auto-contouring. Several institutes worldwide are working on fast auto-contouring algorithms.[49] At the UMCU, we have shown that artificial intelligence (AI) can already support the radiation oncologist in pre-treatment contouring by giving a contour proposal for the contours of interest.[50] The radiation oncologist then only needs to verify and, if necessary, adjust the AI-generated contours, resulting in a significant reduction of contouring time. Auto-contouring software is rapidly improving. Also, MRI-sequences with enhanced tissue contrast and shorter acquisition times are being developed.[28,51] Once auto-contouring becomes accurate enough to use for treatment planning without the need for manual interference, and both auto-contouring and auto-planning can be performed fast enough, they can be clinically implemented on the MR-Linac.[52,53] With online auto-contouring, plan adaptation and dose delivery, we can work towards treatment planning with a CTV to PTV margin of (near) 0 mm. Furthermore, it will lead to a substantial reduction in treatment time, as most of the time during treatment fractions is currently spent on manual contouring and plan adjustment.

Margin reduction allows for dose escalation and (ultra)hypofractionation.[54–58] A reduced fractionation scheme may lower the treatment burden for patients and potentially reduce treatment costs for the health care system.[1,59] At our institution, intermediate-risk prostate cancer patients are treated with 36.25 Gy in five fractions using MRI-guided radiotherapy. Currently, two studies are assessing the effect of an even further hypofractionated scheme. One is the HERMES trial, running within the MOMENTUM study, which is evaluating a two-fraction scheme with a total dose of 24 Gy to the prostate (boost of 27 Gy to the tumor) against standard radiotherapy in five fractions on a 1.5 T MR-Linac for patients with Gleason score 3 + 4 or 4 + 3, MRI stage T3a or less, and PSA < 25 ng/ml.[60,61] The other study is the FORT trial, which is investigating a similar two-fraction scheme against a five-fraction scheme on a 0.35 T MR-Linac.[62]

Another advantage of MRI-guidance is the improved dominant intraprostatic lesion (DIL) visibility during treatment, as the MR-Linac supports multiparametric MRI. This enables focal tumor-boosting treatments.[12,63] Studies have shown that most tumor recurrences occur at the site of the initial DIL.[64] Therefore, focal tumor boosting has been proposed

to increase biochemical disease-free survival without increasing toxicity. The FLAME trial demonstrated a biochemical disease-free survival benefit for intermediate- and high-risk patients (NCCN risk criteria[65]) who received an integrated focal boost of 95 Gy to the multiparametric MRI-defined tumor(s) while the remainder of the prostate received 77 Gy in 35 fractions, compared to patients who received 77 Gy without a boost.[66] The boost improved biochemical disease free survival from 85% to 92% at 5-years follow-up and did not increase genitourinary and gastrointestinal toxicity. The subsequent single-arm hypo-FLAME trial investigated patients treated with extreme hypofractionated doses of 35 Gy in five weekly fractions to the whole prostate gland with a simultaneous integrated boost up to 50 Gy to the multiparametric MRI-defined tumor(s).[67] The investigators chose acute toxicity as the primary endpoint and demonstrated acceptable acute genitourinary and gastrointestinal toxicity. The hypo-FLAME 2.0 trial currently investigates the feasibility and safety of the same dose/fraction scheme delivered in half the total treatment time (15 days instead of 29 days).[68] The randomized hypo-FLAME 3.0 trial has just started accrual of patients, aiming to confirm the efficacy of the hypo-FLAME regimen by comparing it to the current standard treatment of 3.1 Gy in 20 fractions (without boost). In the future, focal tumor boosting can not only improve biochemical disease free survival but can also facilitate a relative dose reduction to the remainder of the prostate with the aim of reducing toxicity.[69] Future studies that will investigate focal tumor boosting using MRI-guided radiotherapy are in development.

Cost-effectiveness is an important consideration in the implementation of MRI-guided radiotherapy and the selection of standard-of-care treatment for localized prostate cancer. Implementing medical innovations without evidence of (cost-)effectiveness can increase healthcare costs without improving treatment quality.[70,71] Payers and policy-makers are becoming increasingly reluctant to approve and reimburse costly, unproven medical innovations.[72] MRI-guided radiotherapy is more expensive than conventional radiotherapy due to higher device costs, maintenance costs, overhead costs, and workload.[1,13,73,74] In practice, proving the superiority or inferiority of a treatment in terms of cost-effectiveness is complex. Treatment costs, follow-up costs, and costs that are accompanied by post-treatment toxicity and tumor recurrence, for which a patient may need additional treatment, can be calculated relatively objectively. On the other hand, the costs that can be made for gained quality of life or (biochemical recurrence-free) survival years are much more subjective and vary between countries and cultures.[75] Early health economic evaluations are useful to explore areas where new technologies have the potential to become a cost-effective alternative or addition to standard treatment and determine conditions that need to be met to achieve cost- effectiveness.[76] In these early evaluations, empirical data is lacking for costs and treatment outcomes. Therefore, assumptions about costs and clinical effects must be made,

using the best available sources.[77] Hehakaya et al. have demonstrated that five-fraction MRI-guided radiotherapy on a 1.5 T MR-Linac for localized prostate cancer is found to be cost-effective compared to 20 and 39 fractions CT-guided radiotherapy at baseline.[1] For five-fraction MRI-guided radiotherapy to become cost-effective compared to five-fraction CT-guided radiotherapy and low-dose-rate brachytherapy, it needs to substantially reduce toxicity or be offered at lower costs. Future health economic evaluation for MRI-guided radiotherapy can incorporate empirical data from the UPC and the MOMENTUM study for assessment.

Further development of MRI-guided radiotherapy may lead to a substantial reduction in costs, as online auto-contouring and plan adaptation will reduce the workload for radiation oncologists, radiotherapy technologists, and planners, and will reduce treatment time. This will result in a reduction in workload and an increased number of patients that can be treated within the same timeframe, which can even be further increased with (ultra)hypofractionation. Additionally, better tumor control and less toxicity will lower the need for care after treatment. Moreover, an automated workflow for MRI-guided radiotherapy provides a consistent treatment that minimizes the chance of unexpected outcomes, in contrast to many invasive treatments that require a learning curve for providers.[78–80] These are important developments, as the incidence of localized prostate cancer is expected to increase, while staffing is becoming scarcer.[81–84]

There is a need for patient-specific outcome prediction to guide prostate cancer patients towards the appropriate treatment.[7] Using AI and machine learning algorithms, it is now possible to integrate and analyze complex data from multiple sources to predict outcomes for individual patients.[85,86] Large real-world datasets such as UPC can be used to develop prediction models for individualized toxicity and survival outcomes for different treatment options based on patient characteristics. For MRI-guided radiotherapy, prediction models can be taken a step further. MRI-guided radiotherapy enables more accurate delivered dose estimation.[87] For every patient treated on the MR-Linac, an online position verification MRI scan is collected prior to each fraction, and additional position verification scans may be made during fractions.[88] With these scans, the accumulated dose can be calculated to approximate the actual delivered dose received by the target volumes and the organs at risk (OAR) more accurately.[89] In combination with the patient- and physician-reported toxicity and tumor response data collected within the UPC and the MOMENTUM study databases, dose/toxicity and dose/tumor-response relationship models can be established.[18] Willigenburg et al. performed such analyses for urinary toxicity after MRI-guided radiotherapy to the prostate with a dose of 36.25 Gy in five fractions using the UPC data and found a dose threshold for the bladder wall for urinary toxicity, which can be used to evaluate the current bladder dose

constraint.[90] This study can be considered a starting point for the development of dose/toxicity and dose/tumor response models using the UPC and the MOMENTUM study data. Similar studies can be performed for bowel and sexual toxicity, analyzing dose to OAR such as the rectum and the NVB, as well as for focal tumor-boosting strategies and (ultra)hypofractionation schemes.[59,60,66] The development of elaborate dose/toxicity and dose/tumor-control models may even enable patient-specific dose constraints based on the patient's characteristics and patient's preferences.[85] The pre-treatment plan of a patient can be analyzed for dose that will be received by the prostate and tumor, as well as urinary, bowel, and erectile structures. As we previously described, tumor coverage and sparing of OAR can be a tradeoff. This tradeoff can be discussed with the patient to determine the desired balance, and the treatment plan can be adjusted accordingly. Adaptive models fed with the patient's specific parameters and outcome preferences can guide the optimal planned dose distribution. In the future, with the increasing capability of AI, this may even be modeled and discussed in real time during clinic visits.

Conclusion

MRI-guided radiotherapy holds the promise to reduce toxicity and improve tumor control for patients with localized prostate cancer, but the theoretical advances need to be proven in practice. Several prospective cohorts have been established to evaluate MRI-guided radiotherapy, serving as platforms for trials and technical and clinical treatment development. We developed neurovascular-sparing MRI-guided radiotherapy and initiated the first trial to test neurovascular-sparing MRI-guided radiotherapy for localized prostate cancer, assessing the effect of neurovascular-sparing MRI-guided radiotherapy on erectile function and tumor control. Ongoing technical and clinical treatment development is aimed at decreasing treatment burden, reduce toxicity, and increase survival. Online auto-contouring and adaptive plan adaptation are expected to reduce margins to improve outcomes while reducing workload and treatment time, and therefore costs. Outcome prediction models may assist in choosing the right treatment for a patient and help establish a tailor-made MRI-guided radiotherapy dose distribution plan adhering to the patient's needs and wishes. These innovations need to be evaluated within the UPC and will define the place of MRI-guided radiotherapy in the treatment of localized prostate cancer and guide the optimal patient-specific treatment. If MRI-guided radiotherapy can prove its promises, it may lead to a paradigm shift toward radiotherapy as the primary choice for radical treatment of localized prostate cancer.

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APPENDICES

Nederlandse samenvatting (Summary in Dutch)

Scientific publications

Dankwoord (Acknowledgements)

Curriculum vitae

Nederlandse samenvatting (Summary in Dutch)

Uitwendige radiotherapie is één van de drie standaardbehandelingen voor gelokaliseerde prostaatkanker, naast het operatief verwijderen van de prostaat (prostatectomie) en inwendige bestraling (brachytherapie). Deze behandelingen worden “radicale” behandelingen genoemd. Voor bepaalde laag- en matig-risicogroepen is ook *active surveillance* (actief volgen) een optie. MRI-gestuurde radiotherapie is een nieuwe vorm van uitwendige radiotherapie waarbij gebruik wordt gemaakt van een MR-Linac, een integratie van een MRI-scanner en een lineaire versneller. De MR-Linac apparaat maakt het mogelijk om vóór en tijdens de bestraling MRI-scans te maken om zo het te bestralen gebied en de omliggende weefsels te visualiseren. Dit is extra van belang bij organen die tijdens en tussen de bestralingssessies (fracties) kunnen veranderen van vorm en positie, zoals de prostaat onder invloed van onder andere de darmperistaltiek en de vulling van de blaas. Tegenwoordig worden prostaatkankerpatiënten die reguliere uitwendige bestraling krijgen in de meeste gevallen in 5 tot 35 fracties bestraald. De hypothese is dat MRI-gestuurde radiotherapie accurater en preciezer stralingsdosis kan afleveren. Dat resulteert in minder straling op gezond weefsel, waardoor er minder bijwerkingen (toxiciteit) optreden. Ook kan accuratere en preciezere bestraling op de prostaat en de tumor in de prostaat leiden tot betere tumorcontrole. Bovendien maakt deze techniek het mogelijk om de stralingsdosis per fractie te verhogen. Patiënten kunnen daardoor in minder fracties worden bestraald, zonder negatieve invloed op de uitkomsten.

De MOMENTUM-studie (acroniem voor: *The Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac study*) werd parallel aan de klinische introductie van de MR-Linac geïnitieerd voor de klinische evaluatie van deze nieuwe behandelmethode. In de MOMENTUM-studie worden patiënten gevolgd die zijn behandeld op een 1,5 Tesla MR-Linac in verschillende centra wereldwijd. Hoofdstuk 2 beschrijft de uitkomsten in het eerste jaar na de behandeling van patiënten in de MOMENTUM-studie die zijn behandeld voor gelokaliseerde prostaatkanker met vijf fracties van 7,25 Gy (stralingsdosis uitgedrukt in Gray ofwel Gy). Dit is de standaard bestralingsbehandeling voor matig-risico gelokaliseerde prostaatkanker in het universitair medisch centrum Utrecht. Onder andere de waarden van het prostaatspecifieke-antigeen (PSA), en de arts- en patiëntgerapporteerde uitkomsten werden geanalyseerd. We vonden dat de mediane PSA-waarde significant daalde tot en met 1 jaar na behandeling. Er werd een piek in arts-gerapporteerde gastro-intestinale en genito-urinaire toxiciteit gerapporteerd op 3 maanden na behandeling, die zich herstelde op 6 en 12 maanden na de behandeling. De patiëntgerapporteerde uitkomsten lieten een significante toename van mictieklachten zien op alle vervolgmomenten, vergeleken met de waarden aan het begin van de behan-

deling. Bovendien rapporteerden zowel artsen als patiënten een achteruitgang van de erectiele functie bij patiënten gedurende het eerste jaar na de behandeling. Deze studie laat zien dat MRI-gestuurde bestraling van vijf fracties van 7,25 Gy op een 1,5 Tesla MR-Linac veilig en effectief is, maar dat er sprake is van bijwerkingen. De gerapporteerde bijwerkingen zijn vergelijkbaar met de literatuur over MRI-gestuurde bestraling. De MOMENTUM-studie blijft patiënten en data verzamelen en *real-world* data leveren over de uitkomsten van MRI-gestuurde bestraling. Daarbij maakt de MOMENTUM-studie het mogelijk om vergelijkende studies te verrichten.

Hoofdstuk 3 beschrijft de ontwikkeling en de eerste resultaten van het Utrecht Prostaat Cohort (UPC). Het UPC is het eerste *trials within cohorts*-platform (TwiCs) voor prostaatkanker. Het gaat een stap verder dan de MOMENTUM-studie door naast patiënten die door middel van MRI-gestuurde bestraling zijn behandeld, patiënten te includeren die met de standaard behandelopties zijn behandeld voor prostaatkanker zonder metastasen op afstand. Dit maakt het mogelijk om die behandelingen direct met elkaar te vergelijken. Patiënten die deelnemen aan het UPC geven toestemming voor het opslaan van hun klinische en technische gegevens en arts- en patiëntgerapporteerde uitkomsten tot 10 jaar na de behandeling. Daarbij kunnen patiënten toestemming geven om in de toekomst deel te nemen aan gerandomiseerde studies voor experimentele behandelingen (TwiCs). In het geval van een TwiCs studie zal alleen de groep die de experimentele behandeling zal ondergaan worden geïnformeerd over die behandeling en kunnen zij aanvullend toestemming geven voor deelname. We hebben de patiënt-gerapporteerde uitkomsten uit het UPC geanalyseerd van patiënten die met verschillende methoden werden behandeld voor prostaatkanker. We zagen bij patiënten die werden behandeld met MRI- of CT-gestuurde uitwendige bestraling een voorbijgaande maar significante toename van irritatieve en obstructieve mictieklachten en darmklachten op één maand na de behandeling. Patiënten die een prostatectomie ondergingen lieten vergeleken met vóór de behandeling een significante toename zien van urine-incontinentie op alle vervolgmomenten, maar een significante afname van irritatieve en obstructieve mictieklachten op 9 en 12 maanden na de behandeling. Alle patiënten die een radicale behandeling ondergingen lieten significante verslechtering zien van gerapporteerde scores in het seksuele domein gedurende het eerste jaar na behandeling. Patiënten die actief gevolgd werden en dus niet radicaal werden behandeld, lieten geen significante verandering van klachten zien op enig domein. Deze eerste resultaten geven inzicht in de toxiciteitsprofielen van de verschillende behandelingen en laten zien waar zij kunnen verbeteren. Het UPC breidt snel uit met nieuwe deelnemers. Het biedt een doorlopend prospectief observationeel cohort en een infrastructuur voor onderzoeken en vergelijkende studies voor de evaluatie van nieuwe behandeling voor prostaatkanker, zoals MRI-gestuurde bestraling.

Patiënten met gelokaliseerde prostaatkanker kunnen in aanmerking komen voor verschillende behandelingen. Voor patiënten en artsen kan dat een moeilijke beslissing zijn. Hoofdstuk 4 bespreekt de voorkeuren voor de verschillende behandelingen voor gelokaliseerde prostaatkanker. Patiënten uit het UPC die werden behandeld voor gelokaliseerde prostaatkanker en gezonde vrijwilligers werden uitgenodigd om een vragenlijst in te vullen. Voordat zij informatie hadden gekregen over de behandeling, rangschikten de deelnemers zes verschillende behandelingen van meest tot minst gewenst (actief volgen, robot-geassisteerde prostatectomie, conventionele uitwendige radiotherapie, brachytherapie, MRI-gestuurde uitwendige radiotherapie en focale therapie door middel van irreversibele elektroporatie). In het volgende onderdeel werd aan de deelnemers een gedetailleerde beschrijving gegeven over de behandelprocedures, kans op bijwerkingen, risico of terugkeer van kanker en vervolgbeleid voor elk van de zes behandelopties en werd gevraagd om de behandelingen nogmaals te rangschikken. Ook gaven de deelnemers onder andere een visueel analogeschaalscore (VAS-score) van 1 tot 10 voor elk scenario. Actief vervolgen en niet-invasieve behandelingen zoals MRI-gestuurde radiotherapie kregen de hoogste VAS-scores toebedeeld, en bleken de meest gewenste opties van patiënten en gezonde vrijwilligers.

Hoofdstuk 2 en 3 laten zien dat achteruitgang van de erectiele functie na radicale behandeling van gelokaliseerde prostaatkanker een belangrijk probleem is en hoofdstuk 4 benadrukt de voorkeur van de patiënt voor niet-invasieve behandelingen. Dit geeft aan dat er behoefte is aan een niet-invasieve behandeling voor prostaatkanker waarbij tegelijkertijd wordt geprobeerd de erectiele functie te behouden. Hetgeen heeft geleid tot onze ontwikkeling van een zenuw- en vaatsparende MRI-gestuurde bestralingsbehandeling voor gelokaliseerde prostaatkanker. Het doel van deze behandeling is om de erectiele functie te behouden door zenuw- en vaatstructuren zoals de neurovasculaire bundel, de arteria pudenda interna, het corpus cavernosum en de bulbus penis die dicht bij de prostaat liggen, en van belang zijn voor de erectiele functie, te sparen tijdens bestraling. Dit zijn structuren die tijdens reguliere radiotherapie substantiële stralingsdosis ontvangen. Juist de ondersteuning van de MRI-beelden bij de MRI-gestuurde bestraling stellen ons in de gelegenheid deze structuren goed te visualiseren en dus mogelijk ook te sparen. Omdat deze behandelmethode niet eerder is uitgevoerd op een MR-Linac, moest er een aantal stappen aan vooraf gaan voor klinische implementatie mogelijk en verantwoord was. De eerste stap wordt beschreven in hoofdstuk 5. Dit was een studie om de mate van overeenstemming van het intekenen van de zenuw- en vaatstructuren tussen radiotherapeuten te meten. In deze studie hebben vier radiotherapeuten afzonderlijk bij twintig patiënten de neurovasculaire bundel en de arteria pudenda interna aan weerszijden van de prostaat ingetekend op de MRI-scan die voorafgaand aan de bestraling werd gemaakt. Dit zijn “nieuwe” structuren voor de radiotherapeut,

omdat die tijdens reguliere bestralingsbehandelingen niet worden ingetekend. In een tussentijdse analyse na de eerste vijf patiënten werd gezien dat de overeenstemming tussen de contouren van de intekenaars kon verbeteren. Dat gebeurde ook nadat de MRI-sequentie werd aangepast voor beter contrast van de structuren en na aanvullende intekentraining. De overeenstemming was het grootst in het inferieure deel van de neurovasculaire bundel. Dit deel van de neurovasculaire bundel ligt het dichtst bij de prostaat en is dus extra relevant voor zenuw- en vaatsparend MRI-gestuurd bestralen omdat op die locatie het conflict tussen hoge stralingsdosis op de prostaat enerzijds, en zo min mogelijk stralingsdosis op de zenuw- en vaatstructuren anderzijds, het grootst is. Een juiste intekening van dit deel van de neurovasculaire bundel is dus in het bijzonder van belang. De resultaten van deze studie geven voldoende zekerheid dat afzonderlijke radiotherapeuten met voldoende overeenstemming de zenuw- en vaatstructuren kunnen intekenen om de behandeling consistent te kunnen verrichten in de klinische praktijk. Daarbij verwachten we dat met ervaring ook de overeenstemming tussen intekenaars verder zal verbeteren.

Aansluitend hebben we onderzocht of het technisch haalbaar is om klinisch acceptabele zenuw- en vaatsparende bestralingsplannen te maken voor de MR-Linac, specifiek voor patiënten met matig-risico gelokaliseerde prostaatkanker die in vijf fracties worden bestraald. Voorafgaand aan de bestraling wordt in het bestralingsplan berekend hoeveel straling het doelgebied (de prostaat) en de omliggende weefsels (onder andere de darmen en blaas) bereikt. De plannen worden zo gemaakt dat er voldoende straling op de tumor komt, voor voldoende tumorcontrole, maar niet te veel op het omliggende weefsel dat kan zorgen voor onacceptabele bijwerkingen. Voor twintig patiënten met gelokaliseerde prostaatkanker werden hypothetische zenuw- en vaatsparende MRI-gestuurde radiotherapie-plannen gemaakt. De maximaal toegestane stralingsdosis voor de neurovasculaire bundel, de arteria pudenda interna, het corpus cavernosum en de bulbus penis werden vastgesteld op basis van de beschikbare literatuur. De voorgeschreven stralingsdosis voor de prostaat en de tumor in de prostaat werd aangepast met het doel om het sparen mogelijk te maken zonder dat het ten koste gaat van de tumorcontrole. In de zenuw- en vaatsparende plannen was het mogelijk om onder de maximaal toegestane dosis te blijven voor het corpus cavernosum en de bulbus penis. In het geval van de arteria pudenda interna was dat mogelijk bij negentien (95%) patienten aan beide zijden en bij één (5%) patiënt aan één zijde. Voor de neurovasculaire bundel was het mogelijk om bij acht (40%) patiënten beiderzijds onder de maximaal toegestane dosis te blijven en bij acht (40%) aan één zijde. Bij vier (20%) van de patiënten was het niet mogelijk om onder de maximaal toegestane dosis te blijven. Wel is er in die gevallen een relatieve vermindering van de dosis op de neurovasculaire bundel haalbaar, ten opzichte van standaard (MRI-gestuurde) bestraling waarbij de zenuw- en

vaatstructuren niet actief worden gespaard. In de gevallen waarbij de neurovasculaire bundels niet konden worden gespaard, lag de tumor in de prostaat doorgaans aan dorsolaterale zijde, dicht bij de bundel. In dergelijke gevallen gaat het bereiken van voldoende straling op de tumor boven het sparen van de neurovasculaire bundel. We concluderen uit deze studie dat het technisch haalbaar is om zenuw- en vaatsparende plannen te generen voor de MR-Linac en dat de mate waarin de arteria pudenda interna en met name de neurovasculaire bundel gespaard kan worden afhangt van de anatomie en tumorlocatie van de patiënt.

Hoofdstuk 7 bouwt voort op de technische haalbaarheid van zenuw- en vaatsparend MRI-gestuurd bestralen door te onderzoeken welke patiënten met matig-risico gelokaliseerde prostaatkanker in aanmerking komen voor deze behandeling en in welke mate zenuw- en vaatsparing mogelijk is bij die patiënten. In een studie hebben we een serie opeenvolgende patiënten geïncludeerd die op de standaard manier in vijf fracties zijn bestraald voor gelokaliseerde prostaatkanker op de MR-Linac. Bij deze patiënten werd met behulp van vragenlijsten bepaald wat de uitgangswaarde was van de erectiele functie voorafgaand aan de behandeling. Ook werd in deze patiëntengroep gekeken in hoeverre het mogelijk zou zijn geweest om de neurovasculaire bundel te sparen, dat wil zeggen: onder de maximale toegestane stralingsdosis te blijven, zonder te veel in te leveren op de dosis die zou worden afgegeven aan de prostaat en de tumor. We vonden dat de helft van de patiënten aangaf een goede erectiele functie of slechts een milde erectiestoornis te hebben. Bij die patiënten zou het technisch mogelijk zijn geweest om de neurovasculaire bundel dubbelzijdig te sparen bij 20,0% en enkelzijdig bij 68,0%. Dit geeft aan dat een grote groep patiënten met een matig-risico gelokaliseerde prostaatkanker in aanmerking zou kunnen komen voor zenuw- en vaatsparende MRI-gestuurde bestraling, omdat er in de helft van de gevallen een goede erectiele functie is voorafgaand aan behandeling, waarbij gepoogd kan worden die te behouden. Bij die groep is het in de meeste gevallen haalbaar om de neurovasculaire bundel uni- of bilateraal te sparen tijdens bestraling. In hoofdstuk 6 zagen we al dat het sparen van de arteria pudenda interna, het corpus cavernosum en de bulbus penis in vrijwel alle gevallen mogelijk moet zijn. Deze uitkomsten benadrukken het potentieel van de behandeling en de behoefte aan klinisch bewijs.

Eén van de huidige ontwikkelingen in MRI-gestuurd bestralen is de mogelijkheid om voorafgaand aan elke fractie het bestralingsplan aan te passen aan de vormverandering van de prostaat en omliggende structuren (*adapt to shape*) en niet alleen de positieverandering (*adapt to position*). Bij de conventionele adapt to position-procedure worden de contouren niet aangepast, maar alleen verschoven in x, y, z richting gebaseerd op de positie van alleen de prostaat. Tijdens adapt to shape worden de contouren van

alle structuren die van belang zijn om te bestralen en te sparen opnieuw ingetekend op basis van de dagelijkse anatomie. Het idee is dat door de toevoeging van adapt to shape in het behandelproces er gerichter kan worden bestraald en beter kan worden gespaard. De 1,5 Tesla MRI op de MR-Linac maakt het mogelijk om structuren met een laag contrast, zoals neurovasculaire structuren in kaart te brengen waardoor ook adapt to shape voor die structuren kan worden toegepast. In hoofdstuk 8 beschrijven we een studie die de geplande stralingsdosis per fractie voor de neurovasculaire bundel en de arteria pudenda interna tussen de twee strategieën bij zenuw- en vaatsparend bestralen vergelijkt. De studie laat zien dat bij de bestralingsplannen die werden aangepast na adapt to shape de mediane dosis die de neurovasculaire bundel bereikte lager was dan na adapt to position. Ook zat er bij de bestralingsplannen die aangepast werden na de adapt to shape-procedure minder verschil in dosis op de neurovasculaire bundel en de arteria pudenda interna tussen de vijf fracties per patiënt, resulterend in consistentere bestralingsplannen. Onze resultaten ondersteunen het gebruik van adapt to shape en de ontwikkeling van software voor snelle automatische intekeningen en directe plan-adaptatie tijdens MRI-gestuurde bestraling. Zo kan adapt to shape ook tijdens de bestraling kan worden uitgevoerd, en kan men optimaal zenuw- en vaatsparend bestralen bij patiënten met gelokaliseerde prostaatkanker.

MRI-gestuurde radiotherapie is voortdurend in ontwikkeling met verbeteringen op technisch en klinisch gebied. De MOMENTUM-studie en het UPC verzamelen data om MRI-gestuurde radiotherapie voor gelokaliseerde prostaatkanker te evalueren en te vergelijken met andere therapieën. Zenuw- en vaatsparend MRI-gestuurd bestralen is technisch en klinisch mogelijk en op moment van schrijven is de eerste trial gaande die de effectiviteit van zenuw- en vaatsparend bestralen onderzoekt.

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Curriculum vitae

Freek was born in ’s-Hertogenbosch in 1993 and grew up in Vught, the Netherlands. After graduating from gymnasium education at Maurick College in Vught, he began his medical studies at VU University in Amsterdam. During medical school, he undertook internships in Aruba and Saint Martin, Dutch Caribbean, and Al Ain, United Arab Emirates. He did his research internship at the Department of Orthopedic Surgery at Massachusetts General Hospital in Boston, USA. In 2018, he started working as a resident at the Department of Pediatric Urology at Sophia Children’s Hospital in Rotterdam. Six months later, he began his PhD research at the Department of Radiation Oncology at University Medical Center Utrecht under the supervision of Prof. Dr. Lenny Verkooijen, Dr. Jochem van der Voort van Zyp, and Dr. Harm van Melick, which led to this thesis. During this three-year research period, he earned his master’s degree in epidemiology from Utrecht University. Subsequently, he worked as a resident at the Department of Urology at St. Antonius Hospital in Nieuwegein and Diakonessenhuis in Utrecht for a year. In October 2023, he started his residency in radiation oncology at Radboud University Medical Center in Nijmegen.