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ONCOLOGY

Neurovascular-Sparing MR-Guided Adaptive Radiotherapy in Prostate Cancer; Defining the Potential Population for Erectile Function-Sparing Treatment

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ABSTRACT

Background: Magnetic resonance-guided adaptive radiotherapy (MRgRT) enables neurovascular-sparing treatment for localized prostate cancer (PCa). 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. PCa 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.

Aim: To define the eligibility and technical feasibility for neurovascular-sparing MRgRT in intermediate-risk localized PCa patients.

Methods: A consecutive series of men that received 5 × 7.25 gray (Gy) MRgRT for localized PCa 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 MRgRT for localized PCa and indicate the proportion in which the NVB can technically be spared.

Strength & 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 MRgRT. Trials need to assess the effect of neurovascular-sparing MRgRT on erectile function. **Teunissen FR, van der Voort van Zyp JRN, Verkooijen HM, et al., Neurovascular-Sparing MR-Guided Adaptive Radiotherapy in Prostate Cancer; Defining the Potential Population for Erectile Function-Sparing Treatment. J Sex Med 2022;19:1196−1200.**

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INTRODUCTION

Erectile dysfunction (ED) is a common adverse effect of radical treatments for localized prostate cancer (PCa) 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 1.5T MRI scanner.[10] MR-guided adaptive radiotherapy (MRgRT) 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] MRgRT is therefore very suitable for neurovascular-sparing (or erectile function-sparing) radiotherapy treatment.

During neurovascular-sparing MRgRT 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 MRgRT for intermediate-risk PCa has been implemented in standard clinical practice, whereas MRgRT with neurovascular-sparing has recently become available in clinical-trial setting. Ideally, neurovascular-sparing MRgRT is applied in intermediate-risk PCa 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 PCa patients that choose to undergo novel MRgRT 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 MRgRT is technically feasible.

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

METHODS

Patients

We included all intermediate-risk (National Comprehensive Cancer Network category) PCa 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 gray (Gy) to the prostate in 5 fractions using MRgRT, which is is standard treatment for patients with intermediate-risk PCa 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 MRgRT 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 PCa in the Netherlands were recorded. For our analysis we extracted type of treatment (ie, 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 $\geq$ 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 MRgRT patients received a pre-treatment 3Tesla (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 (Figure 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 (Figure 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.

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 PCa 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 PCa 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).

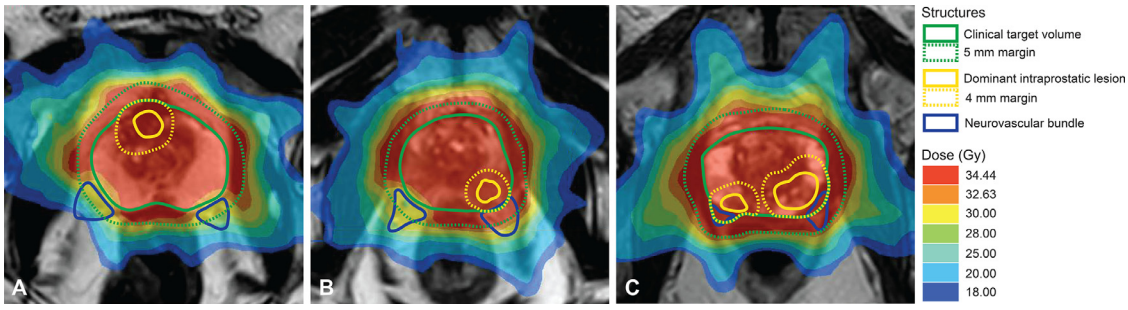

Figure 1. Pre-treatment planning dose distribution, representing the variation in tumor location in relation to the neurovascular bundle (NVB) and ability of NVB sparing (axial plane). Yellow dashed line (i.e., high-dose area): represents the dominant intraprostatic lesion (DIL) with a 4 mm isotropic 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. Figure 1 is available in color online at www.jsm.jsexmed.org.

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 PCa treatment. This study is the first to estimate the potential patient population that will be eligible for erectile function-sparing treatment and to identify the proportion of patients in which the NVB can be spared during neurovascular-sparing MRgRT.

Almost all patients that were treated for intermediate-risk localized PCa with MRgRT 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: (i) that efforts to preserve sexual function are extremely relevant within the MRgRT patient population, and (ii) 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 MRgRT is already attracting a relatively younger group of patients. Neurovascular-sparing MRgRT, which holds the promise to further reduce ED after radical PCa treatment, may induce a further paradigm shift by drawing younger and healthier PCa patients towards EBRT.

Neurovascular-sparing MRgRT for PCa 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 MRgRT in 70 men with intermediate-risk PCa 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 MRgRT 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.

CONCLUSIONS

At baseline 49.0% of patients receiving novel MRgRT for intermediate-risk localized PCa 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 MRgRT on erectile function.

CONFLICT OF INTEREST AND FUNDING

Conflict of Interest: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HV receives research funding from Elekta. The remaining authors declare no potential competing interests.

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REFERENCES

1. Sánchez-Cruz JJ, Cabrera-León A, Martín-Morales A, et al. Male erectile dysfunction and health-related quality of life. **Eur Urol 2003;44:245–253. doi:** 10.1016/S0302-2838(03)00215-X.
2. Downing A, Wright P, Hounsome L, et al. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. **Lancet Oncol 2019;20:436–447. doi:** 10.1016/S1470-2045(18)30780-0.
3. Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. **J Urol 1982;128:492–497. doi:** 10.1016/S0022-5347(17)53012-8.
4. Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. **Eur Urol 2012;62:418–430. doi:** 10.1016/j.eururo.2012.05.046.
5. Wortel RC, Incrocci L, Pos FJ, et al. Acute toxicity after image-guided intensity modulated radiation therapy compared to 3D conformal radiation therapy in prostate cancer patients. **Int J Radiat Oncol Biol Phys 2015;91:737–744. doi:** 10.1016/j.ijrobp.2014.12.017.
6. Wortel RC, Incrocci L, Pos FJ, et al. Late side effects after image guided intensity modulated radiation therapy compared to 3d-conformal radiation therapy for prostate cancer: results from 2 prospective cohorts. **Int J Radiat Oncol Biol Phys 2016;95:680–689. doi:** 10.1016/j.ijrobp.2016.01.031.
7. Lee JY, Spratt DE, Liss AL, et al. Vessel-sparing radiation and functional anatomy-based preservation for erectile function after prostate radiotherapy. **Lancet Oncol 2016;17:e198–e208. doi:** 10.1016/S1470-2045(16)00063-2.
8. McLaughlin PW, Narayana V, Meriowitz A, et al. Vessel-sparing prostate radiotherapy: dose limitation to critical erectile vascular structures (internal pudendal artery and corpus cavernosum) defined by MRI. **Int J Radiat Oncol Biol Phys 2005;61:20–31. doi:** 10.1016/j.ijrobp.2004.04.070.
9. Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. **Phys Med Biol 2017;62:L41–L50. doi:** 10.1088/1361-6560/aa9517.
10. Lagendijk JJW, Raaymakers BW, van Vulpen M. The magnetic resonance imaging-linac system. **Semin Radiat Oncol 2014;24:207–209. doi:** 10.1016/j.semradonc.2014.02.009.
11. Chin S, Eccles CL, McWilliam A, et al. Magnetic resonance-guided radiation therapy: a review. **J Med Imaging Radiat Oncol 2020;64:163–177. doi:** 10.1111/1754-9485.12968.
12. Zachiu C, Denis De Senneville B, Willigenburg T, et al. Anatomically-adaptive multi-modal image registration for image-guided external-beam radiotherapy. **Phys Med Biol 2020;65. doi:** 10.1088/1361-6560/abad7d.
13. Teunissen FR, Wortel RC, Hes J, et al. Adaptive magnetic resonance-guided neurovascular-sparing radiotherapy for preservation of erectile function in prostate cancer patients. **Phys Imaging Radiat Oncol 2021;20:5–10. doi:** 10.1016/j.phro.2021.09.002.
14. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. **Int J Impot Res 1999;11:319–326. doi:** 10.1038/sj.ijir.3900472.
15. Szymanski KM, Wei JT, Dunn RL, et al. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. **Urology 2010;76:1245–1250. doi:** 10.1016/j.urology.2010.01.027.
16. Teunissen FR, Wortel RC, Wessels FJ, et al. Interrater agreement of contouring of the neurovascular bundles and internal pudendal arteries in neurovascular-sparing magnetic resonance-guided radiotherapy for localized prostate cancer. **Clin Transl Radiat Oncol 2022;32:29–34. doi:** 10.1016/J.CTRO.2021.11.005.
17. Skolarus TA, Dunn RL, Sanda MG, et al. Minimally important difference for the expanded prostate cancer index composite short form. **Urology 2015;85:101–105. doi:** 10.1016/j.urology.2014.08.044.
18. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. **N Engl J Med 2016;375:1415–1424. doi:** 10.1056/nejmoa1606220.
19. van Stam MA, Pieterse AH, van der Poel HG, et al. Shared decision making in prostate cancer care—encouraging every patient to be actively involved in decision making or ensuring the patient preferred level of involvement? **J Urol 2018;200:582–589. doi:** 10.1016/j.juro.2018.02.3091.
20. de Muinck Keizer DM, van der Voort van Zyp JRN, de Groot-van Breugel EN, et al. On-line daily plan optimization combined with a virtual couch shift procedure to address intrafraction motion in prostate magnetic resonance guided radiotherapy. **Phys Imaging Radiat Oncol 2021;19:90–95. doi:** 10.1016/j.phro.2021.07.010.