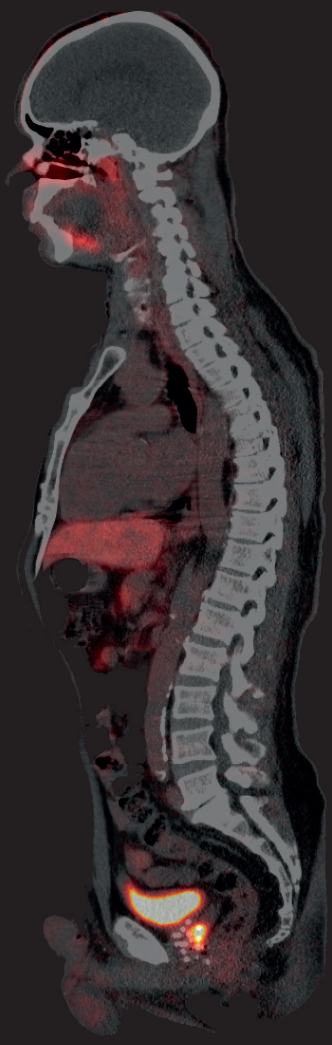
FOCAL THERAPY FOR (RECURRENT) PROSTATE CANCER

TREAT THE LESION, PRESERVE THE MAN?



MARIEKE VAN SON

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Treat the lesion, preserve the man?

Marieke van Son

COLOFON

Focal therapy for (recurrent) prostate cancer, Marieke van Son
ISBN: 978-94-6416-627-9

Publication of this thesis was financially supported by the UMC Utrecht department of Radiation Oncology, KWF Kankerbestrijding, ChipSoft, Elekta B.V. and Ipsen Farmaceutica B.V.

Layout and design by Anna Bleeker | persoonlijkproefschrift.nl
Printing: Ridderprint | www.ridderprint.nl

Focal therapy for (recurrent) prostate cancer

Treat the lesion, preserve the man?

Plaatselijke behandeling van (teruggekeerde) prostaatkanker

Doelgerichte therapie met behoud van functie?

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 1 juli 2021 des middags te 4.15 uur

door

Marieke Juliet van Son
geboren op 7 november 1991
te Rotterdam

Promotor:
Prof. dr. ir. J.J.W. Lagendijk

Copromotoren:
Dr. J.R.N. van der Voort van Zyp
Dr. M. Peters

CONTENT

CHAPTER 1

General Introduction and Thesis Outline

The present thesis constitutes an investigation of the role of focal therapy in the treatment of prostate cancer. Considering the complexity of the topic, this introduction offers a comprehensive insight into all aspects of the disease including the current established treatment options, before zooming in on the concept and rationale of focal therapy. The aim is to provide a wide basis for a well-founded vision on its potential.

Epidemiology

Prostate cancer is the second most common cancer in men (after skin cancer), affecting 1 in 9 men over the course of their lifetime(1). Incidence rates increased rapidly in the early 1990s (Figure 1) due to a screening surge using prostate specific antigen (PSA) testing to detect latent prostate cancers in asymptomatic men(2). In more recent years, incidence rates have declined because of recommendations against the routine use of PSA-screening, although this remains controversial. Main arguments against screening involve the risk of over-diagnosis of indolent cancers and unnecessary treatments which carry a financial, emotional and physical burden(3). Main arguments in favor of screening involve the risk of delaying the diagnosis of a more aggressive or advanced prostate cancer, diminishing survival rates substantially(4, 5). Although the peak in PSA-testing in the early 1990s was accompanied by a relative increase in prostate cancer-specific mortality (Figure 2), which is most likely explained by the larger pool of evident prostate cancer patients at the time, the steady decline of mortality rates afterwards shows no clear survival advantage for population-wide PSA-screening. Current guidelines recommend the decision to screen should be an individual one, balancing benefits and harms based on individual characteristics and patient preference(6, 7).

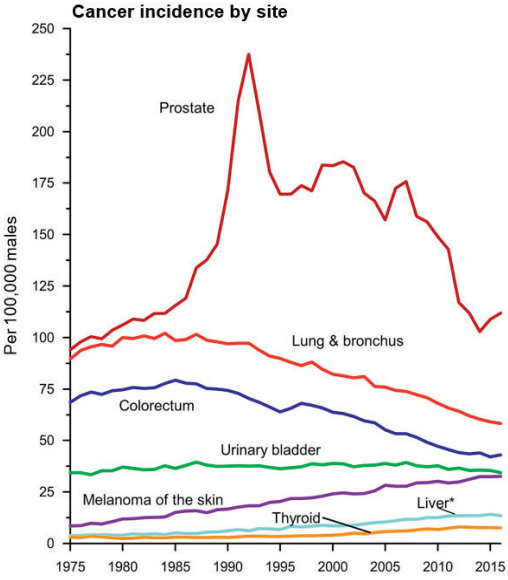

Figure 1 – Trends in age-standardized cancer incidence rates among males in the United States. Image adapted from: Siegel et al., 2020(2)

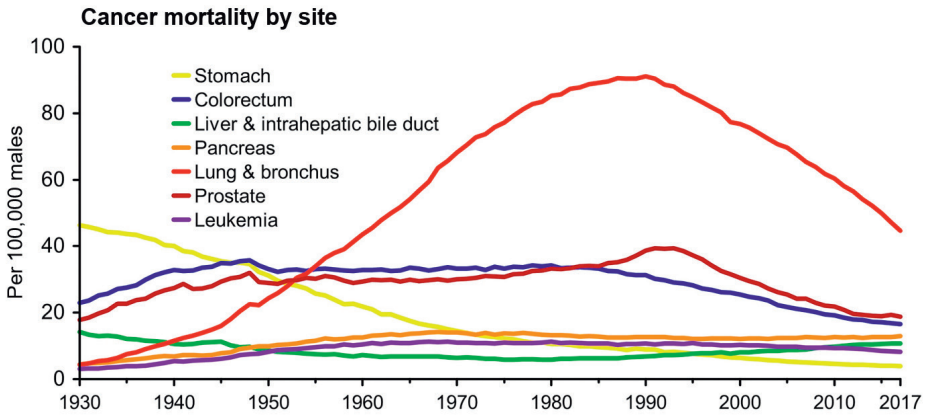

Figure 2 – Trends in age-standardized cancer mortality rates among males in the United States. Image adapted from: Siegel et al., 2020(2)

Prostate cancer is most frequently diagnosed among men aged 65-74, and it is more common in men of African ancestry, men with a genetic predisposition (e.g., Lynch syndrome and BRCA1 and BRCA2 mutations) or a family history of close relatives diagnosed with prostate cancer, especially before the age of 65(8). At presentation, ±80% of patients have localized disease, ±15% has regional lymph node involvement and ±5% has distant metastases(9). Stage at diagnosis has a dramatic impact on 5-year relative survival rates, with excellent survival for patients with localized or regional disease (>99%) and much lower survival for patients presenting with metastases (31%)(8). This not only reflects the aggressive nature of late-stage disease, but also the indolent nature of early-stage disease and potentially the effectiveness of local treatments for these tumors.

Diagnosis and staging

To improve accurate staging (and to provide a better framework for suitable choice of treatment), there has been a heavy focus on improving diagnostic imaging over the last years. Although several developments have led to improved cancer detection and potentially better patient selection, the challenge remains how to incorporate these new techniques in diagnostic pathways and, consequently, in treatment decisions.

Although local tumor staging (Figure 3) is historically performed using digital rectal examination (DRE) and current guidelines still refer to DRE-findings for determination of the clinical T-stage(10), the role of multiparametric magnetic resonance imaging (mp-MRI) seems to become more prominent. Its added value in terms of initial cancer screening in biopsy-naïve patients has been under debate, considering its low specificity and therefore high number of false positives(11). Nevertheless it has been suggested that the combination of mp-MRI with clinical and biochemical data in a multivariate prediction model may aid in the decision process of whether or not to biopsy at all, thereby reducing the number of unnecessary biopsies(12). More established is its role as pre-biopsy visual aid, since mp-MRI allows for targeted biopsies which seem to im-

prove the diagnostic yield of clinically significant cancer, while reducing over-diagnosis of low-risk disease as compared to systematic biopsies(13-15). The clinical utility of systematic biopsies in such an "MRI pathway" has even been questioned in more recent work, showing that the detection of clinically significant cancer in exclusively non-targeted biopsies can be as low as 2%(16). In the pre-treatment setting, mp-MRI also provides a predictive ability of extracapsular extension, aiding urologists in their preoperative planning and radiation oncologists in selecting their treatment regimen(17-19). To improve inter-reader reproducibility, much effort has been put into creating clear guidelines to ensure standardized mp-MRI acquisition and interpretation(20).

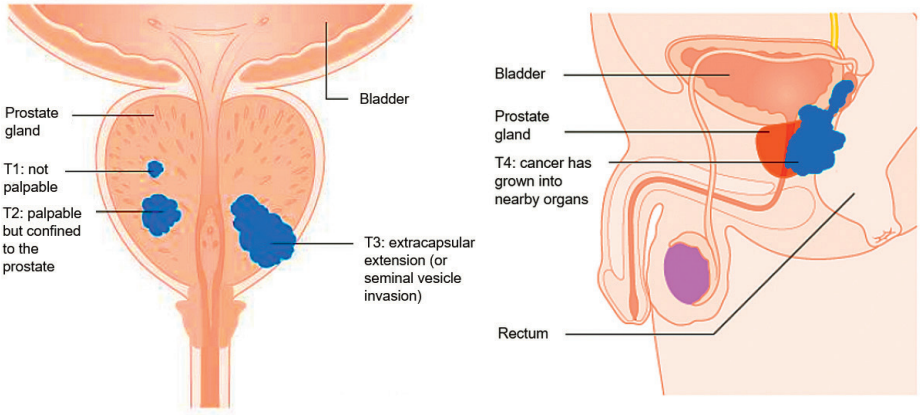

Figure 3 - Four main prostate cancer tumor stages.
T1 is divided into T1a (cancer unexpectedly found in <5% of removed tissue), T1b (cancer unexpectedly found in ≥5% of removed tissue) and T1c (cancer found by biopsy). T2 is divided into T2a (≤half of one side of the gland), T2b (>half of one side of the gland) and T2c (both sides). T3 is divided into T3a (broken through the capsule) and T3b (spread into the vesicles). Image adapted from: Cancer Research UK (www.cancerresearchuk.org).

After manual and radiological examination, a definitive prostate cancer diagnosis requires histopathological verification of adenocarcinoma. The International Society of Urological Pathology (ISUP) constructed the Gleason score system, which consists of a score for the most extensive pattern plus the second most common pattern and a sum score. Nowadays, Gleason scores are reported by the classification of five grade groups, i.e. sum score ≤6 (group 1), 3+4=7 (group 2), 4+3=7 (group 3), sum score 8 (group 4) and sum score 9-10 (group 5)(21). There are several definitions of what is considered "clinically significant prostate cancer" (i.e. cancer that requires treatment), ranging from any ISUP grade 2 or 3 to ISUP grade 3 / ≥6mm of ISUP grade 1 or ISUP grade 2 / ≥4mm of ISUP grade 1(22).

A combination of these features (clinical T-stage, ISUP grade group, serum PSA-level) allows for stratification of patients into prognostic groups based on risk of recurrence after treatment. Low-, intermediate- and high-risk groups have been identified by several guideline committees(23-26), all with minor differences regarding the definition of intermediate- and high-risk disease (Table 1). To further aid individualized treatment

decisions, patients in the intermediate-risk group are frequently subdivided into favorable (ISUP grade 2) and unfavorable (ISUP grade 3) risk groups(27).

Table 1 – Risk stratification groups for patients with localized prostate cancer

Low-risk	(all) PSA <10 and ISUP 1 and cT1-T2a
Intermediate-risk	D'Amico/EAU/NICE – PSA 10-20 and/or ISUP 2-3 and/or cT2b NCCN – PSA 10-20 and/or ISUP 2-3 and/or cT2b-c
High-risk	D'Amico/NICE – PSA >20 and/or ISUP 4-5 and/or cT2c-T3 EAU – PSA >20 and/or ISUP 4-5 and/or cT2c or any PSA/ISUP with cT3-4 or cN+ NCCN – PSA >20 and/or ISUP 4-5 and/or cT3 or ≥2 intermediate risk features

PSA: prostate specific antigen, ISUP: grade group by the International Society of Urological Pathology, EAU: European Association of Urology, NICE: National Institute for health and Care Excellence (UK), NCCN: National Comprehensive Cancer Network (US).

Beyond local staging, further nodal and metastatic screening is strongly advised for unfavorable intermediate- and high-risk patients(24, 28). Although relatively modern imaging modalities (prostate specific membrane antigen [PSMA]-PET/CT and diffusion-weighted MRI) provide the most sensitive detection of lymph node and bone metastases(29-32), there remains hesitation regarding treatment of modern imaging-only detectable lesions since its clinical benefit in terms of overall survival has not yet been established(33). Although current guidelines still advise using a classical work-up with bone scan and abdominopelvic CT, recent level 1 evidence supports offering PSMA-PET/CT to high-risk patients(34).

Treatments in the primary setting

For patients with clinically localized non-metastatic prostate cancer, there are local treatment options with curative intent. Among these, surgery and radiotherapy are the two major contemporary approaches, with apparent equivalence in terms of overall survival. As long-term data from a randomized study (among predominantly low-risk patients) have shown, 10-year prostate cancer-specific mortality is very low (±1%)(35), which shifts the attention towards treatment-related side-effects.

Radical prostatectomy (RP) entails the complete removal of the prostate and seminal vesicles, nowadays usually performed using a laparoscopic (LRP) or robot-assisted (RARP) approach(36). On average, intra- and peri-operative complications such as need for blood transfusion, organ injury, infection, or anastomotic leak are rare (<5%)(37), although patients with existing comorbidities are at higher risk of surgical complications(38). Post-operative morbidity is a more common problem, mainly presenting in the form of urinary incontinence (±20% one year post-treatment) and erectile dysfunction (ED) (±70-75% one year post-treatment)(39). Both are the direct result of surgically compromised critical structures, such as the external urethral sphincter and neurovascular bundles. Studies assessing the effect of sphincter reconstruction or bladder

neck suspension have failed to show continence improvement compared to standard anastomosis with no reconstruction(40, 41). Depending on tumor location and size, nerve-sparing techniques such as intra-fascial dissection and athermal, traction-free handling of neurovascular bundles may be used in an attempt to preserve erectile function(42). Depending on age and pre-operative function, this may significantly improve post-operative potency(43).

Radiotherapy uses high doses of ionizing radiation to treat cancerous tissue, which can be delivered as an external beam (EBRT) or through internal implantation (brachytherapy). Modern techniques to shape the radiation beam and modulate its intensity (IMRT, VMAT) and the integration of imaging modalities into the radiation machine (IGRT) have evolved EBRT from large-field to more conformal treatment, enabling dose escalation to the tumor while reducing exposure to surrounding healthy organs(44). Common acute toxicities after radiotherapy include dysuria, urinary frequency, urinary retention, diarrhea and rectal bleeding, although these usually resolve over weeks-months(45). Although severe toxicity requiring invasive intervention is rare (±2%), long-term side-effects caused by radiation-induced inflammation are more common, such as irritative urinary complaints (±10-20%) and symptoms of proctitis (±15-30%)(46, 47). The occurrence of rectal morbidity is generally lower after brachytherapy compared with EBRT(48). Radiation-induced ED develops slowly over time, increasing from low impotence rates directly after treatment to rates around 50% after 5 years(49, 50).

Other sources of energy for treatment are investigated within clinical trial settings. Most investigational data is available from freezing (-40°C, i.e. cryotherapy) and heating (>65°C, i.e. high-intensity focused ultrasound [HIFU]), which are techniques to induce cell death by ischemic necrosis(51, 52). Both ablative treatments have been introduced as a minimally invasive approach which can be performed in an outpatient setting at a lower cost than conventional EBRT or RP(53). Comparative outcome data is sparse, with only two randomized controlled trials (RCT) comparing cryotherapy to EBRT. At a median follow-up nearing 9 years, cryotherapy seems most suited for less bulky prostate cancer (<T2c) although no clear difference was found in overall or disease-specific survival as compared to EBRT(54, 55). Short-term procedural complications of cryotherapy are rare, such as acute urinary retention (±4%), urethral stricture (±1%), recto-urethral fistula formation (0-6%) and rectal pain (±3%). One year post-cryotherapy morbidity seems limited with ±20% ED and ±3% urinary incontinence. No RCT's are available comparing HIFU to standard treatment. From what is described in case series, acute side-effects are more common, including dysuria (±20%), urinary retention (±10%), urethral stricture (±8%), rectal pain (±11%) and recto-urethral fistula (0-5%). Major long-term effects include ±23% ED and ±10% urinary incontinence(53).

Treatment guidelines vary by risk group (Figure 4), reflecting the differences in the critical trade-off between cancer control and potential harm from treatment.

Low-risk	Intermediate-risk	High-risk
Active surveillance	(Active surveillance)	PLND
No PLND	PLND at LNI risk >5%	Active treatment (RP, RT)
Active treatment (RP, RT)	Active treatment (RP, RT)	EBRT+36 months ADT
	EBRT+6 months ADT	+/-brachy boost
	+/-brachy boost	RP +/-adjuvant RT or ADT

Figure 4 – General treatment guidelines per prostate cancer risk group.
PLND: pelvic lymph node dissection, RP: radical prostatectomy, RT: radiotherapy, LNI: lymph node involvement, ADT: androgen deprivation therapy.
Image adapted from: The Sunshine Coast Urology Clinic (www.sunshinecoasturology.com.au).

Low- and favorable intermediate-risk patients are eligible for both surgery and radiotherapy, which carry equal but distinct risk-benefit profiles(56). However, as long-term observational cohort studies on (initial) conservative management have shown, the natural course of clinically localized disease is relatively mild, with cancer-specific survival rates of 80-90% after 10 years(57, 58). In an effort to reduce over-treatment of indolent non-lethal tumors, active surveillance (AS) has therefore emerged as the recommended strategy for patients with low-risk disease or highly selected favorable intermediate-risk patients (i.e. <10% Gleason pattern 4)(59, 60). In principle, AS is a deferred treatment strategy with curative intent, aiming to treat no earlier than necessary. To monitor the need for treatment, follow-up should at least include PSA-testing and DRE every 3-6 months, and standard repeat prostate biopsy after one year and every three years thereafter. PSA progression, clinical progression on DRE and/or radiological progression on mp-MRI (if performed) require interim repeat biopsy(61). This strict follow-up protocol is a downside of AS, with decreasing patient compliance over time, particularly regarding repeat biopsies(62). From a patient's perspective, the burden of follow-up combined with fear of progressively growing cancer may favor immediate active treatment. Both AS and active treatment require a life expectancy of at least 10 years to expect any benefit from (potential) local treatment above a conservative watchful waiting strategy.

Unfavorable intermediate- and high-risk patients require a more aggressive approach, with a more extensive diagnostic evaluation (extended pelvic lymph node dissection [ePLND])(63) and use of multi-modal treatment, consisting of EBRT with systemic androgen deprivation therapy (ADT) and/or brachytherapy boost or RP with adjuvant radiotherapy to the prostate bed or ADT(24). Patients with ePLND-proven

(pN+) or image-suspected (iN+M+) metastatic disease represent a heterogeneous and complex group (often referred to as "very high risk"), for whom a clear consensus regarding optimal treatment is lacking. A subdivision based on metastatic volume (low- or high-volume) has been adopted as a predictor for survival and as a guideline for treatment decisions(64).

ADT, which lowers androgen levels to prevent prostate cancer cells from growing, has been the standard of care for disseminated disease for over 50 years(65). However the timing of initiation, type of androgen blockade and its role in asymptomatic stages remains poorly defined. ADT has a temporary suppressive effect on the disease, halting its progression for a mean of 2-3 years before the tumor becomes hormone-resistant(66). It is therefore a palliative treatment with no potential of cure. Moreover, ADT is associated with significant side-effects, including impotence, fatigue, gynecomastia, breast pain, hot flushes, metabolic and cardiovascular events and psychological distress(67). ADT is therefore usually deferred until the patient suffers symptoms of metastatic prostate cancer or has evident radiological tumor progression. However the ideal timing remains controversial, with a recent Cochrane review concluding that early ADT may extend time to death(68). Further research in the field of systemic palliative treatments has led to the adoption of novel therapeutic approaches, particularly the wide-spread use of combination therapies (ADT with chemotherapy or second generation antiandrogens)(69) and the concept of adding local treatment for cytoreductive purposes in patients with "low volume" metastatic disease(70).

Recurrence of disease

Although the average 10-year overall survival rate is as high as 98%(8), prostate cancer recurrences are quite common after local treatment. Depending on the primary risk group, 10-40% of patients have recurrence of disease within 10 years after radiotherapy or surgery(71, 72). A relapse is diagnosed based on rising PSA, with different definitions of biochemical failure after RP (PSA >0.4 ng/mL and rising) and radiotherapy (PSA increase >2 ng/mL above nadir value)(73). The management of recurrent disease is controversial since its natural history is very heterogeneous, ranging from indolent cancer that remains clinically undetectable to aggressive recurrences that are rapidly lethal(74). Nonetheless, on average, biochemical failure precedes progression to distant metastases by ±5 years and prostate cancer-specific mortality by ±10 years(75). As concluded in a recent review, the impact of biochemical recurrence on survival seems most outspoken in a subgroup of patients with specific clinical risk factors (short PSA doubling time, short interval to biochemical failure, high Gleason score)(76). Just as in the primary setting, the decision to initiate salvage treatment should be carefully balanced between the risk of disease progression and the risk of treatment morbidity.

For patients with a localized recurrence after radiotherapy ("radiorecurrent" disease), there is potential to re-treat the prostate gland. In this setting, modern imaging has a more established role in staging the disease and guiding local salvage treatment. PSMA/PET-CT is the most sensitive tool for the detection of distant metastases(77), while

mp-MRI is the best technique to evaluate local recurrence(78). Available whole-gland salvage treatments include salvage RP, cryotherapy, HIFU and brachytherapy. Although salvage RP and HIFU are associated with worse rates of urinary incontinence (40-50%) than salvage cryotherapy or brachytherapy (7-12%), all modalities have high impotence rates (±75%) and high rates of urethral stricture (±20%). Reported overall relapse rates are similar across all treatments, with 45-55% of patients experiencing post-salvage recurrence after 4.5 years(79). Due to these unfavorable oncologic and functional outcomes, ±90% of patients with radiorecurrent disease is currently treated with ADT(80).

Introduction to focal therapy

To reduce the burden of treatment-related side-effects, preservation of normal prostate tissue and surrounding structures is warranted. Focal therapy, which entails the targeted ablation of only the malignant area of the prostate, has been suggested as a way to accomplish this(81). However, efforts to adopt a focal therapy approach for prostate cancer have been challenged by the multifocal nature of the disease, with only 20-30% of men having unifocal or unilateral cancer(82).

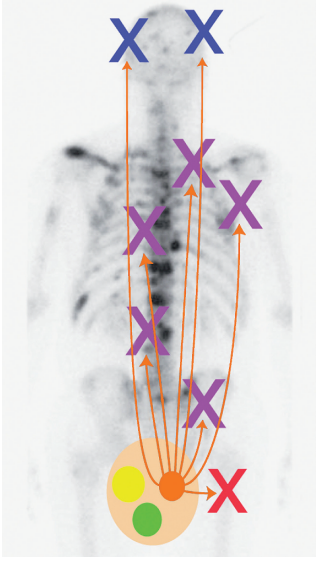

Figure 5: Monoclonal origin of metastatic prostate cancer.
Adapted from: Liu et al., 2009 (81)

Despite the notion of multiple lesions harboring clones of cancer cells, considerable evidence suggests that one lesion in the prostate (the index lesion or dominant intraprostatic lesion) may be the most important predictor for the course of the disease and its prognosis(83). Furthermore, genetic studies on pathologic characteristics of metastatic prostate cancer indicate that a single precursor cell from one type of clone could be responsible for driving the cancer to metastasize and become lethal

(Figure 5)(84, 85). Adding these two concepts together has led to the idea that even in multifocal prostate cancer, focused treatment of the index lesion alone might control clinical progression of the disease.

To enable focal treatment, adequate imaging becomes essential. Herein, the introduction of mp-MRI has made it possible to reliably determine the location of cancer foci within the gland(86). However, with multifocal prostate cancer the question remains how to determine the index lesion. Although it has been suggested that it is usually the largest or highest grade lesion, there is also evidence that small, relatively low-grade tumors sometimes harbor the lethal clone(87). Furthermore, mp-MRI has the limitation of often underestimating the size of cancer lesions, necessitating the use of a certain treatment margin to avoid incomplete ablation(88). Therefore, ablation patterns may range from targeting the lesion only (ultrafocal ablation) to treating half the gland (hemi-gland ablation) or three-quarters in a "hockey stick" shape. Different modalities such as cryotherapy, HIFU and brachytherapy are available to achieve focal ablation.

Position in the primary setting

Despite excellent long-term cancer control rates of contemporary surgery and radiotherapy (especially in low-risk disease), patients face an increased risk of both transient and chronic side-effects affecting their daily living, as described in previous sections. Although the adoption of AS has caused a shift towards reducing (unnecessary) treatment, strict inclusion criteria and invasive follow-up protocols restrict the number of patients able or willing to choose such a strategy. Furthermore, ±50% of patients under AS convert to active treatment within 10 years and are therefore still exposed to side-effects(89). Given these disadvantages of whole-gland treatment and active surveillance, focal therapy might be a reasonable treatment option for selected patients.

Position in the salvage setting

After primary EBRT, the most common site of recurrence is within the prostate gland and/or seminal vesicles(90), with relapses usually occurring at the site of the primary largest (index) lesion(91). Organ-confined, targetable recurrences are eligible for focal salvage treatment, which could be offered as a safer alternative to whole-gland salvage treatment and as a way to prevent or postpone the need for palliative ADT.

AIMS OF THE THESIS

In summary, the role of focal therapy will be explored in two settings: the primary treatment setting and the salvage treatment setting. Besides a general outline, the use of high-dose-rate brachytherapy as a focal treatment modality will be explored specifically. This thesis aims to answer the following general and more specific questions:

I. Primary treatment setting

- How does focal therapy compare to conventional EBRT and RP?

Specifically:

- What are the results of MRI-guided ultrafocal high-dose-rate brachytherapy?

II. Salvage treatment setting

- What is the current status of focal salvage treatments?

Specifically:

- What are the results of MRI-guided ultrafocal salvage high-dose-rate brachytherapy?
- What is the effect on patient-reported quality of life?
- How does this compare to physician-reported toxicity?
- What are the potential predictors of treatment failure?
- Upon recurrence, can we repeat focal salvage treatment?

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: a cancer journal for clinicians. 2020;70(1):7-30.
3. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. The Cochrane database of systematic reviews. 2013(1):CD004720.
4. Sheng IY, Wei W, Chen YW, Gilligan TD, Barata PC, Ornstein MC, et al. Implications of the United States Preventive Services Task Force Recommendations on Prostate Cancer Stage Migration. Clinical genitourinary cancer. 2020.
5. Hugosson J, Roobol MJ, Mansson M, Tammela TLJ, Zappa M, Nelen V, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol. 2019;76(1):43-51.
6. Force USPST, Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. Jama. 2018;319(18):1901-13.
7. Horwich A, Hugosson J, de Reijke T, Wiegel T, Fizazi K, Kataja V, et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24(5):1141-62.
8. American Cancer Society. Cancer Facts & Figures 2020. Atlanta: American Cancer Society; 2020.
9. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Prostate Cancer. [Available from: https://seer.cancer.gov/statfacts/html/prost.html.
10. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2017.
11. Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. The Cochrane database of systematic reviews. 2019;4:CD012663.
12. Schoots IG, Roobol MJ. Multivariate risk prediction tools including MRI for individualized biopsy decision in prostate cancer diagnosis: current status and future directions. World journal of urology. 2020;38(3):517-29.
13. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;378(19):1767-77.
14. Rouviere O, Puech P, Renard-Penna R, Claudon M, Roy C, Mege-Lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. The Lancet Oncology. 2019;20(1):100-9.
15. van der Leest M, Cornel E, Israel B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. Eur Urol. 2019;75(4):570-8.
16. Connor MJ, Eldred-Evans D, van Son M, Hosking-Jervis F, Bertoncelli Tanaka M, Reddy D, et al. A Multicentre Study of the Clinical Utility of Non-targeted Systematic Transperineal Prostate Biopsies in Patients Undergoing Pre-biopsy mpMRI. The Journal of urology. 2020:101097JU0000000000001184.

17. Rayn KN, Bloom JB, Gold SA, Hale GR, Baiocco JA, Mehralivand S, et al. Added Value of Multiparametric Magnetic Resonance Imaging to Clinical Nomograms for Predicting Adverse Pathology in Prostate Cancer. The Journal of urology. 2018;200(5):1041-7.

18. Feng TS, Sharif-Afshar AR, Wu J, Li Q, Luthringer D, Saouaf R, et al. Multiparametric MRI Improves Accuracy of Clinical Nomograms for Predicting Extracapsular Extension of Prostate Cancer. Urology. 2015;86(2):332-7.

19. Chang JH, Lim Joon D, Nguyen BT, Hiew CY, Esler S, Angus D, et al. MRI scans significantly change target coverage decisions in radical radiotherapy for prostate cancer. Journal of medical imaging and radiation oncology. 2014;58(2):237-43.

20. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol. 2019;76(3):340-51.

21. Egevad L, Delahunt B, Srigley JR, Samaratunga H. International Society of Urological Pathology (ISUP) grading of prostate cancer - An ISUP consensus on contemporary grading. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica. 2016;124(6):433-5.

22. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. The Journal of urology. 2011;186(2):458-64.

23. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network : JNCCN. 2019;17(5):479-505.

24. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71(4):618-29.

25. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Jama. 1998;280(11):969-74.

26. Dasgupta P, Davis J, Hughes S. NICE guidelines on prostate cancer 2019. BJU international. 2019;124(1):1.

27. Serrano NA, Anscher MS. Favorable vs Unfavorable Intermediate-Risk Prostate Cancer: A Review of the New Classification System and Its Impact on Treatment Recommendations. Oncology (Williston Park, NY). 2016;30(3):229-36.

28. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. The Journal of urology. 2018;199(3):683-90.

29. van Kalmthout LWM, van Melick HHE, Lavalaye J, Meijer RP, Kooistra A, de Klerk JMH, et al. Prospective Validation of Gallium-68 Prostate Specific Membrane Antigen-Positron Emission Tomography/Computerized Tomography for Primary Staging of Prostate Cancer. The Journal of urology. 2020;203(3):537-45.

30. Corfield J, Perera M, Bolton D, Lawrentschuk N. (68)Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. World journal of urology. 2018;36(4):519-27.

31. Thoeny HC, Froehlich JM, Triantafyllou M, Huesler J, Bains LJ, Vermathen P, et al. Metastases in normal-sized pelvic lymph nodes: detection with diffusion-weighted MR imaging. Radiology. 2014;273(1):125-35.

32. Pasoglou V, Larbi A, Collette L, Annet L, Jamar F, Machiels JP, et al. One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI): toward an upfront simplified "all-in-one" imaging approach? The Prostate. 2014;74(5):469-77.

33. Hicks RJ, Murphy DG, Williams SG. Seduction by Sensitivity: Reality, Illusion, or Delusion? The Challenge of Assessing Outcomes after PSMA Imaging Selection of Patients for Treatment. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2017;58(12):1969-71.

34. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020;395(10231):1208-16.

35. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-24.

36. Myers RP. Practical surgical anatomy for radical prostatectomy. The Urologic clinics of North America. 2001;28(3):473-90.

37. Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N, et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health technology assessment. 2012;16(41):1-313.

38. Alibhai SM, Leach M, Tomlinson G, Krahn MD, Fleshner N, Holowaty E, et al. 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity. Journal of the National Cancer Institute. 2005;97(20):1525-32.

39. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderang U, Thorsteinsdottir T, et al. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol. 2015;68(2):216-25.

40. Sutherland DE, Linder B, Guzman AM, Hong M, Frazier HA, 2nd, Engel JD, et al. Posterior rhabdosphincter reconstruction during robotic assisted radical prostatectomy: results from a phase II randomized clinical trial. The Journal of urology. 2011;185(4):1262-7.

41. Stolzenburg JU, Nicolaus M, Kallidonis P, Do M, Dietel A, Hafner T, et al. Influence of bladder neck suspension stitches on early continence after radical prostatectomy: a prospective randomized study of 180 patients. Asian journal of andrology. 2011;13(6):806-11.

42. Walz J, Epstein JI, Ganzer R, Graefen M, Guazzoni G, Kaouk J, et al. A Critical Analysis of the Current Knowledge of Surgical Anatomy of the Prostate Related to Optimisation of Cancer Control and Preservation of Continence and Erection in Candidates for Radical Prostatectomy: An Update. Eur Urol. 2016;70(2):301-11.

43. Stolzenburg JU, Kallidonis P, Do M, Dietel A, Hafner T, Rabenalt R, et al. A comparison of outcomes for interfascial and intrafascial nerve-sparing radical prostatectomy. Urology. 2010;76(3):743-8.

44. Zaorsky NG, Harrison AS, Trabulsi EJ, Gomella LG, Showalter TN, Hurwitz MD, et al. Evolution of advanced technologies in prostate cancer radiotherapy. Nature reviews Urology. 2013;10(10):565-79.

45. Matzinger O, Duclos F, van den Bergh A, Carrie C, Villa S, Kitsios P, et al. Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991. European journal of cancer. 2009;45(16):2825-34.

46. Pederson AW, Fricano J, Correa D, Pelizzari CA, Liauw SL. Late toxicity after intensity-modulated radiation therapy for localized prostate cancer: an exploration of dose-volume histogram parameters to limit genitourinary and gastrointestinal toxicity. Int J Radiat Oncol Biol Phys. 2012;82(1):235-41.

47. Ohri N, Dicker AP, Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. The Canadian journal of urology. 2012;19(4):6373-80.

48. Lesperance RN, Kjorstadt RJ, Halligan JB, Steele SR. Colorectal complications of external beam radiation versus brachytherapy for prostate cancer. Am J Surg. 2008;195(5):616-20; discussion 20.

49. Mahmood J, Shamah AA, Creed TM, Pavlovic R, Matsui H, Kimura M, et al. Radiation-induced erectile dysfunction: Recent advances and future directions. Adv Radiat Oncol. 2016;1(3):161-9.

50. Incrocci L. Radiotherapy for prostate cancer and sexual health. Translational andrology and urology. 2015;4(2):124-30.

51. Rees J, Patel B, MacDonagh R, Persad R. Cryosurgery for prostate cancer. BJU international. 2004;93(6):710-4.

52. Madersbacher S, Marberger M. High-energy shockwaves and extracorporeal high-intensity focused ultrasound. Journal of endourology. 2003;17(8):667-72.

53. Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health technology assessment. 2015;19(49):1-490.

54. Chin JL, Al-Zahrani AA, Autran-Gomez AM, Williams AK, Bauman G. Extended followup oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). The Journal of urology. 2012;188(4):1170-5.

55. Donnelly BJ, Saliken JC, Brasher PM, Ernst SD, Rewcastle JC, Lau H, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer. 2010;116(2):323-30.

56. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016;375(15):1425-37.

57. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Outcomes of localized prostate cancer following conservative management. Jama. 2009;302(11):1202-9.

58. Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med. 1994;330(4):242-8.

59. Chen RC, Rumble RB, Loblaw DA, Finelli A, Ehdaie B, Cooperberg MR, et al. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(18):2182-90.

60. Lam TBL, MacLennan S, Willemse PM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur Urol. 2019;76(6):790-813.

61. van den Bergh RC, Roemeling S, Roobol MJ, Roobol W, Schroder FH, Bangma CH. Prospective validation of active surveillance in prostate cancer: the PRIAS study. Eur Urol. 2007;52(6):1560-3.

62. Bokhorst LP, Alberts AR, Rannikko A, Valdagni R, Pickles T, Kakehi Y, et al. Compliance Rates with the Prostate Cancer Research International Active Surveillance (PRIAS) Protocol and Disease Reclassification in Noncompliers. Eur Urol. 2015;68(5):814-21.

63. Abdollah F, Suardi N, Gallina A, Bianchi M, Tutolo M, Passoni N, et al. Extended pelvic lymph node dissection in prostate cancer: a 20-year audit in a single center. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24(6):1459-66.

64. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(11):1080-7.

65. Pagliarulo V, Bracarda S, Eisenberger MA, Mottet N, Schroder FH, Sternberg CN, et al. Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol. 2012;61(1):11-25.

66. Karantanos T, Corn PG, Thompson TC. Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches. Oncogene. 2013;32(49):5501-11.

67. Lee RJ, Smith MR. Hormone Therapy for Prostate Cancer. In: Chabner BA, Longo DL, editors. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5th ed: Wolters Kluwer: Lippincott Williams & Wilkins; 2011.

68. Kunath F, Jensen K, Pinart M, Kahlmeyer A, Schmidt S, Price CL, et al. Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer. The Cochrane database of systematic reviews. 2019;6:CD003506.

69. Sathianathen NJ, Philippou YA, Kuntz GM, Konety BR, Gupta S, Lamb AD, et al. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. The Cochrane database of systematic reviews. 2018;10:CD012816.

70. Burdett S, Boeve LM, Ingleby FC, Fisher DJ, Rydzewska LH, Vale CL, et al. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. Eur Urol. 2019;76(1):115-24.

71. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2013;85(3):686-92.

72. Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. Nature clinical practice Urology. 2005;2(4):174-82.

73. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.

74. Punnen S, Cooperberg MR, D'Amico AV, Karakiewicz PI, Moul JW, Scher HI, et al. Management of biochemical recurrence after primary treatment of prostate cancer: a systematic review of the literature. Eur Urol. 2013;64(6):905-15.

75. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Polkinghorn W, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol. 2015;67(6):1009-16.

76. Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol. 2019;75(6):967-87.

77. De Visschere PJL, Standaert C, Futterer JJ, Villeirs GM, Panebianco V, Walz J, et al. A Systematic Review on the Role of Imaging in Early Recurrent Prostate Cancer. Eur Urol Oncol. 2019;2(1):47-76.

78. van der Poel H, Grivas N, van Leeuwen P, Heijmink S, Schoots I. The role of MRI for detection and staging of radio- and focal therapy-recurrent prostate cancer. World journal of urology. 2019;37(8):1485-90.

79. Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. European urology focus. 2016;2(2):158-71.

80. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR, Cancer of the Prostate Strategic Urological Research E. Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. Cancer. 2008;112(2):307-14.

81. Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? Nature clinical practice Oncology. 2007;4(11):632-42.

82. Eggener SE, Scardino PT, Carroll PR, Zelefsky MJ, Sartor O, Hricak H, et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. The Journal of urology. 2007;178(6):2260-7.

83. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009;361(17):1704-6.

84. Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nature medicine. 2009;15(5):559-65.

85. Van Etten JL, Dehm SM. Clonal origin and spread of metastatic prostate cancer. Endocr Relat Cancer. 2016;23(4):R207-17.

86. Zhen L, Liu X, Yegang C, Yongjiao Y, Yawei X, Jiaqi K, et al. Accuracy of multiparametric magnetic resonance imaging for diagnosing prostate Cancer: a systematic review and meta-analysis. BMC cancer. 2019;19(1):1244.

87. Haffner MC, Mosbruger T, Esopi DM, Fedor H, Heaphy CM, Walker DA, et al. Tracking the clonal origin of lethal prostate cancer. The Journal of clinical investigation. 2013;123(11):4918-22.

88. Wysock JS, Lepor H. Multi-parametric MRI imaging of the prostate-implications for focal therapy. Translational andrology and urology. 2017;6(3):453-63.

89. Kinsella N, Helleman J, Bruinsma S, Carlsson S, Cahill D, Brown C, et al. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. Translational andrology and urology. 2018;7(1):83-97.

90. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Kollmeier M, et al. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer. The Journal of urology. 2015;194(6):1624-30.

91. Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys. 2002;53(3):595-9.

CHAPTER 2

Conventional radical versus focal treatment for localized prostate cancer: a propensity score weighted comparison of 6-year tumour control

Authors: Marieke J. van Son, Max Peters, Deepika Reddy, Taimur T. Shah, Feargus Hosking-Jervis, Stephen Robinson, Jan J.W. Lagendijk, Stephen Mangar, Tim Dudderidge, Stuart McCracken, Richard G. Hindley, Amr Emara, Raj Nigam, Raj Persad, Jaspal Virdi, Henry Lewi, Caroline Moore, Clement Orczyk, Mark Emberton, Manit Arya, Hashim U. Ahmed, Jochem R.N. van der Voort van Zyp, Matt Winkler, Alison Falconer
Joint senior authors: J.R.N. van der Voort van Zyp, M. Winkler, A. Falconer

PROSTATE CANCER AND PROSTATIC DISEASES

ABSTRACT

Background

For localized prostate cancer, focal therapy offers an organ-sparing alternative to radical treatments (radiotherapy or prostatectomy). Currently, there is no randomised comparative effectiveness data evaluating cancer control of both strategies.

Methods

Following the eligibility criteria PSA <20 ng/mL, Gleason score ≤7 and T-stage ≤T2c, we included 830 radical (440 radiotherapy, 390 prostatectomy) and 530 focal therapy (cryotherapy, high intensity focused ultrasound or high-dose-rate brachytherapy) patients treated between 2005-2018 from multicentre registries in the Netherlands and the UK. A propensity score weighted (PSW) analysis was performed to compare failure-free survival (FFS), with failure defined as salvage treatment, metastatic disease, systemic treatment (androgen deprivation therapy or chemotherapy) or progression to watchful waiting. Secondary outcome was overall survival (OS). Median (IQR) follow-up in each cohort was 55 (28–83) and 62 (42–83) months, respectively.

Results

At baseline, radical patients had higher PSA (10.3 versus 7.9) and higher-grade disease (31% ISUP 3 versus 11%) compared to focal patients. After PSW, all covariates were balanced (SMD <0.1). 6-year weighted FFS was higher after radical therapy (80.3%, 95% CI 73.9-87.3) than after focal therapy (72.8%, 95% CI 66.8-79.8) although not statistically significant (p=0.1). 6-year weighted OS was significantly lower after radical therapy (93.4%, 95% CI 90.1-95.2 versus 97.5%, 95% CI 94-99.9; p=0.02). When compared in a three-way analysis, focal and LRP patients had higher risk of treatment failure than EBRT patient (p<0.001), but EBRT patients had higher risk of mortality than focal patients (p=0.008).

Conclusions

Within the limitations of a cohort-based analysis in which residual confounders are likely to exist, we found no clinically relevant difference in cancer control conferred by focal therapy compared to radical therapy at 6 years.

INTRODUCTION

For localized prostate cancer, whole-gland treatments such as radiotherapy or prostatectomy confer excellent long-term cancer control, with 10-year biochemical disease-free survival rates between 65-90%[1,2] and 10-year prostate cancer-specific survival rates of nearly 100%[3-5]. However, these favourable oncological outcomes are often accompanied with detrimental side-effects, most notably urinary leakage requiring pads after prostatectomy, rectal side-effects (bleeding, loose stools, discomfort) following radiotherapy and erectile dysfunction for both types of radical therapies[6-8]. In an effort to avoid over-treatment and its associated morbidity, many low-risk patients can be safely managed with active surveillance[9].

Tissue-preserving focal therapy (FT) has been suggested as "the middle ground" and has undergone a phased evaluation over the last 14 years. Early to medium-term outcomes from cohort studies on focal high-intensity focused ultrasound (HIFU), focal cryotherapy and focal brachytherapy have shown pad-free continence rates between 93-100% and potency preservation between 58-100% with rectal toxicity being rare[10-17].

Randomised comparative effectiveness trials comparing FT to radical therapy are underway, although delivery of such trials may be difficult[18,19]. If successful, it will take almost a decade before conclusions can be drawn[20]. Awaiting this, the best available evidence comes from cohort-based analyses. This report is a follow-up study to our previously published work[21], comparing cancer control following radical therapy (external beam radiotherapy [EBRT] and laparoscopic radical prostatectomy [LRP]) versus FT, using a propensity score weighted (PSW) analysis.

MATERIALS AND METHODS

Study design and setting

EBRT data was collected from a UK single-centre retrospective registry of patients treated between January 2011-December 2018. LRP data was collected from a UK multicentre prospective registry between May 2007-September 2018. FT data was collected from three prospective registries: the focal HIFU HEAT registry, focal cryotherapy ICE registry in the UK and HDR-brachytherapy in the Netherlands, including patients between November 2005-February 2018. Data collection was approved by local medical research ethics committees and informed consent was obtained from all prospectively followed patients. Our study is compliant with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[22].

Patients

Eligibility criteria were: PSA <20 ng/mL, ≤ISUP 3 and T-stage ≤T2c (National Comprehensive Cancer Network [NCCN] low- to intermediate-risk). Patients with a history of previous prostate cancer treatment were excluded.

Interventions

EBRT

Radiation was administered using intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT). Until 2013, the indicated protocol for patients with low-risk disease (stage T1-2b, ISUP 1) was 70Gy in 35 fractions. After 2013, this protocol was changed to 60Gy in 20 fractions. For patients with a Roach seminal vesicle score[23] >15%, the seminal vesicles were included into the clinical target volume (CTV). Up to 2016, intermediate-risk patients (ISUP 2-3) received 74Gy in 37 fractions, with the base of the seminal vesicles included in the CTV. From 2016 onwards, this was changed to 72Gy in 32 fractions. All protocols included a margin of 5mm (0mm posteriorly) to the CTV for the planning target volume (PTV). Neo-adjuvant short-course (usually 3-6 months) ADT was prescribed for all EBRT patients unless contra-indicated.

LRP

Surgery was performed as a standardised laparoscopic procedure without pelvic lymph node dissection, using unilateral or bilateral nerve sparing at the discretion of the operating surgeon. If, for any reason, surgery had to be delayed, patients received neo-adjuvant short-course (usually ≤3 months) ADT as a bridging strategy. In case of post-operative adverse pathologic findings (positive surgical margins, upstaging to pT3-4), patients received adjuvant radiotherapy to the prostate bed (66Gy in 33 fractions) only if they had concomitant PSA progression.

FT

Focal HIFU (Sonablate, Sonacare) was offered to patients with peripheral or posterior tumours or those anteriorly based in which the anterior-posterior height was ≤3.5cm. Focal cryotherapy (SeedNet or Visual ICE cryotherapy device, Boston Scientific) was the preferred technique in anterior tumours, larger prostates with an anterior-posterior distance of >3.5cm or those with prostatic calcifications. Focal HDR-brachytherapy (1x19Gy) was performed without restrictions regarding tumour location or prostate size. Detailed descriptions of treatment procedures can be found in previous reports[13,14,24]. Salvage or repeat therapy following focal therapy was advised after histological confirmation of recurrent or residual disease. All focal patients had regular PSA monitoring, with an MRI performed in the case of two consecutive PSA rises with no identifiable benign cause. If a lesion of PI-RADS 3 or above was identified the patient underwent biopsy.

Data collection

ISUP grade and maximum cancer core length (MCCL) were determined from either TRUS-guided systematic sampling (LRP patients until 2016, EBRT and focal HDR-brachytherapy patients), MRI-targeted biopsies with peripheral zone sampling (focal HIFU/cryotherapy) or MRI-targeted biopsies with contralateral sampling (LRP

from 2017 onwards). All patients underwent MRI either for staging prior to focal therapy and radiotherapy, or to guide surgical technique regarding nerve sparing prostatectomy.

Outcome assessment

The primary outcome was failure-free survival (FFS), a composite endpoint of (1) need for local salvage treatment, (2) development of metastatic disease, (3) use of systemic treatment (ADT or chemotherapy) or (4) progression to a watchful waiting (WW) strategy. Secondary outcome was overall survival (OS). Prostate cancer-specific survival could not be assessed, as causality of death was often difficult to gauge. Salvage treatment was defined as any secondary treatment after EBRT, prostate bed radiotherapy for rising PSA after LRP if there were no adverse pathologic findings and >1 focal re-do or any whole-gland treatment after FT. WW was defined as no intention to treat despite biochemical recurrence after EBRT (PSA nadir+2 ng/mL) or LRP (PSA>0.2 ng/mL) or histologically proven recurrence after focal (ISUP ≥2 of any length). Prostate biopsies were mostly taken after two consecutive PSA rises and suspected recurrence on mp-MRI, with a small proportion of patients undergoing standard prostate biopsies as part of the FT protocol.

Statistical analysis

All analyses were performed using R version 3.5.0. To compare treatments, a PSW-analysis was performed using the matching weights approach[25,26]. Missing data was considered to be missing at random and was imputed upfront with single imputation (mice package). Each patient was assigned a propensity score based on age, PSA, ISUP grade, MCCL, T-stage and year of treatment (VGAM package). Patients were then weighted to correct for imbalances between treatment groups, with more weights applied to patients with equal probabilities of assignment to either treatment group. After weighting, covariates with a standardized mean difference (SMD) <0.1 were considered sufficiently balanced between treatment groups. Next, a weighted Cox regression analysis was performed to estimate the average treatment effect on hazard of failure and mortality (survey package). To visualize survival over time, PSW-adjusted Kaplan Meier survival curves were fitted, using a weighted log-rank test to detect differences in FFS and OS (survey package). All analyses were also performed in a three-way setting (EBRT versus LRP versus FT), comparing multiple pairs at once. For all three-way analyses, the significance level was set at $p<0.017$ (Bonferroni correction). For all two-way comparisons, significance was set at $p<0.05$.

RESULTS

Overall, 440 EBRT, 390 LRP and 530 FT patients were eligible. Treatment details are summarised in Table 1. Although patients may have had different types of treatment failure, the total number of failures represents each patient's first event. Local salvage treatment after EBRT consisted of focal HIFU (n=2). LRP patients received either

salvage EBRT to the prostate bed (n=72) or EBRT+ADT (n=9). Among FT patients, 17 had a second focal re-do, 29 had salvage whole-gland radiotherapy (EBRT or I-125 brachytherapy), 4 had salvage whole-gland HIFU and 21 had salvage prostatectomy. Mortality was higher in the EBRT group (5.9%) than the LRP (2.8%) and FT (1.9%) groups. Follow-up time ranged from median 41 months (EBRT) to 62 months (focal) to 77 months (LRP).

Table 1 – Treatment characteristics and outcomes

		Median (IQR) or number (%)	Missing (%)
EBRT (n=440)			
Neoadjuvant ADT		418 (95%)	5 (1.1%)
Treatment protocol	60Gy in 20# 70Gy in 35# 72Gy in 32# 74Gy in 37# Other	101 (23%) 9 (2%) 80 (18.2%) 243 (55.2%) 7 (1.6%)	
BED (Gy)		173 (173 – 180)	
EQD_2 (Gy)		74 (74 – 77)	
Treatment failure		31 (7%)	
Salvage treatment		2 (0.4%)	
Metastases		7 (1.6%)	
Systemic treatment		10 (2.3%)	
Watchful waiting		17 (3.9%)	
Death		26 (5.9%)	
Follow-up time (months)		41 (21 – 61)	
LRP (n=390)			
Neoadjuvant ADT		17 (4.4%)	2 (0.5%)
Adjuvant treatment			
EBRT		28 (7.2%)	
EBRT+ADT		12 (3.1%)	
Treatment failure		93 (23.8%)	
Salvage treatment		81 (20.8%)	
Metastases		8 (2%)	
Systemic treatment		19 (4.9%)	
Watchful waiting		2 (0.5%)	
Death		11 (2.8%)	
Follow-up time (months)		77 (45 – 102)	

Table 1 Continued

	Median (IQR) or number (%)	Missing (%)
Focal therapy (n=530)		
Neoadjuvant ADT	57 (10.8%)	
Type		
Focal HIFU	419 (79.1%)	
Focal cryotherapy	81 (15.3%)	
Focal HDR-brachytherapy	30 (5.7%)	
Treatment failure	113 (21.3%)	
Salvage treatment	71 (13.4%)	
Metastases	13 (2.4%)	
Systemic treatment	6 (1.1%)	
Watchful waiting	32 (6%)	
Death	10 (1.9%)	
Follow-up time (months)	62 (42 – 83)	

Legend: IQR: interquartile range, BED: biologically effective dose, EQD_2: equivalent dose to 2 Gy fractionation scheme, ADT: androgen deprivation therapy, EBRT: external beam radiotherapy, LRP: laparoscopic radical prostatectomy, HIFU: high intensity focused ultrasound, HDR-brachytherapy: high-dose-rate brachytherapy.

Two-way analysis

Baseline patient and tumour characteristics are displayed in the "unweighted" column in Table 2. Missing data was <2% for all variables except MCCL, which was missing in 5% (focal) and 25% (radical). Most pronounced baseline differences between groups were PSA and ISUP grade, with radical patients presenting with higher PSA than focal patients (mean 10 versus 8) and harbouring higher-grade disease (22% ISUP 3 versus 11%). After PSW, balance was achieved for all covariates (SMD <0.1). The remaining effective sample size (ESS), indicating the size of a hypothetical unweighted cohort that would yield similar precision (the larger the better), was ±380 patients per group.

Table 2 – Balance assessment before and after applying propensity score matching weights

	Unweighted			Weighted		
	Radical	Focal	SMD	Radical	Focal	SMD
Age (mean, SD)	66.4 (7.5)	65.7 (7.4)	0.105	66 (7.3)	66 (7.4)	0.001
PSA (mean, SD)	9.6 (4)	7.9 (3.8)	0.441	8.6 (3.5)	8.5 (3.9)	0.022
ISUP grade						
1 (%)	25.4%	28.5%	0.309	31.4%	31.7%	0.011
2 (%)	52.3%	60.6%		56.4%	55.8%	
3 (%)	22.3%	10.9%		12.2%	12.5%	
MCCL (mean, SD)	6.6 (3.9)	6.5 (4)	0.034	6.3 (3.8)	6.3 (3.4)	0.003
T-stage						
T1 (%)	12%	13.8%	0.051	12.7%	12.7%	0.002
T2 (%)	88%	86.2%		87.3%	87.3%	
Year (mean)	2014	2011	1.040	2011	2011	0.026
N or ESS (weighted)	830	530		385.2	376.5	

Legend: SMD=standardized mean difference, SD=standard deviation, PSA=prostate specific antigen, ISUP=International Society of Urological Pathology, MCCL=maximum cancer core length, *N*=number of patients, ESS=effective sample size.

Table 3 displays the Cox-estimated average treatment effect on hazard of failure and mortality after weighting, showing no significant differences between both groups. Figure 1 shows the PSW-adjusted Kaplan Meier survival curves estimating FFS (Figure 1a) and OS (Figure 1b). Overall, median time to treatment failure was 36 months (IQR 20-62) and median time to death was 43 months (IQR 25-66). Although there was no clear difference during the first five years of follow-up, FT patients had faster declining FFS afterwards (6-year FFS 80.3%, 95% CI 73.9-87.3 [radical] versus 72.8%, 66.8-79.8 [focal]; *p*=0.10). After radical treatment, 6-year OS was significantly lower (93.4%, 90.1-95.2 versus 97.5%, 94-99.9; *p*=0.02).

Table 3 – Estimated average treatment effect on treatment failure and overall mortality

	Propensity score weighted		
	HR (95% CI)	*SE*	*p-value*
Treatment failure			
Focal versus radical	1.29 (0.96-1.75)	0.15	0.10
Overall mortality			
Focal versus radical	0.49 (0.22-1.09)	0.41	0.08

Legend: HR=hazard ratio, 95% CI=95% confidence interval, SE=standard error.

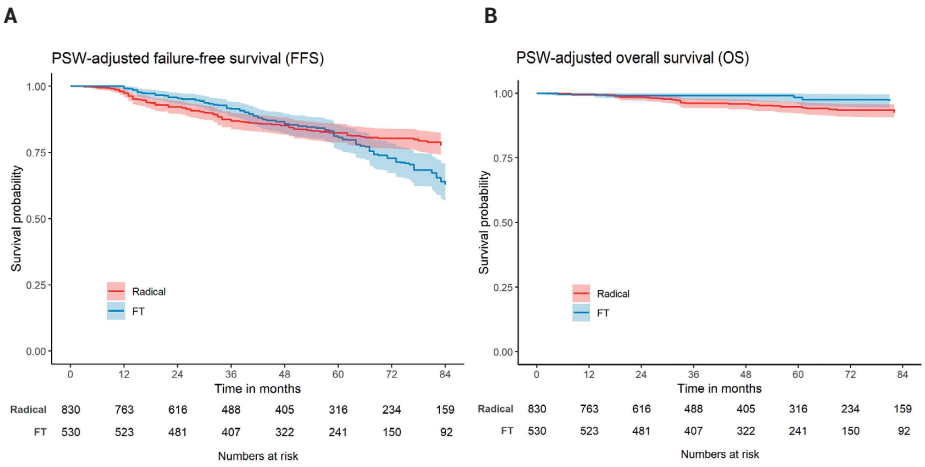

Figure 1 – two-way survival analysis, displaying propensity weighted failure-free survival and overall survival against time for patients treated with radical (EBRT or LRP) and focal therapy.

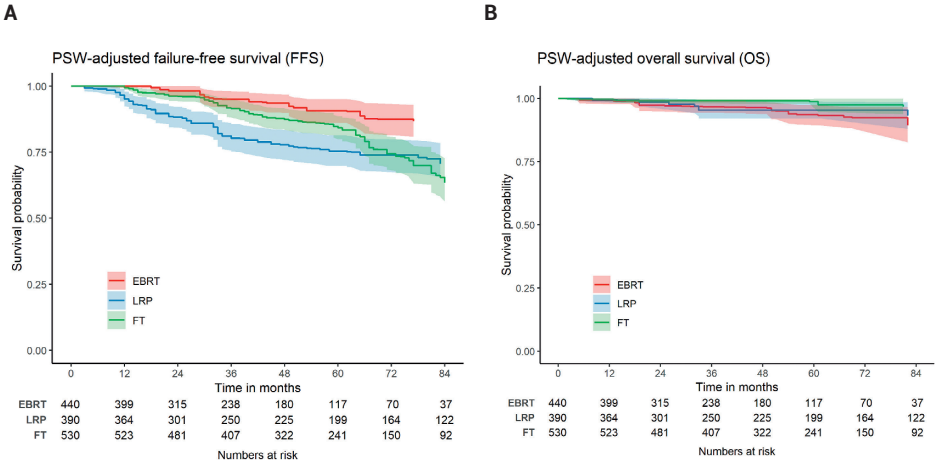

Figure 2 – three-way survival analysis, displaying propensity weighted failure-free survival and overall survival against time for patients treated with EBRT, LRP and focal therapy.

Three-way analysis

Results from the three-way PSW-analysis (EBRT versus LRP versus FT) are displayed in Supplementary Table 1 (covariate balance assessment) and Supplementary Table 2 (Cox regression estimates). Balance was achieved for most covariates except for age (mean 66.2 versus 65.3 versus 66.6, SMD 0.161).

Both FT and LRP patients had a higher risk of treatment failure than the EBRT group (both $p<0.001$), but there was no statistically significant difference between FT and LRP ($p=0.69$). In terms of overall mortality, the only significant difference was between focal and EBRT patients, with a lower risk of death after FT (HR 0.29, 95% CI 0.11-0.76; $p=0.008$).

Figure 2 shows the PSW-adjusted Kaplan Meier survival curves estimating FFS (Figure 2a) and OS (Figure 2b) for the three separate treatment groups. After six years, estimated FFS was 87.4% (95% CI 79.9-93.9) in the EBRT group, 73.9% (68-80.9) in the LRP group and 74.4% (68.4-81.5) in the focal group (p<0.001). Estimated 6-year OS was 92.3% (83.5-95.8), 95.3% (88.9-98.3) and 97.5% (94.9-100), respectively (p=0.05).

DISCUSSION

Within the limitations of a cohort-based analysis, our study provides comparative effectiveness data on cancer control showing no clear difference between FT and radical therapies after 6 years follow-up. Due to the observational nature of the data, systematic baseline differences between groups may affect treatment outcomes. To minimize this effect, we used PSW to equalise the distribution of measured baseline covariates.

The first assumption of a PSW-analysis is that the set of observed pre-treatment covariates is sufficiently rich such that the propensity score is constructed without missing important unmeasured or unknown confounders[27]. To this end, this study had limitations. We had no data of important characteristics such as PSA doubling time and a robust measurement of tumour volume. Instead we used MCCL, which appears to be an independent predictor of cancer volume[28]. We also used simplified T-stage categories (stage T1 or T2) due to a large proportion of missing data (40-65%) on sub-classifications of T2. Furthermore, we had no data on comorbidity profiles or socioeconomic status. EBRT patients were more likely to have comorbidities, considering that they were (on average) 5-8 years older and had higher mortality rates than LRP or FT patients. Although we did have data on history of neo-adjuvant ADT, this was not used for construction of propensity scores because the difference between groups (96% before EBRT versus 4% and 11% before LRP and FT) was too large to achieve sufficient balance. These differences in use of neoadjuvant ADT are likely to account for the FFS rates favouring EBRT, considering that residual effects of LHRH agonist use is known to continue in approximately 25% of men for many months after cessation[29,30].

The second assumption is that each patient has a probability of receiving each treatment and that there are no values of pre-treatment variables that could occur only among patients receiving one of the treatments[27]. We therefore chose inclusion criteria (PSA <20 ng/mL, ≤ISUP 3 and T-stage ≤T2c) that represent patients who could have been eligible for all treatments. Baseline variables that were used to construct propensity scores (age, PSA, ISUP grade, MCCL, T-stage and year of treatment) generally have no values that are exclusively seen in one of the treatment groups.

The demonstrated FFS advantage for patients treated with EBRT was most surprising. From randomized comparative trials, there is evidence that at least prostatectomy and radiotherapy are comparable in terms of oncologic outcomes[3,31] . Although these trials were conducted between 1989-2009 and both treatment techniques have markedly improved since, updated results from recent observational studies have only confirmed oncologic equivalence[32]. There are several concerns potentially causing biased results

in favour of EBRT in our study. First, EBRT data was collected in a retrospective manner, while focal and LRP data were collected prospectively. Second, unknown or unmeasured confounders may have distorted results. Although EBRT patients had higher PSA and higher-grade disease, they may have had smaller tumours or longer PSA doubling time, potentially indicating less aggressive disease. Third, as discussed above, the widespread use of neo-adjuvant ADT among EBRT patients may have substantially improved FFS within the available medium length follow-up.

For the focal group, estimated FFS seemed to decline faster beyond six years follow-up in both the three-way and two-way Kaplan Meier curves. Although this estimation is limited by smaller numbers of patients at risk at later time points, this may reflect emergence of residual cancer cells in the treated area or de novo lesions emerging in untreated tissue. This requires further research.

We selected patients with NCCN low- to intermediate-risk disease, assuming eligibility for both radical treatment and FT. Besides active treatment, current guidelines however recommend offering active surveillance (AS) to patients with (very) low-risk disease[33-35]. Following general AS eligibility criteria (Gleason score ≤6, clinical T1c or T2a/b and PSA ≤10 ng/mL, not taking into account PSA density or number of positive cores)[36], 222/1360 (16.3%) of patients in our study could have been offered AS. This is important because it is generally agreed that FT should only be considered in men who are likely to benefit from active treatment. Nonetheless, the only randomized focal study available compared focal ablation (using vascular targeted photodynamic therapy [VTP]) to AS, randomizing 413 men. At four years, they concluded that conversion to radical treatment was less likely in the focal group (24% vs 53%), lowering the risk of treatment-related morbidity[37]. There has been criticism of this study recruiting men with very low risk disease and not incorporating a confirmatory MRI targeted biopsy when a lesion was seen prior to randomisation.

As our primary outcome we studied the composite endpoint treatment failure, consisting of salvage treatment, metastatic disease, systemic treatment or progression to WW. Here, the frequently used endpoint biochemical progression-free survival is of limited value due to the lack of a biochemical failure definition after FT[38]. Although OS is the most valid and reliable endpoint, treatment failure serves as a clinically meaningful surrogate endpoint within the time frame of this study. We considered prostate bed EBRT after LRP as adjuvant treatment (i.e. part of primary treatment) when given as a consequence of rising PSA and positive surgical margins. Before LRP, patients are explained that surgery entails the risk of incomplete resection, which then requires adjuvant radiotherapy. Therefore, we did not consider such adjuvant treatment as failure. In the same setting, we allowed one focal re-do as part of initial focal treatment. WW was added to the treatment failure definition to account for the fact that EBRT patients were older and more likely to have comorbidities, potentially preventing them from undergoing salvage treatment upon recurrence.

Our study did not have comparative toxicity or patient-reported outcome data. Within randomized trials comparing radiotherapy and prostatectomy, no discernible differ-

ences were found in patient-reported quality of life, although the variation of reported symptoms differed[7,39]. With respect to FT, there is evidence from observational retrospective and prospective studies on different sources of ablative energy, showing that it has a significantly lower impact on genitourinary function[11].

The effectiveness of FT is currently being investigated within randomized clinical trials (RCT). A first feasibility study in the UK (PART) has completed recruitment of 80 patients with either unilateral clinically significant (ISUP 2-3 or >4mm grade 1) intermediate-risk prostate cancer or dominant unilateral cancer with small contralateral low-risk disease (ISRCTN 99760303). They concluded that it is feasible to randomize patients between prostatectomy and focal HIFU, with an achieved randomization rate of 50%, although the recruitment period had to be extended and the target lowered from 100 to 80. Compliance in the radical prostatectomy arm was also just under 80%[18]. A follow-up RCT is expected, aiming to randomize 800 patients between radical treatment (prostatectomy, EBRT or LDR-brachytherapy) and focal VTP. Another UK-based RCT (CHRONOS) is currently testing feasibility of recruiting patients to either an RCT of focal (cryotherapy or HIFU) versus radical therapy (EBRT or low-dose-rate brachytherapy or prostatectomy) or a separate multi-arm multi-stage RCT comparing focal alone to focal with neoadjuvant finasteride or bicalutamide (ISRCTN 17796995).

In conclusion, within the confines and limitations of residual confounding that might be present, we found no clinically relevant difference in 6-year treatment failure-free survival between conventional radical treatments and FT. Awaiting longer follow-up data from cohorts and initial results from RCTs, this study offers an insight into the potential of FT, potentially supporting its use in select patients with localized prostate cancer.

Supplementary Table 1 – Three-way balance assessment before and after applying propensity score matching weights

	Unweighted				Weighted			
	EBRT	LRP	FT	SMD	EBRT	LRP	FT	SMD
Age (mean ± SD)	70.4 ± 6.7	62 ± 5.7	65.7 ± 7.4	0.857	66.2 ± 6.6	65.3 ± 4.2	66.6 ± 6.2	0.161
PSA (mean ± SD)	10.3 ± 3.9	8.9 ± 3.9	7.9 ± 3.8	0.418	9.3 ± 3.7	9 ± 3.6	9.5 ± 4.1	0.098
ISUP grade								
1 (%)	15.2%	36.7%	28.5%	0.448	23.1%	21.4%	25.5%	0.083
2 (%)	54.1%	50.2%	60.6%		57.8%	60%	58.7%	
3 (%)	30.7%	13.1%	10.9%		19.1%	18.6%	15.8%	
MCCL (mean ± SD)	6.7 ± 3.9	6.5 ± 3.9	6.5 ± 4	0.033	6.7 ± 4.1	6.4 ± 3.8	6.3 ± 3.3	0.054
T-stage								
T1 (%)	13.2%	10.8%	13.8%	0.061	11.8%	13.8%	13.3%	0.038
T2 (%)	86.8%	89.2%	86.2%		88.2%	86.2%	86.7%	
Year (mean)	2015	2012	2011	0.620	2012	2012	2014	0.098
N or ESS (weighted)	440	390	530		165.8	171.1	164.4	

Legend: LRP=laparoscopic radical prostatectomy, EBRT=external beam radiotherapy, FT=focal therapy, SMD=standardized mean difference, SD=standard deviation, PSA=prostate specific antigen, ISUP= International Society of Urological Pathology, MCCL=maximum cancer core length, *N*=number of patients, ESS=effective sample size.

Supplementary Table 2 – Three-way estimated average treatment effect on treatment failure and overall mortality

	Propensity score weighted		
	HR (95% CI)	*SE*	*p-value*
Treatment failure			
LRP versus EBRT	2.41 (1.44-4.05)	0.26	**0.0005**
FT versus EBRT	2.24 (1.4-3.64)	0.25	**0.0002**
FT versus LRP	0.93 (0.65-1.33)	0.18	0.69
Overall mortality			
LRP versus EBRT	0.54 (0.23-1.29)	0.44	0.17
FT versus EBRT	0.29 (0.11-0.76)	0.48	**0.008**
FT versus LRP	0.54 (0.19-1.52)	0.53	0.24

Legend: HR=hazard ratio, 95% CI=95% confidence interval, SE=standard error, LRP=laparoscopic radical prostatectomy, EBRT=external beam radiotherapy, FT=focal therapy.

REFERENCES

1. Tamada S, Ninomiya N, Kitamoto K, et al. Comparative effectiveness of radical prostatectomy and curative radiotherapy in localized prostate cancer: long-term follow-up. *Journal of radiation research.* 2017;58(4):552-558.
2. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU international.* 2012;109 Suppl 1:22-29.
3. 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(15):1415-1424.
4. Sooriakumaran P, Nyberg T, Akre O, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. *Bmj.* 2014;348:g1502.
5. Taguchi S, Fukuhara H, Shiraishi K, et al. Radical Prostatectomy versus External Beam Radiotherapy for cT1-4N0M0 Prostate Cancer: Comparison of Patient Outcomes Including Mortality. *PloS one.* 2015;10(10):e0141123.
6. Vernooij RWM, Cremers R, Jansen H, et al. Urinary incontinence and erectile dysfunction in patients with localized or locally advanced prostate cancer: A nationwide observational study. *Urol Oncol.* 2020.
7. Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med.* 2016;375(15):1425-1437.
8. Lardas M, Liew M, van den Bergh RC, et al. Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review. *Eur Urol.* 2017;72(6):869-885.
9. Lam TBL, MacLennan S, Willemse PM, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). *Eur Urol.* 2019;76(6):790-813.
10. McClure TD, Margolis DJ, Hu JC. Partial gland ablation in the management of prostate cancer: a review. *Current opinion in urology.* 2017;27(2):156-160.
11. Valerio M, Cerantola Y, Eggener SE, et al. New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. *Eur Urol.* 2017;71(1):17-34.
12. Stabile A, Orczyk C, Hosking-Jervis F, et al. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. *BJU international.* 2019;124(3):431-440.
13. Guillaumier S, Peters M, Arya M, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. *Eur Urol.* 2018;74(4):422-429.
14. Shah TT, Peters M, Eldred-Evans D, et al. Early-Medium-Term Outcomes of Primary Focal Cryotherapy to Treat Non-metastatic Clinically Significant Prostate Cancer from a Prospective Multicentre Registry. *Eur Urol.* 2019;76(1):98-105.
15. Barqawi A, Pessoa RR, Al-Musawi M, MacDermott T, O'Donnell CI. The Impact of Performing a 3D Mapping Biopsy Prior to Primary Cryotherapy for the Treatment of Prostate Cancer. *Urology.* 2020;144:171-176.
16. Tourinho-Barbosa RR, Sanchez-Salas R, Claros OR, et al. Focal Therapy for Localized Prostate Cancer with Either High Intensity Focused Ultrasound or Cryoablation: A Single Institution Experience. *The Journal of urology.* 2020;203(2):320-330.

17. Oishi M, Gill IS, Tafuri A, et al. Hemigland Cryoablation of Localized Low, Intermediate and High Risk Prostate Cancer: Oncologic and Functional Outcomes at 5 Years. *The Journal of urology.* 2019;202(6):1188-1198.

18. Hamdy FC, Elliott D, le Conte S, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. *Health technology assessment.* 2018;22(52):1-96.

19. Ahmed HU, Berge V, Bottomley D, et al. Can we deliver randomized trials of focal therapy in prostate cancer? *Nature reviews Clinical oncology.* 2014;11(8):482-491.

20. Reddy D, Shah TT, Dudderidge T, et al. Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer (IP4-CHRONOS): A prospective, multi-centre therapeutic phase II parallel Randomised Control Trial. *Contemporary clinical trials.* 2020:105999.

21. Shah TT, Reddy D, Peters M, et al. Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score-matched study. *Prostate cancer and prostatic diseases.* 2021.

22. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med.* 2007;4(10):e297.

23. Diaz A, Roach M, 3rd, Marquez C, et al. Indications for and the significance of seminal vesicle irradiation during 3D conformal radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 1994;30(2):323-329.

24. Peters M, van Son MJ, Moerland MA, et al. MRI-Guided Ultrafocal HDR Brachytherapy for Localized Prostate Cancer: Median 4-Year Results of a feasibility study. *Int J Radiat Oncol Biol Phys.* 2019;104(5):1045-1053.

25. Li L, Greene T. A weighting analogue to pair matching in propensity score analysis. *Int J Biostat.* 2013;9(2):215-234.

26. Yoshida K, Hernandez-Diaz S, Solomon DH, et al. Matching Weights to Simultaneously Compare Three Treatment Groups: Comparison to Three-way Matching. *Epidemiology.* 2017;28(3):387-395.

27. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res.* 2011;46(3):399-424.

28. Simopoulos DN, Sisk AE, Jr., Priester A, et al. Cancer core length from targeted biopsy: an index of prostate cancer volume and pathological stage. *BJU international.* 2019;124(2):275-281.

29. Nascimento B, Miranda EP, Jenkins LC, Benfante N, Schofield EA, Mulhall JP. Testosterone Recovery Profiles After Cessation of Androgen Deprivation Therapy for Prostate Cancer. *The journal of sexual medicine.* 2019;16(6):872-879.

30. Nam W, Choi SY, Yoo SJ, et al. Factors associated with testosterone recovery after androgen deprivation therapy in patients with prostate cancer. *Investig Clin Urol.* 2018;59(1):18-24.

31. Akakura K, Suzuki H, Ichikawa T, et al. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months. *Japanese journal of clinical oncology.* 2006;36(12):789-793.

32. Taguchi S, Shiraishi K, Fukuhara H. Updated evidence on oncological outcomes of surgery versus external beam radiotherapy for localized prostate cancer. *Japanese journal of clinical oncology.* 2020;50(9):963-969.

33. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2019;17(5):479-505.

34. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol.* 2017;71(4):618-629.

35. Dasgupta P, Davis J, Hughes S. NICE guidelines on prostate cancer 2019. *BJU international.* 2019;124(1):1.

36. Komisarenko M, Martin LJ, Finelli A. Active surveillance review: contemporary selection criteria, follow-up, compliance and outcomes. *Translational andrology and urology.* 2018;7(2):243-255.

37. Gill IS, Azzouzi AR, Emberton M, et al. Randomized Trial of Partial Gland Ablation with Vascular Targeted Phototherapy versus Active Surveillance for Low Risk Prostate Cancer: Extended Follow-up and Analyses of Effectiveness. *The Journal of urology.* 2018;200(4):786-793.

38. Tay KJ, Amin MB, Ghai S, et al. Surveillance after prostate focal therapy. *World journal of urology.* 2019;37(3):397-407.

39. Lennernas B, Majumder K, Damber JE, et al. Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes. *Acta oncologica (Stockholm, Sweden).* 2015;54(6):875-881.

CHAPTER 3

MRI-guided ultrafocal HDR-brachytherapy for localised prostate cancer: median 4 year results of a feasibility study

Authors: Max Peters, Marieke J. van Son, Marinus A. Moerland, Linda G.W. Kerkmeijer, Wietse S.C. Eppinga, Richard P. Meijer, Jan J.W. Lagendijk, Taimur T. Shah, Hashim U. Ahmed, Jochem R.N. van der Voort van Zyp
Joint first authors: M. Peters and M.J. van Son

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS

ABSTRACT

Introduction

For the treatment of localised prostate cancer, focal therapy has the potential to cure with less side-effects than traditional whole-gland treatments. We report an update of toxicity, quality of life (QoL) and tumour control of our MRI-guided ultrafocal high-dose-rate (HDR) brachytherapy cohort.

Materials and methods

Disease status was evaluated by systematic biopsies and 3T multiparametric MRI. The brachytherapy implant procedure under fused transrectal ultrasound/MRI guidance was followed by 1.5T MRI for contour adjustments and catheter position verification. In a single dose, 19Gy was delivered to the tumour with a margin of 5 mm. Genitourinary (GU) toxicity, gastro-intestinal (GI) toxicity and erectile dysfunction (ED) were graded with the CTCAE 4.0. QoL was measured with RAND-36, EORTC QLQ-C30 and EORTC QLQ-PR25. IPSS and IIEF scores were obtained. PSA was monitored, with biochemical recurrence defined as nadir+2ng/ml (Phoenix).

Results

Thirty patients with NCCN low(13%) to intermediate(87%) risk prostate cancer were treated between May 2013 and April 2016. Median follow-up was 4 years. Median age was 71 years (interquartile range 68-73), median iPSA 7.3 ng/ml (5.2-8.1). Maximum Gleason score was 4+3=7 (in 2 patients). All tumours were radiological (MRI) stage T2. No grade >2 GU or >1 GI toxicity occurred. IPSS only deteriorated temporarily. Pre-treatment IIEF mild ED deteriorated to moderate/severe ED in 50% of patients.. Long-term clinically relevant QoL deterioration was seen in sexual activity and tiredness, while emotional and cognitive functioning improved. At 4 years, biochemical disease-free survival (BDFS) was 70% (95% CI 52-93%), metastases-free survival 93% (85-100%) and overall survival 100%. Of intraprostatic recurrences, 7/9 were out-of-field.

Conclusion

Ultrafocal HDR-brachytherapy conveys minimal GU/GI toxicity and has a marginal effect on QoL. An early decline in erectile function was seen. Tumour control outcomes are poor (BDFS 70% [52-93%] at 4 years), most likely as a result of poor patient selection.

INTRODUCTION

Due to PSA-screening and diagnostic advancements prostate cancer has undergone a stage migration to more localised disease(1). Traditionally, whole-gland radical prostatectomy and radiotherapy are standard of care. However, neither showed an overall survival advantage when compared to active monitoring in the ProtecT trial, while side-effects were frequent(2,3). Even though most patients in this trial had low-risk disease potentially eligible for active surveillance, approximately 20% of patients represented an intermediate-risk subgroup who could benefit from curative treatment(2).

Focal therapy (FT) could offer a suitable alternative for men with clinically significant prostate cancer in terms of cancer control, while decreasing genitourinary (GU) and gastro-intestinal (GI) toxicity, and erectile dysfunction (ED)(4). The largest cohorts of FT after a median follow-up of 5 years reported biochemical disease-free survival (BDFS) rates of 88-92%(5,6), with favourable toxicity profiles(4,6).

Recent advancements in magnetic resonance imaging (MRI) and MRI-guidance during treatment have made an ultrafocal approach possible, as opposed to segmental ablation. We have previously described preliminary results of our prospective feasibility study of MRI-guided ultrafocal high-dose-rate (HDR)-brachytherapy at median 2 years follow-up(7). In the current paper, we report updated results regarding toxicity, quality of life (QoL) and tumour control at 4 years median follow-up.

MATERIALS AND METHODS

Between May 2013 and April 2016, 30 consecutive patients underwent MRI-guided ultrafocal HDR-brachytherapy within a feasibility study. The study was approved by the Institutional Review Board (IRB) of the UMC Utrecht and written informed consent was obtained from all patients. Patient selection criteria, treatment procedures and follow-up assessment have been described previously(7,8). They are briefly discussed below.

Patient selection criteria

Patients were eligible if they had the following clinical characteristics: 1. Age >65 years, 2. Karnofsky score ≥70, 3. T-stage ≤T2c, 4. Gleason sum score ≤7, 5. PSA <10 ng/mL, and 6. IPSS <15.

Diagnostic procedures and treatment

Imaging of the intraprostatic lesion was performed using 3T multiparametric (mp)-MRI, consisting of T2-weighted, diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) sequences. PET-scans were not part of the diagnostic work-up. Tumour lesions were pathologically verified using systematic biopsies. Radiological concordance with positive biopsy location was required. All MRI-sequences were used for delineations of the gross tumour volume (GTV), prostate and organs at risk (urethra, bladder, rectum). An intraprostatic margin of 5mm was applied around the GTV to

indicate the clinical target volume (CTV), allowing coverage of microscopic spread(9). Using a treatment planning system (Oncentra Prostate; Elekta Nucletron,Veenendaal, the Netherlands), a pre-treatment plan was constructed with the following goals and constraints: 1. CTV D95%≥19Gy, or minimal CTV D90%≥17Gy, 2. Bladder and rectum D1cc<12Gy and 3. urethra D10%<21Gy(10). Intra-operatively, live transrectal ultrasound (TRUS)-images were rigidly fused with the pre-treatment MR-delineations. MR-compatible self-anchoring catheters were inserted in and around the CTV transperineally. After insertion, an intra-operative MRI was performed for catheter reconstruction and adaptation of delineations to account for anatomical changes, after which the treatment plan was updated. A final MRI was performed for position verification, after which irradiation was given.

Outcome assessment

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used for GU, GI and ED toxicity assessment. QoL was measured using the RAND-36, EORTC-QLQ-C30 and PR-25 questionnaires(11-14). In addition, International Prostate Symptoms Score (IPSS) and the International Index of Erectile Function (IIEF) were assessed. Serial PSA measurements were performed at 1, 3, 6, 9 and 12 months, subsequently every 6 months until 24 months and yearly afterwards until 10 years. The nadir+2 ng/ml (Phoenix) definition was used to assess biochemical failure (BF), which was an indication for a PET/CT-scan. If localised intraprostatic recurrence was found without metastatic disease, an mp-MRI was performed. Tumour control and toxicity risk were carefully weighed to decide whether focal or whole-gland salvage treatment should be performed. If focal salvage treatment was contemplated, MRI-guided biopsy confirmation was performed.

Statistical analyses

Continuous variables are described as medians with interquartile ranges (IQR) and categorical variables as absolute numbers with percentages. Differences in continuous variables were tested with the Wilcoxon signed rank test. To correct for multiple testing, statistical significance was pragmatically set at $p<0.001$. Median QoL-score differences of ≥10 points were deemed clinically relevant, apart from statistical considerations(14). BDFS, metastases-free survival (MFS) and overall survival (OS) were assessed using the Kaplan-Meier method. An explorative univariable Cox-regression analysis was performed for the first BF event including the variables age (before treatment), American Joint Committee on Cancer (AJCC) grade group, T-stage, PSA, pre-treatment PSA doubling time (PSADT; as calculated with Memorial Sloan Kettering Cancer Center online tool), AJCC prognostic stage group and PSA nadir post-treatment. IBM SPSS v23.0 was used for descriptives and R v3.5.1 for graphs and survival analyses (https://www.R-project.org/, 'survminer', 'rms', 'ggplot2' packages).

RESULTS

Baseline characteristics

Median age was 71 years (IQR 68-73). MRI prostatic volume was 40cc (32.3-41.7). Median PSA was 7.3 ng/ml (5.2-8.1) and median PSADT was 4.7 years (2.4-10.6). Radiological T-stage was T2a in 13 (43.3%), T2b in 4 (13.3%) and T2c in 13 (43.3%) patients. Gleason score was 3+3=6 in 16 (53.3%), 3+4=7 in 12 (40%) and 4+3=7 in 2 (6.7%) patients. Other baseline characteristics are shown in table 1.

Table 1 – Baseline and treatment characteristics of the focal HDR-brachytherapy cohort

	Median / n	IQR / %	Unknown (%)
Pre-treatment characteristics			
Age(years)	71	68-73	0 (0%)
Biopsy technique			
TRUS-guided	13	43.3%	16 (53.3%)
MRI-guided	1	3.3%	
Tumour location			
Base	2	6.7%	0 (0%)
Midgland	13	43.3%	
Apex	8	26.7%	
Combination	7	23.3%	
Total number of cores	10	8-11	0 (0%)
Number of positive cores	3	2-4	0 (0%)
MRI volume prostate(cc)	40	32.3-41.7	0 (0%)
Gleason score			
3+3=6	16	53.3%	0 (0%)
3+4=7	12	40%	
4+3=7	2	6.7%	
Clinical T-stage			
T1c	16	53.3%	0 (0%)
T2a	13	43.3%	
T2c	1	3.3%	
Radiological T-stage			
T2a	13	43.3%	0 (0%)
T2b	4	13.3%	
T2c	13	43.3%	
AJCC prognostic stage group			
Stage I	15	50%	0 (0%)
Stage IIA	1	3.3%	
Stage IIB	12	40%	
Stage IIC	2	6.7%	
iPSA (ng/ml)	7.3	5.2-8.1	0 (0%)
PSADT (months)	56.8	28.8-126.7	7 (23.3%)

Table 1 Continued

	Median / n	IQR / %	Unknown (%)
Treatment characteristics			
Number of catheters	14	12-15	0 (0%)
GTV(cc)	3.3	2.1-4.9	0 (0%)
CTV(cc)	20.8	12.6-25.0	0 (0%)
D90 CTV (Gy)	20.8	19.4-22.6	0 (0%)
D95 CTV (Gy)	19.1	17.9-20.5	0 (0%)
D10 urethra (Gy)	17.0	13.1-18.6	0 (0%)
D1cc rectum (Gy)	11.5	8.2-12.3	0 (0%)
D1cc bladder (Gy)	6.5	5.0-10.1	0 (0%)

Abbreviations: HDR=high-dose-rate; IQR=interquartile range; TRUS=transrectal ultrasound; MRI=magnetic resonance imaging; AJCC=American Joint Committee on Cancer; iPSA=initial prostate specific antigen; PSADT=PSA doubling time.

Treatment characteristics and dosimetry

A median of 14 brachytherapy catheters were implanted. The GTV had a median volume of 3.3cc (2.1-4.9), which corresponded to a median CTV volume of 20.8cc (12.6-25). The median CTV D95% was 19.1Gy (17.9-20.5): in 14 patients, D95% was below 19Gy. Median CTV D90% was 20.8Gy (19.4-22.6), with 2 patients having a D90% below 17Gy. Reasons for suboptimal implant dosimetry were mainly transgression of organs at risk constraints, due to tumour position or size of the tumour volume. The urethral constraint was met in all patients. The rectal constraint was slightly exceeded in 10 patients (up to a maximum of 12.8Gy) and the bladder constraint in 2 patients (up to a maximum of 12.4Gy).

Toxicity

GU, GI toxicity and ED scores are depicted in figure 1 and table 2. In our previous report, we described one grade 3 GU toxicity: acute prostate haemorrhage resulting in gross haematuria and hospital admittance due to improper post-operative removal of an unfolded catheter. However, since this was not a direct side-effect of the radiation treatment itself, we consider this a perioperative complication in the current report. New grade 2 GU toxicity developed in 4 patients, including urinary frequency (n=3) and cystitis (n=1), all successfully treated with temporary medication. No grade 2 or higher GI toxicity occurred. New grade 2 ED after treatment was observed in 6 patients, new grade 3 ED occurred in 12 patients.

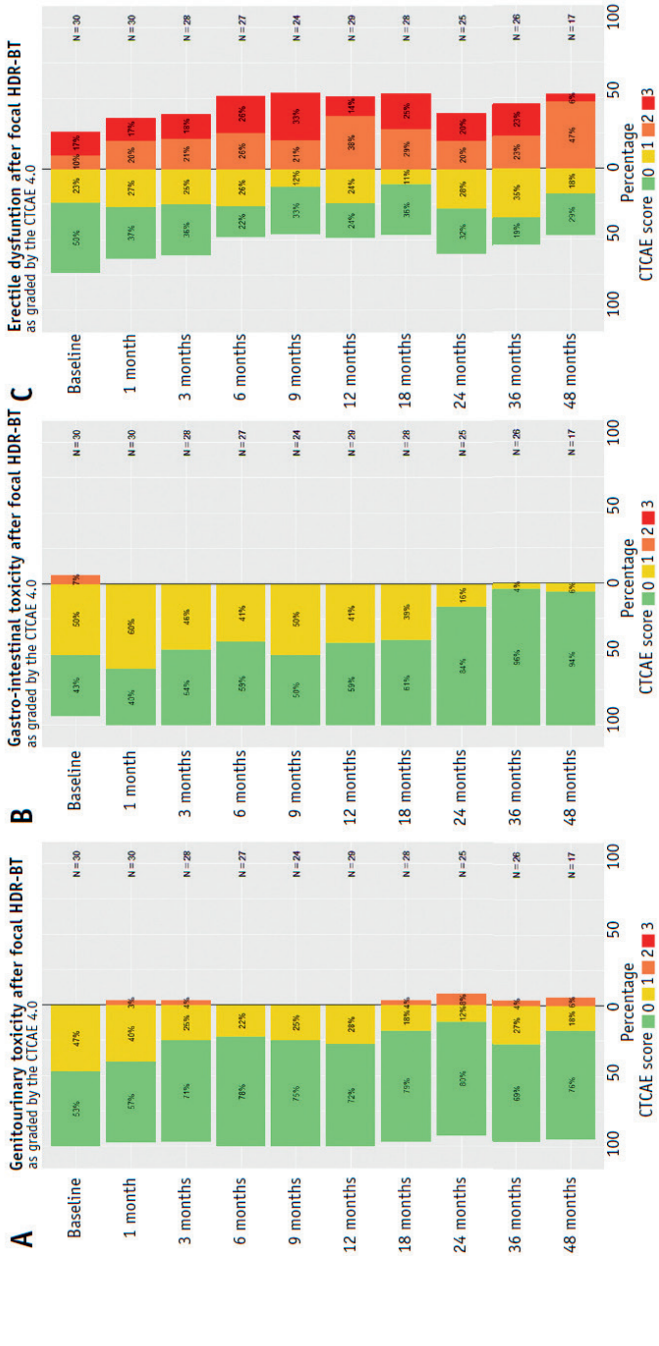

Figure 1 – Genitourinary (A) and gastrointestinal (B) toxicity and erectile dysfunction (C).

Table 2 – Toxicity

	Baseline N=30	1 mo N=30	3 mo N=28	6 mo N=27	9 mo N=24	12 mo N=29	18 mo N=28	24 mo N=25	36 mo N=26	48 mo N=17
GU										
Grade 1	14	12	7	6	6	8	5	3	7	3
Grade 2	0	1	1	0	0	0	1	2	1	1
Grade 3	0	0	0	0	0	0	0	0	0	0
GI										
Grade 1	15	18	13	11	12	12	11	4	1	1
Grade 2	2	2	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0
ED										
Grade 1	7	8	7	7	3	7	3	7	9	3
Grade 2	3	6	6	7	5	11	8	5	6	8
Grade 3	5	5	5	7	8	4	7	5	6	1

Abbreviations: GU=genitourinary; GI-gastro-intestinal; ED=erectile dysfunction, mo=months

IPSS showed the largest increase in the first month, from median score 5 (IQR 4-7) to 8 (6-13), corresponding to progression from mild symptoms to moderate symptoms.. Median IIEF score decreased from 19 (5-22) at baseline to 6 at 6 months, (significant at the 0.001 level), and remained at a lower level until 48 months follow-up. This corresponds to a clinical decrease from mild to moderate/severe ED. IPSS and IIEF are depicted in figure 2.

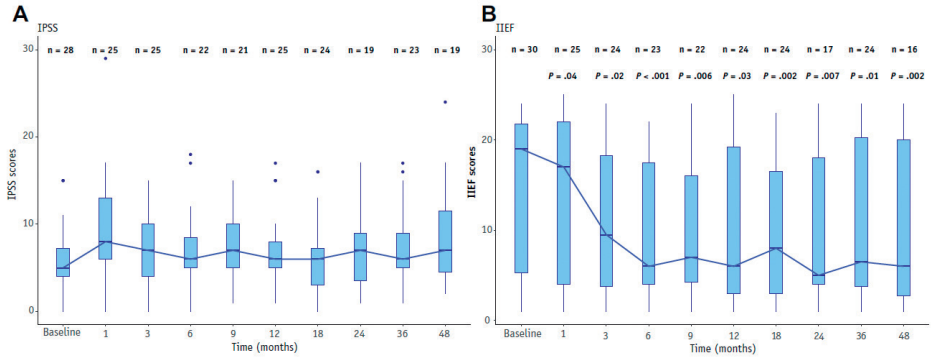

Figure 2 – International Prostate Symptom Score (A) and International Index of Erectile Function (B) scores. Medians with interquartile ranges are depicted.

QoL

Supplementary figures 1-3 (available online at https://doi.org/10.1016/j.ijrobp.2019.03.032) give an overview of RAND-36, EORTC QLQ-C30 and PR-25 questionnaire scores. Within the RAND-36 domains, clinically relevant decrease was seen in social functioning (>10 points after 1 and 24 months), vitality (10 points after 9 months) and pain (>10 points after 1 month). All scores returned to baseline value. Mental and general health showed no increase >10 points, contrary to our previous report(7). No significant differences at the 0.001 level were seen.

The QLQ-C30 showed clinically relevant deterioration in the domains for tiredness (>10 points after 48 months) and sleeping disturbances (only at 24 months). On the contrary, improvement was seen in the domains for emotional functioning (>10 points after 48 months) and cognitive functioning (>10 points after 36 months). There were no statistically significant differences from baseline.

Within the PR-25, urinary symptoms increased from 10 at baseline to 17 in the first month, after which scores recovered to baseline. Bowel symptoms remained stable at 0. Treatment-related symptoms went from 0 at baseline to a score of 6 at all follow-up time points. A clinically relevant decrease of >10 points was seen in sexual activity at all follow-up times. Sexual functioning, on the contrary, remained relatively stable. Again, there were no statistically significant differences.

Tumour control

Ten patients experienced BF, with local prostatic recurrence in 9 patients on PET/CT (18F-Choline [n=1] and later 68Ga-prostate specific membrane antigen [PSMA] [n=9], both in combination with mp-MRI). Of all intraprostatic recurrences, 7/9 were out-of-field lesions with respect to the primary tumour. Comparing the original CTVs of the primary HDR-procedure to the recurrent lesions on PSMA PET-CT, most (5/7) were located on the contralateral prostate lobe. Two patients had a recurrence in the same lobe, but with a distinct distance between primary and recurrent lesion sites.

Three patients had local and metastatic disease. Two were referred to their urologist for deferred ADT. One patient underwent stereotactic body radiotherapy (SBRT, 1x18Gy) twice to different solitary bone metastases, before receiving whole-gland salvage Iodine-125 brachytherapy. One year later, PSA-levels rose again after which ADT was initiated.

Of 6 patients with solitary localized recurrence, 4 received local salvage: either ultrafocal salvage HDR-brachytherapy (n=2) or whole-gland salvage Iodine-125 brachytherapy (n=2). Until now, PSA-levels remain low in all re-treated patients between 1- and 3-years follow-up. The remaining 2 patients requested an active surveillance strategy.

One patient with BF presented with a solitary metastasis in L4 without local prostatic recurrence, for which he received SBRT (1x18Gy). Unfortunately, there was no PSA-response and he subsequently received ADT.

The 4-year BDFS rate was 70% (95% CI 52-93%). MFS was 93% (85-100%) and OS was 100% at 4 years (Figure 3). An explorative Cox-regression analysis only showed a significant hazard ratio (HR) for age: 1.27 (95% CI 1.01-1.59; p=0.04), meaning higher age conveyed higher risk of BF in these patients.

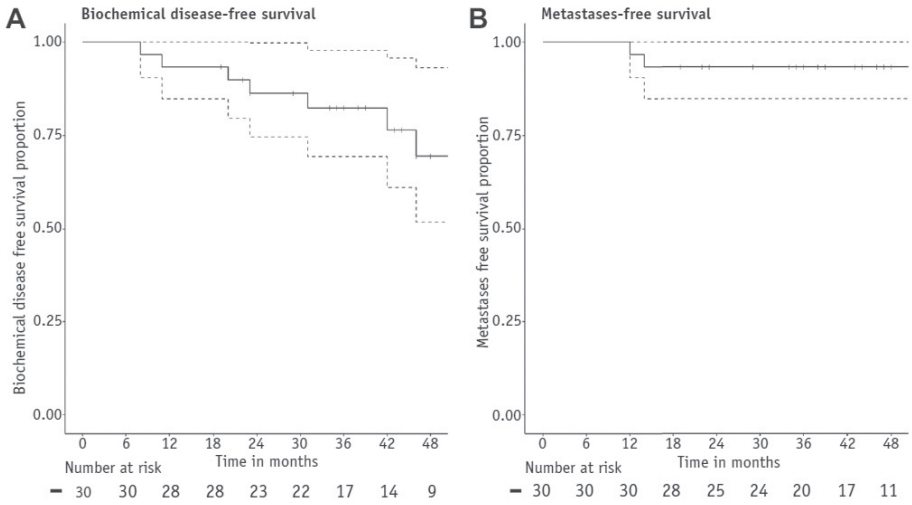

Figure 3 – Kaplan-Meier analysis for biochemical disease-free survival (A) and metastases-free survival (B).

DISCUSSION

The main goal of ultrafocal ablation of localised prostate cancer is to reduce treatment-related side-effects and thereby maintain QoL while not compromising tumour control. The medium-term results of this study show that it is feasible to treat with limited toxicity and minimal impact on QoL. However, 70% BDFS at 4 years is an unfavourable tumour control outcome, which needs comprehensive evaluation to assess the position of ultrafocal HDR-brachytherapy in the primary prostate cancer setting.

Toxicity and QoL outcomes were mostly in line with our previous report, with no treatment-related severe GU or GI toxicity and a minor impact on patient-reported QoL. A distinct result was a clear downward trend in erectile function, as reflected by deteriorating IIEF scores and CTCAE-graded ED scores, with more patients experiencing grade 2-3 ED during follow-up compared to the previous analysis. The IIEF classifies ED into five categories: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25). Defining potency as satisfactory capacity of having an erection, this may involve submaximal rigidity or capability to sustain the erection, corresponding to IIEF scores >17 as a reasonable cut-off point. Within our study group, 16 patients had pre-treatment IIEF score >17 (initial potency), of which 8 had IIEF scores below 17 at last follow-up (50% new onset impotence).

The decrease of erectile function might in part be attributable to radiation sensitivity of the neurovascular bundles, although the relation between neurovascular bundle dose and erectile dysfunction remains hypothetical(15). With 43% of our patients having bilateral (T2c) disease, this potentially could have led to a higher dose burden on the neurovascular bundles. However, we do not have dosimetry data and there is a lack of established delineation guidelines for the neurovascular bundles(16). Moreover, part of the deterioration could be explained by the natural course of developing ED with increasing age.

Further evaluation of QoL showed only transient deterioration of general health (RAND-36 subdomains). Patients reported more tiredness, but at the same time improvement of emotional and cognitive functioning (QLQ-C30). There was a transient increase in urinary symptoms and a decrease in sexual activity (although relatively stable sexual functioning), but no bowel symptoms (PR-25). To our knowledge, no other FT studies have reported such extended QoL analyses. This provides new and detailed insight into the domains that are affected.

Direct comparison of our data with others is difficult as no other literature on ultrafocal HDR-brachytherapy is available. When comparing our results to a small focal Iodine-125 brachytherapy series (n=21), contrasting results are shown with stable IIEF at a mean score of 20 after 12 months follow-up(17). Possible explanations could be their smaller target volumes or substantially lower patient age (mean 62 versus median 71 in our cohort). It is also possible that HDR-brachytherapy inherently has a larger influence on erectile function than Iodine-125 brachytherapy. Similar to our report, this study showed an early temporary increase in IPSS. Another small study on ultrafocal

Iodine-125 brachytherapy (n=17) reported no grade >1 toxicity, no significant deterioration in IIEF and a similar transient IPSS increase(18).

A comparison with other FT modalities confirms the common theme with a minimum impact on QoL and genitourinary functions(4). A single-centre study evaluated prospective data on multiple FT modalities including cryotherapy (n=50, hemi-ablation), HIFU (n=21, hemi-ablation), photodynamic therapy (n=23, focal) and brachytherapy (n=12, focal)(19). Between baseline and 12 months follow-up, IPSS remained stable (<5 points median difference). However, IIEF deteriorated in all groups (median 5-10 points change).

Alternatively, comparing our results to whole-gland HDR-brachytherapy series which are usually performed in multiple fraction schedules(20), we find that late grade 3 GU and GI toxicity were observed in 0-16% and 0-2% of patients, respectively. Late grade 2 GU and GI toxicity were seen in 0-40% and 0-13%. These results are inferior to our toxicity numbers: no grade 3 GU toxicity, only 13% grade 2 GU toxicity (4/30), and no grade >1 GI events.

Morton et al. compared single-dose 19Gy (n=87) with 2x13.5Gy (n=83) in a randomised controlled trial of low/intermediate-risk patients with a median follow-up of 20 months(21). Grade 2 GU toxicity was frequent in both treatment arms (51% acute and 31% late) and grade 3 GU toxicity occurred in 2 patients. Grade 2 acute and late GI toxicity was limited to 2% (single-dose) and 3% (two fractions). Grade 2 ED occurred in 12% and in 29%. As measured by the Expanded Prostate Cancer Index Composite (EPIC), patient-reported ED occurred in 34% and in 58%. Although CTCAE-graded ED scores are favourable compared to our results (40% newly developed grade 3 ED), patient-reported erectile function seems comparable. A potential explanation for the favourable ED results of Morton et al. could be their lower patient age: 65 versus 71 years in our patient group.

A study by Prada et al. (n=60, low/intermediate-risk patients, 1x19Gy, median follow-up 72 months) reported even lower toxicity: no new grade 2 GU or GI toxicity occurred. Rectal spacers were used to limit rectal dose. Potency was not reported(22). Their subsequent study (n=60, low/intermediate-risk patients, 1x20.5Gy, median follow-up 51 months) similarly showed no grade 2 GU or GI toxicity(23). A critical note to these results is the lack of data on patient-reported QoL, which may have yielded a different outcome.

Our 4-year BDFS of 70% is clearly lower than the 79-100% BDFS at 3-10 years in fractionated whole-gland HDR-brachytherapy series(20). Lower BDFS was also reported by Prada et al. after 1x19Gy whole-gland HDR-brachytherapy: 66% for low-risk and 63% for intermediate-risk patients after 6 years(22). In contrast, BDFS after 1x20.5Gy whole-gland HDR-brachytherapy was much higher (82% at 6 years), even though a higher proportion of intermediate-risk patients were treated (57% in the 20.5Gy study vs. 27% in the 19Gy study)(23). Although the α/β ratio of prostate cancer is thought to be low (approximately 1.5)(24), which is an argument for hypofractionation, single-dose 19Gy might be a suboptimal therapeutic dose.

Even more so, inadequate patient selection could be the reason behind our poor tumour control, with 7/9 out-of-field recurrences. First, systematic biopsies could have led to under sampling of clinically significant tumours. According to the PRECISION trial, the diagnostic yield of MRI-targeted biopsies is higher than TRUS-guided systematic biopsies(25), which means we potentially missed higher-risk disease. Even with systematic biopsies, almost half of this cohort already had Gleason sumscore 7. Gleason grade is a well-established independent predictor of BDFS, with grade 3+4 and 4+3 tumours at biopsy corresponding to 82-91% and 65-85% 4 to 5-year BDFS, respectively(26,27). In our cohort, 6/10 biochemical recurrences occurred in patients with Gleason 7 tumours.

Second, for low/intermediate-risk patients (predominant Gleason pattern <4), the EAU-guidelines do not advise additional imaging for staging purposes in the primary setting, due to a lack of evidence(28). This means there is a risk of missing intraprostatic multifocality, although even mp-MRI has a false negative rate of 10-20% regarding clinically significant disease(29). Well-designed controlled trials regarding PET/CT imaging for nodal and metastatic staging are lacking, but evidence is increasing that a more sensitive metastases detection can be achieved than with classical bone scan and abdominopelvic CT(30).

Overall, a combination of more extensive diagnostic staging and further dose escalation could be the next step in evaluating the validity of ultrafocal HDR-brachytherapy.

Another point of discussion is the interpretation of the Phoenix definition for failure after FT, which leaves more biologically active untreated prostate tissue than whole-gland treatment. There is a need for a tailored definition for BF after FT. An alternative outcome measure is to consider only progression beyond curative treatment options as failure. A sub-analysis using this definition for disease-free survival offers a different perspective on tumour control. As recommended by an FT consensus meeting(31), considering successful focal salvage treatment as no failure yields a BDFS of 73% (54-97%). Taking into account both successful focal and whole-gland salvage treatments, BDFS increases to 91% (79-100%) (Supplementary figure 4, available online at https://doi.org/10.1016/j.ijrobp.2019.03.032). Importantly, focal and whole-gland salvage radiotherapy were well tolerated without exacerbated toxicity (grade 2 urinary frequency among both patents who underwent whole-gland salvage, deterioration of erectile function in 1 patient who was still potent). With the absence of increased toxicity and stable patient-reported QoL after primary FT, a strategy of repeated treatments could favour FT over a primary whole-gland approach, especially with increased adoption of ultrafocal targeting.

The explorative univariable Cox-analysis showed a higher risk of first BF with increasing age. We do not have a definitive explanation for this association. Age did not correlate with other prognostic variables such as PSA, PSADT and AJCC stage group. With only 10 BF events, there is a possibility of a type I error.

A disadvantage of ultrafocal HDR-brachytherapy is the labour-intensiveness. Total procedure time is currently 3-4 hours and this will inherently remain time-consuming,

considering all procedure steps: MRI/TRUS-guided insertion of catheters, subsequent transport to the MRI, catheter reconstruction and dose planning, another MRI scan for verification just before dose delivery and, if necessary, adjustment of the plan. In the future, MRI-guided external radiotherapy systems could provide hypofractionated ultrafocal stereotactic radiation treatment(32), potentially matching ultrafocal HDR-brachytherapy in terms of tumour control and morbidity.

CONCLUSION

MRI-guided ultrafocal HDR-brachytherapy for localised prostate cancer conveyed minimal grade 2 GU toxicity and no grade >1 GI toxicity. Erectile function significantly deteriorated over time, with a rapid decline after treatment. Accordingly, patient-reported QoL was marginally affected, although clinically relevant deteriorations were seen in the domains tiredness and sexual activity. After 4 years, BDFS was 70%. Even in the light of very low toxicity, this is an unfavourable outcome which predominantly seems to result from inadequate patient selection. However, the remaining potential for successful (focal or whole-gland) local salvage treatment may substantiate the use of focal therapy, especially if patient selection is improved in the future.

REFERENCES

1. Shao YH, Demissie K, Shih W, Mehta AR, Stein MN, Roberts CB, et al. Contemporary risk profile of prostate cancer in the United States. J Natl Cancer Inst 2009 Sep 16;101(18):1280-1283.
2. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med 2016 Oct 13;375(15):1415-1424.
3. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med 2016 Oct 13;375(15):1425-1437.
4. Valerio M, Cerantola Y, Eggener SE, Lepor H, Polascik TJ, Villers A, et al. New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. Eur Urol 2017 Jan;71(1):17-34.
5. Nguyen PL, Chen MH, Zhang Y, Tempany CM, Cormack RA, Beard CJ, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. J Urol 2012 Oct;188(4):1151-1156.
6. Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol 2018 Oct;74(4):422-429.
7. Maenhout M, Peters M, Moerland MA, Meijer RP, van den Bosch MAAJ, Frank SJ, et al. MRI guided focal HDR brachytherapy for localized prostate cancer: Toxicity, biochemical outcome and quality of life. Radiother Oncol 2018 Aug 18.
8. Maenhout M, van der Voort van Zyp,J.R.N., Borot de Battisti M, Peters M, van Vulpen M, van den Bosch M, et al. The effect of catheter displacement and anatomical variations on the dose distribution in MRI-guided focal HDR brachytherapy for prostate cancer. Brachytherapy 2018 Jan - Feb;17(1):68-77.
9. Groenendaal G, Moman MR, Korporaal JG, van Diest PJ, van Vulpen M, Philippens ME, et al. Validation of functional imaging with pathology for tumor delineation in the prostate. Radiother Oncol 2010 Feb;94(2):145-150.
10. Holly R, Morton GC, Sankreacha R, Law N, Cisecki T, Loblaw DA, et al. Use of cone-beam imaging to correct for catheter displacement in high dose-rate prostate brachytherapy. Brachytherapy 2011 Jul-Aug;10(4):299-305.
11. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993 Mar 3;85(5):365-376.
12. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998 Nov;51(11):1055-1068.
13. van Andel G, Bottomley A, Fossa SD, Efficace F, Coens C, Guerif S, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008 Nov;44(16):2418-2424.
14. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998 Jan;16(1):139-144.

15. van der Wielen GJ, Mulhall JP, Incrocci L. Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review. Radiother Oncol 2007 Aug;84(2):107-113.

16. Lee JY, Spratt DE, Liss AL, McLaughlin PW. Vessel-sparing radiation and functional anatomy-based preservation for erectile function after prostate radiotherapy. Lancet Oncol 2016 May;17(5):e198-208.

17. Cosset JM, Cathelineau X, Wakil G, Pierrat N, Quenzer O, Prapotnich D, et al. Focal brachytherapy for selected low-risk prostate cancers: a pilot study. Brachytherapy 2013 Jul-Aug;12(4):331-337.

18. Graff P, Portalez D, Lusque A, Brun T, Aziza R, Khalifa J, et al. IDEAL 2a Phase II Study of Ultrafocal Brachytherapy for Low- and Intermediate-risk Prostate Cancer. Int J Radiat Oncol Biol Phys 2018 Nov 15;102(4):903-911.

19. Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol. 2013 Apr;63(4):618-22.

20. Tselis N, Hoskin P, Baltas D, Strnad V, Zamboglou N, Rodel C, et al. High Dose Rate Brachytherapy as Monotherapy for Localised Prostate Cancer: Review of the Current Status. Clin Oncol (R Coll Radiol) 2017 Jul;29(7):401-411.

21. Morton G, Chung HT, McGuffin M, Helou J, D'Alimonte L, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19Gy or two fractions of 13.5Gy. Radiother Oncol 2017 Jan;122(1):87-92.

22. Prada PJ, Cardenal J, Blanco AG, Anchuelo J, Ferri M, Fernandez G, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results. Radiother Oncol 2016 Jun;119(3):411-416.

23. Prada PJ, Ferri M, Cardenal J, Blanco AG, Anchuelo J, Diaz de Cerio I, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results. Brachytherapy 2018 Nov - Dec;17(6):845-851.

24. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9-2.2) Gy. Int J Radiat Oncol Biol Phys 2012 Jan 1;82(1):e17-24.

25. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018 May 10;378(19):1767-1777.

26. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013 May;111(5):753-60.

27. Loeb S, Folkvaljon Y, Robinson D, Lissbrant IF, Egevad L, Stattin P. Evaluation of the 2015 Gleason Grade Groups in a Nationwide Population-based Cohort. Eur Urol. 2016 Jun;69(6):1135-41.

28. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017 Apr;71(4):618-629.

29. Moldovan PC, Van den Broeck T, Sylvester R, Marconi L, Bellmunt J, van den Bergh RCN, et al. What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017 Aug;72(2):250-266.

30. Eiber M, Herrmann K, Fendler WP, Maurer T. (68)Ga-labeled Prostate-specific Membrane Antigen Positron Emission Tomography for Prostate Cancer Imaging: The New Kid on the Block-Early or Too Early to Draw Conclusions? Eur Urol 2016 Dec;70(6):938-940.

31. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol 2015 Apr;67(4):771-777.

32. Pathmanathan AU, van As NJ, Kerkmeijer LGW, Christodouleas J, Lawton CAF, Vesprini D, et al. Magnetic Resonance Imaging-Guided Adaptive Radiation Therapy: A "Game Changer" for Prostate Treatment? Int J Radiat Oncol Biol Phys 2018 Feb 1;100(2):361-373.

CHAPTER 4

Focal salvage treatment of radiorecurrent prostate cancer: a narrative review of current strategies and future perspectives

Authors: Marieke J. van Son, Max Peters, Marinus A. Moerland, Linda G.W. Kerkmeijer, Jan J.W. Lagendijk, Jochem R.N. van der Voort van Zyp

CANCERS

ABSTRACT

Over the last decades, primary prostate cancer radiotherapy has seen improving developments such as more conformal dose administration and hypofractionated treatment regimes. Still, prostate cancer recurrences after whole-gland radiotherapy remain common, especially in patients with intermediate- to high-risk disease. The vast majority of these patients is treated palliatively with androgen deprivation therapy (ADT), which exposes them to harmful side-effects and is only effective for a limited amount of time. For patients with a localized recurrent tumor, local treatment with curative intent seems more rational. However, whole-gland salvage treatments such as salvage radiotherapy or salvage prostatectomy are associated with significant toxicity and are therefore uncommonly performed. Treatments that are aimed at the recurrent tumor itself, thereby better sparing the surrounding organs at risk, potentially provide a safer salvage treatment option in terms of toxicity. To achieve tumor-targeted treatment, imaging developments have made it possible to better exclude metastatic disease and accurately discriminate the tumor. Currently, focal salvage treatment is being performed with different modalities, including brachytherapy, cryotherapy, high intensity focused ultrasound (HIFU) and stereotactic body radiation therapy (SBRT). Oncologic outcomes seem comparable to whole-gland salvage series, but with much lower toxicity rates. In terms of oncologic control, these results will improve further with better understanding of patient selection. Other developments, such as high-field diagnostic MRI and live adaptive MRI-guided radiotherapy will further improve precision of the treatment.

INTRODUCTION

Prostate cancer is the most diagnosed male cancer in developed countries. Frequently diagnosed at an early stage, with opportunistic PSA-screening increasing the incidence, the search for optimal and patient-tailored treatment is of growing significance. In the setting of localized recurrent prostate cancer after primary whole-gland radiotherapy, standard of care now consists of palliative androgen deprivation therapy (ADT). This only has a temporary suppressive effect and is associated with harmful side-effects. On the other hand, treatments with curative intent such as salvage prostatectomy or whole-gland radiotherapy also convey serious toxicity risks and should only be offered to highly selected patients [1]. This leaves a gap in the treatment arsenal for radiorecurrent prostate cancer. Here, focal ablative treatment might meet the need: with lower toxicity risks, it could postpone palliative hormonal treatment or perhaps even avoid it altogether. Within this narrative review, an overview is provided of the developments in primary prostate cancer care, current strategies on how to deal with localized prostate cancer recurrences and future perspectives with respect to focal salvage treatment.

Whole-gland primary radiotherapy

For whole-gland treatment of intermediate- to high-risk prostate cancer in the primary setting, radiotherapy has evolved as a suitable modality. It is comparable to prostatectomy in terms of cancer control, while both are associated with their respective side-effects [2]. Several developments over the last decades have increased the use of radiotherapy for the primary treatment of prostate cancer. Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) are increasingly adopted as external beam radiation therapy (EBRT) techniques, using fiducial gold markers for position verification. Both are able to substantially reduce the dose to surrounding organs at risk (in particular rectum and bladder) due to a more conformal dose distribution [3,4]. Although radiation therapy traditionally entailed a lengthy treatment with smaller daily fractions over 6-7 weeks' time, hypofractionation seems to provide comparable tumor control, against acceptable toxicity profiles [5-9]. The rationale behind using higher dose in fewer fractions comes from data describing a lower α/β-ratio of prostate cancer than previously thought. Despite ambiguous recommendations from different large trials, hypofractionated radiotherapy is increasingly adopted in guidelines worldwide [10].

While external beam techniques are generally delivered fractionated, internal radiation using brachytherapy is increasingly performed in a single procedure. Originally, low-dose-rate brachytherapy (using Iodine-125 seeds) was mainly used for low- to intermediate-risk patients. Nowadays, there is an increase in the treatment of higher-risk disease with high-dose-rate brachytherapy, providing comparable cancer control rates to other primary treatments [11-13]. As compared to Iodine-125 seeds, high-dose-rate brachytherapy offers the advantage of higher dose control by the approach of adjusting source dwell times and positions. The steep dose decline of brachytherapy makes

it possible to further escalate the dose to the tumor, without compromising the dose constraints for the organs at risk [13]. This feature can also be used to deliver a concurrent tumor boost next to whole-gland EBRT techniques, thereby further increasing the therapeutic efficacy for intermediate- to high-risk disease [14].

Recurrence risk and location

Although dose escalation is increasingly adopted, recurrent prostate cancer after primary radiotherapy remains common. A recent series of 2.694 patients treated with doses above 78 Gy revealed 10-year biochemical recurrence risks of approximately 10%, 23% and 44% in low-, intermediate- and high-risk patients, respectively [15]. Biochemical recurrences according to the Phoenix definition (i.e. PSA nadir + 2.0 ng/ml) preceded the development of distant metastases and death due to prostate cancer by 5.4 years and 10.5 years, respectively. In patients with a reasonable life-expectancy, management of these recurrences is therefore often necessary to prevent cancer-related complications and mortality.

Primary prostate cancer is often a multifocal process [16,17], with a hypothesized 'index lesion' driving metastatic potential [18,19]. Within this hypothesis, it is thought that synchronous lesions outside the index lesion are secondary insignificant cancers which lie dormant [20]. After primary whole-gland radiotherapy, several series have shown that recurrences nearly all (89-100%) regrow at the site of the primarily largest and/or highest grade index lesion [21-25]. This indicates that the malignant remnant causes biochemical failure, while secondary indolent tumor foci have been successfully treated by the primary radiation course. Building on this, the rationale behind focal treatment in the localized radiorecurrent setting becomes clear. Although the index lesion hypothesis remains controversial due to a lack of robust evidence, long-term oncological efficacy data of focal treatments in the future might help to either support or undermine this view.

Traditional approach to radiorecurrent prostate cancer

The treatment of prostate-confined recurrences after primary radiotherapy is called salvage and will be denoted as such in the subsequent part of this review. Within the literature there are reasonably large series available describing the results of salvage treatments directed at the entire prostatic volume. These series include salvage radical prostatectomy (SRP) [26], whole-gland salvage cryotherapy [27,28], whole-gland salvage high intensity focused ultrasound (HIFU) [29,30], and in increasingly larger series, whole-gland salvage brachytherapy [31-33]. These studies show an approximate 5-year biochemical failure-free survival (bFFS) of 50-60%, thereby postponing the use of palliative ADT with its associated toxicity [34]. However, due to previous radiation damage to organs at risk, toxicity of secondary surgery or radiation can be deleterious. Severe genitourinary (GU) and gastro-intestinal (GI) toxicity, requiring operative intervention to resolve, are observed in about 30% of patients, with erectile dysfunction (ED) often present in 100% of cases post-salvage [35]. For this reason, whole-gland techniques

remain unpopular amongst treating physicians, with only 2% of patients receiving any form of salvage curative treatment. The other 98% receives ADT, either immediately or deferred [36]. These patterns are also observed in large national databases, such as the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database from the U.S. [37].

Focal treatment of radiorecurrent prostate cancer

With recurrences often being localized and unifocal (mainly at the 'index lesion' site), a salvage treatment directed solely at the recurrent tumor lesion seems rational. Especially considering the narrow therapeutic ratio (treatment efficacy versus treatment-related toxicity) in the recurrent setting, focal treatment provides a promising alternative: a second chance at achieving local control, with minimal burden to the patient in terms of side-effects.

DIAGNOSTIC ASSESSMENT

Excluding metastatic disease

The success of focal salvage treatment starts with adequate exclusion of metastatic disease. More dated series of whole-gland salvage treatments often show substantial failure rates due to inadequate pre-treatment diagnosis of metastases. For example, technetium-99m bone scintigraphy was often used to exclude bone metastases, which only achieves acceptable diagnostic accuracy in patients with higher-risk disease characteristics (PSA>20, Gleason ≥8) [38]. Furthermore, studies regarding computed tomography (CT) and/or magnetic resonance imaging (MRI) for nodal disease staging have demonstrated poor diagnostic accuracy [39], since lymph node diameter and morphology are inadequate predictors for nodal invasion. Positron-emission computed tomography (PET/CT), however, is recommended as the standard diagnostic modality to assess metastatic disease in the recurrent setting. It offers the advantage of concurrently evaluating bony and nodal metastatic disease. Different PET tracers have been used, with choline and fluoride as originally most abundant [40-42]. Negative predictive values of up to 100% have been reported, although the range observed in the reported literature is substantial. Thus far, the most promising PET-technique seems to be (68)Ga prostate-specific membrane antigen (PSMA)-PET/CT, with a radiotracer binding more specifically to a cellular protein overexpressed on 95% of prostate cancer cell-membranes. High diagnostic accuracy is attained for both intra-prostatic lesions as well as lymph node and bone metastases, even at low PSA-values (<2 ng/ml) [43,44]. Available since 2013 [45], PSMA-PET/CT has quickly become a routine form of targeted molecular imaging in countries across Asia, Australia, and Europe [46]. Currently, diffusion-weighted whole-body MRI is also being investigated for assessment of bone metastases in the recurrent setting, although PET/CT seems superior [47,48].

Assessing and targeting intra-prostatic disease

After exclusion of metastatic disease, assessment of intra-prostatic disease is necessary to adequately target the recurrent lesion. In the past, salvage treatments had to be aimed at the whole prostate gland since localization of the recurrent nodule was inadequate. Nowadays, this has become possible with the use of multi-parametric MRI (mp-MRI), offering both morphological and functional information with T2-weighted, dynamic contrast-enhanced (DCE) and diffusion-weighted imaging (DWI). In the primary setting, diagnostic accuracy of mp-MRI for the detection of clinically significant intra-prostatic disease seems adequate with a sensitivity of 93% [49,50]. Although smaller (secondary) tumor foci are still occasionally being missed (even when harboring higher grade cancers), mp-MRI is often able to detect the larger index tumor [51]. Because of the relatively high contrast of fibrotic prostatic tissue with viable tumor tissue in a previously irradiated prostate, DCE and DWI-MRI are especially capable of adequately detecting radiorecurrent lesions [52-54].

However, in the setting of treatment failure evaluation, the interpretation of mp-MRI is often complicated by treatment-related anatomic and functional changes. Radiologists should be familiar with the findings that are associated with the type of treatment the patient previously received. For instance, T2 hypo-intense intraprostatic lesions can be difficult to distinguish within a diffusely hypo-intense prostate caused by previous irradiation. Although there are no established guidelines for characterizing possible local tumor relapses on mp-MRI, there is an increasing amount of literature discussing the differences between normal post-treatment patterns and suspicious recurrence findings [55-59].

The combination of (68)Ga-PSMA-PET/CT with mp-MRI could provide an even higher accuracy in detecting and delineating intra-prostatic disease [60] (see Figure 1 for image example). A retrospective analysis on the diagnostic value of (68)Ga-PSMA-PET/CT in the recurrent setting revealed a negative predictive value (NPV) and positive predictive value (PPV) of 91.4% and 100%, detecting recurrent prostate cancer in a high number of patients [61]. In line with these promising results, the impact of using (68)Ga-PSMA-PET/CT in patients with recurrent prostate cancer is large, altering the therapeutic management in approximately half of all patients. Specifically, the use of dose escalation to boost the target volume and the proportion of focal salvage treatments seems to increase, while systemic treatment decreases [62].

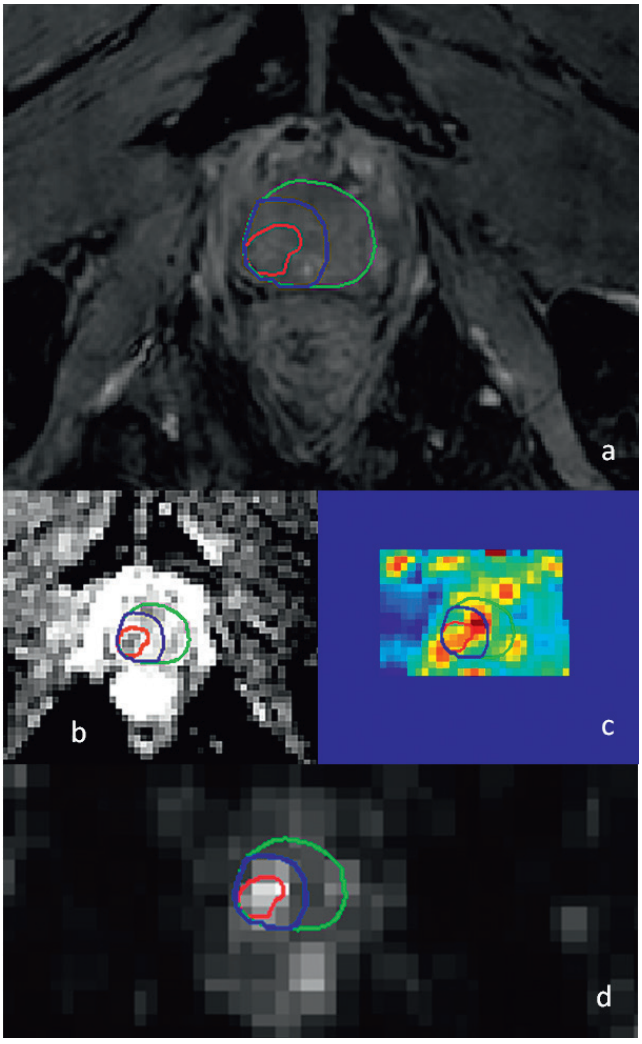

Figure 1 – Recurrent prostate cancer lesion on diagnostic 3T multiparametric-magnetic resonance imaging (mp-MRI) (a,b,c) and PSMA-PET/CT (d). The suspect lesion is visible in the right peripheral zone of the apex. Delineations of the prostate (green), gross tumor volume (GTV, red) and clinical target volume (CTV, blue) are displayed.
(a) T2-weighted MRI, (b) ADC map of DWI-MRI, (c) K-trans map of DCE-MRI, (d) 68Ga-PSMA-PET/CT

Biopsies

In the primary setting it was shown that MRI-targeted biopsies, as opposed to transrectal ultrasonography (TRUS)-guided biopsies, decrease the detection of insignificant disease, while the yield of clinically relevant cancers increases [63]. A study in which patients subsequently underwent mp-MRI, TRUS-biopsies and transperineal template prostate mapping (TPM) biopsies (sampling the whole gland every 5 mm), calculated that up to 18% more cases of clinically significant cancer might be detected if TRUS-bi-

opsies were guided by MRI findings [50]. Adding mp-MRI information to subsequent TPM biopsies seems to achieve the highest diagnostic accuracy, with a sensitivity and specificity of 97% and 61%, a positive predictive value of 83% and a negative predictive value of 91% [64]. Different approaches to achieve biopsy under MRI-guidance (i.e. in-bore, MRI-TRUS fusion or cognitive registration) yield similar detection rates of clinically significant prostate cancer [65]. Interestingly, the definition of clinically significant cancer differs between studies, ranging from Gleason score 6 and cancer core length >3 mm to Gleason score ≥4+3.

In the radiorecurrent setting, prostate biopsy evaluation is hampered by radiation effects, which sometimes mimic higher grade disease. Approximately 30% of indeterminate biopsies seem to resolve into negative disease status. On the other hand, local failure can also be interpreted as radiation effect and indeterminate biopsies should therefore not be considered negative. Furthermore, delayed tumor regression may cause false positives. Biopsies should therefore not be taken before 24 months of follow-up [66]. Even after two years, routine post-radiotherapy biopsies are of limited added value to regular PSA-testing, and should only be considered in case of biochemical failure [67]. According to the EAU guidelines, biopsy after radiotherapy is only indicated if local recurrence affects treatment decisions [68].

In case of localized recurrence, one could argue that biopsies might aid in the selection of patients for focal salvage treatment. A study comparing cognitive targeted biopsies with TPM biopsies showed that targeted biopsies had similar or at most 10% less detection rates, depending on the definition of clinically significant cancer. Targeted biopsies were efficient, requiring fewer biopsies compared to TPM biopsies for detection of clinically significant disease [69]. However, clinical significance was determined based on either maximum cancer core length or Gleason score. Since the effect of altered architecture from previous radiotherapy on the Gleason score is poorly understood, it does not seem appropriate for grading radiorecurrent lesions [70-72]. Validation studies on the use of the Gleason scoring system in the radiorecurrent setting are lacking in the current available literature. Furthermore, there seems to be no consensus on the Gleason score definition for clinically significant disease. Histological confirmation of recurrence is therefore limited (i.e. adenocarcinoma yes/no) and does not provide any information on the clinical significance (tumor aggressiveness) of the recurrent lesion.

With advancements in imaging modalities as outlined above, and the burden of invasive biopsy procedures on patients, it is questionable whether these biopsies are mandatory for adequate disease assessment. There is no literature describing the accuracy of combined mp-MRI and PET-CT with pathology verification in the radiorecurrent setting. Currently, we are investigating a cohort of patients with a positive recurrent lesion on (68)Ga-PSMA-PET/CT and at least one mp-MRI sequence, who underwent subsequent MRI-targeted biopsies, to determine the added value of histologic verification for adequate disease assessment.

CURRENT FOCAL SALVAGE SERIES

Today, focal salvage treatment of radiorecurrent prostate cancer is performed with a variety of techniques: focal cryotherapy [73-75], focal HIFU [76], focal brachytherapy (both low-dose-rate [77,78] and high-dose-rate [79-81]) and, in smaller series, stereotactic body radiation therapy (SBRT) [82,83]. The extend of ablation differs per ablation method and between series, ranging from ultrafocal to hemi- and subtotal ablation. Focal cryotherapy usually entails hemi-ablation by achieving a lethal freezing temperature of –40 °C in the prostate lobe containing the cancer. Focal HIFU can be hemi-ablation or quadrant ablation (one half of a lobe), using focused ultrasonic waves for tissue destruction by means of thermal, mechanical and cavitation effects. With brachytherapy, ultrafocal ablation can be achieved by administering radiation to a small target volume, using the steep dose fall-off with distance from the radiation source. Iodine-125 seeds are used for low-dose-rate brachytherapy, delivering a prescribed dose of 144-145 Gy. High-dose-rate brachytherapy delivers radiation from an Iridium-192 source through temporarily implanted catheters, which allow for dose painting by varying the dwell positions and times of the radiation source. High-dose-rate schedules vary from 18-19 Gy in a single dose to 27 Gy divided over two implants. CyberKnife-based SBRT has been performed with dose schedules between 30-35 Gy in 5 fractions. While this technique offers a high degree of conformity, it is also likely to increase the integral dose to the surrounding healthy tissues. Furthermore, without real-time MRI-guidance, planning target volume (PTV) margins for correction of intrafraction motion remain necessary to avoid geographical miss. Different focal ablation methods have varying limitations with respect to tumor recurrence location: HIFU is less suited for treating anterior-located lesions due to insufficient length of most devices, while cryotherapy can be less effective in the apical and peri-urethral region due to organ-protective warming tools. With brachytherapy it is usually possible to cover all sides of the prostate [84,85].

Studies that report 5-year bFFS seem to reach an approximate 50% rate [86], which is comparable to whole-gland salvage series. Only one study presented a direct comparison between focal and whole-gland using cryotherapy: 5-year bFFS rates were 54 and 86%, respectively [73]. However, differences in patient characteristics and primary radiation schedules make it hard to interpret these results. Though most literature comes from relatively recent studies, patient selection methods are often already outdated. Exclusion of metastatic disease was often performed with either CT or MRI for nodal assessment, bone scintigraphy for bony disease and, in some series, PET/CT in a small number of patients. A modern multimodal radiologic approach with mp-MRI and (68)Ga-PSMA-PET/CT outperforms the other modalities in selecting patients with true localized, non-metastatic recurrence [44,87]. In the future, better patient selection could therefore improve oncologic outcomes of focal salvage series even further. Follow-up times are still too short to assess the impact of focal salvage treatment in terms of

overall survival. However, the main impact lies in delaying the need for palliative hormonal treatment, while providing a chance of cure through local control.

With this in mind, it is important to consider treatment-related side effects of focal salvage treatments. Although toxicity might be underreported in many current series due to the retrospective nature of data collection, the general trend seems favorable. Severe GU and GI toxicity seem limited to a maximum of 5-10%. Potency preservation (measured with the international index of erectile function [IIEF] or CTCAE) is observed in the majority of patients in many of the series. Treatment effects on patient-reported quality of life was only reported in focal salvage brachytherapy series, revealing no significant changes in most domains, except an increase in urinary symptoms after focal low-dose-rate brachytherapy [78].

Table 1 provides an overview of functional and oncologic outcomes of the different focal salvage treatment modalities.

To determine which patients benefit the most from focal salvage treatment, it is important to consider other patient and tumor characteristics, too. In the above mentioned studies, patients with stage T1-T3b recurrent tumors, total Gleason score ≤6-10 and PSA-levels between 0.01 and ≥20 ng/ml were treated. This indicates that a wide range of patients, classified from (very) low-risk to high-risk disease, were included. Most studies did not report on the pre-treatment PSA doubling time (PSADT). In a Delphi consensus study among 18 experts in the field of salvage brachytherapy for radiorecurrent prostate cancer, 88% of participants indicated that stage T3b should be the maximum tumor classification to be eligible for salvage treatment. A total of 94% agreed that the Gleason score should not be used as a criterion (with over half of participants stating that the Gleason score cannot be determined in case of relapse after primary radiotherapy). In terms of PSA kinetics, a maximum PSA-level of 10 ng/mL and minimum PSADT of 6 months was preferred by most participants [88]. A prediction study on factors associated with failure after focal salvage HIFU revealed that the length of the interval between primary treatment and radiologic recurrence, prostatic volume, T-stage, PSA-level, PSADT and primary tumor Gleason score are potential predictors of failure [89]. More research is warranted to better understand which combination of patient and tumor characteristics is best served by (which) focal salvage treatment. The decision-making process before and after focal salvage treatment is displayed in a flow chart in Figure 2.

Table 1 – Summary of studies on functional and oncologic outcomes of different focal salvage treatment modalities for localized radiorecurrent prostate cancer.

Focal salvage treatment	Study	Ablation extent	N	Median follow-up	bFFS	GU/GI Toxicity	QoL
LDR	Kunogi et al [77]	Ultrafocal (145 Gy)	12	56 months	78% at 4 years	No grade 3	NA
	Peters et al [78]	Ultrafocal (144 Gy)	20	36 months	60% at 3 years	5% grade 3 GU	Increase in urinary symptoms
HDR	Zamboglou et al [79]	Ultrafocal (18 Gy)	2	6 months	100% at 6 months	No grade 3	NA
	Maenhout et al [80]	Ultrafocal (19 Gy)	17	10 months	92% at 1 year	6% grade 3 GU	NA
	Murgic et al [81]	Quadrant (27 Gy in 2 fractions)	15	36 months	61% at 3 years	7% grade 3 GU	No significant change
Cryotherapy	de Castro Abreu et al [73]	Hemi	25	31 months	54% at 5 years	No incontinence, no fistula	NA
	Kongnyuy et al [74]	Hemi	65	27 months	48% at 3 years	6% incontinence	NA
	Li et al [75]	NA	91	15 months	47% at 5 years	6% incontinence, 7% retention, 3% fistula	NA
HIFU	Kanthabalan et al [76]	Ultrafocal (11%) Quadrant (55%) Hemi (34%)	150	35 months	48% at 3 years	8% bladder neck stricture, 2% fistula	NA
SBRT	Jereczek-Fossa et al [82]	Ultrafocal (30 Gy in 5 fractions)	15	10 months	22% at 2.5 years	7% grade 3 GU	NA
	Mbeutcha et al [83]	Ultrafocal (35 Gy in 5 fractions)	18	15 months	56% at 1 year	No grade 3	NA

Abbreviations: bFFS: biochemical failure-free survival, GU: genitourinary, GI: gastrointestinal, QoL: quality of life, LDR: low-dose-rate, HDR: high-dose-rate, HIFU: high intensity focused ultrasound, NA: not available, SBRT: stereotactic body radiation therapy.

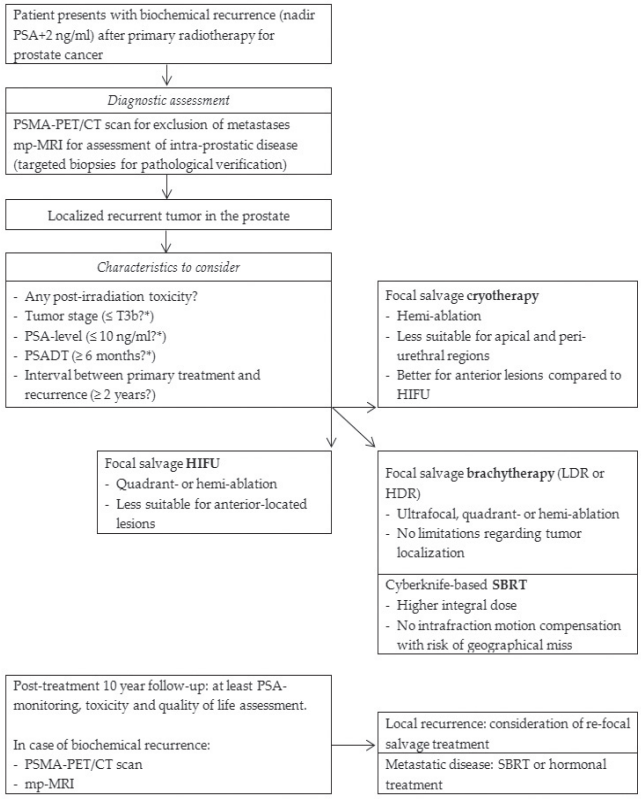

Figure 2 – Flow chart for decision-making before and after focal salvage treatment of localized radiorecurrent prostate cancer.
*As proposed by Delphi consensus study among 18 experts in the field of salvage brachytherapy for radiorecurrent prostate cancer (conducted by UroGEC group of GEC-ESTRO) [88].

Future prospects regarding MRI-guided radiotherapy

It is clear that accurate targeted ablation requires precise localization of the recurrent prostatic lesion. Over the years, the use of (mp-)MRI for treatment planning has substantially increased. The superior resolution of soft tissue enables more accurate delineation of the tumor volume and organs at risk [91]. New developments such as ultra-high field MRI with 7T systems have the potential to enhance the spatial resolution even further [92]. Although it seems that 7T T2- and diffusion-weighted imaging deliver clinically adequate anatomical images within acceptable acquisition times, there are still several technical challenges to overcome before a 7T mp-MRI protocol for the prostate can be achieved [93].

Imaging developments are not only used for the treatment planning phase, but are also increasingly incorporated into the treatment itself. Currently, MRI-guidance during treatment can be achieved using image registration of pre-operative MR-images (1.5T or 3T) with intra-operative TRUS-images (MRI-TRUS fusion). With this technique,

software is used to register the pre-operatively delineated tumor location to real-time prostate images. Image registration may be either rigid (overlay of images without adjustment for possible prostate deformation during treatment) or non-rigid (using algorithms that compensate for deformation). Some factors that contribute to prostate deformation are unavoidable, such as swelling of the prostate due to catheter insertion during a brachytherapy implant procedure. Prostate motion can also be caused by surrounding organ movement, such as rectal distension due to flatulence or introduction of an ultrasound probe. Evidently, non-rigid registration is challenging: a variety of registration methods using different algorithms have been presented in the search for the most optimal solution [94].

The next step in the development of MRI-guided intervention is the incorporation of live MR-images into the treatment workflow, thereby achieving direct treatment guidance and avoiding any registration errors. Although early experiences with real-time MRI-guided brachytherapy date back to 1997, this approach has not been widely adopted yet due to logistical issues such as resource demand and procedural time prolongation [95]. One of the obvious challenges of in-bore intervention is the limited workspace. Open MRI units that provide access to the patient while imaging are available, but these deliver low image quality and need increased scanning time due to the inherently lower signal-to-noise ratio.

To overcome these shortcomings, a robotic MRI-compatible implantation device for prostate brachytherapy was developed at our institution (see Figure 3). The robot system fits in a 1.5T MRI scanner and can be placed between the patient's legs. In 2010, the first clinical proof of principal study was performed with the UMCU robot, successfully implanting gold fiducial markers into the prostate for external beam radiation [96]. It was shown that the in vivo use of the robot was feasible. After this first clinical test, the UMCU robot was further developed and optimized for the application of brachytherapy implant procedures. We are currently working on a study investigating the in vivo technical feasibility of robotic insertion of a brachytherapy needle into the prostate. It is expected that this study will be a step forward in the development of MRI-guided focal salvage brachytherapy with a robotic device. In the future, a full MRI-guided robotic implantation procedure may allow for a reduction of needles needed for the implant [97], with expected lower toxicity rates and a reduction of time necessary for the procedure.

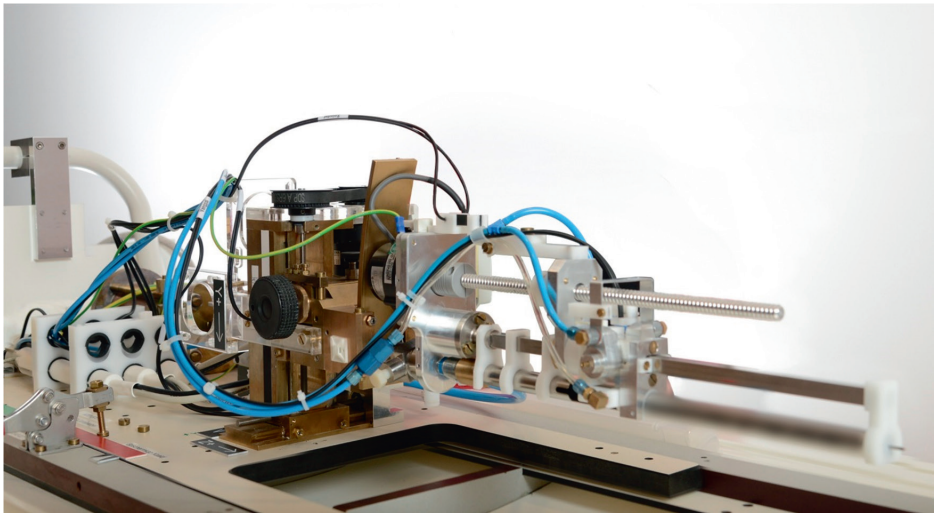

Figure 3 – Magnetic resonance imaging (MRI)-compatible robotic implantation device for prostate brachytherapy. A cylindrical weight that is pneumatically driven hits the needle holder to tap a brachytherapy needle into the prostate. Placed between the patient's legs inside an MRI scanner, the needle can be tracked using live images.

Regarding external beam radiotherapy, MRI-guided radiotherapy systems such as the MR-Linac will provide another way to accomplish live MRI-guided intervention. By using online fast MR-sequences for auto-contouring and auto-planning, a full MRI-based online adaptive workflow can be achieved [98]. Changes in anatomy can be accounted for with inter-beam re-planning. This will further reduce the target volume margins needed, reducing normal tissue radiation exposure and thereby decreasing the risk of toxicity. This enables safe dose escalation, potentially in the form of delivering a single ablative dose, which would be of benefit to both patient comfort and hospital logistics. It should however be noted that external beam radiotherapy is inherently less conformal than brachytherapy, and it remains to be seen whether this treatment modality will be suitable for focal treatment in the recurrent prostate cancer setting.

CONCLUSION

Localized radiorecurrent prostate cancer seems susceptible for focal salvage treatment. Treating the tumor while sparing the surrounding healthy tissue leads to a reduction of treatment-related side effects, where whole-gland salvage treatments or palliative ADT are often less well-tolerated. Focal salvage therapy thereby provides an intermediate step between primary curative treatment and (if necessary) palliative hormonal treatment. Diagnostic innovations have led to more adequate patient selection in terms of exclusion of metastatic disease and accurate tumor targeting. This is a constant developing field, as new diagnostic techniques are warranted to provide greater insight into prostate tumor profiling. With MRI-guidance, focal treatment becomes more and more precise, especially with emerging technologies enabling live and online adaptive MRI-guided radiotherapy.

REFERENCES

1. Cornford, P.; Bellmunt, J.; Bolla, M.; Briers, E.; De Santis, M.; Gross, T.; Henry, A.M.; Joniau, S.; Lam, T.B.; Mason, M.D., et al. Eau-estro-siog guidelines on prostate cancer. Part ii: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017, 71, 630-642; DOI: 10.1016/j.eururo.2016.08.002.
2. Hamdy, F.C.; Donovan, J.L.; Lane, J.A.; Mason, M.; Metcalfe, C.; Holding, P.; Davis, M.; Peters, T.J.; Turner, E.L.; Martin, R.M., 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.
3. Sheets, N.C.; Goldin, G.H.; Meyer, A.M.; Wu, Y.; Chang, Y.; Sturmer, T.; Holmes, J.A.; Reeve, B.B.; Godley, P.A.; Carpenter, W.R., et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. Jama 2012, 307, 1611-1620; DOI: 10.1001/jama.2012.460.
4. Biegala, M.; Hydzik, A. Analysis of dose distribution in organs at risk in patients with prostate cancer treated with the intensity-modulated radiation therapy and arc technique. Journal of medical physics 2016, 41, 198-204; DOI: 10.4103/0971-6203.189490.
5. Aluwini, S.; Pos, F.; Schimmel, E.; van Lin, E.; Krol, S.; van der Toorn, P.P.; de Jager, H.; Dirkx, M.; Alemayehu, W.G.; Heijmen, B., et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (hypro): Acute toxicity results from a randomised non-inferiority phase 3 trial. The Lancet. Oncology 2015, 16, 274-283; DOI: 10.1016/S1470-2045(14)70482-6.
6. Aluwini, S.; Pos, F.; Schimmel, E.; Krol, S.; van der Toorn, P.P.; de Jager, H.; Alemayehu, W.G.; Heemsbergen, W.; Heijmen, B.; Incrocci, L. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (hypro): Late toxicity results from a randomised, non-inferiority, phase 3 trial. The Lancet. Oncology 2016, 17, 464-474; DOI: 10.1016/S1470-2045(15)00567-7.
7. Dearnaley, D.; Syndikus, I.; Mossop, H.; Khoo, V.; Birtle, A.; Bloomfield, D.; Graham, J.; Kirkbride, P.; Logue, J.; Malik, Z., et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 chhip trial. The Lancet. Oncology 2016, 17, 1047-1060; DOI: 10.1016/S1470-2045(16)30102-4.
8. Musunuru, H.B.; Quon, H.; Davidson, M.; Cheung, P.; Zhang, L.; D'Alimonte, L.; Deabreu, A.; Mamedov, A.; Loblaw, A. Dose-escalation of five-fraction sabr in prostate cancer: Toxicity comparison of two prospective trials. Radiother Oncol 2016, 118, 112-117; DOI: 10.1016/j.radonc.2015.12.020.
9. Catton, C.N.; Lukka, H.; Gu, C.S.; Martin, J.M.; Supiot, S.; Chung, P.W.M.; Bauman, G.S.; Bahary, J.P.; Ahmed, S.; Cheung, P., et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017, 35, 1884-1890; DOI: 10.1200/JCO.2016.71.7397.
10. Dearnaley, D.; Hall, E. How will the chhip trial affect the future of prostate radiotherapy? Expert review of anticancer therapy 2018, 18, 607-609; DOI: 10.1080/14737140.2018.1477595.

11. Grimm, P.; Billiet, I.; Bostwick, D.; Dicker, A.P.; Frank, S.; Immerzeel, J.; Keyes, M.; Kupelian, P.; Lee, W.R.; Machtens, S., et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the prostate cancer results study group. BJU international 2012, 109 Suppl 1, 22-29; DOI: 10.1111/j.1464-410X.2011.10827.x.

12. Morton, G.C.; Hoskin, P.J. Brachytherapy: Current status and future strategies -- can high dose rate replace low dose rate and external beam radiotherapy? Clinical oncology (Royal College of Radiologists (Great Britain)) 2013, 25, 474-482; DOI: 10.1016/j.clon.2013.04.009.

13. Prada, P.J.; Ferri, M.; Cardenal, J.; Blanco, A.G.; Anchuelo, J.; Diaz de Cerio, I.; Vazquez, A.; Pacheco, M.; Raba, I.; Ruiz, S. High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results. Brachytherapy 2018; DOI: 10.1016/j.brachy.2018.06.002.

14. Morris, W.J.; Tyldesley, S.; Rodda, S.; Halperin, R.; Pai, H.; McKenzie, M.; Duncan, G.; Morton, G.; Hamm, J.; Murray, N. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ascende-rt trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017, 98, 275-285; DOI: 10.1016/j.ijrobp.2016.11.026.

15. Zumsteg, Z.S.; Spratt, D.E.; Romesser, P.B.; Pei, X.; Zhang, Z.; Polkinghorn, W.; McBride, S.; Kollmeier, M.; Yamada, Y.; Zelefsky, M.J. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol 2015, 67, 1009-1016; DOI: 10.1016/j.eururo.2014.09.028.

16. Wise, A.M.; Stamey, T.A.; McNeal, J.E.; Clayton, J.L. Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. Urology 2002, 60, 264-269.

17. Andreoiu, M.; Cheng, L. Multifocal prostate cancer: Biologic, prognostic, and therapeutic implications. Human pathology 2010, 41, 781-793; DOI: 10.1016/j.humpath.2010.02.011.

18. Liu, W.; Laitinen, S.; Khan, S.; Vihinen, M.; Kowalski, J.; Yu, G.; Chen, L.; Ewing, C.M.; Eisenberger, M.A.; Carducci, M.A., et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nature medicine 2009, 15, 559-565; DOI: 10.1038/nm.1944.

19. Ahmed, H.U. The index lesion and the origin of prostate cancer. N Engl J Med 2009, 361, 1704-1706; DOI: 10.1056/NEJMcibr0905562.

20. Ahmed, H.U.; Pendse, D.; Illing, R.; Allen, C.; van der Meulen, J.H.; Emberton, M. Will focal therapy become a standard of care for men with localized prostate cancer? Nature clinical practice. Oncology 2007, 4, 632-642; DOI: 10.1038/ncponc0959.

21. Arrayeh, E.; Westphalen, A.C.; Kurhanewicz, J.; Roach, M., 3rd; Jung, A.J.; Carroll, P.R.; Coakley, F.V. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal mri and mrsi study. Int J Radiat Oncol Biol Phys 2012, 82, e787-793; DOI: 10.1016/j.ijrobp.2011.11.030.

22. Cellini, N.; Morganti, A.G.; Mattiucci, G.C.; Valentini, V.; Leone, M.; Luzi, S.; Manfredi, R.; Dinapoli, N.; Digesu, C.; Smaniotto, D. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: Implications for conformal therapy planning. Int J Radiat Oncol Biol Phys 2002, 53, 595-599.

23. Chopra, S.; Toi, A.; Taback, N.; Evans, A.; Haider, M.A.; Milosevic, M.; Bristow, R.G.; Chung, P.; Bayley, A.; Morton, G., et al. Pathological predictors for site of local recurrence after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2012, 82, e441-448; DOI: 10.1016/j.ijrobp.2011.05.035.

24. Pucar, D.; Hricak, H.; Shukla-Dave, A.; Kuroiwa, K.; Drobnjak, M.; Eastham, J.; Scardino, P.T.; Zelefsky, M.J. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: Magnetic resonance imaging and step-section pathology evidence. Int J Radiat Oncol Biol Phys 2007, 69, 62-69; DOI: 10.1016/j.ijrobp.2007.03.065.

25. Jalloh, M.; Leapman, M.S.; Cowan, J.E.; Shinohara, K.; Greene, K.L.; Roach, M., 3rd; Chang, A.J.; Chan, J.M.; Simko, J.P.; Carroll, P.R. Patterns of local failure following radiation therapy for prostate cancer. The Journal of urology 2015, 194, 977-982; DOI: 10.1016/j.juro.2015.04.111.

26. Chade, D.C.; Eastham, J.; Graefen, M.; Hu, J.C.; Karnes, R.J.; Klotz, L.; Montorsi, F.; van Poppel, H.; Scardino, P.T.; Shariat, S.F. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: A systematic review of the literature. Eur Urol 2012, 61, 961-971; DOI: 10.1016/j.eururo.2012.01.022.

27. Wenske, S.; Quarrier, S.; Katz, A.E. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: Long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. Eur Urol 2013, 64, 1-7; DOI: 10.1016/j.eururo.2012.07.008.

28. Williams, A.K.; Martinez, C.H.; Lu, C.; Ng, C.K.; Pautler, S.E.; Chin, J.L. Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. Eur Urol 2011, 60, 405-410; DOI: 10.1016/j.eururo.2010.12.012.

29. Murat, F.J.; Poissonnier, L.; Rabilloud, M.; Belot, A.; Bouvier, R.; Rouviere, O.; Chapelon, J.Y.; Gelet, A. Mid-term results demonstrate salvage high-intensity focused ultrasound (hifu) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol 2009, 55, 640-647; DOI: 10.1016/j.eururo.2008.04.091.

30. Crouzet, S.; Murat, F.J.; Pommier, P.; Poissonnier, L.; Pasticier, G.; Rouviere, O.; Chapelon, J.Y.; Rabilloud, M.; Belot, A.; Mege-Lechevallier, F., et al. Locally recurrent prostate cancer after initial radiation therapy: Early salvage high-intensity focused ultrasound improves oncologic outcomes. Radiother Oncol 2012, 105, 198-202; DOI: 10.1016/j.radonc.2012.09.014.

31. Chen, C.P.; Weinberg, V.; Shinohara, K.; Roach, M., 3rd; Nash, M.; Gottschalk, A.; Chang, A.J.; Hsu, I.C. Salvage hdr brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. Int J Radiat Oncol Biol Phys 2013, 86, 324-329; DOI: 10.1016/j.ijrobp.2013.01.027.

32. Kollmeier, M.A.; McBride, S.; Taggar, A.; Anderson, E.; Lin, M.; Pei, X.; Weiji, S.; Voros, L.; Cohen, G.; Yamada, Y., et al. Salvage brachytherapy for recurrent prostate cancer after definitive radiation therapy: A comparison of low-dose-rate and high-dose-rate brachytherapy and the importance of prostate-specific antigen doubling time. Brachytherapy 2017, 16, 1091-1098; DOI: 10.1016/j.brachy.2017.07.013.

33. Wojcieszek, P.; Szlag, M.; Glowacki, G.; Cholewka, A.; Gawkowska-Suwinska, M.; Kellas-Sleczka, S.; Bialas, B.; Fijalkowski, M. Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure. Radiother Oncol 2016, 119, 405-410; DOI: 10.1016/j.radonc.2016.04.032.

34. Nguyen, P.L.; Alibhai, S.M.; Basaria, S.; D'Amico, A.V.; Kantoff, P.W.; Keating, N.L.; Penson, D.F.; Rosario, D.J.; Tombal, B.; Smith, M.R. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 2015, 67, 825-836; DOI: 10.1016/j.eururo.2014.07.010.

35. Peters, M.; Moman, M.R.; van der Poel, H.G.; Vergunst, H.; de Jong, I.J.; Vijverberg, P.L.; Battermann, J.J.; Horenblas, S.; van Vulpen, M. Patterns of outcome and toxicity after salvage prostatectomy, salvage cryosurgery and salvage brachytherapy for prostate cancer recurrences after radiation therapy: A multi-center experience and literature review. World journal of urology 2013, 31, 403-409; DOI: 10.1007/s00345-012-0928-8.

36. Tran, H.; Kwok, J.; Pickles, T.; Tyldesley, S.; Black, P.C. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol 2014, 32, 701-706; DOI: 10.1016/j.urolonc.2013.12.014.

37. Agarwal, P.K.; Sadetsky, N.; Konety, B.R.; Resnick, M.I.; Carroll, P.R.; Cancer of the Prostate Strategic Urological Research, E. Treatment failure after primary and salvage therapy for prostate cancer: Likelihood, patterns of care, and outcomes. Cancer 2008, 112, 307-314; DOI: 10.1002/cncr.23161.

38. Abuzallouf, S.; Dayes, I.; Lukka, H. Baseline staging of newly diagnosed prostate cancer: A summary of the literature. The Journal of urology 2004, 171, 2122-2127.

39. Hovels, A.M.; Heesakkers, R.A.; Adang, E.M.; Jager, G.J.; Strum, S.; Hoogeveen, Y.L.; Severens, J.L.; Barentsz, J.O. The diagnostic accuracy of ct and mri in the staging of pelvic lymph nodes in patients with prostate cancer: A meta-analysis. Clinical radiology 2008, 63, 387-395; DOI: 10.1016/j.crad.2007.05.022.

40. Evangelista, L.; Guttilla, A.; Zattoni, F.; Muzzio, P.C.; Zattoni, F. Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate- to high-risk prostate cancer: A systematic literature review and meta-analysis. Eur Urol 2013, 63, 1040-1048; DOI: 10.1016/j.eururo.2012.09.039.

41. Evangelista, L.; Zattoni, F.; Guttilla, A.; Saladini, G.; Zattoni, F.; Colletti, P.M.; Rubello, D. Choline pet or pet/ct and biochemical relapse of prostate cancer: A systematic review and meta-analysis. Clinical nuclear medicine 2013, 38, 305-314; DOI: 10.1097/RLU.0b013e3182867f3c.

42. Wallitt, K.L.; Khan, S.R.; Dubash, S.; Tam, H.H.; Khan, S.; Barwick, T.D. Clinical pet imaging in prostate cancer. Radiographics : a review publication of the Radiological Society of North America, Inc 2017, 37, 1512-1536; DOI: 10.1148/rg.2017170035.

43. Perera, M.; Papa, N.; Christidis, D.; Wetherell, D.; Hofman, M.S.; Murphy, D.G.; Bolton, D.; Lawrentschuk, N. Sensitivity, specificity, and predictors of positive (68)ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: A systematic review and meta-analysis. Eur Urol 2016, 70, 926-937; DOI: 10.1016/j.eururo.2016.06.021.

44. Afshar-Oromieh, A.; Zechmann, C.M.; Malcher, A.; Eder, M.; Eisenhut, M.; Linhart, H.G.; Holland-Letz, T.; Hadaschik, B.A.; Giesel, F.L.; Debus, J., et al. Comparison of pet imaging with a (68) ga-labelled psma ligand and (18)f-choline-based pet/ct for the diagnosis of recurrent prostate cancer. European journal of nuclear medicine and molecular imaging 2014, 41, 11-20; DOI: 10.1007/s00259-013-2525-5.

45. Afshar-Oromieh, A.; Malcher, A.; Eder, M.; Eisenhut, M.; Linhart, H.G.; Hadaschik, B.A.; Holland-Letz, T.; Giesel, F.L.; Kratochwil, C.; Haufe, S., et al. Pet imaging with a [68ga]gallium-labelled psma ligand for the diagnosis of prostate cancer: Biodistribution in humans and first evaluation of tumor lesions. European journal of nuclear medicine and molecular imaging 2013, 40, 486-495; DOI: 10.1007/s00259-012-2298-2.

46. Perera, M.; Murphy, D.; Lawrentschuk, N. Prostate-specific membrane antigen positron emission tomography/computed tomography in locally advanced, recurrent, and metastatic prostate cancer. JAMA oncology 2018, 4, 748-749; DOI: 10.1001/jamaoncol.2017.0287.

47. Zacho, H.D.; Nielsen, J.B.; Afshar-Oromieh, A.; Haberkorn, U.; deSouza, N.; De Paepe, K.; Dettmann, K.; Langkilde, N.C.; Haarmark, C.; Fisker, R.V., et al. Prospective comparison of (68)ga-psma pet/ct, (18)f-sodium fluoride pet/ct and diffusion weighted-mri at for the detection of bone metastases in biochemically recurrent prostate cancer. European journal of nuclear medicine and molecular imaging 2018; DOI: 10.1007/s00259-018-4058-4.

48. Kanthabalan, A.; Shah, T.; Arya, M.; Punwani, S.; Bomanji, J.; Haroon, A.; Illing, R.O.; Latifoltojar, A.; Freeman, A.; Jameson, C., et al. The forecast study - focal recurrent assessment and salvage treatment for radiorecurrent prostate cancer. Contemporary clinical trials 2015, 44, 175-186; DOI: 10.1016/j.cct.2015.07.004.

49. Futterer, J.J.; Briganti, A.; De Visschere, P.; Emberton, M.; Giannarini, G.; Kirkham, A.; Taneja, S.S.; Thoeny, H.; Villeirs, G.; Villers, A. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015, 68, 1045-1053; DOI: 10.1016/j.eururo.2015.01.013.

50. Ahmed, H.U.; El-Shater Bosaily, A.; Brown, L.C.; Gabe, R.; Kaplan, R.; Parmar, M.K.; Collaco-Moraes, Y.; Ward, K.; Hindley, R.G.; Freeman, A., et al. Diagnostic accuracy of multi-parametric mri and trus biopsy in prostate cancer (promis): A paired validating confirmatory study. Lancet 2017, 389, 815-822; DOI: 10.1016/S0140-6736(16)32401-1.

51. Le, J.D.; Tan, N.; Shkolyar, E.; Lu, D.Y.; Kwan, L.; Marks, L.S.; Huang, J.; Margolis, D.J.; Raman, S.S.; Reiter, R.E. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: Correlation with whole-mount histopathology. Eur Urol 2015, 67, 569-576; DOI: 10.1016/j.eururo.2014.08.079.

52. Haider, M.A.; Chung, P.; Sweet, J.; Toi, A.; Jhaveri, K.; Menard, C.; Warde, P.; Trachtenberg, J.; Lockwood, G.; Milosevic, M. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys 2008, 70, 425-430; DOI: 10.1016/j.ijrobp.2007.06.029.

53. Roy, C.; Foudi, F.; Charton, J.; Jung, M.; Lang, H.; Saussine, C.; Jacqmin, D. Comparative sensitivities of functional mri sequences in detection of local recurrence of prostate carcinoma after radical prostatectomy or external-beam radiotherapy. AJR. American journal of roentgenology 2013, 200, W361-368; DOI: 10.2214/AJR.12.9106.

54. Arumainayagam, N.; Kumaar, S.; Ahmed, H.U.; Moore, C.M.; Payne, H.; Freeman, A.; Allen, C.; Kirkham, A.; Emberton, M. Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy. BJU international 2010, 106, 991-997; DOI: 10.1111/j.1464-410X.2010.09291.x.

55. Gaur, S.; Turkbey, B. Prostate mr imaging for posttreatment evaluation and recurrence. Radiologic clinics of North America 2018, 56, 263-275; DOI: 10.1016/j.rcl.2017.10.008.

56. Oppenheimer, D.C.; Weinberg, E.P.; Hollenberg, G.M.; Meyers, S.P. Multiparametric magnetic resonance imaging of recurrent prostate cancer. Journal of clinical imaging science 2016, 6, 18; DOI: 10.4103/2156-7514.181494.

57. Panebianco, V.; Barchetti, F.; Grompone, M.D.; Colarieti, A.; Salvo, V.; Cardone, G.; Catalano, C. Magnetic resonance imaging for localization of prostate cancer in the setting of biochemical recurrence. Urol Oncol 2016, 34, 303-310; DOI: 10.1016/j.urolonc.2016.01.004.

58. Patel, P.; Mathew, M.S.; Trilisky, I.; Oto, A. Multiparametric mr imaging of the prostate after treatment of prostate cancer. Radiographics : a review publication of the Radiological Society of North America, Inc 2018, 38, 437-449; DOI: 10.1148/rg.2018170147.

59. Hotker, A.M.; Meier, A.; Mazaheri, Y.; Zheng, J.; Capanu, M.; Chaim, J.; Sosa, R.; Coleman, J.; Hricak, H.; Akin, O. Temporal changes in mri appearance of the prostate after focal ablation. Abdominal radiology 2018; DOI: 10.1007/s00261-018-1715-9.

60. Taneja, S.; Jena, A.; Taneja, R.; Singh, A.; Ahuja, A. Effect of combined (68) ga-psmahbed-cc uptake pattern and multiparametric mri derived with simultaneous pet/mri in the diagnosis of primary prostate cancer: Initial experience. AJR. American journal of roentgenology 2018, 210, 1338-1345; DOI: 10.2214/AJR.17.18881.

61. Afshar-Oromieh, A.; Avtzi, E.; Giesel, F.L.; Holland-Letz, T.; Linhart, H.G.; Eder, M.; Eisenhut, M.; Boxler, S.; Hadaschik, B.A.; Kratochwil, C., et al. The diagnostic value of pet/ct imaging with the (68) ga-labelled psma ligand hbed-cc in the diagnosis of recurrent prostate cancer. European journal of nuclear medicine and molecular imaging 2015, 42, 197-209; DOI: 10.1007/s00259-014-2949-6.

62. Han, S.; Woo, S.; Kim, Y.J.; Suh, C.H. Impact of (68)ga-psma pet on the management of patients with prostate cancer: A systematic review and meta-analysis. Eur Urol 2018, 74, 179-190; DOI: 10.1016/j.eururo.2018.03.030.

63. Kasivisvanathan, V.; Rannikko, A.S.; Borghi, M.; Panebianco, V.; Mynderse, L.A.; Vaarala, M.H.; Briganti, A.; Budaus, L.; Hellawell, G.; Hindley, R.G., et al. Mri-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018, 378, 1767-1777; DOI: 10.1056/NEJMoa1801993.

64. Tran, M.; Thompson, J.; Bohm, M.; Pulbrook, M.; Moses, D.; Shnier, R.; Brenner, P.; Delprado, W.; Haynes, A.M.; Savdie, R., et al. Combination of multiparametric mri and transperineal template-guided mapping biopsy of the prostate to identify candidates for hemi-ablative focal therapy. BJU international 2016, 117, 48-54; DOI: 10.1111/bju.13090.

65. Wegelin, O.; Exterkate, L.; Somford, D.; Barentsz, J.; Van Der Leest, M.; Kummer, A.; Vreuls, W.; De Bruin, P.; Bosch, R.; Van Melick, H. The future trial; a multicenter rct on three techniques of mri targeted prostate biopsy. In EAU 18, Copenhagen, 2018.

66. Crook, J.; Malone, S.; Perry, G.; Bahadur, Y.; Robertson, S.; Abdolell, M. Postradiotherapy prostate biopsies: What do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys 2000, 48, 355-367.

67. Kass-Iliyya, A.; Jovic, G.; Murphy, C.; Fisher, C.; Syndikus, I.; Jose, C.; Scrase, C.D.; Graham, J.D.; Nicol, D.; Sydes, M.R., et al. Two-years postradiotherapy biopsies: Lessons from mrc rt01 trial. Eur Urol 2018, 73, 968-976; DOI: 10.1016/j.eururo.2017.12.017.

68. Cornford, P.; Bellmunt, J.; Bolla, M.; Briers, E.; De Santis, M.; Gross, T.; Henry, A.M.; Joniau, S.; Lam, T.B.; Mason, M.D., et al. Eau-estro-siog guidelines on prostate cancer. Part ii: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017, 71, 630-642; DOI: 10.1016/j.eururo.2016.08.002.

69. Kanthabalan, A.; Abd-Alazeez, M.; Arya, M.; Allen, C.; Freeman, A.; Jameson, C.; Kirkham, A.; Mitra, A.V.; Payne, H.; Punwani, S., et al. Transperineal magnetic resonance imaging-targeted biopsy versus transperineal template prostate mapping biopsy in the detection of localized radio-recurrent prostate cancer. Clinical oncology (Royal College of Radiologists (Great Britain)) 2016, 28, 568-576; DOI: 10.1016/j.clon.2016.04.038.

70. Crook, J.M.; Bahadur, Y.A.; Robertson, S.J.; Perry, G.A.; Esche, B.A. Evaluation of radiation effect, tumor differentiation, and prostate specific antigen staining in sequential prostate biopsies after external beam radiotherapy for patients with prostate carcinoma. Cancer 1997, 79, 81-89.

71. Goldstein, N.S.; Martinez, A.; Vicini, F.; Stromberg, J. The histology of radiation therapy effect on prostate adenocarcinoma as assessed by needle biopsy after brachytherapy boost. Correlation with biochemical failure. American journal of clinical pathology 1998, 110, 765-775.

72. Grignon, D.J.; Sakr, W.A. Histologic effects of radiation therapy and total androgen blockade on prostate cancer. Cancer 1995, 75, 1837-1841.

73. de Castro Abreu, A.L.; Bahn, D.; Leslie, S.; Shoji, S.; Silverman, P.; Desai, M.M.; Gill, I.S.; Ukimura, O. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. BJU international 2013, 112, 298-307; DOI: 10.1111/bju.12151.

74. Kongnyuy, M.; Berg, C.J.; Kosinski, K.E.; Habibian, D.J.; Schiff, J.T.; Corcoran, A.T.; Katz, A.E. Salvage focal cryosurgery may delay use of androgen deprivation therapy in cryotherapy and radiation recurrent prostate cancer patients. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 2017, 33, 810-813; DOI: 10.1080/02656736.2017.1306121.

75. Li, Y.H.; Elshafei, A.; Agarwal, G.; Ruckle, H.; Powsang, J.; Jones, J.S. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: Initial results from the cryo online data registry. The Prostate 2015, 75, 1-7; DOI: 10.1002/pros.22881.

76. Kanthabalan, A.; Peters, M.; Van Vulpen, M.; McCartan, N.; Hindley, R.G.; Emara, A.; Moore, C.M.; Arya, M.; Emberton, M.; Ahmed, H.U. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU international 2017, 120, 246-256; DOI: 10.1111/bju.13831.

77. Kunogi, H.; Wakumoto, Y.; Yamaguchi, N.; Horie, S.; Sasai, K. Focal partial salvage low-dose-rate brachytherapy for local recurrent prostate cancer after permanent prostate brachytherapy with a review of the literature. J Contemp Brachytherapy 2016, 8, 165-172; DOI: 10.5114/jcb.2016.60452.

78. Peters, M.; Maenhout, M.; van der Voort van Zyp, J.R.; Moerland, M.A.; Moman, M.R.; Steuten, L.M.; van Deursen, M.J.; van Vulpen, M. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: A retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol 2014, 112, 77-82; DOI: 10.1016/j.radonc.2014.06.013.

79. Zamboglou, C.; Rischke, H.C.; Meyer, P.T.; Knobe, S.; Volgeova-Neher, N.; Kollefrath, M.; Jilg, C.A.; Grosu, A.L.; Baltas, D.; Kroenig, M. Single fraction multimodal image guided focal salvage high-dose-rate brachytherapy for recurrent prostate cancer. J Contemp Brachytherapy 2016, 8, 241-248; DOI: 10.5114/jcb.2016.61067.

80. Maenhout, M.; Peters, M.; van Vulpen, M.; Moerland, M.A.; Meijer, R.P.; van den Bosch, M.; Nguyen, P.L.; Frank, S.J.; van der Voort van Zyp, J.R.N. Focal mri-guided salvage high-dose-rate brachytherapy in patients with radiorecurrent prostate cancer. Technology in cancer research & treatment 2017, 16, 1194-1201; DOI: 10.1177/1533034617741797.

81. Murgic, J.; Morton, G.; Loblaw, A.; D'Alimonte, L.; Ravi, A.; Wronski, M.; Davidson, M.; Haider, M.; Commisso, K.; Zhang, L., et al. Focal salvage high dose-rate brachytherapy for locally recurrent prostate cancer after primary radiation therapy failure: Results from a prospective clinical trial. Int J Radiat Oncol Biol Phys 2018, 102, 561-567; DOI: 10.1016/j.ijrobp.2018.06.039.

82. Jereczek-Fossa, B.A.; Beltramo G.; Fariselli L.; Fodor C.; Santoro L.; Vavassori A.; Zerini D.; Gherardi F.; Ascione C.; Bossi-Zanetti I.; Mauro R.; Bregantin A.; Bianchi LC.; De Cobelli O.; Orecchia R. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. International journal of radiation oncology, biology, physics 2012, 82, 889-897; DOI: 10.1016/j.ijrobp.2010.11.031.

83. Mbeutcha, A.; Chauveinc, L.; Bondiau, P.Y.; Chand, M.E.; Durand, M.; Chevallier, D.; Amiel, J.; Kee, D.L.; Hannoun-Levi, J.M. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. Radiation oncology (London, England) 2017, 12, 49; DOI: 10.1186/s13014-017-0789-9.

84. Golbari, N.M.; Katz, A.E. Salvage therapy options for local prostate cancer recurrence after primary radiotherapy: A literature review. Curr Urol Rep 2017, 18, 63; DOI: 10.1007/s11934-017-0709-4.

85. Zdrojowy, R.; Dembowski, J.; Malkiewicz, B.; Tupikowski, K.; Krajewski, W. Salvage local therapy for radiation-recurrent prostate cancer - where are we? Central European journal of urology 2016, 69, 264-270; DOI: 10.5173/ceju.2016.832.

86. Duijzentkunst, D.A.; Peters, M.; van der Voort van Zyp, J.R.; Moerland, M.A.; van Vulpen, M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: A comprehensive review. World journal of urology 2016, 34, 1521-1531; DOI: 10.1007/s00345-016-1811-9.

87. Eiber, M.; Weirich, G.; Holzapfel, K.; Souvatzoglou, M.; Haller, B.; Rauscher, I.; Beer, A.J.; Wester, H.J.; Gschwend, J.; Schwaiger, M., et al. Simultaneous (68) ga-psma hbed-cc pet/mri improves the localization of primary prostate cancer. Eur Urol 2016, 70, 829-836; DOI: 10.1016/j.eururo.2015.12.053.

88. Kaljouw, E.; Pieters, B.R.; Kovacs, G.; Hoskin, P.J. A delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a uro-gec study. Radiother Oncol 2016, 118, 122-130; DOI: 10.1016/j.radonc.2015.10.021.

89. Peters, M.; Kanthabalan, A.; Shah, T.T.; McCartan, N.; Moore, C.M.; Arya, M.; van der Voort van Zyp, J.R.; Moerland, M.A.; Hindley, R.G.; Emberton, M., et al. Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: Presentation of risk scores for individual patient prognoses. Urol Oncol 2018, 36, 13 e11-13 e10; DOI: 10.1016/j.urolonc.2017.08.022.

90. Chung H, D.A.L., Loblaw A, et al. Three-year results of a prospective study on focal salvage hdr prostate brachytherapy after previous definitive external beam radiotherapy. Brachytherapy 2017, 16, S63.

91. Barret, E.; Turkbey, B.; Puech, P.; Durand, M.; Panebianco, V.; Futterer, J.J.; Renard-Penna, R.; Rouviere, O. Update on the icud-siu consultation on multi-parametric magnetic resonance imaging in localized prostate cancer. World journal of urology 2018; DOI: 10.1007/s00345-018-2395-3.

92. Ashrafi, A.N.; Tafuri, A.; Cacciamani, G.E.; Park, D.; de Castro Abreu, A.L.; Gill, I.S. Focal therapy for prostate cancer: Concepts and future directions. Current opinion in urology 2018; DOI: 10.1097/MOU.0000000000000539.

93. Lagemaat, M.W.; Philips, B.W.; Vos, E.K.; van Uden, M.J.; Futterer, J.J.; Jenniskens, S.F.; Scheenen, T.W.; Maas, M.C. Feasibility of multiparametric magnetic resonance imaging of the prostate at 7 t. Investigative radiology 2017, 52, 295-301; DOI: 10.1097/RLI.0000000000000342.

94. Onofrey, J.A.; Staib, L.H.; Sarkar, S.; Venkataraman, R.; Nawaf, C.B.; Sprenkle, P.C.; Papademetris, X. Learning non-rigid deformations for robust, constrained point-based registration in image-guided mr-trus prostate intervention. Medical image analysis 2017, 39, 29-43; DOI: 10.1016/j.media.2017.04.001.

95. Tharmalingam, H.; Alonzi, R.; Hoskin, P.J. The role of magnetic resonance imaging in brachytherapy. Clinical oncology (Royal College of Radiologists (Great Britain)) 2018; DOI: 10.1016/j.clon.2018.07.024.

96. van den Bosch, M.R.; Moman, M.R.; van Vulpen, M.; Battermann, J.J.; Duiveman, E.; van Schelven, L.J.; de Leeuw, H.; Lagendijk, J.J.; Moerland, M.A. Mri-guided robotic system for transperineal prostate interventions: Proof of principle. Physics in medicine and biology 2010, 55, N133-140; DOI: 10.1088/0031-9155/55/5/N02.

97. Borot de Battisti, M.; Maenhout, M.; Denis de Senneville, B.; Hautvast, G.; Binnekamp, D.; Lagendijk, J.J.; van Vulpen, M.; Moerland, M.A. An automated optimization tool for high-dose-rate (hdr) prostate brachytherapy with divergent needle pattern. Physics in medicine and biology 2015, 60, 7567-7583; DOI: 10.1088/0031-9155/60/19/7567.

98. Kontaxis, C.; Bol, G.H.; Kerkmeijer, L.G.W.; Lagendijk, J.J.W.; Raaymakers, B.W. Fast online replanning for interfraction rotation correction in prostate radiotherapy. Medical physics 2017, 44, 5034-5042; DOI: 10.1002/mp.12467.

CHAPTER 5

MRI-guided ultrafocal salvage high-dose-rate brachytherapy for localized radiorecurrent prostate cancer: updated results of 50 patients

Authors: Marieke J. van Son, Max Peters, Marinus A. Moerland, Jan J.W. Lagendijk, Wietse S.C. Eppinga, Taimur T. Shah, Hashim U. Ahmed, Jochem R.N. van der Voort van Zyp

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS

ABSTRACT

Purpose

Most patients with local prostate cancer recurrence after radiation therapy undergo palliative androgen deprivation therapy (ADT), since whole-gland salvage treatments have a high risk of severe toxicity. Focal treatment reduces this risk while offering a second opportunity for cure. We report updated outcomes of ultrafocal salvage high-dose-rate brachytherapy (HDR-BT).

Methods and Materials

Prospectively collected data from the first 50 treated patients were analyzed. Disease status was assessed by 3T multiparametric MRI, 18F-Choline or 68Ga-PSMA PET/CT and systematic or tumor-targeted biopsies. Ultrafocal salvage HDR-BT (1x19 Gy) was performed by implanting the clinical target volume (CTV: gross tumor volume + 5mm margin) under fused TRUS/MRI guidance. Follow-up included toxicity grading (using CTCAE 4.0), quality of life (QoL) assessment and PSA-testing.

Results

Median follow-up was 31 months. Median CTV D95% was 18.8 Gy. We observed 2% grade 3 genitourinary toxicity, no grade 3 gastro-intestinal toxicity and 22% newly developed grade 3 erectile dysfunction. Five out of 13 patients (38%) with self-reported pre-treatment potency (IIEF>17) remained potent. Clinically relevant QoL deterioration was reported for only 6/31 items, not statistically significant. Biochemical failure (nadir+2) occurred in 26 patients. Among intraprostatic recurrences, 73% were in-field. After 2.5 years, biochemical disease-free survival (BDFS) was 51% (95% CI 37-69%), metastases-free survival 75% (64-89%), ADT-free survival 90% (82-99%) and overall survival 98% (94-100%). Pre-salvage PSA, CTV size and stage ≥T3 were significantly associated with biochemical failure. Higher-risk patients (stage≥T3, PSA≥10, or PSADT≤9 months) had 25% BDFS at 2.5 years versus 71% for lower-risk patients.

Conclusions

At this early stage, MRI-guided ultrafocal HDR-BT seems to be a safe salvage treatment option, with acceptable biochemical control in a well-selected group of patients, and the potential of effectively postponing ADT.

INTRODUCTION

According to current cancer statistics, about one in nine men will be diagnosed with prostate cancer during their lifetime.[1] Approximately 30% of patients are primarily treated with radiotherapy, either with external beam or brachytherapy.[2] Even with modern technical advancements, post-radiation recurrences occur in 10-40% of patients after 10 years of follow-up.[3-5] The benefit of re-treatment must be weighed against a higher chance of (severe) toxicity in the radiorecurrent setting. Furthermore, the impact on quality of life (QoL) has taken a more prominent role in management decisions.

Although early recurrences are often confined to the prostate,[6] most patients are treated with systemic androgen deprivation therapy (ADT).[7] This has a temporary suppressive effect until the tumor becomes castration-resistant after a median of 3 years.[8] Side-effects range from hot flushes and lowered libido to changes in blood lipids, insulin resistance and loss of bone density.[9] However, due to high toxicity rates, curative whole-gland salvage treatments such as salvage prostatectomy, brachytherapy, cryotherapy or high-intensity focused ultrasound (HIFU) remain unpopular. Common side-effects are urinary incontinence (±10-50%), urethral strictures (±5-25%), fistulas (±2-4%) and impotence (±80-90%).[10]

In contrast, focal ablation spares the healthy surrounding tissue, thereby reducing the risk of severe side-effects and associated QoL deterioration. Although with curative intent, the aim of focal salvage treatment is to postpone or potentially avoid the need for palliative ADT.

At the UMC Utrecht, we perform ultrafocal ablation with MRI-guided high-dose-rate brachytherapy (HDR-BT). In a previous report, we presented clinical outcomes of the first 17 patients with a median follow-up of 10 months.[11] The current report provides an update on those results, with prospectively collected data from an extended patient group with longer follow-up.

METHODS

Patient selection

Since 2013, MRI-guided ultrafocal salvage HDR-BT has been offered to patients with localized radiorecurrent prostate cancer at the UMC Utrecht. A group of 30 patients with PSA-level ≤10 ng/ml, PSA doubling time (PSADT) ≥12 months, tumor stage ≤T2c on MRI and acceptable urinary function (International Prostate Symptom Score [IPSS]<15) was treated within an institutional review board (IRB)-approved prospective feasibility study. Toxicity rates proved to be very low and after two years of inclusion, experience allowed for extended treatment of patients beyond the initial selection criteria. All underwent radiologic disease status assessment with 3T multiparametric (mp)-MRI and 68Ga-PSMA PET-CT (or 18F-Choline PET-CT if treated before 2016) and tumor-targeted (cognitive or MRI-TRUS fusion) prostate biopsies. 24% of patients underwent systematic

biopsies at their referring center. All patients had at least two years recurrence-free interval after primary radiation treatment.

We analyzed the first consecutive 50 patients, treated between July 2013 and April 2017. This group consists of 23 patients from the feasibility study and 27 patients treated off-protocol. All patients were followed in the same prospective manner. Informed consent was obtained from all study patients. For patients treated off- protocol, the IRB waived the requirement for informed consent.

Ultrafocal salvage HDR-BT

The treatment procedure has been described in a previous paper.[11] In summary, the radiation plan is based on delineations of the gross tumor volume (GTV), the clinical target volume (CTV, GTV+5mm margin) and the organs at risk (OAR's), namely bladder, rectum and urethra. Under spinal anesthesia, MR-compatible brachytherapy catheters are perineally inserted into the CTV, guided by fused TRUS/MR images. Another 1.5T MRI is made for catheter reconstruction, contour adaptation and a simulation of dose distribution by the Oncentra Prostate treatment planning system (Elekta, The Netherlands). The dosimetric goal is to deliver ≥19 Gy to 95% of the CTV (CTV D95%), with a lower threshold of >17 Gy to 90% of the CTV (CTV D90%). Dose constraints for bladder and rectum D1cc (minimal dose to the most exposed 1 cc) is <12 Gy and for the urethra D10% (minimal dose to 10% of the urethra) <17.7 Gy. An additional 1.5T MRI-scan is made just before dose administration to check for any catheter displacements to ensure safe delivery of the planned radiation dose.

Outcome assessment

Follow-up is scheduled four weeks after treatment and every three months in the first year, every six months in the second year and annually thereafter for up to 10 years. At each time point, outcome assessment is performed by (1) grading GU, GI and erectile toxicity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and by obtaining IPSS and International Index of Erectile Function (IIEF-5) scores, (2) assessing patient-reported QoL using the RAND-36, EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires and (3) routine PSA-testing. In case of biochemical recurrence after treatment (defined as PSA nadir+2 ng/ml, i.e. Phoenix definition), patients undergo 68Ga-PSMA PET-CT for disease status evaluation, followed by 3T mp-MRI in case of intraprostatic disease.

Statistical analysis

Descriptives were used for patient and tumor characteristics. Follow-up time after treatment was calculated as time from treatment to death or last PSA-measurement. QoL scores were linearly transformed to a 0-100 scale. Wilcoxon signed rank tests were used for testing differences between median scores at baseline and each follow-up time point (with $p<0.001$ considered statistically significant to correct for multiple testing). Apart from statistical definitions, QoL score differences of ≥10 points were considered

clinically relevant change.[12] Time-to-event analyses were performed using the Kaplan Meier-estimator, with no competing events between different outcomes. An explorative risk factor analysis for biochemical failure was performed with a univariable Cox regression for age, American Joint Committee on Cancer(AJCC) grade group, T-stage, PSA, PSADT and CTV size. Based on the resulting risk factors, we divided the cohort into groups of low and high risk of treatment failure to visualize the effect on biochemical disease-free survival (BDFS) curves.

Analyses were performed with R statistical software (version 3.5.1; the R foundation for Statistical Computing, Vienna, Austria) and IBM SPSS statistics (version 25.0).

RESULTS

Baseline patient and tumor characteristics are displayed in Table 1. Median follow-up was 31 months (range 13 – 58 months).

Table 1 – Baseline characteristics

	No. patients (%) / median (range)
Total	50
Primary setting	
iPSA	13 ng/ml (2.1 – 140)
Clinical T-stage	
T1c	26 (52%)
T2a	10 (20%)
T2b	1 (2%)
T3a	13 (26%)
Gleason grade group	
1	33 (66%)
2	6 (12%)
3	2 (4%)
4	3 (6%)
5	3 (6%)
Missing	3 (6%)
AJCC prognostic stage group	
Stage I	31 (62%)
Stage IIA	4 (8%)
Stage IIB	9 (18%)
Stage IIC	3 (6%)
Missing	3 (6%)
Radiation treatment	
EBRT (70-78Gy)	25 (50%)
LDR-BT (145 Gy)	25 (50%)

Table 1 Continued

	No. patients (%) / median (range)
History of ADT around primary treatment [median duration]	
No	39 (78%)
Yes, neo-adjuvant	4 (8%) [5.5 months]
Yes, adjuvant	7 (14%) [36 months]
Interval between primary treatment and biochemical recurrence	101 months (25 – 228)
Recurrent setting	
Age	71 years (59 – 83)
iPSA	5 ng/ml (0.9 – 39)
PSADT	17 months (3 – 73)
Prostate size on MRI	33 cc (15 – 105)
MRI T-stage	
T2a	19 (38%)
T2b	9 (18%)
T2c	3 (6%)
T3a	3 (6%)
T3b	14 (28%)
T4	2 (4%)
Tumor location	
Base	7 (14%)
Midgland	12 (24%)
Apex	8 (16%)
Combination	10 (20%)
Seminal vesicle	13 (26%)
PET-CT tracer	
18F-Choline	11 (22%)
68Ga-PSMA	39 (78%)
Biopsy type [median no. of cores]	
Systematic	12 (24%) [8 cores]
Tumor-targeted	35 (70%) [4 cores]
Both	3 (6%) [11 cores]
Gleason score*	
3+3=6	9 (18%)
3+4=7	17 (34%)
4+3=7	11 (22%)
Sumscore 8	4 (8%)
Sumscore 9/10	6 (12%)
Missing	3 (6%)
GTV size	3 cc (0.3 – 18.5)
CTV size	8.6 cc (3.3 – 34.9)

iPSA: initial prostate specific antigen level, EBRT: external beam radiation therapy, LDR-BT: low-dose-rate brachytherapy using I-125 seeds, ADT: androgen deprivation therapy, PSADT: PSA doubling time, GTV: gross tumor volume, CTV: clinical target volume.

Treatment characteristics

Median nine brachytherapy catheters were used for the implant (range 5-14). The CTV D95% ≥19 Gy prescription dose was achieved in 42%, with a median administered dose of 18.8 Gy (range 11.3-23 Gy). The CTV D90% >17 Gy lower threshold was achieved in 90%, with a median of 20.4 Gy (range 13.5-24.9 Gy). The main reason for underdosing the CTV was to refrain from exceeding dose constraints for the organs at risk. Median urethral D10% was 14.8 Gy (range 3.1-18.2), median bladder D1cc was 8.2 Gy (range 1.3-13.6) and median rectum D1cc was 10 Gy (range 2.3-12.2). The median percentage of target volume receiving 100%, 150% and 200% of the prescribed dose (CTV V100%, V150%, V200%) was 95%, 57% and 25%, respectively.

Toxicity

Figure 1 shows physician-graded GU, GI and erectile toxicity. GU toxicity scoring included the items hematuria, urinary frequency, urinary incontinence, urinary retention, urinary tract pain and cystitis. Severe (grade 3) toxicity occurred in one patient (2%) after 24 months follow-up. The patient underwent surgical dilation for an obstructive urethral stricture, after which he was left with urinary incontinence, requiring several incontinence pads per day. New-onset grade 2 GU toxicity was seen in 26 patients (52%), among which the prescription of medication for urinary frequency in 21 patients, use of incontinence pads for occasional urinary leakage in three patients, mild signs of cystitis in one patient and mild postmictional residue in one patient. 19/21 patients required chronic use (until last follow-up) of urinary medication and 1/3 patients required chronic use of pads.

For GI toxicity, the items abdominal pain, diarrhea, enterocolitis, fecal incontinence, flatulence, hemorrhoids, proctitis, rectal fistula, rectal hemorrhage and rectal pain were graded. No grade 3 GI toxicity occurred. New-onset grade 2 GI toxicity occurred in two patients (4%): one had transient rectal hemorrhage and one developed symptomatic hemorrhoids.

Pre-treatment grade 3 ED (severe dysfunction with insufficient effect from erectile aids) was present in nine patients (18%). New-onset grade 3 ED developed in 11 patients (22%), and new-onset grade 2 ED (dysfunction, but with sufficient effect from erectile aids) developed in another 11 patients (22%).

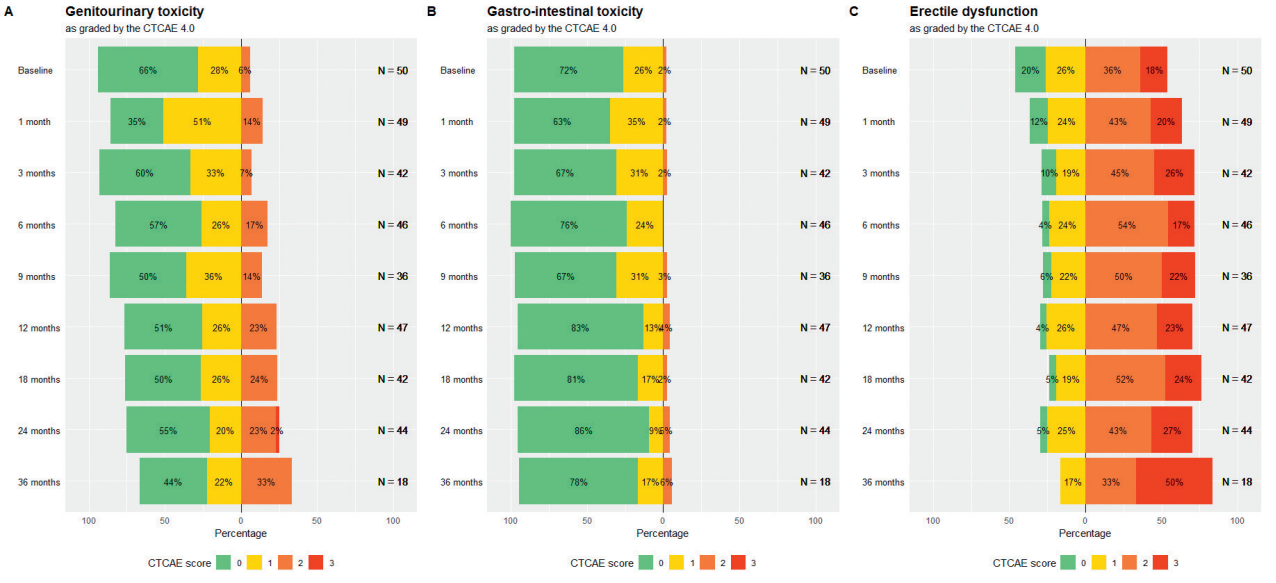

Figure 1 – Physician-graded toxicity.
a) Genitourinary toxicity, b) Gastro-intestinal toxicity, c) Erectile dysfunction.

Figure 2 shows patient-reported urinary and erectile function (IPSS and IIEF-5). For the IPSS, score 0-7 indicates mild symptoms, 8-19 indicates moderate symptoms and 20-35 indicates severe symptoms. Median baseline score was 8, increasing to a median 11.5 at one month follow-up and then returning back to baseline level (median 8 at 36 months follow-up).

For the IIEF-5, score 1-7 indicates severe ED, 8-11 indicates moderate ED, 12-16 indicates mild to moderate ED, 17-21 indicates mild ED, and 22-25 indicates absence of ED. Median baseline score was 11, which quickly deteriorated to a median 7 after the first month, with a further downward trend to median 3 at 36 months follow-up. Out of 13 patients with pre-treatment potency (here defined as IIEF≥17), five patients (38%) remained potent.

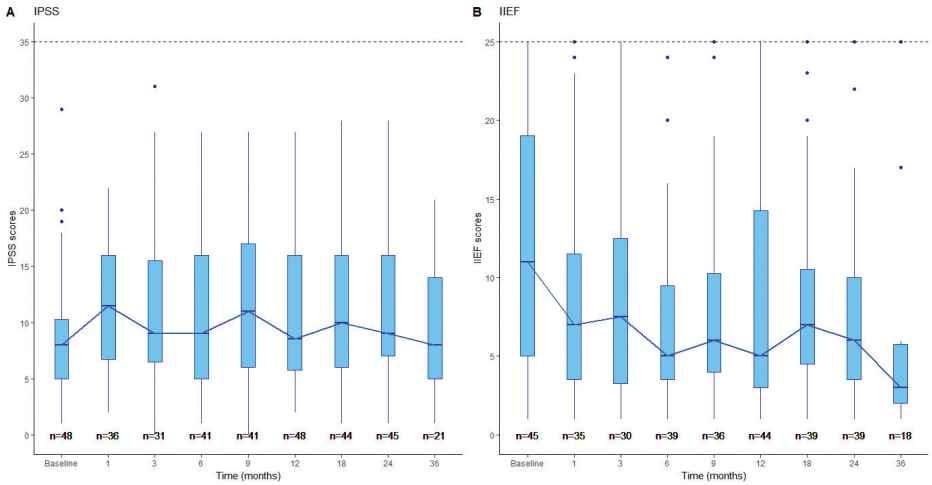

Figure 2 – Patient-reported toxicity. Medians with interquartile ranges (IQR) and complete ranges are shown. The blue dots represent outliers, defined as >1.5 * IQR.
a) IPSS (urinary symptoms), b) IIEF-5 (erectile function).

QoL

Patient-reported QoL over time is depicted in supplementary figures 1-3 (available online at https://doi.org/10.1016/j.ijrobp.2020.01.023), with separate graphs for the different domains within each questionnaire.

Within the general health survey (RAND-36), long-term clinically relevant deterioration of QoL was seen in the domains social functioning (Δ13 points) and mental health (Δ12 points). Patients reported a transient increase in pain symptoms (Δ11 points) after three months follow-up, which recovered afterwards. No statistically significant changes were seen.

Regarding cancer-related health (EORTC QLQ-C30), the domains tiredness and cognitive functioning showed long-term clinically relevant deterioration (Δ11 and 17 points, respectively). A transient increase of sleeping disturbances (Δ33 points) was seen at 24 months follow-up. Again, no statistically significant changes were observed.

Prostate cancer-related health (EORTC QLQ-PR25) was affected in the domains sexual functioning (Δ17 points) and sexual activity (Δ16 points). A clinically relevant transient increase in urinary symptoms was seen at nine months follow-up (Δ11 points), returning to baseline level afterwards. There were no statistically significant changes.

Oncologic outcomes

PSA nadir was reached after a median of 5.5 months (range 1-24 months). Biochemical recurrence (nadir+2) occurred in 26 patients (52%) after a median of 20 months (range 6-44 months).

Using 68Ga-PSMA PET-CT for disease status assessment, 22 out of 26 patients had intraprostatic recurrence. As assessed on a subsequent 3T mp-MRI scan, 16 patients (73%) had a recurrence at the site of the treated lesion (in-field recurrence) and six patients (27%) had an out-of-field recurrence. Out-of-field recurrences were either located on the contralateral lobe (3/6) or with a distinct distance from the previous lesion site (3/6).

Three out of 26 patients with biochemical recurrence had metastases without intraprostatic recurrence on 68Ga-PSMA PET-CT. All had distant metastatic disease: one with extended nodal invasion (suspicious lymph nodes above the aortic bifurcation), one with bony metastases, and one with a suspected metastastic lesion in the right lung with mediastinal lymph node involvement.

In one patient, further imaging upon biochemical recurrence was not deemed clinically relevant due to concurrent progressive metastatic sigmoid cancer.

Two patients underwent re-salvage treatment. One received another ultrafocal salvage HDR-BT treatment which was well tolerated without exacerbated toxicity. The other underwent whole-gland cryoablation at a different center and was left with urinary incontinence requiring several pads per day. After one year follow-up, PSA-levels remain low in both patients.

Six patients started ADT after a median of 15 months (range 8-32 months).

Two patients died of other diseases, after 13 and 33 months respectively.

After 2.5 years follow-up, BDFS was 51% (95% CI 37-69%). Metastases-free survival (MFS) was 75% (95% CI 64-89%). Hormonal treatment-free survival (HFS) was 90% (95% CI 82-99%) and overall survival (OS) was 98% (95% CI 94-100%). The Kaplan Meier survival curves are presented in Figure 3.

The explorative univariable Cox regression analysis for biochemical failure revealed a small but significant hazard ratio for pre-salvage PSA (1.1, p=0.02) and size of the CTV (1.1, p=0.04), and a larger significant hazard ratio for locally advanced (stage ≥T3) tumors (2.6, p=0.02). Results are displayed in Table 2. To visualize survival differences, we stratified between “high risk of treatment failure” (stage≥T3, PSA ≥10, or PSADT ≤9 months) and “low risk of treatment failure” (stage<T3, PSA<10 and PSADT>9 months). Figure 4 shows the Kaplan Meier curves. After 2.5 years, only 25% of the “high risk” patients were free of biochemical failure, versus 71% of “low risk” patients.

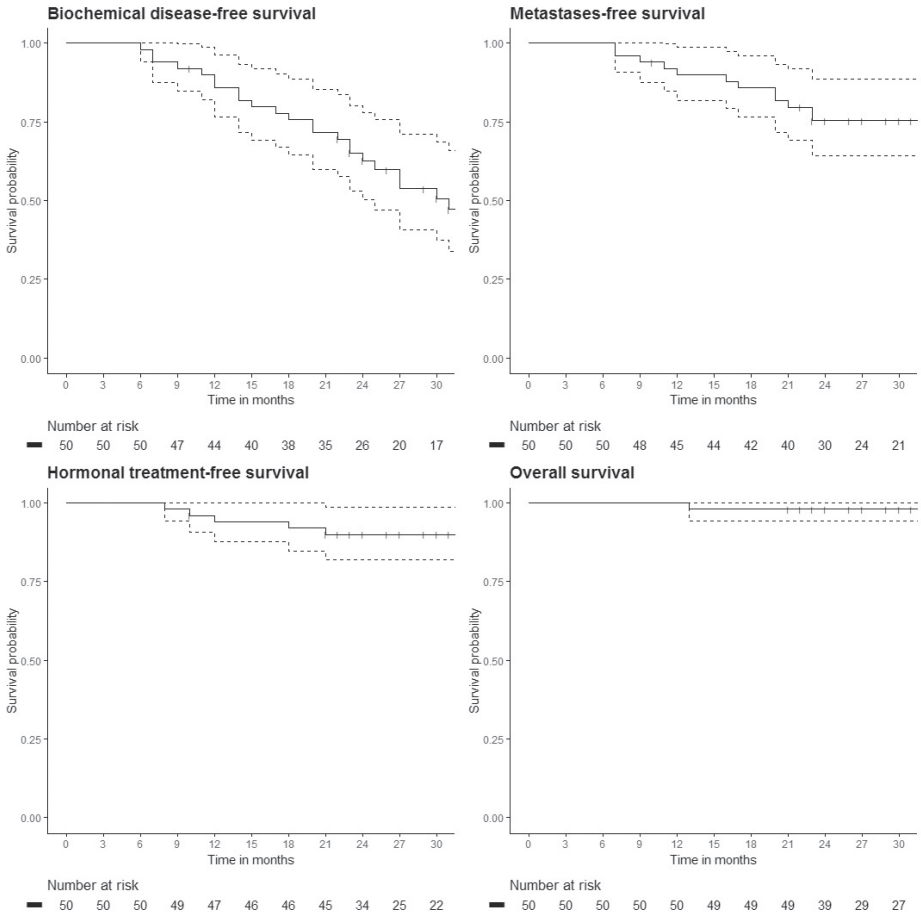

Figure 3 – Kaplan Meier survival curves. The dotted lines represent the upper and lower 95% confidence intervals.
a) Biochemical disease-free survival(BDFS), b) metastases-free survival(MFS), c) hormonal treatment-free survival(HFS), d) overall survival(OS).

Table 2 – Univariable Cox regression analysis for biochemical failure

Risk factor	β	HR	95% CI		p-value
			lower	upper	
Age	-0.06	0.94	0.87	1	0.16
AJCC grade group*					
Group 2 (3+4=7)	0.24	1.27	0.36	4.5	0.71
Group 3 (4+3=7)	0.77	2.16	0.64	7.24	0.21
Group 4 (4+4=8)	-0.8	0.45	0.05	4.03	0.48
Group 5 (9/10)	0.81	2.24	0.56	9.06	0.26
MRI T-stage**					
≥T3	0.95	2.6	1.17	5.78	**0.02**
PSA	0.06	1.1	1	1.1	**0.02**
PSADT	-0.02	0.98	0.95	1	0.2
Size of the CTV (cc)	0.05	1.1	1	1.1	**0.04**

β: estimate of the effect, HR: hazard ratio, 95% CI: 95% confidence interval, AJCC: American joint committee on cancer, PSA: prostate specific antigen level, PSADT: PSA doubling time, CTV: clinical target volume.
*AJCC grade group 1 (3+3=6) as reference category.
**MRI stage T2 as reference category.

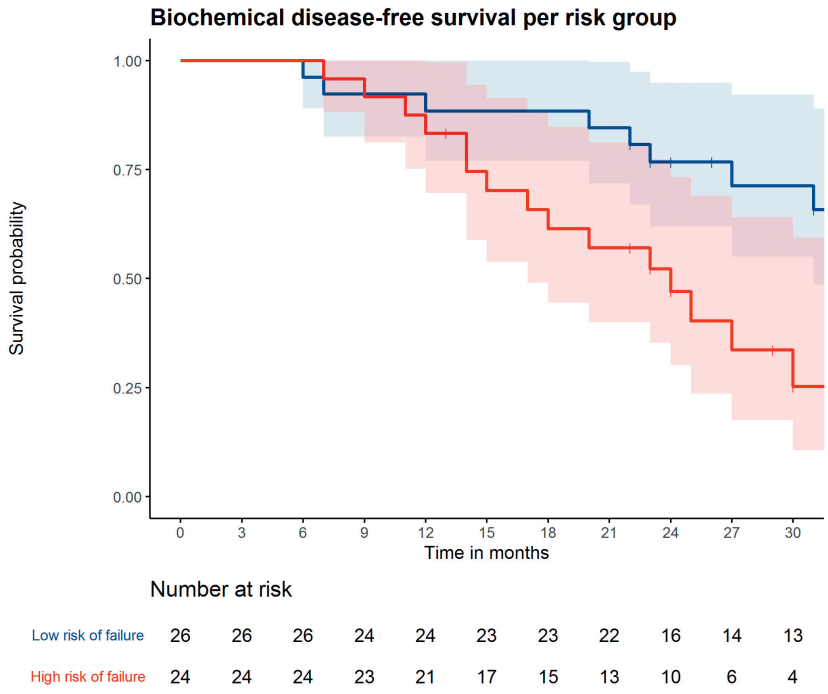

Figure 4 – Kaplan Meier BDFS survival curves stratified for low (stage<T3 and PSA<10 and PSADT>9 months) and high risk of treatment failure (anyone else).

DISCUSSION

From the first 50 patients treated with ultrafocal salvage HDR-BT, we report only 2% severe GU toxicity and no severe GI toxicity. Grade 2 GU toxicity occurred more frequently (52%), but was mostly manageable by medication, resulting in a stable patient-reported IPSS over time. Severe ED occurred in 22% of patients, corresponding to a downward trend in IIEF-5 scores after treatment. QoL was not significantly affected. After 2.5 years, BDFS was 51% (95%-CI 37-69%), MFS was 75% (64-89%) and 90% had not started ADT (82-99%).

These results are consistent with reports on focal salvage treatment modalities, namely LDR/HDR brachytherapy, cryotherapy, HIFU and stereotactic body radiotherapy (SBRT).[13] Severe GU/GI toxicity rarely (≤8%) occurs. The few studies reporting QoL describe a significant deterioration within the sexual domain (using the Expanded Prostate Cancer Index Composite [EPIC]),[14] and a significant increase in urinary symptoms (using EORTC QLQ-PR25).[15] BDFS ranges from 56-92% at 1 year, to 22-61% at 3 years, to 47-54% at 5 years follow-up.[13] The main difference between focal treatment modalities is their accessibility to certain tumor locations: posterior lesions seem best approachable using HIFU, cryotherapy is more appropriate for anterior lesions and apical lesions can be safely treated with brachytherapy.[16] From our own experience, both intraprostatic tumors and seminal vesicle invasion (SVI) are well within reach for a focal brachytherapy implant.

A recent review by Steele et al. showed there are higher and more severe toxicity rates from whole-gland salvage treatments, at similar tumor control rates (5-year BDFS approximately 50–60%). Salvage prostatectomy (total 709 patients, follow-up 3-7.2 years) caused 4-10% operative rectal injury, 22–41% postoperative bladder neck contractures and 48% urinary incontinence. Whole-gland salvage LDR-BT (total 311 patients, follow-up 4.5-9 years) caused 12-19% grade 3 GU/GI toxicity. In comparison, whole-gland HDR-BT (total 94 patients, follow-up 3-5 years) seemed less toxic with 2-7% grade 3 GU toxicity and no grade 3 GI toxicity. Whole-gland salvage cryotherapy (total 665 patients, follow-up 1.4- 7.5 years) resulted in 72% urinary incontinence (dribbling or leakage), 66% medium to severe obstructive symptoms and 8-10% complications requiring additional surgical intervention. Whole-gland salvage HIFU (total 1013 patients, follow-up 1.2-3.3 years) caused 6-9% urethrorectal fistula and 16-30% bladder outlet obstruction.[17]

Despite its low toxicity profile, the role of focal salvage treatment for radiorecurrent prostate cancer is yet to be determined. Longer follow-up data is warranted to assess the effectiveness in terms of oncologic control and delay time to ADT. Herein, there are several aspects to evaluate.

First, adequate patient selection is crucial. Within our cohort, failing patients were slightly younger at the time of treatment (median 70 versus 73 years), had a higher Gleason grade (54% versus 29% ³4+3=7), higher pre-salvage PSA (median 5.5 versus 4.2 ng/ml), shorter PSADT (median 16.5 versus 19 months) and more advanced T-stage

on MRI (50% versus 25% ³T3) than non-failing patients. MRI stage ³T3 and higher PSA were significantly associated with poorer biochemical control. Larger CTV was also a significant risk factor, but this was related to T-stage (p=0.003 by ANOVA test). For the "low risk of failure" group within our cohort, BDFS was very good compared with other focal salvage cohorts, where a vast majority of patients were "low risk".[14,15,18,19]

Another tumor characteristic potentially associated with treatment failure is radioresistance. To evaluate this, we compared within-patient primary and recurrent tumor localizations. Out of 23 primary MRI scans available, 16 patients (70%) had an in-field recurrence with respect to the primary tumor. Stratifying for in- and out-of-field lesions, there was no clear relation between treating an in-field recurrence and salvage treatment failure: 9/16 (56%) "in-field patients" failed and 4/7 (57%) "out-of-field patients" failed.

For local staging, additional functional imaging sequences (most importantly diffusion weighted imaging [DWI] and dynamic contrast enhanced [DCE]) have improved accuracy.[20] Although correct interpretation is challenging and should be performed by expert uro-radiologists, mp-MRI can aid in focal salvage treatment planning, intra-operative guidance and follow-up.[21] Studies comparing mp-MRI assessment to prostate biopsies (n=52) or full histologic prostate mapping (n=13) in patients with a suspected local recurrence report area under the receiver-operator curve (AUC)-values of 0.82-1 and 0.8-0.9, respectively.[22,23] For the detection of extra prostatic extension (EPE) and SVI the sensitivity and specificity are less optimistic, ranging between 50-75% and 70-100%, respectively.[24] PSMA-PET/CT is the indicated modality for metastatic disease assessment, albeit with correct timing: a study on 248 patients with rising PSA reported detection rates of 58% at PSA-levels of <0.5 ng/mL versus 97% at PSA-levels of ≥2 ng/mL.[25] Two studies evaluating 30 and 65 patients with biochemical recurrence and PSMA-suspected lymph node metastases who underwent (extended) salvage lymph node dissection, reported positive and negative predictive values of 100% and 89-100% respectively.[26,27]

For ultrafocal salvage HDR-BT, we delineate the recurrent lesion using both mp-MRI (in particular T2-hypointense and restricted diffusion areas) and PSMA-PET/CT. When these images do not overlap, the GTV is extended to encompass suspected areas from all sequences. This approach is supported by recent reports showing mp-MRI significantly underestimates the tumor volume, where PSMA-PET/CT has better agreement with histopathology.[28,29]

All in all, it seems we can adequately exclude metastatic disease but tend to underestimate the extent of local recurrence. Although we add a 5 mm margin to the GTV to account for this, going from ultrafocal to quadrant treatment could potentially improve oncologic control even further. Dose escalation or dose fractionation could also improve oncologic outcomes, especially considering our relatively high number (73%) of in-field recurrences, of which 13/16 had been underdosed (D95% <19 Gy) and 4/16 did not reach the lower threshold of D90% >17 Gy. By fractionating, tumor cells may become more susceptible to the next radiation course because of enhanced tumor cell division during

a course of radiotherapy.[30] Adversely, an increased number of fractions and associated overall treatment time could affect the radiation tolerance of normal tissue.

In a small study by Murgic et al., 15 patients were treated with focal salvage HDR-BT using a prescription dose of 27 Gy divided over two implants with a one week interval.[14] Treatment was aimed at the quadrant of the prostate containing an MRI-visible recurrent lesion. Staging included 3T mp-MRI, CT and bone scan. Their patient group was comparable to our cohort, except they had no primary T3 tumors versus 26% in our cohort. After three years, BDFS was 61%. One patient (7%) had severe (grade 3) late GU toxicity, 14 patients (93%) had acute grade 2 GU toxicity and no severe GI toxicity occurred. The relative biochemical control benefit of this regimen therefore seems to come with more toxicity.

For the future, our challenges are to improve patient selection and treatment technique. Our cohort represents a wide variety of patient and tumor characteristics, all with varying risks of treatment failure. Overall oncologic control statistics are therefore not generalizable. However, there is a lack of knowledge on how to stratify risk groups in the radiorecurrent setting. A prediction model for failure is warranted to indicate which patients benefit most from focal salvage treatment.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians 2019; 69(1): 7-34.
2. Cancer Research UK. Prostate cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Four (accessed 11 June 2019).
3. Zumsteg ZS, Spratt DE, Romesser PB, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol 2015; 67(6): 1009-16.
4. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2013; 85(3): 686-92.
5. Routman DM, Funk RK, Stish BJ, et al. Permanent prostate brachytherapy monotherapy with I-125 for low- and intermediate-risk prostate cancer: Outcomes in 974 patients. Brachytherapy 2019; 18(1): 1-7.
6. Zumsteg ZS, Spratt DE, Romesser PB, et al. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer. The Journal of urology 2015; 194(6): 1624-30.
7. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR, Cancer of the Prostate Strategic Urological Research E. Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. Cancer 2008; 112(2): 307-14.
8. Elishmereni M, Kheifetz Y, Shukrun I, et al. Predicting time to castration resistance in hormone sensitive prostate cancer by a personalization algorithm based on a mechanistic model integrating patient data. The Prostate 2016; 76(1): 48-57.
9. Lee RJ, Smith MR. Hormone Therapy for Prostate Cancer. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy: Principles and Practice. 5th ed: Wolters Kluwer: Lippincott Williams & Wilkins; 2011.
10. Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Non-surgical Therapies for Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. European urology focus 2016; 2(2): 158-71.
11. Maenhout M, Peters M, van Vulpen M, et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radiorecurrent Prostate Cancer. Technology in cancer research & treatment 2017; 16(6): 1194-201.
12. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1998; 16(1): 139-44.
13. van Son M, Peters M, Moerland M, Kerkmeijer L, Lagendijk J, van der Voort van Zyp J. Focal Salvage Treatment of Radiorecurrent Prostate Cancer: A Narrative Review of Current Strategies and Future Perspectives. Cancers 2018; 10(12).
14. Murgic J, Morton G, Loblaw A, et al. Focal Salvage High Dose-Rate Brachytherapy for Locally Recurrent Prostate Cancer After Primary Radiation Therapy Failure: Results From a Prospective Clinical Trial. Int J Radiat Oncol Biol Phys 2018; 102(3): 561-7.

15. Peters M, Maenhout M, van der Voort van Zyp JR, et al. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: a retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol 2014; 112(1): 77-82.

16. Ganzer R, Arthanareeswaran VKA, Ahmed HU, et al. Which technology to select for primary focal treatment of prostate cancer?-European Section of Urotechnology (ESUT) position statement. Prostate cancer and prostatic diseases 2018; 21(2): 175-86.

17. Steele EM, Holmes JA. A review of salvage treatment options for disease progression after radiation therapy for localized prostate cancer. Urol Oncol 2019.

18. Mbeutcha A, Chauveinc L, Bondiau PY, et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. Radiation oncology (London, England) 2017; 12(1): 49.

19. Li YH, Elshafei A, Agarwal G, Ruckle H, Powsang J, Jones JS. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: initial results from the cryo on-line data registry. The Prostate 2015; 75(1): 1-7.

20. Akin O, Gultekin DH, Vargas HA, et al. Incremental value of diffusion weighted and dynamic contrast enhanced MRI in the detection of locally recurrent prostate cancer after radiation treatment: preliminary results. European radiology 2011; 21(9): 1970-8.

21. van der Poel H, Grivas N, van Leeuwen P, Heijmink S, Schoots I. The role of MRI for detection and staging of radio- and focal therapy-recurrent prostate cancer. World journal of urology 2019; 37(8): 1485-90.

22. Luzurier A, Jouve De Guibert PH, Allera A, et al. Dynamic contrast-enhanced imaging in localizing local recurrence of prostate cancer after radiotherapy: Limited added value for readers of varying level of experience. Journal of magnetic resonance imaging : JMRI 2018; 48(4): 1012-23.

23. Arumainayagam N, Kumaar S, Ahmed HU, et al. Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy. BJU international 2010; 106(7): 991-7.

24. Zattoni F, Kawashima A, Morlacco A, et al. Detection of recurrent prostate cancer after primary radiation therapy: An evaluation of the role of multiparametric 3T magnetic resonance imaging with endorectal coil. Practical radiation oncology 2017; 7(1): 42-9.

25. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid (6)(8)Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2015; 56(5): 668-74.

26. Jilg CA, Drendel V, Rischke HC, et al. Diagnostic Accuracy of Ga-68-HBED-CC-PSMA-Ligand-PET/CT before Salvage Lymph Node Dissection for Recurrent Prostate Cancer. Theranostics 2017; 7(6): 1770-80.

27. Abufaraj M, Grubmuller B, Zeitlinger M, et al. Prospective evaluation of the performance of [(68)Ga]Ga-PSMA-11 PET/CT(MRI) for lymph node staging in patients undergoing superextended salvage lymph node dissection after radical prostatectomy. European journal of nuclear medicine and molecular imaging 2019; 46(10): 2169-77.

28. Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. The Journal of urology 2017; 197(2): 320-6.

29. Bettermann AS, Zamboglou C, Kiefer S, et al. [68Ga-]PSMA-11 PET/CT and multiparametric MRI for gross tumor volume delineation in a slice by slice analysis with whole mount histopathology as a reference standard - Implications for focal radiotherapy planning in primary prostate cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2019.

30. Harrington K, Jankowska P, Hingorani M. Molecular biology for the radiation oncologist: the 5Rs of radiobiology meet the hallmarks of cancer. Clinical oncology (Royal College of Radiologists (Great Britain)) 2007; 19(8): 561-71.

CHAPTER 6

Health-related quality of life after ultrafocal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer: reporting the patient's perspective

Authors: Marieke J. van Son, Evelyn M. Monninkhof, Max Peters, Jan J.W. Lagendijk, Jochem R.N. van der Voort van Zyp

CLINICAL AND TRANSLATIONAL RADIATION ONCOLOGY

ABSTRACT

Purpose

For patients with a localized prostate cancer recurrence after radiotherapy, focal salvage treatment offers a less toxic alternative to whole-gland treatments, with the potential of preserving health-related quality of life (HR-QoL). With a focus on the patient's perspective of treatment, this study aims to describe HR-QoL after ultrafocal salvage high-dose-rate brachytherapy (HDR-BT), and to explore predictive factors affecting HR-QoL.

Material and Methods

We included 100 patients treated with ultrafocal salvage HDR-BT. Prostate cancer-related HR-QoL was assessed by the EORTC QLQ-PR25 questionnaire. Domains were urinary symptoms, bowel symptoms and sexual activity/functioning. For each domain, a mixed effects model was made to estimate HR-QoL trends over time. For domains showing clinically relevant change (≥10 points difference), the mixed effects model was used to explore potential predictors (age, baseline HR-QoL score, T-stage, tumor location, CTV size, dose to organs at risk and history of ADT).

Results

Median follow-up was 20 months (IQR 13-30). Mean questionnaire response rate was 86% (range 72-100%). Median baseline scores were 12 (urinary), 0 (bowel) and 67/50 (sexual activity/functioning). Urinary symptoms and sexual functioning showed clinically relevant deterioration over time (maximum difference of 11 and 12 points, respectively). Worse baseline score and higher administered dose to the urethra (≥16 Gy) were predictive of increased urinary symptoms ($p<0.01$ and $p=0.03$). Better baseline score was predictive of better sexual functioning ($p<0.01$).

Conclusion

Ultrafocal salvage HDR-BT has negligible impact on bowel symptoms but does affect urinary symptoms and sexual functioning. Lower impact is predicted for patients with favorable urinary and sexual function at baseline. Urethral dose constraints should be closely monitored.

INTRODUCTION

As a result of treatment innovations and increased cancer survival, more attention is directed towards patient-reported outcomes such as health-related Quality of Life (HR-QoL). This trend is especially relevant for prostate cancer, with decreasing mortality rates in most countries despite increasing incidences(1).

Depending on tumor stage, prostate cancer recurrences occur in 10-50% of patients 10 years after external beam radiotherapy (EBRT)(2). Most of these patients are treated with (delayed) androgen deprivation therapy (ADT)(3), which is a temporary suppressive treatment associated with significant side effects and deterioration of HR-QoL(4). Although various whole gland salvage treatment modalities are available such as radical prostatectomy, low-dose-rate brachytherapy (LDR-BT), cryotherapy and HIFU, these are unpopular due to high failure and toxicity rates(5). Although salvage prostatectomy and HIFU are associated with higher urinary incontinence rates (40-50%) than salvage cryotherapy or brachytherapy (7-12%), all modalities have high impotence (±75%) and urethral stricture rates (±20%), and 45-55% of patients experience a relapse after 4 years(6). Whole-gland salvage irradiation causes toxicity by accumulation of dose to the surrounding organs at risk. Toxicity reduction is anticipated if the target is reduced from the whole gland to the tumor area alone. Since imaging advancements such as magnetic resonance imaging (MRI) and PSMA-PET/CT have improved detection of the exact tumor location, focal treatment is now clinically feasible(7, 8). Reviews of the available literature on focal salvage treatments (including focal brachytherapy, HIFU and cryotherapy) have consistently shown that they are well tolerated with very limited severe genitourinary and gastro-intestinal toxicity (<5%) and with encouraging biochemical control rates (48-72% after 3 years)(9, 10).

The radiotherapy department at the University Medical Centre Utrecht has a 1.5T MRI high-dose-rate brachytherapy (HDR-BT) facility. Here, ultrafocal treatment of recurrent prostate cancer is performed by internal irradiation of the tumor under MRI-guidance. Due to the steep dose fall-off in brachytherapy, a high dose can be applied to the tumor while the surrounding healthy tissue receives low radiation exposure. It is therefore expected that patients experience less side effects and maintain their HR-QoL. Providing a detailed view on the patient's perspective of this treatment, the current study aims to investigate prostate cancer-specific HR-QoL after ultrafocal salvage HDR-BT and to explore predictive factors that may impact HR-QoL.

MATERIAL AND METHODS

Patients

Between July 2013 and March 2018, the first consecutive 100 patients with localized recurrent prostate cancer after primary radiotherapy were treated with ultrafocal salvage HDR-BT. Treatment was either performed within an institutional review board (IRB)-approved prospective study (Netherlands Trial Register [NTR] number 6123 or

7014) or outside the scope of a study protocol, including patients with higher-risk disease characteristics, such as seven patients with a solitary lymph node or bone metastasis who received upfront stereotactic radiotherapy. For study patients, trial inclusion criteria were PSA <10 ng/ml, PSA doubling time (PSADT) >12 months and MRI tumor stage ≤T2c (NTR 6123) or PSA ≤20 ng/ml, PSADT ≥9 months and MRI tumor stage ≤T3b (NTR 7014). All patients (on- or off-protocol) were prospectively followed in the same manner. Informed consent was obtained from all study patients. For patients treated off-protocol, the IRB waived the requirement for informed consent. For this report it was pragmatically chosen to analyze the first 100 treated patients, since they all had at least three months post-treatment follow-up before the start of the analysis.

Treatment

Using 3T multiparametric MRI (T2-weighted, diffusion-weighted and dynamic contrast enhanced sequences) and 68Ga-PSMA or 18F-Choline PET-CT, we delineated the gross tumor volume (GTV), clinical target volume (CTV, defined as five-millimeter margin around GTV) and organs at risk (OARs: bladder, rectum, and urethra). The rectum was delineated between the level of the sigmoid fold and the anal region, the bladder was delineated within the available field of view and the urethra was delineated one slice above and one slice under the prostate (sagittal plane). No PTV-margin was applied. Under the guidance of rigidly fused MRI/transrectal ultrasound images, MR-compatible catheters were transperineally inserted in and around the CTV. A subsequent 1.5T MRI scan was used for catheter reconstruction and adjustment of delineations. Radiation goal was to administer a single dose of 19 Gy to 95% of the CTV. Dosimetry constraints were D1cc <12Gy for the bladder and rectum and D10% <17.7Gy for the urethra. With the radiation dose fully targeted at the CTV instead of a quarter or half of the gland, this treatment is generally described as ultrafocal.

Outcome assessment

HR-QoL was investigated using the EORTC QLQ-PR25 questionnaire, which was specifically designed for use among prostate cancer patients(11). Questionnaires were sent out before treatment and after 1, 3, 6, 9, 12, 18 and 24 months, and yearly thereafter. The respective domains are urinary symptoms (9 items), bowel symptoms (4 items), sexual activity (2 items) and sexual functioning (4 items). As ADT was not part of this treatment, we did not analyze the domain hormonal treatment-related symptoms. For each item, patients were asked to indicate the extent to which they had experienced symptoms or problems during the past week (1: not at all, 2: a little, 3: quite a bit, 4: very much).

Domain scores were linearly transformed to a 0-100 scale if at least half of the items in the domain were answered. Higher scores either indicated more symptoms (urinary and bowel domains) or higher levels of functioning (sexual domains).

For the QLQ-PR25 questionnaire, no threshold value has been determined as the minimal clinically important difference in scores. In concordance with the QLQ-C30

questionnaire (HR-QoL of cancer patients in general, similar scoring range 0-100), we defined a change of ≥10 points as a clinically relevant difference(12).

Statistical analysis

To estimate average HR-QoL trends over time, a mixed effects model for repeated measures was made for each domain. Differences between baseline HR-QoL scores and follow-up time points were tested by adding time as a categorical variable to the mixed effects model. The significance level for HR-QoL change was set at p=0.01, taking into account multiple testing. Trends were graphically displayed using the group least squares means and their standard errors.

Secondly, we explored potential predictors of change in HR-QoL within each model. This was only analyzed for the domains that showed clinically relevant change. We hypothesized that age, baseline HR-QoL score, T-stage of the tumor (as scored by the AJCC TNM eighth edition staging manual), size of the CTV and dose to the respective organs at risk (OAR) are potential factors predicting HR-QoL change. For the sexual domain, we also included previous use of ADT and dorsolateral location of the tumor. Assessment of the relation between these predictors and change in HR-QoL was performed in a multivariable model, calculating odds ratios and their 95% confidence intervals (CI). Predictors with p-values <0.05 were considered statistically significant.

Statistical analyses were performed with R statistical software (version 3.5.1; the R foundation for Statistical Computing, Vienna, Austria) and IBM SPSS statistics (version 23.0).

RESULTS

The median follow-up time was 20 months (interquartile range [IQR] 13-30 months). Questionnaire response rates were between 72% (3 months) and 100% (36 months), with a mean response rate of 86%. At baseline, patients reported mild urinary symptoms (median score 12, IQR 8-21) and negligible bowel symptoms (median score 0, IQR 0-8). Sexual activity was at a baseline median score of 67 (IQR 50-83), and sexual functioning at median 50 (IQR 42-67). The median CTV D90% was 21.43 Gy (IQR 19-21.5), with a median of 9 brachytherapy catheters used for the implant (IQR 8-11). A summary of baseline patient and tumor characteristics is displayed in Table 1.

Table 1 – Baseline characteristics (n=100)

			Median (IQR) or percentages
Age (years)			71 (67 – 74)
Primary treatment	EBRT		53%
	LDR-BT		44%
	Whole-gland HDR-BT		1%
	Ultrafocal HDR-BT		2%
History of ADT*	No		80%
	Yes, neo-adjuvant		6%
	Yes, adjuvant		14%
TNM-stage on imaging	T	T2	62%
		T3	36%
		T4	2%
	N	N0	96%
		N1	4%
	M	M0	97%
		M1	3%
Size of the CTV (cc)			10 (7 – 16)
Baseline quality of life scores^	Urinary symptoms		12 (8 – 21)
	Bowel symptoms		0 (0 – 8)
	Sexual activity		67 (50 – 83)
	Sexual functioning		50 (42 – 67)

Legend: IQR: interquartile range, EBRT: external beam radiotherapy, LDR-BT: low-dose-rate brachytherapy, HDR-BT: high-dose-rate brachytherapy, ADT: androgen deprivation therapy, TNM-stage: tumor/node/metastasis stage, CTV: clinical target volume.
* As part of primary treatment.
^ EORTC QLQ-PR25, scale 0 – 100.

Figure 1 shows the modeled quality of life trends over time for each HR-QoL domain, displaying least squares means with their standard error (SE) at each follow-up time point. Urinary symptoms (Figure 1-a) increased with +11 points in the first month after treatment ($p<0.01$). Afterwards, the score recovered almost completely back to baseline level (least squares mean difference of 2 points between baseline and 36 months follow-up, $p=0.5$). Bowel symptoms (Figure 1-b) remained stable at a lower level over time, with a maximum least squares mean difference of +3 points at 6 months ($p=0.04$). Sexual activity (Figure 1-c) showed a similar stable trend, with a maximum least squares mean difference of +4 points at 3 months ($p=0.1$). Sexual functioning (Figure 1-d) showed a downward trend over time, with a temporary recovery between six and twelve months, but with a maximum least squares mean difference of -12 points at 24 months ($p<0.01$).

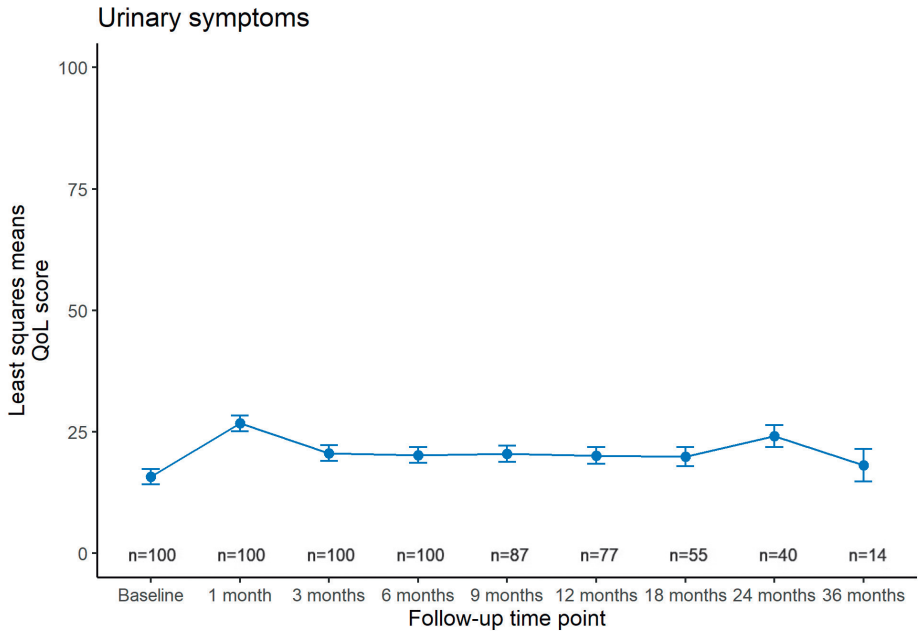

Figure 1-a

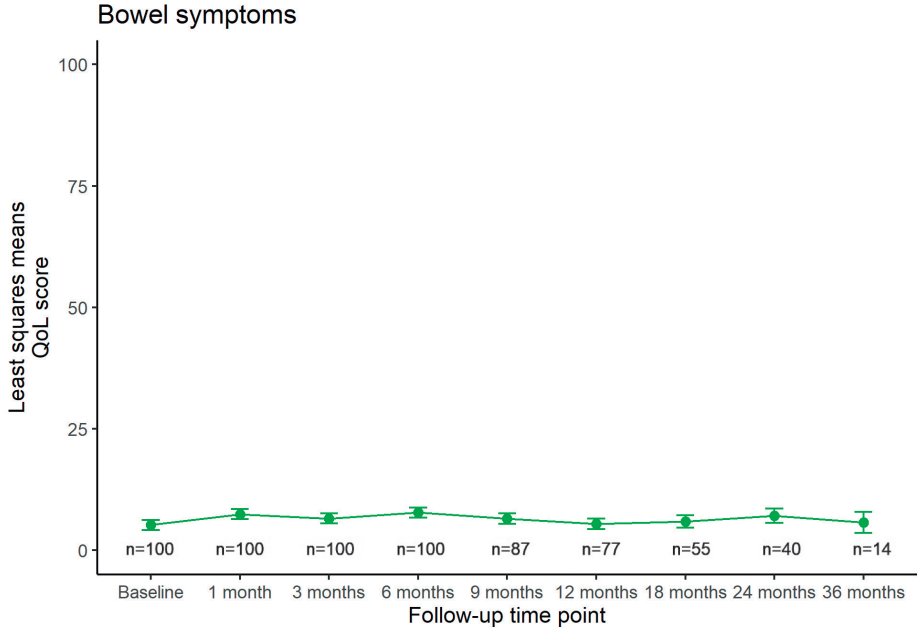

Figure 1-b

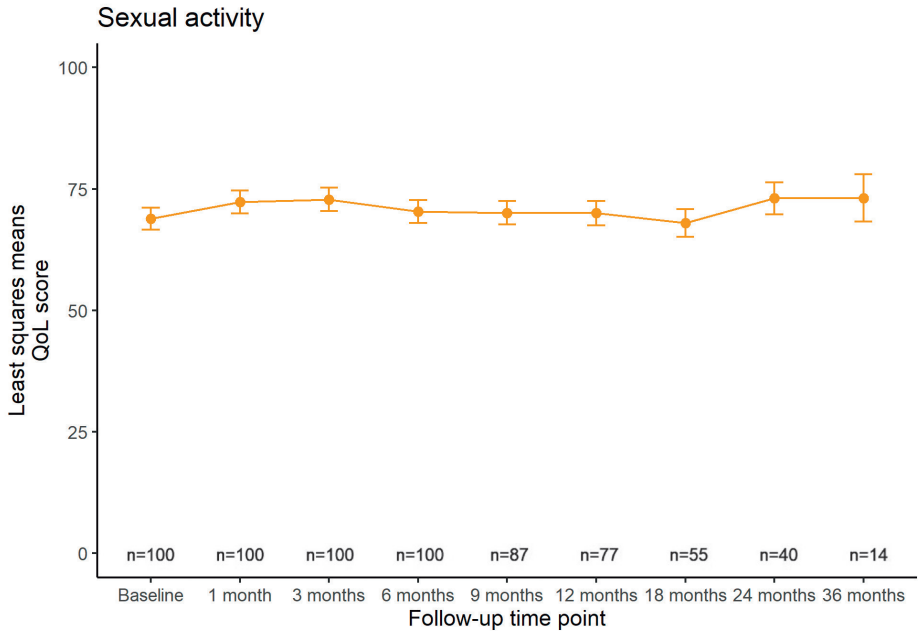

Figure 1-c

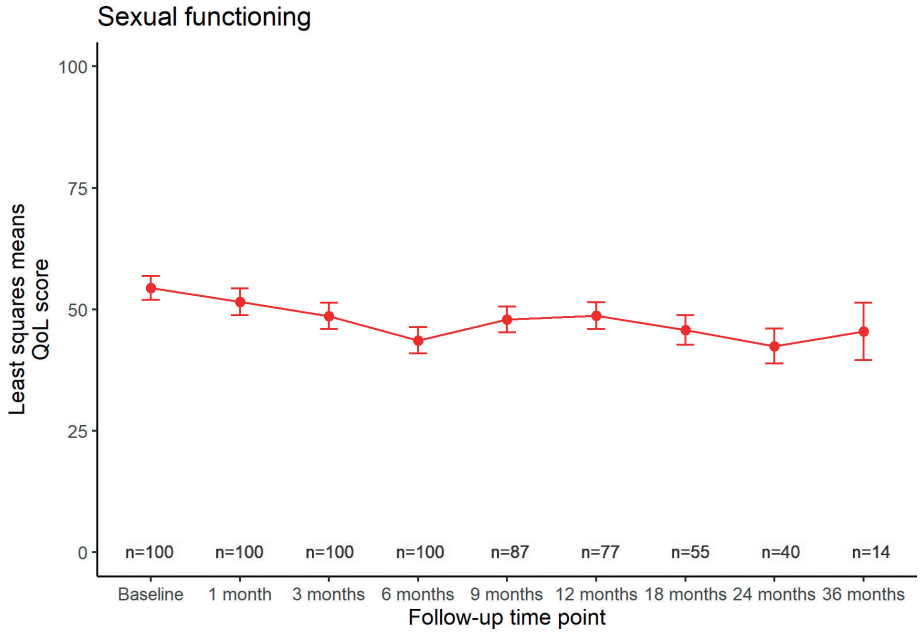

Figure 1-d

Figure 1 a,b,c,d: Modeled quality of life trends over time. Least squares means are displayed with their standard errors at each follow-up time point. Number of patients at risk who received a questionnaire at each time point is displayed on the bottom.

An explorative assessment of potential predictors for HR-QoL change was performed for the domains urinary symptoms and sexual functioning, as these domains showed clinically relevant change over time (Table 2). Higher (i.e. worse) baseline HR-QoL score and higher administered dose to the urethra were significant predictors for urinary symptoms. A post-hoc cut-off analysis revealed that a constraint of 16 Gy was the lowest value at which urethra D10% was a significant predictor in the model. Higher (i.e. better) baseline HR-QoL score (p<0.01) was predictive of better sexual functioning over time.

Table 2 – Association of predictors with HR-QoL change per affected domain

Domain		95% CI			
		β	lower	upper	p-value
Urinary symptoms	Administered dose to the urethra	0.62	0.19	1.06	**<0.01**
	Administered dose to the bladder	-0.47	-1.03	0.09	0.10
	Baseline HR-QoL score	0.73	0.59	0.87	**<0.01**
	Age	-0.03	-0.35	0.28	0.83
	Size of the CTV (cc)	-0.09	-0.36	0.18	0.52
	Tumor stage on MRI >T2	3.76	-0.74	8.78	0.20
Sexual functioning	Previous use of ADT*	7.15	-1.20	15.50	0.07
	Baseline HR-QoL score	0.68	0.48	0.88	**<0.01**
	Age	-0.26	-0.90	0.37	0.42
	Size of the CTV (cc)	0.05	-0.34	0.44	0.81
	Tumor stage on MRI >T2	-5.17	-12.22	1.88	0.15
	Dorsolateral location of the tumor	5.09	-2.86	13.04	0.21

Legend: HR-QoL: health-related quality of life, CTV: clinical tumor volume, ADT: androgen deprivation therapy, β: estimate of the effect, 95% CI: 95% confidence interval. *Aspartofprimary treatment (neo-adjuvant or adjuvant).

A more detailed view on individual HR-QoL items is provided in Supplementary Table 1, with separate item scoring patterns. The table displays the percentage of patients reporting any symptom (score>1) at each follow-up time point. Most reported urinary symptoms in the first month after treatment were dysuria, urgency, difficulty leaving the house and being limited in daily activities. Incontinence was also frequently reported, with a maximum of 14 patients declaring the need to wear an incontinence aid. Sexual functioning was mainly impaired by erectile dysfunction, ejaculation problems and sexual intimacy issues.

DISCUSSION

This study shows that ultrafocal salvage HDR-BT has limited effect on patient-reported bowel function and sexual activity but causes a (temporary) increase in urinary symptoms and a decrease of sexual functioning over time. Predictive factors for deterioration of urinary HR-QoL are increased urinary symptoms at baseline and higher administered

dose to the urethra (≥16 Gy). Higher level of baseline sexual functioning was predictive of better sexual HR-QoL.

A comparison with our previous work on ultrafocal salvage HDR-BT shows similar trends in terms of treatment-related toxicity. Our first report (n=17, median follow-up 10 months) described physician-graded toxicity following the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). There was minor grade 1 rectal toxicity (mild or asymptomatic) and urinary toxicity was limited to approximately 25% grade 2 (moderate) and 5% grade 3 (severe) toxicity. Grade 3 new-onset erectile dysfunction occurred in 1/6 patients with full erectile function at baseline and 1/7 patients with moderate erectile dysfunction at baseline(13).

In a more recent update (n=50, median follow-up 31 months), 4% had new-onset grade 2 rectal toxicity. While severe urinary toxicity was still limited (2%), more patients had developed grade 2 toxicity (52%). Grade 3 new-onset erectile dysfunction was seen in 22%. Regarding patient-reported toxicity, the IPSS revealed a temporary increase of urinary symptoms in the first month after treatment (maximum median score 11.5). The International Index of Erectile Function (IIEF) showed a downward trend of erectile function over time, from median score 11 at baseline to median 3 after 3 years follow-up(14).

Within the current literature on salvage treatments for radiorecurrent prostate cancer, there is limited data of patient-reported HR-QoL. Reports of HR-QoL that have been published are heterogeneous, using a variety of different questionnaires. Two studies reported IPSS and IIEF scores after whole-gland salvage treatments, namely whole-gland salvage LDR-BT (n=19) and whole-gland salvage HIFU (n=81). The questionnaires revealed a peak to moderate urinary symptoms (mean IPSS ±15) and a deterioration to severe ED (mean IIEF ±6) in the first year(15, 16). Another study on whole-gland salvage HIFU in 61 patients used the University of California Los Angeles Prostate Cancer Index (UCLA-PCI) as patient-reported outcome measurement. They reported clinically significant urinary and sexual function deterioration after 1.5 years follow-up. At a scoring range of 0-100, mean urinary function decreased with 12 points ($p<0.01$) and mean sexual function decreased with 15 points ($p<0.01$). Bowel function was not affected(17).

Regarding targeted salvage treatments, only two studies described HR-QoL. A study on ultrafocal salvage LDR-BT (20 patients) used the EORTC QLQ-PR25, reporting a clinically significant increase of median 12 points in urinary symptoms after 3 years ($p<0.01$)(18). A study on focal salvage HDR-BT to a quadrant of the prostate (15 patients) used the Expanded Prostate Cancer Index Composite (EPIC). They reported a significant deterioration of sexual function after 3.5 years (approximately -20 points on a 0-100 scale, $p<0.01$), whereas the urinary and bowel domains were not significantly affected. The median IPSS never exceeded a score of 10(19).

To have a better understanding of what factors predict HR-QoL, we explored the association between several predictors and HR-QoL change. The apparent predictors for the urinary domain confirmed our expectations. We already screen for baseline urinary symptoms using the IPSS questionnaire, with scores >15 being a contra-indication for treatment. Although severe urinary toxicity has been low, we are strict in adhering

to our urethral dose constraint (17.7 Gy) to account for the more frequently occurring moderate urinary symptoms. Following our cut-off analysis, a lower constraint might be an improvement.

For the sexual functioning domain, surprisingly age was not a significant predictor for HR-QoL deterioration, showing that sexual functioning varies among men of similar ages. Interestingly, the level of sexual activity did not seem to be affected over time.

It has been suggested that substantial radiation dose to the dorsolaterally situated neurovascular bundles (NVBs) may cause erectile dysfunction(20). Although we expect the dose to the NVBs to be relatively low with ultrafocal HDR-BT, 87/100 patients had a dorsolaterally located tumor, of which 25% was bilateral. Due to a lack of clear guidelines on identification and delineation of the NVBs, we were not able to directly assess the relation with NVB received dose.

Although outside the scope of this patient-reported outcome study, a recent comparative trial has raised concerns about the oncological effectiveness of a single-dose HDR-BT regimen in the primary setting. This trial randomized 170 patients between whole-gland 1x19Gy and 2x13.5Gy and reported 5-year biochemical control rates of 73.5% (single-dose) versus 95% (two-fraction)(21), with similar low morbidity(22). Unfortunately, there is no comparative data available on single-dose versus two-fraction focal salvage HDR-BT. It is therefore too early to suggest that this translates to the (focal) salvage setting.

A limitation of this study is the relatively short follow-up time. Although it is not expected, late treatment effects from delayed radiation damage may cause more HR-QoL deterioration in the future. Strengths of this study include the prospective nature, the high questionnaire response rates and the large patient group included in the analysis.

CONCLUSION

In conclusion, ultrafocal salvage HDR-BT seems to have a transient effect on patient-reported urinary function and no clinical effect on patient-reported bowel function. While sexual activity does not seem to decrease, patients report a deterioration of sexual functioning over time. Patients with impaired function at baseline (increased urinary symptoms or decreased sexual functioning) may have a higher risk of domain-specific HR-QoL deterioration over time, showing the importance of symptom assessment before treatment. Radiation dose to the urethra should be kept at a minimum to avoid urinary symptoms after treatment. This information may be used to improve treatment planning and patient counseling before treatment.

Supplementary table 1 – Presence of symptoms per HR-QoL scoring item (EORTC QLQ-PR25)

	Baseline	1 month	3 months	6 months	9 months	12 months	18 months	24 months	36 months
No. patients	100	100	100	100	87	77	55	40	14
Urinary symptoms									
Urinary frequency	79	85	76	75	81	81	77	71	64
Nocturia	71	76	75	70	71	77	75	72	79
Urinary urgency	60	76	69	67	70	73	77	69	79
Sleeping disturbances	32	42	36	33	26	36	29	56	21
Difficulty leaving the house	20	36	28	30	36	30	26	39	14
Urinary incontinence	21	43	38	42	40	41	42	40	36
Dysuria	3	41	15	17	16	10	10	8	0
If wearing an incontinence aid:									
Problems with incontinence aid	17	23	22	43	46	38	33	50	50
No. responses	***6***	***13***	***9***	***14***	***11***	***8***	***9***	***6***	***4***
Limited in daily activities	13	25	18	27	26	25	23	38	15
Bowel symptoms									
Limited in daily activities	13	24	20	24	19	17	21	21	15
Fecal incontinence	13	15	12	17	16	11	10	14	21
Rectal bleeding	11	18	15	15	12	8	2	6	7
Abdominal bloating	18	27	26	23	24	21	23	31	7

Supplementary table 1 Continued

	Baseline	1 month	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Sexual activity and functioning									
Sexual desire	80	72	76	76	78	74	77	74	71
Sexually active	64	53	60	57	63	60	60	62	36
If sexually active over last 4 weeks:									
Satisfaction sexual experience	98	94	92	100	95	95	93	95	83
Erectile dysfunction	80	88	92	98	90	90	90	90	100
Ejaculation problems	71	71	78	85	81	82	83	79	100
Sexual intimacy problems	41	55	58	51	60	54	55	61	67
No. responses	***50***	***31***	***39***	***37***	***40***	***39***	***29***	***18***	***6***

Legend: percentage (%) of patients with score >1. For each individual scoring item, patients reported symptoms or problems during the past week, ranging between 1: not at all, 2: a little, 3: quite a bit, and 4: very much.

REFERENCES

1. Wong MC, Goggins WB, Wang HH, Fung FD, Leung C, Wong SY, et al. Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries. Eur Urol. 2016;70(5):862-74.
2. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Polkinghorn W, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol. 2015;67(6):1009-16.
3. Tran H, Kwok J, Pickles T, Tyldesley S, Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol. 2014;32(5):701-6.
4. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67(5):825-36.
5. Golbari NM, Katz AE. Salvage Therapy Options for Local Prostate Cancer Recurrence After Primary Radiotherapy: a Literature Review. Curr Urol Rep. 2017;18(8):63.
6. Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. European urology focus. 2016;2(2):158-71.
7. Lindenberg ML, Turkbey B, Mena E, Choyke PL. Imaging Locally Advanced, Recurrent, and Metastatic Prostate Cancer: A Review. JAMA oncology. 2017;3(10):1415-22.
8. Patel P, Mathew MS, Trilisky I, Oto A. Multiparametric MR Imaging of the Prostate after Treatment of Prostate Cancer. Radiographics : a review publication of the Radiological Society of North America, Inc. 2018;38(2):437-49.
9. Duijzentkunst DA, Peters M, van der Voort van Zyp JR, Moerland MA, van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review. World journal of urology. 2016;34(11):1521-31.
10. Khoo CC, Miah S, Connor MJ, Tam J, Winkler M, Ahmed HU, et al. A systematic review of salvage focal therapies for localised non-metastatic radiorecurrent prostate cancer. Translational andrology and urology. 2020;9(3):1535-45.
11. van Andel G, Bottomley A, Fossa SD, Efficace F, Coens C, Guerif S, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. European journal of cancer. 2008;44(16):2418-24.
12. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16(1):139-44.
13. Maenhout M, Peters M, van Vulpen M, Moerland MA, Meijer RP, van den Bosch M, et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radiorecurrent Prostate Cancer. Technology in cancer research & treatment. 2017;16(6):1194-201.
14. van Son MJ, Peters M, Moerland MA, Lagendijk JJW, Eppinga WSC, Shah TT, et al. MRI-guided ultrafocal salvage high-dose-rate brachytherapy for localized radiorecurrent prostate cancer: updated results of 50 patients. Int J Radiat Oncol Biol Phys. 2020.

15. Barbera F, Triggiani L, Buglione M, Ghirardelli P, Vitali P, Caraffini B, et al. Salvage Low Dose Rate Brachytherapy For Recurrent Prostate Cancer After External Beam Radiotherapy: Results From A Single Institution With Focus On Toxicity And Functional Outcomes. Clin Med Insights Oncol. 2017;11:1179554917738765.

16. Siddiqui KM, Billia M, Arifin A, Li F, Violette P, Chin JL. Pathological, Oncologic and Functional Outcomes of a Prospective Registry of Salvage High Intensity Focused Ultrasound Ablation for Radiorecurrent Prostate Cancer. The Journal of urology. 2017;197(1):97-102.

17. Berge V, Baco E, Dahl AA, Karlsen SJ. Health-related quality of life after salvage high-intensity focused ultrasound (HIFU) treatment for locally radiorecurrent prostate cancer. International journal of urology : official journal of the Japanese Urological Association. 2011;18(9):646-51.

18. Peters M, Maenhout M, van der Voort van Zyp JR, Moerland MA, Moman MR, Steuten LM, et al. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: a retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol. 2014;112(1):77-82.

19. Murgic J, Morton G, Loblaw A, D'Alimonte L, Ravi A, Wronski M, et al. Focal Salvage High Dose-Rate Brachytherapy for Locally Recurrent Prostate Cancer After Primary Radiation Therapy Failure: Results From a Prospective Clinical Trial. Int J Radiat Oncol Biol Phys. 2018;102(3):561-7.

20. van der Wielen GJ, Mulhall JP, Incrocci L. Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review. Radiother Oncol. 2007;84(2):107-13.

21. Morton G, McGuffin M, Chung HT, Tseng CL, Helou J, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol. 2020;146:90-6.

22. Morton G, Chung HT, McGuffin M, Helou J, D'Alimonte L, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19Gy or two fractions of 13.5Gy. Radiother Oncol. 2017;122(1):87-92.

CHAPTER 7

Determining the safety of ultrafocal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer: a toxicity assessment of 150 patients

Authors: Marieke J. van Son, Max Peters, Marinus A. Moerland, Sandrine M.G. van de Pol, Wietse S.C. Eppinga, Jan J.W. Lagendijk, Jochem R.N. van der Voort van Zyp

CLINICAL AND TRANSLATIONAL RADIATION ONCOLOGY

ABSTRACT

Background and purpose

Local re-treatment of radiorecurrent prostate cancer is potentially curative. However, the increased risk of severe toxicity may outweigh the opportunity of cancer control. This study aims to evaluate treatment-related toxicity from ultrafocal salvage high-dose-rate brachytherapy (HDR-BT) and to investigate potential risk factors.

Materials and methods

Toxicity data from 150 treated patients (July 2013-November 2019) was collected from a prospective registry. The treatment aim was to deliver a single dose of 19 Gy to the recurrent lesion as identified on multiparametric MRI and PET-CT. Treating physicians graded genitourinary (GU) and gastro-intestinal (GI) toxicity and erectile dysfunction (ED) using the Common Terminology Criteria for Adverse Events (CTCAE) 4.0, at baseline and during follow-up. Domains with substantial (≥10%) new-onset grade ≥2 toxicity were further evaluated using mixed effects logistic regression to find potential risk factors.

Results

Median follow-up time was 20 months (IQR 12–31). Over time, new-onset grade 2 and 3 toxicity was recorded in 41% and 3% (GU), 5% and 0% (GI) and 22% and 15% (ED). While GI toxicity remained stably low, grade ≥2 GU toxicity and ED were seen twice as frequent in the late phase (>3 months after treatment). Significant risk factors for grade ≥2 toxicity were baseline GU toxicity (grade ≥2), baseline ED (grade ≥2), IPSS (cut-off ≥14) and urethral dose (D10%, cut-off ≥17 Gy).

Conclusion

Ultrafocal salvage HDR-BT is a safe re-treatment option, especially in patients with a favorable symptom profile at baseline. Adherence to urethral dose constraints is important to avoid GU toxicity.

INTRODUCTION

Patients with a local prostate cancer recurrence after radiotherapy are potential candidates for curative salvage treatment, which offers the opportunity to avoid or postpone palliative androgen deprivation therapy (ADT), thereby preventing patients from its associated metabolic, cardiovascular, sexual and psychological side-effects(1, 2). Whole-gland salvage treatments are generally associated with (severe) side-effects. A recent prospective study on whole-gland salvage brachytherapy reported 14% grade 3 toxicity(3). The aim of focal treatment is to solely target the recurrent tumor and therefore further reduce toxicity, potentially with comparable cancer control.

Improvements in imaging for selection and treatment, most notably prostate specific membrane antigen (PSMA)-PET/CT, have advanced the field of focal salvage treatment(4). Across different modalities, toxicity from focal salvage treatment seems limited compared to whole-gland salvage treatment, with event rates of severe (grade 3) genitourinary (GU) and gastro-intestinal (GI) toxicity as low as 5% and erectile dysfunction (ED) often reduced, allowing some patients to preserve their potency(5-7).

However, reported series in literature are mostly retrospective and small, using a wide range of patient- and physician-reported toxicity outcome measures. This leads to bias and prevents adequate assessment of risk factors which could be used to reduce or avoid associated side-effects of treatment.

We previously reported tumor control and functional outcomes of 50 patients after two years follow-up(8) and we investigated patient-reported quality of life of 100 patients treated with MRI-guided ultrafocal salvage high-dose-rate brachytherapy (HDR-BT)(9). With an emphasis on further safety evaluation, the current study reports prospectively collected data of physician-graded GU and GI toxicity and ED in a total of 150 treated patients. Additionally, we analyze potential risk factors for toxicity to improve treatment planning and to guide patient counselling.

MATERIALS AND METHODS

Patients

We used data from a single-center prospective registry of patients treated with ultrafocal salvage HDR-BT. The first consecutive 150 patients were included, treated between July 2013 and November 2019. As described previously(9), patients were either treated within an institutional review board (IRB)-approved study (Netherlands Trial Register 6123 or 7014) or outside the scope of a study protocol if tumor characteristics were incompatible with study inclusion criteria. All patients (on- or off-protocol) were prospectively followed in the same manner. Pre-treatment characteristics varied from lower- to higher-risk disease, but acceptable baseline urinary toxicity (International Prostate Symptom Score [IPSS] <15) was required for all patients. Study patients all signed informed consent. The IRB waived the requirement for informed consent for off-protocol patients.

Intervention

Before treatment, patients underwent 3T multiparametric (mp)-MRI (T2-weighted, diffusion-weighted and dynamic contrast enhanced imaging) without an endorectal coil and 68Ga-PSMA or Choline PET-CT. Both imaging modalities were used to delineate the gross tumor volume (GTV), clinical target volume (CTV, defined as five-millimeter margin around GTV, excluding the urethra) and organs at risk (OARs: bladder, rectum, and urethra). Suspicious areas on MRI- or PET-imaging were included in the GTV, even if exclusively present on one of them. Patients treated before 2018 also underwent systematic (21/150) or (systematic and) MRI-targeted biopsies (67/150). After that, patients were treated without biopsy confirmation. Treatment was performed by trans-perineal insertion of MR-compatible catheters in and around the CTV, with the patient under spinal anesthesia. Rigidly fused MRI/transrectal ultrasound images offered image guidance(10). After the implantation a subsequent 1.5T MRI scan was used for delineation adjustment and catheter reconstruction. The goal was to deliver 1x19 Gy to the CTV (D95%), with dosimetry constraints for the bladder and rectum (D1cc <12Gy) and for the urethra (D10% <17.7Gy). Since radiation is fully targeted at the CTV (and not a quarter or half of the gland), this treatment is generally described as ultrafocal.

Outcome assessment

Toxicity before and after treatment was graded by the treating physician using the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Prostate cancer-specific domains were GU toxicity (6 subdomains), GI toxicity (10 subdomains) and ED. Each domain/subdomain was graded according to the severity of the symptoms, with a general range from grade 1 (asymptomatic or mild) to grade 2 (moderate), grade 3 (severe but not immediately life-threatening), grade 4 (life-threatening) and grade 5 (death). Toxicity grading was performed at baseline and during follow-up visits after 1, 3, 6, 9, 12, 18 and 24 months, and yearly thereafter.

Statistical analysis

To assess the effect of ultrafocal salvage HDR-BT on toxicity, post-treatment toxicity grades were compared to baseline grade. Any score above baseline was considered new-onset toxicity and therefore potentially treatment-related. The overall grade for the domains GU and GI toxicity was determined by the highest score of the respective subdomains.

For the domains showing substantial (≥10%) new-onset grade ≥2 toxicity, an explorative risk factor assessment was performed to study the effect of (pre)-treatment characteristics. Potential risk factors included patient-reported baseline symptoms (IPSS and IIEF-5) and physician-graded baseline toxicity (CTCAE 4.0), dose to the respective OAR, stage/location of the tumor, prostate size, CTV size, primary treatment type, history of previous salvage treatment, interval between primary and current salvage treatment, history of transurethral resection of the prostate (TURP) or ADT and number of brachytherapy catheters used. Using the lme4 package(11), mixed effects logistic

regression was performed to model development of grade ≥2 toxicity over time, with potential risk factors included as fixed effects and a random effect per patient and per follow-up time point. In this multivariable model, odds ratios and their 95% confidence intervals (CI) were calculated to assess the independent effect of each risk factor on the outcome, with p-values <0.05 considered statistically significant.

Statistical analyses were performed with R statistical software (version 3.5.1; the R foundation for Statistical Computing, Vienna, Austria) and IBM SPSS statistics (version 23.0).

RESULTS

Table 1 summarizes baseline characteristics. Most patients were primarily treated with EBRT or low-dose-rate (LDR)-BT, with 20% receiving (neo)-adjuvant ADT in the primary setting. A small group (<5%) had already received a previous salvage treatment. Median interval between primary treatment and current salvage treatment was 8 years. Seven patients presented with a solitary lymph node or bone metastasis for which they received upfront stereotactic radiotherapy. Baseline GU and GI toxicity was limited to 12% and <2% grade 2 toxicity, respectively. Approximately half of all patients had grade ≥2 ED at baseline. Dosimetry constraints were adhered to in 83% of patients, with maximum outliers to 18.5 Gy (urethra D10%), 14.5 Gy (bladder D1cc) and 12.6 Gy (rectum D1cc). Median follow-up time was 20 months (IQR 12–31).

Table 1 – Patient and treatment characteristics (n=150)

			Median (IQR) or number (%)	Missing (%)
Age (years)			72 (68 – 75)	
Primary treatment	EBRT		80 (53.3%)	
	LDR-BT		67 (44.7%)	
	Whole-gland HDR-BT		2 (1.3%)	
	Ultrafocal HDR-BT		1 (0.7%)	
History of ADT*	No		120 (80%)	
	Neo-adjuvant		8 (5.3%)	
	Adjuvant		22 (14.7%)	
Previous salvage treatment	No		143 (95.3%)	
	Whole-gland LDR-BT		4 (2.7%)	
	Ultrafocal HDR-BT		3 (2%)	
History of TURP			10 (6.7%)	
Interval primary–salvage treatment (years)			8 (5.3 – 10.7)	
TNM-stage on imaging	T	T2	85 (56.7%)	
		T3	63 (42%)	
		T4	2 (1.3%)	
	N	N0	146 (97.3%)	
		N1	4 (2.7%)	
	M	M0	147 (98%)	
		M1	3 (2%)	

Table 1 Continued

			Median (IQR) or number (%)	Missing (%)
Dorsolateral location of the tumor			132 (88%)	
Size of the CTV (cc)			8.5 (6 – 12.8)	
Size of the prostate# (cc)			31.4 (25.7 – 39.6)	
Baseline IPSS			8 (5 – 11)	16 (10.7%)
Baseline IIEF			9 (4 – 18)	24 (16%)
Baseline toxicity^	GU	0	73 (48.7%)	6 (4%)
		1	52 (34.7%)	
		2	19 (12.6%)	
		3	0 (0%)	
	GI	0	118 (78.7%)	6 (4%)
		1	24 (16%)	
		2	2 (1.3%)	
		3	0 (0%)	
	ED	0	23 (15.3%)	6 (4%)
		1	40 (26.7%)	
		2	54 (36%)	
		3	27 (18%)	
Number of brachytherapy catheters used			9 (8 – 11)	
CTV D95%			18.8 (17.4 – 19.7)	
Urethra D10% (Gy)			15.2 (10.3 – 17.5)	
Bladder D1cc (Gy)			9.2 (5.2 – 11.6)	
Rectum D1cc (Gy)			10.2 (8.1 – 11.7)	

Legend: IQR: interquartile range, EBRT: external beam radiotherapy, LDR-BT: low-dose-rate brachytherapy, HDR-BT: high-dose-rate brachytherapy, ADT: androgen deprivation therapy, TURP: transurethral resection of the prostate, TNM-stage: tumor/node/metastasis stage, CTV: clinical target volume, IPSS: international prostate symptoms score, IIEF: international index of erectile function.

* As part of primary treatment.

As measured on MRI.

^ As graded by the Common Terminology Criteria for Adverse Events (CTCAE) 4.0.

Cumulative toxicity

Over time, 48/150 (32%) patients had maximum new-onset grade 1 GU toxicity, mainly consisting of mild urinary tract pain, hematuria or frequency. A maximum of grade 2 GU toxicity was seen in 61/150 patients (41%), mostly within the subdomain urinary frequency (49/61), for which medication was usually prescribed. Five patients (3%) experienced grade 3 GU toxicity. One patient had grade 3 cystitis, for which he received intravenous antibiotics during a hospital admission. Two patients had grade 3 urinary retention (urethral stricture), which involved placement of a permanent suprapubic catheter after failed urethral stricture incision. Two patients had grade 3 urinary in-

continence: one had overflow incontinence due to bladder neck stenosis and one had severe stress incontinence.

Highest recorded new-onset GI toxicity was grade 1 in 47/150 patients (31%), which was mainly mild flatulence, rectal discomfort or mild rectal hemorrhage. Maximum grade 2 GI toxicity occurred in 8/150 patients (5%), mainly in the form of rectal hemorrhage needing minor cauterization (4/8). No grade 3 GI toxicity was seen.

In 7/150 (5%) patients, highest recorded new ED was grade 1. Maximum grade 2 ED was seen in 33/150 patients (22%) and maximum grade 3 ED in 22/150 (15%) patients.

Toxicity per time point

A subdivision of new-onset toxicity per follow-up time point is graphically displayed in Figures 1a–c. At each time point, the bars represent toxicity as compared to baseline. New grade 1 GU toxicity was mostly recorded in the first month, while grade 2 and 3 GU toxicity peaked between six and twelve months. GI toxicity generally decreased over time. The occurrence of grade 2-3 ED was relatively stable. For more detail, supplementary Figures 1 a–f and 2 a–j (available online at https://doi.org/10.1016/j.ctro.2020.12.002) display new-onset toxicity per GU/GI subdomain.

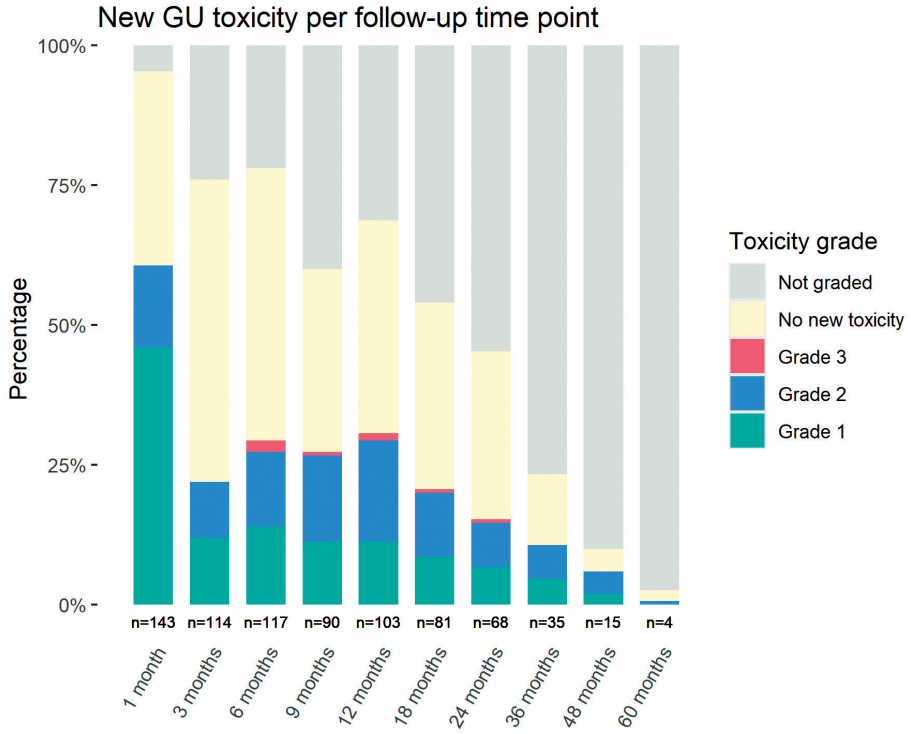

Figure 1-a

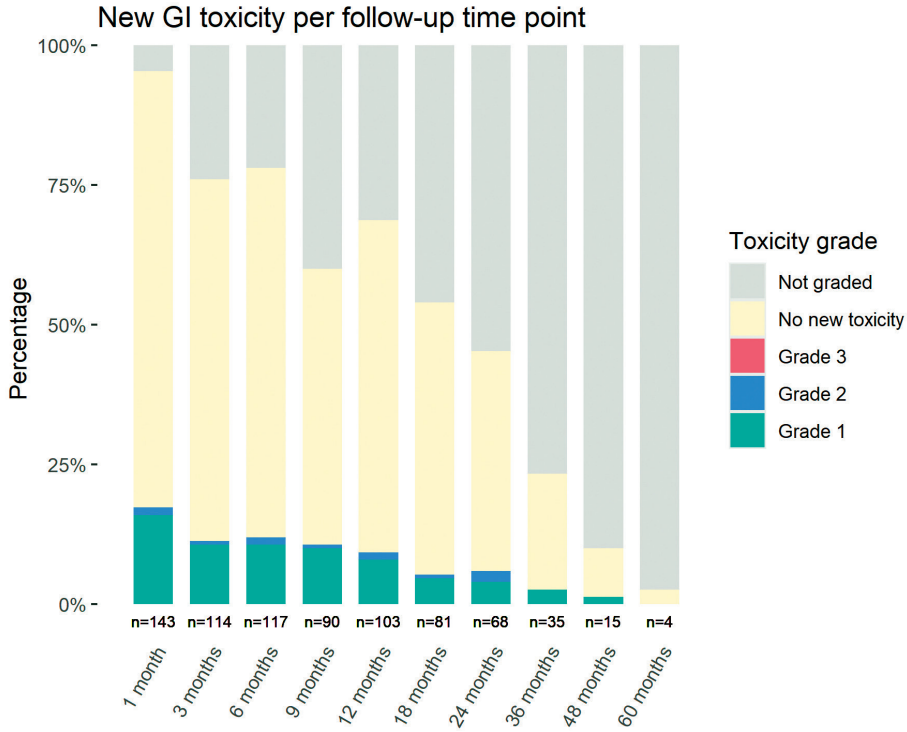
New GI toxicity per follow-up time point
100%
75%
50%
25%
0%
Percentage
n=143
n=114
n=117
n=90
n=103
n=81
n=68
n=35
n=15
n=4
1 month
3 months
6 months
9 months
12 months
18 months
24 months
36 months
48 months
60 months
Toxicity grade
Not graded
No new toxicity
Grade 3
Grade 2
Grade 1

Figure 1-b

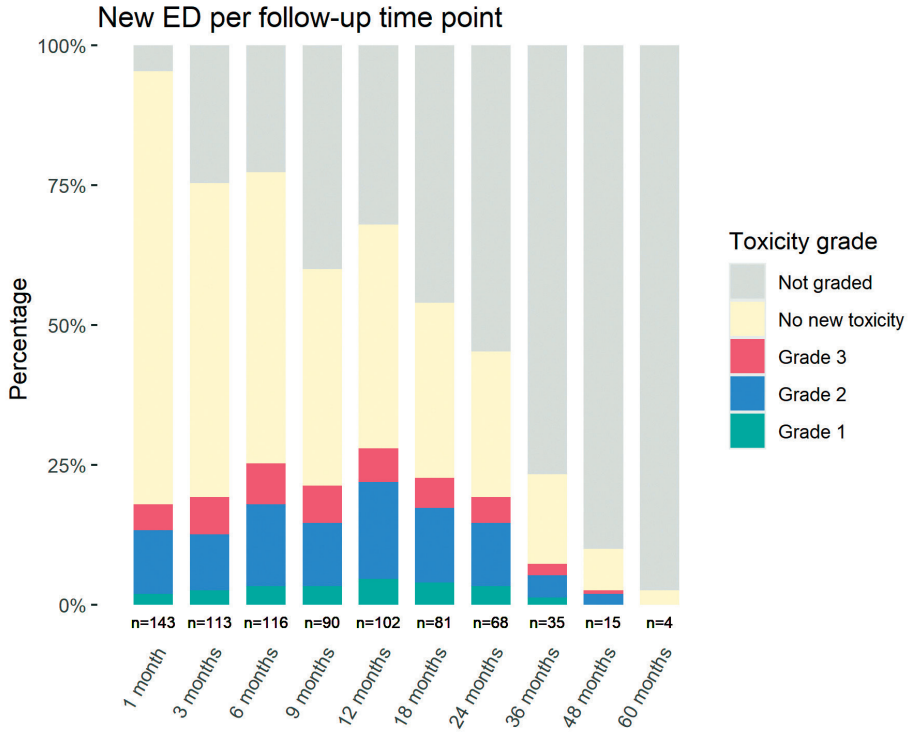

Figure 1-c
Figure 1-a,b,c: Stacked barplots displaying number of patients with new-onset toxicity after ultrafocal salvage HDR-BT. At each follow-up time point, toxicity scores were compared with baseline. Any score above baseline was considered new-onset toxicity.

Acute/late phase

Table 2 shows new-onset toxicity as divided into the acute (≤3 months) and late (>3 months) phase. For the GU domain, grade 2 toxicity increased from 21% (acute phase) to 41% (late phase). Grade 3 GU toxicity only occurred in the late phase. Grade 2 GI toxicity was limited to 2% and 5% in the acute and late phase, respectively. Grade ≥2 ED increased from 22% in the acute phase to 40% in the late phase. Supplementary Table 1 displays acute and late new-onset toxicity for each subdomain.

Table 2 – New-onset acute and late toxicity

Domain	Acute, number (%)	Missing, number	Late, number (%)	Missing, number
Genitourinary toxicity				
No toxicity	48 (33.4%)	6	46 (36.2%)	23
Grade 1	66 (45.8%)		24 (18.9%)	
Grade 2	30 (20.8%)		52 (40.9%)	
Grade 3	0 (0%)		5 (3.9%)	
Gastrointestinal toxicity				
No toxicity	112 (77.8%)	6	89 (70.1%)	23
Grade 1	29 (20.1%)		32 (25.2%)	
Grade 2	3 (2.1%)		6 (4.7%)	
Grade 3	0 (0%)		0 (0%)	
Erectile dysfunction				
No toxicity	108 (75%)	6	69 (54.8%)	24
Grade 1	4 (2.8%)		6 (4.8%)	
Grade 2	21 (14.6%)		32 (25.4%)	
Grade 3	11 (7.6%)		19 (15%)	

Legend: New-onset toxicity after ultrafocal salvage HDR-BT as graded by the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Any score above baseline in the acute (≤3 months) or late (>3 months) phase was considered new-onset toxicity.

For the domains GU toxicity and ED, an explorative risk factor assessment was performed (Table 3). In both domains, baseline toxicity appeared to be the strongest predictor of grade ≥2 toxicity (GU OR 14.8; ED OR 73.7). Within the GU domain, higher baseline IPSS (OR 1.11) and higher dose to the urethra (D10%) (OR 1.28) were also significant risk factors. Post-hoc cut-off analyses showed that the lowest contributive values to the model were IPSS ≥14 and urethra D10% ≥17 Gy. A baseline toxicity score of grade 2 or higher was a significant predictor for both GU toxicity and ED. To clarify the size of the relative risk of developing grade ≥2 GU toxicity or ED, figure 2 shows predicted probabilities at various levels of these risk factors.

Table 3 – Association of pre-treatment characteristics with grade ≥2 toxicity

Domain		95% CI			
		OR	lower	upper	p-value
GU	Baseline toxicity	14.76	6.14	35.50	**<0.01**
	Baseline IPSS	1.11	1.01	1.23	**0.03**
	Urethra D10% (Gy)	1.28	1.05	1.56	**0.01**
	Bladder D1cc (Gy)	1.02	0.84	1.24	0.85
	Prostate size (cc)	1.02	0.98	1.05	0.36
	Tumor stage >T2	1.10	0.29	4.20	0.89
	Size of the CTV (cc)	1.04	0.89	1.21	0.61
	Primary LDR-BT (versus EBRT)	2.79	0.90	8.70	0.08
	Interval primary–salvage treatment (years)	1.07	0.95	1.22	0.26
	Previous salvage treatment	0.72	0.05	11.31	0.81
	History of TURP	2.46	0.34	17.95	0.37
	Number of brachytherapy catheters used	0.83	0.59	1.16	0.28
ED	Baseline toxicity	73.70	15.97	340.03	**<0.01**
	Baseline IIEF	0.97	0.87	1.08	0.56
	Dorsolateral location of the tumor	2.81	0.25	31.19	0.40
	Prostate size (cc)	1.00	0.95	1.05	0.96
	Tumor stage >T2	0.45	0.07	2.76	0.39
	Size of the CTV (cc)	1.04	0.85	1.27	0.70
	Primary LDR-BT (versus EBRT)	1.73	0.28	10.62	0.55
	Interval primary–salvage treatment (years)	1.10	0.88	1.37	0.40
	Previous salvage treatment	0.31	0.01	12.01	0.53
	Previous use of ADT*	1.58	0.17	15.08	0.69
	Number of brachytherapy catheters used	1.04	0.64	1.68	0.88

Legend: GU: genitourinary, ED: erectile dysfunction, IPSS: international prostate symptoms score, CTV: clinical tumor volume, LDR-BT: low-dose-rate brachytherapy, EBRT: external beam radiotherapy, TURP: transurethral resection of the prostate, IIEF: international index of erectile function, ADT: androgen deprivation therapy, OR: odds ratio, 95% CI: 95% confidence interval.
* As part of primary treatment (neo-adjuvant or adjuvant).

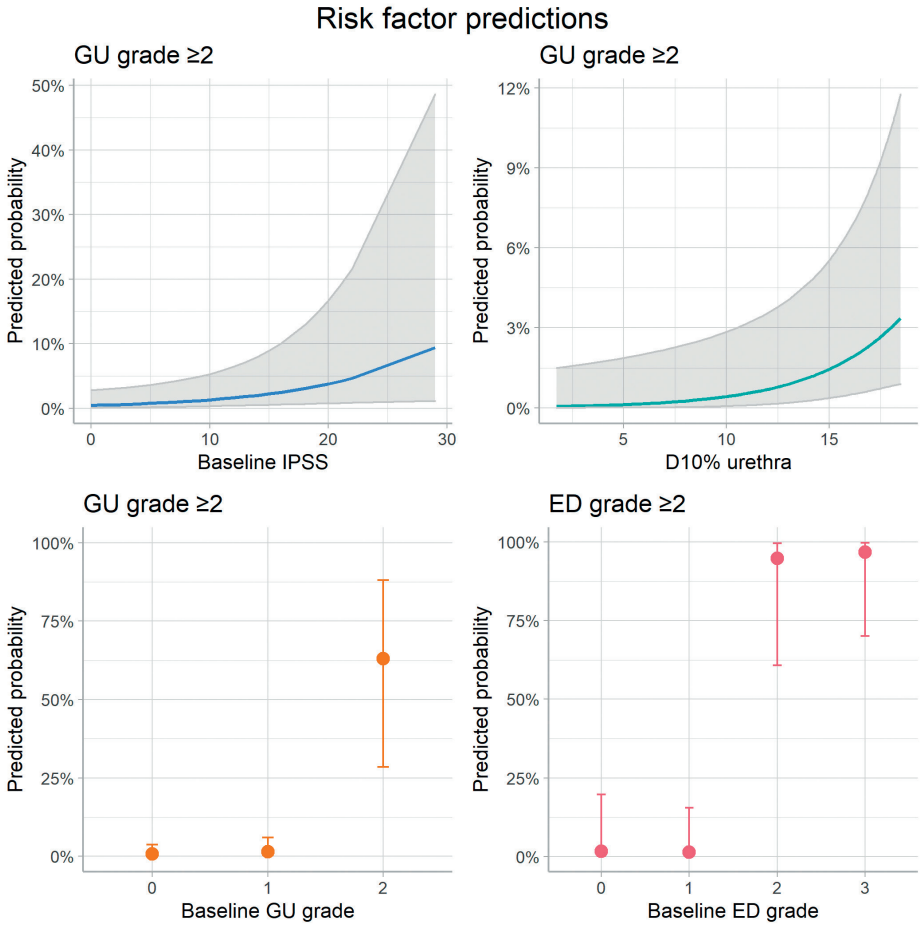

Figure 2 – Predicted probabilities of grade ≥2 GU toxicity or ED at various levels of each risk factor. Modelled marginal means and their confidence intervals are shown, holding the other variables in the model constant.

DISCUSSION

For patients with a local prostate cancer recurrence after radiotherapy, the tradeoff between tumor control and risk of normal tissue damage needs close evaluation when offering salvage treatment. This study provides a comprehensive insight into the occurrence of toxicity after ultrafocal salvage HDR-BT. While severe (grade 3) toxicity was very low (3% GU, 0% GI), proving the safety of this treatment, the number of patients experiencing mild (grade 1) or moderate (grade 2) toxicity was more pronounced (GU 32% and 41%, GI 31% and 5%, respectively). Although almost half of all patients already had grade ≥2 ED at baseline, new grade 2 and 3 ED was seen in 22% and 15%, respectively.

A further evaluation of individual toxicity subdomains and timing of occurrence shows that there are certain patterns of toxicity over time. The acute phase after treatment

was mainly characterized by transient mild symptoms of haematuria, urinary frequency and urinary tract pain, which are common acute symptoms after brachytherapy. In the late phase, moderate urinary frequency became more frequent, as well as moderate urinary incontinence and urinary retention. Erectile function generally decreased over time, with increasing frequencies across the range of mild to severe symptoms.

Although the CTCAE is commonly used to describe treatment-related toxicities, the severity of symptoms and their grading varies between subdomains. The general guideline states that grade 2 toxicity refers to moderate symptoms indicating minimal, local or non-invasive intervention, whereas grade 3 toxicity involves disabling symptoms limiting self-care activities of daily living or (prolongation of) hospitalization(12). Within the subdomain urinary retention, grade 2 toxicity includes placement of a urinary or suprapubic catheter or intermittent catheterization, besides use of medication. In our group, 7 patients with grade 2 urinary retention required a (temporary) urinary catheter (2/7), a (temporary) suprapubic catheter (4/7) or needed self-catheterization (1/7). Since these interventions have substantial impact on daily life activities, we urge to report them separately.

In recent years, an increasing amount of literature on focal salvage HDR-BT has become available. Table 4 summarizes four studies using different focal HDR-BT regimens and targeting strategies, who all reported GU and GI toxicities using the CTCAE 4.0. Across these studies, 2-10% grade 3 GU and 0% grade 3 GI toxicity was reported. Acute and late grade 2 GU toxicity was observed in 54-93% and 42-47% of patients. Two studies specified grade 2 retention: Murgic et al. described that no patient required a urinary catheter, while Chitmanee et al. had patients requiring intermittent catheterization (n=9), urethral dilatation (n=1) and a suprapubic catheter (n=1). Acute and late grade 2 GI toxicity occurred in 0-8% and 0-13%. Grade 1 GU toxicity was observed in 0-36% (acute) and 20-26% (late), and grade 1 GI toxicity in 14-24% (acute) and 14-22% (late).

In comparison, retrospective studies on other focal salvage modalities such as HIFU, cryotherapy and irreversible electroporation (IRE) have described similarly low complication rates(17-19). However, future results from prospective multi-center trials will provide more insight in the role of focal salvage IRE (FIRE trial, ACTRN12617000806369) and focal salvage HIFU/cryotherapy (FORECAST trial, NCT01883128).

Table 4 – Focal salvage HDR-BT studies reporting CTCAE 4.0 toxicity

Study	Year	N	Dose regimen	Target	OAR dose constraints	Median follow-up	Grade 3 toxicity
Jiang et al (13)	2017	22	3 weekly fractions of 10 Gy	Peripheral zone and choline PET-positive area	≤9 Gy to the urethral surface and ≤7 Gy to the visible rectum	73 months	GI: 0% GU: 9% (late phase)
Murgic et al (14)	2018	15	2 weekly fractions of 13.5 Gy	Prostate quadrant with MRI-visible lesion	Urethra D10% <110% and rectal V80% <0.2 ml	36 months	GI: 0% GU: 6.7% (late phase)
Slevin et al (15)	2020	43	Single dose of 19 Gy	Lesion as identified using TRUS, mp-MRI, PET-CT and template-guided biopsies	Urethra D10% <20.9 Gy, rectal V100%=0 ml and rectal D2cc <12.35 Gy	26 months	GI: 0% GU: 2.3% (late phase)
Chitmanee et al (16)	2020	50	Single dose of 19 Gy	Lesion as identified using mp-MRI and template mapping biopsies	Urethra D10% <22 Gy and rectal D2cc <15 Gy	21 months	GI: 0% GU: 10% (late phase)

Legend: CTCAE: Common Terminology Criteria for Adverse Events, N: number of patients, OAR: organs at risk, Gy: Gray, PET: positron emission tomography, mp-MRI: multiparametric magnetic resonance imaging, TRUS: transrectal ultrasound, GU: genitourinary, GI: gastro-intestinal.

In a previous study, we focused on patient-reported quality of life after ultrafocal salvage HDR-BT(9). Patients reported increased urinary symptoms (especially in the first month after treatment) and a decrease of sexual functioning, while bowel symptoms were negligible. The explorative risk factor analysis in that study revealed that increased baseline urinary symptoms and higher urethra D10% (≥16 Gy) were significantly associated with post-treatment urinary symptoms, and impaired sexual functioning at baseline with post-treatment erectile dysfunction. These results are consistent with the current findings, in which baseline GU/ED toxicity, IPSS ≥14 and urethra D10% ≥17 Gy were significant predictors for grade ≥2 toxicity. While these analyses highlight the importance of assessing urinary and sexual function before treatment and the need for a strict urethral dose constraint, it also shows the apparent weak relationship between toxicity and other factors such as dose to the bladder, size or stage of the tumor and number of brachytherapy catheters used for the implant. This is important information to find areas of improvement for treatment planning and patient selection, especially since (ultra) focal salvage HDR-BT is being adopted in an increasing number of centers worldwide.

Out of the five patients who experienced severe GU toxicity, only two had substantial pre-treatment urinary complaints, consisting of increased frequency (hourly urination), hesitation and mild urge. Pre-treatment IPSS values among these patients ranged between 3 and 18. A common denominator was the relatively high received dose by the urethra, with D10% >17 Gy in 4/5 patients.

Although beyond the scope of this study, more research is warranted to explore potential improvements in terms of optimizing tumor control. For instance, dose fractionation may offer biological advantages. As described above, different dosimetry and fractionation schemes are being employed for (ultra)focal salvage HDR-BT. Although toxicity seems comparable between these regimens, estimated 3-year biochemical disease-free survival was higher in the multi-fraction studies (±60%) than the single-dose studies (±44%). Recent results from a comparative trial on the efficacy of whole-gland HDR-BT in the primary setting (1x19 Gy versus 2x13.5 Gy) revealed a clear 5-year cancer control advantage for the two-fraction arm(20). Using patient- and tumor-related characteristics, we are currently in the process of developing a prediction model for biochemical failure to further optimize our patient selection criteria.

CONCLUSION

MRI-guided ultrafocal salvage HDR-BT can be offered as a safe salvage treatment to patients with a local recurrence after primary radiotherapy. Adequate patient selection by baseline symptom assessment and adherence to urethral dose constraints during treatment planning are the most important factors to avoid (severe) toxicity. By offering this treatment, patients may avoid or at least postpone the need for ADT, preventing them from hormone deprivation-related symptoms. Further research in this field should focus on potential areas of improvement in terms of cancer control, aiming to maintain patients ADT-free for as long as possible.

REFERENCES

1. Magee DE, Singal RK. Androgen deprivation therapy: indications, methods of utilization, side effects and their management. The Canadian journal of urology. 2020;27(1S1):11-6.
2. Muniyan S, Xi L, Datta K, Das A, Teply BA, Batra SK, et al. Cardiovascular risks and toxicity - The Achilles heel of androgen deprivation therapy in prostate cancer patients. Biochim Biophys Acta Rev Cancer. 2020:188383.
3. Crook JM, Zhang P, Pisansky TM, Trabulsi EJ, Amin MB, Bice W, et al. A Prospective Phase 2 Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer After External Beam Radiation Therapy (NRG Oncology/RTOG-0526). Int J Radiat Oncol Biol Phys. 2019;103(2):335-43.
4. Fendler WP, Ferdinandus J, Czernin J, Eiber M, Flavell RR, Behr SC, et al. Impact of (68) Ga-PSMA-11 PET on the Management of recurrent Prostate Cancer in a Prospective Single-Arm Clinical Trial. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2020.
5. Duijzentkunst DA, Peters M, van der Voort van Zyp JR, Moerland MA, van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review. World journal of urology. 2016;34(11):1521-31.
6. van Son M, Peters M, Moerland M, Kerkmeijer L, Lagendijk J, van der Voort van Zyp J. Focal Salvage Treatment of Radiorecurrent Prostate Cancer: A Narrative Review of Current Strategies and Future Perspectives. Cancers. 2018;10(12).
7. Haj-Hamed M, Karivedu V, Sidana A. Salvage treatment for radio-recurrent prostate cancer: a review of literature with focus on recent advancements in image-guided focal salvage therapies. International urology and nephrology. 2019;51(7):1101-6.
8. van Son MJ, Peters M, Moerland MA, Lagendijk JJW, Eppinga WSC, Shah TT, et al. MRI-guided ultrafocal salvage high-dose-rate brachytherapy for localized radiorecurrent prostate cancer: updated results of 50 patients. Int J Radiat Oncol Biol Phys. 2020.
9. van Son M, Monninkhof E, Peters M, Lagendijk J, van der Voort van Zyp J. Health-related quality of life after ultrafocal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer: reporting the patient's perspective. Clinical and translational radiation oncology. 2020;25:81-7.
10. Maenhout M, Peters M, van Vulpen M, Moerland MA, Meijer RP, van den Bosch M, et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radiorecurrent Prostate Cancer. Technology in cancer research & treatment. 2017;16(6):1194-201.
11. Bates D, Machler M, Bolker BM, Walker SC. Fitting Linear Mixed-Effects Models Using lme4. J Stat Softw. 2015;67(1):1-48.
12. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
13. Jiang P, van der Horst C, Kimmig B, Zinsser F, Poppe B, Luetzen U, et al. Interstitial high-dose-rate brachytherapy as salvage treatment for locally recurrent prostate cancer after definitive radiation therapy: Toxicity and 5-year outcome. Brachytherapy. 2017;16(1):186-92.
14. Murgic J, Morton G, Loblaw A, D'Alimonte L, Ravi A, Wronski M, et al. Focal Salvage High Dose-Rate Brachytherapy for Locally Recurrent Prostate Cancer After Primary Radiation Therapy Failure: Results From a Prospective Clinical Trial. Int J Radiat Oncol Biol Phys. 2018;102(3):561-7.

15. Slevin F, Hodgson S, Rodda SL, Bownes P, Bottomley D, Adiotomre E, et al. Efficacy and toxicity outcomes for patients treated with focal salvage high dose rate brachytherapy for locally recurrent prostate cancer. Clinical and translational radiation oncology. 2020;23:20-6.

16. Chitmanee P, Tsang Y, Tharmalingam H, Hamada M, Alonzi R, Ostler P, et al. Single-Dose Focal Salvage High Dose Rate Brachytherapy for Locally Recurrent Prostate Cancer. Clinical oncology (Royal College of Radiologists (Great Britain)). 2020;32(4):259-65.

17. Kanthabalan A, Peters M, Van Vulpen M, McCartan N, Hindley RG, Emara A, et al. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU international. 2017;120(2):246-56.

18. Bomers JGR, Overduin CG, Jenniskens SFM, Cornel EB, van Lin E, Sedelaar JPM, et al. Focal Salvage MR Imaging-Guided Cryoablation for Localized Prostate Cancer Recurrence after Radiotherapy: 12-Month Follow-up. J Vasc Interv Radiol. 2020;31(1):35-41.

19. Scheltema MJ, van den Bos W, Siriwardana AR, Kalsbeek AMF, Thompson JE, Ting F, et al. Feasibility and safety of focal irreversible electroporation as salvage treatment for localized radio-recurrent prostate cancer. BJU international. 2017;120 Suppl 3:51-8.

20. Morton G, McGuffin M, Chung HT, Tseng CL, Helou J, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol. 2020;146:90-6.

CHAPTER 8

Development and internal validation of multivariable prediction models for biochemical failure after MRI-guided focal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer

Authors: Thomas Willigenburg, Marieke J. van Son, Sandrine M.G. van de Pol, Wietse S.C. Eppinga, Jan J.W. Lagendijk, Hans C.J. de Boer, Marinus A. Moerland, Jochem R.N. van der Voort van Zyp, Max Peters

SUBMITTED

ABSTRACT

Background and purpose

Magnetic resonance (MR)-guided focal salvage high-dose-rate brachytherapy (FS-HDR-BT) for radiorecurrent prostate cancer (PCa) shows low toxicity rates. However, biochemical failure (BF) rates after treatment remain high. We developed and internally validated two prediction models for BF (Phoenix definition) with the aim of enhancing patient selection, guidance and counselling before FS-HDR-BT and to identify high-risk patients during follow-up.

Materials and methods

A prospective cohort of 150 radiorecurrent PCa patients treated with FS-HDR-BT between 2013 and 2020 at the University Medical Center Utrecht was used for model development and validation. Two multivariable Cox proportional hazards models were developed and internally validated. For model 1, only pre-salvage variables were included as candidate predictors. For model 2, additional (post-)salvage characteristics were tested. The models were calibrated and for each model a nomogram and webtool were constructed. Finally, three risk groups were identified.

Results

Sixty-one patients (41%) experienced BF after a median of 32.9 months (interquartile range 23.5-43.6). At baseline (model 1), age, gross tumor volume, pre-salvage PSA, and pre-salvage PSA doubling time (PSADT) were predictive of BF. During follow-up (model 2), age, pre-salvage PSA and PSADT, seminal vesicle involvement, post-salvage time to PSA nadir, and percentage PSA reduction were predictive of BF. The adjusted C-statistics were 0.73 (95% CI: 0.66-0.81) and 0.84 (95% CI: 0.78-0.90) with acceptable calibration. Estimated 2-year biochemical disease-free survival was 84%, 70%, and 31% (model 1), and 100%, 71%, and 5% (model 2) for the low-, intermediate-, and high-risk group, respectively.

Conclusion

Two models are provided for prediction of BF in patients with radiorecurrent PCa treated with FS-HDR-BT. Based on pre- and post-salvage characteristics, we are able to identify patients with a high risk of BF. These findings can aid patient selection, counselling, and guidance at baseline and during follow-up.

INTRODUCTION

Advances in prostate cancer (PCa) treatment have increased cure rates. However, still up to 50% of high-risk PCa patients treated with radiotherapy develop a recurrence within 10 years of treatment[1–3]. These recurrences are often confined to the prostate and frequently located at the site of the primary index lesion[4,5]. Nowadays, recurrences can be assessed at an earlier stage with prostate specific membrane antigen positron emitting tomography CT (PSMA-PET-CT). In this setting, focal therapy, targeting the recurrent lesion while sparing healthy prostate tissue, is an attractive treatment option with the aim of postponing initiation of androgen deprivation therapy (ADT) [5,6]. The main potential advantage of focal over whole-gland salvage treatments is the reduced chance of side-effects and quality of life deterioration, without affecting oncological outcomes[7–13].

One of the treatment options for radiorecurrent PCa is magnetic resonance imaging (MRI)-guided focal salvage high-dose-rate brachytherapy (FS-HDR-BT)[8,9]. In previous studies, we found that around 50% of patients treated with single fraction FS-HDR-BT show biochemical failure (BF) within 2.5 years, caused by either local recurrences, regional recurrences, metastatic disease, or a combination[9]. While several studies have been published on predictive factors for BF after whole-gland salvage radiotherapy treatments[14–16], no studies have been published in patients undergoing focal salvage radiotherapy. Due to differences in patient-, tumor-, and treatment-characteristics, the results from whole-gland salvage studies are not directly applicable to FS-HDR-BT. In the current study we evaluated the predictive value of several pre- and post-salvage variables for BF after FS-HDR-BT for radiorecurrent PCa. Two models were developed, (1) with the aim of enhancing patient selection, based on pre-salvage characteristics, and (2) including additional (post-)salvage characteristics, with the aim of identifying patients at high-risk of BF during follow-up to support patient guidance and counselling.

MATERIALS AND METHODS

Patient selection

For this study we prospectively included 150 patients treated with FS-HDR-BT for localized radiorecurrent PCa between July 2013 and January 2020 at the Radiotherapy of the University Medical Center Utrecht (UMCU). Initially, patients were treated within an institutional review board (IRB)-approved feasibility study (Netherlands Trial Register number NTR6123), following the criteria: PSA level ≤10 ng/ml, PSA doubling time (PSADT) ≥12 months, tumor stage (MRI) ≤T2c, and acceptable urinary function (International Prostate Symptom Score <15). Because of favourable toxicity results after 2 years of inclusion, patients beyond the initial inclusion criteria were treated off-protocol. In February 2018, a subsequent phase II study initiated ('PRostatE Cancer MRI guided focal SalvagE high-dose-rate brachytherapy', or PRECISE; NTR7014). This study expanded the inclusion criteria from the feasibility study: PSA ≤20 ng/ml, PSADT ≥9

months, and tumor stage ≤T3b. All study patients provided written informed consent. A waiver from the IRB was obtained for patients treated off-protocol. Study and treatment details have been described previously[9,17].

Pre-treatment procedures

Patients underwent pre-treatment 3T multiparametric (mp) MRI (including T2-weighted, diffusion-weighted, and dynamic contrast enhanced sequences) and 68Ga-PSMA-PET-CT or 18F-Choline-PET-CT scans. Initially, PSMA-PET/MRI-targeted biopsies were performed in all patients. However, since the accuracy of Gleason score assessment is debated in irradiated prostate tissue and because biopsies were predominantly positive, biopsies were no longer performed from the end of 2017 onward[18–20].

A dose of 19 Gray (Gy) was prescribed to the clinical target volume (CTV), which consisted of the MRI- and PET-CT-visible lesion (gross tumor volume [GTV]) plus a 5 mm margin. The planning target volume (PTV) was equal to the CTV. Dose constraints to organs at risk were according to protocol and included rectum D1cc and bladder D1cc <12 Gy, and urethra D10% <17.7 Gy [9].

Follow-up and outcome assessment

Follow-up consisted of outpatient clinical visits combined with PSA measurements at 1 and 3 months, every three months the first year, biannually the second year, and annually thereafter up to 10 years. The outcome, BF, was defined according to the Phoenix definition (PSA nadir + 2 ng/ml). In case of BF, follow-up imaging was performed with Ga68-PSMA-PET-CT to assess loco-regional recurrence and/or metastatic disease.

Candidate variables for model building

To minimize the risk of overfitting, a sample size calculation was performed up front to calculate the number of candidate predictors allowed for multivariable testing. Assuming a 0.05 acceptable difference in apparent and adjusted R-squared, an expected R-squared of 0.15, an overall event rate of 0.2 (200 events per 1000 person-years follow-up), and a shrinkage factor of 0.8, would allow for seven candidate variables with 150 patients and 61 events[21]. For model 1, six candidate variables were selected for multivariable testing based on clinical knowledge and literature[10,15,16]. For model 2, three additional variables were tested, thereby accepting a small increase in chance of overfitting. For model 1, the variables assessed pre-salvage included: age at FS-HDR-BT, seminal vesicle involvement, GTV (cm3), PSADT (months), PSA (ng/ml), and MRI-based T-stage (T1, T2, and T3 based on NCCN criteria). PSADT was obtained using the Memorial Sloan Kettering Cancer tool (available via: https://www.mskcc.org/nomograms/prostate/psa_doubling_time). For model 2, CTV D95% (dose to 95% of the CTV, in Gy), time to PSA nadir (months) and PSA reduction (ratio between pre-salvage PSA and PSA nadir, in %) were added.

Statistical analysis

Baseline characteristics and survival

Normally distributed determinants are presented as mean (± standard deviation [SD]). Skewed variables are presented as medians with interquartile ranges (IQR). Frequencies and percentages are used for categorical data. The Kaplan-Meier method was used to estimate biochemical disease-free survival (bDFS). For comparisons between groups, the log-rank test was used.

Missing data handling

Missing data was considered to be missing at random. Multiple imputation by chained equations was used to impute missing data, creating 20 imputation datasets. All predictors listed above, additional patient and treatment characteristics listed in Supplementary File A, the outcome, and the cumulative baseline hazard, calculated with the Nelson-Aalen function, were included in the imputation procedure[22,23]. All subsequent modelling steps were pooled over the 20 imputation datasets.

Functional form of continuous predictors

Before fitting the multivariable model, non-linear relationships between continuous predictors and the outcome were assessed visually by plotting the predictors against log-hazard using restricted cubic splines with three knots (10th, 50th, and 90th percentile). In case of visible non-linearity, spline transformations were tested against linear modelling through univariable and multivariable Cox proportional hazards models (likelihood-ratio test). If model fit improved significantly, a spline-transformation was used. For pre-salvage PSA, a natural logarithm-transformation was used based on literature and model fit in our dataset[24].

Model development

In case correlations between candidate variables were ≥0.75, the clinically most relevant variable was chosen for multivariable testing. MRI-based T-stage showed high correlation with seminal vesicle involvement (correlation coefficient 0.78). Based on clinical judgement, MRI-based T-stage was therefore excluded from multivariable regression analysis. A multivariable Cox proportional hazards regression model was fitted, providing hazard ratios (HR) with 95% confidence intervals (CI). Stepwise backward elimination was performed, using lowest Akaike's Information Criteria (AIC) for selection[25]. No interactions were assessed due to the limited sample size.

Model assumptions

For both models the assumptions of the Cox proportional hazards model were checked. The proportionality assumption was assessed using Log-Log curves and Schoenfeld residuals for categorical and continuous variables, respectively. Linearity of continuous

variables was checked with Martingale residuals. Influential outliers were assessed by calculating dfbeta residuals.

Model performance and internal validation

The discriminative ability of the model was assessed using Harrell's C-statistic. Internal validation was performed through bootstrapping with 2000 resamples for each imputation set, in which all modeling steps were repeated. The optimism of each model and shrinkage factors were calculated, and the β-coefficients and C-statistic were adjusted accordingly. The predictive accuracy of the optimism-corrected models was visualized with calibration plots at 12, 24, and 36 months.

Nomogram and risk group construction

For both models a nomogram and webtool were constructed using the optimism-corrected coefficients. Finally, for each model separately, three risk groups were identified on the basis of the 25th and 75th percentile of the linear predictor. The Kaplan-Meier method was used to display the biochemical disease-free survival curves for each risk group.

All statistical analyses were performed using R studio (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria, https://rstudio.com) and the survival, survminer, rms, pmsampsize, ggplot2, mice, psfmi, DynNom, and regplot packages[26]. Reporting was according to the TRIPOD statement[25].

RESULTS

Baseline characteristics and Kaplan-Meier survival analysis

Baseline characteristics are displayed in Table 1. Median (IQR) follow-up time was 25.1 months (13.5-38.1) for all patients and 18.1 months (9.2-29.6) for patients who did not experience BF (censored). Sixty-one patients (40.7%) experienced BF after a median (IQR) of 32.9 months (23.5-43.6). Median bDFS was 29.7 months (95% CI: 25.0-38.6) (Figure S1 in Supplementary File B).

Table 1 – Baseline patient-, tumour-, and treatment-related characteristics

Primary treatment	n (%) or median (IQR)	Missing (%)
Primary treatment		
EBRT	80 (53.3)	0
LDR brachytherapy	67 (44.7)	
HDR brachytherapy	3 (2)	
EBRT dose (Gy)	76.0 (71.5-77.0)	12.5
LDR dose (Gy)	145.0 (145.0-145.0)	0
HDR dose (Gy)	19.0 (19.0-38.0)	0
PLND at primary treatment	30 (20.0)	0

Table 1 Continued

Primary treatment	n (%) or median (IQR)	Missing (%)
Initial NCCN risk group		
Low risk	27 (18.0)	5.3
Intermediate risk	56 (37.3)	
High risk	59 (39.3)	
ADT use (adjuvant/neoadjuvant)	30 (20.0)	0
ADT duration (months) (n=30)	36.0 (18.0-36.0)	10
PSA nadir post-primary treatment (ng/ml)	0.56 (0.25-1.10)	3.3
FS-HDR-BT	n (%) or median (IQR)	Missing (%)
Pre-salvage PSADT (months)	15.7 (11.6-23.6)	0
Interval between primary and salvage treatment (months)	97 (63-128)	0
Age at FS-HDR-BT (years)	71.5 (±5.0)	0
Pre-salvage PSA (ng/ml)	4.88 (2.80-6.80)	0
Imaging T-stage at FS-HDR-BT		
T1-2a	45 (30.0)	0
T2b-2c	40 (26.7)	
T3a-3b	65 (43.3)	
Gleason at FS-HDR-BT		
3+3=6	14 (9.3)	44.7
3+4=7	27 (18.0)	
4+3=7	21 (14.0)	
Sum score=8	6 (4.0)	
Sum score=9/10	14 (9.3)	
Tumour location		
Base	21 (14.0)	0
Midgland	29 (19.3)	
Apex	21 (14.0)	
Combination base/midgland/apex	31 (20.7)	
Seminal vesicle	23 (15.3)	
Prostate body and seminal vesicle	25 (16.7)	
Seminal vesicle involvement at FS-HDR-BT	48 (32.0)	0
GTV at FS-HDR-BT (cm^3)	3.0 (1.7-5.1)	0.7
D95% CTV (Gy)	18.8 (17.4-19.7)	0
V200% CTV (%)	26.3 (18.4-27.9)	0
Post-salvage PSA nadir (ng/ml)	0.76 (0.26-1.30)	0
Post-salvage time to PSA nadir (months)	6.1 (3.6-9.6)	0
Percentage PSA reduction	84.2 (68.3-92.9)	0
Biochemical recurrence	61 (40.7)	0
Follow-up time (months)	25.1 (13.5-36.1)	0

Abbreviations: IQR=interquartile range. SD=standard deviation. EBRT=external beam radiotherapy. LDR=low-dose rate. HDR=high-dose rate. PLND=pelvic lymph node dissection. NCCN=national comprehensive cancer network. ADT=androgen deprivation therapy. PSA=prostate specific antigen. FS-HDR-BT=focal salvage high-dose-rate brachytherapy. PSADT=PSA doubling time. GTV=gross tumour volume. D95%=dose to 95% of the volume. V200%=volume receiving 200% or more of the prescribed dose. CTV=clinical target volume.

Table 2 – Multivariable Cox proportional hazards regression analysis for biochemical recurrence for model 1 and model 2

	Model 1			Model 2		
Candidate predictor	Corrected* β-coefficient	Corrected* HR (95% CI)	p-value	Corrected# β-coefficient	Corrected# HR (95% CI)	p-value
Age (years)	-0.065	0.94 (0.90-0.98)	0.003	-0.087	0.92 (0.87-0.96)	0.0005
Pre-salvage PSADT (months)	-0.14	0.87 (0.83-0.92)	<0.0001	-0.12	0.89 (0.83-0.94)	0.0001
Pre-salvage PSADT' (months)$	0.16	1.18 (1.09-1.27)	<0.0001	0.15	1.16 (1.07-1.26)	0.0004
Pre-salvage PSA (ng/ml) (natural logarithm)	0.78	2.19 (1.50-3.18)	0.0001	1.50	4.47 (2.94-6.80)	<0.0001
Seminal vesicle involvement	X	X	X	0.40	1.49 (0.87-2.55)	0.14
GTV (cm^3)	0.053	1.05 (1.00-1.11)	0.037	X	X	X
D95% CTV (Gy)	NA	NA	NA	X	X	X
Time to PSA nadir post-salvage (months)	NA	NA	NA	-0.20	0.82 (0.76-0.88)	<0.0001
PSA reduction post-salvage (%)	NA	NA	NA	-0.021	0.98 (0.97-0.99)	0.0003

Baseline survival model 1: $S_0(12) = \exp(-12.82)$; $S_0(24) = \exp(-65.71)$; $S_0(36) = \exp(-159.00)$. Baseline survival model 2: $S_0(12) = \exp(-214.58)$; $S_0(24) = \exp(-1869.63)$; $S_0(36) = \exp(-5167.25)$.

*Corrected for optimism with shrinkage factor = 0.845.

#Corrected for optimism with shrinkage factor = 0.812.

$PSADT is modelled using restricted cubic splines (3 knots at 10^{th}, 50^{th}, and 90^{th} percentile), resulting in one extra parameter, PSADT', which is dependent on PSADT and can be calculated according to the formula for PSADT' in Supplementary File D.

NA = not applicable. X = excluded using backward elimination based on AIC.

Abbreviations: HR=hazard rate. CI=confidence interval. PSA=prostate specific antigen. FS-HDR-BT=focal salvage high-dose-rate brachytherapy. PSADT=PSA doubling time. GTV=gross tumour volume. D95%=dose to 95% of the volume. CTV=clinical target volume. $S_0(t)$=baseline survival at time point t.

Cox proportional hazards models

Table 2 presents the results from multivariable Cox regressions for model 1 and 2. At baseline (model 1), four variables were identified as significant predictors of BF: age (HR 0.94), pre-salvage PSA (HR 2.19), GTV (HR 1.05), and pre-salvage PSADT (HR 0.87 and 1.18 for PSADT and PSADT', respectively). For model 2, six predictors were identified: age (HR 0.92), pre-salvage PSADT (HR 0.89 and 1.16), pre-salvage PSA (HR 4.47), seminal vesicle involvement (HR 1.49), post-salvage time to PSA nadir (HR 0.82), and PSA reduction (HR 0.98). Although seminal vesicle involvement was not statistically significant in model 2 (p=0.14), its exclusion affected AIC notably and therefore it remained in the model. The ranges of the continuous variables in our dataset are displayed in Supplementary File C.

Calibration and internal validation

Calibration curves at 12, 24, and 36 months for both models are depicted in Figure 1. Calibration was reasonable up to 24 months. Internal validation showed an optimism of 0.15 and 0.19 for model 1 and 2, respectively. The β-coefficients were therefore adjusted with a factor of 0.85 (model 1) and 0.81 (model 2). The C-statistic was adjusted from 0.75 to 0.73 (95% CI: 0.66-0.81) for model 1 and from 0.85 to 0.84 (95% CI: 0.78-0.90) for model 2. The full regression equation for both models can be found in Supplementary file D.

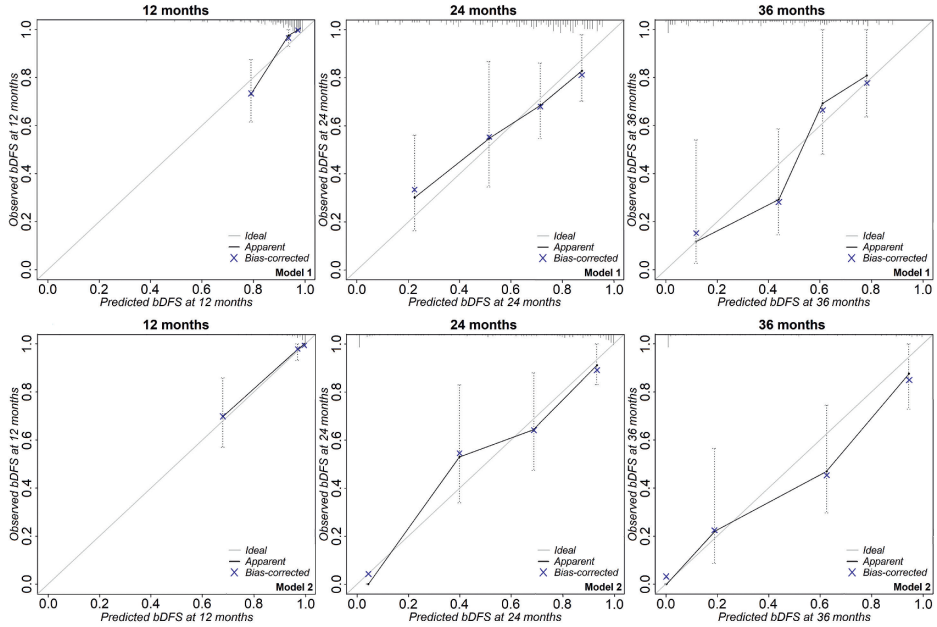

Figure 1 – Calibration plots for model 1 (upper row) and model 2 (lower row) depicting the observed (y-axis) versus the predicted probability (x-axis) of biochemical disease-free survival (bDFS) at 12, 24, and 36 months, respectively. Vertical bars indicate the 95% confidence interval. The grey diagonal line depicts the ideal line for complete concordance between observed and predicted probabilities. The blue crosses indicate the optimism-corrected probabilities.

Nomogram

The static nomograms for model 1 and 2 are depicted in Figure 2 and 3, respectively. An exemplary case is included in the figure caption. The Kaplan-Meier curves for bDFS for low-, intermediate-, and high-risk groups, as identified by model 1 (nomogram score <193, 193-222, and >222, respectively) and model 2 (nomogram score <297, 297-334, and >334, respectively) are shown in Figure 4. Estimated bDFS at 24 months for low-, intermediate, and high-risk groups was 84%, 70%, and 31% for model 1 (p<0.0001) and 100%, 71%, and 5% for model 2 (p<0.0001), respectively. Both models can be used as webtools through: https://fs-hdr-bt-prediction.shinyapps.io/model1/ (model 1) or https://fs-hdr-bt-prediction.shinyapps.io/model2/ (model 2).

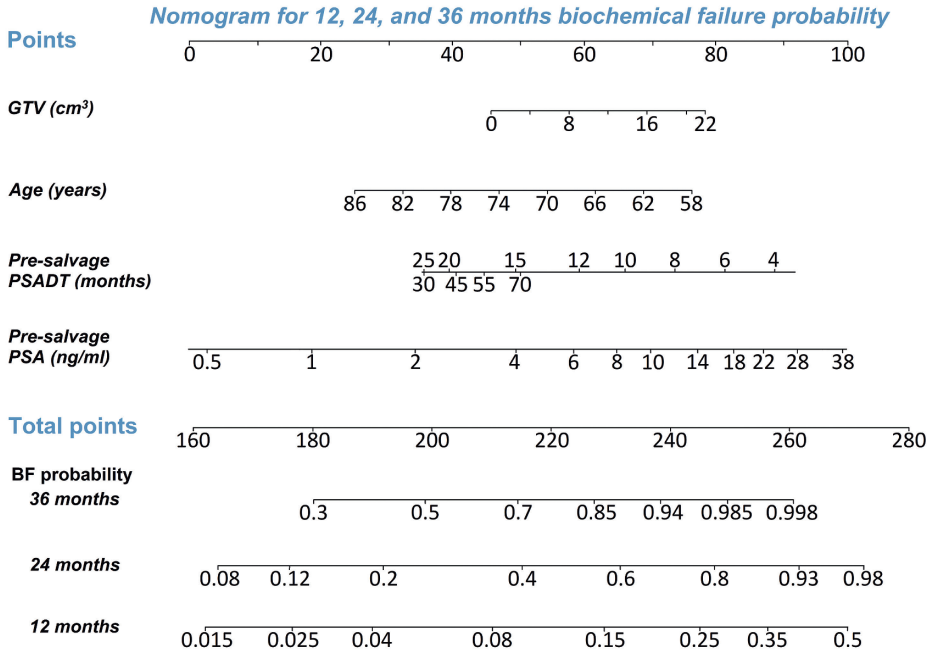

Figure 2 – Nomogram based on **model 1** for prediction of biochemical failure among patients who underwent FS-HDR-BT. Probabilities of biochemical failure within 12, 24, and 36 months can be calculated. Instruction: Locate the patient's GTV (cm3) of the recurrent prostate cancer lesion on the 'GTV (cm3)' axis. Draw a line straight upward to the 'Points' axis to determine the number of points based on the GTV. Repeat this process for each of the four variables. Sum the points that are received for each of the four predictors ('Total points'). Finally, draw a line straight down from the 'Total points' axis to find the patient's probability of having biochemical failure within 36, 24, and 12 months, respectively. An interactive version of the nomogram can be used online through: https://fs-hdr-bt-prediction.shinyapps.io/model1/. As an example, a 72-year-old patient with a GTV of 4.0 cm3, a PSA-level of 6.0 ng/ml, and a pre-salvage PSADT of 25 months has an estimated 12-, 24-, and 36-months bDFS probability of 95% (95% CI: 93-98%), 78% (95% CI: 70-87%) and 53% (95% CI: 40-71%), respectively.

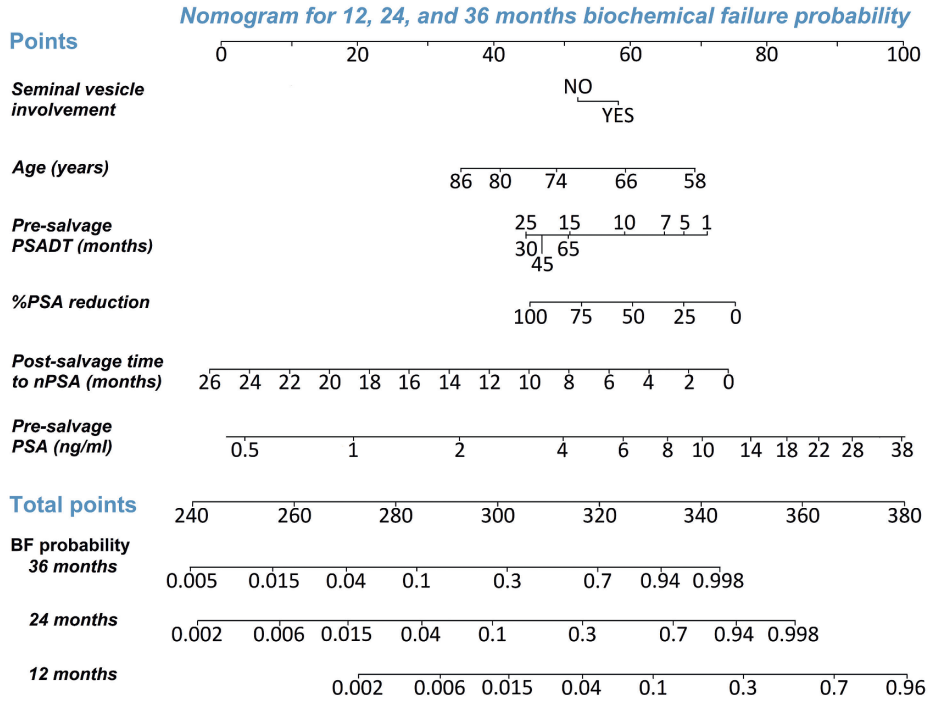

Figure 3 – Nomogram based on **model 2** for prediction of biochemical failure among patients who underwent FS-HDR-BT. Probabilities of biochemical failure within 12, 24, and 36 months can be calculated. The model can be used online through: https://fs-hdr-bt-prediction.shinyapps.io/model2/. As an example, for the same patient (72 years old, PSA-level 6.0 ng/ml, and a pre-salvage PSADT of 25 months) with no seminal vesicle involvement, PSA nadir after 6 months and a PSA reduction of 90%, the score based on model 2 would be 313, with estimated bDFS probabilities of 98% (95% CI: 96-100%), 80% (95% CI: 71-91%) and 52% (95% CI: 36-74%) at 12, 24, and 36 months.

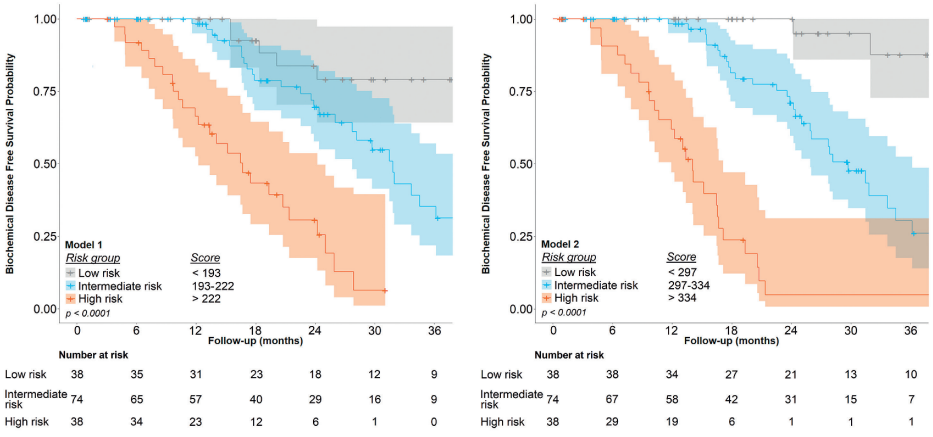

Figure 4 – Kaplan-Meier plots for biochemical disease-free survival for low-, intermediate-, and high-risk groups (based on linear predictor/nomogram score), as identified by model 1 (left, nomogram sum scores <193, 193-222, and >222, respectively) and model 2 (right, nomogram sum scores <297, 297-334, and >334, respectively). Scores are as calculated by the respective nomograms.

DISCUSSION

This study provides two clinically useful multivariable prediction models for BF in patients with radiorecurrent PCa treated with FS-HDR-BT. Model 1 can be used to support clinical decision making and patient guidance at baseline, while model 2 could be used during follow-up to counsel patients regarding their prognosis and potentially adapt follow-up intensity accordingly.

The predictors in both models and the direction of their effects were mostly as expected. Increased age was associated with a lower hazard of BF. Although causal inference is not applicable in prediction, this could be explained by the potentially longer disease-free survival interval (DFSI) between primary and salvage treatment indicating more indolent tumors. DSFI was longer in elderly patients (median 92 versus 108 months for <75 years versus ≥75 years, respectively). Data on pre-salvage Gleason score is mostly lacking in our cohort, which hinders assessing this relation. Both a higher pre-salvage PSA level and larger GTV were associated with an increased hazard. Both indicate higher tumor load and were therefore expected to be correlated with BF. For pre-salvage PSADT, which was non-linearly related to the outcome, hazard decreased with longer doubling times. This was expected given previous reports[15]. However, from approximately 32 months onward, the hazard increased slightly again, as displayed by a HR of 1.18 for PSADT'. PSADT was ≥32 months in only 19 patients (12.7%). Median post-primary PSA nadir, post-salvage PSA nadir, and pre-salvage PSA were higher in these patients compared to those with a PSADT of <32 months (1.1 vs 0.5 ng/ml, 0.9 vs 0.6 ng/ml, and 6.1 vs 4.6 ng/ml, respectively), but the percentage of patients classified as high-risk (NCCN) at primary treatment was comparable (39% vs 42%). Therefore, we have no clear explanation, and these findings might be caused by the limited sample size. Seminal vesicle involvement, which is a sign of extensive disease, was associated with an increased hazard of BF. A longer post-salvage time to PSA nadir was associated with a lower hazard, potentially reflecting tumor biology (a faster response after radiotherapy could be a sign of more malignant/dedifferentiated PCa) as previously observed[27]. Finally, a larger reduction in PSA level was protective of BF.

Several studies have identified predictors for BF in patients with radiorecurrent PCa treated with focal or whole-gland salvage high-intensity focused ultrasound (HIFU), low-dose rate brachytherapy (LDR-BT), and cryotherapy[15,28–30]. However, it is questionable to what extent predictors from whole-gland salvage studies are applicable to focal salvage treatments. Spiess et al. reported a risk stratification model in a whole-gland salvage cryotherapy cohort (n=132), using the Phoenix definition of BF[29]. Upon multivariable analysis, post-salvage PSA nadir and pre-salvage Gleason score were identified as predictors for BF. PSA nadir was also identified as a predictor of BF after salvage whole-gland HIFU in a small cohort of 50 patients[30]. Peters et al. showed that DFSI between primary and salvage treatment, T-stage before salvage, prostate volume (cm3), PSA, and PSADT were predictors of BF in patients treated with focal salvage HIFU[15]. This model shows overlap with our model, indicating that pre-salvage PSA

and PSADT are strong predictors for BF after focal salvage treatment for radiorecurrent PCa. While we did not investigate the predictive value of PSA nadir alone, we did incorporate it in our model by using PSA reduction. We argue that this might be a better predictor than PSA nadir, given its dependence on pre-salvage PSA. Furthermore, PSA nadir is also influenced by other factors, such as prostate volume[10]. We did not assess pre-salvage Gleason score as a potential predictor, as biopsies were not performed from the end of 2017 onwards (leading to 44.7% missing values). Also, while some have identified variables from the primary tumor and/or treatment as predictors, we did not investigate any primary tumor characteristics because of our limited sample size and missing data in these characteristics. Furthermore, the predictive value of these variables in focal salvage studies seems limited[15]. With an extended sample size and follow-up, we could potentially investigate the added value of some of these predictors.

There are several strengths to our study. Missing data for candidate pre-salvage predictors was very low (0.7%) due to prospective data collection. The inclusion of patients treated off-protocol also makes the study sample more representative and increases external validity. Furthermore, candidate predictors for multivariable analysis were selected based on literature and clinical knowledge rather than by performing univariable analysis, thereby minimizing the occurrence of type-I errors[25]. The online dynamic nomograms we created are helpful tools to quickly assess and visualize individual predicted bDFS.

The study has some limitations. First, external validation of this model is necessary. Several other focal salvage strategies have been described, all with minor differences with respect to eligibility of patients. Therefore, such cohorts offer an opportunity for external validation. Especially since both models use predictors that are known to be related to PCa progression and none of them are treatment specific. External validation of our models could lead to adjustment of these models and thereby improve predictive accuracy and be applicable to other focal salvage modalities. Despite taking into account the sample size, some overfitting is indicated by the suboptimal shrinkage factors of 0.85 and 0.81, indicating 15% and 19% optimism, respectively. Furthermore, limiting the number of candidate variables might have led to missing important predictors, such as DSFI [15]. Consequently, the C-statistic of 0.73 of the first model might be improved by including other potential predictors when sample size has increased. Third, length of follow-up was relatively short with a median of 25.1 months, thus the models perform optimal within a timeframe of approximately two years. Fourth, tumor volume was based on the delineated GTV. Although GTV delineation was based on mpMRI and PSMA PET-CT, which improves the estimation of tumor volume compared to mpMRI alone[31], interobserver variability due to the lack of delineation guidelines will be present and influences the accuracy and predictive value of this variable.

CONCLUSION

This study provides two models for BF prediction in patients with radiorecurrent PCa treated with FS-HDR-BT. Our findings support that both pre- and post-salvage PSA characteristics (PSA level, PSADT, time to PSA nadir, and PSA reduction) are important predictors of BF, in addition to age, tumor volume, and seminal vesicle involvement. These models could aid patient selection, counselling, and guidance at baseline and during follow-up. Potentially, these models can also be used for other salvage techniques, for which external validation remains necessary.

SUPPLEMENTARY FILE A

Additional variables used for multiple imputation via chained equations:

- Primary treatment
  EBRT, *LDR brachytherapy*, or *HDR brachytherapy*
- Pelvic lymph node dissection at primary treatment (yes/no)
- Initial NCCN risk group
  Low risk (T1-T2a AND Gleason ≤6 AND PSA <10 ng/ml), Intermediate risk (T2b-T2c OR Gleason 7 OR PSA 10-20 ng/ml), or High risk (³T3a OR Gleason ³8 OR PSA > 20 ng/ml)
- ADT use
  No, ≤36 months, or >36 months
- PSA nadir post-primary treatment (ng/ml)
- Prostate size on pre-salvage MRI (cm^3)
- Maximum tumor diameter on pre-salvage MRI (mm)
- V200% CTV (%)
- PSA velocity (ng/ml/years)
- Interval between primary and salvage treatment (months)
- Previous salvage treatment (yes/no)
- Time to nadir post-primary treatment (months)
- Deceased (yes/no)

SUPPLEMENTARY FILE B

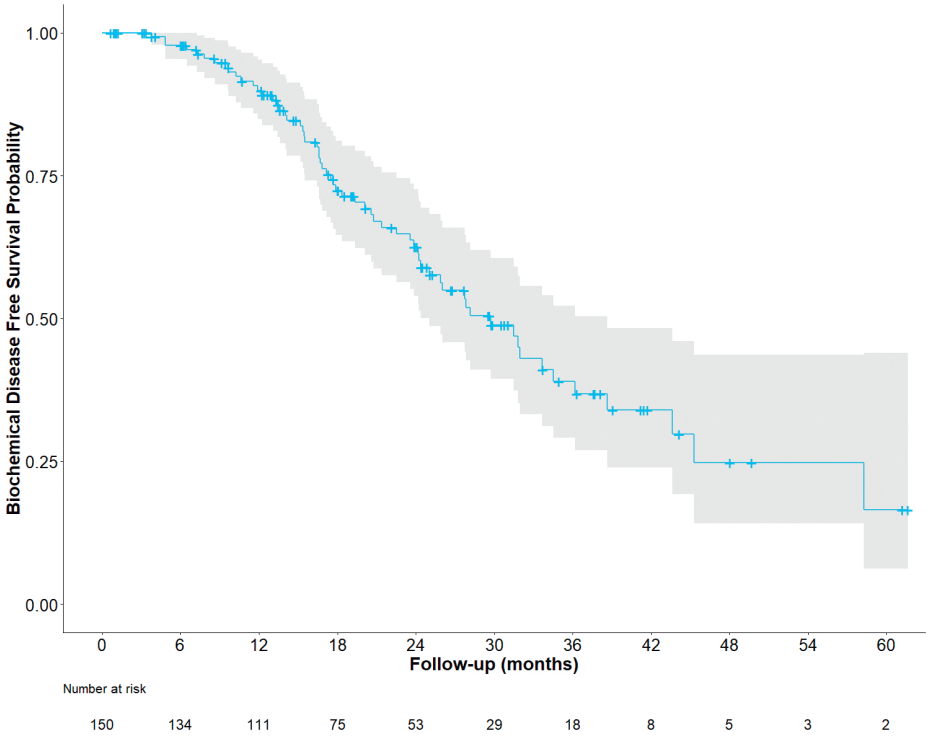

Figure S1 – Kaplan-Meier curve depicting biochemical disease-free survival for the entire FS-HDR-BT group.

SUPPLEMENTARY FILE C

Predictor	Range in dataset used for model building
Pre-salvage PSADT (months)	3 – 73 months
Age at FS-HDR-BT (years)	59 – 85 years
Pre-salvage PSA (ng/ml)	0.4 – 39.0 ng/ml
GTV (cm^3)	0.5 – 22 cm^3
Time to PSA nadir post-salvage (months)	1 – 25 months
PSA reduction post-salvage (%)	0 – 100 %

Abbreviations: PSADT=prostate specific antigen doubling time. FS-HDR-BT=focal salvage high-dose-rate-brachytherapy. PSA=prostate specific antigen. GTV=gross tumor volume.

SUPPLEMENTARY FILE D

Model 1

The full regression equation for model 1 is as follows:

$$h(t) = h_0(t) * \exp(-0.065 * Age + 0.78 * \ln(PSA) + 0.053 * GTV - 0.14 * PSADT + 0.16 * PSADT')$$

Or for calculating the predicted survival probability:

$$s(t) = s_0(t)^{\exp(-0.065*Age + 0.78*\ln(PSA) + 0.053*GTV - 0.14*PSADT + 0.16*PSADT')}$$

Where:
h(t) = the expected hazard at time *t*
$h_0(t)$ = the baseline hazard at time *t*
s(t) = the expected survival probability at time t
$s_0(t)$ = the baseline survival at time *t (see Table 2 for baseline survival at 12, 24, and 36 months)*
Age = age in years at time of FS-HDR-BT
ln = natural logarithm
PSA = pre-salvage PSA level in ng/ml
GTV = gross tumor volume in cm^3
PSADT = PSA doubling time in months
PSADT' can be calculated as follows:

$$PSADT' = \frac{(PSADT - 7.98)_+^3 - 1.43(PSADT - 15.70)_+^3 + 0.44(PSADT - 33.63)_+^3}{657.9225}$$

Model 2

The full regression equation for model 2 is as follows:

$$h(t) = h_0(t) * \exp(-0.087 * Age + 1.50 * \ln(PSA) + 0.40 * Seminal\ vesicle\ involment - 0.12 * PSADT + 0.15 * PSADT' - 0.20 * Time\ to\ PSA\ nadir - 0.021 * \%PSA\ reduction)$$

Or for calculating the predicted survival probability:

$$s(t) = s_0(t)^{\exp(-0.087*Age + 1.50*\ln(PSA) + 0.40*Seminal\ vesicle\ involvement - 0.12*PSADT + 0.15*PSADT' - 0.20*Time\ to\ PSA\ nadir - 0.021*\%PSA\ reduction)}$$

Where:

h(t) = the expected hazard at time *t*

$h_0(t)$ = the baseline hazard at time *t*

s(t) = the expected survival probability at time t

$s_0(t)$ = the baseline survival at time *t (see Table 2 for baseline survival at 12, 24, and 36 months)*

Age = age in years at time of FS-HDR-BT

ln = natural logarithm

PSA = pre-salvage PSA level in ng/ml

Seminal vesicle involvement = 0 when not applicable, 1 when applicable

Time to PSA nadir = post-salvage time to nadir in months

%PSA reduction = PSA reduction (ratio between pre-salvage PSA and post-salvage PSA nadir) in %

PSADT = PSA doubling time in months

PSADT′ can be calculated as follows:

$$PSADT' = \frac{(PSADT - 7.98)_+^3 - 1.43(PSADT - 15.70)_+^3 + 0.44(PSADT - 33.63)_+^3}{657.9225}$$

REFERENCES

1. Ward JF, Pagliaro LC, Pisters LL. Salvage Therapy for Radiorecurrent Prostate Cancer. Curr Probl Cancer 2008;32:242–71. https://doi.org/10.1016/j.currprobl cancer.2008.10.001.
2. Zelefsky MJ, Kuban DA, Levy LB, Potters L, Beyer DC, Blasko JC, et al. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys 2007;67:327–33. https://doi.org/10.1016/j.ijrobp.2006.08.056.
3. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Polkinghorn W, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol 2015;67:1009–16. https://doi.org/10.1016/j.eururo.2014.09.028.
4. Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, et al. Analysis of Intraprostatic Failures in Patients Treated With Hormonal Therapy and Radiotherapy : Implications for Conformal Therapy Planning. Int J Radiat Oncol Biol Phys 2002;53:595–9.
5. Pucar D, Hricak H, Shukla-Dave A, Kuroiwa K, Drobnjak M, Eastham J, et al. Clinically Significant Prostate Cancer Local Recurrence After Radiation Therapy Occurs at the Site of Primary Tumor: Magnetic Resonance Imaging and Step-Section Pathology Evidence. Int J Radiat Oncol Biol Phys 2007;69:62–9. https://doi.org/10.1016/j.ijrobp.2007.03.065.
6. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Kollmeier M, et al. Anatomic Patterns of Recurrence Following Biochemical Relapse in the Dose-Escalation Era for Prostate Patients Undergoing External Beam Radiotherapy. J Urol 2015;194:1624–30. https://doi.org/10.1016/j.juro.2015.06.100.
7. Khoo CC, Miah S, Connor MJ, Tam J, Winkler M, Ahmed HU, et al. A systematic review of salvage focal therapies for localised non-metastatic radiorecurrent prostate cancer. Transl Androl Urol 2020;9:1535–45. https://doi.org/10.21037/tau.2019.08.21.
8. Van Son M, Peters M, Moerland M, Kerkmeijer L, Lagendijk J, Van der Voort van Zyp J. Focal salvage treatment of radiorecurrent prostate cancer: A narrative review of current strategies and future perspectives. Cancers (Basel) 2018;10:480. https://doi.org/10.3390/cancers10120480.
9. van Son MJ, Peters M, Moerland MA, Lagendijk JJW, Eppinga WSC, Shah TT, et al. MRI-Guided Ultrafocal Salvage High-Dose-Rate Brachytherapy for Localized Radiorecurrent Prostate Cancer: Updated Results of 50 Patients. Int J Radiat Oncol 2020. https://doi.org/10.1016/j.ijrobp.2020.01.023.
10. Stabile A, Orczyk C, Giganti F, Moschini M, Allen C, Punwani S, et al. The Role of Percentage of Prostate-specific Antigen Reduction After Focal Therapy Using High-intensity Focused Ultrasound for Primary Localised Prostate Cancer. Results from a Large Multi-institutional Series. Eur Urol 2020. https://doi.org/https://doi.org/10.1016/j.eururo.2020.04.068.
11. Tan WP, ElShafei A, Aminsharifi A, Khalifa AO, Polascik TJ. Salvage Focal Cryotherapy Offers Similar Short-term Oncologic Control and Improved Urinary Function Compared With Salvage Whole Gland Cryotherapy for Radiation-resistant or Recurrent Prostate Cancer. Clin Genitourin Cancer 2019:260–5. https://doi.org/10.1016/j.clgc.2019.11.009.

12. Bomers JGR, Overduin CG, Jenniskens SFM, Cornel EB, van Lin ENJT, Sedelaar JPM, et al. Focal Salvage MR Imaging–Guided Cryoablation for Localized Prostate Cancer Recurrence after Radiotherapy: 12-Month Follow-up. J Vasc Interv Radiol 2020;31:35–41. https://doi.org/10.1016/j.jvir.2019.07.001.

13. Duijzentkunst DAS, Peters M, van der Voort van Zyp JRN, Moerland MA, van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review. World J Urol 2016;34:1521–31. https://doi.org/10.1007/s00345-016-1811-9.

14. Henríquez I, Sancho G, Hervás A, Guix B, Pera J, Gutierrez C, et al. Salvage brachytherapy in prostate local recurrence after radiation therapy: Predicting factors for control and toxicity. Radiat Oncol 2014;9:1–8. https://doi.org/10.1186/1748-717X-9-102.

15. Peters M, Kanthabalan A, Shah TT, McCartan N, Moore CM, Arya M, et al. Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: Presentation of risk scores for individual patient progn. Urol Oncol Semin Orig Investig 2018;36:13.e1-13.e10. https://doi.org/10.1016/j.urolonc.2017.08.022.

16. Peters M, van der Voort van Zyp JRN, Moerland MA, Hoekstra CJ, van de Pol S, Westendorp H, et al. Development and internal validation of a multivariable prediction model for biochemical failure after whole-gland salvage iodine-125 prostate brachytherapy for recurrent prostate cancer. Brachytherapy 2016;15:296–305. https://doi.org/10.1016/J.BRACHY.2016.01.004.

17. Maenhout M, Peters M, van Vulpen M, Moerland MA, Meijer RP, van den Bosch MAAJ, et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radiorecurrent Prostate Cancer. Technol Cancer Res Treat 2017;16:1194–201. https://doi.org/10.1177/1533034617741797.

18. Grignon DJ, Sakr WA. Histologic effects of radiation therapy and total androgen blockade on prostate cancer. Cancer 1995;75:1837–41. https://doi.org/10.1002/1097-0142(19950401)75:7+<1837::AID-CNCR2820751613>3.0.CO;2-S.

19. Crook JM, Bahadur YA, Robertson SJ, Perry GA, Esche BA. Evaluation of radiation effect, tumor differentiation, and prostate specific antigen staining in sequential prostate biopsies after external beam radiotherapy for patients with prostate carcinoma. Cancer 1997;79:81–9. https://doi.org/10.1002/(SICI)1097-0142(19970101)79:1<81::AID-CNCR12>3.0.CO;2-2.

20. Goldstein NS, Martinez A, Vicini F, Stromberg J. The histology of radiation therapy effect on prostate adenocarcinoma as assessed by needle biopsy after brachytherapy boost: Correlation with biochemical failure. Am J Clin Pathol 1998;110:765–75. https://doi.org/10.1093/ajcp/110.6.765.

21. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ 2020;368:1–12. https://doi.org/10.1136/bmj.m441.

22. White IR, Royston P. Imputing missing covariate values for the Cox model. Stastics Med 2009;28:1982–1998. https://doi.org/1.

23. Moons KGM, Donders RART, Stijnen T, Harrell FE. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 2006;59:1092–101. https://doi.org/10.1016/j.jclinepi.2006.01.009.

24. Nieboer D, Vergouwe Y, Roobol MJ, Ankerst DP, Kattan MW, Vickers AJ, et al. Nonlinear modeling was applied thoughtfully for risk prediction: The Prostate Biopsy Collaborative Group. J Clin Epidemiol 2015;68:426–34. https://doi.org/10.1016/j.jclinepi.2014.11.022.

25. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med 2015;162:W1–73. https://doi.org/10.7326/M14-0698.

26. Team RC. R: A language and environment for statistical computing 2019.

27. Ray ME, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA, et al. PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: A multi-institutional analysis. Int J Radiat Oncol Biol Phys 2006;64:1140–50. https://doi.org/10.1016/j.ijrobp.2005.07.006.

28. Spiess PE, Katz AE, Chin JL, Bahn D, Cohen JK, Shinohara K, et al. A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer. BJU Int 2010;106:194–8. https://doi.org/10.1111/j.1464-410X.2009.09078.x.

29. Spiess PE, Levy DA, Mouraviev V, Pisters LL, Jones JS. Predictors of biochemical failure in patients undergoing prostate whole-gland salvage cryotherapy: A novel risk stratification model. BJU Int 2013;112:256–61. https://doi.org/10.1111/j.1464-410X.2012.11695.x.

30. Shah TT, Peters M, Kanthabalan A, McCartan N, Fatola Y, Van Der Voort Van Zyp J, et al. PSA nadir as a predictive factor for biochemical disease-free survival and overall survival following whole-gland salvage HIFU following radiotherapy failure. Prostate Cancer Prostatic Dis 2016;19:311–6. https://doi.org/10.1038/pcan.2016.23.

31. Bettermann AS, Zamboglou C, Kiefer S, Jilg CA, Spohn S, Kranz-rudolph J, et al. [68 Ga-] PSMA-11 PET / CT and multiparametric MRI for gross tumor volume delineation in a slice by slice analysis with whole mount histopathology as a reference standard – Implications for focal radiotherapy planning in primary prostate cancer. Radiother Oncol 2019;d:7–12. https://doi.org/10.1016/j.radonc.2019.07.005.

CHAPTER 9

Re-salvage MRI-guided focal high-dose-rate brachytherapy for locally recurrent prostate cancer

Authors: Marieke J. van Son, Max Peters, Marinus A. Moerland, Juus L. Noteboom, Wietse S.C. Eppinga, Raquel Davila Fajardo, Jan J.W. Lagendijk, Jochem R.N. van der Voort van Zyp

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ABSTRACT

Prostate cancer recurrences are common, even with twenty-first-century primary prostate cancer treatment modalities. The most common salvage treatment is (delayed) hormonal therapy, which is often associated with serious side-effects. Due to the risk of significant toxicity, whole-gland targeted salvage treatments remain unpopular. Consequently, developments in focal therapies have arisen. Magnetic resonance imaging (MRI)-guided focal salvage high-dose-rate brachytherapy (HDR-BT) is a novel treatment aiming for minimal toxicity in recurrent prostate cancer patients. Repeating focal treatment could, therefore, be possible in case of post-salvage recurrence. We report the case of a 77-year-old man who underwent repeat focal HDR-BT.

INTRODUCTION

Despite improvements in primary prostate cancer care, 15%-55% of patients undergoing radiotherapy develop biochemical recurrence after a 10 years' follow-up [1]. Even with external beam radiation therapy (EBRT) dose escalation, the risk of disease progression remains significant, especially in higher-risk groups [2]. In the management of recurrent disease, physicians are faced with difficult considerations regarding salvage treatment options. Although early recurrences are often confined to the prostate without lymph-node or distant metastases, around 98% of patients are still treated with (delayed) androgen deprivation therapy (ADT). This treatment is associated with significant side-effects, such as erectile dysfunction, osteoporosis, increased risk of diabetes, gynaecomastia, hot flashes, and depression. Moreover, hormonal treatment is palliative and castration resistance usually occurs within one to three years [3]. In contrast, curative whole-gland salvage treatments, such as prostatectomy, brachytherapy, high-intensity focused ultrasound (HIFU), and cryosurgery remain unpopular due to high toxicity rates and, in earlier series, a significant risk of failure [4].

In an effort to reduce toxicity in the salvage setting, research has shifted towards organ preserving approaches. Although prostate cancer is usually multifocal, the "index lesion" hypothesis states there is one clinically important tumor focus in the prostate (the index lesion), which harbors the metastatic precursor cell [5]. After whole-gland irradiation, the disease often recurs unifocally [6], indicating that smaller secondary lesions have been treated while the index lesion remains. On that premise, salvage focal therapy aimed at this lesion should achieve the same oncological control as whole-gland treatments. The success of focal salvage treatment depends on the degree of tumor visualization and reliable exclusion of metastases. This has significantly improved with advancements in multiparametric (mp)-MRI and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging.

The Radiation Oncology department of the University Medical Center Utrecht (UMCU) is equipped with a 1.5T MRI treatment facility, enabling brachytherapy treatment under MRI guidance. The convergence of these technologies allows for an optimal implantation procedure, supporting focal treatment. In 2013, the UMCU introduced MRI-guided, single-fraction (19Gy) focal high-dose-rate brachytherapy (HDR-BT) with iridium-192 as the salvage treatment for local radio-recurrent prostate cancer. With this treatment, the radiation dose to the tumor is escalated while exposure to the surrounding organs at risk (OAR) is limited. Results with regard to toxicity are promising and, therefore, the question arises whether re-treatment with focal HDR-BT is possible for future post-salvage recurrences. This could prevent or further delay the initiation of ADT, thereby avoiding hormone-induced toxicity. Furthermore, postponing castration resistance could potentially increase prostate cancer-specific survival. We present a novel case of second MRI-guided focal salvage HDR-BT.

Case Presentation

A 77-year-old male visited the radiation oncology department for a follow-up consultation nine years after initial prostate cancer treatment with whole-gland Iodine-125 brachytherapy (145Gy). His further medical history consisted of an asymptomatic thoracic aortic aneurysm and his medication included antihypertensive drugs, a cholesterol-lowering statin, and an anticoagulant. The initial cT1ciT2aNxMx prostate tumor (staged on MRI) was located in the left peripheral zone (initial prostate-specific antigen (PSA) 7.9 ng/ml). Treatment-related toxicity involved increased urinary frequency and transient obstructive complaints for which he received tamsulosin 0.4 mg once daily for approximately 18 months post-implantation. His erectile function declined but was sufficient for penetrative intercourse without the need for supporting medication. PSA levels dropped to a nadir of 0.2 ng/ml one year after treatment and remained stable during the first three years of follow-up. Later, a steady upward trend was seen with a PSA doubling time (PSADT) of 12 months up to the level of 2.5 ng/ml seven years posttreatment. This was considered a biochemical recurrence according to the Phoenix definition (PSA nadir+2 ng/ml) and radiographic evaluation for recurrent disease was performed using 3T multiparametric-MRI (mp-MRI) and F18-Choline PET-CT. However, there were no signs of local recurrence or distant metastases, nor on repeat imaging one year later.

When the patient returned to our department, the PSA level had further increased to 6.7 ng/ml (prostate-specific antigen doubling time (PSADT) 18 months) and a 68Ga-PSMA PET-CT followed. The scan revealed local high uptake in the right dorsal peripheral zone next to the prostate midline and in the right seminal vesicle (Figure 1). A 3T mp-MRI (Figure 2) and MRI-guided target biopsies confirmed this lesion (25% adenocarcinoma in one out of two cores, suggested Gleason score 4+3=7). Upon this, the patient was treated with MRI-guided focal salvage high-dose-rate brachytherapy (HDR-BT).

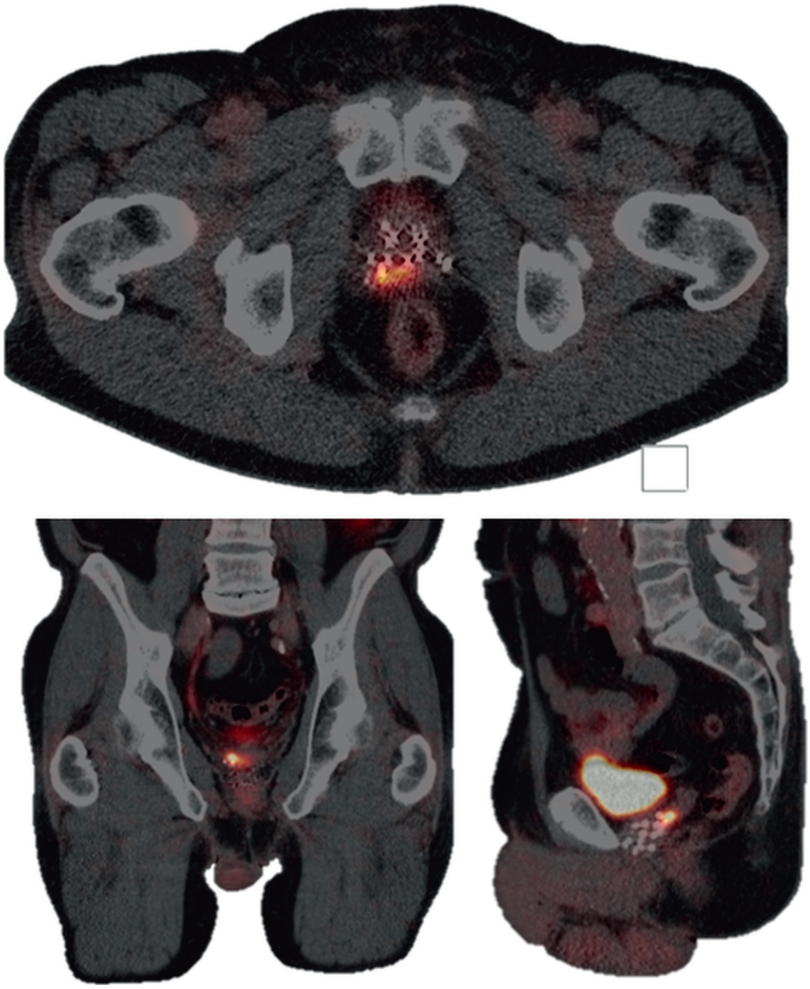

Figure 1 – First recurrence lesion on 68Ga-PSMA PET-CT.
Transversal plane (upper image), coronal plane (lower-left image), and sagittal plane (lower-right image) showing the first recurrence lesion in the right dorsal peripheral zone and in the right seminal vesicle on the 68Ga-PSMA PET-CT, nine years after initial prostate cancer treatment.

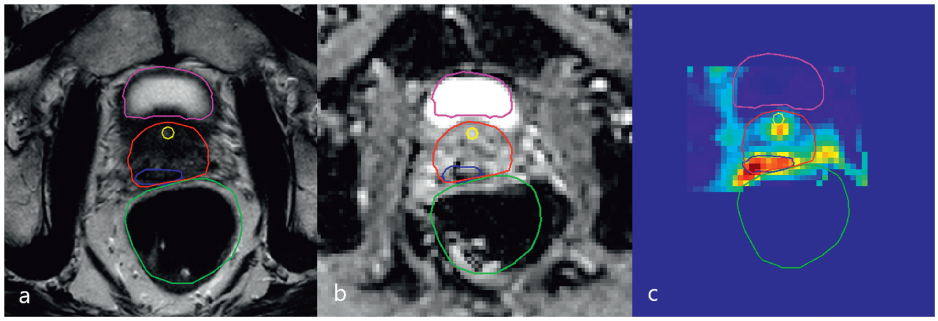

Figure 2 – Diagnostic 3T mp-MRI revealing first recurrence lesion.
Transversal plane of the diagnostic 3T multiparametric-magnetic resonance imaging (mp-MRI) revealing a suspect lesion in the right dorsal peripheral zone next to the prostate midline and in the right seminal vesicle. Delineations of the bladder (purple), urethra (yellow), rectum (green), prostate (red), and gross tumor volume (GTV, blue) are shown. In this case, the clinical target volume (CTV) was considered equal to the GTV because there was mainly seminal vesicle invasion. (a) T2-weighted image, (b) ADC image, (c) K-trans image

Focal salvage treatment

Prior to treatment, the gross tumor volume (GTV), clinical target volume (CTV), defined as GTV with a five-millimeter margin, and the organ at risk (OAR) (prostate, bladder, rectum, and urethra) were delineated based on a 3T mp-MRI and 68Ga-PSMA PET-CT scan. For the CTV to planning target volume (PTV), the margin was 0 millimeter as the source and dose distribution along the tumor in brachytherapy. With the patient in the lithotomy position and under spinal anesthesia, seven MR-compatible catheters were placed in and around the right peripheral zone and seminal vesicle via the perineum (Figure 3). Catheter insertion was guided by fused diagnostic MRI delineations and intraoperative transrectal ultrasound. To evaluate catheter positions with respect to the tumor and OAR, an additional 1.5T MRI scan was made and delineations were adjusted to account for swelling. Next, a simulation of dose distribution was made by the treatment planning system. To ensure the safe delivery of the radiation dose, an additional 1.5T MRI scan was made just before the radiation treatment to check for catheter displacements. The dose to 95% of the GTV (D95) was 20.3Gy (aim: >19Gy). The minimum dose to the most exposed 1 cc of rectum or bladder (D1cc) was limited to 10Gy and the dose to 10% of the urethra (D10) was 5.2Gy. We used constraints of D1cc <12Gy for the rectum and bladder and D10 <17.7Gy for the urethra [7]. Later, all catheters were removed, leaving no source of radioactivity behind in the patient. There were no perioperative complications and the patient was discharged the same day.

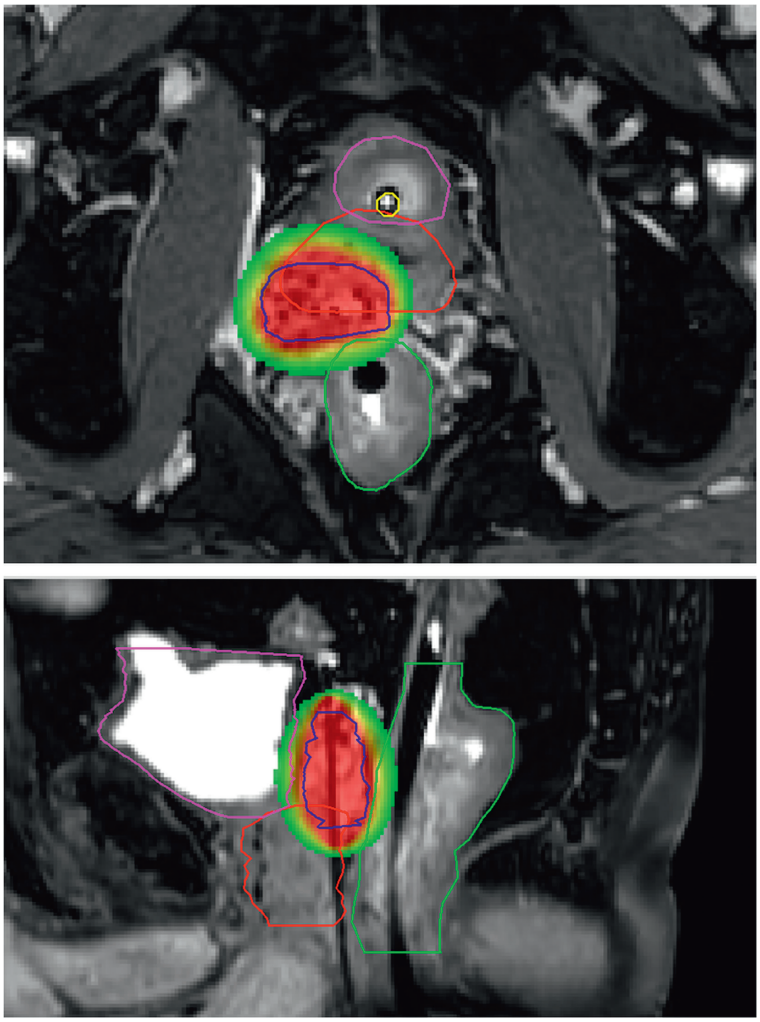

Figure 3 – Dose distribution first MRI-guided focal salvage HDR-BT.
Transversal plane (upper magnetic resonance (MR) image) and sagittal plane (lower MR image) showing delineations of the bladder (purple), urethra (yellow), rectum (green), prostate (red), and gross tumor volume (GTV, blue) in the right dorsal peripheral zone and the right seminal vesicle. The images show signal voids from the catheters and previously implanted iodine 125 seeds. On the sagittal image, one of the catheters is visible within the GTV. In this case, the clinical target volume (CTV) was considered equal to the GTV because there was mainly seminal vesicle invasion. Radiation dose is displayed in colors, with red representing 19Gy and green representing 9.5Gy.

During the first six months of follow-up, tamsulosin 0.4 mg once daily was prescribed due to minor urinary retention and frequency symptoms. His erectile function decreased in the same period but restored without medication. There were no rectal complaints. Three months posttreatment, the nadir PSA was 0.9 ng/ml. An mp-MRI for response evaluation six months after treatment showed no signs of loco-regional malignant disease and post-radiation fibrosis was visible in the right seminal vesicle. Nevertheless, PSA levels started to rise again, up to 3.4 ng/ml one year after treatment (PSADT, six months). Once again, disease status evaluation was performed with 68Ga-PSMA PET-CT and 3T mp-MRI. As compared to the first diagnostic PET-CT scan, less PSMA uptake was visible in the right peripheral zone. A new suspect lesion of approximately 10 millimeters was suggested in the left dorsal peripheral zone, in close relation to the seminal vesicle (Figure 4). Diminutive diffusion restriction and contrast enhancement on the mp-MRI could not verify this lesion (also due to an overall heterogeneous aspect of the prostate).

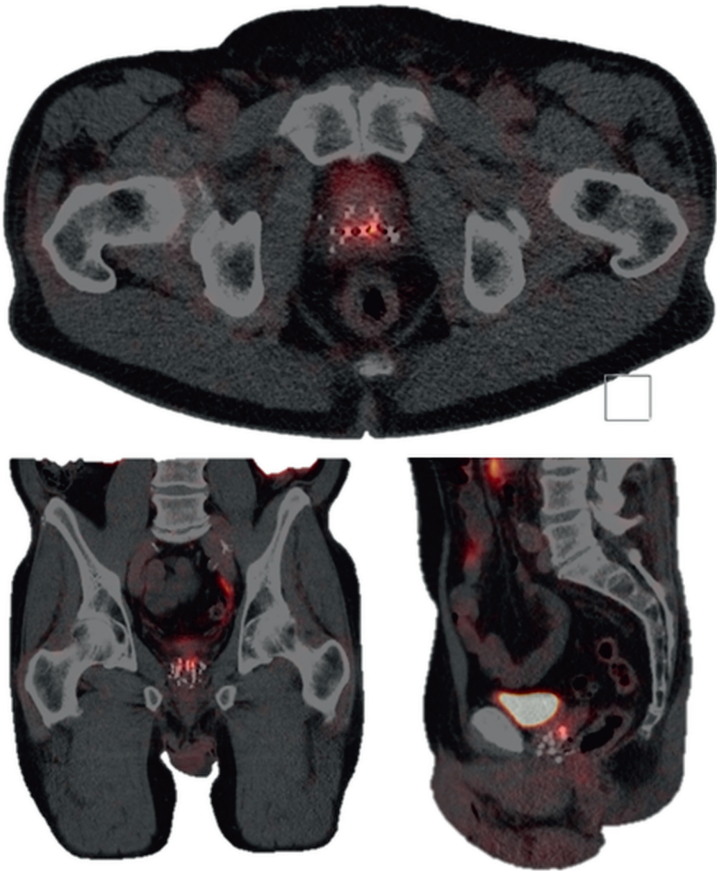

Figure 4 – Second recurrence lesion on 68Ga-PSMA PET-CT
Transversal plane (upper image), coronal plane (lower-left image), and sagittal plane (lower-right image), showing the second recurrence lesion in the left dorsal peripheral zone on the 68Ga-PSMA PET-CT, 11 years after initial prostate cancer treatment.

Both imaging modalities were repeated six months later at a PSA-value of 4.6 ng/ml (PSADT nine months). The same recurrence location was revealed on the 68Ga-PSMA PET-CT and confirmed by the mp-MRI (Figure 5) and MRI-guided target biopsies (<1% adenocarcinoma in one out of four cores, suggested Gleason score 3+3=6).

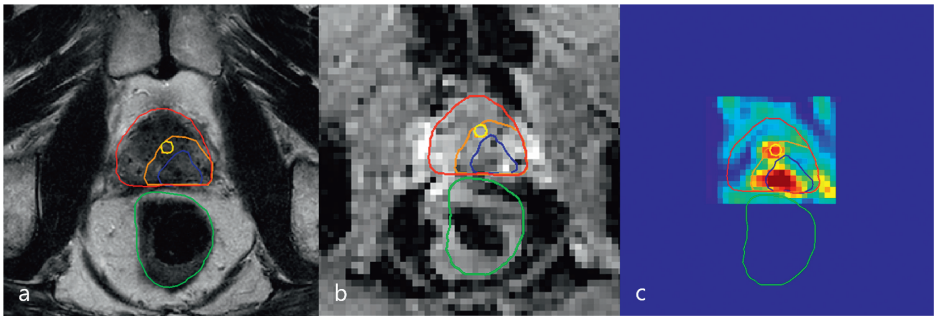

Figure 5 – Diagnostic 3T mp-MRI revealing second recurrence lesion
Transversal plane of the diagnostic 3T mp-MRI revealing a suspect lesion in the left dorsal peripheral zone. Delineations of the urethra (yellow), rectum (green), prostate (red), gross tumor volume (GTV, blue), and clinical target volume (CTV, orange) are shown.
(a) T2-weighted image, (b) ADC image, (c) K-trans image

Re-salvage treatment

Eleven years after the initial prostate cancer treatment and two years after receiving the first MRI-guided focal salvage HDR-BT, the patient was re-treated. A total of eight catheters were placed in and around the recurrence lesion (Figure 6). D95 for the CTV was 19.1Gy, D1cc of rectum and bladder was 11Gy, and D10 of the urethra was 15.1Gy. No perioperative complications occurred. The postoperative PSA values at one, three, and six months were 0.37 ng/ml, <0.10 ng/ml, and <0.10 ng/ml, respectively. The patient experienced transient flatulence complaints without further need for any therapeutic interventions. Three months after treatment, tamsulosin 0.4 mg was again prescribed. No grade ≥3 toxicity occurred. The mp-MRI six months post-treatment revealed a reduction in both diffusion restriction and contrast enhancement at the treated location. An overview of the course of PSA values over time is presented in Figure 7.

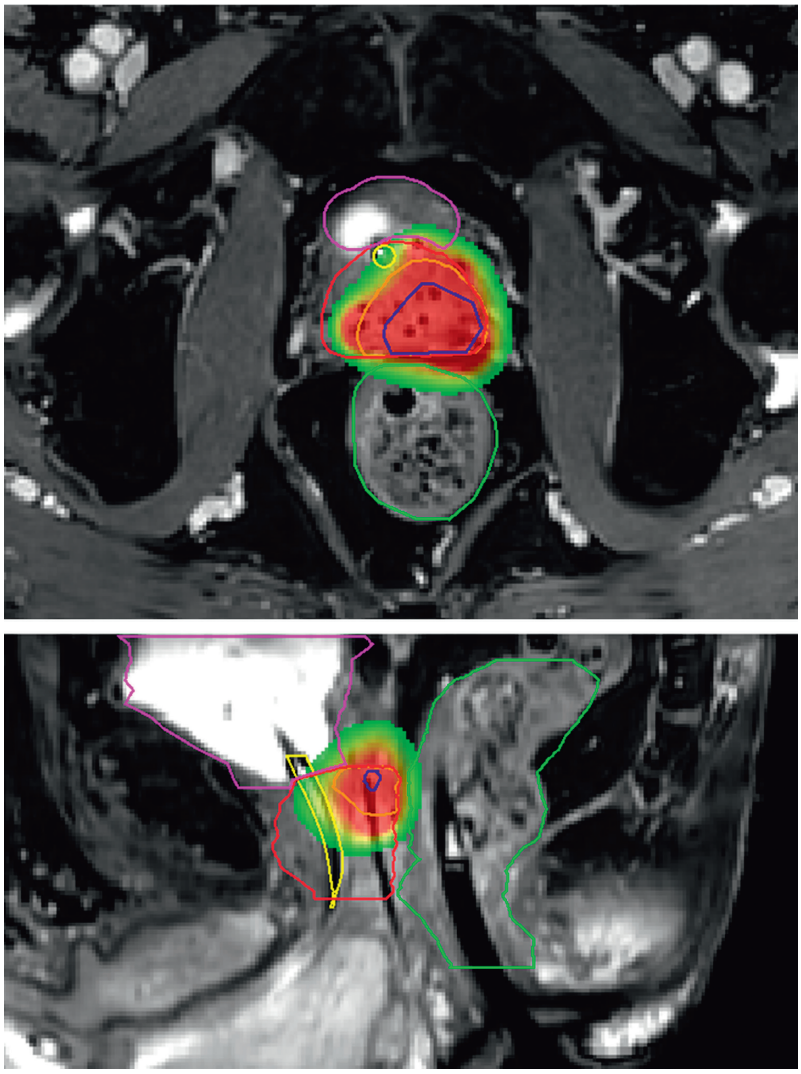

Figure 6 – Dose distribution second MRI-guided focal salvage HDR-BT
Transversal plane (upper MR image) and sagittal plane (lower MR image) showing delineations of the bladder (purple), urethra (yellow), rectum (green), prostate (red), gross tumor volume (GTV, blue), and clinical target volume (CTV, orange) in the left dorsal peripheral zone. The images show signal voids from the catheters and previously implanted iodine 125 seeds. On the sagittal image, one of the catheters is visible within the CTV. Radiation dose is displayed in colors, with red representing 19Gy and green representing 9.5Gy.

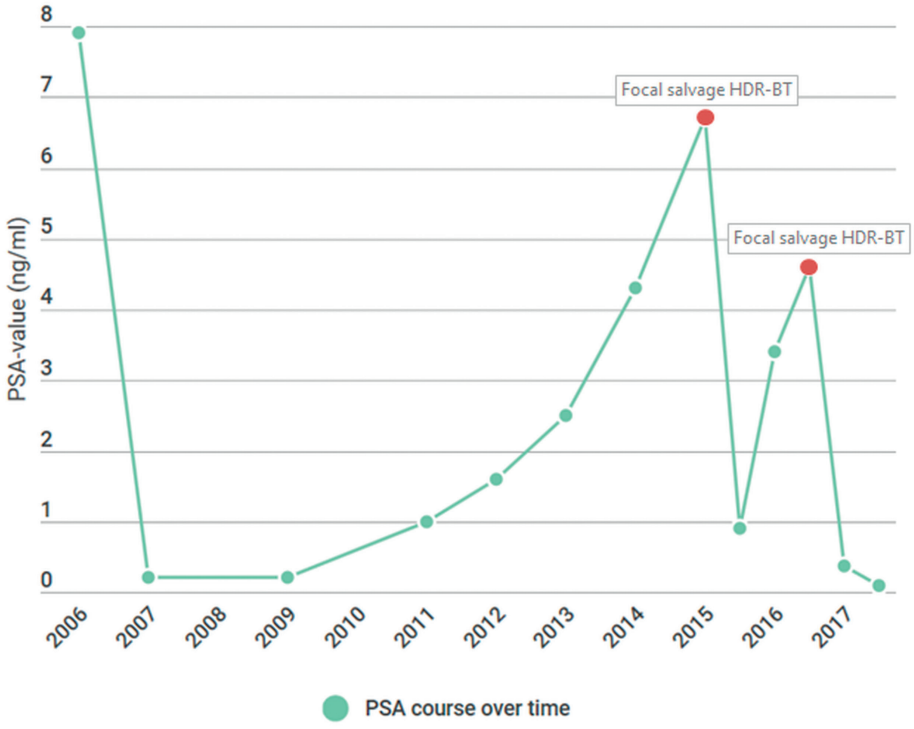

Figure 7 – PSA value timeline
Timeline showing the course of PSA values over time. The first MRI-guided focal salvage HDR-BT was performed at a PSA level of 6.7 ng/ml. The second MRI-guided focal salvage HDR-BT was performed at a PSA-level of 4.6 ng/ml.

DISCUSSION

With local salvage treatments, toxicity is a major issue that must be weighed against the benefits of delaying the onset of metastatic disease or, in particular cases, providing a cure. Focal treatment aimed at the tumor lesion instead of the whole prostate gland is a novel development in the span of salvage treatments. Powered by technical advances in diagnostic modalities and the increasing possibilities of MRI guidance before and during treatment, targeted therapy aims to reduce toxicity. With limited toxicity, repetitive salvage treatment could be possible for future local recurrences and ADT (and its side effects) could be postponed or even prevented.

This report describes the first case of repeat MRI-guided focal salvage HDR-BT for prostate cancer recurrence. After both focal treatments, the patient experienced minor toxicity (maximum grade 2), which was limited to urinary retention and frequency symptoms, transient flatulence complaints, and a temporary decrease in erectile function. Because of the relatively short follow-up time after the second treatment, there is no information on long-term toxicity yet. However, results with regard to acute toxicity

are promising and major complications in the future are not expected due to the high level of dose control with respect to the OAR. The combination of MRI guidance and the steep dose fall-off in brachytherapy allows for high precision in administering the radiation dose to the tumor. In the described case, dose constraints for the OAR were not exceeded during both focal HDR-BT treatments.

Within the literature, there are few papers covering repeat salvage therapy. One case report by Claren et al. on second salvage treatment using whole-gland HDR-BT (5x7Gy) showed limited toxicity (grade 2 urinary incontinence). After 24 months, a PSA nadir of 0.03 ng/ml was reached [8]. More recently, Maenhout et al. described a case series of four patients receiving MRI-guided focal salvage HDR-BT after previous salvage I-125 brachytherapy. No postoperative development of grade ≥2 toxicity was observed. Lymph node metastatic disease was detected in one patient during follow-up [9].

Choosing the appropriate salvage treatment strategy for recurrent prostate cancer is a complex matter and patient selection for focal treatment depends on many factors. To estimate the risk of toxicity, it is essential to establish any pre-existing urinary or bowel symptoms. Time from treatment to biochemical relapse and PSA kinetics, such as PSADT, have prognostic relevance with respect to salvage oncologic outcomes [10]. Appropriate imaging modalities should be deployed for accurate tumor staging and the detection of disseminated disease. We have adopted 68Ga-PSMA PET-CT and mp-MRI as standard imaging techniques. From our experience, the diagnostic accuracy of this imaging combination has rendered prostate biopsies unnecessary since image-guided biopsies were all tumor-positive in the past. In the salvage setting, the assessment of in- or outfield recurrence is important because infield recurrences with a short interval from the previous treatment (less than two years) may indicate radioresistancy and are, therefore, less susceptible to repeat focal salvage irradiation.

CONCLUSIONS

MRI-guided focal salvage HDR-BT is a novel modality within the range of local treatment options for recurrent prostate cancer. This case report highlights the potential of this therapy with regard to re-treating locally recurrent prostate cancer after previous salvage treatment. Re-salvage could further delay or even avoid the need for ADT, thereby minimizing the risk of exposure to hormone-related toxicity. The joint use of MRI guidance and HDR-BT allows for targeted therapy with minimal risk of toxicity. Therefore, focal re-treatment seems possible. Further experience in treating patients with re-recurrent local prostate cancer will yield more knowledge on long-term outcomes.

REFERENCES

1. Mottet N, Bellmunt J, Bolla M, et al.: EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017, 71:618-629. 10.1016/j.eururo.2016.08.003
2. Zaorsky NG, Keith SW, Shaikh T, et al.: Impact of radiation therapy dose escalation on prostate cancer outcomes and toxicities. Am J Clin Oncol. 2016, 41:409-415. 10.1097/COC.0000000000000285
3. James ND, Spears MR, Clarke NW, et al.: Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol. 2015, 67:1028-1038. 10.1016/j.eururo.2014.09.032
4. Golbari NM, Katz AE: Salvage therapy options for local prostate cancer recurrence after primary radiotherapy: a literature review. Curr Urol Rep. 2017, 18:63. 10.1007/s11934-017-0709-4
5. Ahmed HU: The index lesion and the origin of prostate cancer . N Engl J Med. 2009, 361:1704-1706. 10.1056/NEJMcibr0905562
6. Pucar D, Hricak H, Shukla-Dave A, et al.: Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence. Int J Radiat Oncol Biol Phys. 2007, 69:62-69.10.1016/j.ijrobp.2007.03.065
7. Holly R, Morton GC, Sankreacha R, et al: Use of cone-beam imaging to correct for catheter displacement in high dose-rate prostate brachytherapy. Brachytherapy. 2011, 10:299–305.10.1016/j.brachy.2010.11.007
8. Claren A, Gautier M, Feuillade J, Falk AT, Levi JM: Second salvage treatment for local recurrence of prostate cancer using high-dose-rate brachytherapy: a case report. J Contemp Brachytherapy. 2015, 7:244-247. 10.5114/jcb.2015.51852
9. Maenhout M, van Vulpen M, Moerland M, et al.: Second salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer. J Contemp Brachytherapy. 2017, 9:161-166.10.5114/jcb.2017.67015
10. Peters M, Kanthabalan A, Shah TT, et al. : Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: presentation of risk scores for individual patient prognoses. Urol Oncol. 2018, 36:11-13. 10.1016/j.urolonc.2017.08.022

CHAPTER 10

General Discussion and Future Perspectives

Focal therapy was introduced as a potential paradigm shift in the management of localized prostate cancer. The burden of overtreatment and the pursuit of function preservation have generated a growing interest in this approach. While modern biopsy strategies and imaging techniques have transformed our ability to localize and characterize pathological lesions, there are still some uncertainties withholding the widespread adoption of focal therapy. In the primary setting, focal therapy is an organ-sparing alternative to conventional radical treatments with the primary aim of reducing treatment-related toxicity. However, it will take years before clinical evidence on its long-term oncological effectiveness becomes available. In the salvage setting, focal therapy is an opportunity for local re-treatment with the primary aim of postponing or potentially averting the need for androgen deprivation therapy (ADT). Although in this setting functional outcomes are more relevant than long-term oncological effectiveness, it remains crucial to understand which patients truly benefit from re-treatment and who should move on to watchful waiting.

This thesis aimed to explore the role of focal therapy in the primary treatment setting (**part I**) and the salvage treatment setting (**part II**) and, in both settings, focused on the clinical results of MRI-guided ultrafocal HDR-brachytherapy. Besides lessons learned, there are remaining questions that will need to be addressed in future research.

I. Primary treatment setting

Lessons learned:

- After 6 years follow-up, primary focal therapy has no clear inferiority to conventional whole-gland treatments in terms of need for salvage treatment, progression to metastases, need for ADT or mortality (*chapter 2*).
- Long-term cohort data and future RCT evidence are warranted to establish the position of primary focal therapy besides available whole-gland treatments (*chapter 2*).
- Ultrafocal HDR-brachytherapy has a very limited effect on urinary and bowel function, but erectile dysfunction is common (*chapter 3*).
- Based on PSA progression, 4-year tumor control of ultrafocal HDR-brachytherapy seems to be poor (*chapter 3*).

For the establishment of primary focal therapy as a non-investigative, conventional treatment besides available whole-gland treatments, there are several caveats that require further investigation. Among these are the multifocal nature of prostate cancer and shortcomings in the diagnostic accuracy of localizing this multifocality(1). Ideally, focal therapy serves as the “middle ground” option for patients in whom treatment is recommended but where function preservation is highly rated. However, if cancer-free survival is diminished, the advantage of function preservation may no longer hold. A remaining challenge is the long indolent course of localized prostate cancer with progression usually occurring many years after treatment. Long-term assessment (≥10 years) of oncological outcomes is needed before more definitive conclusions can be drawn about the efficacy of primary focal therapy.

Another limitation in primary focal therapy research is the wide variety of different modalities being used for focal ablation, creating a field in which we are reliant upon separate groups investigating (smaller) cohorts, often using non-uniform nomenclature, varying diagnostic work-up, follow-up protocols or study endpoints. Within the available literature there are reports of focal HIFU, cryotherapy, brachytherapy, stereotactic body radiotherapy (SBRT), photodynamic therapy (PDT), irreversible electroporation (IRE), focal laser ablation (FLA), transurethral ultrasound ablation (TULSA) and radiofrequency ablation (RFA). For each energy modality, there are different techniques and/or devices available, often with considerable technological differences. Furthermore, the minimal extent of ablation varies widely, from targeting the tumor with a margin to hemi-gland or "hockey stick" (three-quarters) ablation. Currently, there are no randomized trials available comparing the outcome of different focal therapy technologies. The existing evidence from systematic reviews on the varying treatment strategies does not point to one approach being clearly superior to others(2-5).

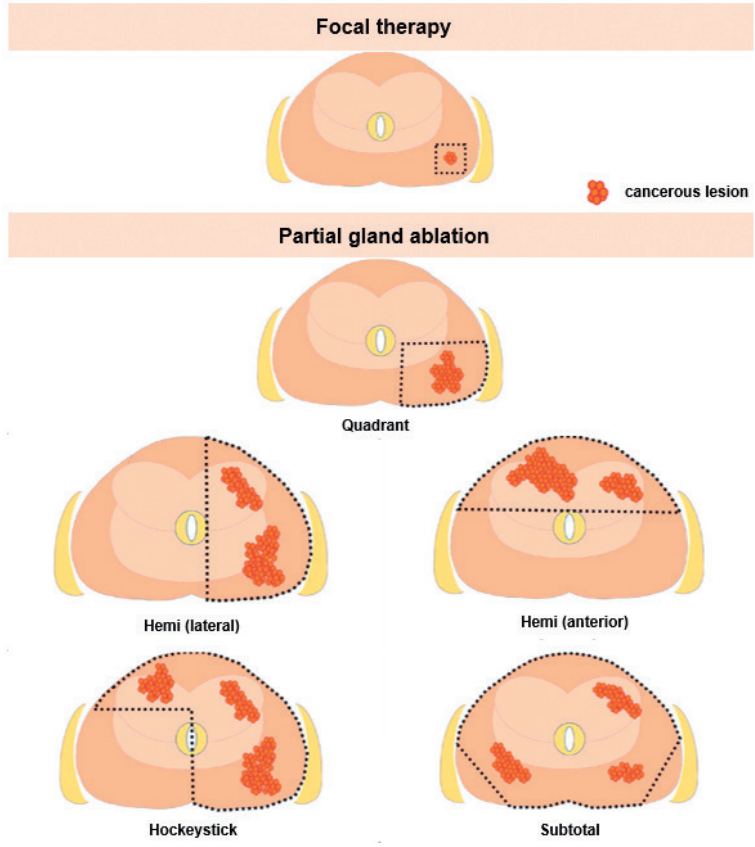

Figure 1 – Terminology for partial treatment of the prostate: "Focal therapy" versus "Partial gland ablation".
Image adapted from: Lebastchi et al., 2020(6)

To facilitate standardized evaluation of treatment outcomes, an international multidisciplinary consensus panel used the modified Delphi method to reach consensus on terminology and adequate post-treatment follow-up(6). They recommended regular PSA-checks (every 3 months in the first year and every 6 months thereafter), multiparametric (mp)-MRI after 6 and 18 months, systematic biopsy combined with targeted biopsy of the treated area after 6-12 months, and functional outcome assessment starting 3-6 months after treatment. In terms of terminology, the panel suggested using the term "focal therapy" to describe guided ablation of an image-defined, biopsy-confirmed lesion with a safety margin surrounding it. All strategies aiming to treat a standardized anatomic part of the gland should be referred to as "partial gland ablation" (Figure 1).

Even the definition of success after primary focal therapy is controversial(7). For patients, the most relevant measure of success is durable disease control, although there are several ways to define this. Among the available hard endpoints there are short-term measures such as presence or absence of positive cores on post-treatment biopsy, and long-term endpoints such as metastatic disease on imaging or death. A more common mid-term endpoint is biochemical disease-free survival, traditionally used as surrogate endpoint for treatment success in whole-gland treatment studies. For radical prostatectomy, the American Urological Association (AUA) and the European Association of Urology (EAU) have recommended a PSA threshold >0.2 ng/mL to define biochemical failure(8, 9), whereas radical radiotherapy uses the American Society for Therapeutic Radiology and Oncology (ASTRO) Phoenix definition of PSA nadir+2(10). With primary focal therapy, defining such a threshold is problematic due to the fact that (substantial) parts of the gland are left untreated and PSA may vary according to the ablative technology, amount of tissue treated, and amount of residual tissue that remains. Because PSA could be the expression from both malignant and benign prostate tissue, the target level after focal therapy is highly individual. A recently proposed definition for treatment success is percentage PSA reduction after treatment, with a PSA reduction of >90% predicting a 20% chance of patients needing additional treatment within 5 years within the studied cohort(11).

An advantage of primary focal therapy is that new (or residual) lesions with clinically significant cancer arising after treatment may be re-treated, potentially again with few undesirable genitourinary and gastro-intestinal side effects. Although there are no guidelines for the management of patients with localized recurrence after primary focal therapy, all therapeutic options are theoretically possible, including radiotherapy, surgery, repeat focal therapy or even active surveillance(12, 13). Whether initial focal therapy jeopardizes the safety and oncological outcomes of subsequent treatment remains largely unknown, with the current evidence being limited to a few retrospective series(14, 15). Repeat focal therapy seems possible, although reports on efficacy remain scarce, with available studies describing either a small proportion (1.5%) of patients receiving focal repeat ablation(16) or refraining from specifically addressing functional and oncological outcomes for the repeat procedures(17). For patients in whom repeat focal therapy is deemed unfeasible, for example due to multifocal or extended disease,

radical salvage therapy may be offered. A large cohort of patients (n=82) undergoing salvage prostatectomy after focal therapy (HIFU or cryotherapy) showed no increase in toxicity when compared to surgery in the primary treatment setting. The oncological effectiveness of salvage treatment depends on the nature of the recurrent lesion: if the recurrence is within the previously treated field, the oncological prognosis seems to be worse as these lesions seem to harbor more aggressive disease(18).

Which patients should be offered primary focal therapy remains subject of debate. Due to the difficulty of accurately localizing significant cancer within the prostate gland, tissue-sparing techniques have been difficult to develop. The wide-spread adoption of mp-MRI has largely improved our radiological assessment, and mapping biopsy techniques are available to overcome remaining uncertainties. Together, imaging and pathology characteristics are vital in determining the significance of prostate cancer being found. In a histological study of 100 consecutive radical prostatectomy specimens, primary tumors were often multifocal (78%) and bilateral (86%), but satellite foci (smaller lesions besides the "index lesion"), were mostly <0.5 cm^3 (87%), usually with ISUP grade 1 (99.4%), indicating non-aggressive disease which may be left untreated(19).

Translation into clinic

The current position of the EAU is that the lack of high-level evidence does not allow the use of primary focal therapy outside the context of clinical trials(20). In the Netherlands, this is currently limited to three clinical centers (st. Antonius, Amsterdam UMC and Radboud) investigating focal IRE or FLA. In terms of patient selection, focal therapy is not an alternative to active surveillance in low-risk men. It should be offered to men with localized, clinically significant cancer without high-risk disease characteristics such as PSA >20 ng/ml or ISUP grade 4-5. Awaiting long-term oncological effectiveness data, it now seems most suitable to men who place greater value on maintaining genitourinary function than certainty over long-term disease control.

II. Salvage treatment setting

Lessons learned:

- Several modalities are available for focal salvage treatment of localized radiorecurrent prostate cancer, all with very low severe urinary and bowel toxicity (*chapter 4*).
- Follow-up of current focal salvage series is still limited (*chapter 4*).
- Ultrafocal salvage HDR-brachytherapy has varying tumor control, depending on individual characteristics indicating tumor aggressiveness (*chapter 5*).
- Whereas bowel symptoms rarely occur, patients do report acute urinary symptoms and deteriorating sexual functioning over time (*chapter 6*).
- Concordantly, physicians observe limited bowel toxicity while moderate urinary symptoms and erectile dysfunction are more prominent (*chapter 7*).
- Ultrafocal salvage HDR-brachytherapy seems to be a safe salvage treatment option with a low risk of severe morbidity (*chapters 6 and 7*).
- Age, tumor volume and baseline PSA kinetics are potential predictors of PSA progression after treatment, indicating treatment failure (*chapter 8*).
- A second salvage treatment with ultrafocal HDR-brachytherapy seems feasible with a low risk of severe side-effects (*chapter 9*).

For patients with a localized recurrence after primary radiotherapy, whole-gland salvage treatments are not without risk due to the high incidence (15-30%) of severe toxicity such as urinary incontinence, rectal injury and erectile dysfunction, irrespective of the modality used(21-23). To minimize the risk of morbidity, focal salvage treatments have emerged as a promising alternative(24). Similar to the primary treatment setting, there are several modalities available for focal salvage treatment, with the most reported being focal salvage HIFU, focal salvage cryotherapy and focal salvage brachytherapy(25). Although technological differences between modalities may lead to different outcomes, there is no randomized evidence available showing superiority of one modality over others. In a retrospective study comparing 300 men undergoing either focal salvage cryotherapy or focal salvage HIFU, the HIFU patients had higher rates of biochemical recurrence and progression to castration resistant prostate cancer, but there were no differences in prostate cancer-specific mortality after 10 years(26). Severe side-effects seem to occur in 5-10% of patients irrespective of the modality used.

For each individual patient, the risk of side-effects should be carefully weighed against potential benefit from treatment. First, truly localized recurrence needs to be distinguished from unrecognized metastatic disease. Metastatic disease staging has improved significantly since the introduction of prostate-specific membrane antigen (PSMA) PET-CT(27, 28). For local disease assessment, mp-MRI has made it possible to largely differentiate glandular atrophy or radiotherapy-induced fibrosis from pathologic restricted diffusion or contrast enhancement(29, 30). Reported anatomical patterns of recurrence 8-10 years after primary radiotherapy are ±35% local relapse, ±25% pelvic nodal invasion and ±40% distant metastatic failure (Figure 2)(31, 32). It is likely that the actual local recurrence rate is even higher, since not all patients with biochemical failure

received local staging in these studies. In contrast with prostate cancer in the primary setting, localized radiorecurrent disease is usually unifocal, occurring predominantly at the site of primary disease(33). It is likely that the primary dose to the dominant lesion within the prostate was often too low while microscopic disease elsewhere in the prostate was eradicated. This supports the use of targeted treatment in the salvage setting.

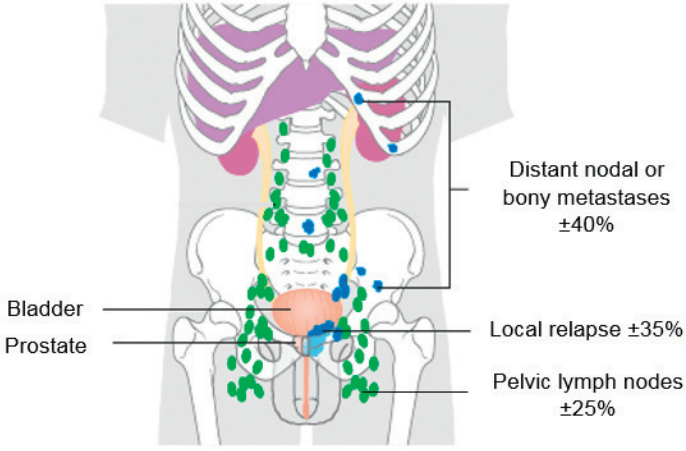

Figure 2 – Anatomical patterns of prostate cancer relapse after primary radiotherapy. Image adapted from: Cancer Research UK, 2020

Beyond detection of prostate cancer presence, radiological findings alone cannot determine the clinical significance of recurrent disease. It has been suggested that prostate biopsies are critical to confirm that the source of PSA progression originates from local disease recurrence(34). However, its interpretation is problematic with high occurrence of false negatives due to sampling error, false positives due to delayed tumor regression, and indeterminate biopsies showing radiation effect in residual tumor(35). Since the pathologic assessment of radiorecurrent disease falls short in accurately distinguishing clinically significant cancer, biopsy results are of limited value in predicting which patients will have long-term benefit from local salvage treatment and whom should be left untreated to avoid unnecessary side-effects.

Understanding the true impact of biochemical recurrence after primary treatment is crucial, since it does not necessarily indicate that a patient will develop clinically relevant (metastatic) disease or will even die from the disease. Studies have shown that only certain patient subgroups, namely those with increased age, high initial ISUP grade, high PSA or short PSA doubling time, are at high risk of progressive disease(36, 37). In a recent systematic review on the natural history of recurrences after primary curative treatment, biochemical relapse after radiotherapy was associated with worse survival rates, but this was limited to men with a short interval to biochemical failure or men with a high initial ISUP grade(38). Within this review, the authors proposed recurrence stratification criteria, stratifying post-radiotherapy patients with an inter-

val to biochemical failure >18 months and an initial ISUP grade <4 into the "low-risk" group, raising awareness that not all patients with biochemical recurrence have similar outcomes or should be offered salvage treatment.

To aid individualized treatment decisions in the salvage setting, research should be aimed at finding a combination of clinical features that allows for stratification of patients into prognostic groups predicting high or low risk of focal salvage treatment failure, similar to the risk groups in the primary treatment setting. From the current available literature on both focal and whole-gland salvage treatments, including several modalities, it seems that initial ISUP grade, interval to biochemical failure, PSA at relapse, PSA doubling time at relapse, T-stage at relapse and prostatic volume all seem to have predictive value(39-43). Common denominators between studies are interval to biochemical failure, PSA-level and PSA doubling time.

If left untreated, localized radiorecurrent disease may disseminate, potentially requiring systemic ADT in a later phase. Taking into account its time-limited effectiveness and the frequent severe side-effects associated with hormonal suppression, ADT seems most beneficial in the setting of metastatic disease, rather than for the treatment of localized radiorecurrent disease. However, the most optimal timing of ADT initiation remains under debate. The EAU guidelines currently recommend a deferred treatment strategy, offering ADT only to patients with symptoms of advanced disease or patients with an increased risk of spinal cord compression, pathological fractures or urethral obstruction. Early ADT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA doubling time (<6-12 months) or a high initial ISUP grade (>3)(44). As compared to a deferred ADT strategy, it would be interesting to assess the amount of ADT-free time that is gained by offering salvage treatment when the recurrent disease is still at a localized stage.

Translation into clinic

In contrast to the primary setting, the EAU has no strong recommendations regarding the use of focal salvage treatments for localized radiorecurrent prostate cancer(44). Awaiting prediction models based on long-term oncological outcome data from focal salvage series, adequate patient selection remains a challenge. Based on the available data, focal salvage treatment seems most beneficial for patients with a reasonable interval to recurrence and with favorable PSA kinetics. Treatment benefit should however be weighed against the potentially mild natural course of locally recurrent disease with favorable characteristics. With the other treatment option being (deferred) ADT, focal salvage treatment seems especially suitable for patients who are reluctant to start ADT or anxious to await the need for ADT in the longer term.

Future perspectives

For the future, the role of focal therapy among whole-gland treatment options will in part depend on the extent to which innovations can further reduce whole-gland treatment-related side effects. In the early 1990s, physicians became more aware of morbidity related to whole-gland prostate cancer treatments. The general view was that with refinements of surgical techniques and radiation advancements, erectile dysfunction and incontinence could be largely reduced(45, 46). Indeed, some improvements have already contributed to reducing complication rates.

For radical prostatectomy, these include nerve-sparing techniques, centralization in high-volume expert centers and (although controversial) robot-assisted surgery(47-49). Although a recent review showed that 82% of patients still reported erectile dysfunction after bilateral nerve-sparing surgery (versus 95% after conventional surgery)(50), the NeuroSAFE technique has now been introduced as an approach to further improve erectile function preservation(51). With this technique, the prostate is removed with bilateral nerve-sparing after which a frozen-section examination is performed to decide whether a secondary resection of the neurovascular bundle is necessary. A cohort-based analysis of 258 patients undergoing NeuroSAFE prostatectomy showed that 25% had positive surgical margins prompting a secondary neurovascular bundle resection. However, in 72% of bundle resections, no tumor was present. The authors concluded that the neurovascular bundle can be spared in the majority of patients and that secondary nerve bundle resection might even be omitted in patients with small positive surgical margins of ≤1 mm with Gleason pattern 3, supporting individual intraoperative clinical decision-making(52). However, such decisions should be made with caution, as the entire approach relies on meticulous pathological examination. If the pathologist misses significant cancer (due to inadequate slice thickness or microscopic inspection), this may compromise the oncological safety of the procedure. Unfortunately, it will take years before long-term oncological outcome data will become available. A future trial planning to randomize between NeuroSAFE prostatectomy and nerve-sparing as per standard of care will aim to investigate both functional outcomes and cancer control(53).

In the field of primary whole-gland radiotherapy, dose escalation without increasing toxicity has become more achievable since the introduction of volumetric arc external beam radiotherapy (VMAT) and intensity-modulated radiation therapy (IMRT) techniques(54). Although most trials have not been able to show a significant prostate cancer-specific or overall survival advantage for patients treated with ≥74 Gy, dose escalation at least seems to reduce the need for secondary therapies(55, 56) and it is now an accepted standard of care with low rates of severe side effects(57). The low estimated α/β ratio of prostate cancer translates into a potential benefit from hypofractionation, with encouraging results from studies investigating external beam radiotherapy in only 4-5 fractions(58, 59). The introduction of the MR-Linac, in which a linear accelerator is integrated with a diagnostic quality MRI-scanner, has made it possible to adapt the radiotherapy plan to anatomic changes during treatment and

therefore deliver high-precision radiotherapy. This enables irradiation of the tumor while sparing the surrounding healthy tissues, potentially allowing for an increased dose to the tumor with smaller margins, a reduction of toxicity and/or a reduction of the number of fractions(60).

Regarding the improvement of focal HDR-brachytherapy, the recent literature has shown increasing evidence favoring a fractionated regimen over single-dose treatment. In the primary whole-gland treatment setting, a prospective randomized controlled trial comparing two fractions of 13.5 Gy to a single dose of 19 Gy HDR-brachytherapy revealed a clear 5-year biochemical disease-free survival advantage in the two-fraction arm (95% versus 73.5%)(61). In the focal salvage treatment setting, the evidence is limited to individual cohort studies which show higher estimated 3-year biochemical disease-free survival among multi-fraction studies (±60% versus ±44%), with comparable toxicity rates(62-66). Although these results support the use of fractionated treatment, selection bias may affect this interpretation. Furthermore, there are also disadvantages to fractionated brachytherapy, particularly the logistical aspects of two (or more) implant sessions. Here, highly conformal external beam radiotherapy would undoubtedly have procedural advantages over brachytherapy. If adequate tumor tracking becomes possible on the MR-Linac(67), there even is a potential for ultrafocal external beam radiotherapy. The trade-off, however, would likely be less target dose coverage and less conformal dose distributions, with therefore higher doses to the rectum and urethra(68).

REFERENCES

1. Bass EJ, Ahmed HU. Focal therapy in prostate cancer: A review of seven common controversies. Cancer treatment reviews. 2016;51:27-34.
2. Kayano PP, Klotz L. Current evidence for focal therapy and partial gland ablation for organ-confined prostate cancer: systematic review of literature published in the last 2 years. Current opinion in urology. 2021;31(1):49-57.
3. Fallara G, Capogrosso P, Maggio P, Taborelli A, Montorsi F, Deho F, et al. Erectile function after focal therapy for localized prostate cancer: a systematic review. International journal of impotence research. 2020.
4. Valerio M, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol. 2014;66(4):732-51.
5. Ahdoot M, Lebastchi AH, Turkbey B, Wood B, Pinto PA. Contemporary treatments in prostate cancer focal therapy. Current opinion in oncology. 2019;31(3):200-6.
6. Lebastchi AH, George AK, Polascik TJ, Coleman J, de la Rosette J, Turkbey B, et al. Standardized Nomenclature and Surveillance Methodologies After Focal Therapy and Partial Gland Ablation for Localized Prostate Cancer: An International Multidisciplinary Consensus. Eur Urol. 2020;78(3):371-8.
7. Ahmed HU, Moore C, Lecornet E, Emberton M. Focal therapy in prostate cancer: determinants of success and failure. Journal of endourology. 2010;24(5):819-25.
8. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. The Journal of urology. 2007;177(2):540-5.
9. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65(2):467-79.
10. Roach M, 3rd, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006;65(4):965-74.
11. Stabile A, Orczyk C, Giganti F, Moschini M, Allen C, Punwani S, et al. The Role of Percentage of Prostate-specific Antigen Reduction After Focal Therapy Using High-intensity Focused Ultrasound for Primary Localised Prostate Cancer. Results from a Large Multi-institutional Series. Eur Urol. 2020;78(2):155-60.
12. Barret E, Harvey-Bryan KA, Sanchez-Salas R, Rozet F, Galiano M, Cathelineau X. How to diagnose and treat focal therapy failure and recurrence? Current opinion in urology. 2014;24(3):241-6.
13. Hamid S, Guillaumier S, Shah T, Arya M, Ahmed HU. Prostate cancer recurrence after Focal Therapy: Treatment options. Archivos espanoles de urologia. 2016;69(6):375-83.

14. Marra G, Gontero P, Walz JC, Sivaraman A, Tourinho-Barbosa R, Cathelineau X, et al. Complications, oncological and functional outcomes of salvage treatment options following focal therapy for localized prostate cancer: a systematic review and a comprehensive narrative review. World journal of urology. 2019;37(8):1517-34.

15. Marra G, Valerio M, Emberton M, Heidenreich A, Crook JM, Bossi A, et al. Salvage Local Treatments After Focal Therapy for Prostate Cancer. Eur Urol Oncol. 2019;2(5):526-38.

16. Wenske S, Quarrier S, Katz AE. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. Eur Urol. 2013;64(1):1-7.

17. Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol. 2018;74(4):422-9.

18. Marconi L, Stonier T, Tourinho-Barbosa R, Moore C, Ahmed HU, Cathelineau X, et al. Robot-assisted Radical Prostatectomy After Focal Therapy: Oncological, Functional Outcomes and Predictors of Recurrence. Eur Urol. 2019;76(1):27-30.

19. Karavitakis M, Winkler M, Abel P, Livni N, Beckley I, Ahmed HU. Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy. Prostate cancer and prostatic diseases. 2011;14(1):46-52.

20. van der Poel HG, van den Bergh RCN, Briers E, Cornford P, Govorov A, Henry AM, et al. Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position in 2018. Eur Urol. 2018;74(1):84-91.

21. Golbari NM, Katz AE. Salvage Therapy Options for Local Prostate Cancer Recurrence After Primary Radiotherapy: a Literature Review. Curr Urol Rep. 2017;18(8):63.

22. Alongi F, De Bari B, Campostrini F, Arcangeli S, Matei DV, Lopci E, et al. Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: a review. Critical reviews in oncology/hematology. 2013;88(3):550-63.

23. Valle LF, Lehrer EJ, Markovic D, Elashoff D, Levin-Epstein R, Karnes RJ, et al. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur Urol. 2020.

24. Haj-Hamed M, Karivedu V, Sidana A. Salvage treatment for radio-recurrent prostate cancer: a review of literature with focus on recent advancements in image-guided focal salvage therapies. International urology and nephrology. 2019;51(7):1101-6.

25. Khoo CC, Miah S, Connor MJ, Tam J, Winkler M, Ahmed HU, et al. A systematic review of salvage focal therapies for localised non-metastatic radiorecurrent prostate cancer. Translational andrology and urology. 2020;9(3):1535-45.

26. Nair SM, Peters M, Kurver P, Lavi A, Verhoeff JJC, van der Voort van Zyp JRN, et al. Long-term outcomes of two ablation techniques for treatment of radio-recurrent prostate cancer. Prostate cancer and prostatic diseases. 2020.

27. Evans JD, Jethwa KR, Ost P, Williams S, Kwon ED, Lowe VJ, et al. Prostate cancer-specific PET radiotracers: A review on the clinical utility in recurrent disease. Practical radiation oncology. 2018;8(1):28-39.

28. Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2020;77(4):403-17.

29. Abd-Alazeez M, Ramachandran N, Dikaios N, Ahmed HU, Emberton M, Kirkham A, et al. Multiparametric MRI for detection of radiorecurrent prostate cancer: added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. Prostate cancer and prostatic diseases. 2015;18(2):128-36.

30. Arumainayagam N, Kumaar S, Ahmed HU, Moore CM, Payne H, Freeman A, et al. Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy. BJU international. 2010;106(7):991-7.

31. Yorozu A, Soyano T, Sutani S, Saito S, Toya K, Shiraishi Y. Patterns of Recurrence for Prostate Cancer Patients Treated with Brachytherapy-based Radiotherapy. Int J Radiat Oncol Biol Phys. 2019;105(1):E316.

32. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Kollmeier M, et al. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer. The Journal of urology. 2015;194(6):1624-30.

33. Chopra S, Toi A, Haider MA, Milosevic M, Bristow RG, Bayley A, et al. Spatial patterns of local recurrence after radiotherapy for prostate cancer. Radiother Oncol. 2009;92:S22.

34. Jones JS. Radiorecurrent prostate cancer: an emerging and largely mismanaged epidemic. Eur Urol. 2011;60(3):411-2.

35. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdolell M. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys. 2000;48(2):355-67.

36. van den Bergh RC, van Casteren NJ, van den Broeck T, Fordyce ER, Gietzmann WK, Stewart F, et al. Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review. Eur Urol. 2016;69(5):802-20.

37. Boorjian SA, Thompson RH, Tollefson MK, Rangel LJ, Bergstralh EJ, Blute ML, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol. 2011;59(6):893-9.

38. Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol. 2019;75(6):967-87.

39. Peters M, Kanthabalan A, Shah TT, McCartan N, Moore CM, Arya M, et al. Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: Presentation of risk scores for individual patient prognoses. Urol Oncol. 2018;36(1):13 e1- e0.

40. Spiess PE, Katz AE, Chin JL, Bahn D, Cohen JK, Shinohara K, et al. A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer. BJU international. 2010;106(2):194-8.

41. Peters M, van der Voort van Zyp JRN, Moerland MA, Hoekstra CJ, van de Pol S, Westendorp H, et al. Development and internal validation of a multivariable prediction model for biochemical failure after whole-gland salvage iodine-125 prostate brachytherapy for recurrent prostate cancer. Brachytherapy. 2016;15(3):296-305.

42. Henriquez I, Sancho G, Hervas A, Guix B, Pera J, Gutierrez C, et al. Salvage brachytherapy in prostate local recurrence after radiation therapy: predicting factors for control and toxicity. Radiation oncology (London, England). 2014;9:102.

43. Spiess PE, Levy DA, Mouraviev V, Pisters LL, Jones JS. Predictors of biochemical failure in patients undergoing prostate whole-gland salvage cryotherapy: a novel risk stratification model. BJU international. 2013;112(4):E256-61.

44. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2020.

45. Walsh PC. Radical retropubic prostatectomy with reduced morbidity: an anatomic approach. NCI monographs : a publication of the National Cancer Institute. 1988(7):133-7.

46. Zelefsky MJ, Fuks Z, Happersett L, Lee HJ, Ling CC, Burman CM, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol. 2000;55(3):241-9.

47. Avulova S, Zhao Z, Lee D, Huang LC, Koyama T, Hoffman KE, et al. The Effect of Nerve Sparing Status on Sexual and Urinary Function: 3-Year Results from the CEASAR Study. The Journal of urology. 2018;199(5):1202-9.

48. Fossati N, Di Trapani E, Gandaglia G, Dell'Oglio P, Umari P, Buffi NM, et al. Assessing the Impact of Surgeon Experience on Urinary Continence Recovery After Robot-Assisted Radical Prostatectomy: Results of Four High-Volume Surgeons. Journal of endourology. 2017;31(9):872-7.

49. Steffens D, Thanigasalam R, Leslie S, Maneck B, Young JM, Solomon M. Robotic Surgery in Uro-oncology: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Urology. 2017;106:9-17.

50. Vernooij RWM, Cremers R, Jansen H, Somford DM, Kiemeney LA, van Andel G, et al. Urinary incontinence and erectile dysfunction in patients with localized or locally advanced prostate cancer: A nationwide observational study. Urol Oncol. 2020;38(9):735 e17- e25.

51. Schlomm T, Tennstedt P, Huxhold C, Steuber T, Salomon G, Michl U, et al. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) increases nerve-sparing frequency and reduces positive surgical margins in open and robot-assisted laparoscopic radical prostatectomy: experience after 11,069 consecutive patients. Eur Urol. 2012;62(2):333-40.

52. van der Slot MA, den Bakker MA, Klaver S, Kliffen M, Busstra MB, Rietbergen JBW, et al. Intraoperative assessment and reporting of radical prostatectomy specimens to guide nerve-sparing surgery in prostate cancer patients (NeuroSAFE). Histopathology. 2020;77(4):539-47.

53. Dinneen E, Haider A, Allen C, Freeman A, Briggs T, Nathan S, et al. NeuroSAFE robot-assisted laparoscopic prostatectomy versus standard robot-assisted laparoscopic prostatectomy for men with localised prostate cancer (NeuroSAFE PROOF): protocol for a randomised controlled feasibility study. BMJ open. 2019;9(6):e028132.

54. Zaorsky NG, Keith SW, Shaikh T, Nguyen PL, Horwitz EM, Dicker AP, et al. Impact of Radiation Therapy Dose Escalation on Prostate Cancer Outcomes and Toxicities. Am J Clin Oncol. 2018;41(4):409-15.

55. Michalski JM, Moughan J, Purdy J, Bosch W, Bruner DW, Bahary JP, et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA oncology. 2018;4(6):e180039.

56. Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2021:JCO2002873.

57. Spratt DE, Michalski JM. Long-Term Benefits of Dose-Escalation in Localized Prostate Cancer. Int J Radiat Oncol Biol Phys. 2019;104(4):798-800.

58. Kishan AU, Dang A, Katz AJ, Mantz CA, Collins SP, Aghdam N, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. JAMA Netw Open. 2019;2(2):e188006.

59. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. The Lancet Oncology. 2019;20(11):1531-43.

60. Pathmanathan AU, van As NJ, Kerkmeijer LGW, Christodouleas J, Lawton CAF, Vesprini D, et al. Magnetic Resonance Imaging-Guided Adaptive Radiation Therapy: A "Game Changer" for Prostate Treatment? Int J Radiat Oncol Biol Phys. 2018;100(2):361-73.

61. Morton G, McGuffin M, Chung HT, Tseng CL, Helou J, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol. 2020;146:90-6.

62. Murgic J, Morton G, Loblaw A, D'Alimonte L, Ravi A, Wronski M, et al. Focal Salvage High Dose-Rate Brachytherapy for Locally Recurrent Prostate Cancer After Primary Radiation Therapy Failure: Results From a Prospective Clinical Trial. Int J Radiat Oncol Biol Phys. 2018;102(3):561-7.

63. Jiang P, van der Horst C, Kimmig B, Zinsser F, Poppe B, Luetzen U, et al. Interstitial high-dose-rate brachytherapy as salvage treatment for locally recurrent prostate cancer after definitive radiation therapy: Toxicity and 5-year outcome. Brachytherapy. 2017;16(1):186-92.

64. Slevin F, Hodgson S, Rodda SL, Bownes P, Bottomley D, Adiotomre E, et al. Efficacy and toxicity outcomes for patients treated with focal salvage high dose rate brachytherapy for locally recurrent prostate cancer. Clinical and translational radiation oncology. 2020;23:20-6.

65. Chitmanee P, Tsang Y, Tharmalingam H, Hamada M, Alonzi R, Ostler P, et al. Single-Dose Focal Salvage High Dose Rate Brachytherapy for Locally Recurrent Prostate Cancer. Clinical oncology (Royal College of Radiologists (Great Britain)). 2020;32(4):259-65.

66. van Son M, Peters M, Moerland M, van de Pol S, Eppinga W, Lagendijk J, et al. Determining the safety of ultrafocal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer: A toxicity assessment of 150 patients. Clinical and translational radiation oncology. 2021;27:1-7.

67. de Muinck Keizer DM, Pathmanathan AU, Andreychenko A, Kerkmeijer LGW, van der Voort van Zyp JRN, Tree AC, et al. Fiducial marker based intra-fraction motion assessment on cine-MR for MR-linac treatment of prostate cancer. Physics in medicine and biology. 2019;64(7):07NT2.

68. Willigenburg T, Beld E, Hes J, Lagendijk J, de Boer H, Moerland M, et al. Focal salvage treatment for radiorecurrent prostate cancer: A magnetic resonance-guided stereotactic body radiotherapy versus high-dose-rate brachytherapy planning study. Physics and Imaging in Radiation Oncology. 2020;15:60-5.

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APPENDICES

DUTCH SUMMARY – NEDERLANDSTALIGE SAMENVATTING

Eén op de negen mannen wordt gedurende het leven gediagnosticeerd met prostaatkanker. Het is daarmee, op huidkanker na, de meest voorkomende kankersoort bij mannen. Prostaatkanker kan zich in verschillende gradaties manifesteren, met zeer uiteenlopende prognoses. Het natuurlijk beloop bij patiënten met gelokaliseerde, laaggradige tumoren is over het algemeen zo mild dat tegenwoordig steeds vaker wordt gewacht met behandeling. Er wordt dan gekozen voor een "actief afwachtend" beleid. Echter, patiënten met hooggradige of vergevorderde tumoren hebben vaak juist langdurige systemische therapie nodig. Over het algemeen is de prognose bij het vinden van prostaatkanker relatief gunstig, met een gemiddelde 10-jaarsoverleving van 98% bij patiënten met gelokaliseerde ziekte.

De behandeling van lokale prostaatkanker wordt traditioneel gericht op de gehele prostaat, waarbij gekozen kan worden voor radiotherapie (bestraling van de prostaat) of prostatectomie (operatie waarbij de prostaat in zijn geheel verwijderd wordt). Beide behandelopties hebben uitstekende resultaten qua tumorcontrole, maar kunnen helaas gepaard gaan met (soms invaliderende) bijwerkingen, zoals plasklachten (aandrang, urine-incontinentie), darmklachten (diarree, rectaal bloedverlies) en erectiestoornissen. Deze bijwerkingen zijn het directe gevolg van schade aan gezonde organen die in de buurt van de prostaat liggen en niet (geheel) ontzien kunnen worden tijdens bestraling of operatie. Om nevenschade aan gezonde organen zoveel mogelijk te beperken en daarmee de bijwerkingen van behandeling te verminderen is er steeds meer aandacht voor focale (plaatselijke) behandeling van lokale prostaatkanker. Hierbij wordt alleen de tumor in de prostaat behandeld, terwijl de rest van de prostaat en de omgevende organen worden ontzien. Daarmee is focale behandeling potentieel curatief, met mogelijk minder bijwerkingen.

Deel I – Primaire behandeling van lokale prostaatkanker

In het eerste deel van dit proefschrift worden de resultaten beschreven van het onderzoek naar focale behandeling bij patiënten die zich in de primaire setting met lokale prostaatkanker presenteren.

Algehele versus focale behandeling

Om de uitkomsten van focale behandeling betrouwbaar te kunnen vergelijken met conventionele radiotherapie of prostatectomie zijn prospectieve klinische studies nodig, waarbij patiënten gerandomiseerd worden tussen de verschillende behandelopties. Deze randomisatie brengt met zich mee dat patiënten binnen elk van de groepen naar verwachting vergelijkbare kenmerken hebben. Gerandomiseerde trials zoals de CHRONOS-trial (ISRCTN 17796995) zijn recent gestart, maar de resultaten hiervan zullen pas over een aantal jaren bekend zijn. In de tussentijd lopen er wereldwijd verschillende

(kleine) cohortstudies waarin verschillende soorten focale behandelingen worden bestudeerd. In **hoofdstuk 2** is de setting van een gerandomiseerde trial zoveel mogelijk nagebootst door gebruik te maken van een propensity score analyse, waarbij cohortdata van 440 radiotherapie en 390 prostatectomie patiënten wordt vergeleken met data van 530 focale therapie patiënten. De kans op falen van de behandeling (gedefinieerd als noodzaak tot opnieuw behandelen, vaststellen van recidief of metastasen) bleek na 6 jaar niet significant groter te zijn na focale therapie. Met inachtneming van de limitaties van een dusdanige statistische analyse kan in elk geval worden geconcludeerd dat focale therapie potentie heeft als behandeling bij een geselecteerde groep patiënten met een klinisch significante gradatie van lokale prostaatkanker.

Focale inwendige bestraling

Een van de modaliteiten die gebruikt worden voor focale therapie, is brachytherapie (inwendige bestraling). Hierbij wordt gebruikt gemaakt van bestralingsbronnen die via holle katheters transperineaal worden ingebracht in de prostaat. In **hoofdstuk 3** worden de resultaten beschreven van eenmalige MRI-geleide focale brachytherapie, waarbij de bestraling zo precies mogelijk wordt gericht op alleen de tumor in de prostaat. Hiervoor wordt de tumor voorafgaand aan de behandeling met een marge van 5 millimeter ingetekend op een multiparametrische MRI-scan. Na implantatie van de brachytherapiekatheters in en rond de tumor, wordt een bestralingsplan gemaakt met strikte voorwaarden ten aanzien van de maximale bestralingsdosis die de gezonde omliggende weefsels mogen ontvangen. Binnen de beschreven studiegroep van 30 patiënten blijkt het gastro-intestinale en urogenitale bijwerkingenprofiel zeer gunstig (geen graad 3, ofwel ernstige bijwerkingen), maar komt erectiele dysfunctie na behandeling wel vaak voor (50% verslechtert van milde dysfunctie naar matig tot ernstige dysfunctie). Met betrekking tot tumorcontrole blijkt de biochemisch recidief-vrije overleving na 4 jaar 70% te zijn, een resultaat dat relatief tegenvalt in vergelijking met de gemiddelde tumorcontrole na conventionele radiotherapie of prostatectomie.

Deel II – Behandeling van teruggekeerde lokale prostaatkanker

Alhoewel de prognose qua overleving relatief gunstig is voor patiënten met prostaatkanker, is de kans op recidief na conventionele primaire behandeling binnen 10 jaar 10-40%. Een recidief wordt vastgesteld door een stijgende PSA-waarde, waarbij voor radiotherapie en prostatectomie verschillende definities worden aangehouden voor PSA-bewezen teruggekeerde ziekte (“biochemisch recidief”). Indien er sprake is van een biochemisch recidief duurt het gemiddeld 5 jaar tot er afstandsmetastasen ontstaan en is de maximale overleving gemiddeld 10 jaar. Het natuurlijk beloop is echter zeer heterogeen, variërend van indolente recidieven die asymptomatisch blijven tot agressieve tumoren die snel dodelijk zijn. Bij patiënten met een redelijke levensverwachting kan opnieuw lokaal behandelen zinvol zijn om complicaties van metastasen of vroegtijdig overlijden te voorkomen. Net zoals in de primaire behandelsetting moet het risico op bijwerkingen van behandeling zorgvuldig

worden afgewogen tegen de voordelen van verlengde overleving. De behandelopties die er zijn hebben echter elk hun eigen nadelen. Een tweede behandeling van de gehele prostaat geeft vaak ernstige bijwerkingen (wederom vanwege de schade aan gezonde omliggende organen) en de beschreven tumorcontrole in de literatuur is matig. Daarom wordt tegenwoordig >90% van de patiënten met een lokaal recidief uiteindelijk behandeld met systemische hormonale therapie. Deze behandeling heeft een tijdelijk remmend effect en kent potentiele bijwerkingen zoals onder andere opvliegers, (pijnlijke) zwelling van borstweefsel, wisselend humeur, impotentie en botontkalking. Qua bijwerkingenprofiel zou focale therapie in de setting van lokale recidieven dus een goed alternatief kunnen zijn.

In het tweede deel van dit proefschrift worden de resultaten beschreven van het onderzoek naar focale behandeling bij patiënten met een lokaal recidief na primaire behandeling met algehele bestraling.

Overzicht van focale behandelingen van lokale recidieven

Uit verschillende studies blijkt dat recidieven na primaire radiotherapie vaak voorkomen op de plek waar zich in de primaire setting de grootste of meest agressieve laesie zich bevond. Tevens is door celbiologische onderzoeken de hypothese ontstaan dat er bij prostaatkanker één aandrijvend focus (ofwel "index laesie") bestaat, met een cel of groepje cellen die als voorloper dienen voor verdere verspreiding van de ziekte. Door deze laesie focaal te behandelen zou het prostaatkankerrecidief in theorie afgeremd of zelfs onschadelijk gemaakt kunnen worden. **Hoofdstuk 4** beschrijft de belangrijkste voorwaarden voor een succesvolle focale behandeling (adequaat uitsluiten van metastasen, detectie en beeldvorming van het recidief) en de resultaten van huidige focale series. De meeste data in de literatuur komt van studies naar focale HIFU, cryotherapie, brachytherapie en stereotactische uitwendige radiotherapie. Bij elke techniek worden verschillende behandelschema's en doelvolumina aangehouden, wat de onderlinge vergelijking tussen cohorten erg ingewikkeld maakt. Over het algemeen lijken ernstige bijwerkingen weinig voor te komen (gastro-intestinaal en urogenitaal 5-10% graad 3) en wordt in de langste studies een biochemisch recidief-vrije overleving van 50% gerapporteerd na 5 jaar.

Focale inwendige bestraling van een lokaal recidief

Het concept van focale brachytherapie zoals eerder in de primaire setting omschreven, kan ook worden toegepast voor de behandeling van lokale recidieven na radiotherapie. De resultaten van deze behandeling worden belicht in **hoofdstuk 5**, waarin een cohortstudie wordt beschreven met 50 patiënten. Voor de stadiering werd gebruik gemaakt van 18F-Choline of 68Ga-PSMA PET/CT om metastasen uit te sluiten en multiparametrische MRI en biopten om lokale recidieven aan te tonen. In deze studie wordt duidelijk zichtbaar gemaakt hoezeer het te verwachten succespercentage van de behandeling afhangt van de patiënt- en tumorkarakteristieken en daarbij behorende risicoprofielen. Binnen de beschreven groep van 50 patiënten zijn uiteenlopende karakteristieken te

onderscheiden, met PSA-waarden variërend tussen 1 en 39, PSA-verdubbelingstijden variërend van 3 maanden tot enkele jaren en tumorstadia van T2a (zeer lokaal) tot T4 (met ingroei tot in de blaas). Om een eerlijker beeld te schetsen van de uitkomsten qua tumorcontrole werd de groep daarom in tweeën opgedeeld: de "laag-risico" groep had een biochemisch recidief-vrije overleving van 71% na 2,5 jaar, terwijl dit in de "hoog-risico" groep slechts 25% was.

Bijwerkingen en kwaliteit van leven

Bijwerkingen en patiënt-gerapporteerde kwaliteit van leven zijn belangrijke uitkomstmaten van focale therapie bij lokale recidieven, omdat hiervan een aanzienlijke verbetering te verwachten valt ten opzichte van een behandeling met hormonale therapie. **Hoofdstukken 6 en 7** beschrijven het perspectief van de patiënt ten aanzien van kwaliteit van leven en de bijwerkingen zoals gerapporteerd volgens de CTCAE 4.0 criteria. Uit data van kwaliteit van leven vragenlijsten van 100 patiënten en data van CTCAE rapportages van 150 patiënten die focale brachytherapie ondergingen blijkt dat er voornamelijk plasklachten (met name vlak na de behandeling) en erectiestoornissen worden gerapporteerd. Patiënten met een slechtere functionele uitgangswaarde voorafgaand aan de behandeling lopen meer risico op het ontwikkelen van plasklachten of erectiestoornissen. Patiënten die een hoge dosis (≥16 Gy) op de urethra krijgen lopen specifiek meer risico op plasklachten. In beide studies blijken darmklachten na focale brachytherapie zeer weinig voor te komen. In alle overige kwaliteit van leven domeinen werd ook geen verslechtering gerapporteerd. Hiermee kan niet alleen rekening gehouden worden bij het informeren van de patiënt over het te verwachten beloop, maar ook bij het bestralingsplan dat gemaakt wordt voorafgaand aan de behandeling.

Voorspelling van de kans op succes

Om in de toekomst een betere selectie te kunnen maken van de patiënten die het meest gebaat zullen zijn bij focale brachytherapie, wordt in **hoofdstuk 8** ingegaan op het ontwikkelen en valideren van predictiemodellen waarmee de kans op succes per patiënt kan worden ingeschat. Het eerste model voorspelt de biochemisch recidief-vrije overleving aan de hand van patiënt- en tumorkarakteristieken voorafgaand aan de behandeling. In deze studiegroep van 150 patiënten zijn de beste voorspellers van een biochemisch recidief leeftijd (negatieve associatie; hoe jonger hoe groter het risico), grootte van de tumor (positieve associatie), PSA-waarde (positieve associatie) en PSA-verdubbelingstijd (negatieve associatie; hoe korter hoe groter het risico). Op basis van patiënt-specifieke waarden van deze voorspellers kan vervolgens per patiënt in een nomogram worden bepaald of de patiënt in de laag-, gemiddeld- of hoog-risico groep valt. Hetzelfde is toegepast in het tweede model, waarbij de biochemisch recidief-vrije overleving na focale brachytherapie wordt ingeschat. Dit model kan worden gebruikt om patiënten gedurende de follow-up een inschatting te bieden van de kans op succes op basis van karakteristieken die meetbaar zijn na de behandeling, zoals de procentuele daling van de PSA-waarde. Alhoewel deze uitkomsten een eerste indicatie geven van

factoren waar rekening mee gehouden kan worden bij de selectie van patiënten, zal externe validatie nog nodig zijn om het nomogram ook toepasbaar te maken op een nieuw cohort.

Herhaling van plaatselijke inwendige bestraling

Als er opnieuw een lokaal recidief ontstaat na focale brachytherapie, zou kunnen worden overwogen om de behandeling nog een keer te herhalen. Omdat er in de literatuur zeer weinig bekend is over de veiligheid en haalbaarheid van het herhalen van een focale behandeling na primaire algehele bestraling, wordt in **hoofdstuk 9** een patiëntcasus gepresenteerd waarbij het beloop nauwgezet beschreven wordt. Deze patiënt kreeg als primaire behandeling jodiumzaadjes, waarna er na 9 jaar een lokaal recidief werd vastgesteld en behandeld met focale brachytherapie. Twee jaar later ontstaat er opnieuw een lokaal recidief, ditmaal op een andere lokalisatie in de prostaat, en hij wordt opnieuw behandeld met focale brachytherapie. Hierna zakt de PSA-waarde in 6 maanden naar onmeetbaar. De belangrijkste bevinding is dat deze patiënt aan beide behandelingen slechte milde of tijdelijke bijwerkingen overhoudt. Daarmee lijkt herhaalde focale brachytherapie veilig en haalbaar.

Vooruitzichten

De rol van focale therapie tussen de huidige conventionele prostaatkankerbehandelingen zal afhangen van de uitkomsten van langlopende cohortonderzoeken en gerandomiseerde klinische trials, maar zal ook deels afhangen van de mate waarin conventionele behandeling nog verbeterd kan worden qua toxiciteit. De ideale patiënt voor focale therapie in de primaire setting lijkt een patiënt met een lokale, klinisch significante prostaattumor, die veel waarde hecht aan het behoud van zijn urogenitale en erectiele functie. In de setting van een lokaal recidief na radiotherapie blijft het moeilijk inschatten welke patiënten echt baat zullen hebben van opnieuw lokale behandeling. Hier is focale therapie met name geschikt voor patiënten die niet met hormonale therapie willen starten of die niet willen afwachten tot hormonale therapie nodig zal zijn. In de toekomst zouden de uitkomsten van focale brachytherapie mogelijk verbeterd kunnen worden door de dosis te verdelen over meerdere sessies, waarbij uiteraard wel logistieke nadelen komen kijken. Mogelijk zou uitwendige bestraling met de MR-Linac hierbij een geschikt alternatief bieden.

REVIEW COMMITTEE

Prof. dr. P.J. van Diest
Professor of Pathology
University Medical Center Utrecht, the Netherlands

Prof. dr. M.G.E.H. Lam
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University Medical Center Utrecht, the Netherlands

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Professor Outcome Evaluation of Image-guided Interventions
University Medical Center Utrecht, the Netherlands

Prof. dr. R.J.A. van Moorselaar
Professor of Oncologic Urology
Amsterdam UMC, the Netherlands

Dr. H.H.E. van Melick
St. Antonius hospital, the Netherlands

LIST OF PUBLICATIONS

1. **van Son MJ**, Peters M, Moerland MA, Noteboom JL, Eppinga WSC, Davila Fajardo R, Lagendijk JJW, van der Voort van Zyp JRN.
Re-salvage MRI-guided Focal High-dose-rate Brachytherapy for Locally Recurrent Prostate Cancer.
Cureus. 2018 Apr 5;10(4):e2429.v doi: 10.7759/cureus.2429.

2. **van Son MJ**, Peters M, Moerland MA, Kerkmeijer LGW, Lagendijk JJW, van der Voort van Zyp JRN.
Focal Salvage Treatment of Radiorecurrent Prostate Cancer: A Narrative Review of Current Strategies and Future Perspectives.
Cancers (Basel). 2018 Dec 3;10(12):480.

3. **van Son MJ**, Lock MTWT, Peters M, Fransen van de Putte EE, Meijer RP.
Treating Benign Ureteroenteric Strictures: 27-Year Experience Comparing Endourological Techniques With Open Surgical Approach.
World J Urol. 2019 Jun;37(6):1217-1223.

4. Peters M, **van Son MJ**, Moerland MA, Kerkmeijer LGW, Eppinga WSC, Meijer RP, Lagendijk JJW, Shah TT, Ahmed HU, van der Voort van Zyp JRN.
MRI-Guided Ultrafocal HDR-Brachytherapy For Localised Prostate Cancer: Median 4 Year Results Of A Feasibility Study.
Int J Radiat Oncol Biol Phys. 2019 Aug 1;104(5):1045-1053.

5. Shah TT, Gao C, Peters M, Manning T, Cashman S, Nambiar A, Cumberbatch M, Lamb B, Peacock A, **van Son MJ**, van Rossum PSN, Pickard R, Erotocritou P, Smith D, Kasivisvanathan V, British Urology Researchers in Surgical Training (BURST) Collaborative MIMIC Study Group.
Factors Associated With Spontaneous Stone Passage In A Contemporary Cohort Of Patients Presenting With Acute Ureteric Colic. Results From The MIMIC Study (A Multi-centre cohort study evaluating the role of Inflammatory Markers In patients presenting with acute ureteric Colic).
BJU Int. 2019 Sep;124(3):504-513.

6. **van Son MJ**, Peters M, Moerland MA, Lagendijk JJW, Eppinga WSC, Shah TT, Ahmed HU, van der Voort van Zyp JRN.
MRI-Guided Ultrafocal Salvage High-Dose-Rate Brachytherapy for Localized Radiorecurrent Prostate Cancer: Updated Results of 50 Patients.
Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):126-135.

7. **van Son MJ**, Monninkhof EM, Peters M, Lagendijk JJW, van der Voort van Zyp JRN.
Health-Related Quality Of Life After Ultrafocal Salvage High-Dose-Rate Brachytherapy For Radiorecurrent Prostate Cancer: Reporting The Patient's Perspective.
Clin Transl Radiat Oncol. 2020 Oct 17;25:81-87.

8. Connor MJ, Eldred-Evans D, **van Son MJ**, Hosking-Jervis F, Bertoncelli Tanaka M, Reddy D, Bass EJ, Powell L, Ahmad S, Pegers E, Joshi S, Sri D, Wong K, Tam H, Hrouda D, Qazi H, Gordon S, Winkler M, Ahmed HU.
A Multicentre Study Of The Clinical Utility Of Non-Targeted Systematic Transperineal Prostate Biopsies In Patients Undergoing Pre-Biopsy mpMRI.
J Urol. 2020 Dec;204(6):1195-1201.

9. **van Son MJ**, Peters M, Moerland MA, van de Pol SMG, Eppinga WSC, Lagendijk JJW, van der Voort van Zyp JRN
Determining The Safety Of Ultrafocal Salvage High-Dose-Rate Brachytherapy For Radiorecurrent Prostate Cancer: A Toxicity Assessment Of 150 Patients.
Clin Transl Radiat Oncol. 2020 Dec 11;27:1-7.

10. Shah TT, Reddy D, Peters M, Ball D, Hyun Kim N, Gomez Gomez E, Miah S, Eldred-Evans D, Guillaumier S, van Rossum PSN, **van Son MJ**, Hosking-Jervis F, Dudderidge T, Hindley RG, Emara A, McCracken S, Greene D, Nigam R, McCartan N, Valerio M, Minhas S, Afzal N, Lewi H, Ogden C, Persad R, Virdi J, Moore CM, Arya M, Emberton M, Ahmed HU, Winkler M.
Focal Therapy Compared To Radical Prostatectomy For Non-Metastatic Prostate Cancer: A Propensity Score Matched Study.
Prostate Cancer Prostatic Dis. 2021 Jan 28.

11. Nair SM, Peters M, Kurver P, Lavi A, Verhoeff JJC, van der Voort van Zyp JRN, **van Son MJ**, Chin JL.
Long Term Outcomes Of Two Ablation Techniques For Treatment Of Radio-Recurrent Prostate Cancer.
Prostate Cancer Prostatic Dis. 2021 Mar;24(1):186-192.

12. Khoo CC, Eldred-Evans D, Peters M, **van Son MJ**, van Rossum PSN, Connor MJ, Hosking-Jervis F, Bertoncelli Tanaka M, Reddy D, Bass E, Powell L, Ahmad S, Pegers E, Joshi S, Sri D, Wong K, Tam H, Hrouda D, Qazi H, Gordon S, McCracken S, Winkler M, Ahmed HU.
A Comparison Of Prostate Cancer Detection Between Visual-Estimation (Cognitive Registration) And Image-Fusion (Software Registration) Targeted Transperineal Prostate Biopsy.
J Urol. 2021 Apr;205(4):1075-1081.

13. **van Son MJ**, Peters M, Reddy D, Shah TT, Hosking-Jervis F, Robinson S, Lagendijk JJW, Mangar S, Dudderidge T, McCracken S, Hindley RG, Emara A, Nigam R, Persad R, Virdi J, Lewi H, Moore CM, Orczyk C, Emberton M, Arya M, Ahmed HU, van der Voort van Zyp JRN, Winkler M, Falconer A.
Conventional Radical Versus Focal Treatment For Localised Prostate Cancer: A Propensity Score Weighted Comparison Of 6-Year Tumour Control.
Prostate Cancer Prostatic Dis. 2021 May 1. Online ahead of print.

ACKNOWLEDGEMENTS – DANKWOORD

Voor u ligt het proefschrift waar ik de afgelopen 3,5 jaar met veel plezier aan heb gewerkt. Het is het resultaat van een leerzame periode waarin ik veel nieuwe mensen heb ontmoet en waarin ik een heel ander deel van de zorg heb ontdekt. Ik wil graag iedereen bedanken die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift. Naast het werk dat er is geleverd heb ik hele mooie herinneringen aan "mijn onderzoekstijd", waarvoor ik een aantal personen in het bijzonder wil bedanken.

Allereerst mijn copromotoren, **dr. J.R.N. van der Voort van Zyp** en **dr. M. Peters**. Jochem en Max, jullie hebben mij met veel enthousiasme laten kennismaken met de wondere wereld van de radiotherapie. Na mijn wetenschappelijke stage mocht ik onder jullie hoede aan de HDR-studies blijven werken, waarbij we al snel de kans kregen om onze resultaten op congressen te presenteren. Ondanks het sensationele congres in Milaan zag ik mezelf geen radiotherapeut worden, maar ik had de HDR-dagjes met broodjes kroket voor geen goud willen missen.

Prof. dr. ir. J.J.W Lagendijk, Jan, als onderzoeker en als uitvinder ben jij natuurlijk een inspiratie voor velen. Veel dank voor jouw kritische blik op mijn stukken, je hulp bij het uitstippelen van mijn promotietraject en de laagdrempeligheid waarmee ik bij jou terecht kon.

Geachte leden van de beoordelingscommissie, **prof. dr. P.J. van Diest**, **prof. dr. M.G.E.H. Lam**, **prof. dr. H.M. Verkooijen**, **prof. dr. R.J.A. van Moorselaar** en **dr. H.H.E. van Melick**, hartelijk dank voor de tijd en aandacht die jullie hebben gestoken in het lezen en beoordelen van mijn proefschrift.

Voor mijn onderzoek heb ik veel tijd doorgebracht in de HDR-brachy ruimte, waar we soms bijna een hele dag kwijt waren met het behandelen van één prostaatkanker patiënt. Voor elke patiënt was een hoop mankracht en expertise nodig en het was dan ook fijn om met een vast clubje mensen te kunnen werken. Allereerst veel dank aan **dr. ir. M.A. Moerland**, Rien: bij jou kon ik onder andere terecht voor fysica-gerelateerde vragen en mooie plaatjes van dosisverdelingen voor mijn stukken. Het is jammer dat ik jouw HDR-robot nooit live in actie heb gezien! Ook wil ik graag **Rogier Schokker, Katelijne van Vliet, Atousa Yazdani, Maarten Kastelijns, Stefan van der Vegt, Danielle Kelder, Paulien Mulder** en **Jacqueline Verkerk** bedanken voor jullie ondersteuning bij het intekenen, plannen, assisteren en op gang houden van de HDR-behandelingen. Daarnaast in het bijzonder veel dank aan **Diana Louis**, zonder jouw hulp met het versturen van de maandelijkse stapel kwaliteit van leven-vragenlijsten had ik waarschijnlijk de handdoek al in de ring gegooid.

De dagjes "prikken op de HDR" waren voor mij een heerlijke afwisseling met de dagen waarop er echt aan het onderzoek geschreven moest worden. Graag zou ik (naast Jochem) **dr. J.L. Noteboom**, Juus, **drs. W.S.C. Eppinga**, Wietse, **drs. R. Davila Fajardo**,

Raquel en **drs. S.M.G. van de Pol**, Sandrine willen bedanken voor de supervisie en het vertrouwen om het mij uiteindelijk helemaal zelf te laten doen.

Uiteraard wil ik graag alle patiënten bedanken die aan het onderzoek hebben meegedaan. “Mijn” studiegroep bestond uit een verzameling uitermate betrokken patiënten en ik werd dan ook vaak verrast met extra verhalen naast de uitgebreide vragenlijsten die zij toch al moesten invullen. In het bijzonder heb ik warme herinneringen aan de patiënt die uiteindelijk ook op de omslag van dit proefschrift is beland.

Dankzij het grote aantal arts-onderzoekers op de afdeling radiotherapie was er altijd wel iemand om mee te sparren over analyses, om te helpen bij de rompslomp van administratie (helaas een onvermijdelijk onderdeel van onderzoek), of om op vrijdag halverwege de middag het terras mee op te duiken. **Lucas Goense, Madelijn Gregorowitsch, Alice Couwenberg, Bart Pielkenrood, Alicia Borggreve, Jeanine Vasmel, Lois Daamen, Sophie de Mol van Otterloo, Marilot Batenburg, Freek Teunissen, Thomas Willigenburg, Steven Nagtegaal** en **Charisma Hehakaya**: veel dank voor de gezelligheid, de lunch om 12.00 en alle support. Ook heb ik erg veel geluk gehad met mijn kamergenoten **Boris Peltenburg, Veerle Groen** en **Ingmar Defize**, waarmee soms hard gewerkt kon worden en soms de concentratie ver, heel ver te zoeken was (maar de sfeer daardoor des te beter).

Met mijn lieve paranimfen **Fieke Prins** en **Sieske Hoendervangers** heb ik het langst een kamer (en daarmee ook lief en leed) gedeeld. Op maandagochtend kon het werk pas beginnen als alle verhalen van het weekend uitgebreid besproken en geanalyseerd waren. Wij zijn alle drie elkaars paranimfen geweest en daarom voelt het extra bijzonder om deze tijd samen met jullie af te sluiten. Ik ben ontzettend trots op wat jullie al bereikt hebben en hoop dat we elkaar in de kliniek nog tegen zullen komen.

Ik denk nog graag terug aan de bonte verzameling artsen, fysici en onderzoekers op de afdeling radiotherapie van het UMC Utrecht, ofwel “de vrienden van de radiotherapie”. Alhoewel ik de werkelijke betekenis van “k-space” nooit zal begrijpen, heb ik grote bewondering voor de manier waarop ingewikkelde materie op deze afdeling wordt omgezet in innovaties die uiteindelijk een grote impact hebben op de kliniek. Ik ben de afdeling dankbaar voor de kans om de master Epidemiologie te kunnen volgen en in de praktijk te brengen op een plek waar kwalitatief goed onderzoek verricht wordt.

Graag zou ik ook mijn huidige collega's van de urologie in het Spaarne gasthuis willen bedanken voor de support de afgelopen tijd om naast mijn ANIOS-baan de laatste loodjes te voltooien (waaronder het schrijven van dit dankwoord).

Dear **professor Ahmed**, Hash, thank you for inviting me to collaborate with your research group in London to finish one of my research projects. It was amazing to be part of

such a hard-working group of researchers, of whom I would like to particularly thank **Deepika, Taimur** and **Feargus** for their warm welcome and help.

Tijdens mijn promotietraject was er ook tijd voor persoonlijke ontwikkeling op andere vlakken. Zo kwam ik via **Ingelise Nieuwenhuijzen** en **Eveline van Rein** in aanraking met de insanity workouts van Shaun T. Dankzij jullie heb ik ontdekt dat sporten de ultieme vorm van ontspanning is en daar heb ik tot de dag van vandaag veel profijt van. In dat opzicht wil ik ook **Brigitte van den Broek** graag bedanken, die met volle overgave eerst het avontuur van insanity en later ook de hikingtrip in Amerika met mij wilde aangaan.

Zonder de liefde en support van familie en vrienden was het schrijven van dit proefschrift een stuk minder leuk geweest. **Constance van Laarhoven**, wij zijn samen begonnen aan de studie geneeskunde en we zijn ook samen afgestudeerd. Wie had aan het begin van die tijd ooit kunnen denken dat wij uiteindelijk allebei een promotietraject zouden afronden? Jij weliswaar met wat meer vaart dan ik, maar voor het grootste deel toch samen. Ik vind het bijzonder dat ik al die fases zo met jou heb kunnen doorlopen en je kunt voor altijd op mijn vriendschap rekenen.

Wat vriendschap betreft wil ik ook graag mijn jaarclub bedanken voor de inmiddels 10+ jaar dat we het al met elkaar uithouden. Langzaamaan gaan we een volwassener fase in, maar ik had me geen mooiere studententijd dan met jullie kunnen wensen.

Lieve **Joris**, door ons leeftijdsverschil van 4 jaar duurde het even voordat ik niet meer alleen jouw kleine zusje was. Inmiddels hebben we een hechte band opgebouwd en doen we veel samen. Ik kijk uit naar de zomeravonden die we straks op onze sloep kunnen gaan doorbrengen en de vele wintersportvakanties die hopelijk nog zullen volgen. Ik ben blij dat we dat kunnen delen!

Lieve papa en mama, **Ben** en **Annelies**, jullie hadden nooit kunnen bedenken dat jullie kinderen zulke andere carrières zouden kiezen dan jullie zelf gedaan hebben. Al was het niet altijd even goed te volgen, jullie zijn altijd enorm geïnteresseerd geweest in de vorderingen van mijn onderzoek. Ik wil jullie bedanken voor jullie onvoorwaardelijke steun, liefde en de vrijheid die jullie mij geven om mijn leven vorm te geven. Jullie hebben mij geleerd dat niet iedereen met dezelfde hoeveelheid geluk geboren wordt en daardoor besef ik mij goed welke kansen ik heb gekregen. Al krijg je mij niet meer mee op fietsvakantie, kijk ik toch met een goed gevoel terug op de eindsprint als de laatste bocht in zicht kwam.

Lieve **Tim**, samen hebben we de afgelopen tijd een hoop werk verzet in de vrije uren. Jij wist mij altijd te motiveren om nog even een uurtje “iets te doen”, zodat uiteindelijk alles mooi op z'n pootjes terecht is gekomen. Dankjewel voor je support, de manier waarop je alles omzet in iets positiefs en de drive die je daardoor bij mij teweegbrengt om ergens echt voor te kunnen gaan. Ik ben trots om deel uit te mogen maken van jouw team.

CURRICULUM VITAE

Marieke van Son was born on the 7th of November in Rotterdam, where she grew up with her older brother and parents. After graduating from Gymnasium at CSG Calvijn, she took a gap year and went on an exchange program to the United States. She attended High School in Boardman, a small town in the state of Oregon, and lived with a host family. In 2010, she started Medical School at the University Medical Center Utrecht (UMCU).

During the course of Medical School, she had several part-time jobs which all involved her passion for (hands-on) healthcare. She worked nightshifts enucleating eyes from tissue donors for a corneal transplantation clinic (NIIOS, Rotterdam), performed electrocardiograms on call throughout the UMCU, extended her general practitioner's internship by doing evening consultations, supervised during practical anatomy classes in the dissecting room and worked as a surgery assistant for (non-medical) circumcisions.

Between internships, part-time jobs and enjoying life as a student, she developed a specific interest for Urology. She started her first research project at the UMCU Urology department, supervised by dr. M.T.W.T. Lock and dr. R.P. Meijer. Sparked by the academic side of medicine, she started her PhD research right after graduating from Medical School in 2017. Under supervision of prof. dr. ir. J.J.W. Lagendijk, dr. J.R.N. van der Voort van Zyp and dr. M. Peters, she coordinated several trials involving focal brachytherapy for prostate cancer at the UMCU Radiotherapy department. Her focal therapy research developed further by collaborating with the research group of prof. dr. H.U. Ahmed at Imperial College London, where she enjoyed a research fellowship in 2019. To enhance her academic skills, she finished the post-graduate master Epidemiology at the University Utrecht in 2020.

Marieke currently works as a resident not in training (ANIOS) at the Urology department of the Spaarne Gasthuis, under supervision of dr. M.A. Noordzij. Besides her clinical career, she finds balance in doing CrossFit workouts, buying flowers at the local florist and entertaining friends with home-cooked dinners.