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Stereotactic body radiation therapy for prostate cancer after surgical treatment of prostatic obstruction: Impact on urinary morbidity and mitigation strategies

Constance Huck [a], Vérane Achard [b,c], Priyamvada Maitre [d], Vedang Murthy [d], Thomas Zilli [c,e,f,*]

[a] Division of Radiation Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[b] Division of Radiation Oncology, Fribourg Cantonal Hospital, Fribourg, Switzerland
[c] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[d] Tata Memorial Hospital and Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Homi Bhabha National Institute (HBNI), Mumbai, India
[e] Division of Radiation Oncology, Oncology Institute of Southern Switzerland (IOSI), EOC, Bellinzona, Switzerland
[f] Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland

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ABSTRACT

In the past decade, stereotactic body radiation therapy (SBRT) has emerged as a valid treatment option for patients with localized prostate cancer. Despite the promising results of ultra-hypofractionation in terms of tolerance and disease control, the toxicity profile of SBRT for prostate cancer patients with a history of surgical treatment of benign prostate hyperplasia is still underreported. Here we present an overview of the available data on urinary morbidity for prostate cancer patients treated with SBRT after prior surgical treatments for benign prostate hyperplasia. Technical improvements useful to minimize toxicity and possible treatments for radiation-induced urethritis are discussed.

Introduction

Modern radiotherapy techniques and better knowledge of radiobiology have led to the emergence of ultra-hypofractionation as a valid curative treatment option for patients with localized prostate cancer (PCa). Large prospective studies have shown the good tolerance and outcome results of stereotactic body radiotherapy (SBRT), with randomized clinical trials demonstrating the non-inferiority of ultra-hypofractionation in terms of disease control and toxicity compared to standard fractionation or moderate hypofractionation [1–4].

Despite these premises, a thorough understanding and evaluation of the treatment-related side effects of these emerging therapeutic modalities remains critical to ensure their safe adoption in clinical practice. Toxicities affecting the genitourinary (GU) system are undoubtedly a significant problem, greatly affecting the quality of life of PCa patients undergoing curative external beam radiotherapy (EBRT). This is particularly evident in patients with a previous history of surgical treatment of benign prostate hyperplasia (BPH), one of the most commonly benign disease observed in aging men.

Current standard of care for BPH that do not respond to standard medication includes transurethral resection of the prostate (TURP) or adenomectomy through open prostatectomy for patients with prostate glands larger than 80 g [5,6]. Due to the high prevalence of PCa and BPH in aging men, it is therefore not uncommon to observe a prior history of TURP or adenomectomy in patients who are candidates for an EBRT treatment.

While the correlation between EBRT and an increased risk of GU toxicity in patients with a prior TURP treated with standard fractionation has already been demonstrated [7], the impact of ultra-hypofractionated SBRT on the occurrence of urinary side effects after a previous TURP has been less clearly reported.

Prostate SBRT and TURP: current evidence

In a retrospective study on 208 PCa patients treated with definitive SBRT, Gurka *et al.* observed with a median follow-up of 48 months up to 18.3 % of the patients experiencing hematuria, with history of prior procedure(s) for BPH being significantly associated with this event [8]. In another study, Murthy *et al.* used a database to select 50 PCa patients with a previous history of TURP treated with definitive SBRT. These

* Corresponding author at: Radiation Oncology, Oncology Institute of Southern Switzerland (IOSI), EOC CH-6500 Bellinzona, Switzerland.
E-mail address: Thomas.Zilli@eoc.ch (T. Zilli).

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patients were matched by propensity score to a cohort of patients without a prior TURP treated with SBRT during the same time period [9]. With a median follow-up of 26 months, there was no statistically significant difference between non-TURP versus TURP patients in terms of cumulative occurrence of grade ≥ 2 acute (8 % *vs* 6 %) and late GU toxicities (8 % *vs* 12 %), urethral stricture (4 % *vs* 6 %), and incontinence rates (0 % *vs* 4 %).

Four other studies reported the GU toxicity outcomes of patients treated with SBRT with a prior history of BPH treatment. Tambas *et al.* compared prostate-specific antigen kinetics, toxicity, and quality of life of 20 patients treated with a conventionally fractionated volumetric arc therapy (VMAT) technique with 28 patients treated with SBRT. Both cohorts were well balanced regarding the rate of pre-treatment TURP (17.9 % in the VMAT group *vs* 20 % in the SBRT group). All the five patients (17.9 %) with a previous history of TURP treated with SBRT presented a grade 3 GU toxicity compared to only one single patient in the VMAT group (5 %) [10]. In a retrospective study of 47 patients with a history of prior TURP (including multiple TURP) treated with SBRT, Pepin *et al.* found a cumulative late grade ≥ 2 and grade ≥ 3 GU toxicity rate of 49 % and 6.4 %, respectively. At least one episode of transient hematuria was observed in more than 50 % of the patients [11]. In another single-institution series of 24 patients with a history of surgery for BPH treated with a 5-fraction SBRT, cumulative late grade 2 and 3 GU toxicities were observed in 8 (33 %) and 4 (16.7 %) patients, respectively [12]. Notably, patients with a prior adenomectomy or multiple TURPs were at a higher risk of developing severe GU toxicities.

In one of the largest series of PCa patients with a prior history of TURP presented during the last ESTRO 2023 meeting, Maitre *et al.* analyzed the occurrence of late toxicity in 204 patients treated with either moderate hypofractionation (64–68 Gy/25fx, n = 116) or SBRT (35–37.5 Gy/5fx, n = 88). When regarding cumulative late grade 2 GU toxicities, rates were similar among patients treated with moderate hypofractionation or SBRT, 24.3 % and 27 %, respectively. Nevertheless, cumulative grade 3 late urinary toxicity was 7.4 % for the whole cohort, significantly higher with moderate hypofractionation compared to SBRT (11.3 % *vs* 2.2 %, p = 0.01), with hematuria (9.6 % *vs* 2.2 %) and urinary obstruction (4.3 % *vs* 0 %) as the most contributory symptoms for the higher toxicity observed with moderate hypofractionation [13].

Even if the majority of the analyzed studies used SBRT treatments delivering doses between 33.5 Gy and 40 Gy with state of the art daily image-guidance mostly using cone beam computed tomography imaging [8,9,12], strict comparison of the results of these studies remains challenging (Table 1). The different time intervals between TURP and SBRT could possibly have impacted the healing capacity of the surgical cavity [14] and different optimization strategies to the urethra could have influenced the development of long-term GU toxicity. Noteworthy, in the Tambas *et al.* study, urethra and the surgical cavity were not defined as organ at risk, possibly explaining the GU toxicity of grade 3 occurring in all patients treated with SBRT [10].

Despite differences in treatment planning and delivery, it seems that the late GU toxicity rates of patients with a prior history of TURP treated with SBRT and reported in Table 1 are higher than the late GU toxicity

Table 1
Stereotactic Body Radiation Therapy series in prostate cancer patients with transurethral resection of the prostate.

Reference Year of publication	*n* (total/ TURP)	Type of RT	IGRT technique	RT dose, schedule and prescription	Median time between TURP and RT (range)	Median follow-up	GU toxicity grading scale	With TURP GU toxicity grade ≥ 2	Without TURP GU toxicity grade ≥ 2	Other worsening factors
Gurka *et al.* 2015 [8]	208/24	SBRT	Daily IGRT	36.25 Gy and 35 Gy in 5 fx	NA	48 months	CTCAE v 4.0 Hematuria	18.3 %		Use of alpha-blockers Prostate volume
Murthy *et al.* 2019 [9]	100/50	SBRT	Daily kV/ CBCT	35 Gy and 37.5 Gy in 5 fx, EOD	10 months (3–96)	26 months	RTOG/ CTCAE v 4.0 GU ≥ G2	Acute: 6 % (1 patient with G3) Late: 12 % (1 patient with G3 et 1 patient with G4)	Acute: 8 % Late: 8 % (1 patient with G3)	Diabetes mellitus
Tambas *et al.* 2016 [10]	SBRT arm: 28/5 VMAT arm: 20/4	SBRT VMAT	NA	33.5 Gy in 5 fx EOD 75.6 Gy in 35 fx	NA	23 months	CTCAE v 4.0 G3 urinary retention	SBRT arm: 5 patients with G3 VMAT arm: 1 patient with G3		
Pepin *et al.* 2020 [11]	47/47	SBRT	NA	35 and 36.5 Gy in 5 fx, EOD	NA (1–5 years)	56.4 months (Mean FU)	CTCAE v 4.0 GU ≥ G2	Acute: 15 % (No G3) Late: 54 % (5 patients with G3)		Use of alpha- blockers, 5 alpha reductase inhibitors and antimuscarinics
Huck *et al.* 2022 [12]	24/24 (5 adenectomy)	SBRT	Daily kV/ CBCT	35 Gy, 36.25 Gy, and 40 Gy in 5 fx, EOD	54 months (2–204)	45 months	CTCAE v 4.0 GU ≥ G2	Acute G3: 4.2 % Late G2: 33 % Late G3: 17 %		Multiple TURP, adenomectomy
Maitre *et al.* 2023 [13]	204/204	SBRT IMRT (MHRT)	NA	36.25 Gy in 5 fx 68 Gy in 25 fx	10 months (7–16)	37 months	CTCAE v 5.0 GU ≥ G2	SBRT: 27 % G2, 2.2 % G3 MHRT: 24.3 % G2, 11.3 % G3		

Abbreviations: TURP, Transurethral resection of the prostate; NS, not significant; NA, not available; SBRT, Stereotactic Body Radiotherapy; GU, Genitourinary; VMAT, Volumetric Modulated Arc Therapy; MHRT, moderate hypofractionated radiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; EOD, every-other-day; IGRT, Image-guided radiotherapy; kV, kilovoltage.

rates reported in some of the landmark trials of SBRT for localized PCa [2–4]. In the HYPO-RT trial, aiming to show the non-inferiority of a 7-fraction regimen compared to conventional fractionation up to 78 Gy, patients treated with ultra-hypofractionation experienced only a 5 % grade $\geq$ 2 late GU toxicity, according to the Radiation Therapy Oncology Group (RTOG) grading scale. [2]. Similarly, in the PACE-B trial comparing conventionally fractionated radiotherapy to SBRT, 24-month cumulative incidence rates of RTOG grade $\geq$ 2 GU toxicity was observed in 18.3 % of the patients treated in the SBRT arm. [4]. Based on these results, it seems reasonable to assume that patients with a previous history of surgery for BPH are at higher risk of developing late GU toxicities when treated with SBRT than patients who have not undergone this type of treatment.

Mechanisms, mitigation, and management of urinary toxicity post-TURP

Mechanisms of urinary toxicity post-TURP

The urethra and bladder neck are critical structures particularly sensitive to high radiation doses. A correlation between the dose received by prostatic urethra and the bladder neck and the risk of GU toxicity has been demonstrated in several brachytherapy studies [15]. Even for SBRT, in a combined analysis of 23 prospective clinical trials the dose of radiation delivered to the intraprostatic urethra has been associated with the occurrence of acute and late GU toxicity. In this study, each 1 Gy increase in urethral dose was associated to a 0.8 % and 1.0 % increase in acute and late grade 2 toxicity, respectively, after adjusting for age, prostate size, bladder dosimetry, and initial urinary function [16].

It might be speculated that after TURP, the resection cavity and the largest exposure of urothelial mucosa may explain the higher sensitivity to radiation observed in these patients. Fibroblast proliferation, replacement of elastic tissue and muscle fibers following TURP, combined with radiation-induced intravascular coagulation, extensive tissue degeneration and necrosis, represent the main pathophysiological mechanisms increasing the risk of late GU toxicity [17–19]. Interestingly, in favor of this hypothesis, a linear correlation between the volume of the intraprostatic post-surgical cavity and the occurrence of severe GU toxicity has been observed in the study by Huck *et al.* [12]. Using multiparametric magnetic resonance (MR) imaging to delineate the intraprostatic post-surgical cavity, among the 24 SBRT patients analyzed, the five who developed grade 3 GU toxicities had a mean post-surgical intraprostatic cavity volume of 6.3 cc, six-fold larger than the cavity of patients without severe toxicity (1 cc).

Although TURP remains one of the gold standard surgical treatment of BPH [20], other mini-invasive ablative techniques such as Holmium laser enucleation of the prostate (HoLEP) [21–23], or laser vaporization (Greenlight) [24] have been developed to reduce operating time, hospitalization duration, and morbidity. Urolift [25] or prostatic artery embolization [26] are other non-ablative techniques preserving the urethral tissues currently proposed as alternative to standard ablative procedures for patients with symptomatic BPH [27]. Although these less invasive techniques may potentially mitigate the risk of radiation-induced toxicity occurring after SBRT, their supposed preventive effect remains yet to be demonstrated.

Mitigation of urinary toxicity post TURP

Minimizing the dose to the urethra or the resection cavity by limiting hot spots or by reducing the dose delivered compared to the whole gland could be a promising approach to limit the rate of GU toxicities occurring in PCa patients undergoing SBRT after a previous TURP [28]. Of note, long-term results of a phase II randomized trial of PCa patients treated with a linac-based technique to 36.25 Gy in 5 fractions and limiting the dose to the urethra at 32.5 Gy (equivalent to 74 Gy in 2 Gy per fraction using a $\alpha/\beta = 1.5$ Gy), showed that 5 year late grade $\geq$ 2 GU toxicity rates were below 25 %, with only one patient presenting late grade 3 GU toxicity [29]. By analogy, protection of the resection cavity in TURP-treated patients, with a much larger surface of exposed healthy tissue, would likely be an attractive strategy to reduce the risk of radiation-induced GU toxicity. Proper visualization and definition of the urethra and resection cavity using dedicated MR imaging protocols as well as routine implementation of standard of care image-guidance modalities remain the essential requirements needed to implement a "cavity-sparing" SBRT technique for mitigating urinary toxicity post-TURP [30]. Of note, use of MRI-guided SBRT techniques with daily online adaptive represents certainly an appealing treatment technique for treating these patients. As observed in a systematic review and *meta*-analysis, acute grade 2 or higher GU or GI toxicity can significantly be reduced using a MRI-guided adaptive SBRT technique compared to a fiducial or CT-guided non-adaptive prostate SBRT (12 % and 5 % on average, respectively) [31].

Management of urinary toxicity post TURP

If prevention of GU toxicity fails, several treatment approaches of post radiation cystitis and urethritis are currently proposed. The approach to managing radiation cystitis depends on the extent of symptoms. For cases classified as Grade 1 and Grade 2, the main goal is usually to relieve symptoms. When symptoms mainly involve increased frequency and urgency, anticholinergic drugs are commonly used to provide relief. In addition, for all levels of severity, initial treatment may involve bladder irrigation, which can also help remove blood clots in cases of evident macrohematuria [32]. In selected cases, procedures such as fulguration using alum or silver nitrate might be employed directly to stop macrohematuria [33,34]. Hyperbaric oxygen therapy (HBOT) represents another approach proposed to treat refractory cases of post-radiation cystitis or urethritis after failure of standard drug medication. By promoting oxygenation of the tissues, it participates in healing by restoring fibroblast growth and collagen synthesis, as well as by promoting neoangiogenesis and the development of epithelialization [35]. Its use in post-radiation bladder and urethral lesions has been demonstrated in several retrospective studies [36,37] and confirmed by a phase II-III randomized controlled trial (RICH-ART) [38].

Conclusions

Based on literature, appropriate patient selection is needed when SBRT is proposed in patients with a history of surgical treatment of BPH, especially when multiple TURPs or adenomectomy procedures have been performed. Use of adaptive MRI-guided SBRT implementing "cavity-sparing" techniques may represent an interesting strategy for mitigating urinary toxicity in patients with a prior history of TURP of the prostate, although its use requires further investigation.

Author's contributions

All authors contributed, read, and approved the final manuscript.

CRediT authorship contribution statement

Constance Huck: Data curation, Formal analysis, Writing, Validation. **Vérane Achard:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Validation. **Priyamvada Maitre:** review & editing, Validation. **Vedang Murthy:** review & editing, Validation. **Thomas Zilli:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial

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