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INVITED REVIEW

The march toward single-fraction stereotactic body radiotherapy for localized prostate cancer—*Quo Vadimus*?

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Abstract

Purpose Stereotactic body radiotherapy (SBRT) is an emerging treatment option for localized prostate cancer. There is increasing interest to reduce the number of fractions for prostate SBRT.

Methods We provide a narrative review and summary of prospective trials of different fractionation schedules for prostate SBRT, focusing on efficacy, toxicities, and quality of life outcomes.

Results There are two randomized phase 3 trials comparing standard external beam radiotherapy with ultra-hypofractionated radiotherapy. HYPO-RT-PC compared 78 Gy in 39 fractions vs 42.7 Gy in 7 fractions (3D-CRT or IMRT) showing non-inferiority in 5-year biochemical recurrence-free survival and equivalent tolerability. PACE-B trial compared 78 Gy in 39-fraction or 62 Gy in 20-fraction vs 36.25 Gy in 5-fraction prostate SBRT, with no significant differences in toxicity outcomes at 2 years. Five-year efficacy data for PACE-B are expected in 2024. Five-fraction prostate SBRT is currently the most common and well-established fractionation schedule with multiple prospective phase 2 trials published to date. There is more limited data on 1–4 fraction prostate SBRT. All fractionation schedules had acceptable toxicity outcomes. Experience from a high-dose-rate brachytherapy randomized trial showed inferior efficacy with single-fraction compared to two-fraction brachytherapy. Hence, caution should be applied in adopting single-fraction prostate SBRT.

Conclusion Two-fraction SBRT is likely the shortest fractionation schedule that maintains the therapeutic ratio. Several randomized trials currently recruiting will likely provide us with more definite answers about whether two-fraction prostate SBRT should become a standard-of-care option. Enrollment of eligible patients into these trials should be encouraged.

Keywords Prostate cancer · Stereotactic body radiotherapy · Hypofractionation

Introduction

Radiotherapy is an effective curative treatment option for men with localized prostate cancer. External beam radiotherapy (EBRT) for prostate cancer is conventionally delivered as daily fractions of 1.8–2.0 Gy, five fractions per week, over approximately 8 weeks. The advent of radiotherapy technologies along with better understanding of the radiobiology of prostate cancer have allowed for treatment delivery using stereotactic body radiotherapy (SBRT) techniques over fewer number of fractions. The optimal number of fractions for prostate SBRT, however, remains to be determined. In this review, we summarize the rationale of, evidence for, and future direction of prostate SBRT.

Rationale for ultra-hypofractionated radiotherapy

The probability of cell survival following fractionated radiotherapy is classically governed by the linear-quadratic model, which is characterized by a parameter called the alpha–beta (α/β) ratio. While the α/β ratio for most tumour is generally 10 Gy and above, Brenner and Hall first hypothesized in 1999 that the α/β ratio for prostate

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cancer is much lower at approximately 1.5 Gy [1]. It is still debatable as to the precise α/β ratio for prostate cancer, and in the most recent meta-analyses using data of more than 10,000 patients from 14 randomized trials, Vogelius et al. suggested that the best estimate of α/β ratio for prostate cancer is 1.6 Gy (95% confidence interval of 1.3–2.0 Gy) [2]. On the other hand, the α/β for late complications for adjacent dose-limiting organ-at-risk (OAR), such as rectum, has been estimated to be around 3 Gy [3, 4], which is higher than that for prostate cancer. Exploiting the differential α/β ratio between prostate cancer and the OAR has allowed us to improve the therapeutic ratio of radiotherapy for prostate cancer by increasing the fraction size for prostate radiotherapy. Several phase 3 randomized trials, including CHHiP [5], PROFIT [6], and RTOG0415 [7], have shown that moderate hypofractionation radiotherapy (2.4–3.4 Gy per fraction) is non-inferior to conventionally fractionated radiotherapy in terms of toxicities. The moderate hypofractionated schedule is now adopted as the standard-of-care treatment for prostate cancer, and endorsed by ASTRO, ASCO and AUA [8]. There is now increasing interest to further increase the fraction size, delivering >5 Gy per fraction (i.e., ultra-hypofractionated schedule), and to reduce the number of fractions for prostate SBRT. At the same time, it is important to recognize that there are uncertainties in the α/β ratio for prostate cancer in the ultra-hypofractionated setting, whereby the α/β ratio is postulated to increase with increased fraction size [2].

Evidence for ultra-hypofractionated radiotherapy

Seven fractions

HYPO-RT-PC is the first phase 3 randomized trial comparing conventional fractionated (78 Gy in 39 fractions) with ultra-hypofractionated schedule (42.7 Gy in 7 fractions) for prostate cancer [9]. At a median follow-up of 5 years, the 7-fraction schedule was reported to be non-inferior to 39-fraction schedule in terms of failure-free survival—84% in both treatment groups. There was slight increase in acute physician-reported grade ≥ 2 urinary toxicities and patient-reported urinary and bowel symptoms with seven-fraction radiotherapy [9], while late toxicities and patient-reported quality of life were similar in both treatment groups [10]. However, it is important to note that approximately 80% of treatment in both treatment arms in the trial was delivered using three-dimensional conformal radiotherapy technique (3D-CRT) while 20% had intensity-modulated radiotherapy (IMRT), and none had SBRT techniques by today's standard.

Five fractions

Early experience of prostate SBRT was most commonly delivered over five fractions, with multiple prospective phase 2 trials published over the past decades (Table 1) [11–21]. Pooling data from more than 2000 men enrolled in multiple phase 2 trials treated between 2000 and 2012, Kishan et al. reported excellent efficacy outcomes with 7-year cumulative incidence of biochemical failure of 4.5% and 10.2% in patients with low-risk and intermediate-risk prostate cancer, respectively [22]. The overall incidence of grade 2 toxicities was low in the acute (9.0% for GU toxicities and 3.3% for GI toxicities) and late setting (10-year cumulative incidence, 13.4% GU toxicities and 4.5% GI toxicities). However, it is important to note that there is large range of toxicity rate reported in each individual trials (Table 1). This could potentially be attributed to the varying prescribed dose, and SBRT techniques such as planning target volume (PTV) margin, immobilization devices as well as image guidance used.

There is, however, only one phase 3 randomized multicenter international trial (PACE-B) that has compared conventional (78 Gy in 39 fractions) or hypofractionated (62 Gy in 20 fractions) schedule with ultra-hypofractionated schedule (36.25 Gy in 5 fractions) delivered using high-precision SBRT techniques [23, 24]. This trial again confirmed the overall low toxicities associated with five-fraction prostate SBRT. In the most recent publication of the 2-year toxicities' outcomes from PACE-B trial, which was the co-primary endpoints, the overall RTOG grade ≥ 2 GU and GI toxicities were low, with no significant differences between the SBRT and conventional/ hypofractionated arms [24]. The grade ≥ 2 GU toxicities assessed using RTOG scale was 3% in the SBRT arm, and 2% in the conventional/ hypofractionated arm ($P=0.39$). However, using the CTCAE scoring system, the grade ≥ 2 GU toxicities were statistically significantly higher in the SBRT arm (11.8%) compared to conventional/ hypofractionated arm (5.8%) ($P=0.006$) [24]. This highlighted the sensitivity of different toxicity scoring system in toxicity detection, which may yield varying results, and it is important to take into consideration the scoring system used when comparing toxicities rate across trials. The co-primary endpoint of 5-year biochemical recurrence-free survival is expected to be reported in 2024.

Four fractions

There were several phase 2 trials that investigated four-fraction prostate SBRT (Table 1) [25–29]. One of the largest cohorts was from a multi-institutional phase 2 trial of

Table 1 Selected prospective trials of five or fewer fractions prostate SBRT

Study	Year	Number of patients	Dose/ fractions	Median follow-up, months	Oncological outcomes	Acute toxicity outcomes	Late toxicity outcomes
Five fractions							
Madsen et al. [11]	2000–2004	40	33.5 Gy in 5 fx	41	4-yr BFS: 90%	G2 + GU: 22.5% G2 + GI: 12.5%	G2 + GU: 20% G2 + GI: 7.5%
King et al. [12]	2003–2009	67	36.25 Gy in 5 fx	32	4-yr BFS: 94%	NR	G2 + GU: 8.5% G2 + GI: 2%
Katz et al. [13]	2006–2010	515	35–36.25 Gy in 5 fx	84	8-yr BFS: 94% (LR), 84% (IR), 65% (HR)	NR	NR
Musunuru et al. [14] Alayed et al. [15]	2006–2008	84	35 Gy in 5 fx	115	5-yr BF: 2.5% 10-yr BF: 12.8%	G2 + GU: 20% G2 + GI: 10%	G2 + GU: 5% G2 + GI: 7%
McBride et al. [16]	2006–2011	45	36.25–37.5 Gy in 5 fx	44.5	3-yr BFS: 97.7%	G2 + GU: 19% G2 + GI: 7%	G2 + GU: 17% G2 + GI: 12%
Meier et al. [18]	2008–2011	309	40 Gy in 5 fx	61	5-yr BFS: 97%	G2 + GU: 26% G2 + GI: 8.1%	G2 + GU: 13.3% G2 + GI: 2%
Kataria et al. [19]	2008–2011	145	35–37.5 Gy in 5 fx	67.2	5-yr BFS: 98.5% (LR), 95% (IR)	NR	NR
Musunuru et al. [14] Alayed et al. [15]	2010	30	40 Gy in 5fx	83	5-yr BF: 3.3%	G2 + GU: 17% G2 + GI: 10%	G2 + GU: 13% G2 + GI: 20%
Alayed et al. [20]	2012–2013	152	40 Gy in 5 fx	62	5-yr BF: 3–7%	G2 + GU: 34% G2 + GI: 14%	G2 + GU: 55% G2 + GI: 22%
Kishan et al. [21]	2020–2021	156	40 Gy in 5 fx	3	NR	G2 + GU: 24.4%[a]–43.4%[b] G2 + GI: 0%[a]–10.5%[b]	NR
Four fractions							
Fuller et al. [25]	2007–2012	259	38 Gy in 4 fx	60	5-yr BFS: 100% (LR), 89% (IR)	G2 + GU: 36.2% G2 + GI: 6.9%	G2 + GU: 14.7% G2 + GI: 3.4%
Jabbari et al. [27]	NR	20	38 Gy in 4 fx	18	BF: 0%	G2 + GU: 42% G2 + GI: 11%	NR
Aluwini et al. [26]	2008–2011	50	38 Gy in 4 fx	23	2-yr BFS: 100%	G2 + GI: 23% G2 + GI: 14%	G2 + GU: 16% G2 + GI: 3%
Pontoriero et al. [28]	2008–2013	21	38 Gy in 4 fx	21	NR	G2 + GU: 0% G2 + GI: 5%	G2 + GU: 5% G2 + GI: 5%
Kawakami et al. [29]	2015–2018	55	36 Gy in 4 fx	36	3-yr BFS: 89.8%	G2 + GU: 9% G2 + GI: 11%	G2 + GU: 15% G2 + GI: 9%
Three fractions							
Magli et al. [30]	2015–2019	59	40 Gy in 3 fx	20	NR	G2 + GU: 14% G2 + GI: 9%	NR
Two fractions							
Alayed et al. [31]	2014	30	26 Gy in 2 fx	49	4-yr BF: 0%	G2 + GU: 67% G2 + GI: 3%	G2 + GU: 63% G2 + GI: 20%
Ong et al. [32]	2018	30	26 Gy in 2 fx (DIL boost 32 Gy)	44	4-yr BF: 8.3%	G2 + GU: 57% G2 + GI: 3%	G2 + GU: 50% G2 + GI: 10%
One fraction							
Greco et al. [36]	2015–2017	15	24 Gy in 1 fx	48	4-yr BFS: 64%	G2 + GU: 0% G2 + GI: 0%	G2 + GU: 7% G2 + GI: 0%
Zilli et al. [37]	2017–2018	6	19 Gy in 1 fx	3	NR	G2 + GU: 50% G2 + GI: 0%	NR

Gy Gray, *fx* fractions, *NR* not reported, *LR* low risk, *IR* intermediate risk, *HR* high risk, *EOD* every other day, *BF* biochemical failure, *BFS* biochemical failure-free survival

[a]MR-guided arm (2 mm PTV margin)

[b]CT-guided arm (4 mm PTV margin)

259 men treated with a non-coplanar robotic SBRT system to a dose of 38 Gy in 4 fractions [25]. The 5-year biochemical recurrence-free survival were 100% and 89% in men who had low-risk and intermediate-risk prostate cancer, respectively [25]. The acute grade ≥ 2 GU and GI toxicities were 36.2% and 6.9%, respectively, while the 5-year cumulative grade ≥ 2 GU and GI toxicities were 15% and 3.4%, respectively. There was one patient (0.4%) who had cystoprostatectomy for cystourethritis. Overall, across all four-fraction prostate SBRT trials, the risk of acute and late GU and GI toxicities were low (Table 1).

Three fractions

Only one multi-institutional phase 2 trial of three-fraction prostate SBRT has been reported to date (Table 1) [30]. All men in the trial were treated to 40 Gy in three fractions, with urethra-sparing approach, limiting the urethra maximum dose to 33 Gy in three fractions. The study met its primary endpoint in terms of acute toxicity, with 14% and 8% acute grade ≥ 2 GU and GI toxicities, respectively.

Two fractions

There were two published phase 2 trials of two-fraction prostate SBRT—2STAR and 2SMART—both from the Sunnybrook Odette Cancer Centre (Table 1) [31, 32]. In the 2STAR trial, 30 men with low- to intermediate-risk prostate cancer were treated with 26 Gy in 2 fractions weekly [31], while in the 2SMART trial, another 30 men with low- to intermediate-risk prostate cancer were treated with 26 Gy in 2 fractions with addition of DIL boost to 32 Gy [32]. In both trials, men were treated with GU-Lok™, a rectal immobilization device [33], which allowed for tighter PTV margins of 2–3 mm. In the updated pooled analyses of both trials with median follow-up of close to 6 years, there was one biochemical failure reported in each trial—at 62 months in 2STAR and 44 months in 2SMART [34]. There were no significant differences in GU and GI toxicities with or without DIL boost. The cumulative acute and late CTCAE grade ≥ 2 GU toxicities were 62% (37/60) and 57% (34/60), respectively, while the cumulative acute and late GI toxicities were 3% (2/60) and 15% (9/60), respectively. However, higher proportion of patients who had DIL boost reported minimal clinical important changes in late urinary quality of life assessed using the EPIC-26 questionnaire (50% vs 21%).

While the overall grade ≥ 2 GU toxicities in both two-fraction prostate SBRT trials appear higher than most of the five-fraction prostate SBRT trials (Table 1), it is important to recognize that these grade ≥ 2 GU toxicities were likely artificially over-estimated due to the low threshold for alpha blocker initiation in both trials, which by definition is considered 'grade 2 GU toxicity'. The authors investigated this further by differentiating 'medication-related' vs 'non-medication-related' GU toxicities in the 2SMART trial, and reported that 15/30 (50%) and 2/30 (7%) acute grade ≥ 2 GU toxicities were medication and non-medication related, while 15/30 (50%) and 0/30 (0%) late grade ≥ 2 GU toxicities were medication and non-medication related—almost all grade ≥ 2 GU toxicities were due to alpha blocker prescription [32]. This, again, highlighted caution in direct cross-trial comparison of treatment-related toxicities rate in the literature. In fact, when the authors compared the patient-reported urinary quality of life (QOL) between two-fraction and five-fraction prostate SBRT from the same institution, there were no significant differences in urinary QOL outcomes between the two prostate SBRT fractionation schedules [35].

Single fraction

There were two prospective trials on single-fraction prostate SBRT [36, 37]. In a phase 2 PROSINT trial, 30 men were randomized to either 24 Gy in 1-fraction or 40 Gy in 5-fraction prostate SBRT [36]. No statistically significant differences in the acute and late GU and GI toxicities between the arms were observed. There were three patients in the single-fraction prostate SBRT arm who developed biochemical failure at a median of 27 months, with 4-year biochemical disease-free survival of 77%. There was a separate phase 1 prostate SBRT trial whereby six men were treated with 19 Gy in one fraction [37]. A urethra-sparing technique was applied limiting the prostatic urethra (defined based on foley catheter) to 17 Gy. All patients were followed-up to 3 months, with half of the patients (50%) reporting grade ≥ 2 GU toxicities, and no grade ≥ 2 GI toxicities.

Lessons learnt from high-dose-rate (HDR) brachytherapy

The move toward single treatment for prostate cancer is an appealing option from patients' convenience and potential healthcare cost saving point of view. Currently, low-dose-rate (LDR) brachytherapy is the only established 'single-treatment' radiotherapy option for localized prostate cancer with long-term outcome data [38]. However, the underlying radiobiology and mechanisms of cell kill with LDR brachytherapy is different from that of fractionated SBRT [39]. On the other hand, high-dose-rate (HDR) brachytherapy in some way resembles SBRT with delivery of high ablative dose over single or few fractions. However, based on experience and data from HDR brachytherapy, caution is advised in adopting single-fraction SBRT for prostate cancer [40]. In the phase 2 randomized trial of 27 Gy in 2-fraction vs 19 Gy in 1-fraction HDR brachytherapy monotherapy in

Table 2 Ongoing trials comparing five-fraction vs two-fraction stereotactic body radiotherapy (SBRT) for prostate cancer

Trial	Trial number	Treatment platform	Number of patients	Control arm	Experimental arm	Primary endpoint
HERMES	NCT04595019	MR-Linac	46	36.25 Gy in 5 fx (DIL boost 40 Gy)	24 Gy in 2 fx (DIL boost 27 Gy)	Acute GU toxicities (CTCAE)
FORT	NCT04984343	MR-Linac	136	37.5 Gy in 5 fx	25 Gy in 2 fx	GI QOL (EPIC 26)
ISMART	NCT05600400	CT-Linac	144	40 Gy in 5 fx	27 Gy in 2 fx	Sexual QOL (EPIC-26)
SABR-DUAL	MOH_2022-08-30_012007	CT-Linac	608	40 Gy in 5 fx	27 Gy in 2 fx	Freedom from disease progression

170 patients, Morton et al. reported the 5-year biochemical disease-free survival and cumulative incidence of local failure of 95% and 3% in the 2-fraction arm, and 74% and 29% in the single-fraction arm, respectively [40]. Updated results presented at the American Brachytherapy Society meeting 2023 showed 8-year biochemical disease-free survival of 82% and 61% in the two-fraction and single-fraction arm respectively (personal communication, G. Morton June 2023; abstract citation in press).

Subsequent trials aimed to investigate whether dose escalation in single-fraction HDR brachytherapy may improve the efficacy [41, 42]. In a phase 2 Canadian trial in 60 patients treated with 19 Gy single-fraction HDR brachytherapy to the whole gland, dose escalation of the DIL (median D90% of 27.2 Gy) had similar efficacy outcomes as the single-fraction arm of the abovementioned Morton trial [43]—the 3-year and 4-year cumulative incidence of biochemical failure were 15% and 32%, respectively [41]. In separate phase 2 UK trial of 50 patients treated with 19 Gy in single-fraction HDR brachytherapy with dose escalation of DIL up to 21 Gy (D90% ranging from 21.8–25.8 Gy), the 5-year biochemical free survival was in the range of 76–88%, depending on prescription methods to the non-DIL prostate [42]. Overall dose escalation to the DIL did not significantly improve the efficacy in single-fraction HDR brachytherapy. In fact, in a dosimetric analyses of local failure following single-fraction HDR brachytherapy, large proportion of local failure occurred in the DIL, which was dose escalated [44].

These data suggest that the poor efficacy from single-fraction HDR brachytherapy is not simply explained by inadequate dose, and that there is likely other radiobiological mechanism at play [40]. The radiobiological rationales for fractionated radiotherapy include overcoming hypoxia and allowing redistribution of cells through different phases of cell cycles. Previous hypoxia functional imaging studies have suggested that fractionated radiotherapy induces early prostate tumor reoxygenation [45]; however, there is no opportunity for reoxygenation if treatment is delivered over single fraction [40]. Similarly, single-fraction treatment limits the opportunities for cell kill whereby some cancer cells may be in relatively radioresistant phases of cell cycle during the single-fraction treatment, whereas treatment over two or more fractions may allow redistribution of cancer cells into more radiosensitive phases of cell cycle in the subsequent fraction(s). While there is currently limited data in single-fraction SBRT [36, 37], it makes sense to apply the lessons learnt from single-fraction HDR brachytherapy to single-fraction SBRT. Hence, we believe that two-fraction prostate SBRT is as low as we could safely achieve from efficacy point of view. A recent comparison of prospective data from two-fraction SBRT and two-fraction HDR brachytherapy suggested that two-fraction SBRT yields similar efficacy, toxicities, and quality of life outcomes as two-fraction HDR brachytherapy [46].

The future of ultra-hypofractionated prostate SBRT

Five-fraction prostate SBRT is currently the most common fractionation schedule, supported by phase 3 randomized data [23, 24]. While reducing prostate SBRT to two fractions is an appealing option, there is a need for randomized evidence with long-term follow-up data to confirm both the efficacy, toxicity, and quality of life outcomes before it will become a standard-of-care treatment option. Currently, there are at least four recruiting trials comparing two-fraction vs five-fraction prostate SBRT, including the HERMES trial (NCT04595019) [47], FORT trial (NCT04984343), iSMART trial (NCT05600400), and SABR-DUAL trial (Table 2).

In our zest to move toward fewer fractions SBRT, it is paramount that effort is also put into further reducing or minimizing SBRT-related toxicities and the impact on QOL. This is especially important given that majority of men with localized prostate cancer will be cured and will be living with long-term treatment-related sequelae. While the overall toxicities of prostate SBRT are already reasonably low, there is various armamentarium available in the space of radiation oncology to further improve this. Advancement

in technology with the integration of on-board magnetic resonance imaging (MRI) scanners with Linac machines [48] allows for more accurate delineation of prostate, capacity to replan for anatomy of the day, as well as monitoring of prostate motion during treatment [49]. Collectively, all these advantages allow us to reduce the PTV margins, thereby reducing dose to neighboring organs at risk, which is expected to translate into reduced treatment-related toxicities. The benefits of PTV margin reduction on MR-Linac for prostate SBRT has been shown in the MIRAGE trial, whereby men treated on MR-Linac with 2 mm PTV margin had significantly lower acute GU and GI toxicities compared to those treated on standard CT-Linac with 4 mm PTV margin (Table 1) [21]. The introduction of rectal spacing device is also another approach to reduce prostate SBRT-related toxicities [50]. By increasing the spatial separation between prostate and the rectum, rectal spacing device allows us to deliver ablative radiation dose to the prostate while respecting the dose constraints of the rectum. This has been shown in a randomized trial in hypofractionated radiotherapy to result in improved rectal dosimetry and reduced acute grade ≥ 2 GI toxicities [51]. Other rectal immobilization devices, such as GU-Lok [33] and endorectal balloon [52], are different ways that can be used in conjunction with prostate SBRT to reduce treatment-related toxicities.

Conclusion

In summary, there is early prospective evidence to suggest that five or fewer fractions prostate SBRT is safe with low toxicities. While single-fraction prostate SBRT is appealing in many ways, experience from HDR brachytherapy suggests caution in clinical implementation of single-fraction prostate SBRT. Two-fraction prostate SBRT, we believe, is likely to be as low as we could go. However, randomized data with long-term efficacy and toxicity outcomes are required before two-fraction prostate SBRT may become the standard of care for localized prostate cancer.

Declarations

Conflict of intrest Dr Ong: no conflicts. Dr Loblaw: Grants/Research Support: TerSera, Tolmar. Honoraria/Travel: Astellas, Bayer, Janssen, Knight, Sanofi, TerSera Advisory Boards/Consulting: Astellas, Bayer, Janssen, Sanofi, TerSera. Financial Group: Sunnybrook Radiation Oncology Associates Patents/Licenses: Endorectal immobilization device (GU-Lok), Molli.

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