Current Urology Reports (2019) 20: 53
https://doi.org/10.1007/s11934-019-0918-0

PROSTATE CANCER (S PRASAD, SECTION EDITOR)

Hypofractionated Radiotherapy for Localized Prostate Cancer: When and for Whom?

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Published online: 29 July 2019

Abstract

Purpose of Review To summarize recent evidence concerning the use of moderately hypofractionated external beam radiotherapy, defined as 2.4–3.4 Gy per fraction, and ultrahypofractionated external beam radiotherapy (also known as stereotactic body radiotherapy [SBRT]), defined as at least 5 Gy per fraction, in men with localized prostate cancer.

Recent Findings Taken together, a number of recently completed randomized trials show that moderately hypofractionated radiotherapy confers similar biochemical control compared to conventionally fractionated radiotherapy without increasing late toxicity. These effects appear to extend across all baseline clinical risk groups. Several single-arm phase II studies, as well as a recently published large-scale randomized trial comparing SBRT with conventional fractionation, show very promising biochemical control and favorable acute and late treatment-related morbidity with the use of SBRT in predominantly low- and intermediate-risk prostate cancer.

Summary As it is associated with similar prostate cancer control and toxicity while improving patient convenience and reducing cost, moderate hypofractionation is a preferred alternative to conventional fractionation in a majority of men with localized prostate cancer choosing radiotherapy as their primary treatment modality. To date, studies conducted largely in low- and intermediate-risk prostate cancer report encouraging oncologic outcomes and acceptable toxicity with SBRT. Mature results of phase III trials evaluating five-fraction SBRT regimens are eagerly awaited.

Keywords Prostate cancer · Hypofractionated radiotherapy · External beam radiotherapy

Introduction

External beam radiotherapy (RT) is a curative local treatment option in patients with localized prostate cancer. In the ProtecT trial, radical prostatectomy and prostate RT combined with 3–6 months of androgen deprivation therapy (ADT) yielded equivalent prostate cancer-specific survival (PCSS) and progression-free survival at 10 years in patients with PSA screening-detected localized prostate cancer [1]. The combination of RT and ADT has been shown to confer greater overall survival (OS) compared to either therapy alone in patients with high-risk localized and locally advanced prostate cancer in large-scale randomized trials [2–5].

The biological effect of radiation therapy on a tissue has been modeled and is described by the tissue's alpha-beta ratio. Tissues with lower alpha-beta ratios demonstrate relatively greater fractionation sensitivity. Specifically, relatively large changes in isoeffective dose arise when dose per fraction is changed for tissues with low alpha-beta ratios compared to those with higher ratios [6]. Prostate cancer is uncommon among solid tumors in that its alpha-beta ratio is estimated to be lower than that of surrounding organs at risk [7–9]. This relationship makes the use of hypofractionation, namely, the delivery of more than the conventional 2 Gy per fraction, attractive as a means of potentially improving the therapeutic ratio. Hypofractionated RT has been somewhat arbitrarily subdivided into two distinct approaches: moderate hypofractionation, defined here as 2.4–3.4 Gy per fraction,

This article is part of the Topical Collection on *Prostate Cancer*

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and ultrahypofractionation or SBRT, defined as at least 5 Gy per fraction [10•]. In either form, it has the obvious added advantage of reducing the number of treatment fractions and overall treatment time. On this basis, it has been found to be more cost-effective than conventionally fractionated RT [11•, 12].

Numerous prospective trials, including a number of large-scale randomized trials, evaluating hypofractionated RT have been reported in the past few years [13, 14, 15•, 16, 17•]. A sizeable increase in the utilization of hypofractionation in localized prostate cancer has been observed in a population-based study conducted in the USA over this period. Interestingly, use of SBRT has accounted for a far greater proportion of this increase than has moderate hypofractionation, despite generally higher-level evidence supporting use of the latter [18•]. In what follows, taking account of recent findings, we review the indications, patient selection, and benefits and adverse effects of hypofractionated RT in localized prostate cancer.

Methods

For the purposes of this narrative review, we have adopted the subdivision of hypofractionated RT regimens into moderate hypofractionation and ultrahypofractionation/SBRT as defined above [10•]. Regarding the moderate hypofractionation literature, only randomized trials were considered in this review. Regarding the SBRT literature, randomized trials, prospective nonrandomized studies, or pooled analyses of nonrandomized studies were considered. While there is some heterogeneity in the reporting of efficacy in trials of RT in localized prostate cancer, an endpoint that includes biochemical recurrence as the predominant event is almost universal. Accepting slight differences in endpoint definitions across trials, for the purposes of this review, the primary efficacy endpoint is defined as biochemical or clinical disease-free survival (bDFS). Other outcomes of interest in this review include PCSS and OS (where reported), clinician and patient-reported toxicities, and quality of life (QOL).

Results

Moderate Hypofractionation

Three large phase III randomized controlled trials (RCTs)—CHHiP, PROFIT, and RTOG 0415—have demonstrated the non-inferiority of moderately hypofractionated RT to conventionally fractionated RT [13••, 15•, 17•]. Beyond this, a number of single-institution RCTs have also compared various schedules of moderate hypofractionation with conventional fractionation [16, 19, 20]. The design details and principal results of the multicenter studies are summarized in Table 1.

Table 1 Completed multicenter randomized controlled trials comparing moderate hypofractionation with conventional fractionation

Study (sample size)	Risk group distribution	ADT use	Dose	$EQD2_{1.5}$/$EQD2_3$	Efficacy			Clinician-reported toxicity		
					5-year bDFS	HR	CI	Any grade ≥ 3	Late GU grade ≥ 2	Late GI grade ≥ 2
CHHiP (n = 3216)	Low: 15%	97% (3–6 months)	74Gy/37Fx	74/74	88.3%	–	–	< 1%	9.1%	13.7%
	Int: 73%		60Gy/20Fx	77/72	90.6%	0.84	0.68–1.03	< 1%	11.7%	11.9%
	High: 12%		57Gy/19Fx	73/68	85.9%	1.2	0.99–1.46	< 1%	6.6%	11.3%
PROFIT (n = 1206)	Int	None	78Gy/39Fx	78/78	85%	–	–	3%	22%	13.9%
			60Gy/20Fx	77/72	85%	0.96	0.77–1.2	2%	22%	8.9%*
RTOG 0415 (n = 1092)	Low	None	73.8Gy/41Fx	70/71	85.3%	–	–	2.4%	22.8%	14%
			70Gy/28Fx	80/77	86.3%	0.85	0.64–1.14	4.1%	29.7%*	22.4%*
HYPRO (n = 820)	Int: 26%	67%	78Gy/39Fx	78/78	77.1%	–	–	39%[a]	12.9% (grade ≥ 3)	17.7%[b]
	High: 74%		64.6Gy/19Fx	90.4/82.7	80.5%	0.86	0.63–1.16	41.3%[a]	19% (grade ≥ 3)*	21.9%[b]

*Statistically significant difference

[a] Cumulative incidence at 2 years

[b] Cumulative incidence at 3 years

ADT androgen deprivation therapy, *EQD2* equivalent dose at 2 Gy per fraction, *bDFS* biochemical or clinical disease-free survival, *HR* hazard ratio, *CI* confidence interval, *Int* intermediate, *mos* months

90% confidence intervals are quoted for the CHHiP and PROFIT trials and 95% confidence intervals for the ROTG 0415 and HYPRO trials.

Efficacy

In the CHHiP trial, 3216 men with predominantly intermediate-risk prostate cancer were randomly assigned (1:1:1) to conventionally fractionated RT (74 Gy in 37 fractions) or one of two moderately hypofractionated schedules (60 Gy in 20 fractions or 57 Gy in 19 fractions over 4 weeks) using intensity-modulated radiotherapy (IMRT) and 3–6 months of ADT [13••, 21]. The primary endpoint was bDFS. To establish non-inferiority, the upper limit of the two-sided 90% confidence interval (CI) for the hazard ratio (HR) for bDFS needed to be < 1.208, corresponding to at most a 5% absolute decrement in bDFS. Median follow-up was 62.4 months. The regimen of 60 Gy in 20 fractions was found to be non-inferior to the conventionally fractionated regimen (HR 0.84, 90% CI 0.68–1.03, $p = 0.0018$ for non-inferiority). By contrast, 57 Gy in 19 fractions was not found to be non-inferior to conventional fractionation (HR 1.20, 90% CI 0.99–1.46, $p = 0.48$).

In the Ontario Clinical Oncology Group PROFIT study, 1206 men with exclusively intermediate-risk localized prostate cancer were randomized to a conventionally fractionated regimen of 78 Gy in 39 fractions or a moderately hypofractionated regimen of 60 Gy in 20 fractions utilizing image-guided IMRT [17•]. The threshold for non-inferiority in this trial was set such that the upper limit of the two-sided 90% CI of HR for bDFS was < 1.32. ADT use was not permitted. A total of 82% of patients had PSA ≥ 5 ng/mL, 63% had Gleason score of 3 + 4, and 79% had T1c-T2a disease. With a median follow-up of 6 years, the moderately hypofractionated schedule was found to be non-inferior (HR 0.96, 90% CI 0.77–1.2). The trial results are not mature with respect to PCSS; overall, only 10 deaths from prostate cancer were observed in the experimental arm compared with 12 in the standard arm (HR 0.76, 95% CI 0.32–1.82).

The Radiation Therapy Oncology Group conducted a phase III non-inferiority trial (RTOG 0415) comparing moderate hypofractionation and conventional fractionation in men with low-risk localized prostate cancer [15•]. A non-inferiority margin of 7.65% was chosen, corresponding to a critical HR of 1.52 for bDFS. A total of 1115 men were randomized to conventional fractionation (73.8 Gy in 41 fractions) or moderate hypofractionation (70 Gy in 28 fractions). With a median follow-up of 5.8 years, the moderately hypofractionated regimen was non-inferior with respect to bDFS (HR 0.85, 95% CI 0.64–1.14) to the conventionally fractionated schedule.

Unlike the other large-scale randomized non-inferiority trials, HYPRO, conducted in the Netherlands, had a superiority design. A total of 820 patients with intermediate- or high-risk localized prostate cancer were randomized to 64.6 Gy in 19 fractions (three fractions weekly for 6.5 weeks) or 78 Gy in 39 fractions [22•, 23, 24]. Approximately two-thirds of the patients received ADT, with a median duration of ADT use of 32 months. At a median follow-up of 60 months, the relapse-free survival (RFS) was 80.5% and 77.1% in the hypofractionated and standard arms (adjusted HR 0.86, 95% CI 0.63–1.16, $p = 0.36$), and thus, superiority was not observed. Five-year OS was similar across the two regimens (86.2% vs. 85.9%, HR 1.02, 95% CI 0.71–1.46, $p = 0.92$).

A number of single-institution randomized studies comparing conventional fractionation and hypofractionation have also been conducted. In a trial undertaken at Fox Chase Cancer Center, 303 men with intermediate- or high-risk prostate cancer were randomized to 76 Gy in 38 fractions over 7.6 weeks or 70.2 Gy in 26 fractions over 5.2 weeks [16, 25]. High-risk patients, who constituted about one-third of the study population, received long-term ADT. The 5-year cumulative incidence of failure was 21.4% and 23.3%, respectively, for the conventional and moderate hypofractionation arms ($p = 0.75$). A study conducted at Istituto Regina Elena in Rome compared 80 Gy in 40 fractions with 62 Gy in 20 fractions in 168 patients with high-risk prostate cancer [19, 26–28]. All patients received 9 months of ADT. At a median follow-up of 9 years, 10-year freedom from biochemical failure (BF) was 72% in the hypofractionated arm compared to 65% in the conventional arm (HR 1.62, 95% CI 0.88–2.97). Ten-year PCSS and OS with moderate hypofractionation were 95% and 75% compared to 88% and 64% with conventional fractionation ($p = 0.22$ and $p = 0.066$, respectively). In a trial conducted at MD Anderson Cancer Center, 206 men with localized prostate cancer were randomized to 75.6 Gy in 42 fractions over 8.4 weeks vs. 72 Gy in 30 fractions over 6 weeks [20, 29]. Approximately three-quarters of patients had cT1 cancer, and ≥ 90% patients had Gleason score ≤ 7 and PSA ≤ 10 ng/mL. Approximately one-quarter of patients received ADT. At a median follow-up of 8.5 years, the 10-year failure rate was lower with moderate hypofractionation (10.7% vs. 15.4%, $p = 0.036$) while no difference in OS was observed.

Treatment Effect from Moderate Hypofractionation Across Subgroups of Interest

Among all the published studies, CHHiP had by far the largest patient population. Risk group was a pre-specified stratification factor in this study. There was no heterogeneity of fractionation effect among the low-, intermediate-, or high-risk subgroups ($p = 0.45$) [13••]. Similar findings were noted in the HYPRO study. In this study, the HRs for RFS were 0.87 (95% CI: 0.63–1.22) in the high-risk and 0.85 (95% CI: 0.4–1.79) in the intermediate-risk subgroup with no statistical evidence of heterogeneity across subgroups ($p = 0.95$) [22•].

Interestingly, there appeared to be an interaction between the benefit from moderate hypofractionation and age in the CHHiP trial. The 60-Gy regimen was associated with a 41% relative improvement in the risk of failure (HR 0.59, 90% CI 0.43–0.81) in patients with age ≥ 70 years compared to 11%

increase in failure risk in patients < 70 years (test for heterogeneity, $p = 0.01$) [13••]. In a separate exploratory post hoc analysis from CHHiP trial, the authors concluded that there was no difference in bDFS between men aged < 75 years and ≥ 75 years for any of the fractionation schedules [30]. In the elderly subgroup, 5-year bDFS marginally favored the 60-Gy regimen (84.7% for 74 Gy, 91% for 60 Gy, and 87.7% for 57 Gy), corresponding to a hazard ratio of 0.54 (95% CI 0.28–1.05, $p = 0.064$) for the comparison between the 60-Gy and 74-Gy arms. These findings should be interpreted with some caution; none of the other completed trials have shown a similar interaction between treatment effect and age and thus it is unclear whether this is a chance finding in a relatively small subgroup—only 15% of the CHHiP population was ≥ 75 years of age—or one that generalizes more broadly.

Toxicity and QOL

All of the randomized studies investigating moderate hypofractionation have collected information on clinician-reported toxicity and a number have also collected patient-reported outcome data. In general, the moderate hypofractionation regimens studied had favorable toxicity profiles. A forest plot presenting the odds ratios for the crude incidence of late grade ≥ 2 genitourinary (GU) and gastrointestinal (GI) toxicity across the completed trials is presented in Fig. 1. The incidence of reported late grade ≥ 3 toxicity was remarkably low (1–4%) in the RTOG 0415, PROFIT, and CHHiP trials [13••, 15•, 17•]. In RTOG 0415, there was a modest increase in late grade ≥ 2 GU (GU) and GI toxicity in the moderate hypofractionation arm whereas in PROFIT, late grade ≥ 2 GI morbidity favored the moderate hypofractionation arm. In a post hoc analysis, minimum dose to the 5% of the rectal volume receiving the highest dose correlated with late GI toxicity in the RTOG study [31]. In CHHiP, there was substantially higher acute grade ≥ 2 bowel toxicity with the moderate hypofractionation regimens (38%) compared with conventional fractionation (25%). About 50% of patients had acute grade ≥ 2 bladder toxicity across all three study arms. However, by 18 weeks, the majority of acute GI toxicity had subsided and the rates of GI and GU toxicities across all the arms were approximately 5% by this time. In a recent presentation of patient-reported outcomes, the CHHiP investigators reported a low incidence of moderate or substantial symptoms for bowel, urinary, and sexual bother at 5 years in all treatment schedules [32]. Changes in bowel or urinary symptoms up to 5 years were similar across schedules. Sexual bother symptoms worsened over time in all arms but were more favorable with hypofractionation. There was no notable difference in the patient-reported toxicity outcomes at 5 years compared to those at 2 years [21].

In updated results from the MD Anderson study, there was a non-significant increase in late grade 2/3 GI toxicity with moderate hypofractionation compared to conventional fractionation (8-year incidence 12.6% vs. 5%, $p = 0.08$); however, late GU toxicity was similar ($p = 0.84$) across the two treatment regimens [20]. There was no incidence of grade 4 toxicity. Long-term results from a phase 2 trial from Princess Margaret Hospital are also reassuring with 2% incidence of grade 3 toxicity after > 10 years of follow-up with the moderately hypofractionated regimen of 60 Gy in 20 fractions [33]. However, dose escalation to 66 Gy in 22 fractions led to significantly worse late toxicity with a 4% ($n = 1$) grade 4 GI and GU toxicity observed in this cohort.

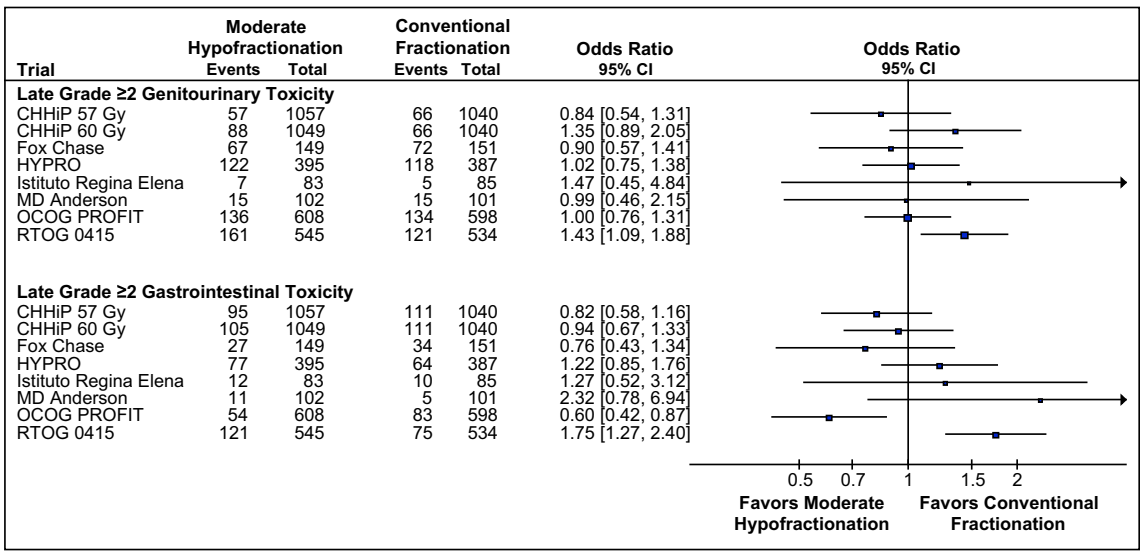

Fig. 1 Forest plots of odds ratios for crude events of late grade ≥ 2 genitourinary and gastrointestinal toxicity in the completed randomized trials comparing moderately hypofractionated RT with conventionally fractionated RT. Given the heterogeneity in radiotherapy dose-fractionation regimens used across trials, pooled estimates have not been calculated.

Long-term results of the Fox Chase trial did not identify a statistically significant difference between the two treatment arms in terms of the scores from a number of validated instruments including the Expanded Prostate Cancer Index Composite (EPIC), International Prostate Symptom Score (IPSS), and EQ-5D [25]. A trend toward lower EPIC urinary incontinence scores was observed, however, with moderate hypofractionation. On multivariable analysis, there was no association between fractionation schema and any quality of life (QOL) parameter. A post hoc analysis showed worse GU function after moderate hypofractionation than conventional fractionation in patients with baseline IPSS > 12; this finding has not been confirmed in any of the larger studies [16].

In contrast to the other randomized trials, HYPRO identified increased late toxicities with moderate hypofractionation. Specifically, a higher cumulative incidence of grade ≥ 2 GI (HR 1.19, 90% CI 0.93–1.52) and GU toxicities (HR 1.16, 90% CI 0.98–1.38) were observed at 3 years and both violated the pre-specified upper limit of non-inferiority [24]. There was a significant correlation between receipt of moderate hypofractionation and cumulative incidence of grade ≥ 3 GU adverse events, but no such association was seen for late grade ≥ 3 GI morbidities. The relatively higher rate of treatment-related morbidities in this study might be attributed to the higher biological effective dose used in the moderate hypofractionation arm in this study, essentially due to the superiority design with respect to the co-primary endpoint of RFS.

Summary of Evidence on Moderate Hypofractionation

While the median follow-up duration of 5–6 years in majority of the completed randomized studies could be considered relatively short for localized prostate cancer, the existing evidentiary base nonetheless constitutes several thousand patients and tens of thousands of patient-years of follow-up. The oncologic outcome and toxicity data accumulated to date consolidate the hypothesis that moderate hypofractionation is a viable, and indeed preferred, alternative to the more prolonged 7–9-week conventionally fractionated schedules in patients with localized prostate cancer. Use of moderately hypofractionated prostate radiotherapy as the only modality of local therapy does, however, warrant caution in a subset of highest-risk patients including those with Gleason score ≥ 9 or Gleason score 8 with clinical stage T3 disease as these patients were relatively poorly represented in the completed randomized trials. The same caveat applies to patients receiving conventionally fractionated prostate RT as their only local treatment. Such patients at highest risk of treatment failure may be better served by intensified local therapy approaches incorporating brachytherapy boosts and/or pelvic nodal radiotherapy. Moderate hypofractionation requires further prospective study in the setting of elective pelvic nodal irradiation (ENI) [10•, 34]. Although studies have shown a modest increase in acute GI toxicity with moderate hypofractionation, the overall risk of acute and late GU and late GI toxicity is similar to that of conventional fractionation (Fig. 1). Moreover, additional measures including use of prostate-rectal spacers might be helpful in reducing the risk of late rectal toxicity [35]. No specific contraindications to the use of moderate hypofractionation related to gland size, voiding dysfunction, or prior transurethral resection of prostate have been identified.

The most commonly utilized hypofractionated schedules are 60 Gy in 20 fractions over 4 weeks or 70 Gy in 28 fractions over 5.5 weeks. There is no conclusive randomized evidence to prefer one schedule over the other, and therefore, the choice is essentially guided by institutional policy and patient and physician preference. It is noted, however, that the 60 Gy in 20 fraction regimen has been more robustly evaluated in a larger population across several risk groups and with or without adjuvant ADT; on these grounds, it may be favored as a preferred regimen. Irrespective of the regimen chosen, meticulous attention should be paid to the technical aspects of treatment planning and delivery with emphasis on image guidance, intensity modulation, and following the dose-volume constraints for the nearby OARs based on the existing guidelines [10•] and protocols.

Ultrahypofractionated Radiotherapy/SBRT

Until recently, the evidentiary base for ultrahypofractionated RT (SBRT) consisted largely of prospective nonrandomized studies reporting feasibility, efficacy, and adverse effects [36–52]. Table 2. summarizes those studies with a minimum of 4 years of follow-up. The eligible study populations were mainly limited to men with low- and intermediate-risk prostate cancer, gland volume < 100 cc, and baseline IPSS < 20. Recently, the first efficacy and toxicity results of a large-scale randomized trial comparing SBRT and conventional fractionation were published [14••]. Three other large-scale randomized studies, at various stages of completion and discussed further below, are directly comparing the outcome of five-fraction SBRT regimens with conventional fractionation or moderate hypofractionation.

Efficacy

HYPO-RT-PC, a large-scale trial conducted in Scandinavia, constitutes the only published level 1 evidence for prostate SBRT [14••]. In this trial, 1200 patients with intermediate- and favorable high-risk localized prostate cancer were randomized to receive either 78 Gy in 39 fractions over 8 weeks or 42.7 Gy in 7 fractions, 3 days per week, over 2.5 weeks. Specifically, patients with one or two of the following factors were eligible: clinical stage T3a, Gleason score ≥ 7, and

Table 2 Phase II trials of ultrahypofractionated radiotherapy/SBRT in localized prostate cancer with at least 4 years of follow-up

Trial	Median follow-up	Dose	$EQD2_{1.5}$	5-year bDFS	Acute G3+ toxicity		Late G3+ toxicity		
					GU	GI	GU	GI	ED
Pham, 2010 ($n = 40$)	5 years	34 Gy/5Fx over 1 week	80.6	93%	2%	0%	3%	0%	50%
Kupelian, 2013 ($n = 135$)	5 years	35–40 Gy/4–5 Fx over 1–2 weeks	85–108.6 Gy	97%	NR	NR	NR	NR	NR
Mantz, 2014 ($n = 102$)	> 5 years	40 Gy/5 Fx in 2 weeks	108.6 Gy	100%	2%	0%	NR	0%	NR
Hannan, 2016 ($n = 91$)	4.5 years	45–50 Gy/5 Fx over 1 week	135–164.3 Gy	99%	0%	2%	5%	7%	26%
Musunuru, 2016 ($n = 84$)	6.2 years	35 Gy/5Fx over 4 weeks	85 Gy	97%	1%	0%	0%	1%	43%
Zimmerman, 2016 ($n = 80$)	6.9 years	45 Gy/9 Fx over 9 weeks	83.6 Gy	96%	NR	NR	4%	13%	NR
Meier, 2018 ($n = 309$)	5.2 years	36.25 Gy in 5 Fx over 5–11 days	90.73 Gy	97.1% (DFS)	0	0	1.3%	0	NR
Kataria, 2018 ($n = 145$)	5.6 years	35–37.5 Gy in 5 Fx	85–96.4 Gy	98.5% (LR) 95% (IR)	NR	NR	NR	NR	NR
Fuller, 2018 ($n = 259$)	5 years	38 Gy in 4 Fx	119.4 Gy	100% (LR) 88% (IR)	1.1%	0%	2.3%[a]	0	NR[b]
Fuller, 2018 ($n = 79$)	5 years	38 Gy in 4 Fx	119.4 Gy	100% (LR) 92% (IR)	0%	0%	6%	0%	35%

[a] Cumulative incidence of G3 or higher GU toxicity at 5 years

[b] There was decrease in sexual quality of life with time

bDFS biochemical disease-free survival, *ED* erectile dysfunction, *EQD2* equivalent dose in 2-Gy fractions, *Fx* fraction, *GI* gastrointestinal, *GU* genitourinary, *int.* intermediate, *NR* not reported, *G* grade

PSA ≥ 10 ng/mL. Patients with baseline PSA > 20 ng/mL were ineligible. It is noteworthy that the use of ADT in conjunction with RT was not permitted. The primary endpoint was time to biochemical or clinical failure. A non-inferiority design was used, with a pre-specified non-inferiority margin of 4% in absolute terms at 5 years, corresponding to a critical HR limit of 1.338.

Ultimately, 89% of the enrolled population was intermediate risk and just 11% high risk. Efficacy results have been published at a median follow-up of 5.0 years. Five-year freedom from biochemical or clinical failure was 84% in both the conventionally fractionated and SBRT arms (adjusted HR 1.002, 95% CI 0.758–1.325); thus, the SBRT regimen was confirmed to be non-inferior to the conventionally fractionated regimen. There was no significant interaction between efficacy of SBRT and a number of baseline factors, including age, Gleason score, clinical T stage, baseline PSA, and risk group. The SBRT and conventionally fractionated arms were also found to have similar efficacy across a range of secondary endpoints, including distant failure and overall survival.

Alayed et al. reported late outcomes from a pooled analysis of two prospective single-institution studies of SBRT in low- and intermediate-risk prostate cancer [39]. One of them employed a schedule of 35 Gy in five fractions (33.25 Gy to the planning target volume [PTV]) given weekly while the other study used 40 Gy in five fractions (38 Gy to PTV). Results for the two studies have been published at a median follow-up of 9.6 years and 6.9 years, respectively. The cumulative incidence of biochemical failure was 2.5% and 3.3% at 5 years with 35 Gy and 40 Gy, respectively ($p = 0.78$). There were no deaths from prostate cancer in either study.

Kishan et al. reported outcomes of SBRT in low- and intermediate-risk prostate cancer from a pooled analysis of 12 phase II studies ($n = 2142$) in which individual patient data were analyzed [36]. Approximately 55% of the study population was low-risk while 32% were favorable intermediate-risk and 12% were unfavorable intermediate-risk. Approximately 5% of patients received ADT. Results were reported at a median follow-up of 6.9 years. The cumulative incidence of biochemical failure at 7 years in the three risk groups was 4.5%, 8.6%, and 14.9%, respectively, whereas overall survival at 7 years was 91.4%, 93.7%, and 86.5%, respectively. Neither radiotherapy dose nor the use of ADT was significantly associated with a prolongation in time to biochemical failure.

A recent meta-analysis of over 6000 patients treated with SBRT demonstrates encouraging results with 5-year bDFS of 96.7% and 92.1% in low- and intermediate-risk patients, respectively [53•]. A significant correlation was identified in this study between biochemical control and prescribed dose. Despite a substantial proportion of patients being in the intermediate-risk category, no stratification was carried out between favorable and unfavorable subsets of the intermediate-risk population.

Prospective evidence supporting use of SBRT in high-risk localized prostate cancer is sparse. As noted above, only 11% of the HYPO-RT-PC population was high risk. Alayed et al. compared two prospective phase II trials using SBRT in high-risk localized prostate cancer, with and without elective pelvic nodal radiotherapy [54]. Patients in the first trial received 40 Gy in five fractions to the prostate and 30 Gy in five fractions to the seminal vesicles while those in the second trial received 40 Gy in five fractions to the prostate and 25 Gy in five fractions to the pelvic nodes and seminal vesicles. Rates of biochemical failure at 5 years were 14.6% and 0% in the first and second trials, respectively. Overall survival at 5 years was 93.2% and 96.7% ($p = 0.86$).

Toxicity and QOL

In the HYPO-RT-PC trial, physician-reported toxicity was recorded using the RTOG morbidity scale while patient-reported QOL was assessed using the Prostate Cancer Symptom Scale questionnaire. There was a suggestion of greater grade ≥ 2 acute GU toxicity with the SBRT arm at the end of treatment (28% vs. 23%, no formal statistical comparison), but these differences vanished beyond 1 year of follow-up [14••]. The prevalence of grade ≥ 2 GU toxicity at 5 years was 5% in both arms. No significant differences in the frequency of physician-reported grade ≥ 2 GI toxicity were noted throughout follow-up. Patients reported greater GU and GI symptoms at the end of treatment in the SBRT arm compared to the conventionally fractionated arm ($p = 0.0066$ for GU symptoms and $p < 0.0001$ for GI symptoms), but no differences between the arms persisted beyond 2 years. There was no difference between the arms in patient-reported erectile function.

The first results from a large-scale randomized trial investigating a five-fraction SBRT regimen were recently presented in abstract form. PACE-B was conducted in the United Kingdom and Canada and enrolled patients with low-risk or favorable intermediate-risk prostate cancer (clinical stage T1c-T2c, Gleason score ≤ 3 + 4, and presenting PSA ≤ 20 ng/mL) unsuitable for surgery or preferring RT [55•]. Patients were randomized between SBRT (36.25 Gy in five fractions over 1–2 weeks) and the investigator's choice of a conventionally fractionated regimen (78 Gy in 39 fractions over 7.8 weeks) or moderately hypofractionated regimen (62 Gy in 20 fractions over 4 weeks). ADT use was not permitted. A total of 430 patients were assigned to moderate hypofractionation or conventional fractionation (of which 69% received the moderately hypofractionated schedule) while 414 received SBRT. RTOG grade ≥ 2 toxicity was not significantly different for GI events (12.1% vs. 10.1% $p = 0.368$) or GU events (27.2% vs. 23.2%, $p = 0.179$) in the conventional/moderate hypofractionation and SBRT arms, respectively. Late toxicity results and efficacy results are awaited.

In the pooled analysis of single-arm phase II studies by Kishan et al., acute grade ≥ 3 GU and GI toxicity event rates were 0.6% and 0.09%, respectively [36]. Seven-year cumulative incidence of late grade ≥ 3 GU and GI toxicity was 2.4% and 0.4%, respectively. The meta-analysis by Jackson et al. reported similar late grade ≥ 3 GU and GI toxicity rates of 2.0% and 1.1%, respectively [53•].

A comparative evaluation of two dose-fraction regimens by Musunuru et al. revealed a higher cumulative incidence of GU (5% vs. 24.2%) and GI (7.6% vs 26.2%) toxicities with dose escalation to 40 Gy compared to 35 Gy in five fractions given weekly [43]. However, longitudinal QOL analysis of the same studies by Quon et al. did not reveal any significant difference between the two treatment groups with respect to the minimum clinically important change in QOL defined as a decrease in QOL from baseline to follow-up, which exceeded half of the standard deviation of that value at baseline [56].

Kim, Timmerman, and colleagues observed a similar dose-toxicity relationship. In a multicenter phase 2 dose escalation trial of 45, 47.5, and 50 Gy in five fractions, the cumulative incidence of late grade ≥ 2 GI toxicity was 6.7%, 33.3%, and 32.8% while that of grade 3/4 GI toxicity was 0%, 1.6%, and 8.2% [57]. Late grade ≥ 3 GI toxicity was significantly correlated with the volume of rectal wall receiving at least 50 Gy ($p < 0.0001$).

Finally, Quon et al. compared the toxicity and QOL outcomes of men with low- and intermediate-risk prostate cancer treated with 40 Gy in five fractions on either a weekly or alternating-day schedule [37]. The primary endpoint was the proportion with a minimum clinically important change in QOL during the acute (≤ 12 weeks) period. At a median follow-up of 4 years, acute urinary and bowel QOL were better with the alternating-day schedule while there were no significant differences in late urinary or bowel QOL at 2 years or last follow-up.

Summary of Evidence on Ultrahypofractionation/SBRT

Based on the available literature, SBRT is an emerging radiotherapeutic management option in men with localized low- or intermediate-risk prostate cancer. The evidentiary base for this treatment approach is accumulating rapidly and both cancer control outcomes and acute and late toxicity profiles are very promising. The 7-fraction regimen studied in a predominantly intermediate-risk population in the HYPO-RT-PC trial has been shown to be as effective as conventional fractionation and without any significant excess in late toxicity.

Evidence supporting the use of SBRT nonetheless remains less robust currently than that supporting moderate hypofractionation. Specifically, the evidentiary base for the 5-fraction SBRT regimens commonly used in North America remains relatively weak in intermediate- and high-risk disease. Mature results from the PACE-B

(NCT01584258), NRG-GU005 (NCT03367702), and HEAT (NCT01794403) trials are eagerly awaited and will provide definitive comparative evidence on the oncologic outcomes and toxicity of 5-fraction SBRT as well as its impact on QOL. When SBRT is selected, careful attention to the technical aspects of treatment planning and delivery—including image guidance, intensity modulation, adherence to published dose-volume constraints, and use of prostate-rectal spacer devices where available—is recommended. Routine dose escalation beyond PTV doses of 36.25 Gy in 5-fraction schedules, as it has not been shown to consistently yield improvements in biochemical outcome, and has been associated with excess toxicity in some cohorts, is not recommended at this time [10•].

Cost-Effectiveness of Hypofractionated Radiotherapy

A number of analyses exploring the cost-effectiveness of hypofractionation in relation to conventional fractionation in localized prostate cancer have been reported. A secondary analysis of the MD Anderson randomized trial showed moderate hypofractionation to be more cost effective than conventional fractionation even after considering the costs related to late radiation toxicities [11•]. Specifically, a per-patient savings of US$7000 was identified with the use of moderate hypofractionation. Another study from Hungary explored the cost-effectiveness of radiotherapy in localized prostate cancer using a Markov model to calculate the incremental quality-adjusted life years and costs [12]. Transition probabilities, adverse events, and utilities were derived from relevant systematic reviews. The authors concluded that hypofractionation was a cost-effective approach and it had the potential for improving access to radiotherapy and reducing burden on the public payers. Finally, a study in Ontario, Canada, showed that both moderate hypofractionation and SBRT are cost-effective alternatives to conventional fractionation and that SBRT was the single most cost-effective treatment approach among those studied [58]. It is emphasized that analyses of cost-effectiveness are inevitably influenced by the nature of the particular health care system in which they are conducted and findings therefore may not generalize to other jurisdictions.

Conclusion

Taken together, the results of four multicenter randomized trials and a number of smaller single-institution randomized trials clearly demonstrate that moderately hypofractionated radiotherapy is as effective and no more toxic over the long term than conventionally fractionated radiotherapy and offers significant benefits in terms of patient convenience and reduced costs. The current evidentiary base therefore supports the routine use of moderate hypofractionation in localized prostate cancer across all risk groups, with the proviso that approaches employing prostate RT as the only local therapy may be suboptimal in highest-risk patients.

Published randomized data now exist demonstrating that a 7-fraction ultrahypofractionated regimen yields similar outcomes to conventional fractionation in intermediate-risk localized prostate cancer. Extensive non-randomized evidence shows promising results in men with low-risk and intermediate-risk disease with the more commonly used SBRT regimens in North America, in which a PTV dose of 35–36.25 Gy is delivered over five fractions. Efficacy results from randomized trials investigating 5-fraction SBRT are awaited for definitive evidence of the value of this treatment approach in localized prostate cancer. Whichever form of hypofractionation is chosen, rigorous quality assurance in relation to treatment planning and delivery is of critical importance in order to confidently replicate the results of the trials on which these treatment approaches are based.

It should finally be acknowledged that whereas the prevailing radiobiological model predicts that hypofractionation should improve the therapeutic ratio in localized prostate cancer compared to conventional fractionation, the results from the randomized clinical trials completed to date do not appear to bear this out. When regimens of similar biological effective dose are compared, hypofractionation and conventional fractionation appear to have similar efficacy and toxicity, and no consistent improvements in either have been observed with hypofractionation. Nonetheless, moderate hypofractionation, insofar as it is more convenient for patients and less costly, is a preferred approach on these grounds alone. Whether gains in efficacy can be achieved with SBRT will be evaluated in the randomized trials in progress.

Compliance with Ethical Standards

Conflict of Interest Soumyajit Roy declares no potential conflicts of interest.

Scott C. Morgan is on the advisory board and consults for Astellas, Bayer Healthcare, and Janssen.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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