

# The Case for Hypofractionation of Localized Prostate Cancer

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An optimal treatment regimen for localized prostate cancer (PCa) is yet to be determined. Increasing evidence reveals a lower  $\alpha/\beta$  ratio for PCa with hypofractionated radiation therapy (HFRT) regimens introduced to exploit this change in therapeutic ratio. HFRT also results in shortened overall treatment times of 4 to 5 weeks, thus reducing staffing and machine burden, and, more importantly, patient stress. This review evaluates pretreatment characteristics, outcomes, and toxicity for 15 HFRT studies on localized PCa. HFRT results in comparable or better biochemical relapse-free survival and toxicity and is a viable option for localized PCa.

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## KEY WORDS

Localized prostate cancer • Hypofractionation • Short-course radiotherapy • Dose escalation • Biologic equivalence

**M**ultiple randomized dose-escalation trials for localized prostate cancer (PCa) have shown improved biochemical relapse-free survival (bRFS) rates for higher total doses using conventionally fractionated radiotherapy (CFRT), though at a cost of longer treatment duration.<sup>1-4</sup> The increased treatment time requires increased access to radiation treatment facilities, with additional burden on both patients and staff. To address the issue of prolonged treatment duration while

maintaining equivalent bRFS, an increasing number of studies have pursued the role of hypofractionated radiotherapy (HFRT) with higher daily doses delivered in a shorter total amount of time. This treatment paradigm assumes a low  $\alpha/\beta$  ratio for PCa, as demonstrated in several recent studies, with higher  $\alpha/\beta$  ratios for normal surrounding tissues.<sup>5-7</sup> By employing HFRT, the increased daily radiation doses exploit the aforementioned  $\alpha/\beta$  ratios by allowing equivalent tumor kill as with

CFRT, while also allowing for normal tissue repair.

With longer-term and randomized HFRT data now reported in the literature, it seems appropriate to address whether the time has come to make HFRT the new standard. This article seeks to review the current literature and the role of HFRT in the modern era of radiotherapy for localized PCa.

## Materials and Methods

This systematic review was undertaken to investigate the bRFS, distant metastasis rates, and acute and late toxicity rates for HFRT versus CFRT for patients with localized PCa. An electronic PubMed search was performed using the terms: “localized prostate cancer”, “dose escalation”, “hypofractionation”, “short-course radiotherapy”, and “biologic equivalence”. Relevant references were then identified and also reviewed. Hypofractionation was defined for this review as a treatment schema with daily radiation doses of more than the standard 1.8 to 2.0 Gy fractions used for CFRT.

## Results

### Pretreatment Characteristics

Patient characteristics are summarized in Table 1. In total, 15 studies using HFRT for localized PCa were identified and analyzed, of which five were randomized trials.<sup>8-22</sup> The median number of total patients per trial was 130 (range, 36-1092). The median number of patients treated with HFRT across all studies was 102 (range, 36-705). Within the randomized studies, the median number of total patients enrolled was 168 (range, 91-936); the median number of patients randomized to HFRT was 83 (range, 47-466). The median age was 70 (range, 63-75) across all studies.

**TABLE 1**

**Pretreatment Patient Characteristics in 15 HFRT Trials**

Variable	Patients (N)
Age, y (range)	
70 (63-75)	
Clinical stage	752
T1	1024
T2	283
T3	
Gleason score	
<6	1250
7	714
8-10	162
PSA	
< 10	711
11-20	581
> 20	303
ADT	Trials (N)
Yes	8
No	5
Not reported	2

ADT, androgen deprivation therapy; HFRT, hypofractionated radiotherapy; PSA, prostate-specific antigen.

On average, the majority of patients had T2 lesions, followed by T1, then T3. Average Gleason score was < 6, followed by 7, then 8 to 10. Average prostate-specific antigen (PSA) was < 20 (PSA ≤ 10 was slightly more prevalent than PSA 11 to 20, but not statistically significant). A total of eight studies allowed androgen deprivation therapy (ADT), five studies did not, and two studies did not report.

### Radiation Therapy

Radiation therapy, outcomes, and toxicity results are summarized in Table 2. Six studies allowed intensity-modulated radiation therapy (IMRT), and the remaining nine treated with three-dimensional conformal radiation therapy (3DCRT). The median total dose for HFRT was 60 Gy (range, 50-70.2) delivered in a range of 3.5 to 5.5 weeks with a median treatment

duration of 4.5 weeks. The median daily dose per fraction was 3 Gy (range, 2.5-4.5).

### Outcomes

The median follow-up was 36.5 months (range, 2-90). For all patients treated with HFRT, the median bRFS was 73% (range, 3.3%-95.4%), compared with a median of 66% (range, 34%-79%) in the CFRT arms. Rate of distant metastases was reported in only five studies with a median of 4.3% (range, 0%-82%).

### Toxicity

Due to reporting differences, only Radiation Therapy Oncology Group (RTOG) grade I-II acute rectal toxicity and RTOG grade II to III late rectal toxicity were evaluated in this report. For acute toxicity, a median of 29% (range, 0%-75%) was reported for HFRT,

TABLE 2

## Radiation Regimens, Outcomes, and Toxicity Profiles for 15 HFRT Trials

Author	Daily Fx (Gy)	Total Dose (Gy)	No. Weeks	FU (Mos)	IMRT	bRFS	DM Rate	Acute GI Toxicity, Grade 1-2	Long-term GI Toxicity, Grade 2-3
Norkus D et al <sup>8</sup>	3×13; 4.5×4	57	3.5	12	No	54.5%	NR	NR	NR
Kupelian P et al <sup>9</sup>	2.5	70	5.5	30	Yes	87% (88%CF)	NR	70% (88%CF)	5% (12%CF)
Arcangeli G et al <sup>10</sup>	3.1	62	4	35	No	82% (79%CF)	82% (88%CF)	NR	16% (11%CF)
Arcangeli S et al <sup>11</sup>	3.5	56	4	2	Yes	NR	NR	38%	NR
Leborgne F et al <sup>12</sup>	3-3.15	60-63	5	66	No	89.40%	NR	NR	4.4% (4.4%CF)
Leborgne and Fowler <sup>13</sup>	3-3.15	60-63	5	2-3	No	NR	NR	3-4.5%, 3.15-29% (4%CF)	NR
Livsey JE et al <sup>14</sup>	3.13	50	4	48	No	by stage	NR	NR	5%
Rene N et al <sup>15</sup>	3	66	4.5	51	No	2.30%	2.3%	4%	1.5%
Pollack A et al <sup>16</sup>	2.7	70.2	5.5	3	Yes	NR	NR	0% (2%CF)	NR
Martin JM et al <sup>17</sup>	3	60	4	38	Yes	97% 53%	4.3%	NR	4%
Yeoh EE et al <sup>18</sup>	2.75	55	4	90	No	60% (34%CF)	NR	2.80%	2.8%
Lukka H et al <sup>19</sup>	2.63	52.5	5.5	67	No	53% (53%CF)	NR	NR	3.2% (3.2%CF)
Faria S et al <sup>20</sup>	3	66	4.5	51	No	95.4%	4.4%	NR	2%
Soete G et al <sup>21</sup>	3.5	56	4	2	Yes	NR	NR	75%	NR
Junius S et al <sup>22</sup>	2.64	66	5	20	Yes	8.0%	0.0%	47%	3%

bFRS, biochemical relapse-free survival; CF, conventional fractionation; DM, distant metastases; Fx, fraction; FU, follow-up; GI, gastrointestinal; HFRT, hypofractionated radiotherapy; IMRT, intensity-modulated radiation therapy; NR, not reported.

compared with a range of 2% to 88% for CFRT. For late toxicity, a median of 3.6% (range, 1.5%-16%) was reported for HFRT, whereas a range of 3.2% to 12% was reported for CFRT. In separating studies between those that used daily fractions  $\leq 3$  Gy versus those with  $> 3$  Gy, acute toxicity had a median of 4.3% (range, 0%-70%) and 38% (range, 29%-75%), respectively.

## Discussion

Increasing data shows a low  $\alpha/\beta$  ratio for PCas, in the range of 1.0 to 3.0 Gy,<sup>5-7</sup> which has opened the door for the use of HFRT for locally invasive PCa. This treatment regimen assumes similar or higher  $\alpha/\beta$  ratios for normal surrounding structures, which allows the therapeutic ratio to be exploited with

larger daily fraction sizes. In the currently available data, no single HFRT treatment regimen is uniformly used, although a dose of 3 Gy per fraction for a total of 60 Gy in 20 fractions seems to be emerging as a promising standard.

Several randomized trials are now open in the United States, Europe, and Canada, also with varying regimens and modalities. With CFRT, the use of IMRT has increased dramatically over the past decade in order to spare normal surrounding structures, but in the aforementioned data, the use of IMRT versus 3DCRT is variable and appears to have no impact on outcomes or toxicity for HFRT. In addition to maximizing the lower  $\alpha/\beta$  ratio for PCa with HFRT, additional goals and benefits of

treatment are the decrease in strain on treatment center workloads and decreased patient stress with shortened treatment time. These latter goals appear to also be met with the equal efficacy of 3DCRT, as 3DCRT requires less planning and execution time, as well as decreased cost to patient than that with IMRT.

Acute and late toxicity have also been evaluated extensively for CFRT, especially in the age of dose escalation, with minimal toxicity for both 3DCRT and IMRT with 2 Gy fractions.<sup>23-25</sup> In the data just discussed, HFRT appears to have similar and often less acute and late toxicities than CFRT. The one striking exception is when HFRT uses daily fractions  $> 3$  Gy, at which point acute toxicity outpaces that of CFRT.<sup>11,13,21</sup> Leborgne and Fowler<sup>13</sup>

demonstrated this with two HFRT arms of either 3 Gy daily or 3.15 Gy daily, with a dramatic rise in acute toxicity from 4.5% to 29% with larger fraction size. Interestingly, however, this increased acute toxicity does not seem to translate into increased late toxicity.<sup>11,12</sup> Caution must be taken in this interpretation, though, as studies varied in their dosimetric constraints and

increased responsiveness to HFRT, and continues to exploit the therapeutic ratio.

With regard to staging, stratification did vary among studies, but, on average, low- to intermediate-risk groups dominated, and high-risk groups were included in all but two studies.<sup>15,20</sup> This grouping is not surprising, though, as earlier-stage and lower-risk cancers pre-

scheme of Kupelian and colleagues<sup>9</sup> in low-risk patients without ADT versus the Prostate Fractionated Irradiation Trial (PROFIT) in Canada testing the HFRT regimen of Martin and associates<sup>17</sup> in intermediate-risk patients with ADT allowed. It is evident that a more systematic approach is necessary.

### Conclusion

This review provides ample evidence for the use of HFRT for localized PCa, with the inclusion of nonrandomized as well as several large randomized trials. Although there is variation in patient profiles and inclusion criteria among studies, the improved bRFS rates and the similar or improved toxicity profiles for HFRT underscore its enhanced therapeutic ratio with higher daily doses, as well as providing additional evidence for a lower  $\alpha/\beta$  ratio for PCa. Because doses  $> 3$  Gy per day lead to increased toxicity, it is proposed that appropriate patients with localized PCa can now be reasonably treated with 3 Gy daily fractions to a total dose of 60 Gy in

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tolerances, and patient reports were subjective with possible adjustment in tolerance as time progressed.

In addition, bRFS was greatly improved with HFRT in all trials. In a subset analysis of the five randomized studies evaluated here, three provided bRFS data for both the HFRT and CFRT arms, along with improved bRFS for HFRT.<sup>11,18-19</sup> This strengthens the argument for a lower  $\alpha/\beta$  ratio for PCa, as the aforementioned data demonstrates

dominate in the PSA era, and this is representative of current trends. As such, the inclusion of high-risk patients in HFRT trials does not appear detrimental to patient outcomes or toxicity.

In the current review, a trend also points toward improved outcomes with ADT, although the timing, dose, and use varied among studies. This needs to be further evaluated; the recently closed RTOG 0415 trial is testing the HFRT

### MAIN POINTS

- Currently, no single hypofractionated radiotherapy (HFRT) treatment regimen is uniformly used for the treatment of prostate cancer (PCa), although a dose of 3 Gy per fraction for a total of 60 Gy in 20 fractions seems to be emerging as a promising standard.
- HFRT appears to have similar and often less acute and late toxicities than conventionally fractionated radiotherapy (CFRT). The one striking exception is when HFRT uses daily fractions  $> 3$  Gy, at which point acute toxicity outpaces that of CFRT.
- Biochemical relapse-free survival (bRFS) was greatly improved with HFRT in all trials. In a subset analysis of the five randomized studies evaluated, three provided bRFS data for both the HFRT and CFRT arms, along with improved bRFS for HFRT.
- A trend also points toward improved outcomes with androgen deprivation therapy, although the timing, dose, and use varied among studies.
- This review provides ample evidence for the use of HFRT for localized PCa. Although there is variation in patient profiles and inclusion criteria among studies, the improved bRFS rates and the similar or improved toxicity profiles for HFRT underscore its enhanced therapeutic ratio with higher daily doses.

20 fractions, given over 4 weeks at a rate of 5 fractions per week. ■

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