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Authors: Abhishek Soni, Ganesh K Jadhav, Sapna Manocha, Sunil Chauhan, Brijesh Goswami, Monica Verma

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Comparative evaluation of hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate and high risk prostate cancer

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Abhishek Soni[1], Ganesh K Jadhav[2], Sapna Manocha[2], Sunil Chauhan[2], Brijesh Goswami[2], Monica Verma[1]

[1]*Department of Radiation Oncology, PT Bhagwat Dayal Sharma, Rohtak, India*
[2]*Department of Radiation Oncology, Indraprastha Apollo Hospital, New Delhi, India*

Corespondence to: Abhishek Soni, PT Bhagwat Dayal Sharma, Department of Radiation Oncology, Rohtak, India; e-mail: abhisheksoni246@gmail.com

Abstract

Background: The purpose of this study was to comparatively evaluate an efficacy and toxicity profile of hypofractionated radiotherapy (67.5 Gy in 25 fractions) to conventionally fractionated radiotherapy (78 Gy in 39 fractions) in prostate cancer patients with intermediate and high-risk disease.

Materials and methods: From January 2015 to December 2018, 168 patients were randomized to hypofractionated radiation treatment and conventional fractionated radiation treatment schedules of volumetric modulated arc therapy (VMAT) to the prostate and seminal vesicles. All the patients also received androgen deprivation therapy (ADT) and radiation therapy started after ADT.

Results: The median (range) follow-up was 51 (31–63) and 53 (33–64) months in the hypofractionated and conventionally fractionated regimes, respectively. The 3-year biochemical

no evidence of disease (bNED) rates were 86.9% and 73.8% in the hypofractionated and conventionally fractionated groups, respectively (p = 0.032, significant). The 3-year bNED rates in patients at a high risk [i.e., pretreatment prostate-specific antigen (PSA) > 20 ng/mL, Gleason score ≥ 8, or T ≥ 2 c], were 87.9% and 73.5% (p = 0.007, significant) in the hypofractionated and conventionally fractionated radiotherapy groups, respectively. No statistically significant difference was found for late toxicity between the two groups, with 3-year grade 2 gastrointestinal toxicity rates of 19% and 16.7% and 3-year grade 2 genitourinary toxicity rates of 15.5% and 11.9% in the hypofractionated and conventionally fractionated radiotherapy groups, respectively.

Conclusion: Hypofractionated schedule is superior to the conventional fractionation schedule of radiation treatment in terms of bNED in intermediate and high grade prostate cancer patients. Also, the late toxicity is found to be equivalent between the two treatment groups.

Key words: hypofractionation; prostate; radiotherapy; conventional; toxicities; high grade

Introduction

Prostate cancer is the second most common cancer worldwide and it is among the leading causes of death from cancer in men worldwide [1]. Since the entry of prostate specific antigen testing, prostate cancer is diagnosed in a localized stage. Management options include external beam radiotherapy (EBRT), surgery, brachytherapy and active surveillance (in low risk cases only). EBRT is the appropriate treatment modality for intermediate and high risk prostate cancer patients and it has achieved long term disease control. Different trials have provided evidence of improvement in biochemical control after dose escalated EBRT with dose of 78 Gy in 2 Gy conventional fractionation schedule, but at the cost of increased gastrointestinal and genitourinary toxicity; which makes further dose escalation not preferable [2–5]. Various studies showed a low α/ß ratio for prostate cancer in the range of 1 to 3 Gy, which is lower than bladder and rectum [6–9]. Hence, hypofractionated EBRT could be used to enhance the therapeutic ratio with increased biological effective dose but without increasing the toxicity [7, 10, 11]. There is data available with hypofractionated radiation delivered to high total equivalent doses as in CHHiP trial, HYPRO trial, trial by Regina Elena and many more [12–21]. Hypofractionated

radiation is less uncomfortable for elderly prostate cancer patients and is more cost effective with shorter waiting periods and less frequent hospital visits for patients. Various trials depicted results in favor of hypofractionated radiation [11, 15–26]. Some of the trials were carried out before the studies indicating a low α/ß ratio for prostate cancer and did not provide any conclusive evidence with regard to outcomes and toxicities [24,27]. This study was designed to comparatively evaluate the efficacy and toxicity profile of hypofractionated radiotherapy to conventionally fractionated radiotherapy in intermediate and high-risk prostate cancer patients.

Materials and methods

Study design and sample size

This was a prospective, phase III randomized controlled trial framed to randomize intermediate and high risk prostate cancer patients to either 67.5 Gy in 25 fractions in 5 weeks (5 fractions per week) at 2.7 Gy per fraction (Group 1, hypofractionated radiation) or 78 Gy in 39 fractions in 7.4 weeks at 2.0 Gy per fraction (Group 2, conventional fractionated radiation). Assuming an α/β value of 2 Gy, the two groups were hypothesized to be isoeffective for tumor control. With regard to late complications, hypothesizing that the same dose would be absorbed by the organs at risk (OARs) assuming an α/β value of 3 Gy for normal tissue, this hypofractionated radiation regimen should be equivalent to an EQD2 (equivalent dose at 2.0 Gy/fraction) of 76.95 Gy. EQD2 was calculated based on the linear quadratic radiobiological model of Fowler et al. [28]. From the data available in the literature, the 3-year toxicity rates of Grade 2 or higher late rectal toxicity were estimated to be approximately 29% and 12% after 80 or 75 Gy, respectively, for 2 Gy per fraction [29-31]. On the basis of an 80% power to detect a significant difference ($p < 0.05$, two-sided), 84 patients were required in each group (168 total).

Eligibility and risk definition

Between January 2015 and December 2018, 185 patients diagnosed as adenocarcinoma prostate with intermediate and high risk were enrolled for the study. But 17 patients were not included in the study as they were lost to follow up. Total 168 patients were included in the present study. Inclusion criteria were as follows: (1) histopathological proven adenocarcinoma prostate with intermediate and high risk; (2) age ≤ 80 years; (3) no distant metastases; (4) no prior pelvic

radiotherapy; (5) no prior hormonal therapy; (6) no contraindication to hormonal therapy; (7) no history of pelvic surgery other than transurethral resection of the prostate (TURP); (8) no evidence of ulcerative colitis; (9) no pelvic lymph node >1 cm at the computed tomography (CT) or magnetic resonance imaging (MRI) evaluation; (10) no prior malignant tumors; (11) World Health Organization performance status less than or equal to 2; (12) comply with follow up; and (13) written informed consent.

Intermediate risk was defined as clinical stage T2b to T2c, Gleason score (GS) of 7 or grade group 2–3/5, and pretreatment PSA level (iPSA) of 10–20 ng/mL. High risk was defined as clinical stage T3a, GS of 8–10 or grade group 4-5/5, and iPSA > 20 ng/mL. The study protocol was approved by the institutional ethics committee. Detailed informed consent was obtained from all patients.

Treatment regimens

All patients received androgen deprivation therapy (ADT). ADT consisted of the nonsteroidal antiandrogen bicalutamide at a dose of 50 mg per day orally, and subcutaneous luteinizing hormone-releasing hormone (LHRH) analogue depot, which was started seven days after oral ADT, and further doses administered three and six months thereafter. ADT duration was 6 months in intermediate risk cases and 24 months in high risk cases.

Radiotherapy was started six to eight weeks after the first dose of LHRH analogue depot. For simulation and treatment, patients were immobilized in a supine position by using a personalized pelvic thermoplastic mold. Planning CT scan of the pelvis was performed from mid-abdomen to 3 cm below the ischial tuberosities at 3 mm intervals. The planning CT data was transferred to the Eclipse treatment planning system version 13.6 on Novalis Tx Linear Accelerator (Varian Medical Systems, Palo Alto, CA) for contouring. Prostate, seminal vesicles, rectum (from the level of sigmoid flexure to anus), bladder, penile bulb, testis and femoral heads were contoured. The clinical target volume (CTV) included prostate and seminal vesicles. CTV to planning target volume (PTV) expansion margin was taken as 1 cm, except at the prostate-rectum interface where a 0.6 cm margin was used to decrease the rectum involvement. Patients were treated with volumetric modulated arc therapy. The prescription dose was 67.5 Gy in 25 fractions at 2.7 Gy per fraction in the hypofractionated radiation group and 78 Gy in 39 fractions

at 2 Gy per fraction in conventional fractionated radiation group, respectively. The following dose constraints were used; V65Gy ≤ 25% and V40Gy ≤ 50% for the bladder wall, and V65Gy ≤ 17% and V40Gy ≤ 35% for the rectal wall [32]. Dose constraints for organs at risk were: bowel - V68% < 17cc, femoral heads – V100% < 70% and V68% < 50%.

Study endpoints and follow up

In this study, treatment outcomes were compared in terms of biochemical control of prostate cancer, late gastrointestinal (GI) and genitourinary (GU) toxicity. Late toxicity was evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria [33]. The American Urology Association symptom index for benign prostatic hyperplasia (BPH) was used to evaluate obstructive / irritative urinary symptoms [34]. Late toxicity was evaluated using clinical Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale [35]. Late toxicity was defined as rectal or urinary symptoms occurring or persisting 6 months or more after the end of radiotherapy. bNED (biochemical no evidence of disease) was defined as time interval from the first day of radiotherapy to the biochemical relapse/rising PSA level, according to the Phoenix definition of nadir PSA +2 ng/mL [36]. Monitoring of the patients was done weekly during radiation treatment and then one month after the end of radiation, then three monthly for 3 years and six monthly thereafter. PSA levels were not assessed during radiation. However, PSA levels were assessed one month after radiation and at each visit thereafter according to the follow up schedule. At each visit, a history regarding treatment related morbidity was obtained, and the worst toxicity was recorded for each patient. In case of suspected clinical local or distant failure and/or increased PSA level, patients underwent PET CT scan to detect the disease relapse or progression.

Statistical analysis

Overall outcomes and patterns of biochemical and clinical recurrence were analyzed according to the intention-to-treat principle. Actuarial curves of the biochemical failure, late toxicity and distant recurrence were calculated by the Kaplan-Meier product–limit method. The comparison of the actuarial curves was evaluated by the Log-Rank test. Tests for statistical significance were performed with the chi-square and t-test for categorical and continuous variables, respectively. Shapiro-Wilk test was used to check normal distribution of the variables. Hazard ratios were

estimated by applying the Cox proportional hazard model. All times were calculated from the day of radiotherapy beginning. The advantages of hypofractionated radiation for subgroup of the patients with different prognostic factors were estimated by Forest Plot of the hazard ratios (HR) and 95% confidence interval (CI). SPSS software version 26 was used for statistical analysis.

Results

The baseline characteristics regarding age, clinical (c) T stage, PSA level and Gleason score appeared to be balanced between the two arms (as outlined in Tab. 1). Median follow up from the beginning of radiotherapy was 51 (range, 31–63) and 53 (range, 33–64) months for the hypofractionated and conventional arms, respectively. A total of 168 patients were included and analyzed in the study. The dose in the hypofractionated arm was converted to EQD2 for smooth comparison between the two arms.

Table 2 shows the dose-volume characteristics of both treatment arms in terms of D98%, D50% and D2% (% of the prescribed dose delivered to 98%, 50% and 2% of PTV). The recorded dose-volume characteristics for the bladder and rectum were V87.5% and V62.5%, which represent the percent of the organ volumes receiving 87.5% (59 and 68 Gy) and 62.5% (42 and 49 Gy), respectively, of the prescribed dose in the two treatment arms.

Table 3 shows the number of patients and disease status in both of the arms. A nadir PSA (nPSA) ≤ 0.5ng/mL was achieved in 159 (94.6%) patients, 82 (97.6%) patients in the hypofractionated arm and 77 (91.7%) in the conventional arm ($p = 0.0814$). bNED came out to be significantly different for patients in the hypofractionated arm versus conventional arm, with 3 year bNED rates of 86.9% and 72.6% ($p = 0.0235$), respectively. This difference was even larger in high risk prostate cancer patients, with 3 year bNED rates of 87.9% and 70.6% ($p = 0.002$), respectively, in the hypofractionated and conventional arms. Local recurrence was seen in 2.4% patients in the hypofractionated arm and 4.8% in the conventional arm ($p = 0.4126$, NS). Distant metastasis was seen in 5.9% patients in the hypofractionated arm and 8.3% in the conventional arm ($p = 0.5512$, NS). 3-year relapse free survival is 88.1% in the hypofractionated arm and 81% in the conventional arm, respectively. Overall, survival at 3 years was 96.4% in the hypofractionated arm and 94% in the conventional arm, respectively.

Figure 1 shows Forest Plot of the hazard ratios (HR) and 95% confidence interval (CI) for hypofractionated radiation for different prognostic factors. A HR < 1 indicates decreased risk of biochemical failure in the hypofractionated arm. The HR of bNED of the hypofractionated arm relative to the conventional arm was HR = 0.654 (95% CI: 0.23–0.88). Hypofractionation came out to be more beneficial in patients with high risk group, such as PSA ≥ 20, GS > 7 or both, T ≥ T2c. In multivariate Cox proportional hazard analysis, PSA and GS > 7 proved to be independent prognostic factors.

The 3 year rates of grade 2 or more late gastrointestinal toxicities were 19.1% and 16.7%, and genitourinary toxicities were 15.5% and 11.9%, respectively, in the hypofractionated and conventional arms, with no significant difference. Grade 3 late rectal / urinary toxicities were seen only in three patients, one patient with rectal toxicity in the hypofractionated arm and two patients with urinary toxicity in the conventional arm. No grade 4 late toxicities were observed.

Grade 2 acute toxicity was more commonly observed in the hypofractionation arm (38%) in comparison to the conventional arm (33.3%), but not statistically different (p = 0.459). In only one patient in each of the hypofractionated and conventional arm, grade 3 acute toxicity was seen. Grade 4 acute toxicity was not seen.

Discussion

Various trials have been published to explore the results of hypofractionated radiation therapy delivering 77 to 82 Gy (EQD2) to the prostate, and the dose was calculated assuming α/β value of 1.5 Gy [12, 14]. In many of these studies, follow up of the patients was relatively short and grade two or more rectal late toxicities were in the range of 6-9%, and these were lower than the average 26–28% which is demonstrated by conventional radiation therapy delivering 78 Gy to the primary [3, 30]. Two randomized studies which compared hypofractionated radiation to conventional radiation therapy found no statistically significant difference in the results in terms of bNED rates and late toxicities [24, 27].

The present study was designed to evaluate the tumor control while reducing the late rectal complications, assuming α/β value of 1.5 Gy for tumor of prostate and 3 Gy for the late responding normal tissue. Grade 2 or more late rectal toxicity was approximately 29% after 80

Gy of conventional fractionated radiation [29–31]. But grade 2 or more late urinary and rectal toxicities came out to be not statistically significant between the two arms. The bNED was higher in the hypofractionated arm than the conventional arm, which was statistically significant ($p = 0.023$). The three-year incidence of grade 2 or more late rectal toxicities of 11.9–15.5% in this study was significantly lower than 25–35% rates previously demonstrated by phase three trials delivering 78 Gy at conventional fractionation of 2 Gy, and came out to be higher than 6%-9% rates published by prior hypofractionated radiation trials in literature [3, 12, 30]. Lehrer et al. demonstrated that late grade 2 or more genitourinary toxicity were 19.4% for the conventionally fractionated and 20.4% in the hypofractionated arm which is slightly higher than the present study [15].

HYPRO trial showed 19% grade 3 or more late genitourinary toxicity in the hypofractionated arm, which is slightly higher than the present study, and 13% in the conventional arm, which is lower than the present study [16]. 3-year relapse free survival was 93.6% in the hypofractionated arm and 93.7% in the conventional arm, which is slightly higher than the present study [16]. CHHiP trial demonstrated grade 2 or more bowel and bladder toxicity as 13.7% and 9.1% in conventional arm and 11.9% and 11.7% in hypofractionated arm, which are in line with the present study [17]. A study from Italy revealed 10-year freedom from biochemical failure and 10-year overall survival as 72% and 75% in the hypofractionated arm and 65% and 64% in the conventional arm, respectively, which are in line with the present study favoring the hypofractionation arm [18]. PROFIT trial by Catton et al. demonstrated that the hypofractionated radiation regimen was not inferior to conventional radiation and was not associated with increased late toxicity [19]. A study by Fox Chase Cancer Centre demonstrated the 10-year local recurrence rate of 4.7% and 4% in the conventional and hypofractionated arm, respectively, and similar rates reported in the present study. The 10-year biochemical and/or clinical disease failure was seen in 25.9% in the conventional arm and 30.6% in the hypofractionated arm, which was higher than the present study. This might be due to the fact that 3-year biochemical failure rates were reported in the present study whereas 10-year rates were reported in the above mentioned study [20]. Study from MD Anderson Cancer Centre demonstrated that the 8-year failure rate was 10.7% with the hypofractionated arm and 15.4% with conventional radiation, which are in concordance with the present study [21].

In the present study, the toxicity rate was not statistically significantly different in the conventional fractionated arm than in the hypofractionated radiation arm. One of the possible explanations for this effect could be α/β value of less than 3 Gy for OARs, such as the rectum and bladder or some other different mechanisms of radiation induced damage or repair resulting in late bladder and rectal effects in the hypofractionated arm possibly modified by the androgen deprivation therapy [9, 32]. The acute grade 2 rectal toxicity like tenesmus started earlier and was slightly higher in the hypofractionated radiation arm than the conventional radiation arm as has been seen in other studies [37]. Rapid recovery however was seen in the hypofractionated radiation arm.

Biochemical failure is common in high risk prostate cancer patients. Various studies published outcomes for prostate cancer patients receiving 78 Gy, with 3 year bNED rates of 72–75% in high risk patients [2, 3]. Another study reported 5-year PSA relapse free survival rates of 66%, 61% and 40% in high risk patients receiving 81 Gy, 75.6 Gy and 72 Gy or fewer doses at conventional radiation dose of 1.8 Gy per fraction [38]. Literature shows that 1.8 Gy per fraction delivers 4% to 6% less dose equivalent to 2 Gy, for late toxicities assuming α/β of 3 Gy [38]. Arcangeli et al. reported 3 year bNED rates of 78% in conventional radiation fractionation [26].

In the present study, equivalent dose was administered in the hypofractionated radiation arm as compared to conventional fractionation arm. But, bNED rates came out to be statistically significantly improved in the hypofractionated radiation arm. This improvement was more significant in high risk prostate cancer patients with high PSA levels and GS of more than seven.

Conclusion

To conclude, this study shows a statistically significant improvement in biochemical control in the hypofractionated radiation regimen in comparison to the conventional dose escalated radiation regimen, with no statistically significant rates of late radiation toxicities. Longer follow up and additional studies are required to translate this biochemical improvement into improved long term clinical results.

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Conflict of interest

None declared.

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Table 1. Baseline characteristics of the patients treated with hypofractionated or conventional radiotherapy

	Hypofractionated	**Conventional**	**p-value**
Number of patients	84	84	1.0000
Age [years]			
Median (range)	66 (49–74)	64 (48–72)	0.7734
T stage			
T1a	03 (3.7%)	03 (3.7%)	0.8521
T1b	08 (9.5%)	09 (10.7%)	
T1c	05 (5.6%)	06 (7.2%)	
T2a	19 (22.7%)	20 (23.9%)	
T2b	21 (25.0%)	22 (26.2%)	
T2c	17 (20.2%)	13 (15.5%)	
T3a	08 (9.6%)	09 (10.7%)	
T3b	03 (3.7%)	02 (2.4%)	
PSA concentration [ng/mL]			
< 10	28 (33.3%)	27 (32.1%)	0.8632

10–20	37 (44.0%)	36 (42.9%)	
> 20	19 (22.7%)	21 (25.0%)	
Gleason score			
≤ 6	29 (34.5%)	28 (33.3%)	0.8743
7	36 (42.9%)	35 (41.7%)	
8–10	19 (22.7%)	21 (25.0%)	
Risk group			
Intermediate	51 (60.7%)	50 (61.9%)	0.8645
High	33 (39.3%)	34 (38.1%)	
Comorbidities (HTN/DM)	36 (42.9%)	34 (40.5%)	0.7743
Prostate volume [cm^3]			
≤ 50	38 (45.2%)	40 (47.6%)	0.7665
> 50	46 (54.8%)	44 (52.4%)	

PSA — prostate specific antigen; HTN — hypertension; DM — diabetes mellitus

Table 2. Dose-volume characteristics of hypofractionated and conventional radiotherapy arms

	Hypofractionated	**Conventional**	**p-value**
Rectum wall			
Total volume ± σ [cc]	46 ± 14	44 ± 12	0.8423
$V_{87.5\%}$ (Gy) ± σ (%)	30 ± 6	29 ± 5	0.2378
$V_{62.5\%}$ (Gy) ± σ (%)	45 ± 9	42 ± 8	0.1634
Bladder wall			
Total volume ± σ [cc]	38 ± 12	42 ± 14	0.1826
$V_{87.5\%}$ (Gy) ± σ (%)	36 ± 8	34 ± 11	0.1754
$V_{62.5\%}$ (Gy) ± σ (%)	41 ± 11	45 ± 13	0.1334
PTV			
Total volume ± σ [cc]	181 ± 39	184 ± 41	0.5145
$D_{98\%}$ ± σ (% prescribed dose)	89% ± 1%	88% ± 1%	0.5937
$D_{50\%}$ ± σ (% prescribed dose)	100% ± 1%	100% ± 1%	0.2172
$D_{2\%}$ ± σ (% prescribed dose)	105% ± 1%	105% ± 1%	0.4745

PTV — planning target volume; cc — cubic centimeter; Gy — gray

Table 3. Outcomes in hypofractionated and conventional arms after a median follow up of 51 and 53 months respectively

	Total **n (%)**	**Hypofractionated**	**Conventional**	**p-value**
nPSA ≤ 0.5 ng/mL	159 (94.6%)	82 (97.6%)	77 (91.7%)	0.0814
3 year bNED	134 (79.8%)	73 (86.9%)	61 (72.6%)	0.0235
Biochemical failure	23 (13.7%)	09 (10.7%)	14 (16.7%)	0.2634
Local recurrence	06 (3.6%)	02 (2.4%)	04 (4.8%)	0.4126
Metastases	12 (7.1%)	05 (5.9%)	07 (8.3%)	0.5512
Death from other causes	05 (2.9%)	02 (2.4%)	03 (3.6%)	0.6454
Death from tumor	03 (1.8%)	01 (1.2%)	02 (2.4%)	0.5663

nPSA — nadir prostate specific antigen; bNED — biochemical no evidence of disease

Figure 1. Forest plot of biochemical no evidence of disease hazard ratios (HRs) and 95% confidence intervals (CIs) for subgroup of patients with various prognostic factors. PSA — prostate specific antigen; GS — Gleason score