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Long-term Survival Outcomes of Prostate Cancer Treated by a Moderately Hypofractionation Regimen (70Gy in 28 fractions): A Single-Center Experience

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ABSTRACT

OBJECTIVE This study aimed to assess the survival outcomes of localized prostate cancer patients treated with moderately hypofractionationated radiation therapy (70Gy in 28 fractions).

METHODS Between 2013 and 2018, a total of 96 patients with localized prostate cancer underwent radical radiotherapy. The prescribed dose for the prostate gland was 70Gy delivered in 28 fractions. In cases where elective pelvic lymph node treatment was indicated, the prescribed dose for the elective area was 50.4Gy in 28 fractions. Patient characteristics, dose parameters, treatment outcomes, and toxicities were recorded and analyzed. Treatment results were evaluated following the ASTRO-Phoenix recommendations.

RESULTS Out of the 96 patients, 86 were eligible for evaluation. The average age of the patients was 74 years, with 73 of the 86 patients (84.9%) categorized as high-risk. Eighty-one of the 86 patients (92.2%) received hormonal treatment. With a median follow-up time of 52 months, the 4-year biochemical control, disease-free survival, and overall survival rates were 100%, 100%, and 91.4%, respectively. Among this cohort, three patients experienced grade 3 gastrointestinal (GI) or genitourinary (GU) toxicities.

CONCLUSIONS The results of our study, utilizing 70Gy in 28 fractions for localized prostate cancer treatment, are promising and are comparable to findings reported in other publications. Only three patients in our cohort developed grade 3 or higher toxicity.

KEYWORDS prostate cancer, moderate hypofractionation, survival, outcomes

INTRODUCTION

Prostate cancer is one of the male cancers and is found mostly in high income countries. There are many ways to treat prostate cancer. Selection of treatment is related to stage, initial prostatic specific antigen (PSA), and grade group. Current treatment options include active surveillance, surgery, radiotherapy, hormonal therapy and focal treatments. In radiotherapy, both external beam radiotherapy (EBRT) and brachytherapy (BT) have a role in the treatment. Presently, EBRT has rapidly improved, reaching

high conformality to target with the technique of intensity-modulated radiation therapy (IMRT) with dose escalation .Based on low alpha/beta ratio, hypofractionation in theory has a role in prostate cancer treatment. Moderate hypofractionation (2.5-5Gy per fraction) has been investigated in many randomized studies and has shown non-inferiority to a dose-escalation regimen (1-3). In cases of moderate hypofractionation, two schedules are the most frequently recommended: 60Gy in 20 fractions and 70Gy in 28 fractions (4). Our hospital implemented a regimen of moderate hypofractionation in 2013 using a 70Gy in 28 fractions that has based on long-term studies by Kupelian et al. (5-7). From then through 2019, more than 90 patients were treated using this regimen. This study evaluated the survival outcomes of patients in our hospital who were treated by 70Gy in 28 fractions.

METHODS

This retrospective study evaluated the survival outcome of prostate cancer patients treated by moderate hypofractionation (70Gy in 28 fractions). The study was approved by the institutional review board (IRB) of the Faculty of Medicine, Chiang Mai University and assigned the study code RAD-2565-09210.

The study evaluated the outcomes of using 70Gy in 28 fractions in prostate cancer patients treated between 2013 through 2018. All patients were at least 18 years old and had a biopsy-proven prostatic adenocarcinoma. No uncontrolled medical conditions were observed and no previous pelvic radiotherapy or surgery was reported for any of the patients.

All patients were treated using the IMRT technique. Simulation was performed using 3-mm slice thickness CT simulation in the supine position with ankle support. Bladder protocol was followed to maintain stable bladder volume during treatment. CT datasets were uploaded to a workstation, then contouring and planning processes were conducted. Clinical target volume (CTV) was composed of prostate gland (and elective pelvic lymph node (LN)). 70Gy in 28 fractions was applied to the prostate gland and 50.4Gy in 28 fractions was applied selectively to the pelvic LN using the simultaneous integrated boost (SIB) technique. The International Commission on Radiation Units and Measurements report 83 (ICRU 83) was followed to evaluate the dose to targets. Figure 1 shows images used in planning this study.

After completion of treatment, patients were scheduled for follow-up by PSA and physical examination. In the first 2 years, every 3-6

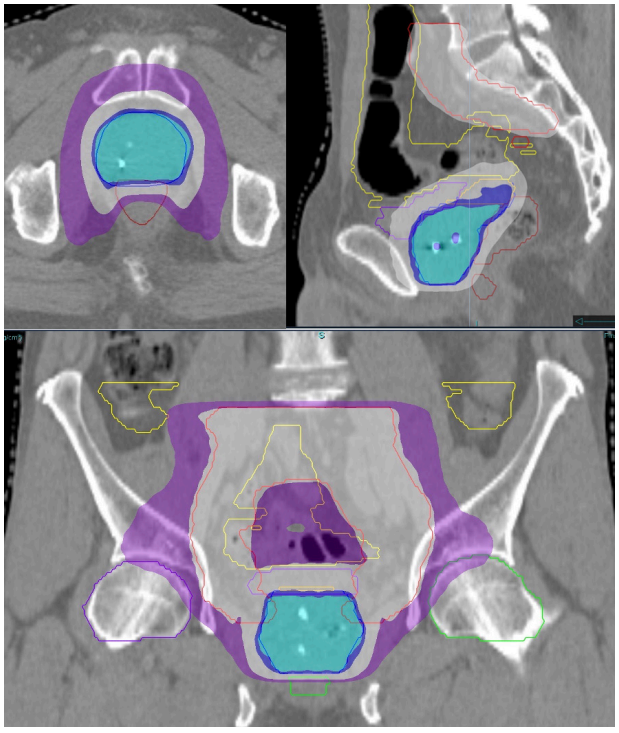

Figure 1. Dose distribution of 70Gy in 28 fractions (marine blue = 70 Gy; light yellow = 50.4 Gy)

months were designed and during 3rd-5th year, every 6 months were designed. For the first two years, examinations were scheduled every 3 to 6 months, then every 6 months during the 3rd to 5th years. ASTRO-Phoenix recommendations (nadir +2 ng/mL of PSA value) were used to evaluate the biochemical recurrence after radiotherapy (8). Overall survival is defined as the status from the start of treatment to death. Descriptive statistics are used to evaluate the quantitative data. SPSS version 22 was used for statistical evaluation.

Table 1. Patient characteristic data

Parameters	Details
Age	74 years (range 50-93)
Initial PSA	57.4 ng/mL (range 2.4-406)
PSA value	
Up to 20 ng/mL	41(47.7%)
More than 20 ng/mL	45(52.3%)
Gleason score	
Less than 6	19 (22.1%)
7	17 (19.7%)
8-10	50 (59.2%)
Tumor stage	
T1	2 (2.3%)
T2	35(40.7%)
T3	36 (41.9%)
T4	13 (15.1%)
Risk group	
Low risk	1 (1.2%)
Intermediate risk	12 (13.9%)
High risk	73 (84.9%)
Elective nodal treatment	
Yes	74 (86%)
No	12 (14%)
Androgen deprivation treatment	
No	5 (5.8%)
Short-term treatment	8 (9.3%)
Long-term treatment	73 (84.9%)
Treatment Technique	
Helical TomoTherapy	52 (60.5%)
Volumetric-modulated arc therapy	34 (39.5%)

PSA, prostatic specific antigen; ng/mL, nanograms per millimeter

RESULTS

From 2013 to 2018, 96 patients were treated in our hospital. Of those, 10 patients were excluded due to missing data; the remaining 86 patients were evaluated. The mean age of the evaluated patients was 74 years. The most common Gleason Score was 8-10 and the median PSA value was 21ng/ml. Seventy-four patients were treated by combined pelvic LN irradiation. Patient characteristics are shown in Table 1.

The mean dose to the target (D50 of PTV) was 70.7Gy. The mean dose to the D10% of the bladder and rectum were 67.9Gy and 64.7Gy, respectively. The median total treatment time was 41 days. Table 2 shows the dose characteristics for the cohort.

With a median follow-up time of 52 months, 20 patients died, 4 patients had biochemical recurrence and 3 patients had distant metastasis. The 4-year biochemical control, progression-free survival, and overall survival rates were 100%, 100%, and 91.8%, respectively. During this period, 10 patients experienced toxicity events. Three patients had grade 3-4 toxicity. Details of toxicity are shown in Table 3.

Table 2. Dose characteristic data

Parameters	Details (mean ± SD)
Volume of PTV prostate	129 cc (range 57 cc-358 cc)
D50 of PTV	70.7±0.7Gy
D98 of PTV	67.2±1Gy
D2 of PTV	72.6±1.1Gy
D10 bladder	67.9±2.7Gy
D15 bladder	65.5±4.3Gy
D25 bladder	60.7±5.9Gy
D50 bladder	49.9±7.9Gy
D10 rectum	64.7±4.5Gy
D15 rectum	61.5±5.3Gy
D25 rectum	55.8±6.3Gy
D50 rectum	44.4±7.2Gy
D50 penile bulb	32.1±14.6Gy
D5 right head of femur	30.7±7.7Gy
D5 left head of femur	30.5±8.1Gy

Dx , dose as a percentage of volume; Gy, gray; PTV, planning target volume; SD, standard deviation

Table 3. Late toxicities

Parameters	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cystitis (GU)	79 (91.9%)	4 (4.6%)	1 (1.2%)	2 (2.3%)	0
Proctitis (GI)	83 (96.5%)	0	2 (2.3%)	1 (1.2%)	0

GI, gastrointestinal; GU, genitourinary

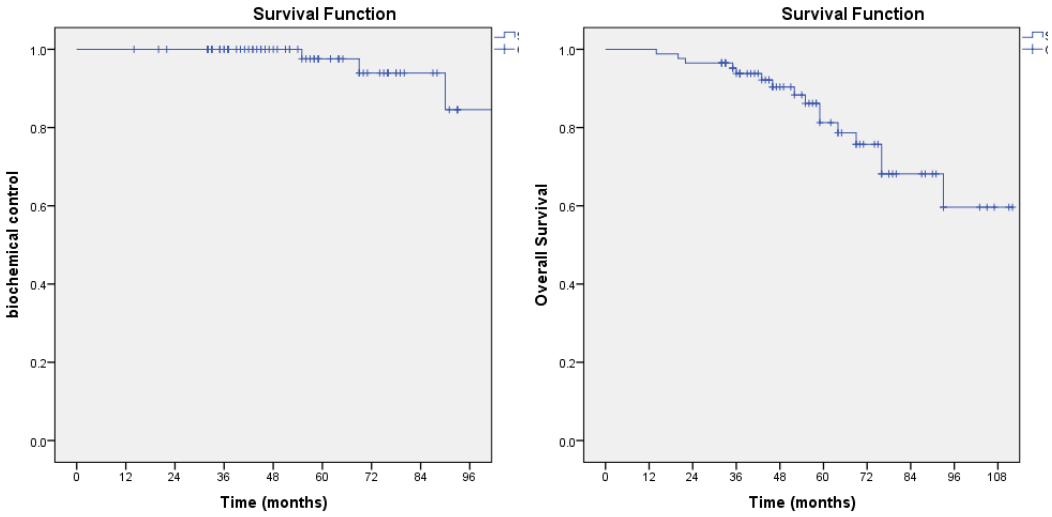

Figure 2. Kaplan-Meier survival curve of Biochemical Control and Overall Survival

DISCUSSION

Radiotherapy is one option for treatment of localized prostate cancer. Recently, moderately hypofractionated radiotherapy has come to be the standard treatment for localized prostate cancer based on randomized controlled studies showing non-inferiority results in comparisons with a dose-escalated conventional regimen. Presently, the schedules of 70Gy in 28 fractions and 60Gy in 20 fractions are supported internationally (9).

The regimen of 70Gy in 28 fractions was initially introduced by Kupelian, et al. in 2001 (6,10,11). This regimen is supported for utilization in all-risk localized prostate cancer. Ten-year results of 70Gy in 28 fractions was published in 2019. Those results showed the 10-year biochemical relapse-free survival rates were 88% for low risk, 78% for favorable intermediate risk, 71% unfavorable intermediate risk, and 42% for high-risk patients. For all patients, the 10-year actuarial overall survival rate was 69% (95% confidence interval, range 66%-73%) (12). Table 4 shows the results of selected studies of moderately hypo-fractionated regimens for localized prostate cancer. Our study reported the results of treatment of prostate cancer in our center with 70Gy in 28 fractions. The 4-year biochemical relapse-free survival and overall survival rates in our analysis were 100%, and 91.8%, respectively. These results are comparable to a study by Kupelian et al. which reported a 5-year biochemical relapse-free survival rate of 88% (6). Results of our study are closest to those in a study by Kim et al. which also used 70Gy in 28 fractions) (13).

Our study had some limitations. First, the number of patients in the study was small (86 patients) due to the low number of prostate cancer patients receiving radical radiotherapy at our hospital during the period 2013-2018. Second, our study has shorter follow-up time than some other international publications. Third, this study used a retrospective approach. Finally, the follow-up program was disrupted by the COVID-19 outbreak. Notwithstanding, our study reported the results of a moderately hypo-fractionated regimen on localized prostate cancer of various risk levels (especially high risk). In our analysis, the 4-year b-RFS and OS rates were 100% and 91.8%, respectively, results comparable to other studies with the same schedule (6,13).

CONCLUSIONS

Use of 70Gy in 28 fractions for localized prostate cancer treatment is promising, with results comparable to previous reports and only three patients developing grade 3 or higher toxicity.

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Table 4. Selected studies of moderately hypo-fractionated regimens

Study	N	Patients	FU	RT schedule	Results	Toxicity
CHHiP (1)	3,216	pT1b-T3aN0M0, prostate cancer	62.4 mos.	Group I: 74Gy in 37Fx Group II: 60Gy in20Fx Group III: 57Gy in 19Fx	5-yr. biochemical or clinical failure-free survival rate Group I: 88.3% Group II: 90.6% Group III: 85.9%	Gr2+ GI and GU Group I:13.7% and 9.1% Group II:11.9% and 11.7% Group III: 11.3% and 6.6%
RTOG 0415 (2)	1092	Low prostate cancer risk group	5.8 yrs.	73.8Gy in 41fx vs.70Gy in 28fx	5-yr. DFS 85.3% in the conventional arm and 86.3% in the hypo-fractionated arm	Late grade 2 and 3 GI and genitourinary adverse events were increased (HR, 1.31 to 1.59) in patients who were treated with H-RT.
HYPRO (14,15)	820	Stage T1b–T4 N0M0, iPSA up to 60ng/mL,	60 mos.	64.6Gy in 19fx vs. 78Gy in 39fx	5-yr. RFS was 80.5% for hypo-fractionated arm and 77.1% for conventional arm	G3+GI 17.7% vs. 21.9% (NS) G3+GU 39.0% vs. 41.3%(NS)
Abu-Gheida et al. (12)	834	LR 266, IR 344, HR 244	11.3 yrs.	70Gy in 28 fractions	10-yr. OS 69%	Gr3+ GU or GI 2% and 1%, respectively.
Kupelien et al. (6)	100	LR36 IR30 HR34	66 mos.	70Gy in 28Fx	5 yr. b-RFs 88%	Gr3+GI 3% Gr3+GU 1%
Kim et al. (13)	30	LR 5 IR 5 HR 20	74.4 mos.	70Gy in 28Fx	5 yr. b-RFS 92.9% in hypo-fractionated arm	Gr2+GU 3.3% Gr2+GU 6.6%
Our study	86	LR 1 IR 12 HR 73	52 mos.	70Gy in 28Fx	4-yr. b-RFS 100% 4-yr. OS 91.8%	Gr2+GU 3.5% Gr2+GI 3.5%

GI,gastrointestinal; GU, genitourinary; Fx, fraction; HR,high risk; IR, intermediate risk; iPSA, initial PSA before treatment; LR, low risk; FU, follow-up; mos, months; OS, overall survival; b-RFS, biochemical relapse-free survival; WHO, World Health Organization

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ADDITIONAL INFORMATION

Contribution

E.T.: concept design, data grouping, data calculation, data analysis, and manuscript writing; P.M.: data collection, S.C.: data collection; P.K.: data collection, WO: data collection, B.J.: data collection; P.T.: data collection; W.N.: physics data collection; A.W.: physics data collection; I.C., V.S, and V.L.: consultant. This manuscript was reviewed by all authors.

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