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ORIGINAL ARTICLE **CME**

Moderately Hypofractionated Versus Conventionally Fractionated Volumetric Modulated Arc Therapy for Definitive Treatment of Localised Prostate Cancer

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ABSTRACT

Introduction: *This retrospective study compares the treatment outcome of a reduced dose with moderate hypofractionation (60 Gray in 20 fractions [60 Gy/20 fr]) with conventionally fractionated (76 Gy/38 fr) volumetric modulated arc therapy for definitive treatment of localised prostate cancer in a public hospital in Hong Kong.*

Methods: *All patients with low- or intermediate-risk prostate cancer (defined according to the National Comprehensive Cancer Network Guidelines) who received definitive radiotherapy from 1 January 2017 to 30 June 2022 were included.*

Results: *A total of 105 patients were identified (58 receiving moderate hypofractionation and 47 receiving conventional fractionation). The median follow-up period was 38.3 months. Grade 2 acute gastrointestinal (GI) toxicity was more common with moderate hypofractionation than with conventional fractionation (15.5% vs. 2.1%, 95% confidence interval = 1.03-69.33; p = 0.02). In the moderate hypofractionation cohort, the planning target volume (PTV) in patients who experienced grade ≥2 acute genitourinary (GU) toxicity was significantly higher than those who did not (p = 0.03). None of the patients developed grade ≥3 acute GI toxicity. The incidence of grade 3 acute or late GU and late GI toxicities was rare with both fractionation schedules.*

Conclusion: *This study shows that moderately hypofractionated radiotherapy is a safe, effective and feasible alternative to conventionally fractionated radiotherapy for low- and intermediate-risk prostate cancer in the Chinese community. Patients should be counselled on the potential increase in low-grade acute GI toxicity with moderate hypofractionation, which is usually self-limited and is not associated with increases in long-term toxicity. Close monitoring for acute GU toxicity in patients with larger PTVs is warranted.*

Key Words: *Neoplasms; Prostate; Radiotherapy*

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Ethics Approval: The research was approved by the Hong Kong East Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: HKECREC 2022-068). The requirement of patient consent was waived by the Committee due to the retrospective nature of the research.

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中文摘要

中等強度大分割及傳統大分割體積調控弧型放射治療作為局部前列腺癌根治性治療方案的比較

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引言：本回顧性研究旨在比較在香港一所公立醫院進行的已減劑量的中等強度大分割（60 Gy分20次）及傳統大分割（76 Gy分38次）體積調控弧型放射治療作為局部前列腺癌根治性治療方案。

方法：本研究納入在2017年1月1日至2022年6月30日期間接受根治性放射治療的所有低風險及中風險前列腺癌患者（根據美國國家綜合癌症網絡指引定義）。

結果：我們共找到105名患者（58名接受中等強度大分割，47名接受傳統大分割）。隨訪時間中位數為38.3個月。第2級急性腸胃道毒性於中等強度大分割中較常見，在傳統大分割則較少見（15.5%與2.1%，95%置信區間 = 1.03-69.33；p = 0.02）。在中等強度大分割隊列中，有第2級或以上急性泌尿生殖系統毒性的患者的治療計劃靶體積顯著高於沒有相關毒性的患者（p = 0.03）。沒有患者有第3級或以上急性腸胃道毒性。第3級急性或晚期泌尿生殖系統毒性及晚期腸胃道毒性在兩個分割治療計劃中均屬罕見。

結論：本研究顯示對於低風險及中風險前列腺癌華裔患者而言，中等強度大分割放射治療是傳統大分割放射治療的安全、有效且可行的替代方案。患者應獲告知中等強度大分割的低級急性腸胃道毒性有可能增加，而該增加通常具自限性，並與長期毒性增加無關。醫護人員應密切監察治療計劃靶體積較高的患者的急性泌尿生殖系統毒性。

INTRODUCTION

Globally, prostate cancer ranks second in cancer incidence and fifth in cancer mortality among males; it has become the most frequently diagnosed cancer in >100 countries.[1] In Hong Kong, prostate cancer ranks fourth in cancer incidence.[2]

For low- or intermediate-risk prostate cancer, external beam radiotherapy (EBRT) and radical prostatectomy are associated with lower incidence of disease progression and metastasis compared to active surveillance. There is no difference in 10-year overall survival or disease-free survival between the two treatments.[3] Radiotherapy has the benefit of sparing patients from surgical and anaesthetic risks, which is especially relevant for patients of advanced age or with medical co-morbidities.

Dose escalation in definitive radiotherapy for prostate cancer increases tumour biological effective dose which leads to improvement in relapse-free survival.[4,5] On the other hand, the location of the prostate near organs at risk (OARs) such as the rectum and bladder leads to inevitably heightened gastrointestinal (GI) and genitourinary (GU) toxicities.[4-8] Recent advances in planning techniques and image guidance have led to improvement in treatment precision. Volumetric modulated arc therapy (VMAT) allows better dose conformation than traditional conformal EBRT, thus minimising dose to surrounding OARs. Image guidance strategies such as cone beam computed tomography (CT), in contrast to traditional two-dimensional kilovoltage imaging, allows more accurate definition and verification of targets and pelvic organs, thereby allowing tighter margins and smaller treatment volumes.

In the past decade, moderately hypofractionated EBRT (generally fractional doses of 2.4 Gray [Gy] to 3.4 Gy[9]) has been increasingly adopted to overcome the limitations of dose escalation in conventional radiotherapy by exploiting the low alpha/beta ratio of prostate cancer. The alpha/beta ratio is inversely correlated to the effect of change in fractional size in normal or malignant tissues. Most cancers have an alpha/beta ratio of approximately 10, whereas OARs typically have an alpha/beta ratio of about 3. Prostate cancer, in contrast to other cancers, has a lower alpha/beta ratio of approximately 1.5.[10,11]

Hypofractionation takes advantage of the low alpha/beta ratio of prostate cancer relative to surrounding OARs to enhance biologically equivalent tumour doses while minimising toxicity to normal tissues.[10,12-16]

Multiple studies have shown the comparable efficacy of moderate hypofractionation to conventional fractionation schedules.[17-22] The guidelines published by ASTRO/ASCO/AUA (the American Society for Radiation Oncology, the American Society of Clinical Oncology, and the American Urological Association) in 2018 recommended moderately hypofractionated EBRT over conventional schedules, especially when nodal irradiation was not required.[9] One of the most widely adopted regimens in clinical practice is 60 Gy in 20 daily fractions (60 Gy/20 fr).

The most relevant toxicities in prostate cancer radiotherapy include GU and GI toxicities as well as sexual dysfunction due to the target's proximity to the bladder, rectum, small bowel, and penile bulb. Most prospective clinical trials had demonstrated slightly increased acute GI toxicity in moderate hypofractionation compared to conventional schedules. Some trials had shown increases in late GU and GI side-effects (mostly of low grade), while others showed no significant differences. Overall, in all trials, there was no significant safety concern with moderately hypofractionated EBRT.[18-20,23-25]

The patient population of most large-scale prospective clinical trials has consisted mainly of Caucasians. So far, there are relatively scarce data reporting on the clinical utility, safety, and efficacy of moderately hypofractionated EBRT in Chinese populations.[26,27] Furthermore, most randomised trials did not necessitate the use of modern radiotherapy techniques such as VMAT,[17,18,22] nor the mode or intensity of image verification.[17-19,22]

Moderately hypofractionated VMAT for definitive treatment of low- and intermediate-risk prostate cancer was introduced in the Department of Clinical Oncology of Pamela Youde Nethersole Eastern Hospital in Hong Kong in January 2017. Since then, both moderate hypofractionation and conventional fractionation can be used for low- and intermediate-risk prostate cancer graded according to the National Comprehensive Cancer Network (NCCN) Guidelines at the clinician's discretion, although the former has been more commonly prescribed in recent years. In this study, we report our 6-year institutional experience in both treatment strategies, which provides real-world data on the toxicity and early treatment outcomes using modern EBRT technique in the local Chinese community under a public hospital setting. This is particularly relevant considering that moderate hypofractionation for prostate cancer has not been universally adopted in Hong Kong.

METHODS

Patients

This study included 105 consecutive patients with NCCN low- or intermediate-risk localised prostate cancer who received moderately hypofractionated or conventionally fractionated VMAT as definitive treatment from 1 January 2017 to 30 June 2022 at the Department of Clinical Oncology of Pamela Youde Nethersole Eastern Hospital. Patients had histologically confirmed prostate carcinoma, with clinical tumour (T) stage ≥2 disease by clinical and multiparametric magnetic resonance imaging staging, as well as a pretreatment prostate-specific antigen (PSA) level of ≤20 ng/mL and a Gleason score of ≤7. A bone scan or ^{68}Gallium–prostate-specific membrane antigen–HBED-CC positron emission tomography–CT was used for staging when clinically indicated.

Treatment Method

Moderate Hypofractionation

For moderate hypofractionation, EBRT consisted of inversely planned VMAT of 60 Gy/20 fr, administering 5 fractions per week. Patients were simulated and treated in the supine position on a flat tabletop in a customised vacuum bag (or alpha cradle). They were instructed to maintain a comfortably full bladder and empty rectum (using micro-enema). Non-contrast CT images of the pelvis with slice thickness of 3 mm were acquired and fused with diagnostic multiparametric magnetic resonance imaging images for radiotherapy planning. Perirectal spacer was not employed in all cases.

The clinical target volume (CTV) was the whole prostate and proximal 1 cm of seminal vesicles for low- and favourable intermediate-risk disease, while the seminal vesicles were included in their entirety for unfavourable intermediate-risk disease. The planning target volume (PTV) was an 8-mm circumferential expansion from the CTV, except 5 mm posteriorly (towards the rectum). Online verification with cone beam CT was performed before each treatment fraction, complemented by the 6 degrees-of-freedom treatment couch for corrections. Typical dose distribution of moderately hypofractionated VMAT is illustrated in the Figure.

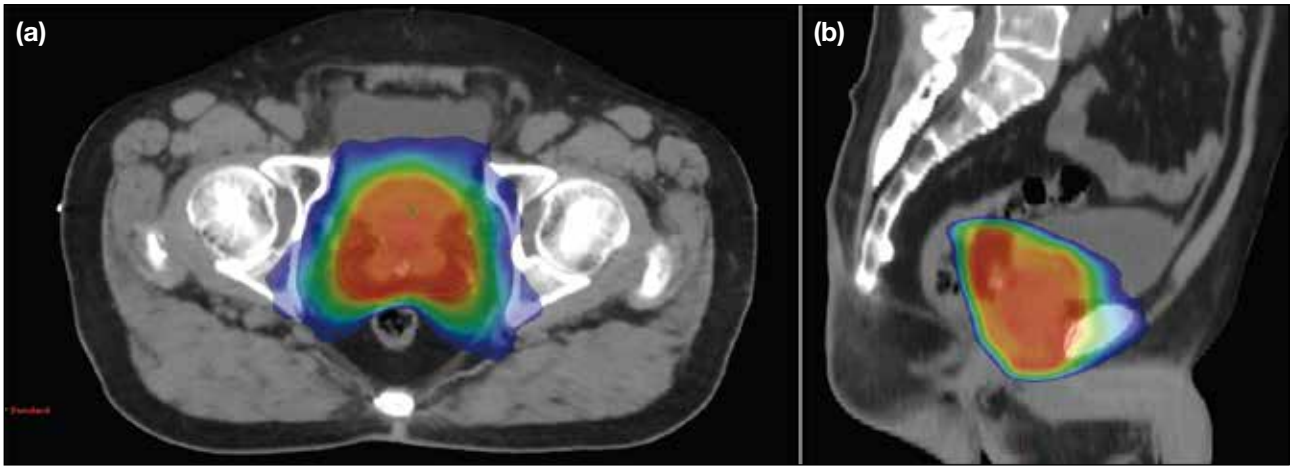

Figure. Typical dose distribution of moderately hypofractionated volumetric modulated arc therapy in axial (a) and sagittal (b) planes. Red colour maps the target volume receiving at least 100% dose.

Conventional Fractionation

For conventional fractionation, EBRT consisted of inversely planned VMAT of 76 Gy/38 fr, administering 5 fractions per week. Patients were simulated and treated in the same setup as that used for moderate hypofractionation.

The CTV was the same as that of moderate hypofractionation, i.e., the whole prostate and proximal 1 cm of seminal vesicles for low- and favourable intermediate-risk disease, while the seminal vesicles were included in their entirety for unfavourable intermediate-risk disease. The PTV was a 10-mm circumferential expansion from the CTV, except 5 mm posteriorly (towards the rectum). Online verification consisted of daily on-board orthogonal kilovoltage imaging, and then with cone beam CT before the first three treatment fractions weekly. Planning objectives and dose constraints to OARs followed the standard institutional protocol (online supplementary Table). Normal organ and target dosimetric priorities were rectum and bladder and PTV coverage.

Neoadjuvant-concurrent luteinising hormone-releasing hormone analogue for 6 months was permitted for intermediate-risk patients in both treatment groups with adverse risk features. If given, this was initiated 3 months prior to radiotherapy.

Follow-up

Clinical assessment was performed at least twice weekly during, at the end of, and 2 weeks after radiotherapy treatment, followed by every 3 to 6 months in the first 5 years, and annually thereafter. Post-treatment PSA level was checked at least half-yearly after radiotherapy.

Assessment

The acute and late GI and GU toxicities arising from radiotherapy were scored according to the National Cancer Institute's CTCAE (Common Terminology Criteria for Adverse Events) version 5.0.[28] Acute treatment toxicities in this study were defined as events occurring within 18 weeks from the start of radiotherapy. Late toxicities were those appearing >18 weeks from the start of radiotherapy.

Biochemical failure was defined by the Phoenix criteria (rise of PSA level of ≥2 ng/mL above the nadir PSA level).[29] Clinical recurrence was defined by any clinical or radiological evidence of disease recurrence at local, regional, or distant sites.

Endpoints and Statistical Analyses

The primary endpoint was the development of radiotherapy-related toxicity. Time-to-event was defined from the first fraction of radiotherapy to the appearance of treatment toxicity at follow-up. The data cut-off was 30 June 2023. Patients were censored at death or at data cut-off, whichever occurred first.

The influence of clinicopathological characteristics and radiotherapy-related parameters on radiotherapy-related toxicities were analysed. For acute toxicities, continuous variables were analysed by logistic regression;

categorical variables were analysed by Pearson's Chi squared test and Fisher's exact test. For late toxicities, continuous variables were analysed by univariate Cox regression; categorical variables were analysed by log-rank test.

A p value of < 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States).

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was implemented in the preparation of the manuscript.

RESULTS

Patient Characteristics

Of the 105 patients identified, 58 had undergone moderate hypofractionation and 47 had undergone conventional fractionation. Table 1 shows the clinicopathological and treatment characteristics of both groups.

Clinical Manifestations of Acute Genitourinary Toxicity

Among patients with any grade acute GU toxicities, the most frequently reported symptoms were urinary frequency (65.4% in the moderate hypofractionation group and 52.3% in the conventional fractionation group), followed by nocturia (13.5% in the moderate hypofractionation group and 25.0% in the conventional fractionation group) and dysuria (7.7% in the moderate hypofractionation group and 9.1% in the conventional fractionation group). Two patients in the moderate hypofractionation group had grade 3 acute GU toxicity, one presented as haematuria and another one as acute urinary retention. One patient in the conventional fractionation group had grade 3 acute GU toxicity, which presented as acute urinary retention (Table 2).

Clinical Manifestations of Acute Gastrointestinal Toxicity

Among patients with any grade acute GI toxicities, the most reported symptoms were diarrhoea (75.0% in the

Table 1. Clinicopathological and treatment characteristics.*

	Moderate hypofractionation (n = 58)	Conventional fractionation (n = 47)	p Value
Age, y	71 (56-81)	71 (59-83)	0.16
ECOG performance status score			
0	16 (27.6%)	7 (14.9%)	
1	39 (67.2%)	39 (83.0%)	
2	3 (5.2%)	1 (2.1%)	0.22
Charlson Comorbidity Index score			
1	3 (5.2%)	1 (2.1%)	
2	19 (32.8%)	7 (14.9%)	
3	26 (44.8%)	18 (38.3%)	
4	7 (12.1%)	12 (25.5%)	
≥5	3 (5.2%)	9 (19.1%)	0.02
Gleason score			
3 + 3	22 (37.9%)	14 (29.8%)	
3 + 4	23 (39.7%)	12 (25.5%)	
4 + 3	13 (22.4%)	21 (44.7%)	0.05
Baseline PSA, ng/mL	8.5 (0.8-19.9)	9.0 (0.8-19.1)	0.46
Tumour (T) stage			
T1	33 (56.9%)	39 (83.0%)	
T2	25 (43.1%)	8 (17.0%)	0.004
NCCN risk			
Low	10 (17.2%)	4 (8.5%)	
Favourable intermediate	21 (36.2%)	16 (34.0%)	
Unfavourable intermediate	27 (46.6%)	27 (57.4%)	0.35
Use of ADT	46 (79.3%)	43 (91.5%)	0.08
Prostate volume on planning CT, cm^3	45.0 (10.4-166.3)	166.6 (81.9-408.3)	0.89
PTV, cm^3	125.4 (49.0-393.4)	166.6 (81.9-408.3)	< 0.001
Follow-up, mo	28.3 (12.2-73.6)	56.1 (14.8-77.6)	< 0.001

Abbreviations: ADT = androgen deprivation therapy; CT = computed tomography; ECOG = European Cooperative Oncology Group; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; PTV = planning target volume.
* Data are shown as No. (%) or median (range).

Table 2. Incidence of toxicities in moderate hypofractionation versus conventional fractionation groups.* †

	Acute GU toxicity		Acute GI toxicity	
	Moderate hypofractionation (n = 58)	Conventional fractionation (n = 47)	Moderate hypofractionation (n = 58)	Conventional fractionation (n = 47)
Grade 1	35 (60.3%)	29 (61.7%)	6 (10.3%)	9 (19.1%)
Grade 2	15 (25.9%)	14 (29.8%)	9 (15.5%)	1 (2.1%)
Grade 3	2 (3.4%)	1 (2.1%)	0	0
	Late GU toxicity		Late GI toxicity	
	Moderate hypofractionation (n = 58)	Conventional fractionation (n = 47)	Moderate hypofractionation (n = 58)	Conventional fractionation (n = 47)
Grade 1	35 (60.3%)	22 (46.8%)	8 (13.8%)	3 (6.4%)
Grade 2	4 (6.9%)	8 (17.0%)	9 (15.5%)	7 (14.9%)
Grade 3	2 (3.4%)	3 (6.4%)	1 (1.7%)	4 (8.5%)

Abbreviations: GI = gastrointestinal; GU = genitourinary.
* Data are shown as No. (%).
† No grade 4 acute and late urinary or bowel toxicity were recorded.

moderate hypofractionation group and 80.0% in the conventional fractionation group), followed by rectal bleeding (16.7% in the moderate hypofractionation group and 10.0% in the conventional fractionation group).

Clinical Manifestations of Late Genitourinary Toxicity

Among patients with any grade late GU toxicities, the most reported symptoms in the moderate hypofractionation group were nocturia (43.9%), followed by urinary frequency (29.3%) and incontinence (9.8%); the most reported symptoms in the conventional fractionation group were nocturia (51.5%), followed by urinary frequency (24.2%), haematuria (15.2%), and incontinence (3.0%). Two patients in the moderate hypofractionation group had grade 3 late GU toxicity, both present as haemorrhagic cystitis. Three patients in the conventional fractionation group had grade 3 late GU toxicity, two presented as haemorrhagic cystitis and one presented as urethral stricture (Table 2).

The median time to develop grade ≥2 late GU toxicity was 32.6 months for the moderate hypofractionation group and 26.4 months for the conventional fractionation group. There was no statistically significant difference between the two groups in time for occurrence of grade ≥2 late GU toxicity ($p = 0.48$).

Clinical Manifestations of Late Gastrointestinal Toxicity

Among patients with any grade late GI toxicities, the most reported late GI toxicity was predominantly proctitis (88.9% in the moderate hypofractionation group and 100% in the conventional fractionation group). No faecal incontinence was reported. The incidence of grade ≥2 late GI toxicity was 17.2% in the hypofractionation group and 23.4% in the conventional fractionation group. One patient in the moderate hypofractionation group and four patients in the conventional fractionation group had grade 3 GI toxicity, all presented as proctitis (Table 2).

The median time to grade ≥2 late GI toxicity was 20.1 months for the moderate hypofractionation group and 22.4 months for the conventional fractionation group. There was no statistically significant difference between the two groups in time for occurrence of grade ≥2 late GI toxicity ($p = 0.48$).

Erectile Dysfunction

The incidence of any grade erectile dysfunction was 6.9% in the moderate hypofractionation group and 10.6% in the conventional fractionation group. The median time to develop erectile dysfunction was 13.1 months in the moderate hypofractionation group and 6.5 months in the conventional fractionation group. There was no statistically significant difference between the two groups in the probability of developing erectile dysfunction ($p = 0.17$).

Effect of Radiotherapy Parameters on Radiotherapy Toxicities

Table 3 shows the effect of radiotherapy parameters on radiotherapy toxicities. The PTV in patients who experienced grade ≥2 acute GU toxicity is significantly higher those who did not ($p = 0.03$). No significant clinical or treatment parameters were found to be predictive of other toxicity endpoints for the two fractionation schedules.

Table 3. Effect of radiotherapy parameters on treatment toxicities.*

	Grade ≥2 acute GU toxicity		Grade ≥2 acute GI toxicity		Grade ≥2 late GU toxicity		Grade ≥2 late GI toxicity	
	OR (95% CI)	p Value	OR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
				Moderate hypofractionation				
Prostate volume	1.02 (1.00-1.04)	0.11	1.01 (0.99-1.04)	0.30	1.02 (0.99-1.05)	0.28	1.01 (0.98-1.03)	0.54
PTV	1.01 (1.001-1.02)	0.03	1.00 (0.98-1.01)	0.53	1.02 (1.00-1.04)	0.13	1.00 (0.98-1.01)	0.76
Rectum V_{60}			0.59 (0.21-1.68)	0.33			0.62 (0.20-1.91)	0.40
Rectum V_{58}			0.91 (0.71-1.16)	0.45			0.94 (0.77-1.16)	0.57
Bladder V_{60}	1.22 (0.86-1.73)	0.27			0.83 (0.41-1.68)	0.60		
Bladder V_{50}	1.05 (0.95-1.16)	0.33			0.93 (0.80-1.09)	0.37		
				Conventional fractionation				
Prostate volume	0.99 (0.97-1.01)	0.43	0.99 (0.92-1.06)	0.80	1.00 (0.98-1.02)	0.79	0.99 (0.97-1.01)	0.43
PTV	1.00 (0.99-1.01)	0.57	1.00 (0.97-1.03)	0.82	1.00 (0.99-1.01)	0.77	1.00 (0.99-1.01)	0.35
Rectum V_{70}			0.80 (0.45-1.43)	0.45			0.96 (0.81-1.14)	0.66
Rectum V_{50}			0.87 (0.62-1.24)	0.44			0.93 (0.85-1.03)	0.16
Bladder V_{70}	1.07 (0.96-1.20)	0.22			1.07 (0.97-1.18)	0.21		
Bladder V_{55}	1.04 (0.97-1.12)	0.25			1.04 (0.98-1.11)	0.20		

Abbreviations: 95% CI = 95% confidence interval; GI = gastrointestinal; GU = genitourinary, HR = hazard ratio; OR = odds ratio; PTV = planning target volume.
* In the first column, V_{60} means the volume of the organ-at-risk of interest receiving ≥60 Gy of the prescribed radiation dose, and so on.

Table 4. Comparison of characteristics and toxicity of moderate hypofractionation among landmark studies and the current study.

	CHHiP[19]	HYPRO[22,24,25,30]	PROFIT[18]	RTOG 0415[17,23]	Current study
Fractionation and dose	60 Gy/20 fr; 5 fr/week	64.6 Gy/19 fr; 3 fr/week	60 Gy/20 fr; 5 fr/week	70 Gy/28 fr; 5 fr/week	60 Gy/20 fr; 5 fr/week
NCCN low risk	15%	Excluded	Excluded	100%	17.2%
NCCN intermediate risk	73%	26%	100%	Excluded	82.8%
NCCN high risk	12%	74%	Excluded	Excluded	Excluded
Use of concurrent ADT	97%	66%	Excluded	Excluded	79.3%
Grade ≥2 acute GU toxicity	49%	60.5%	30.9%	27.0%	29.3%
Grade ≥2 acute GI toxicity	38%	42%	16.7%	10.7%	15.5%
Grade ≥2 late GU toxicity	11.7%*	41.3%*	22.2%*	29.7%*	10.3%
Grade ≥2 late GU toxicity	6%*	19.0%*	2.2%*	3.5%*	3.4%
Grade ≥2 late GI toxicity	11.9%*	21.9%*	8.9%*	22.4%*	17.2%
Grade ≥3 late GI toxicity	3%*	3.3%*	1.5%*	4.1%*	1.7%
Biochemical recurrence-free survival/DFS	5-year biochemical or clinical failure-free rate: 90.6% (95% CI = 88.5%-92.3%)	5-year relapse-free survival: 80.5% (95% CI = 75.7%-84.4%)	5-year DFS: 85% (95% CI = 82%-88%)	5-year DFS: 86.3% (95% CI = 83.1%-89.0%)	No biochemical failure/clinical recurrence in follow-up period

Abbreviations: 95% CI = 95% confidence interval; ADT = androgen deprivation therapy; DFS = disease-free survival; GI = gastrointestinal; GU = genitourinary; NCCN = National Comprehensive Cancer Network.
* Till the end of study.

Biochemical Failure and Clinical Recurrence

There was one biochemical failure with clinical recurrence in the conventional fractionation arm and none in the moderate hypofractionation arm.

DISCUSSION

Landmark trials including CHHiP,[19] HYPRO (HYpofractionated irradiation for PROstate cancer),[22,24,25,30] PROFIT (Prostate Fractionated Irradiation Trial),[18] and RTOG 0415[17,23] have shown that moderately hypofractionated radiotherapy to prostate is as effective as conventional fractionation. However, the data on toxicities were less consistent (Table 4).

Our real-world data showed that the increased acute GI toxicity from moderately hypofractionated radiotherapy was limited to grade 2 and did not lead to increase in long-term toxicity. As recommended by the ASTRO/ASCO/AUA 2018 guideline, patients should be counselled on the small increased risk of acute GI

Table 5. Risk of genitourinary and gastrointestinal toxicities in moderate hypofractionation versus conventional fractionation groups.

	OR (95% CI)	p Value
Grade ≥2 acute GU toxicity	0.89 (0.38-2.04)	0.77
Grade ≥2 acute GI toxicity	8.45 (1.03-69.33)	0.02
	HR (95% CI)	p Value
Grade ≥2 late GU toxicity	0.77 (0.28-2.14)	0.62
Grade ≥2 late GI toxicity	1.29 (0.54-3.12)	0.57

Abbreviations: 95% CI = 95% confidence interval; GI = gastrointestinal; GU = genitourinary; HR = hazard ratio; OR = odds ratio.

toxicity with moderate hypofractionation.[9] Both the CHHiP[19] and PROFIT[18] trials showed lower rates of late GI toxicities with moderately hypofractionated EBRT. In contrast, the late GI toxicity rate was higher with moderate hypofractionation in the RTOG 0415 trial.[17] In our study, no difference was detected between the fractionation schedules for grade ≥2 late GI toxicity (p = 0.57) [Table 5]. For the incidence of grade 3 late GU and GI toxicities in the moderate hypofractionation cohorts, the rates were low in the current study (Table 2).

In general, the incidence of radiotherapy-related toxicities in the current study was lower than that reported in the landmark trials on moderate hypofractionation. There may be several reasons. First, the lower late toxicities may be attributed to shorter follow-up time. The landmark trials had a median follow-up of at least 60 months (62.4 months in CHHiP,[19] 60 months in HYPRO,[22] 72 months in PROFIT,[18] and 70 months in RTOG 0415[17,23]), while the median follow-up time in the current study was 38.3 months (range, 12.2-77.6). We expect more mature late toxicity data with longer follow-up. The long-term radiotherapy-related toxicities may not be fully reflected; nevertheless, it is worth noting that in the landmark prospective trials, the majority of grade ≥2 late toxicity occurred within the first 2 years of follow-up. Second, we adopted inversely planned VMAT with stringent planning aims and dose constraints for OARs, together with daily cone beam CT verification for moderate hypofractionation. Most of the landmark prospective trials did not mandate the use of intensity-modulated radiotherapy or VMAT,[17,18,22] nor did they require the technique or intensity of image verification.[17-19,22] In our study, modern dose planning with VMAT technique and intensive image guidance allowed tight PTV margins and more precise treatment delivery, which could be a contributing factor to the lower incidence of treatment-related toxicities. Third, due to the retrospective nature of this study that reflects on real-world clinical practice, meticulous and frequent documentation of toxicity was difficult. Our reporting on toxicities was limited by inter-clinician variation in toxicity charting (especially for low-grade events), and lack of formal reporting of patient-reported outcome. In addition, there may be cultural variations in toxicity reporting by patients, especially sexual dysfunction, which is often considered a sensitive topic and often underrepresented in the local Chinese population.

The PTV in patients who experienced grade ≥2 acute GU toxicity is significantly higher those who did not (p = 0.03). Interestingly, bladder V_{60} and V_{50}, which reflect the bladder volume receiving high doses (≥60 Gy and ≥50 Gy, respectively), were not significant predictors of acute GU toxicity (Table 3). This may be due to interfractional variation in bladder filling during the course of radiotherapy, which may result in variation between planned and actual bladder doses. Nevertheless, in real life practice, it would be helpful to offer close monitoring of acute GU toxicities for patients with larger PTVs.

There was only one biochemical failure in the conventional fractionation arm and none in the moderate hypofractionation arm. The relatively lower incidence of biochemical or clinical failure in our local cohort compared to other landmark trials may be explained by shorter follow-up duration, differences in patient selection, and use of androgen deprivation therapy (ADT). As discussed above, the landmark trials had a median follow-up of at least 60 months, in contrast to 38.3 months in the current study, making it difficult to conclude on long-term disease control based on the current results. Furthermore, in this study, all patients were classified into low- or intermediate-risk categories according to the NCCN Guidelines. The presence of high-risk patients in CHHiP[19] and HYPRO[22] trials may be a reason for the higher biochemical or clinical failure rate in these trials. In PROFIT[18] and RTOG 0415 trials,[17] the use of ADT was not allowed. On the other hand, 79.3% patients in the hypofractionation cohort received ADT in the current study, which likely contributed to better biochemical control (Table 4).

We have observed a gradual but significant shift in practice from conventional fractionation to moderate hypofractionation over the years. Among patients treated between 2017 and 2019, adoption of moderate hypofractionation was 24.1%. The rate rose to 80.9% in 2020 to 2022. This reflects the evolution in treatment

paradigms with increasing clinical data and local experience to support moderate hypofractionation.

Limitations

Other limitations of our current study include imbalance in baseline characteristics including Charlson Comorbidity Index score, tumour stage, PTV, and median follow-up time, which may be confounders on toxicity outcomes. This was due to the intrinsic nature of a retrospective study. The difference in follow-up duration between the two patient cohorts reflects real-world gradual adoption of moderate hypofractionation and growth in local experience in this technique. Despite the above limitations, it is worth noting that the study cohort represents local real-world data of all consecutive patients treated in the same institution over 5 years, using contemporary radiotherapy planning and intensive image guidance, for which similar reports in Chinese patients are scarce.

Future Directions

Further dose escalation with an intraprostatic boost may improve disease control. The FLAME trial (Fluoxetine for motor recovery after acute ischaemic stroke) demonstrated superior biochemical disease-free survival with a focal 95-Gy boost to macroscopic tumour whilst toxicities and quality of life were not compromised.[31] The ongoing multicentre phase III PIVOTALboost trial may offer phase III data on dose escalation to the prostate (using brachytherapy or EBRT) on top of moderately hypofractionated EBRT in high-intermediate to high-risk patients.[32]

In recent years, there has been growing interest in ultra-hypofractionated EBRT for definitive treatment of prostate cancer (using ≥5 Gy per fraction) to further exploit the biological advantage of its low alpha/beta ratio. The HYPO trial showed comparable 5-year failure-free survival and late toxicities but increased acute GU and GI toxicities for ultra-hypofractionation compared to conventional schedules.[33] The 2-year toxicity data of the PACE-B trial[34,35] and early toxicity data of HEAT (The Helicobacter Eradication Aspirin Trial)[36] had not shown significant safety concerns with ultra-hypofractionated radiotherapy. The long-term data of these studies are eagerly awaited. Considering the encouraging results so far, the ASTRO/ASCO/AUA 2018 guidelines conditionally recommended that ultra-hypofractionated radiotherapy may be offered for low- and intermediate-risk prostate cancer but strongly encouraged treatment of intermediate-risk patients in a clinical trial or multi-institutional registry.[9] It is noteworthy that stereotactic ablative radiotherapy demands high precision in setup, planning, dosimetry, verification, and quality assurance.

The availability of biodegradable spacers placed between the rectum and prostate has been reported to reduce the volume of rectum irradiated and thus further mitigates GI toxicity. Both hydrogel and hyaluronic acid spacers have been demonstrated in phase III clinical trials to improve rectal sparing and reduce GI toxicity.[37,38] As moderately hypofractionated EBRT has been reported to result in more acute GI toxicity compared to conventional schedules, use of perirectal spacers may play a role in improving the therapeutic window in suitable patients.

The effect of high dose volumes (i.e., the volume receiving high dose) of rectum and bladder on radiotherapy-related toxicities was reported in this study. These OAR parameters were chosen due to the more established dose-response relationship with radiotherapy-related toxicities and reflected our local OAR constraints. Low dose volumes to OARs are potential predictors of low-grade toxicities, and it will be a meaningful future research direction to explore the dose-response relationship between low dose volumes to OARs (e.g., V_{20}) and radiotherapy-related toxicities.

CONCLUSION

A major advantage of moderate hypofractionation is the reduction of ≥40% treatment visits, translating to improved patient convenience, alleviation of clinical manpower pressures, and demands on healthcare resources. With the demanding workload in the healthcare system, moderately hypofractionated radiotherapy is considered a cost-effective treatment strategy.[39]

Local institutional outcomes suggested that image-guided moderately hypofractionated radiotherapy using VMAT technique is a safe, effective, and feasible alternative to conventionally fractionated radiotherapy for low- and intermediate-risk prostate cancer in the Chinese community in a public hospital setting. Patients should be counselled on the potential increase in acute GI toxicity that is likely to be low-grade. It is encouraged to take note of the PTV during radiotherapy planning and to offer close monitoring for acute toxicities.

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