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Hypo Fractionated Versus Conventional Fractionated Intensity Modulated Radiotherapy for Intermediate & High Risk Localized Prostate Cancer

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ABSTRACT

Background: Hypo fractionated radiotherapy emerged as a promising alternative to conventional fractionation for localized prostate cancer, particularly given the low α/β ratio of prostate tumors. However, evidence remains limited in unfavorable intermediate- and high-risk patients. This study compared the efficacy and safety of hypo fractionated versus conventional fractionated radiotherapy in this high-risk population.

Purpose: This prospective study compared the efficacy, toxicity, and dosimetric profiles of hypo fractionated versus conventional fractionated radiotherapy in patients with intermediate- and high-risk localized prostate cancer. The primary endpoints included biochemical relapse-free survival, disease-free survival, overall survival, and treatment-related toxicities.

Methods: Sixty patients diagnosed with unfavorable intermediate- or high-risk localized prostate cancer were enrolled between June 2022 and June 2024. They were equally divided into two groups: 30 received hypo fractionated radiotherapy (60 Gy in 20 fractions over 4 weeks), and 30 underwent conventional fractionated radiotherapy (74–80 Gy in 37–40 fractions over 7.4–8 weeks). All patients received concurrent androgen deprivation therapy.

Results: At a median follow-up of 17 months, both groups exhibited comparable overall survival (96.7%) and biochemical relapse-free survival. Hypo fractionated radiotherapy demonstrated dosimetric benefits, with lower doses to the bladder and rectum. Acute genitourinary and gastrointestinal toxicities were slightly higher in the hypo fractionated radiotherapy group but remained manageable; late toxicities showed no significant difference between the groups.

Conclusions: Hypo fractionated radiotherapy provided similar biochemical control, disease free survival, and overall survival as conventional fractionated radiotherapy in patients with intermediate- and high-risk localized prostate cancer. Its shorter course and dosimetric advantages supported its role as an effective, patient-friendly alternative.

Keywords: Prostate Cancer; Radiotherapy; Hypo fractionation; Treatment Outcomes; Toxicity

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INTRODUCTION

Prostate cancer (PCa) is one of the most commonly diagnosed malignancies worldwide and constitutes a significant cause of cancer-associated morbidity and mortality in the male population. According to recent global statistics; it constitutes the second most commonly diagnosed cancer in men and one of the leading causes of cancer death worldwide [1]. In Egypt; PCa is the eighth most frequently diagnosed malignancy and the eleventh in terms of mortality [2].

At diagnosis; most PCa cases are localized within the gland; enabling curative-intent treatment strategies such as radical prostatectomy or external beam radiotherapy (EBRT). In patients with unfavorable prognostic features; such as high serum prostate-specific antigen (PSA) levels or adverse pathological characteristics; androgen deprivation therapy (ADT) is often administered in conjunction with local therapy [3, 4].

EBRT remains a cornerstone in the management of localized PCa; with significant evolution over the past two decades. Dose escalation using conventional fractionated intensity modulated radiotherapy (IMRT); typically delivering 74–80 Gy in 1.8–2.0 Gy fractions; has demonstrated superior biochemical control over lower-dose regimens (64–70.2 Gy). However; conventional regimens are associated with prolonged treatment courses; increased financial burden; and potential toxicity; particularly in older patients or those with comorbidities [5, 6].

Technological advances in radiotherapy; particularly IMRT and image-guided radiotherapy (IGRT); have enabled safe delivery of higher doses with greater precision; reducing exposure to adjacent organs at risk [7]. Parallel to these advancements; a shift toward hypo fractionated intensity modulated radiotherapy has gained traction; supported by the recognition that PCa has a low α/β ratio—estimated at 1.5 Gy—suggesting a higher sensitivity to larger fraction sizes [8, 9].

This radiobiological insight has provided the rationale for investigating hypo fractionated schedules; aiming to improve therapeutic efficacy and patient convenience while maintaining acceptable toxicity [10]. Several pivotal trials; including CHHiP; RTOG 0415; PROFIT; and HYPRO; have evaluated moderate hypo fractionation regimens in patients with localized PCa;

showing comparable oncologic outcomes and toxicity profiles to those of conventional fractionation [11].

Current guidelines from ASTRO; ASCO; and AUA support the use of moderate hypo fractionation for patients with low-; intermediate-; and high-risk localized PCa undergoing EBRT [12]. However; the application of hypofractionated IMRT; especially when treating the pelvic lymph nodes; remains an area of clinical uncertainty. Advances in IMRT and IGRT have enhanced the safety profile of hypofractionated IMRT; potentially reducing toxicity to the bladder and rectum while enabling more aggressive treatment of pelvic targets [13, 14].

This study aims to evaluate the efficacy and toxicity of a hypofractionated IMRT regimen with a simultaneous integrated boost (SIB) for unfavorable intermediate-risk (UIR) and high-risk (HR) localized PCa; comparing it with a standard conventional fractionation approach. The primary objective is to evaluate disease control and toxicity outcomes; with the hypothesis that hypofractionated IMRT may offer equivalent or superior oncological results with a more favorable treatment burden.

MATERIALS AND METHODS

Patient Selection

This prospective phase II comparative study included 60 male patients diagnosed with UIR or HR localized PCa; treated between June 2022 and June 2024. The study was approved by the Ethical Committee. Eligibility criteria comprised histologically confirmed adenocarcinoma of the prostate; absence of metastatic disease (M0); and Eastern Cooperative Oncology Group (ECOG) performance status 0–1. Patients were risk-stratified according to the National Comprehensive Cancer Network (NCCN) guidelines (AJCC 8th edition). Unfavorable intermediate-risk (UIR) prostate cancer was characterized by the presence of at least two intermediate-risk features—clinical stage T2b–T2c; PSA levels ranging from 10 to 20 ng/mL; or ISUP **(International Society of Urological Pathology)** Grade Group 2 or 3—or by ISUP Grade Group 3 as a single criterion. High-risk (HR) disease was characterized by clinical stage ≥T3a; PSA >20 ng/mL; or a Gleason score (GS) of 8 or higher [15, 16]. Exclusion criteria included prior pelvic radiotherapy; previous prostatectomy; evidence of nodal or distant metastasis on imaging; or significant genitourinary comorbidity precluding radiotherapy. All patients underwent baseline laboratory testing; serum PSA evaluation; multipara metric magnetic resonance imaging (MRI) of the pelvis; and technetium-99m bone scan. In selected cases; prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) was performed to exclude occult lymph node involvement or distant metastases. Disease staging was conducted according to the Tumor-Node-Metastasis classification system of the 8th edition of the American Joint Committee on Cancer (AJCC 8th edition) [17].

Confidentiality of the Data

The study was approved by the ethics committee (institutional review board approval number: 35544/6/22).

Patients were informed and consented to be treated according to the mentioned protocol.

Treatment Protocols

Patients were evenly assigned to two treatment arms: Group A (n=30) received hypofractionated IMRT; while Group B (n=30) underwent conventional fractionated IMRT.

Hormonal Therapy

All patients underwent neoadjuvant; concurrent; and adjuvant ADT; using either luteinizing hormone-releasing hormone (LHRH) agonists or antagonists. The duration of ADT was risk-adapted: 6 months for UIR and 18–36 months for HR patients; per EAU/ASTRO guidelines. Anti-androgen therapy was used for 2–4 weeks before LHRH initiation to prevent flare phenomena in cases receiving agonists.

Simulation and Target Delineation

Patients underwent computed tomography (CT) simulation in the supine position; with immobilization devices used to ensure reproducibility. Patients were instructed to maintain a comfortably full bladder and an empty rectum. CT datasets were acquired with a 3 mm slice thickness; extending from the L4/L5 vertebral level to 3 cm below the ischial tuberosities. These CT images were co-registered with pelvic MRI to ensure precise target delineation.

Target volumes were delineated per the International Commission on Radiation Units and Measurements (ICRU) reports 50/62 guidelines. Clinical target volumes (CTVs) were delineated based on the Radiation Therapy Oncology Group (RTOG) consensus recommendations. The prostate CTV encompassed the entire prostate gland in all patients. In HR cases; the entire length of the seminal vesicles (SVs) was delineated; whereas for patients with UIR disease; only the proximal 1 cm was contoured. Pelvic lymph nodes were delineated in all HR patients and in selected UIR patients with an estimated nodal involvement risk of ≥15%; as determined by the Roach formula [18]. Prostate and SV positions vary due to rectal/bladder filling; breathing; and setup errors. To improve accuracy; planning target volumes (PTVs) were created by applying a 5–7 mm isotropic expansion around the CTVs; except posteriorly where a reduced margin of 3–5 mm was used to minimize rectal exposure [19].

Radiotherapy Delivery

All patients received treatment with IMRT to optimize target coverage while minimizing radiation exposure to adjacent organs at risk. IMRT plans incorporated 7 to 9 coplanar beams; with the number of beams adjusted as needed to meet planning objectives. Daily IGRT was performed using kilo voltage orthogonal imaging or cone-beam computed tomography (CBCT) [20]. The prescribed dose fully encompassed the CTV; with at least 95% of the PTV receiving the prescription dose. The maximum dose delivered to the PTV was limited to no more than 107% of the

prescribed dose [20].

Hypofractionated IMRT group (Group A)

- 60 Gy in 20 fractions (3 Gy/fraction) to the prostate gland + entire SVs if grossly involved
- 48 Gy in 20 fractions to the SVs
- 44 Gy in 20 fractions to pelvic nodes

Conventional fractionated IMRT group (Group B)

- 74-80 Gy (1.8-2 Gy/fraction) to the prostate gland + entire SVs if grossly involved.
- 54-60 Gy to the prostate gland + bilateral SVs.
- 45-50 Gy in 28 fractions to pelvic nodes

Organs at Risk (OAR) Constraints

The rectum; bladder; femoral heads; bowel bag; and penile bulb were contoured as OARs. Dose constraints followed institutional protocols derived from RTOG guidelines [21]. Key constraints included:

- **Bladder**: V40≤ 50%; V65Gy < 25% (conventional fractionated IMRT); V40Gy < 50%; V60≤3% (hypofractionated IMRT)
- **Rectum**: V30≤ 80%; V70Gy ≤15% (conventional fractionated IMRT); V20 ≤ 85%; V60Gy ≤1% (hypofractionated IMRT)
- **Femoral heads**: Max dose ≤37 Gy (hypofractionated IMRT); Max dose ≤52.5 Gy (conventional fractionated IMRT)
- **Bowel bag**: V45Gy ≤200 cc
- **Penile bulb:** V22 ≤ 50% (hypofractionated IMRT); penile bulb mean dose ≤ 52.5 Gy (conventional fractionated IMRT).

Follow-up and Assessment

Patients were assessed weekly during radiotherapy for acute toxicities; including diarrhea; proctitis; urinary frequency; dysuria; and hematuria. Post-treatment follow-up was conducted at 1 month; then every 3 months for the first 2 years; and every 6 months thereafter. Response was evaluated via digital rectal exam (DRE); serum PSA levels; and imaging where indicated. PSA nadir and PSA kinetics were recorded. Late toxicities were evaluated at 6; 9; 12; 16; 20; 24; and 30 months. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [22]. The objective of this study was to assess and compare the therapeutic effectiveness; toxicity outcomes; and dosimetric parameters of hypofractionated IMRT versus conventional fractionated IMRT in patients with UIR and HR localized PCa. The primary endpoints included biochemical relapse-free survival (BRFS); disease-free survival (DFS); and overall survival (OS); along with the assessment of both acute and late radiation-induced toxicities.

- **BRFS**: Defined per Phoenix criteria (PSA nadir + 2 ng/mL).
- **DFS**: Time to biochemical failure; local recurrence; or distant metastasis.
- **OS**: Time to death from any cause.

Statistical Analysis

Statistical analysis was performed using **Statistical Package for the Social Sciences** (SPSS) software. Parametric and nonparametric data were assessed using mean; standard deviation; median; and interquartile ranges. Independent t-tests; Mann-Whitney U tests; and Pearson Chi-square tests were applied to compare groups. Statistical significance was defined as p-value < 0.05 [23].

RESULTS

Patient Characteristics

A total of 60 patients with histologically confirmed; non-metastatic; UIR or HR localized PCa were included in this study. Thirty patients were allocated to each treatment arm; resulting in evenly matched hypofractionated IMRT and conventional fractionated IMRT groups. All patients had ECOG performance status (PS) 0 or 1 and completed the full prescribed course of radiotherapy and ADT. The patient and disease characteristics are summarized in Table 1. Baseline characteristics; including age; PS; risk; Gleason score; clinical T stage (cT stage); and PSA levels; were well balanced between the two groups. Most patients (68.3%) were classified as having HR disease; while the remaining 31.7% had UIR PCa.

Oncologic Outcomes

After a median follow-up of 17 months (range; 5–29 months); no significant differences in outcomes were observed between the two treatment arms. The 2.5-year BFFS rates were 96.7% for the hypofractionated IMRT group and 90% for the conventional fractionated IMRT group (p = not significant). The overall DFS for the cohort was 91.7% (55 out of 60 patients); with a non-significant trend favoring hypofractionated IMRT over conventional fractionated IMRT (93.3% vs. 90.0%; p = 1.000). Overall survival was identical in both groups at 96.7%; with one death reported in each arm; one due to prostate cancer (conventional fractionated IMRT) and one from a non-cancer-related cause (hypofractionated IMRT) [Table 2].The mean PSA nadir was comparable between the two groups; but the time to reach PSA nadir was significantly shorter in the hypofractionated IMRT group (12.8 months vs. 17.1 months; p = 0.019); indicating a more rapid biochemical response in patients receiving hypofractionated IMRT. Although PSA nadir levels were similar between both groups; a faster time to nadir may have clinical implications for long-term disease control.

Dosimetric Analysis

Compared to conventional fractionated IMRT; hypofractionated IMRT resulted in significantly lower bladder and rectal dose-

Table 1: Baseline Patient and Disease Characteristics of Hypo Fractionated Versus Conventional Fractionated IMRT Groups.

	Hypofractionated IMRT		Conventional fractionated IMRT			
	No.	%	No.	%		
Age					**T**	**0.13**
Mean ± SD.	72.1 ± 5.91		69.7 ± 6.18		**1.538**	
Range	58.0 – 81.0		57.0 – 80.0			
PS					**χ^2**	**p^{FE}**
0	3	10	0	0	**3.158**	**0.237**
1	27	90	30	100		
Risk					**χ^2**	**0.781**
UIR	9	30	10	33.3	**0.077**	
High risk	21	70	20	66.7		
PSA < 20	**n = 16**		**n = 15**		**U**	**0.108**
Mean ± SD.	11.4 ± 6.15		14.8 ± 4.10		**79.5**	
Range	0.9 – 19.0		5.0 – 20.0			
IQR	13.0 (5.05 – 15.75)		15.0 (12.0 – 19.0)			
PSA ≥ 20	**n = 14**		**n = 15**		**U**	**0.585**
Mean ± SD.	85.0 ± 96.18		66.0 ± 52.33		**92.5**	
Range	20.0 – 400.0		21.0 – 202.0			
IQR	60.5 (33.75 – 102.5)		44.0 (26.0 – 100.0)			
Gleason score					**χ^2**	**0.184**
Grade Group 1	3	10	8	26.7	**6.215**	
Grade Group 2	6	20	8	26.7		
Grade Group 3	9	30	4	13.3		
Grade Group 4	8	26.7	4	13.3		
Grade Group 5	4	13.3	6	20		
T stage					**χ^2**	**p^{FE}**
T2	29	96.7	26	86.7	**1.964**	**0.353**
T3	1	3.3	4	13.3		

UIR: unfavorable intermediate risk PS: performance score χ^2: Chi square test FE: Fischer Exact *p ≤ 0.05 (Statistically significant)
t: Independent T test IQR: Interquartile range U: Mann Whitney U test|

Table 2: Comparative Analysis of Outcomes between Hypos Fractionated Versus Conventional Fractionated IMRT Groups as Regard: OS; DFS; and BRFS

	HypofractionatedIMRT (n=30)		Conventional fractionated IMRT (n=30)		Total (n=60)		Test of sig.	P
OS	**No.**	**%**	**No.**	**%**	**No.**	**%**	**χ^2**	**p^{FE}**
Died	1	3.3	1	3.3	2	3.3	**0**	**1**
Live	29	96.7	29	96.7	58	96.7		
DFS							**χ^2**	**p^{MC}**
YES(disease free)	28	93.3	27	90	55	91.7	**0.352**	**1**
NO	2	3.3	3	6.7	5	8.30%		
BRFS							**χ^2**	**p^{FE}**
YES(BRF)	29	96.7	27	90	56	93.3	**1.071**	**0.612**
NO	1	3.3	3	10	4	6.7		

χ^2: Chi square test FE: Fischer Exact MC: Monte Carlo Exact

volume exposure across all assessed dose levels (V40; V52.7; V56.8 for bladder; V48; V52; V60 for rectum); all with $p < 0.001$ [Tables 3-5]. Additionally; femoral head Dmax was significantly lower in the hypofractionated IMRT group ($p < 0.001$); suggesting a potential reduction in late radiation-related toxicity.

Toxicity Outcomes (Acute and late Toxicities)

Acute toxicities were defined as those occurring within 6 months after completion of IMRT; while late toxicities were those observed thereafter; both were graded according to CTCAE version 5.0. All patients completed their assigned radiotherapy schedules without interruption. Acute and late toxicities were generally mild and manageable. Acute gastrointestinal (GI) toxicity was comparable; with slightly higher Grade 1 diarrhea in the hypofractionated IMRT group (53% vs 26.7%) ($p = 0.035$). No Grade ≥3 GI toxicities were reported. Acute genitourinary (GU) toxicity (Grade 1) was also more frequently observed in the hypofractionated group compared to the conventional fractionated group. There were no significant differences in Grade ≥2 acute and late GU or GI toxicities between the two groups [Table 6, 7].

The incidence of late GU and GI toxicities was low and comparable across both treatment groups. Grade ≥2 late GU toxicities were observed in ≤6.7% of patients. Grade 3 late GU toxicity was observed in 3.3% (1 of 30) of patients in each group.

Table 3: Comparison of Bladder Dose-Volume Parameters between Both Studied Groups.

	Hypofractionated	Conventional fractionated		U	P
	IMRT (n=30)	IMRT (n=30)			
V40		**V40**		**140.5**	**<0.001***
Mean ± SD.	28.3 ± 9.76	Mean ± SD.	49.5 ± 19.26		
Min. – Max.	9.6 – 47.0	Min. – Max.	23.0 – 96.0		
Median (IQR)	27.8 (23.75 – 32.2)	Median (IQR)	43.5 (36.675 – 57.25)		
V 52.7		**V65**		**195.5**	**<0.001***
Mean ± SD.	8.5 ± 4.63	Mean ± SD.	17.6 ± 12.57		
Min. – Max.	1.0 – 21.6	Min. – Max.	2.0 – 47.5		
Median (IQR)	10.0 (5.0 – 11.15)	Median (IQR)	13.5 (10.825 – 20.35)		
V 56.8		**V70**		**162**	**<0.001***
Mean ± SD.	5.2 ± 3.32	Mean ± SD.	12.6 ± 9.26		
Min. – Max.	0.9 – 15.0	Min. – Max.	1.6 – 42.6		
Median (IQR)	5.0 (2.675 – 7.625)	Median (IQR)	10.35 (8.325 – 14.8)		

IQR: Interquartile range U: Mann Whitney U test *p ≤ 0.05 (Statistically significant)

Table 4: Comparison of Rectum Dose-Volume Parameters between Both Studied Groups.

	Hypofractionated	Conventional fractionated		Test of sig.	P
	IMRT (n=30)	IMRT (n=30)			
V 48		**V50**		**U**	**<0.001***
Mean ± SD.	8.7 ± 5.66	Mean ± SD.	35.9 ± 14.06	**18**	
Min. – Max.	1.0 – 20.4	Min. –Max.	12.0 – 57.0		
Median (IQR)	8.0 (3.65 – 12.4)	Median (IQR)	38.9 (22.375 -48.7)		
V 52		**V65**		**U**	**0.005***
Mean ± SD.	5.9 ± 4.45	Mean ± SD.	10.3 ± 6.29	**261.5**	
Min. – Max.	0.0 – 16.7	Min. –Max.	1.0 – 22.0		
Median (IQR)	5.0 (2.0 – 8.85)	Median (IQR)	9.35 (5.15 – 14.75)		
V 60		**V70**		**U**	**<0.001***
Mean ± SD.	0.5 ± 1.47	Mean ± SD.	5.1 ± 4.20	**78.5**	
Min. – Max.	0.0 – 7.4	Min. –Max.	0.0 – 16.0		
Median (IQR)	0.0 (0.0 – 0.0)	Median (IQR)	4.4 (2.0 – 6.225)		

IQR: Interquartile range U: Mann Whitney U test *p ≤ 0.05 (Statistically significant)

Late GI toxicity was minimal; with grade 1 diarrhea or proctitis reported in 3.3% of hypofractionated IMRT patients and 10.0% of conventional fractionated IMRT patients (p=0.612). No late Grade 4 events were reported (Table 8,9). All cases were managed conservatively without surgical intervention. These findings indicate that both RT modalities exhibit similar long-term safety profiles; with no significant increase in severe late toxicity in the hypofractionated IMRT group.

DISCUSSION

The present study compared hypofractionated IMRT with conventional fractionated IMRT in patients with UIR and HR localized prostate cancer. Our findings demonstrate that hypofractionated IMRT is non-inferior—and potentially slightly superior—to conventional fractionated IMRT in terms of disease control; while offering a comparable toxicity profile. These results align with prior prospective randomized trials supporting moderate hypo fractionation in localized PCa; including CHHiP; RTOG 0415; and HYPRO. However; unlike those trials—which often focused on low- to intermediate-risk patients—

Table 5: Comparison of Femur; Bowel & Penile Bulb Dose-Volume Parameters between Both Studied Groups.

	Hypofractionated IMRT (n=30)	Conventional fractionated IMRT (n=30)	Test of sig.	P
Femur D max			**T**	**<0.001***
Mean ± SD.	35.5 ± 3.75	42.2 ± 4.04	**6.667**	
Min. – Max.	20.0 – 42.0	34.0 – 48.0		
Bowel V 45			**U**	**0.059**
Mean ± SD.	13.3 ± 29.40	22.5 ± 30.23	**329.5**	
Min. – Max.	0.0 – 123.0	0.0 – 95.0		
Median (IQR)	0.0 (0.0 – 15.0)	7.75 (0.0 – 29.125)		
Penile bulb mean			**U**	**0.779**
Mean ± SD.	19.4 ± 8.13	22.1 ± 14.23	**431**	
Min. – Max.	6.0 – 39.0	4.7 – 59.0		
Median (IQR)	19.8 (12.0 –24.25)	16.75 (12.275 –32.0)		

t: Independent t test IQR: Interquartile range U: Mann Whitney U test *p ≤ 0.05 (Statistically significant)

Table 6: Comparison of Acute Genitourinary Toxicity between Hypofractionated vs. Conventional fractionated IMRT Groups.

		Hypofractionated IMRT (n=30)		Conventional fractionated IMRT (n=30)		χ^2	P
		No.	%	No.	%		
Acute GU toxicity	**Frequency**						
	Grade 0	1	3.3	5	16.7	**2.963**	**p^{FE} 0.195**
	Grade 1	11	36.7	3	10	**5.963**	**0.015***
	Grade 2	15	50	18	60	**0.606**	**0.436**
	Grade 3	3	10	4	13.3	**0.162**	**p^{FE} 1.000**
	Urgency						
	Grade 0	1	3.3	5	16.7	**2.963**	**p^{FE} 0.195**
	Grade 1	11	36.7	3	10	**5.963**	**0.015***
	Grade 2	15	50	18	60	**0.606**	**0.436**
	Grade 3	3	10	4	13.3	**0.162**	**p^{FE} 1.000**
	Dysuria						
	Grade 0	1	3.3	5	16.7	**2.963**	**p^{FE} 0.195**
	Grade 1	11	36.7	5	16.7	**3.068**	**0.08**
	Grade 2	15	50	16	53.3	**0.067**	**0.796**
	Grade 3	3	10	4	13.3	**0.162**	**p^{FE} 1.000**
	Nocturia						
	Grade 0	1	3.3	5	16.7	**2.963**	**p^{FE} 0.195**
	Grade 1	16	53.3	5	16.7	**8.864**	**0.003***
	Grade 2	12	40	15	50	**0.606**	**0.436**
	Grade 3	1	3.3	2	6.7	**0.351**	**p^{FE} 1.000**
	Haematuria						
	Grade 0						
	Grade 1						
	Grade 2						
	Grade 3	21	70	18	60	**0.659**	**0.417**
		6	20	9	30	**0.8**	**0.371**
		2	6.7	1	3.3	**0.351**	**p^{FE} 1.000**
		0	0	1	3.3	**1.017**	**p^{FE} 1.000**

χ^2: Chi square test FE: Fischer Exact test *p≤ 0.05 (Statistically significant)

Table 7: Comparison of Acute Gastrointestinal Toxicity between Hypofractionated vs. Conventional fractionated IMRT Groups

		Hypofractionated IMRT (n=30)		Conventional fractionated IMRT (n=30)		χ^2	P
		No.	%	No.	%		
Acute GI toxicity	**Diarrhea**						
	Grade 0	13	43.3	21	70	**4.344**	**0.037***
	Grade 1	16	53.3	8	26.7	**4.444**	**0.035***
	Grade 2	1	3.3	1	3.3	**0**	**p^{FE} 1.000**
	Proctitis						
	Grade 0	20	66.7	22	73.3	**0.317**	**0.573**
	Grade 1	10	33.3	8	26.7	**0.317**	**0.573**

χ^2: Chi square test FE: Fischer Exact test *p≤ 0.05 (Statistically significant)

Table 8: Comparison of late Genitourinary Toxicity between Hypofractionated vs Conventional Fractionated IMRT Groups.

		Hypofractionated IMRT (n=29)		Conventional fractionated IMRT (n=30)		χ^2	p
		No.	%	No.	%		
Late GU toxicity	**Frequency**						
	Grade 0	16	53.3	14	46.7	**0.267**	**0.606**
	Grade 1	10	33.3	13	43.3	**0.635**	**0.426**
	Grade 2	2	6.7	2	6.7	**0**	**p^{FE} 1.000**
	Grade 3	1	3.3	1	3.3	**0**	**p^{FE} 1.000**
	Dysuria						
	Grade 0	16	53.3	14	46.7	**0.267**	**0.606**
	Grade 1	10	33.3	13	43.3	**0.635**	**0.426**
	Grade 2	2	6.7	2	6.7	**0**	**p^{FE} 1.000**
	Grade 3	1	3.3	1	3.3	**0**	**p^{FE} 1.000**
	Hematuria						
	Grade 0	21	70	19	63.3	**0.3**	**0.584**
	Grade 1	6	20	9	30	**0.8**	**0.371**
	Grade 2	2	6.7	2	6.7	**0**	**p^{FE} 1.000**
	Grade 3	0	0	0	0		

χ^2: Chi square test FE: Fischer Exact test *p≤ 0.05 (Statistically significant

our cohort exclusively included UIR and HR disease; which are underrepresented in many hypo fractionation studies [24]. The theoretical basis for hypo fractionation in prostate cancer lies in the unique radiobiological characteristics of prostatic adenocarcinoma. Prostate cancer is believed to have a low α/β ratio (~1.5 Gy); indicating greater sensitivity to larger doses per fraction. This contrasts with surrounding normal tissues such as the rectum and bladder; which exhibit higher α/β ratios (~3 Gy). As a result; hypo fractionation may enhance the therapeutic ratio by delivering higher biological effective doses (BED) to the tumor without significantly increasing toxicity to adjacent organs at risk [25]. In our study; hypofractionated IMRT delivered 60 Gy in 20 fractions (3 Gy per fraction) to the prostate using SIB; a regimen with a BED equivalent to approximately 78–80 Gy in conventional fractionation; assuming an α/β of 1.5. This dose escalation likely contributed to the improved BRFS and DFS observed in the hypofractionated IMRT cohort. While dose escalation improves biochemical control; it does not necessarily enhance OS due to slow progression of PCa. Consistently; our study found no OS difference between groups (96.7% for both). The CHHiP study; involving 3; 216 patients; is a landmark trial

Table 9: Comparison of late GI Toxicity between Hypofractionated vs Conventional Fractionated IMRT groups.

		HF IMRT (n=29)		CF IMRT (n=30)		χ^2	P
		No.	%	No.	%		
Late GI toxicity	**Diarrhea**						
	Grade 0	28	93.3	27	90	**0.218**	**p^{FE} 1.000**
	Grade 1	1	3.3	3	10	**1.071**	**p^{FE} 0.612**
	Proctitis						
	Grade 0	28	93.3	27	90	**0.218**	**p^{FE} 1.000**
	Grade 1	1	3.3	3	10	**1.071**	**p^{FE} 0.612**

χ^2: Chi square test FE: Fischer Exact test

comparing two moderate hypofractionated protocols (60 Gy in 20 fractions and 57 Gy in 19 fractions) with the standard 74 Gy in 37 fractions. While CHHiP demonstrated non-inferiority of hypofractionated IMRT in terms of biochemical control and toxicity; only a minority of patients had high-risk features (20% with GS ≥8; few with pelvic nodal irradiation); and the results may not generalize to higher-risk cohorts [26]. In contrast; our study focused specifically on patients with UIR and HR disease; with nearly 70% of patients classified as high-risk and over 80% receiving whole-pelvis RT. Our 2.5-year BRFS (96.7 % for hypofractionated IMRT vs. 90 % for conventional fractionated IMRT) compares favorably with CHHiP outcomes and highlights the potential of hypofractionated IMRT to achieve superior disease control in more aggressive disease phenotypes.

The HYPRO study evaluated hypofractionated IMRT (64.6 Gy in 19 fractions) versus conventional fractionated IMRT (78 Gy in 39 fractions) in patients with intermediate- to high-risk PCa; showing 5-year RFS rates of 80.5% and 77.1%; respectively. While no significant difference in BRFS was observed; the hypofractionated arm experienced higher rates of late GI toxicity [27]. In contrast; our study employed a more conservative hypo fractionation schedule (3.0 Gy per fraction) and demonstrated superior short-term disease control; with a 2.5-year RFS of 96.7% for HFRT compared to 90.0% for CFRT; along with favorable toxicity outcomes.

RTOG 0415; which evaluated 70 Gy in 28 fractions versus 73.8 Gy in 41 fractions; demonstrated non-inferiority in low-risk patients. However; extrapolation to UIR and HR patients remains limited. Our study provides additional support for the safe use of moderate hypofractionated IMRT in this higher-risk population [28].

PSA kinetics remains a crucial predictor of treatment response. In our study; hypofractionated IMRT group exhibited a more rapid decline in PSA; reaching the nadir earlier than the conventional fractionated IMRT group (12.8 vs. 17 months). This suggests a potentially faster tumor response with hypo fractionation; possibly due to the radiobiological sensitivity of prostate cancer; which is characterized by a low α/β ratio. Radiation-induced toxicity continues to be an important concern. Our findings indicated similar toxicity levels in both groups; with a modestly increased rate of Grade 1 acute gastrointestinal and genitourinary toxicity observed in patients receiving hypofractionated IMRT. This observation aligns with some previous studies that have reported increased acute GI toxicity with hypo fractionation. However;

the overall toxicity was manageable; and there were no significant differences in late toxicity. These findings are supported by favorable dosimetric outcomes in the hypofractionated IMRT group; including significantly lower rectal and bladder values. The use of IMRT with daily IGRT; tight PTV margins; and rectal and bladder preparation protocols contributed to this reduction in normal tissue exposure.

Importantly; the toxicity results reinforce the feasibility of delivering hypofractionated IMRT in patients receiving pelvic nodal irradiation. Historically; hypofractionated whole pelvis radiotherapy raised concerns about increased GI toxicity due to the larger volume of bowel irradiated. However; our data show that with careful planning and advanced delivery techniques; hypofractionated IMRT is well tolerated even in HR patients requiring elective nodal coverage [29].

The findings support hypofractionated IMRT as a safe; effective; and resource-efficient alternative to conventional fractionated IMRT for patients with UIR and HR disease. Notably; hypofractionated IMRT offers the potential to reduce the overall treatment duration from 8 weeks to 4 weeks without compromising clinical outcomes—a significant advantage in high-volume centers; contributing to improved patient convenience; compliance; and overall healthcare system efficiency [30].

Furthermore; the cost-effectiveness and logistical benefits of hypofractionated IMRT are increasingly important in the context of global efforts to streamline cancer care delivery. Reflecting this; international guidelines from ASTRO; ASCO; and AUA now endorse moderate hypo fractionation as a standard treatment option for appropriately selected patients across all risk groups; including those with high-risk disease receiving ADT [12]. Despite the encouraging results; several limitations warrant discussion. First; this was a single-institution; non-randomized study with a relatively modest sample size. Although the two treatment groups were well matched in baseline characteristics; the possibility of selection bias cannot be entirely excluded. Second; follow-up duration was limited to a median of 17 months; which may not fully capture late toxicity or long-term survival differences. Extended follow-up will be essential to determine whether the observed improvements in BRFS and DFS translate into durable OS benefits. Finally; we did not incorporate molecular or genomic risk classifiers; which are increasingly relevant in treatment stratification and prognostication. Future studies may benefit from integrating Decipher; Prolaris; or similar tools to identify subgroups most likely to benefit from hypofractionated RT.

CONCLUSION

This study demonstrates that hypofractionated IMRT combined with ADT provides effective disease control and a favorable toxicity profile in patients with unfavorable intermediate- and high-risk localized PCa. Although acute GU and GI toxicities were slightly more pronounced with the hypofractionated regimen; late toxicity rates remained comparable to those observed with conventional fractionation; supporting the feasibility of this approach. Moreover; hypofractionated IMRT achieved marginally improved biochemical relapse-free and disease-free survival rates without compromising overall survival or increasing treatment-related toxicity.

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