

HYPOFRACTIONATED INTENSITY MODULATED HELICAL TOMOTHERAPY FOR LOCALIZED PROSTATE CANCER

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Abstract

This study aimed to compare Moderate Hypofractionated Radiotherapy (H-RT) and Conventional Fractionated Radiotherapy (CFRT) in terms of toxicity and quality of life in patients with localized prostate cancer.

Patients who were delivered 70 Gy H-RT at 2.5 Gy per fraction in 28 fractions, and 72 Gy CFRT at 2 Gy per fraction in 36 fractions, were evaluated retrospectively. The Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) toxicity scales were used to evaluate treatment-related acute and late toxicities in the patients. The Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) and International Prostatism Symptom Score (IPSS) questionnaire surveys were used to evaluate baseline, completion RT and post-RT quality of life (QoL) follow-ups.

Forty patients were included in our study with 20 patients each in the H-RT and CFRT groups. The mean age of the patients was 68.5 old years and the median follow-up duration was 26.2 months. Grade 3–4 toxicity was not observed in any of the patients in our study. When the patients were evaluated in terms of QoL based on the EPIC-CP questionnaire, urinary incontinence, bowel symptoms, hormonal and sexual symptoms were comparable for both groups, but EPIC-CP urinary irritation scores were unfavourably higher in the Control Group ($p < 0.05$). The IIEF-5 score, which evaluates the quality of erectile function, was found to be unfavourable decreasing with erectile function over time in the study group compared to control group ($p = 0.038$).

Moderate H-RT delivered with the Helical Tomotherapy system is an effective treatment radiotherapy regimen that reduces toxicity without impairing patient QoL and well tolerated by patient.

Key words: tomotherapy, prostate cancer, radiotherapy, quality of life

Introduction. Prostate cancer (PCa) is among the most common cancers in men worldwide and the second most common cause of cancer-related deaths in men, with approximately 1 600 000 cases and 366 000 deaths worldwide annually [1].

Active surveillance, radical prostatectomy, cryotherapy, hormonotherapy and radiotherapy (RT) are treatment options for PCa. Recent developments in RT have made it possible to apply high total doses with minimal side effects in PCa with the use of new technologies such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) [2, 3]. In localized PCa, with the Helical Tomotherapy (HT) system, in which tumour volume and dose control are performed in each treatment fraction, curative treatment can be applied with hypofractionated IMRT with a high fraction dose and in a shorter time. With the increase in overall cancer survival with technological and newly developed diagnostic and treatment methods, treatment-related toxicities and quality of life (QoL) have become as important as disease control.

In this study, we investigated the therapeutic efficacy and toxicity profiles of two definitive radiotherapy delivery schemes for patients with low-, intermediate-, and high-risk localized PCa. Compared to conventional fractionated radiotherapy (CFRT), hypofractionated radiotherapy (H-RT) administered with the HT system showed no statistically significant difference in terms of the side effect profile and QoL.

Materials and methods. Patients treated with moderate hypofractionated (70 Gy/2.5 Gy/2.5 Gy/28fr) or conventional fractionation (72 Gy/2 Gy/36fr) EBRT for localized PCa in our institution between January 2017 and November 2021 and followed up for at least 6 months were retrospectively analyzed.

RT treatment planning and implementation. All patients included in the study were informed of the treatment, side effects, and points to be considered during treatment, and written informed consent was obtained before starting treatment. After rectal enema, an intravenous line was opened in all patients, and 50 cc of contrast material was injected 20 min before the computerized tomography (CT) simulation. The patients were asked to drink 1 L of water 30 min before the CT scan to urinate. Patients with mild urinary urgency were placed in the Radiotherapy CT Simulator unit with a half-filled bladder and immobilized in the supine position. The obtained images were transferred to the treatment planning system (TPS) via Digital Imaging and Communications in Medicine (DICOM).

In patients undergoing CFRT, a single Clinical Target volume (CTV) as CTV72 (Clinical Target Volume receiving 72 Gy), was contoured to include only

the prostate in low-risk patients, and the prostate gland and all seminal vesicles in high-risk patients. In patients in the intermediate-risk group, the prostate gland and proximal (up to 1 cm) seminal vesicles were contoured as CTV54, whereas only the prostate was included in CTV72. No patients underwent Elective Nodal Irradiation. In patients undergoing H-RT, in low-risk patients, only the prostate was contoured; in high-risk group patients, only CTV70 was contoured to include the prostate gland and both seminal vesicles. The PTV margins were more limited in the H-RT Study Group than in the CFRT Control Group to reduce the expected potential increase in toxicity. This planning approach was inspired by the experience of the Cleveland Clinic hypofractionated radiotherapy [4].

The IMRT plan was made using Precise Planning System. In the HR-T study group, contouring was performed by the same radiation oncologist using the Monaco (Elekta Medical Systems, Crawley, UK) contouring system and was approved by an expert faculty member. After physician contouring, the data sets were sent via network to the Tomotherapy Hi-ART TPS.

Assessment of toxicity and quality of life (QoL). Toxicity assessment was performed weekly during RT and at 1, 3, 6, 12, 18, and 24 months of follow-up, according to the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC) side effect scale revised in 2011. To assess QoL, patient-reported results were obtained before treatment, at the end of treatment, and at follow-up at 3, 6, 12, and 24 months after treatment according to the definitions in the questionnaires, including urinary, gastrointestinal, sexual, and hormonal subgroups of symptoms and functions. EPIC-CP (Expanded Prostate Cancer Index Composite for Clinical Practice) and IPSS (International Prostatism Symptom Score) were used. The EPIC-CP prostate cancer-related questionnaire enabled patients to evaluate their QoL in five subgroups. These include urinary incontinence, urinary irritation, bowel symptoms, and hormonal function [5,6].

Statement of ethics. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and the study protocol was received and approved by Institutional Review Board at University of Health Sciences Gülhane Training and Research Hospital (IRB NO: 46418926/2021-03-11).

Results. The mean age of all patients in our study was 68.5 years and the mean follow-up period was 26.2 months. Patient and tumour characteristics are shown in Table 1.

GI toxicity results. Acute GI toxicity. In both groups, the Gleason score, baseline PSA value, prostate volume, baseline IPSS value, and PTV volume were found to be significantly higher in patients with acute GI toxicity than in those without acute GI toxicity ($p = 0.0001$, $p = 0.007$, $p = 0.033$, $p = 0.030$, respectively). Rate of ADT use, D'Amico risk group, and tumour T stage were significantly higher in patients who developed acute GI toxicity than in those who

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Patients and tumour characteristics

Characteristics		CHRT(n:20)		H-RT(n:20)		p
		Number of patients(%)	Mean±SD Median (min-max)	Number of patients(%)	Mean±SD Median (min-max)	
Age (years)			68.5±8.3 68(57–82)		68.5±8.7 69(54–81)	0.989
ADT usage	No	11 (55.0)		8 (40.0)		0.527
	Yes	9 (45.0)		12(60.0)		0.527
Duration of ADT usage (month)			16.2±10.1 24 (3–24)		13.2±9.5 14.6±9.7	0.722
Gleason score	≤ 6	11 (55.0)		11 (55.0)		1.000
	7	5 (25.0)		5 (25.0)		
	≥ 8	4 (20.0)		4 (20.0)		
Initial PSA value (ng/dl)	<10	9 (45.0)		7 (35.0)		0.723
	10–20	7 (35.0)		7 (35.0)		
	>20	4 (20.0)		6 (30.0)		
D’Amica risk group	Low	7 (35.0)		7 (35.0)		0.924
	Interm.	7 (35.0)		7 (35.0)		
	High	6 (30.0)		6 (30.0)		
Tumour T stage	T1	4 (20.0)		7 (35.0)		0.524
	T2	11 (55.0)		8 (40.0)		
	T3	5 (25.0)		5 (25.0)		
Smoking	No	8 (40.0)		7 (35.0)		1.000
	Yes	12 (60.0)		13 (65.0)		
Prostate volume (cc)			54.2±17.9 53 (25–88)		50.8±17.5 46 (25–72)	0.253
TURP history	No	16 (80.0)		15 (75.0)		1.000
	Yes	4 (20.0)		5 (25.0)		
Baseline IPSS score			7.0±5.0 6 (1–18)		6.5±4.5 5.5	0.883
Diabetes	No	13 (65.0)		12 (60.0)		1.000
	Yes	7 (35.0)		8 (40.0)		
Hypertension	No	16 (80.0)		17 (85.0)		1.000
	Yes	4 (20.0)		3 (15.0)		
Hyperlipidemia	No	12 (60.0)		12 (60.0)		1.000
	Yes	8 (40.0)		8 (40.0)		

Values are presented as mean±standard deviation or number (%) and chi-square test was used. CHRT: conventional fractionated radiotherapy, H-RT: hypofractionated radiotherapy, SD: standard deviation, Min: minimum, Max: maximum, ADT: androgen deprivation therapy, TURP: transurethral resection of the prostate, IPSS: international prostatism symptom score

did not ($p = 0.009$, $p = 0.009$, $p = 0.009$, and $p = 0.0001$, respectively). A multivariate logistic regression model was created using parameters that were significant in the univariate analyses. However, no independent risk factors affecting the occurrence of acute GI toxicity have been identified.

Late GI toxicity. Gleason score, baseline PSA value and prostate volume were found to be statistically significantly higher in patients with late GI toxicity compared to those without late GI toxicity ($p = 0.0001$, $p = 0.023$, $p = 0.046$). The rate of ADT use in patients with late GI toxicity compared to those without, higher D’Amico risk group and tumour T stage were found to be statistically significant ($p = 0.021$, $p = 0.003$, $p = 0.002$, respectively). A multivariate logistic regression model was created with the parameters that were significant in univariate analyses.

GU toxicity results. *Acute GU toxicity.* Gleason and baseline IPSS scores were found to be significantly higher in patients with acute GUS toxicity than in those without ($p = 0.006$ and $p = 0.0001$, respectively). Higher D'Amico risk group, tumour T stage, and presence of DM were found to be statistically significant in patients with acute GUS toxicity compared to those without ($p = 0.005$, $p = 0.003$, $p = 0.008$). A multivariate logistic regression model was created with the parameters that were significant in univariate analyses. As a result, the baseline IPSS score and the presence of DM were found to be independent risk factors affecting the development of acute GU toxicity (95% CI: 1.12–1.92, $p = 0.005$ and 95% CI: 1.10–1.19, $p = 0.050$, respectively).

Late GU toxicity. Gleason score, baseline PSA value and baseline IPSS value were found to be statistically significantly higher in patients with late GUS toxicity compared to patients without GU toxicity ($p = 0.0001$, $p = 0.003$, $p = 0.0001$). Presence of ADT, higher D'Amico risk group, tumour T stage, history of TURP, and presence of hyperlipidemia were found to be statistically significant in patients with late GU toxicity as compared to those without late GU toxicity ($p = 0.046$, $p = 0.003$, $p = 0.002$, $p = 0.0001$, $p = 0.02$, respectively). A multivariate logistic regression model was created using parameters that were significant in univariate analyses. However, only the baseline IPSS score was found to be an independent risk factor affecting the development of late GU toxicity. As the baseline IPSS score of the patient increased, the likelihood of developing late GU toxicity was 1.8 (95% CI: 1.2–2.6; $p = 0.002$) times higher.

QoL outcomes. When the control and study groups were compared in terms of EPIC-CP Urinary Incontinence scores at baseline, RT completion, post-RT 3, 6, 12 and 24 months, no statistically significant difference was found ($p > 0.05$). The EPIC-CP Urinary Irritation scores were higher in the control group than in the study group. When the EPIC-CP Urinary Irritation scores were compared in both groups at baseline, RT completion, and postRT at 6, 12, and 24 months, a statistically significant difference was found ($p = 0.009$, $p = 0.003$, $p = 0.026$, $p = 0.028$, $p = 0.023$). No significant difference was observed at 3 months ($p = 0.253$). Although a significant increase in EPIC-CP Urinary Irritation scores was observed at the completion of RT and at 3 months post-RT compared to baseline in both treatment arms, EPIC-CP Urinary Irritation scores approached baseline levels at 6, 12, and 24 months post-RT in both groups (Fig. 1). When the control and study groups were compared in terms of the EPIC-CP Bowel Symptom scores at baseline, RT completion, and post-RT at 3, 6, 12, and 24 months, no statistically significant differences were observed ($p > 0.05$). When the control and study groups were compared in terms of EPIC-CP Sexual Symptom scores at baseline, RT completion, post-RT 3, 6, 12 and 24 months, no statistically significant difference was found ($p > 0.05$). When the control and study groups were compared in terms of EPIC-CP Hormonal Symptom scores at baseline, RT completion, and post-RT 3, 6, 12, and 24 months, no statistically significant difference was found

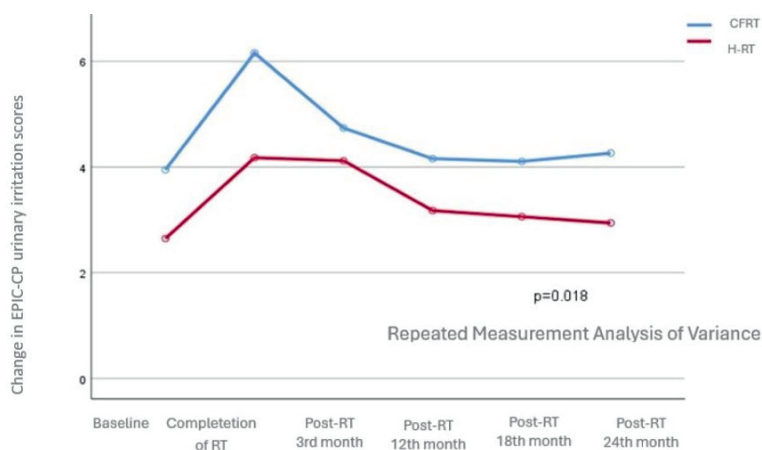


Fig. 1. Change in EPIC-CP urinary irritation scores over time in groups

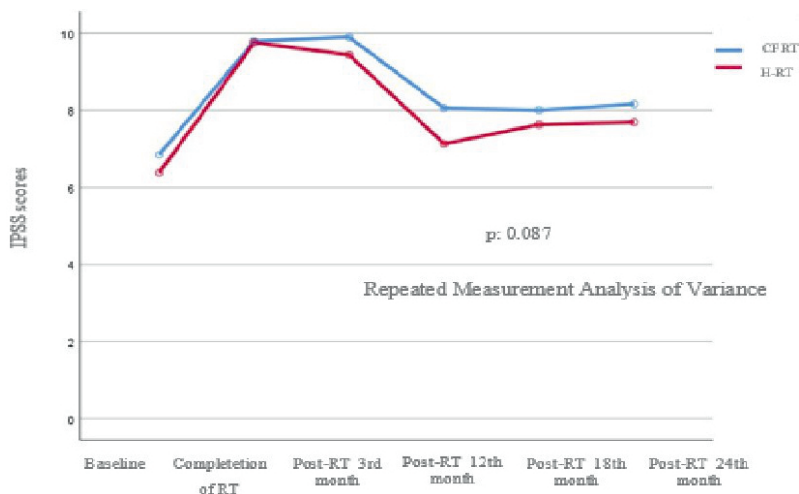


Fig. 2. Change in IPSS scores over time in groups

($p > 0.05$). When the control and study groups were compared in terms of IPSS scores at baseline, RT completion, and post-RT at 3, 6, 12, and 24 months, no statistically significant difference was found ($p > 0.05$). Although IPSS scores were found to be statistically higher than the baseline level in both groups at the end of treatment and at 3 months post-RT, the study arm approached the baseline level at 6 and 12 months post-RT (Fig. 2).

Discussion. Many dose escalation studies have shown that dose escalation from 68–70 Gy to 76–79 Gy reduces biochemical relapses [7–10]. With hypofractionation, effective doses can be administered to the prostate in a shorter total treatment time, and improved therapeutic gain can be achieved without an increase in side effects. Unlike many other epithelial cancers, prostate cancer has

been shown to be more sensitive to high doses per fraction because the α/β ratios of prostate cancer cells are lower than those of the surrounding high-risk normal organs and tissues [11,12]. In addition, H-RT is a good alternative to CFRT for the treatment of localized PCa because it increases patient compliance, allows more efficient use of health equipment and personnel, and reduces treatment costs [13].

In this study, parameters that may affect the occurrence of acute toxicity were analyzed using univariate and multivariate analyses. The presence of DM and IPSS scores of the patients before treatment were found to be independent risk factors for the development of acute GU toxicity ($p = 0.05$, $p = 0.005$, respectively). However, no independent risk factors for acute GI toxicity have been identified. In addition, in the HYPRO study, the most important factor for the development of acute grade ≥ 2 GI toxicity was the presence of GI complications before treatment (grade ≥ 2 GI toxicity according to the patient's baseline RTOG score) [14]. Considering that the IPSS score is also a questionnaire questioning the lower GU symptoms related to prostatism, our study result was found to be very similar to that of the HYPRO study in this respect. In the HYPRO study, acute toxicities occurred earlier (4–5 weeks) in the H-RT arm than in the CFRT arm. Similarly, in the CHHiP study, acute GI toxicities were reported to be more frequent in the H-RT arm during the early weeks [15]. In our study, no difference was found between the arms in this respect, and parameters that may affect the occurrence of late toxicity were examined by univariate and multivariate analyses. In the Fox Chase study, a baseline IPSS score of ≥ 12 was associated with increased late IPSS toxicity [16]. Similarly, in our study, the IPSS scores of patients before treatment were found to be an independent risk factor for the development of late-term GU toxicity ($p = 0.002$). However, no association was found between IPSS and late GU toxicity in the MD Anderson study [17]. Many parameters such as GS, pretreatment PSA value, Prostate volume, Rectum volume, Rectum V40, V50, V60 and Dmax values, ADT use, D'Amico risk group and T stage of the tumour, which were found to be significant for late GI toxicity in univariate analysis, were examined in multivariate analysis. However, no independent risk factors have been identified for late GI toxicity.

There are very few studies in the literature examining QoL in moderate H-RT regimens. When the patients in our study were evaluated in terms of QoL, it was observed that although EPIC-CP urinary incontinence and bowel symptom scores were high immediately after RT completion and until the 3rd month post-RT in both groups, the scores approached the RT baseline level in a relatively short period of time, such as 6 months after RT completion. Although the EPIC-CP Urinary Irritation scores increased significantly in both treatment arms after RT completion and at 3 months post-RT compared to pre-RT baseline levels, they approached baseline levels at 6 months post-RT in both groups. In addition, the EPIC-CP Urinary Irritation scores were higher in the CFRT arm (Repeated Measures Analysis of Variance $p = 0.018$).

Although there was no statistically significant difference between the two groups in terms of IPSS scores, it was observed that IPSS scores reached peak levels at RT completion and post RT 3rd month in both treatment groups and approached the baseline level at 6–12 months in the H-RT arm, while in the CFRT arm, they did not return to the baseline level in the follow-ups. A possible reason for both this situation and the higher EPIC-CP Urinary Irritation scores in the CFRT arm may be that the bladder has high doses such as V40. When EPIC-CP Hormonal Symptom scores were analyzed, it was observed that they peaked between RT completion and post-RT 3 months in both groups, plateaued at 3–6 months, then decreased and approached baseline levels at 12 and 24 months. This may have been influenced by whether the patients used ADT or not and, if so, whether they used ADT for the short or long term.

Our study has some limitations. Firstly, our study is a retrospective single-centre study. Secondly, the results of CFRT and H-RT were examined using radiotherapy techniques and dose limitations. Finally, our patient number is lower compared to other studies in the literature. Despite these limitations, we believe that our study is important in this respect because there are very few studies in the literature comparing H-RT and CFRT regimens in terms of acute-chronic toxicities and QoL.

Conclusion. The most important advantage of H-RT scheme compared to CFRT scheme applied in PCa is that it provides dose escalation. In our study, although the number of patients and follow-up periods were short, both grade 0–1 and grade 2 GI and GUS toxicities in the acute and late periods were similar in the H-RT arm compared to those in the CFRT arm during a median follow-up period of 26.2 months and no grade 3–4 toxicity was observed in any patient. When both treatment groups were compared in terms of EPIC-CP, IPSS, and IIEF-5 QoL questionnaires, urinary irritation, bowel symptoms, hormonal, and sexual functions, no statistically significant difference was found between each group, and the H-RT regimen was found to be well tolerated by the patients.

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