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ACUTE TOXICITY IN MODERATE HYPOFRACTIONATION OVER THREE WEEKS FOR LOCALIZED PROSTATE CANCER WITHOUT MARKER IMPLANTATION

TOXICIDAD AGUDA EN HIPOFRACCIONAMIENTO MODERADO DURANTE TRES SEMANAS PARA EL CÁNCER DE PRÓSTATA LOCALIZADO SIN IMPLANTACIÓN DE MARCADORES

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Acute Toxicity in Moderate Hypofractionation Over Three Weeks for Localized Prostate Cancer Without Marker Implantation

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ABSTRACT

Purpose: prospective observational study of patients with localized prostate cancer referred for radiotherapy using a hypofractionation scheme without marker implantation with the advantages offered by shorter treatments in lower-middle-income countries. Our objective was to establish the acute genitourinary and gastrointestinal toxicity using hypofractionation radiotherapy scheme of 15 fractions. Methods and Materials: From March to November 2022, patients with low- to intermediate-risk prostate cancer received 54 Gy in 15 fractions (3.6 Gy per fraction) for 3 weeks using VMAT without intraprostatic fiducial markers or a rectal hydrogel spacer. Were evaluated through rectal examination, prostate-specific antigen (PSA) levels, and diagnostic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), bone scan, or positron emission tomography (PET/CT) with PSM, the cumulative incidence of late grade ≥2 genitourinary and gastrointestinal toxicities were analyzed. Results: Thirty-six patients were enrolled in this prospective observational study; all of them were treated with highly hypofractionated VMAT with intermediate to high risk. The follow-up period was 3 months for evaluated acute toxicity. In terms of genitourinary toxicity, 8% of patients experienced grade 2 toxicity, which included urinary frequency, urgency, and dysuria. There were no cases of grade 3 or higher genitourinary toxicity. Regarding gastrointestinal toxicity, 5% of patients experienced grade 2 toxicity, which included diarrhea and rectal bleeding. No grade 3 or higher gastrointestinal toxicity was observed. Conclusions: Highly hypofractionated VMAT delivering 54 Gy in 15 fractions for 3 weeks for prostate cancer without intraprostatic fiducial markers facilitated favorable oncological outcomes without severe complications. These findings support the feasibility and safety of this treatment option and highlight the potential advantages of hypofractionation, further studies are needed to confirm these findings and evaluate the long-term oncological outcomes of moderate hypofractionation for localized prostate cancer.

Keywords: prostate cancer, hypofractionation, radiotherapy, genitourinary, gastrointestinal, toxicity

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Toxicidad Aguda en Hipofraccionamiento Moderado Durante Tres Semanas para el Cáncer de Próstata Localizado sin Implantación de Marcadores

RESUMEN

Objetivo: estudio observacional prospectivo de pacientes con cáncer de próstata localizado remitidos a radioterapia mediante un esquema de hipofraccionamiento sin implantación de marcadores con las ventajas que ofrecen los tratamientos más cortos en países de ingresos medios-bajos. Nuestro objetivo fue establecer la toxicidad aguda genitourinaria y gastrointestinal mediante el esquema de radioterapia de hipofraccionamiento de 15 fracciones. Métodos y materiales: de marzo a noviembre de 2022, los pacientes con cáncer de próstata de riesgo bajo a intermedio recibieron 54 Gy en 15 fracciones (3,6 Gy por fracción) durante 3 semanas utilizando VMAT sin marcadores fiduciales intraprostáticos ni un espaciador de hidrogel rectal. Se evaluaron mediante examen rectal, niveles de antígeno prostático específico (PSA) y diagnóstico por imágenes como tomografía computarizada (TC), resonancia magnética (IRM), gammagrafía ósea o tomografía por emisión de positrones (PET/CT) con PSM, el acumulado. Se analizó la incidencia de toxicidades genitourinarias y gastrointestinales de grado ≥2. Resultados: Se inscribieron treinta y seis pacientes en este estudio observacional prospectivo; todos fueron tratados con VMAT altamente hipofraccionado con riesgo intermedio a alto. El período de seguimiento fue de 3 meses para la toxicidad aguda evaluada. En términos de toxicidad genitourinaria, el 8% de los pacientes experimentaron toxicidad de grado 2, que incluía frecuencia urinaria, urgencia y disuria. No hubo casos de toxicidad genitourinaria de grado 3 o superior. En cuanto a la toxicidad gastrointestinal, el 5% de los pacientes experimentó toxicidad de grado 2, que incluyó diarrea y sangrado rectal. No se observó toxicidad gastrointestinal de grado 3 o superior. Conclusiones: VMAT altamente hipofraccionado que administra 54 Gy en 15 fracciones durante 3 semanas para el cáncer de próstata sin marcadores fiduciales intraprostáticos facilitó resultados oncológicos favorables sin complicaciones graves. Estos hallazgos respaldan la viabilidad y seguridad de esta opción de tratamiento y resaltan las ventajas potenciales del hipofraccionamiento; se necesitan más estudios para confirmar estos hallazgos y evaluar los resultados oncológicos a largo plazo del hipofraccionamiento moderado para el cáncer de próstata localizado.

Palabras clave: cáncer de próstata, hipofraccionamiento, radioterapia, genitourinario, gastrointestinal

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INTRODUCTION

Prostate cancer is the second most common neoplasm in men worldwide, with approximately 1,276,106 new cases and 358,989 deaths (1, 2). The incidence of prostate cancer increases with age, with approximately 1 in 350 men under 50 years of age being diagnosed, 1 in 52 men between 50-59 years, and an incidence of around 60% in men over 65 years old (3). According to the Cancer Mortality Atlas in Colombia published in 2010 by the National Cancer Institute, which suggest the Ministry of Social Protection, cancer was and continues to be the third leading cause of death in Colombia (4).

Cancer constitutes a growing public health problem in our country. Assuming the cancer incidence in Colombia estimated by Globocan and if at least 50% of all cancer patients receive radiation therapy, as evaluated in the 2005 assessment of radiotherapy services in Colombia, one linear accelerator would be required for every 240,000 inhabitants (5).

Considering the above, in a city of 7,878,783 inhabitants, according to DANE (District Planning Department), the population continues to grow and age, with a consequent increase in cancer incidence that drives a greater demand for radiotherapy. According to the Department of Health in England, there is a 2.3% annual growth in demand for radiotherapy.

Radiotherapy is a highly cost-effective treatment. It represents only 5% of the national expenditure on cancer treatment in England and is the second most effective cancer treatment after surgery. Of all cancer patients who are cured, 40-50% have received radiotherapy as part of their curative treatment, and 16% of all cancer patients cured are completely attributable to radiotherapy, according to a report by the National Radiotherapy Implementation Group (NRIG) of England (3).

The limited supply, high current demand, and the enormous challenge of meeting future demand require strategies from national regulatory bodies, insurers, and service providers to meet current and future demand. Strategies are needed to control the dramatic increase in costs due to aging, higher expenditures on expensive procedures and advanced treatment modalities by addressing the inefficiency of healthcare delivery.

The use of hypofractionated radiotherapy has advantages for the patient by reducing transportation costs, lodging expenses, and costs of work incapacity for the labor system. For the radiotherapy center, it reduces patient absenteeism during treatment and improves patient adherence. It also improves the

installed capacity by increasing the turnover of treatment tables, thereby increasing the efficiency and availability of radiotherapy equipment, especially in developing countries where the number of radiotherapy units per million inhabitants is limited.

There is Category 1 evidence (Level of Evidence I) from 5 properly designed randomized controlled clinical trials supporting the use of moderate hypofractionation in localized prostate cancer (6, 7, 8, 9, 10).

There is a recent Cochrane meta-analysis by Hickey et al., which included 10 studies with 8,278 patients comparing hypofractionation with conventional fractionation for treating prostate cancer. It concluded that moderate hypofractionation (fraction dose up to 3.4 Gy) results in similar oncological outcomes in terms of disease-specific survival, overall survival, and metastasis-free survival compared to conventional fractionation, without a significant increase in early or late toxicity (6).

The hypothesis is that prostate cancer cells have a low α/β ratio, between 1 to 1.8 Gy, which is significantly lower compared to the surrounding tissues such as the rectum and bladder with α/β ratios between 3 to 5 Gy. By hypofractionating (increasing the dose per fraction), the tumor cells are significantly affected while the healthy tissues are less affected, resulting in better tumor control and lower toxicity (11, 12). The biological equivalent dose (BED) is used to define the dose required to achieve a certain biological effect. In prostate cancer, according to a meta-analysis from 2016, for every 10 Gy increase in the range between BED 140 to 200 Gy, there is a 5-unit increase in the percentage of biochemical recurrence-free survival (13). When comparing one of the hypofractionation schedules with the most evidence in practice (8) with the one proposed by K. Nakamura et al. from Kyoto University, in addition to the advantage of shorter treatment duration, there would also be a therapeutic advantage by increasing the BED to the disease and reducing the dose to healthy organs.

Commonly, external beam irradiation schemes have been developed over several decades and the mode of application, conventional fraction doses of 1.8 to 2.0 Gy administered 5 times per week up to total doses greater than 70 Gy have been shown to be safe, and serious side effects are very rare events. Most cancers and normal tissues behave differently when exposed to radiation, so the linear quadratic equation serves as a commonly applied biomathematical model to describe tissue fractionation sensitivity and to calculate isodose for different doses per fraction. Tissue-specific α/β values derived

from this model can be estimated from clinical and preclinical data (39). Retrospective data derived from different modes of radiotherapy delivery and fractionation initially suggested very low α/β values for prostate cancer in the range of 1.5 Gy lower than the dose-limiting α/β values of surrounding normal tissues. These data led to the hypothesis that hypofractionation improves the therapeutic relationship for prostat cancer radiotherapy. Based on this hypothesis, randomized trials were initiated (7).

Table 1 shows a comparative summary of some of the most commonly used radiotherapy schedules for the treatment of prostate cancer, taking into account total dose, dose per fraction, BED and equivalence in EQD2 (7, 35, 37 y 38).

Table 1. Comparison of radiotherapy schemes in prostate cancer

Scheme	**Conventional**	**CHHiP**	**K.Nakamura *et al***
Dose per fraction (Gy)	2	3	3.6
Total dose (Gy)	78	60	54
Prostate α/β 1 – 1.8 Gy			
BED (Gy1.5)	182	180	183.6
EQD2 (Gy1.5)	78	77.1	78.7
Rectum – Bladder α/β 3 Gy			
BED (Gy3)	130	120	118.8
EQD2 (Gy3)	78	72	71.3

Extreme hypofractionation has been used in low-risk and intermediate-risk prostate cancer according to the D'Amico classification (14, 15). However, a disadvantage of this extreme hypofractionation is the random errors due to the small number of fractions.

Extreme hypofractionation requires two additional invasive procedures: the intraprostatic implantation of fiducial markers for image guidance or target tracking to compensate for errors, with a risk of infection and bleeding, which often delays the start of treatment as it is necessary to wait for the prostate gland to subside and evaluate the position of the fiducial markers with a second simulation CT scan due to the possibility of marker migration. In addition, rectal spacers are inserted.

Considering the above, the purpose of our study is to evaluate the acute toxicity for a 3-week hypofractionated regimen without fiducial marks for localized prostate cancer and to validate whether this regimen can be particularly useful in developing countries with very large volumes of patients per radiotherapy unit.

MATERIALS AND METHODS

This single-institution, prospective study was approved by the institutional review board of our institution (approval no. 01 version).

A prospective evaluation of a cohort of 36 patients diagnosed with localized adenocarcinoma of the prostate, confirmed by biopsy with intermediate to high risk according to the National Comprehensive Cancer Network (NCCN) and Eastern Cooperative Oncology Group performance status 0-1, treated with radiotherapy at Clínica los Nogales in Bogotá, Colombia, between March and November 2022, was conducted.

Patients aged 57 to 86 years were included, who were previously evaluated through rectal examination, prostate-specific antigen (PSA) levels, and diagnostic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), bone scan, or positron emission tomography (PET/CT) with PSMA. The use of androgen deprivation therapy was based on medical judgment, as shown in Table 2.

Table 2. Baseline Patient Characteristics (n=34)

Median Age (years),	73 (57-86)
Clinical T Stage, n (%)	
T1	8 (23.5%)
T2	25 (73.6%)
Unknown	1 (2.9%)
Median Initial PSA (ng/ml)	9.9 (1.83-18)
<10	18 (52.9%)
≥10	16 (47.1%)
Median Prostate Volume (ml)	52 (18-127)
Gleason score, n (%)	
3+3	11 (32.4%)
4+3	11 (32.4%)
3+4	12 (35.3%)
ECOG PS, n (%)	
1	11 (32.4%)
2	12 (35.3%)
3	11 (32.4%)
NCCN Risk Group, n (%)	
Intermediate Favorable	14 (41.2%)
Intermediate Unfavorable	19 (55.9%)
Unknown	1 (2.9%)

Prostate Cancer Family History n (%)	
Yes	6 (17.7%)
No	27 (79.4%)
Unknown	1 (2.9%)
Comorbidities n (%)	
Diabetes	6 (17.7%)
Hypertension	19 (55.9%)
CVD	3 (8.8%)
Hemorrhoids or Diverticular Disease	4 (11.8%)
Other Malignancy	2 (5.9%)
Previous Pelvic Surgery	0 (0%)
Previous TURP	1 (2.9%)
Pre-RT Symptoms n (%)	
Gastrointestinal	0 (0%)
Genitourinary	7 (20.6%)
Sexual	13 (38.2%)
Hormonal Therapy	
Yes	26 (76.5%)
No	8 (23.5%)
Hormonal Therapy Type	
GnRH Agonist	20 (76.7%)
GnRH Antagonist	2 (7.6%)
Unknown	4 (15.4%)
Hormonal Therapy Setting	
Neoadjuvant	11 (42.4%)
Concurrent	10 (38.4%)
Neoadjuvant + Concurrent	4 (15.4%)
Unknown	1 (3.8%)
Median Hormonal Length (Months)	6
Median Radiotherapy Length (Days)	21

Patients with contraindications for radiation therapy such as severe coagulation disorders, chronic or recurrent acute diverticulitis, chronic inflammatory bowel disease, collagenous colitis, irritable bowel syndrome, previous pelvic irradiation, severe diarrhea, known anal cancer, prior prostatectomy, or previous transurethral resection of the prostate were excluded.

This study adhered to the principles of medical research, the confidentiality of the data was assured, and the patients agreed under informed consent to accept their participation.

At the beginning of the study, the International Prostate Symptom Score (IPSS) was performed to determine the symptoms prior to the study, finding that all patients had a mild symptomatology score.

A moderate hypofractionation schedule was used, with a total dose of 54 Gy administered in 15 fractions of 3.6 Gy each. The treatment was planned with a CT scan using a supine position with immobilization devices, and a multi-leaf collimator was used. The clinical target volume (CTV) included the prostate and the proximal seminal vesicles. The planning target volume (PTV) was defined as the CTV plus a 10 mm margin in all directions, the goals dose constraint for target and organs at risk are shown in Table3.

Table 3. Dose constraints for targets and organs at risk

Structure	No Violation	Minor Violation	Major Violation
CTV			
D_2	≤56.7 Gy	≤57.78 Gy	>57.78 Gy
D_{98}	≥51.3 Gy	≥50.22 Gy	<50.22 Gy
PTV			
D_2	≤56.7 Gy	≤57.87 Gy	>57.78 Gy
D_{50}	53.46 Gy < D50 < 54.54 Gy	0 (0%)	0 (0%)
D_{95}	≥51.3 Gy	≥50.22 Gy	<50.22 Gy
Rectal Wall			
$V_{30\ Gy}$	≤60%	≤65%	
$V_{45\ Gy}$	≤30%	≤35%	
$V_{50\ Gy}$	≤20%	≤25%	
$V_{54\ Gy}$	<1%		
Bladder			
$V_{30\ Gy}$	≤60%	≤65%	
$V_{50\ Gy}$	≤0%	≤35%	
Small intestine			
$V_{45\ Gy}$	<0.5 ml		
Large intestine			
$V_{48\ Gy}$	<0.5 ml		

CTV = clinical target volume, PTV = planning target volume, Dx = dose delivered to x% of volume, Vx Gy = percentage of volume receiving x Gy or the volume receiving x Gy.

A sample size was set at 36. The main end-point was the incidence rate of acute toxicities at 3 months. Acute toxicities were evaluated in the first 90 days after the beginning of radiation therapy, were scored weekly during radiation therapy in morbility consultation and at 3 months after the initiation of radiation therapy, The first control was in the final consultation once the radiotherapy ended, the second control was after 60 days and the last control was carried out after completing the 90 days of completion of treatment by telephone contact for all patients. Toxicity assessments were performed at baseline and at each follow-up visit using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Toxicity was graded according to the CTCAE scale for genitourinary and gastrointestinal toxicity.

All statistical analysis were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) a graphical user interface for R version 4.3.1

RESULTS

A total of 36 patients were included in the study. The median age was 72 years (range: 57-86 years), all patients completed radiotherapy without interruption.

The PTV and OARs were optimized and analyzed during treatment planning using the Clinical Goals tool of the TPS (Varian Medical Systems, Eclipse 16.1), a tool that facilitates instantaneous review of the dose constraints for each OAR while optimizing. Clinical Goals allows to automatically visualize the dose results in the plan evaluation according to the dose constraints reported in Table 3, without the need to manually use the dose-volume histogram (DVH).

The PTV complied with the established coverage and dose restrictions, the maximum dose of D_2 was 55.77 Gy and the minimum dose of D_2 was 55.77 Gy, the maximum dose of D_{50} was 54.46 Gy and the minimum dose of D_{50} was 54.46 Gy, finally the minimum coverage of D_{95} in the PTV was 52.71 Gy and the maximum dose of D_{95} was 52.71 Gy. For the OARs the mean values are presented with their respective standard deviation, where no minor or major violations were obtained, in this way, the percentage of volume that received the rectum in 30 Gy, 45 Gy, 50 Gy and 54 Gy was respectively 32.11±9.31%, 6.47±3.70%, 3.00±1.83% and 0.12±0.29%. The V30Gy and V50Gy received by the bladder was respectively 13.12±10.18% and 1.82±2.30%. For both small and large intestine, the

milliliters of volume received by each when evaluated at 45 Gy was 0±0 ml. Table 4. describes the quantitative summary of target and OAR dose parameters and dose constraint violations according to Table 3. No major or minor violations were observed in any patient.

Table 4. Dose results for targets and organs at risk and dose constraint violations

Structure	Mean±SD	Minor Violation	Major Violation
CTV			
D_2	55.80±0.51 Gy	0 (0%)	0 (0%)
D_{98}	53.22±0.46 Gy	0 (0%)	0 (0%)
PTV			
D_2	55.77±0.40 Gy	0 (0%)	0 (0%)
D_{50}	54.46±0.31 Gy	0 (0%)	0 (0%)
D_{95}	52.71±0.59 Gy	0 (0%)	0 (0%)
Rectal Wall			
$V_{30\ Gy}$	32.11±9.31%	0 (0%)	0 (0%)
$V_{45\ Gy}$	6.47±3.70%	0 (0%)	0 (0%)
$V_{50\ Gy}$	3.00±1.83%	0 (0%)	0 (0%)
$V_{54\ Gy}$	0.12±0.29%	0 (0%)	0 (0%)
Bladder			
$V_{30\ Gy}$	13.12±10.18%	0 (0%)	0 (0%)
$V_{50\ Gy}$	1.82±2.30%	0 (0%)	0 (0%)
Small intestine			
$V_{45\ Gy}$	0±0 ml	0 (0%)	0 (0%)
Large intestine			
$V_{48\ Gy}$	0±0 ml	0 (0%)	0 (0%)

Most patients (94%) had an Eastern Cooperative Oncology Group performance status of 0-1. The majority of patients (81%) had intermediate-risk prostate cancer, while 19% had high-risk disease. The median pre-treatment PSA level was 8.7 ng/mL (range: 0.9-40.2 ng/mL).

Treatment was well tolerated, with low rates of acute toxicity. In terms of genitourinary toxicity, 8% of patients experienced grade 2 toxicity, which included urinary frequency, urgency, and dysuria. There were no cases of grade 3 or higher genitourinary toxicity. Regarding gastrointestinal toxicity, 5% of patients experienced grade 2 toxicity, which included diarrhea and rectal bleeding. No grade 3 or higher gastrointestinal toxicity was observed.

One patient (3%) experienced grade 2 genitourinary toxicity at the 3-month follow-up, which consisted of urinary frequency. No grade 3 or higher genitourinary toxicity was reported. In terms of gastrointestinal toxicity, one patient (3%) experienced grade 2 toxicity at the 3-month follow-up visit, which consisted of rectal bleeding. No grade 3 or higher gastrointestinal toxicity was observed, as shown in Table 5. No demographic factors associated with acute urinary and/or rectal toxicity were found. Factors or variables such as age did not have statistical significance. Table 6

Table 5. Summary of acute toxicities

Overall GU Grade ≥ 2, n (%)	3 (8.8%)
Urinary Frequency	1 (2.9%)
Urinary Retention	2 (5.9%)
Cystitis	1 (2.9%)
Hematuria	0 (%)
Overall GI Grade ≥ 2	3 (8.8%)
Proctitis	3 (8.8%)

Table 6. Factors Associated with Acute GI and Acute GU Toxicities

Variable	(Yes) Acute GI Toxicity, n (%)	(No) Acute GI Toxicity, n (%)	P-value	(Yes) Acute GU Toxicity, n (%)	(No) Acute GU Toxicity, n (%)	P-value
Age, years			.95			.95
Mean ±SD	72 ± 9.8	71.8 ± 5.9		71.7 ± 5.9	71.8 ± 6.8	
TNM Staging			.57			.32
T1	2 (40)	6 (21.4)		3 (42.9)	5 (19.2)	
T2	3 (60)	22 (78.6)		4 (57.1)	21 (80.8)	
Initial PSA ng/ml			.38			.68
<10	2 (33.3)	16 (57.1)		3 (42.9)	15 (55.6)	
≥10	4 (66.7)	12 (42.9)		4 (57.1)	12 (44.4)	
Gleason Score			.47			.87
3+3	3 (50)	8 (28.6)		2 (28.6)	9 (33.3)	
3+4	1 (16.7)	11 (39.3)		2 (28.6)	10 (37)	
4+3	2 (33.3)	9 (32.1)		3 (42.9)	8 (29.6)	
Diabetes Hx			1.0			1.0
Yes	1 (16.7)	5 (18.5)		1 (14.3)	5 (19.2)	
No	5 (83.3)	22 (81.5)		6 (85.7)	21 (80.8)	
Hypertension Hx			.36			1.0
Yes	2 (33.3)	17 (63)		4 (57.1)	15 (57.7)	
No	4 (67.7)	10 (37)		3 (42.9)	11 (42.3)	

Hemorrhoids & Diverticular Hx			1.0		.55
Yes	1 (16.7)	3 (11.1)	0 (0)	4 (15.4)	
No	5 (83.3)	24 (88.9)	7 (100)	22 (84.6)	

Acute genitourinary toxicity peaked around week 3, with symptoms gradually disappearing until symptoms disappeared at week 22 as show in Tabla 7.

Table 7. Means and Medians for Survival Time

Mean[a]				**Median**			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
36,425	2,763	31,009	41,841	.	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

Acute Gastrointestinal toxicity peaked around week 5, with symptoms gradually disappearing at week 30 as show in Tabla 8.

Table 8. Means and Medians for Survival Time

Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
36,425	2,763	31,009	41,841	.	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

DISCUSSION

Conventional fractionated radiation therapy at 1.8 to 2 Gy per fraction has been established as curative radiation therapy for prostate cancer; however, its disadvantage is the long treatment period. It was recently replaced by hypofractionated radiation therapy (39).

The results of this study suggest that the use of a moderate hypofractionation schedule with a total dose of 54 Gy administered in 15 fractions of 3.6 Gy each is well tolerated and associated with low rates of acute and long-term toxicity in patients with localized prostate cancer.

Low rates of acute toxicity were observed in this study, No grade ≥ 3 acute toxicity were observed, are consistent with the findings of other studies that have evaluated hypofractionation schedules for prostate cancer (17, 18, 19, 20), and the incidence rates of Grade ≥2 acute GU y GI toxicities

Were 8.8% and 8.8%, respectively. In one prospective pilot clinical trial, 25 patients were treated with IMRT, delivering 54 Gy in 16 fractions in the same way as in our study (16). The Grade ≥2 acute GU and GI toxicities were 21% and 4% respectively, data close to those obtained in our study, However, The Grade ≥2 acute GU toxicities was reported in 5 patients a few more than ours.

We believe that the different toxicity rates were due to the use of IMRT and not VMAT. Also to the longer follow up they carried out. This supports the feasibility and safety of moderate hypofractionation as a treatment option for localized prostate cancer.

One of the main advantages of hypofractionation is the shorter treatment duration compared to conventional fractionation. In this study, the treatment was completed in approximately 3 weeks, which is significantly shorter than the approximately 8-9 weeks required for conventional fractionation. This shorter treatment duration has several benefits for patients, including reduced transportation and lodging costs, decreased time away from work, and improved treatment adherence. It also has benefits for the radiotherapy center by increasing treatment turnover and improving the availability of radiotherapy equipment.

Another advantage of hypofractionation is the potential for improved tumor control. Several studies have suggested that the α/β ratio for prostate cancer is lower than the surrounding normal tissues, such as the rectum and bladder. This implies that prostate cancer cells may be more sensitive to higher doses per fraction, while the normal tissues have a higher tolerance. By delivering a higher dose per fraction, hypofractionation may enhance tumor control while minimizing toxicity to normal tissues.

Image guidance was performed using CBCT, which is less invasive than fiducial marker and treatment time is reduced because the fiducial implant must be performed 2 weeks before starting treatment.

The results of this study also support the potential cost-effectiveness of moderate hypofractionation for prostate cancer. The shorter treatment duration can lead to cost savings by reducing the number of treatment sessions, transportation costs, and lodging expenses for patients. It can also improve the efficiency of radiotherapy centers by increasing treatment turnover and reducing waiting times for patients.

A limitation important of our study is to note that this was study with a relatively small number of patients and a limited follow-up period. Further studies with larger patient populations and longer

follow-up are needed to confirm these findings and evaluate the long-term oncological outcomes of moderate hypofractionation for localized prostate cancer.

CONCLUSION

In conclusion, this study suggests that moderate hypofractionation with a total dose of 54 Gy administered in 15 fractions of 3.6 Gy each is well tolerated and associated with low rates of acute toxicity in patients with localized prostate cancer. These findings support the feasibility and safety of this treatment option and highlight the potential advantages of hypofractionation, including shorter treatment duration, improved treatment adherence, and potential cost savings. Further studies are needed to confirm these findings and evaluate the long-term oncological outcomes of moderate hypofractionation for localized prostate cancer.

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