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Moderate hypofractionated radiotherapy to the prostate bed with or without pelvic lymph nodes: a prospective trial

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ABSTRACT

Background: Hypofractionated radiotherapy in the treatment of prostate cancer has been widely studied. However, in the postoperative setting it has been less explored. The objective of this prospective study is to evaluate the safety and efficacy of hypofractionated radiotherapy in postoperative prostate cancer.

Materials and methods: A prospective study was designed to include patients with prostate cancer with an indication of postoperative radiotherapy as adjuvant or salvage. A hypofractionated radiotherapy scheme of 51 Gy in 17 fractions was performed with the possibility of treating the pelvis at a dose of 36 Gy in 12 fractions sequentially. Safety was evaluated based on acute and late toxicity [according to the Radiation Therapy Oncology Group (RTOG) scale and Common Terminology Criteria Adverse Events (CTCAE) v4.03], International Prognostic Scoring System (IPSS) over time, and quality of life.

Results: From August 2020 to June 2022, 31 patients completed treatment and were included in this report. 35.5% of patients received elective treatment of the pelvic nodal areas. Most patients reported minimal or low acute toxicity, with an acute gastrointestinal (GI) and genitourinary (GU) grade 3 or greater toxicity of 3.2% and 0%, respectively. The evolution in time of the IPSS remained without significant differences ($p = 0.42$). With the exception of a significant improvement in the domains of hormonal and sexual symptoms of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, the rest of the domains [EPIC, European Organization for Research and Treatment of Cancer (EORTC) Core quality of life questionnaire (C-30) and Prostate Cancer module (PR-25)] were maintained without significant differences over time. With a follow-up of 15.4 months, late GI and GU grade 2 toxicity was reported greater than 0% and 9.6%, respectively.

Conclusions: Hypofractionated radiotherapy in postoperative prostate cancer appears to be safe with low reports of relevant acute or late toxicity. Further follow-up is required to confirm these results.

Trial registration: The protocol was approved by the accredited Medical Ethical Committee of Pontificia Universidad Católica de Chile. All participants accepted and wrote informed consent.

Key words: prostate cancer; postoperative radiotherapy; hypofractionated radiotherapy

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Introduction

Prostate cancer is the most prevalent non-cutaneous neoplasm in men both in Chile and worldwide. It is estimated as the fifth cause of death from cancer worldwide and the third in our country [1]. Approximately 30% of patients are treated primarily with radical prostatectomy, and of these, a third will require adjuvant radiation therapy (ART) for high-risk factors or salvage radiotherapy (SRT) for biochemical recurrence [2].

ART and SRT have been shown to be safe and beneficial in terms of local and biochemical control of the disease in several phase III trials [3–5]. Recently, data have been published suggesting that ART could be omitted in favor of early SRT in three phase III trials [6–8] and a meta-analysis [9]. These studies used standard radiation therapy fractionation regimens (60–66 Gy in 30–33 fractions), which entails long duration treatments (6–7 weeks) associated with high operational cost and daily attendance of users at the radiotherapy center during the treatment period.

In several reports of radiotherapy treatment for prostate cancer a low α/β has been found (1.3–3 Gy), this characteristic of this tumor supports the hypothesis that hypofractionated radiotherapy could increase tumor cell death while sparing the surrounding acute responding tissue [10]. Additionally hypofractionated radiotherapy have been described as more cost-effective and convenient for the patient [11, 12].

Hypofractionated radiotherapy as a primary treatment for prostate cancer has been shown to be non-inferior to conventional fractionation and has not been associated with greater toxicity, being a recommended scheme by international guidelines [13].

It should be noted that hypofractionated radiotherapy in postoperative settings has not been fully elucidated. Therefore, a prospective trial was designed to evaluate the safety and efficacy of hypofractionated treatment in the case of ART or SRT.

Materials and methods

Trial Design

This is a prospective clinical trial, conducted at an academic center ("UC-Christus Cancer Center") that explored hypofractionated radiation therapy in the context of SRT or ART. The protocol and design were approved by the local ethics committee (March 5, 2020 (Study number 191016002) and its implementation was under the guidelines of Good Clinical Practice and the Declaration of Helsinki.

Patients

Patients older than 18 years with a diagnosis of prostate cancer, with histopathological confirmation of adenocarcinoma, who underwent radical prostatectomy and indication for adjuvant or salvage radiotherapy were recruited; the need for ART was defined by the presence of risk factors (pT3a-b and/or positive surgical borders or nodal involvement in lymph node dissection) or the need for SRT due to biochemical recurrence (two prostate-specific antigen (PSA) elevations above 0.2 ug/mL). the exclusion criteria were: pT4, macroscopic nodule concordant with persistent disease in the prostate bed or pelvic positive adenopathy concordant with regional or distant metastasis by imaging; history of previous pelvic radiotherapy; severe urinary incontinence, inflammatory bowel disease and/or genetic disease with greater predisposition to radiation therapy toxicity.

Intervention

After defining the need for radiotherapy, the patient was simulated with a pelvic computed tomography (CT) for radiotherapy planning, with rectum and bladder preparation according to the local protocol of the cancer center with an empty rectum and a full bladder.

The prostate bed was defined as "clinical target volume" (CTV) according to the Radiation Therapy Oncology Group (RTOG) contouring guide [14]. The treatment of the nodal areas of the pelvis was according to the preference of treating radiation oncologist, the contouring of the volume was according to the RTOG guideline [15], and after 2021 according to the NRG guide [16]. A "planning target volume" (PTV) was created with a 5 mm expansion of the CTV in all directions.

The prescribed dose to the prostate bed/seminal vesicles was 51 Gy in 17 daily fractions (3 Gy per fraction) for a total of 3.5 weeks. Intensity modulated radiotherapy (IMRT) technique with "volumetric arc therapy" (VMAT) Technique was used for planning. When treatment to the pelvis was planned, the pelvis was prescribed to 36 Gy in 12

daily fractions and, then, a sequential boost to the prostate bed to complete to 51 Gy in 3 Gy fractions was used. The decision of elective treatment to the pelvis was left to the discretion of the treating physician.

The planning objectives were as follows: 99% coverage of the PTV was > 48.45 Gy, allowing a maximum dose in the PTV of < 54.57 Gy. The dose to the tumor bed (51 Gy) is biologically equivalent to 66 Gy (assuming α/β 1.3–1.5 Gy). 36 Gy in 12 fractions to the pelvis was decided based on a calculation of a biologically effective dose (BED) 108, which is similar to the BED of 106 from a standard fractionation scheme of 2 Gy per fraction up to 46 Gy total to the pelvis (assuming α/β of 1.5). The dose restrictions for organs at risk were as follows: rectum V42 < 40% and V18 < 33%; bladder V48 < 40%; bowel V40 < 2 cc and V34 < 17 cc (with maximum dose < 50 Gy) and femoral heads V25 < 5%. All dosimetric plans were evaluated and approved by the treating physician, and quality control was also carried out by the team of physicists prior to each treatment. The positioning and adequate preparation of the bladder and rectum were evaluated with cone beam computed tomography images (CBCT) in each treatment.

Endpoints and statistical methods

The primary endpoint was GU and/or GI late toxicity grade > 2 and the secondary objectives was gastrointestinal and genitourinary acute toxicity, disease-related quality of life and biochemical failure-free survival, defined as an absolute serum PSA > 0.4 ng/ml, rising compared to the previous value.

A sample size calculation of 30 patients was planned, based on a reported risk of grade 3 or greater late toxicity of 2% with standard treatment in historical series [17, 18], and calculating that the upper limit of the confidence interval is 12%. If G3 toxicity less than 12% is confirmed, a randomized phase II study will continue.

In relation to the analysis of the quality of life and the domains of the Expanded Prostate Cancer Index Composite (EPIC) 2.0, the results were transformed into a percentage value of 0–100 [according to European Organization for Research and. Treatment of Cancer (EORTC) manual], and the average, the maximum and minimum baseline value of each of these were reported. For symptom scales a higher score indicates a worse situation, while a higher score for functional and global health status is an indicator for a good condition.

Follow-up and toxicity assessment

Acute toxicity was evaluated weekly by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and International Prostate Symptoms Score (IPSS), during radiotherapy and 4.8 and 12 weeks after its completion. Late toxicity was defined as that presented 6 months after radiotherapy was completed. The disease-related quality of life, urinary, gastrointestinal, sexual and hormonal function were evaluated with EPIC 2.0, Quality of Life of Cancer Patients (QLQ C-30) and Prostate Cancer module (PR-25) questionnaires at baseline before the start of radiotherapy and then every 6 months. A digital rectal examination and PSA measurement were performed every 6 months.

Results

From August 2020 to June 2022, 39 patients were registered. Of these, 3 refused to enter the trial protocol and 5 were excluded due the inability to comply with dosimetric restrictions and/or poor bladder function (4 patients) and were treated with standard fractionation or interruption of radiotherapy (1 patient). Thirty-one patients completed treatment and are included in this report. The summary of the clinical characteristics of the patients who received the protocol is in Table 1. The median patient age was 65 years and most patients had a International Society of Urological Pathology (ISUP) 2 (41.9%), 18 patients had a pT3 (35.7%) and 16 patients had negative surgical margins (51.6%). All patients underwent a lymph node dissection with a median of 11 lymph nodes resected. Five patients (16.1%) were staged as pN1, with a median of two lymph nodes positive for metastasis. The intention to treat in most cases was by salvage (51.6%), with an average PSA prior to the start of RT of 0.24 ng/mL.

Most patients received hormone deprivation treatment (80.6%), all for a period of six months. Before starting salvage radiotherapy, 15 patients were staged with positron emission tomography

Table 1. Patients characteristics

	N or Median	% or Range
Age	65	46–75
PSA at diagnostic [ng/mL]	12	2.6–67.7
ISUP score		
1	1	3.2%
2	12	41.9%
3	11	35.5%
4	2	6.5%
5	4	12.9%
pT		
pT1	2	6.5%
pT2a	6	19.4%
pT2b	3	9.7%
pT2c	14	45.1%
pT3a	4	12.9%
pT3b	1	3.2%
pT4	0	0%
Unknow	1	3.2%
Surgical margins		
Positive	15	48.4%
Negative	16	51.6%
Number lymph nodes dissection	11	2-40
pN		
pN0	26	83.9%
pN1	5	16.1%
PSA pre-EBRT [ng/mL]	0.24	0-0.9
Treatment intention		
Adjuvant	15	48.4%
Salvage	16	51.6%
ADT with EBRT		
Yes	25	80.6%
No	6	19.4%
Image pre-EBRT		
CT or BS	17	31.5%
PET-PSMA	15	55.6%
None	4	12.9%
EBRT volume		
Prostate bed only	20	64.5%
Prostate bed and Elective pelvic	11	35.5%
Time from surgery to EBRT (months)	13.7	4.8-84.47

PSA — prostate-specific antigen; EBRT — external beam radiotherapy; ISUP — International Society of Urological Pathology; CT — computed tomography; BS — bone scintigraphy; ADT — androgen deprivation therapy; PET-PSMA — positron emission tomography with increased prostate-specific membrane antigen

with increased prostate-specific membrane antigen (PET-PSMA) (48.4%). Eleven patients received treatment to the pelvis (35.5%).

Table 2. Acute toxicity gastrointestinal and genitourinary according to the Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria Adverse Events (CTCAE)

RTOG		CTCAE	
Gastrointestinal			
0	32.25%	0	51.61%
1	45.16%	1	35.48%
2	22.58%	2	9.67%
3	0%	3	3.22%
Genitourinary			
0	25.8%	0	19.35%
1	48.38%	1	51.61%
2	25.8%	2	29.03%
3	0%	3	0%

The cumulative acute toxicity according to RTOG and CTCAE v 4.03 is described in Table 2. Most patients reported minimal or low acute radiation effects in terms of gastrointestinal (GI) and genitourinary (GU) problems. According to the RTOG and CTCAE scale, acute GI grade 2 or major toxicity was experienced by 22.58% and 12.89% of the patients, respectively, while acute GU grade 2 toxicity was experienced by 25.8% and 29.03%, respectively. Grade 3 or higher GI/GU toxicity was present in 3.22% of the patients (1 patient had diarrhea G3 according to CTCAE v4.03 and received treatment to prostate bed only).

The median baseline IPSS was 2.73 [standard deviation (SD): 0.42; 95% confidence interval (CI): 2.01–3.68) with a mean increase to 4.69 (SD: 0.62; 95% CI: 3.61–6.04) at the end of treatment and to 3.2 (SD: 0.49; 95% CI: 2.35–4.3) at 12 weeks post-treatment (Fig. 1). In the beta regression analysis, the variation of the IPSS mean remained stable without significant variation over time [odds ratio (OR): 1.04; $p = 0.42$].

The median follow-up was 15.4 months. Late grade ≥ 2 GI and GU toxicity was observed in 0 (0%) and 3 (9.6%) patients, respectively. One (3.2) patient experienced grade 3 late GU toxicity (stricture of urethral anastomosis and actinic cystitis).

27 (87.1%) and 16(51.6%) patients completed the questionnaires at baseline and at 18 months, respectively. Patient-reported urinary symptoms, detriment is shown in continence function on the EPIC questionnaire; however, it remains stable over time without significant difference ($p = 0.08$),

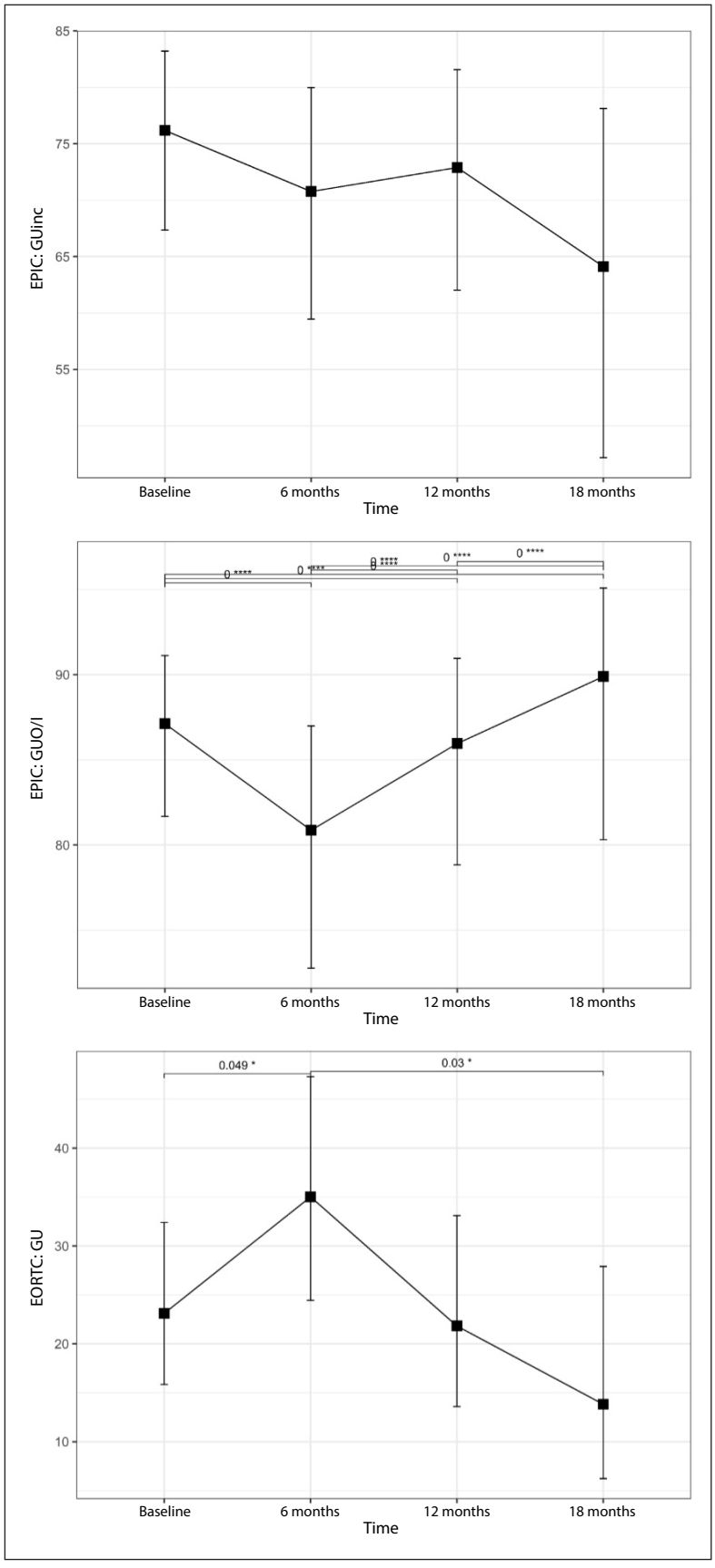

Figure 2. Evolution over time of urinary symptoms in the Expanded Prostate Cancer Index Composite (EPIC) and European Organization for Research and Treatment of Cancer (EORTC) questionnaires

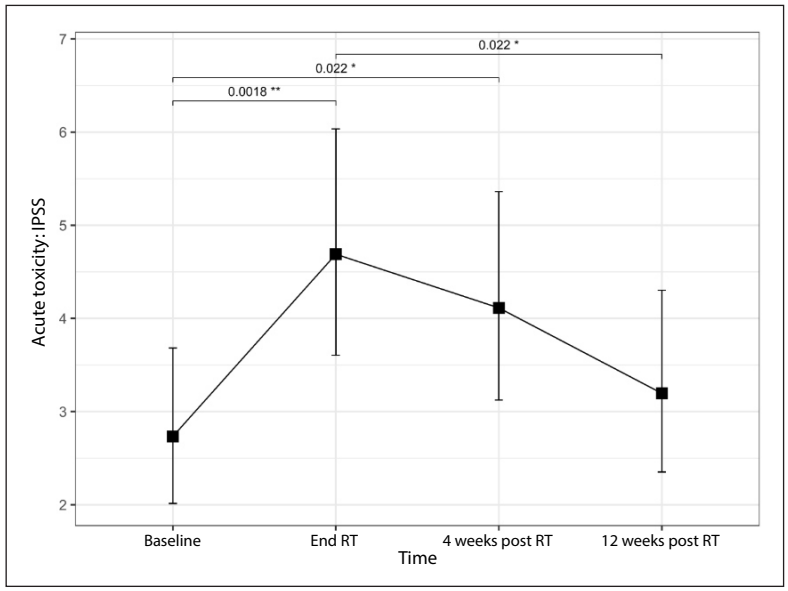

Figure 1. Evolution of the International Prognostic Scoring System (IPSS) over time. RT — radiotherapy

Table 3. Summary of the results of the Expanded Prostate Cancer Index Composite (EPIC) and the European Organization for Research and Treatment of Cancer (EORTC) questionnaires over time

	Baseline (SD)	6 Months (SD)	12 Months (SD)	18 Months (SD)	p-value (SD)
EPIC					
Bowel	86.47 (2.12)	82.71 (2.98)	86.93 (2.54)	93.24 (2.65)	0.23
Urinary Incontinence	76.18 (4.06)	70.22 (5.29)	72.9 (6.11)	64.11 (8.14)	0.08
Urinary Irritative/obstructive	87.12 (2.39)	80.87 (3.62)	85.96 (3.06)	89.89 (3.61)	0.94
Hormonal	83.56 (3.08)	84.55 (3.32)	86.75 (3.12)	92.27 (3.22)	0.04
Sexual	15.27 (2.89)	17.23 (3.55)	17.79 (3.92)	33.99 (7.51)	0.01
EORTC					
Global Health Status	81.66 (3.26)	77.12 (4.36)	78.69 (4.41)	92.02 (3.22)	0.55
Bowel	6.75 (1.52)	9.88 (2.37)	8.32 (2.17)	5.54 (3.01)	0.59
Urinary	23.1 (4.24)	35 (5.92)	21.82 (4.99)	13.82 (5.36)	0.31
Hormonal	11.02 (2.08)	11.37 (2.54)	11.58 (2.86)	10.48 (3.95)	0.95
Incontinence	15.23 (3.74)	23.65 (5.73)	25.07 (6.2)	11.68 (5.55)	0.39
Sexual activity	33.11 (5.19)	37.07 (7.02)	32.02 (6.9)	56.82 (13.44)	0.35
Sexual function	49.27 (10.36)	37.44 (10.71)	59.01 (10.98)	71.43 (22.21)	0.31

SD — standard deviation

there is no major difference in relation to obstructive-irritative symptoms. QLQ-PR25 urinary toxicity shows stability over time of incontinence and genitourinary symptoms (Tab. 3, Fig. 2).

In relation to bowel symptoms, the evaluation of both questionnaires (EPIC and QLQ-PR25) shows stability over time without significant differences (Tab. 3, Fig. 3).

Hormonal symptoms and sexual function show a significant improvement over time in the EPIC questionnaire. However, this is not replicated in the results in the EORTC QLQ-C30. An increase in Global Health Status is observed, however, without demonstrating significance (Tab. 3).

Discussion

Hypofractionated radiation therapy is widely used in the definitive treatment setting. However, its use in the context of postoperative radiotherapy

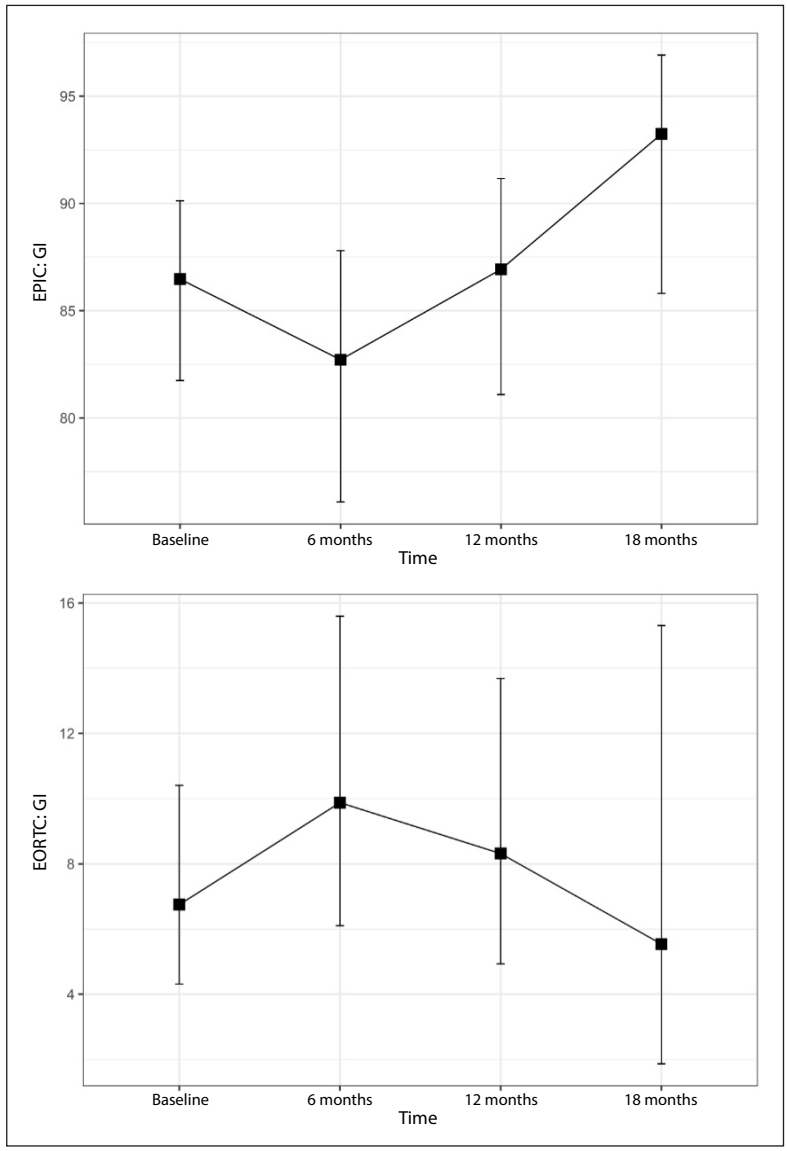

Figure 3. Evolution over time of intestinal symptoms (GI) in the Expanded Prostate Cancer Index Composite (EPIC) and European Organization for Research and Treatment of Cancer (EORTC) questionnaires

is not common in part due to the lack of studies. The potential of a hypofractionated radiotherapy in the postoperative setting would be related to greater radiobiological efficacy and optimization of health resources. Nevertheless, the apprehension for these schemes is due to the eventual greater toxicity of late-responding tissues.

In this report we present the implementation of a hypofractionated radiotherapy of postoperative radiotherapy in prostate cancer of 51 Gy in 17 fractions (3 Gy per fraction), similar to the report by Gladwish et al. [17]. However, our scheme allows elective treatment of the pelvis according to the indication of the physician.

Although hypofractionated radiotherapy has been studied in several series, the treatment of the pelvis has been less evaluated in these. Elective treatment of the pelvis is described in 8 studies [19–27] at doses of 1.7–2 Gy per fraction up to 45–56.1 Gy. The irradiation of the pelvis in these studies was simultaneous to that of the prostate bed, using a simultaneous integrated boost to the prostate bed. To our knowledge this is the first study to use a moderate hypofractionated radiotherapy to the pelvis at doses for subclinical disease with a sequential boost to the prostate bed. Additionally, most patients had a PET PSMA prior to salvage radiotherapy, allowing the identification and exclu-

sion of patients with local or systemic recurrence in a more reliable way [28].

This study shows that severe acute toxicity (grade 3 or greater) is low and similar to what has been published in other series with hypofractionated radiotherapy in the setting of postoperative prostate cancer. Gladwish et al. [17] reports grade 3 toxicity GU and GI of 3% and 0%, respectively, while we publish 0% and 3.2%, respectively. However, in Grade 2 toxicity, we report up to 29%, compared to only 3%. This could be because our study allowed treatment of the pelvis. Ippolito et al. [20] allowed treatment of the pelvis with acute grade 2 toxicity between 20–36% with no grade 3 or higher toxicity, similar to what was reported by us. The largest series of patients was published by Macchia et al. [24] with 124 patients undergoing a scheme of 65.5 Gy in 25 fractions. Only 2 patients (1.6%) experienced grade 3 or greater toxicity. Recently, in 2021, Leite [30] published the experience of 61 patients treated with a hypofractionated radiotherapy scheme of 51 Gy in fractions of 3.4 Gy per fraction (15 fractions in total). Acute toxicity grade 3 or higher GI and GU was 1.6% and 0%, respectively, similar to the series presented. One patient (3.2%) experienced grade 3 late toxicity, similar to the 1.6% reported by Leite et al. [30].

In the context of salvage radiotherapy, international recommendations [29] indicate that the use of androgen deprivation therapy (ADT) should be discussed with the patient, pointing out possible unwanted effects and the potential benefit in preventing recurrence. Consequently, the use of ADT varies significantly, ranging from 13% in the study by Martell et al. [18] to 73% in the study by Massaccesi et al. [21]. In our study, 85.7% of the patients received some type of ADT, which could be related to higher GI toxicity, as reported in other series [31].

This study replicates good results in quality of life with hypofractionated radiotherapy in the postoperative period in prostate cancer. We report a baseline EPIC GI domain of 86% with a relative stability over time of 93% at 18 months. These results are consistent with what was published in NRG GU003, which shows stability of quality of life at 24 months with hypofractionated radiotherapy to the prostate bed [32]. In the series by Martell et al. [18] the mean bowel domain score at 5 years was 93%.

Baseline urinary function in our series is similar to that reported in the literature and does not present significant differences over time. While Martell et al. [18] report a baseline GU between 75–90% with a 5-year estimate of 83%, in this study the patients have a baseline of 76–87% with an average of between 64–89% at 18 months.

Baseline sexual function in EPIC of our series presented was very poor (15%), compared to that reported by Leite [30] of approximately 25%. However, this variable, together with the hormonal domain of the EPIC, were the only ones that significantly improved at 18 months, which could be explained by the use of androgen blockade for 6 months.

Recent research has highlighted substantial shifts (ranging from 30% to 70%) in treatment decision, dose and volumes of radiotherapy in case of biochemical recurrence with the early integration of PSMA-PET/CT [33]. Half of the patients in our series underwent PSMA PET before undergoing radiotherapy, in line with current recommendations. Moreover, our patients underwent PSMA PET with PSA values < 0.5 ng/mL, aligning with the guidelines from recent series [34].

This study allows us to evaluate the safety profile of hypofractionated schemes in postoperative prostate cancer and the feasibility of including elective treatment of the pelvis, which is in line with what is recommended by area experts in the region [35]. However, this protocol has some limitations. It is a mono-institutional study , which must be validated in several centers in the region. It is a study of a single arm without randomized comparison and with the inclusion of elective treatment of the pelvis according to the criteria of the treater. In addition, more follow-up is required. In the future, randomized trials comparing hypofractionated with standard fractionation and the role of elective pelvic treatment in patients at high risk of subclinical lymph node involvement could shed light on the best treatment for this population.

Conclusions

The implementation of a protocol with adjuvant and salvage radiotherapy with moderate hypofractionation in patients after radical prostatectomy, including treatment of the pelvis, is feasible in an academic center in a developing country. Our results

show the low GU and GI severe toxicity. The high prevalence of low-grade GI toxicity may be related to elective pelvic treatment with larger volumes based on recent recommendations and the use of ADT.

The use of moderate hypofractionation seems to be an important strategy to optimize health resources; however, long-term follow-up is required to evaluate late toxicity and biochemical control of the illness.

Conflict of interest

The authors declare no conflict of interest.

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