



Biochemical failure and toxicity in treatment with brachytherapy and external beam radiotherapy compared with radical prostatectomy in localized prostate cancer

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ABSTRACT

Background: Localized prostate cancer (T1-3N0M0) has therapeutic options such as radical prostatectomy (RP), external beam radiation therapy (EBRT) and brachytherapy (BT). However, the evidence of the outcome of these treatments is limited and no studies have been conducted comparing biochemical failure (BF) and toxicity associated with surgical treatment and EBRT + high-dose brachytherapy (HDBT) in the region.

Materials and methods: Retrospective cohort study, clinical records of patients diagnosed with localized prostate cancer between 2014 and 2018 were reviewed at one of the main private neoplasm centers in Lima, Peru; Cox regression was used for both the BF outcome and the grade 2 toxicity outcome, calculating the hazard ratio (HR) with 95% confidence interval (CI).

Results: Of 549 patients, 76.3% (419) received RP as primary treatment, and 72% were between 50 and 70 years old at the time of diagnosis. The patients treated with EBRT + HDBT presented worse characteristics. The EBRT + HDBT group had a 40% lower risk of presenting BF (HR = 0.6; 95% CI: 0.4-0.9), and also a 50% greater risk of presenting toxicity greater than or equal to grade 2 (HR = 1.5; 95% CI: 1.0-2.0) than the group treated with RP.

Conclusion: Our results show that when comparing patients treated with EBRT + HDBT and RP, BF was greater in RP, and post-treatment toxicity was greater in EBRT + HDBT.

Key words: prostate neoplasm; radiotherapy; brachytherapy; prostatectomy; biochemical failure; toxicity

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Introduction

Prostate cancer had approximately ten million deaths in 2020 [1], being the most common neoplasm and the main cause of death in men in Peru [2, 3]. According to risk stratification [4], there are multiple therapeutic options with curative intent for localized prostate cancer (T1-3N0M0) [5]. Among these options, there is brachytherapy

(BT), external beam radiotherapy therapy (EBRT) and surgical treatments such as radical prostatectomy (RP). These therapeutic options have similar levels of evidence; however, to our knowledge, there are no studies that have compared these treatments in the Latin American region.

Biochemical failure (BF) represents an early sign of therapeutic failure after primary treatment [6], both according to the ASTRO definition [3

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consecutive increases in prostate specific antigen (PSA) values after treatment or the start of salvage treatment] [7] and the Phoenix definition (increase greater than or equal to 2 ng/mL in prostate specific antigen (PSA) nadir or the start of salvage treatment) [8]. On the other hand, toxicity is defined as any adverse effect with possible, probable, or definitive attribution to treatment according to the fifth version of the Common Toxicity Criteria for Adverse Effects (CTCv5) [9]. This study compared the development of BF and gastrointestinal (GI) and genitourinary (GU) toxicity among patients treated with PR and EBRT + high-dose brachytherapy (HDBT) in localized prostate cancer of intermediate and high risk.

Material and methods

A retrospective cohort study was carried out in order to determine the prognosis of EBRT + HDBT through the outcomes of BF and toxicity \geq grade 2 after treatment.

Population

The target population was male patients between 50 and 90 years old who had been diagnosed with localized prostate cancer of intermediate and high risk between 2014 and 2018 in the private health center “Oncosalud” in Lima, Peru. Inclusion criteria were having the diagnosis and characteristics of the target population, being treated with RP or EBRT + HDBT and having medical records with complete data. On the other hand, patients were excluded if they had a history of transvesical adenectomy for benign prostate hyperplasia (BPH) or were treated with previous pelvic irradiation. All data were obtained by reviewing medical records and laboratory reports with the previous authorization of the Radiology Service of the Oncosalud Center. The EBRT received was given by volumetric modulated arc therapy (VMAT). The androgen deprivation therapy (ADT) received by the patients at the Oncosalud health center is given, on average, between 6 months and 2 years.

Study variables

Exposure variables were defined as the primary treatment received by the patient: EBRT + HDBT and RP. Likewise, dependent variables included in

the study were BF defined by ASTRO and Phoenix, and GI and GU toxicity \geq grade 2 according to the definitions of the CTCv5. Finally, control variables included were age (years), department of residence, level of education, prostate volume (cc3), Gleason score modified by International Society of Urological Pathology (ISUP), tumor–node–metastasis (TNM) stage, body mass index (BMI), PSA at the time of diagnosis, ADT, history of hypertension, history of diabetes mellitus type 2, and history of personal cancer.

Procedure/data collection

A census was conducted, and potency was calculated using the survival scenario in Epidat 4.2. A ratio of 0.5 was used between the EBRT + HDBT group and the RP group. The potency was calculated with a minimum sample size of 549 patients, a confidence level of 95% and a loss percentage of 10% for both outcomes, obtaining a power of 99.9% and 86.2% for toxicity and BF, respectively.

For the data collection, we went through all medical records of the patients selected in the first half of 2021. These data were digitized in Microsoft Excel 2019 and underwent a quality control via double typing. There was no direct contact with the patients and all the information was handled only by the researchers. Personal data were protected and replaced by codes to ensure patient confidentiality.

All data were analyzed with STATA version 14. For the descriptive analysis, percentages were calculated for the categorical variables while median and interquartile range were calculated for the quantitative variable. P values were calculated with Shapiro-Wilk. For the bivariate analysis of both outcomes, BF and toxicity, p value was calculated with the Log-rank test, while Fisher test was used for the analysis between degrees and types of toxicity according to the primary treatment received. For the multiple variable analysis, Cox Regression was used along with the HR and a 95% CI for both outcomes. All variables of the adjusted model were selected by the epidemiological / theoretical criteria. The “stphtest” command was used to evaluate the assumption of the model and the VIF greater than 2 was used to determine the existence of collinearity. Finally, the adjusted model of BF was stratified considering ADT within the “strata” option.

Results

Descriptive analysis

Of the total 1,125 patients initially considered in the study, 690 were excluded for not meeting the selection criteria and for loss of follow-up. Of the remaining 565, 16 did not have complete data in their clinical history. Only 549 patients were considered of whom 130 (23.7%) received EBRT + HDBT and 419 (76.3%) received RP (Tab. 1).

The mean follow-up of BF was 42.02 months (SD ± 20.3). Patients treated with HDBT + EBRT had a mean follow-up of 33.81 months (SD ± 20.3) and those treated with radical RP, 41.19 months (SD ± 20.40). For the toxicity outcome, the mean follow-up was 37.36 months (SD ± 22.71). The EBRT + HDBT group had a mean follow-up of 28.27 months (SD ± 19.02) and the group RP, a mean of 40.01 months (SD ± 23.13). Regarding some demographic factors, 79.74% of the patients came from Lima and 72% were between 50 to 70 years old. Almost 40% of patients were classified as clinical stage IIIB and 36.98% as stage IIC. Furthermore, within the EBRT + HDBT cohort, 48 patients (43.64%) received 265 Gy, and 62 (56.36%) received 290 Gy, while mostly patients received 70 Gy in 28 fractions. Finally, results showed that 34.6% and 37% of the patients developed BF and toxicity ≥ grade 2, respectively.

As for statistically significant differences (p < 0.05), it was found that patients treated with EBRT + HDBT had a higher percentage of elevated Gleason grades (4 and 5), more advanced clinical stage (primarily stages IIIB and IIIC), older ages (> 70 years) and higher PSA values than those treated with PR. Also, more patients in the EBRT + HDBT group received ADT and had an established diagnosis of hypertension.

Bivariate analysis

For the bivariate analysis of BF (Tab. 2), results evidenced that a higher Gleason score modified by the ISUP, a higher initial PSA values and a more advanced clinical stage were associated with a greater development of BF (p < 0.001). Likewise, 42.5% of those who received ADT developed BF.

For the toxicity outcome (Tab. 3), the study showed that older ages were associated with a greater development of toxicity ≥ grade 2, with those between 70 and 79 years presenting the highest percentage

Table 1. Baseline characteristics of patients with prostate cancer treated with external beam radiation therapy (EBRT) plus high-dose brachytherapy (HDBT) versus radical prostatectomy (RP) in a private center in Lima, Peru

Characteristics	EBRT + HDBT	RP
	n (%)	n (%)
Age [years]		
50–59	10 (7.7)	72 (17.2)
60–69	32 (24.6)	166 (39.8)
70–79	59 (45.4)	140 (33.6)
80–89	29 (22.3)	39 (9.4)
Level of education		
Unlettered	23 (17.8)	47 (11.2)
Incomplete elementary	0 (0.0)	0 (0.0)
Complete elementary	0 (0.0)	0 (0.0)
Incomplete secondary	0 (0.0)	0 (0.0)
Completed secondary	6 (4.7)	45 (10.7)
Higher education	100 (77.5)	327 (78.1)
Origin		
Lima	108 (83.7)	329 (78.5)
Other	21 (16.3)	90 (21.5)
Gleason Score modified by ISUP		
Grade 1	7 (5.4)	12 (2.9)
Grade 2	18 (13.9)	55 (13.1)
Grade 3	55 (42.3)	220 (52.5)
Grade 4	27 (20.8)	113 (27.0)
Grade 5	23 (17.6)	19 (4.5)
Clinical stage		
IIA	1 (0.8)	10 (2.4)
IIIB	10 (7.6)	48 (11.5)
IIC	40 (30.8)	163 (38.9)
IIIA	7 (5.4)	9 (2.1)
IIIB	48 (36.9)	170 (40.6)
IIIC	24 (18.5)	19 (4.5)
TNM stage		
cT2A	4 (3.1)	20 (4.8)
cT2B	15 (11.5)	31 (7.4)
cT2C	48 (36.9)	182 (43.4)
cT3A	15 (11.5)	81 (19.3)
cT3B	44 (33.9)	92 (22.0)
cT3C	4 (3.1)	13 (3.1)
NCCN Risk Category		
Intermediate	61 (46.9)	227 (54.2)
High	69 (53.1)	192 (45.8)
ADT		
Yes	96 (73.9)	123 (29.4)
No	34 (26.1)	296 (70.6)

Table 1. Baseline characteristics of patients with prostate cancer treated with external beam radiation therapy (EBRT) plus high-dose brachytherapy (HDBT) versus radical prostatectomy (RP) in a private center in Lima, Peru

Characteristics	EBRT + HDBT	RP
	n (%)	n (%)
Body mass index		
Normal weight	31 (23.9)	117 (27.9)
Overweight	68 (52.3)	211 (50.4)
Obesity	31 (23.8)	91 (21.7)
Prostate volume [cc ³]*	49.3 (40;57)	46.1 (36.5;58.1)
Initial PSA [ng/mL]		
≤ 10	35 (26.9)	178 (42.5)
10.1–20.9	71 (54.6)	197 (47.0)
≥ 21	24 (18.5)	44 (10.5)
History of HT		
Yes	62 (47.7)	154 (36.7)
No	68 (52.3)	265 (63.3)
History of DM		
Yes	21 (16.1)	61 (14.6)
No	109 (83.9)	358 (85.4)
Personal oncological history		
Yes	2 (1.5)	7 (1.7)
No	128 (98.5)	412 (98.3)

ISUP — International Society of Urological Pathology; TNM — tumor-node-metastasis; NCCN — National Comprehensive Cancer Network; ADT — androgen deprivation therapy; *median (IQR); PSA — prostate specific antigen HT — hypertension; DM — diabetes mellitus

($p < 0.001$). A second analysis was performed between the degrees and types of toxicity according to the primary treatment received (Tab. 4). Even if the findings were not statistically significant ($p > 0.05$), results showed that for both types, GI and GU toxicities, those treated with EBRT + HDBT mostly developed G2 toxicity, while those treated with PR evidenced toxicities of greater degrees.

Multiple variable analysis

The analysis of the BF (Tab. 5) results showed that patients treated with EBRT + HDBT had a 40% lower hazard of developing BF ($p = 0.02$). Similarly, those who received ADT showed 80% more hazard of developing BF, as did those with a previous diagnosis of hypertension, who showed 40% more hazard of developing the outcome ($p < 0.001$). On the other hand, regarding the toxicity outcome (Tab. 6), analysis of the results showed that patients treated with EBRT + HDBT had 50% more hazard of presenting toxicity \geq grade 2 ($p = 0.04$).

Table 2. Biochemical failure according to associated factors in patients with prostate cancer in a private center in Lima, Peru

Variable	Biochemical failure	No biochemical failure	p-value
	n (%)	n (%)	
Treatment			
RP	156 (37.2)	263 (62.8)	0.57
EBRT + HDBT	34 (26.1)	96 (73.9)	
Age [years]			
50–59	28 (33.3)	56 (66.7)	0.83
60–69	67 (33.8)	131 (66.2)	
70–79	73 (36.7)	126 (63.3)	
80–90	22 (32.4)	46 (67.6)	
Gleason score modified by ISUP			
Grade 1	5 (26.3)	14 (73.7)	< 0.001
Grade 2	15 (20.6)	58 (79.4)	
Grade 3	85 (30.9)	190 (69.1)	
Grade 4	66 (47.1)	74 (52.9)	
Grade 5	19 (45.2)	23 (54.8)	
Initial PSA [ng/mL]			
≤ 10	55 (25.8)	158 (74.2)	< 0.001
10.1–20	107 (39.9)	161 (60.1)	
≥ 21	28 (41.2)	40 (58.8)	
Clinical stage			
IIA	6 (25.0)	18 (75.0)	<0.001
IIB	13 (28.3)	33 (71.7)	
IIC	60 (26.1)	170 (73.9)	
IIIA	39 (40.6)	57 (59.4)	
IIIB	64 (47.1)	72 (52.9)	
IIIC	8 (47.1)	9 (52.9)	
ADT			
Yes	93 (42.5)	126 (57.5)	< 0.001
No	97 (29.4)	233 (70.6)	
Body mass index			
Normal weight	51 (34.4)	97 (65.6)	0.09
Overweight	88 (31.5)	191 (68.5)	
Obesity	51 (41.8)	71 (58.2)	
HT history			
Yes	84 (38.9)	132 (61.1)	0.11
No	106 (31.8)	227 (68.2)	
DM history			
Yes	28 (34.1)	54 (65.9)	0.84
No	162 (34.7)	305 (65.3)	

RP — radical prostatectomy; EBRT — external beam radiation therapy; HDBT — high-dose brachytherapy; ISUP — International Society of Urological Pathology; PSA — prostate specific antigen; ADT — androgen deprivation therapy; HT — hypertension; DM — diabetes mellitus; The log rank test was used for all crosses

Table 3. Toxicity ≥ grade 2 according to factors associated with prostate cancer in a private center in Lima, Peru

Variables	Toxicity ≥ 2	Toxicity < 2 or no toxicity	p value
	n (%)	n (%)	
Treatment			
RP	150 (35.8)	269 (64.2)	0.05
EBRT + HDBT	53 (40.8)	77 (59.2)	
Age [years]			
50–59	26 (31.7)	56 (68.3)	< 0.001
60–69	75 (37.9)	123 (62.1)	
70–79	80 (40.2)	119 (59.8)	
80–90	21 (30.9)	47 (69.1)	
Gleason score modified by ISUP			
Grade 1	7 (36.8)	12 (63.2)	0.50
Grade 2	26 (35.6)	47 (63.4)	
Grade 3	105 (38.2)	178 (61.8)	
Grade 4	46 (32.9)	94 (67.1)	
Grade 5	19 (45.2)	23 (54.8)	
Clinical stage			
IIA	9 (37.5)	15 (62.5)	0.22
IIB	16 (34.8)	30 (65.2)	
IIC	76 (33.0)	154 (67.0)	
IIIA	45 (46.9)	51 (53.1)	
IIIB	121 (55.5)	97 (44.5)	
IIIC	5 (29.4)	12 (70.6)	
ADT			
Yes	80 (36.5)	139 (63.5)	0.82
No	123 (37.3)	207 (62.7)	
History of HT			
Yes	90 (41.7)	126 (58.3)	0.11
No	113 (33.9)	220 (66.1)	
History of DM			
Yes	27 (32.9)	55 (67.1)	0.31
No	176 (37.7)	291 (62.3)	

RP — radical prostatectomy; EBRT — external beam radiation therapy; HDBT — high-dose brachytherapy; ISUP — International Society of Urological Pathology; ADT — androgen deprivation therapy; HT — hypertension; DM — diabetes mellitus; The log rank test was used for all crosses

Discussion

We found that the patients treated with EBRT + HDBT had a lower hazard of BF, yet a greater hazard of ≥ grade 2 toxicity when compared with patients treated with RP. Secondly, the majority (76.3%) were treated with RP. Also, 34.6% developed BF and 37.0% toxicity ≥ grade 2.

Regarding the outcome of BF, our results coincide with those reviewed in the literature. A similar study carried out in Germany with 7,515 patients concluded that the patients treated with EBRT + BT presented less risk of BF than those treated with RP ($p < 0.001$) [10]. Another study showed that patients treated with HDBT, despite having worse clinical characteristics, had less BF than those treated with RP [11]. These findings also match the characteristics of the patients treated with EBRT + HDBT that were included in the present investigation.

Despite this, other studies did not find significant differences in these treatments when evaluating low-risk prostate cancer [12]. In addition, a single study that evaluated only patients with Gleason grades 9–10 in the United States found greater BF in patients treated with EBRT + HDBT compared to those treated with RP [13]. However, it is important to emphasize that these studies evaluated populations with characteristics different from ours, like patients of any Gleason grade with intermediate and high-risk prostate cancer.

In addition, regardless of the treatment chosen, it has been shown that the clinical outcome is very similar in the literature reviewed. Long-term follow-ups have identified a similar progression to metastasis between surgical and radiotherapeutic treatments such as EBRT and RP [13–15], and EBRT + BT and RP [14]. Similarly, most of the existing investigations to this date have not

Table 4. Grades and type of toxicity according to the primary treatment with prostate cancer in a private center in Lima, Peru

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal toxicity					
EBRT + HDBT	9 (25.7)	14 (40.0)	7 (20.0)	5 (14.3)	0 (0.0)
RP	15 (31.3)	14 (29.2)	16 (33.3)	3 (6.2)	0 (0.0)
Genitourinary toxicity					
EBRT + HDBT	6 (18.8)	13 (40.6)	11 (34.4)	2 (6.2)	0 (0.0)
RP	35 (23.0)	79 (52.0)	32 (21.0)	6 (4.0)	0 (0.0)

EBRT — external beam radiation therapy; HDBT — high-dose brachytherapy; RP — radical prostatectomy

Table 5. Multivariate analysis by Cox regression for biochemical failure with prostate cancer in a private center in Lima, Peru

	HRC	95% CI	p-value	HRa	95% CI	p-value
Treatment						
EBRT + HDBT	0.9	(0.6–1.3)	0.57	0.6	(0.4–0.9)	0.02
RP	ref			ref		
Age [years]						
50–59	ref			ref		
60–69	1.0	(0.6–1.5)	0.98	0.9	(0.6–1.4)	0.56
70–79	1.1	(0.7–1.8)	0.53	1.0	(0.6–1.5)	0.87
80–90	1.0	(0.6–1.8)	1.00	0.8	(0.4–1.4)	0.33
Gleason Score modified by ISUP						
Grade 1	ref			ref		
Grade 2	0.8	(3.1–2.3)	0.74	0.9	(0.3–2.7)	0.96
Grade 3	1.3	(0.5–3.2)	0.55	1.6	(0.6–4.0)	0.33
Grade 4	2.2	(0.9–5.4)	0.10	2.3	(0.9–6.0)	0.07
Grade 5	2.4	(0.9–6.4)	0.89	2.6	(1.0–7.4)	0.06
Initial PSA [ng/mL]						
≤ 10	ref			ref		
10.1–20.9	1.5	(1.1–2.1)	0.009	1.5	(1.1–2.1)	0.01
≥ 21	2.0	(1.3–3.1)	0.003	1.5	(0.9–2.4)	0.12
Clinical stage						
IIA	ref					
IIB	1.2	(0.5–3.2)	0.69			
IIC	1.1	(0.5–2.5)	0.89			
IIIA	1.9	(0.8–4.5)	0.15			
IIIB	2.4	(1.0–5.6)	0.04			
IIIC	2.6	(0.9–7.5)	0.08			
ADT						
Yes	1.8	(1.3–2.4)	< 0.001			
No	ref					
Body mass index						
Normal weight	ref			ref		
Overweight	0.8	(0.6–1.2)	0.33	0.8	(0.5–1.1)	0.11
Obesity	1.2	(0.8–1.8)	0.28	1.0	(0.7–1.5)	0.99
History of HT						
Yes	1.3	(1.0–1.7)	0.11	1.4	(1.0–1.9)	0.03
No	ref			ref		
History of DM						
Yes	1.0	(0.6–1.4)	0.85			
No	ref					

HR — hazard ratio; CI — confidence interval; EBRT — external beam radiation therapy; HDBT — high-dose brachytherapy; RP — radical prostatectomy; ISUP — International Society of Urological Pathology; PSA — prostate specific antigen; ADT — androgen deprivation therapy; HT — hypertension; DM — diabetes mellitus

identified differences in long-term survival in patients with localized prostate cancer after any of the primary treatments studied in the present

investigation [11, 12, 16–19]. Although there is a multicenter long-term follow-up study which found that mortality was lower in high-risk pros-

Table 6. Multivariate analysis by Cox regression for toxicity \geq grade 2 with prostate cancer in a private center in Lima, Peru

	HRC	IC 95%	p value	HRa	IC 95%	p value
Treatment						
EBRT + HDBT	1.4	(1.0–1.9)	0.05	1.5	(1.0–2.0)	0.04
RP	ref			ref		
Age (years)						
50–59	ref			ref		
60–69	1.3	(0.8–2.0)	0.29	1.3	(0.8–2.0)	0.27
70–79	1.4	(0.9–2.2)	0.15	1.3	(0.9–2.1)	0.20
80–90	1.0	(2.6–1.8)	0.99	1.0	(0.5–1.7)	0.88
Clinical stage						
IIA	ref					
IIB	0.9	(0.4–2.1)	0.88			
IIC	0.9	(0.4–1.7)	0.66			
IIIA	1.4	(0.7–2.8)	0.40			
IIIB	1.1	(0.5–2.2)	0.85			
IIIC	0.7	(0.3–2.2)	0.59			
ADT						
Yes	1.0	(0.7–1.3)	0.83	0.9	(0.6–1.2)	0.40
No	ref			ref		
Initial PSA [ng/mL]						
≤ 10	ref			ref		
10.1–20	0.9	(0.7–1.3)	0.60	0.9	(0.7–1.2)	0.52
≥ 21	1.8	(0.8–1.8)	0.5	1.1	(0.7–1.8)	0.61
History of HT						
Yes	1.3	(1.0–1.7)	0.11	1.2	(0.9–1.6)	0.17
No	ref			ref		
History of DM						
Yes	0.8	(0.5–1.2)	0.31	0.8	(0.5–1.2)	0.31
No	ref			ref		

HR — hazard ratio; CI — confidence interval; EBRT — external beam radiation therapy; HDBT — high-dose brachytherapy; RP — radical prostatectomy; ISUP — International Society of Urological Pathology; PSA — prostate specific antigen; ADT — androgen deprivation therapy; HT — hypertension; DM — diabetes mellitus

tate cancer patients treated with RP [20] at 18 years follow up, the comparison group that received radiotherapeutic treatments was made up of a much smaller number of people.

There is a significant association with other variables that could also influence the development of BF. In the first place, it has been identified that the type of combination of radiotherapeutic regimens may have an important role in the development of BF. In a study carried out in 217 patients, those treated only with EBRT presented higher BF in less time than those treated with EBRT + HDBT [21]. Whereas in another study with 2,279 patients, the application of BT had good biochemical results

[22]. Secondly, there are studies that associate high Gleason score with an increased risk of BF, both in patients treated with EBRT + BT and BT alone [23, 24], also coinciding with the results identified in our investigation. In addition, there is literature associating Gleason grade with metastasis-free survival at 10-year follow-up [25]. On the other hand, there is research that has determined that an elevated PSA level at the time of diagnosis may play a relevant role as a prognostic factor in the development of BF, since a higher value may mean a higher stage. However, it remains a controversial issue as there is also similar literature in which a significant association between elevated PSA levels at the time

of diagnosis and a poorer biochemical prognosis was not identified [26, 27].

Other variables that could influence the outcome were analyzed. However, their association was not significant in our study. In this investigation, age wasn't associated with a greater risk of BF. Although there is an investigation where it was established that the older the age, the greater the risk of developing the outcome, it only compared surgical treatment with BT alone [18], unlike the present study where they are compared with EBRT + HDBT. Additionally, an attempt has been made to associate high BMI with a worse clinical and biochemical prognosis. However, an association between overweight and obesity with an increased risk of BF has not been evidenced. This finding coincides with other studies where BMI was not a predictor of BF in patients treated with RP [28]. Similarly, it's important to mention that, although TNM staging allows us to classify cancer based on size and invasion of nearby anatomical structures in such a way that higher stages refer to a greater progression of the malignant process, the results evidenced in the present study don't associate higher TNM staging with an increased risk of BF. This was also found in a retrospective cohort study carried out in the United States, in which a higher TNM staging was not significantly associated with an increased risk of BF, both in patients treated with EBRT + BT [14, 23], BT alone [24], and when comparing EBRT + BT with RP [29].

As a secondary finding, the frequency of BF was 34.6%. This represents a lower value when compared with other studies, where BF in high-risk patients showed that the BF frequency was 43% and 56.1% at 3 and 5 years of follow-up in RP, respectively [30]. In contrast, another study carried out in high-risk patients treated with EBRT + BT identified a BF rate of 14% at 5 years of follow-up [31]. However, other studies found lower biochemical failure-free survivals than those of the study, such as 53.3% at 5 years [32].

For the toxicity \geq grade 2 outcome, our results are not consistent with the majority of the literature reviewed. A similar study carried out in Italy that measured toxicity levels, didn't identify differences between EBRT + HDBT and RP [33]. However, the study mentioned used the Expanded Prostate Cancer Index Composite (EPIC), while we used the CTCv5, which could account for

the discrepancies in the results. Additionally, there is literature that shows that patients treated with RP have much higher rates of GU toxicity than the group treated with BT (34), as well as poorer sexual function [35]. In this way, we consider it important to analyze the results of the present study with other similar ones available.

Although there are few studies with results similar to those evidenced in the present investigation, a prediction nomogram of intestinal dysfunction in patients with localized prostate cancer identified that radiotherapeutic treatments (EBRT or BT) increase GI toxicity [36].

There are variables that can also influence the toxicity outcome. In the first place, several studies have identified much higher toxicity levels in combined radiotherapeutic treatments, as evaluated in our research, compared to monotherapy [37, 38]. Also, another study that used the IPSS (International Prostate Symptom Score) found that the main toxicities were greater incontinence, hematuria, and clinically important dysuria [39]. Although we found no association between ADT and toxicity, a study showed that patients treated with EBRT + HDBT and ADT developed loss of libido and erectile dysfunction, among others [40].

Studies showed that it is expected for GU effects, mainly urinary incontinence, to be more common after surgical procedures [41–43]. In addition to other expected effects, such as worsening of function and urinary discomfort, the following are also expected [44]; while GI side effects, such as rectal bleeding, are more common after radiation therapies [45]. Also, studies that evaluated patients' perceptions reported that 92% mentioned an effect in their sexual life after the treatment [42], while 23% expressed regret about the chosen treatment [43], regardless of the therapy they were subjected to.

In this way, we emphasize the importance of assessing the toxicity of therapeutic options, like their effect on intimacy, physical relationships and mental health [40]. A direct impact of the toxicity associated with the treatment has been observed on the economic aspect of the patients, bringing unfavorable consequences due to the total costs that the management of each of these adverse effects may entail in the short and long term [46].

As a secondary finding, the frequency of toxicity \geq grade 2 was 37.0% and 15.3% developed tox-

icity \geq grade 3. Among these patients, 4.6% were treated with EBRT + HDBT and 10.75% with RP. A study identified a cumulative grade 3 toxicity in 3.4% of patients treated with EBRT at 5 years of follow-up [47]. On the other hand, a study carried out in Germany identified that of the group of patients treated with RP, 16.67% developed severe adverse effects at 5 years of follow-up [38].

This study has some limitations. First, as it was focused on one private center, it's not possible to extrapolate the results to populations with different characteristics from those of the present study. Second, some variables that could also be associated with both outcomes, such as race [35, 47] or the dose of radiotherapy [49] weren't included. Third, different definitions of BF had to be used for each treatment; however, the sensitivity and specificity of both definitions are similar [50]. Finally, it's important to consider that currently there are studies that do not consider the value of PSA as a good predictor of outcomes after primary treatment of prostate cancer [51]. However, it has been found that increases in PSA values are associated with a higher risk of disease progression [52] and can serve for adequate control [53], so we consider that the measurement of PSA values is suitable for prostate cancer monitoring.

It is in this way that we recommend the use of the prospective methodology for future research, as well as the evaluation and comparison of these results with other toxicity scales, and to replicate it both in public institutions and in other countries. We also recommend including sociodemographic and ethnic characteristics, as well as assessing the radiation dose received. Finally, we suggest replicating this comparison for longer achievements that allow evaluation of other outcomes (distant metastasis, overall survival, and late toxicities).

Conclusions

This was the first study that compared EBRT + HDBT and RP in the Latin American region. We found that those patients treated with EBRT + HDBT had 40% less hazard of BF, but a 50% greater hazard of developing toxicity \geq grade 2, when compared with those patients with RP. Our results must be analyzed in comparison with those available in the literature and future research. The final therapeutic decision should be based on a com-

prehensive assessment of each patient, taking into account the risk of BF but also the impact of the treatment on the quality and functionality of the patients.

Conflict of interest

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