

# Outcomes of Salvage Prostate Cryotherapy: Real-life Experience of a Portuguese Oncologic Hospital

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## What's known on the subject? and What does the study add?

Our study presents the outcomes of an underused therapeutic tool on recurrent prostate cancer setting. Until RCTs are performed and available, series such as ours may help to select the best candidates to perform salvage prostate cryotherapy.

## Abstract

**Objective:** This study aimed to analyze the outcomes of patients with recurrent prostate cancer (PCa) who received salvage cryotherapy (SC) in our institution. Biochemical recurrence (BCR) after definitive radiotherapy or brachytherapy for PCa is usually managed with long-term androgen-deprivation therapy (ADT). In selected cases, salvage therapies might delay ADT and its side effects.

**Materials and Methods:** All patients who received SC from 2014 to 2018 in our institution were evaluated retrospectively.

**Results:** A total of 17 patients were included, with a median age at SC of 72.0 (range 60-77) years. The median prostate-specific antigen (PSA) before SC was 4.25 [interquartile range (IQR) 3.1-7.6] ng/mL. The median time to BCR was 18.8 (IQR 13.5-32.1) months after SC. The median PSA nadir after SC was 0.49 (IQR 0.09-1.0) ng/mL. With a median follow-up of 43 (range, 11-78) months, 7 (41%) patients had a recurrence. Of those patients, two received ADT, while others were managed conservatively. The biochemical progression-free survival (bPFS) time of patients with PSA nadir <0.5 ng/mL was 56.0 vs. 22.5 months (log-rank test,  $p=0.012$ ). Gleason score  $\geq 8$  at diagnosis and PSA before SC >8 ng/mL were also associated with shorter bPFS (log-rank test,  $p<0.05$ ). *De novo* urinary incontinence was reported in 5 (29.4%) patients. The 3- and 5-year PCa-specific survival rates were 93.3% and 85.6%, respectively.

**Conclusion:** SC might be considered with acceptable oncological and functional results. Until randomized controlled trials are performed and available, series such as ours may help widen our views on all therapeutic possibilities after primary treatment failure in PCa.

**Keywords:** Recurrent prostate cancer, biochemical recurrence, salvage prostate cryotherapy

## Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide and is currently the second cause of cancer-related deaths in the USA and Europe (1). After primary curative treatment with radical prostatectomy or radiotherapy (RT), approximately 27%-53% of patients will experience biochemical recurrence (BCR) (2). Biochemical failure after definitive RT or brachytherapy (BT) is usually managed conservatively or with long-term androgen-deprivation therapy (ADT), and only a small proportion of the patients received salvage treatment (3).

Imaging is the cornerstone of proper staging, allowing distinguishing between local and distant recurrence and, ultimately, selecting those who might benefit from local treatment, such as radical prostatectomy, high-intensity focused ultrasound (HIFU), or prostate cryoablation. Salvage cryotherapy (SC) has gained increasing attention as it has a lower morbidity rate than salvage radical prostatectomy (SRP) (4). In this study, we aimed to report the oncological and functional outcomes of SC in our institution.

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## Materials and Methods

We reviewed medical records of 17 patients who submitted to SC from 2014 to 2018 after PCa recurrence following low-dose BT or RT.

The International Society of Urological Pathology (ISUP) grading system was used to report all prostate biopsies (including prognostic Gleason scores 1-5). Patients with PSA levels increasing after RT or BT underwent multiparametric-prostate magnetic resonance imaging (mpMRI), PET-prostate-specific membrane antigen, and prostate transperineal template guided mapping biopsy (TPMB), as appropriate. TPMB was performed following the template proposed by Ginsburg Study Group, which comprises a systematic distribution of prostatic cores in defined sectors (anterior, middle, and posterior sectors), in number 4 from the medial to the lateral in each sector and lobe (5).

After a multidisciplinary meeting, SC was offered to patients with PSA level <20 ng/mL, with exclusive local PCa recurrence and life expectancy superior to 10 years.

Salvage focal cryoablation (SFC) was defined as hemi-ablation of a single lobe of the prostate, while salvage total cryoablation (STC) included the whole gland. SFC was proposed to patients with biopsy-proven unilateral recurrent PCa.

Cryoprobes were placed transperineally using a free-hand technique under ultrasound guidance. Then, two freeze-thaw cycles were performed with a urethral warming device to prevent urethral tissue damage. Rapid freezing causes ice ball formation, monitored by ultrasonography, reaching -40 °C in the target zone. A thermal sensor was positioned in the pre-rectal fatty tissue, and as soon as the temperature reached 0 °C, passive thawing was started. Patients were discharged on day 1, and the bladder catheter was removed on postoperative day 7. Analgesics on-demand and an alpha-blocker for 30 days were prescribed.

PSA levels and functional outcomes were assessed at 3, 6, and 12 months on the first year after surgery and then every 6 months. *De novo* urinary incontinence (UI) was defined as the use of any pad, and *de novo* sexual dysfunction was defined as a new onset of erection inability during sexual intercourse, with or without the use of inhibitors of phosphodiesterase type 5.

BCR was defined according to the Phoenix criteria (nadir PSA plus 2 ng/mL) either following primary (first BCR) or salvage (second BCR) therapies. The primary endpoint was biochemical progression-free survival (bPFS) after SC. Additionally, the overall survival and functional outcomes were assessed.

The institutional ethics committee conceded the approval for data collection, analysis, and publication of this retrospective study.

## Statistical Analysis

Statistical analyses were performed with SPSS version 24. Categorical variables were compared using the chi-square test. Survival curves were established using the Kaplan-Meier method and compared using the log-rank test. Multivariable analysis using the Cox proportional hazards model was performed to evaluate the effect of risk factors on BCR after SC. In all tests,  $p < 0.05$  was considered to indicate significance.

## Results

Patient characteristics are listed in Table 1. A total of 17 patients were included, with a median age of 72 (range, 60-77) years. Of those, 15 (88%) received primary RT and 2 (12%) received BT. Nine patients from the RT group received adjuvant ADT, and all had ISUP grade  $\geq 3$  or ISUP grade 2 with >50% positive cores on prostate systematic biopsy. At diagnosis, the median PSA level was 9.0 [interquartile range (IQR) 7.4-12.2] ng/mL, and 8 (47%) patients belonged to the high-risk group, according to the D'Amico classification. The median time to the first BCR was 77.0 (IQR 64.6-107.1) months. Two patients whose diagnosis were based on prostate mpMRI did not undergo TPMB. Eleven patients received STC, and six patients received SFC with a median PSA level of 4.25 (IQR 70-74.6) ng/mL at the time of the procedure. All patients stayed at the hospital stay for 2 days, and no major surgical complications were recorded. Two cases of acute urinary retention were reported in the STC group, which was managed conservatively. Long-term postoperative complications are described in Table 2. Eight patients had post-SC PSA nadir <0.5 ng/mL, with a median PSA nadir of 0.49 (IQR 0.09-1.0) ng/mL.

Figure 1 illustrates the Kaplan-Meier curve of bPFS after SC of all patients. The 3-year and 5-year bPFS rates were 47.5% and 17.8%, respectively. At a median follow-up of 43.2 (IQR 32.3-40.4) months, 7 (41%) patients experienced recurrence. Of these patients, one was diagnosed with a regional lymph node recurrence and received stereotactic body radiation therapy, two patients received ADT, and the remaining patients were managed conservatively. The median time to the second BCR was 18.8 (IQR 13.5-32.1) months.

The bPFS times were significantly different according to the pre-SC PSA level, with an estimated mean bPFS time of 46.1 months in patients with pre-SC PSA level <8 ng/mL, compared with 18.8 months in patients with pre-SC PSA level  $\geq 8$  ng/mL (log-rank test,  $p=0.03$ ) (Figure 2a). Furthermore, the post-SC PSA nadir  $\geq 0.5$  ng/mL was also associated with shorter bPFS, with a mean of 22.5 months compared with 56.0 months of those with post-SC PSA nadir <0.5 ng/mL (log-rank test,  $p=0.012$ ) (Figure 2b). ISUP  $\geq 4$  and clinical T-stage  $\geq 3a$  at diagnosis and the extent of

SC (STC vs. SFC) did not show significant difference regarding bPFS (Log-rank test,  $p > 0.05$ ).

Table 3 lists the clinicopathological parameters that may predict the second BCR as analyzed by univariate Cox regression analysis.

As shown in the table, ISUP at diagnosis  $\geq 4$ ; hazard ratio (HR) 9.51, 95% confidence interval (CI) 1.32-68.80,  $p = 0.026$ , time to first BCR ( $< 6$ ; HR 2.22; 95% CI 0.46-10.79,  $p = 0.035$ ), pre-

Patient characteristics	Total (n=17)
Age at SC, median (range), years	72 (60-77)
PSA at diagnosis, median (IQR), ng/mL	9.0 (7.4-12.2)
D'Amico risk at diagnosis, n (%)	
Low	3 (17.6)
Intermediate	6 (35.3)
High	8 (47.1)
Clinical stage at diagnosis, n (%)	
T1c	5 (29.4)
T2a	5 (29.4)
T2c	3 (17.6)
$\geq T3$	4 (23.5)
ISUP grade at biopsy at diagnosis, n (%)	
1	7 (41.2)
2	6 (35.3)
3	2 (11.8)
$\geq 4$	2 (11.8)
Type of 1 <sup>st</sup> -line treatment	
RT	15 (88.2)
BT	2 (11.8)
Adjuvant ADT, n (%)	9 (52.9)
PSA-nadir post 1 <sup>st</sup> -line treatment, median (IQR), ng/mL	0.5 (0.08-1.05)
Time to 1 <sup>st</sup> -PSA-nadir, median (IQR), mo	19.0 (11.5-31)
Time to 1 <sup>st</sup> -BCR, median (IQR), mo	77.0 (64.6-107.1)
Cryotherapy, n (%)	
Whole-gland (STC)	11 (64.7)
Hemi-gland (SFC)	6 (35.3)
PSA-pre SC, median (IQR), ng/mL	4.3 (3.1-7.6)
PSA-nadir post SC, median (IQR), ng/mL	0.5 (0.09-1.0)
Time to 2 <sup>nd</sup> -PSA-nadir, median (IQR), mo	3.9 (3.0-7.0)
Time to 2 <sup>nd</sup> -BCR, median (IQR), mo	18.8 (13.5-32.1)
Follow-up period, median (IQR), mo	43.2 (32.3-50.4)

IQR: Interquartile range, PSA: Prostate-specific antigen, ISUP: International Society of Urological Pathology, RT: Radiation therapy, BT: Brachytherapy, ADT: Androgen deprivation therapy, BCR: Biochemical recurrence, Mo: months, SC: Salvage cryotherapy

SC PSA ( $\geq 8$ ; HR 3.94, 95% CI 1.04-14.99,  $p = 0.044$ ), and post-SC PSA nadir ( $\geq 0.5$ ; HR 0.10, 95% CI 0.12-0.88,  $p = 0.038$ ) and pathological T stage at diagnosis ( $\geq 3a$ ; HR 2.33, 95% CI 1.03-5.29,  $p = 0.043$ ) were associated with the second BCR.

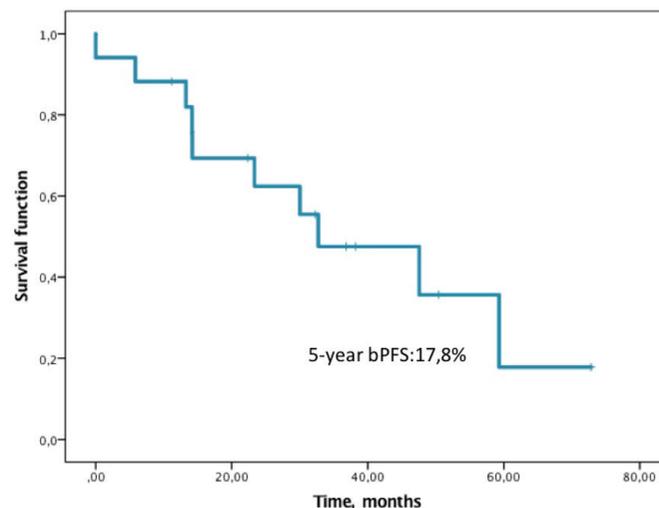
Multivariate Cox regression analysis was performed with the time to the first BCR  $< 6$  years (HR 3.94, 95% CI 0.65-23.94,  $p = 0.137$ ), pre-SC PSA level  $\geq 8$  ng/mL (HR 5.05, 95% CI 0.63-

Long-term complications	STC (n=11)	SFC (n=6)	Total (n=17)
De novo urinary incontinence, n (%)	4 (36.4)	1 (16.7)	5 (29.4)
De novo erectile dysfunction, n (%)	1 (9.1)	1 (16.7)	2 (11.8)
Chronic perineal pain, n (%)	2 (18.2)	1 (16.7)	3 (17.6)

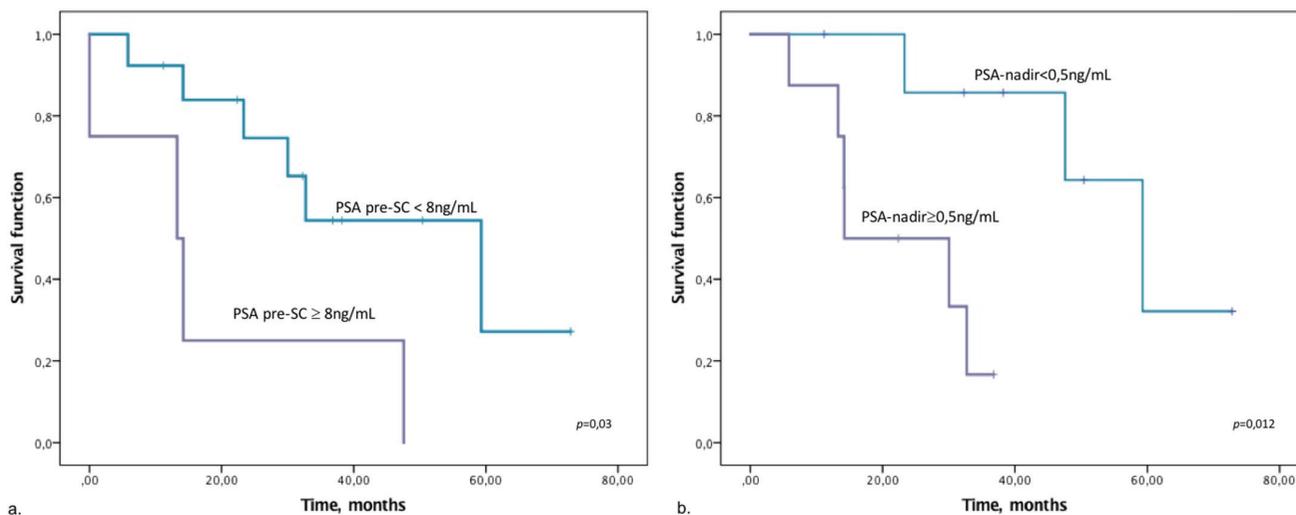
STC: Salvage total cryotherapy, SFC: Salvage focal cryotherapy

Variables	Category	Univariate		
		HR	95% CI	p-value
Pathological T-stage	$< 3a$ vs $\geq 3a$	1.65	0.32-8.60	0.55
High-risk D'Amico at diagnosis	0 vs 1	0.89	0.24-3.23	0.89
Time-to-1 <sup>st</sup> -BCR (years)	$\geq 6$ vs $< 6$	2.22	0.46-10.79	0.035
PSA pre-SC (ng/mL)	$< 8$ vs $\geq 8$	3.94	1.04-14.99	0.044
PSA-nadir post SC	$< 0.5$ vs $\geq 0.5$	0.10	0.12-0.88	0.038

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen, BCR: Biochemical recurrence, SC: Salvage cryotherapy, HR: Hazard ratio, CI: Confidence interval



**Figure 1.** Kaplan-Meier curves of the biochemical progression-free survival of patients with recurrent prostate cancer treated with salvage cryotherapy in our institution



**Figure 2.** Kaplan–Meier curves of the biochemical progression-free survival of patients with recurrent prostate cancer treated with salvage cryotherapy (SC) stratified according to pre-SC prostate-specific antigen (PSA) (<math>< 8 \text{ vs } \geq 8 \text{ ng/mL}</math>, log-rank test  $p=0.030$ ) (a.) and post-SC PSA nadir (<math>< 0.5 \text{ vs } \geq 0.5 \text{ ng/mL}</math>, log-rank test  $p=0.012$ ) (b.)

40.28,  $p=0.126$ ), and PSA nadir  $\geq 0.5 \text{ ng/mL}$  (HR 0.51, 95% CI 0.004–0.62,  $p=0.02$ ) as covariates.

The 3- and 5-year PCa-specific survival rates were 93.3% and 85.6%, respectively. The PCa-specific mortality of the studied population was 11% ( $n=2$ ) with a mean survival time of 70.8 (SE=4.5) months.

## Discussion

Over the past years, local salvage therapies for recurrent PCa have gained increasing attention as they might provide cancer control with minimal well-known side effects of ADT. Nevertheless, consensus about the best candidates for salvage treatment or the best approach is still not established. The current National Comprehensive Cancer Network guidelines suggest the following selection criteria: original clinical stage T1-T2, Nx, or N0, with pre-SC PSA level  $\leq 10 \text{ ng/mL}$ , no distant metastasis, and a positive confirmatory biopsy (6). The European Urology Association guidelines recommend SRP to patients with biopsy-proven recurrent PCa and consider alternative therapies such as HIFU or SC in the clinical trial setting. Although SRP remains the standard of care, no strong evidence supported its widespread use in this context (7). SRP carries significant morbidity with UI rate of 21%–90% and erectile dysfunction nearly in all patients (8). Furthermore, surgical complications are more common in SRP than in primary RP, such as urinary retention (25.3% vs 3.5%), urinary fistula (4.2% vs 0.06%), and rectal injury (9.2% vs 0.6%) (9). Cryoablation, also known as cryotherapy, has emerged as a valid option to achieve cancer control and experience fewer side effects. It involves the placement of probes within the prostate, which will reach extremely low temperatures using

argon. The procedure comprises at least two freeze-thaw cycles. Rapid tissue freezing results in ice crystal formation and cell death (10). The free-hand technique, compared with the grid-template guided technique, allows the surgeon to make easier adjustments of the cryoprobes and anatomical landmarks. The main drawback of this technique is the requirement of a higher level of operator's expertise in prostate ultrasound imaging (11).

In an attempt to decrease the possible side effects of STC, namely, urinary retention (3.0%–8.5%), incontinence (4.4%–13.0%), rectourethral fistula (0%–3.3%), and erectile dysfunction (61.5%–100%) (11–13), investigators tried to apply SFC in patients with biopsy-proven unilateral recurrence. The technique was firstly described in 2008 by Eisenber (14).

In a study by Li et al. (15), SFC appears to be an effective treatment with encouraging potency preservation. However, SFC did not proved to be superior to STC regarding incontinence and rectourethral fistula. In this study, we found a higher rate of urinary acute retention and long-term UI in STC ( $p>0.05$ ).

Tan et al. (16) found no significant difference in bPFS between the SFC and STC groups, after a median follow-up of 24 months, reporting a low rate of acute urinary retention in the SFC group.

One of the major concerns about focal therapy in PCa is its multifocality. Interestingly, recurrences after RT are more likely to be found at the same site of the primary tumor as a single index cancer (17), which when efficiently ablated reduces the postoperative PSA level by  $\geq 80\%$  (11). Although the index lesion is usually defined as the biopsy core with higher GS, radiation induces histological changes that limit Gleason interpretation in this setting (18) and can lead to a considerable false-positive (up to 60%) and false-negative (up to 20%) rates (19). Despite

these limitations, in our institution, all positive biopsy cores were considered to define the candidates to SFC.

Another disadvantage of SFC is that, by leaving a prostate lobe untreated, postoperative PSA might remain high even with successful cancer control, which can be difficult for patient follow-up.

The 5- and 10-year bPFS rates of prostate SC vary between 47% and 63% and 35% and 30%, respectively, based on data published retrospectively (20,21). Early identification of candidates to salvage therapies is important as the tendency to delay treatment after recurrence appears to be associated with higher failure rates (22). We report a 5-year bPFS rate of 17.8%, which can indicate that a significant proportion of patients had high pre-SC PSA levels. In our analysis, pre-SC PSA level  $\geq 8$  ng/mL was associated with a higher risk of tumor relapse with shorter bPFS (18.8 vs 46.1 months). Furthermore, patients with post-SC PSA nadir of  $\geq 0.5$  ng/mL showed inferior long-term outcome results, being an independent risk factor for bPFS.

A review published in 2012 reported that pre-SC PSA level  $\geq 10$  ng/mL is a predictor of PSA failure post-SC, which is in line with our results. Beyond that, PSA kinetics can be useful in predicting local or systemic recurrences, as a longer PSA-doubling time ( $>6-10$  months) is associated with a higher likelihood of local recurrence (23).

After a median follow-up of 43.2 months, only 2 (11.8%) patients received ADT. The possibility of sparing patients from the side effects of a non-curative treatment with ADT such as depression, loss of libido, diabetes, metabolic syndrome, and osteoporosis, is noteworthy (24).

### Study Limitations

The main limitations of this study include its retrospective design, small sample size, and heterogeneous cohort.

### Conclusion

SC appears to be a valid choice of salvage treatment for recurrent PCa with acceptable functional morbidity. Although SC showed inferior oncological results (cancer-specific survival and progression-free survival) to SRP, this disadvantage must be weighed against better functional outcomes. The superiority of SRP in a more durable biochemical control might be explained by the effect of lymph node dissection on controlling micrometastatic disease and recurrence pattern of PCa, i.e., in periurethral zone, which might be undertreated with SC. The selection of patients is important to tailor salvage treatments in recurrent PCa, and series such as ours may help widen our views of an underused therapeutic method in recurrent PCa setting.

### Ethics

**Ethics Committee Approval:** The institutional ethics committee conceded the approval for data collection, analysis, and publication of this retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: L.A., R.C., R.F., A.M., Design: L.A., R.C., R.F., Data Collection or Processing: L.A., R.C., J.P., Analysis or Interpretation: L.A., R.C., J.P., R.F., I.B., A.M., Literature Search: L.A., R.C., Writing: L.A., R.C.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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