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ORIGINAL PAPER

Salvage cryotherapy for prostate cancer

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Summary ***Background: Most men diagnosed with prostate cancer will be candidates for active treatment and 20 to 50% of patients treated with organ preserving strategies recur within the prostate. Optimal treatment of recurrence is controversial. Prostate cryosurgery has been increasingly used as primary, recurrence and focal treatment for prostate cancer.***

Methods: We analysed 55 patients submitted to cryotherapy as salvage treatment after recurrence.

Results: Study population presented with a mean age of 70.9 ± 6.2 years, mean initial PSA of 7.6 ng/ml and average prostate volume by ultrasound of 43.2 ± 14.7 grams. Mean follow-up was of 18.0 months. Biochemical free survival at one year of follow-up was of 85%.

Conclusions: Cryotherapy can be an effective and safe treatment for recurrence after primary curative treatment failure.

KEY WORDS: Prostate cancer; Recurrence; Cryotherapy.

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INTRODUCTION

Most men diagnosed with prostate cancer will be candidates for active treatment, being, in most cases, treated with radiotherapy with external beams or brachytherapy or radical surgery (1, 2). Depending on risk factors, about 20 to 50% of patients treated with organ preserving strategies recur within the prostate with some of them benefiting from additional treatments(2-4). Most patients receive *androgen deprivation treatment* (ADT) for recurrence although they still are candidates for curative treatment with local salvage treatment (3, 5, 6).

Recurrence after radical surgery (two PSA values superior to 0.2 ng/mL after previous undetectable PSA) involves different treatment options when compared to recurrence after radiotherapy (PSA values higher than 2 ng/mL plus nadir) (7). Treatment options for recurrence after surgery include observation, salvage radiotherapy (ideally when the PSA is lower than 2 ng/mL) and ADT while most patients treated with previous radiotherapy cannot be irradiated again (7).

Progression of prostate cancer is highly dependent on testosterone and this represents the rationale for treatment with ADT (8, 9). Hormonal therapies are associated with side effects derived from hypogonadism, such as increased cardiovascular risk, cognitive deterioration, sarcopenia among other important effects (8, 10-13). For this reason, treatments that prevent or delay ADT may be beneficial.

Salvage radical prostatectomy for recurrence after radiotherapy is an accepted alternative although it is a demanding surgical procedure involving serious morbidity and risk of surgical complications (14) .

Optimal local treatment of recurrence is controversial, with alternative treatments depending on availability of instrumentation and risk, age and comorbidities of the patient (2, 15).

New treatment modalities with minimally invasive techniques such as percutaneous cryotherapy and thermal ablation, have gained popularity for treatment of men with prostate cancer (2).

Use of cryotherapy for treatment of *prostate cancer* (PCa) dates back to 1960, although at the time it was associated with multiple and drastic complications (16). With technical advances, cryotherapy has resurfaced as a safe and interesting technique in treating prostate cancer in the recurrence and primary setting, with little toxicity (16, 17). Cryoablation implies the freezing of tissue to promote tissue destruction with direct and indirect mechanisms of action, with a fast freeze phase, followed by slow heating and a repeat cycle (18-20). Optimal duration of freezing and temperature are debatable with various protocols existing, but most studies report critical cellular damage at temperatures below -20ºC (20).

Prostate cryosurgery has been increasingly used for focal treatment of primary and recurrent for prostate cancer, utilizing the same thermal and biological principles for different settings (6, 21, 22).

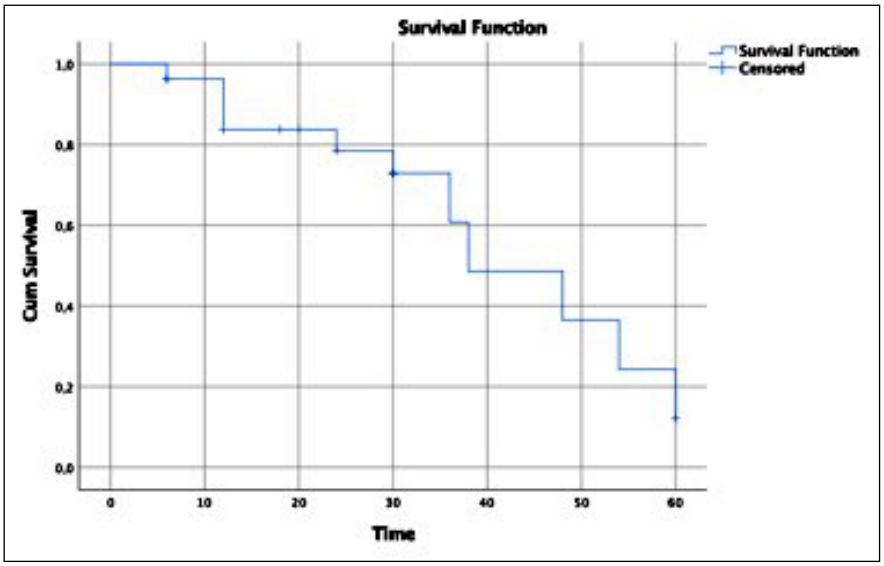
In our centre cryosurgery has been utilized mostly in the context of recurrence, therefore our study aims to evaluate recurrence free survival and time to further treatments associated with cryotherapy.

MATERIAL AND METHODS

Patient selection and variables

All male patients submitted to cryotherapy as salvage treatment during follow-up for prostate cancer in our institution between January 2014 and December 2022 were evaluated. Patients with localized recurrence submitted to hormone treatment were excluded. All patients were submitted to conventional staging with CT to the chest, abdomen and pelvis and a bone scintigraphy previously to treatment

Figure 1.
Patients survival.



in order to exclude extra prostatic disease and in case of doubt with PET-PSMA. Biopsy to the prostate was not performed in most patients. Patients were evaluated at baseline and at 3,6,12,18,24 and after every 6 months until change of treatment due to biochemical failure under Phoenix criteria. Continence was evaluated at every evaluation and a basal reference was obtained.

Surgical technique

Patients were submitted to whole gland prostate cryotherapy utilizing *CryoCare CS*™ (third generation cryoablation system). Cryoprobes were introduced transperineally, using a hands-free, under real-time bi-plane transrectal ultrasonography guidance. The procedure was conducted utilizing argon gas. A rectal thermal sensor was introduced as well as a sensor placed at the external sphincter and a urethral warmer was introduced. Two freeze cycles are performed (10-min freezing per cycle), with active warming in the first cycle and passive after the second cycle; the formed ice-ball and the temperatures are monitored up to 5 min after the second freezing cycle is completed; the cryoprobe, sensors and warming catheter device are removed after the second cycle, and a Foley catheter is placed to be removed after one week. Patients are discharged on the same day.

Statistical analysis

Pearson chi-square, Mann-Whitney and Kolmogorov Smirnov tests were used to compare quantitative and categorical variables. Unconditional binary logistic regression was used to evaluate the independent association between possible predictors of recurrence. Statistical significance in this study was set as $p < 0.05$. Statistical analysis was performed using IBM SPSS®, version 27.0 for Windows.

Results

Of a total of 70 patients submitted to cryotherapy were considered; 55 were evaluated after exclusion of 15 to current usage of androgen deprivation treatment. Patients were then divided in two groups for comparison: patients with biochemical failure (group 1) and patients with no failure of treatment (group 2).

As a whole, study population presented with a mean age of 70.9 ± 6.2 years, a mean initial PSA of 7.6 ng/ml and average prostate volume by ultrasound of 43.2 ± 14.7 grams.

Mean follow-up was of 18.0 (± 13.4) months.

Regarding previous treatments, 36 (65,4%) patients were submitted to radiotherapy, 16 (29.1%) to brachytherapy and 3 (5.5%) to previous cryotherapy.

A total of 19 (34.5%) patients presented with recurrence at a mean of 23.2 ± 16.7 months.

Biochemical free survival at one year of follow-up was of 85%, with 43 patients achieving this length of follow up and 2 patients with recurrence at six months.

Minimum follow-up was of 6 months, achieved by all 55 patients (date of first patients treatment failure), and maximum of 60 months.

In regards of immediate post-operative complications (first week) the most frequent was perineal hematoma in 6 (10.9%) patients, followed by urinary retention in 2 (3.6%) patients. Long term complications are described in Table 1. Mean PSA values in group 1 and group 2 are described in Table 2. When comparing between ISUP

Table 1.
Long term side effects of treatment.

Complication	Number	Percentage
None reported	34	61.8
Light urinary incontinence	7	12.7
Severe urinary incontinence	3	5.5
Haematuria	1	1.8
Fistula	1	1.8
Urge incontinence	7	12.7
Ureteral stenosis	2	3.6

Table 2.
Average PSA values between groups.

	Group 1	Group 2	P
PSA	8.6	7.8	0.4
PSA at 3 months	3.2	1.6	0.03
PSA at 6months	3.9	1.4	0.001
PSA at 12 months	4.3	1.5	0.000
Prostate Volume	44 cc	43cc	0.27
Mean follow-up	29.5 months	23.8 months	0.20
Age	69.5	71.0	0.53

Table 3.
Population characteristics.

	Number	Percentage
ISUP 1	11	20.0
ISUP 2	23	41.8
ISUP 3	13	23.6
ISUP 4	5	9.1
ISUP 5	3	5.5
No Prostate MRI	25	45.5
Prostate MRI	30	54.5
No PET-PSMA	42	76.4
PET PSMA	13	23.6

grades, volume and age between groups a non-significant p value were obtained. Other population characteristics are summarized in Table 3.
Over half of patients were submitted to an MRI and 23.6% to PET PSMA previous to treatment allowing for the exclusion of extra prostatic disease and better treatment planning, that can explain our low rates of incontinence, due to better patient selection.

Discussion

Patients with localized recurrence present with an opportunity for salvage therapies with a curative intent, although with the current widespread usage of ADT, most patients receive hormonal therapies for biochemical failure after curative treatment (23). Androgen deprivation treatment can be responsible for considerable side effects and worse quality of life (24). In our cohort of patients treatment failure, defined by the Phoenix criteria (as currently no validated definition exists for cryotherapy) occurred in 19 (34.5%), with an average time to recurrence of 23.2 months, signifying that patients were spared the side effects of testosterone deprivation therapy for almost two years, with little morbidity associated. A recent study analysing biochemical failure after treatment found rates of recurrence at 12 months of 15% and 19% at two years. Our data in terms of recurrence are similar to these studies although longer follow-up is needed (25).
Most surgical options are associated with considerable morbidity for the patient, with great impact on quality of life and very high degrees of incontinence and fistula (7, 26). Salvage radical surgery presents with a biochemical recurrence free rate of 34-83% at five years, depending on the study considered, that is similar to the rates for minimal invasive procedures (14, 27). Functional outcomes differ significantly between treatment options although most patients present already with a low erection capacity after previous treatment with radiotherapy. After surgery (salvage radical prostatectomy), almost no patient retains erectile function and 25% of patients presents with severe incontinence and significantly lower rates of continence compared to other salvage treatments or surgery as primary treatment (28, 29).
High intensity focused ultrasound (HIFU) is also available for treatment for localized prostate cancer with continence rates superior to 50% but inferior to what has been reported for cryotherapy (26).
In our study, 34 patients 61.8% did not report any significant side effects, a rate higher than average. The most common side effects were both urge incontinence and mild urinary incontinence reported in 7 patients, less severe when compared to side effects reported after salvage prostatectomy where severe continence is present in 25% of patients (7, 26, 29). Only one patient presented with a fistula; he was a 72-year-old patient submitted to prior brachytherapy with combined radiotherapy for ISUP 5 disease. On the contrary, many patients submitted to radical surgery suffer from bladder neck contracture, anastomotic leakage with one third of patients presenting with Clavien 3 or higher complications (26).
Our study shows that, with the currently improved equipment and technique, cryosurgery should be considered as a valid and important option for patients after failure of primary treatment with little toxicity.
Although patients were not biopsied previously to treatment previous histology reported 5 patients with ISUP 4 and 3 with ISUP 5: only 2 patients of the ISUP 4 group presented with failure and none in the other group at an average follow-up of 21.6 and 18.6 months respectively, indicating a possibly important role in high grade disease.
When PSA values between the two groups were considered, initial PSA was non-significantly different, as all other variables considered for direct comparison.
Differences of values at 3,6 and 12 months were statistically significant with p values of 0.03,0.001 and 0.000 respectively. Accordingly, lower PSA values at these intervals predicts treatment success and longer recurrence free survival, similarly to what was reported (25).
Limitations of our study include utilization of the Phoenix criteria to determine biochemical failure, designed initially for radiotherapy, as no current guidelines exist to define failure after cryotherapy, the retrospective nature of our study, relative short average follow-up time and lack of confirmatory biopsy of assumed failure.

Conclusions

Cryotherapy can be an effective and safe treatment for recurrence after primary curative treatment failure, allowing for delay or even eliminate the need for ADT, sparing patients the unnecessary toxicity and complications from salvage radical prostatectomy with little and in most cases manageable side effects.

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