



## Original Article

# Single-institution comparative study on the outcomes of salvage cryotherapy versus salvage robotic prostatectomy for radio-resistant prostate cancer

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## ABSTRACT

**Background:** Although primary treatment of localized prostate cancer provides excellent oncologic control, some men who chose radiotherapy experience a recurrence of disease. There is no consensus on the most appropriate management of these patients after radiotherapy failure. In this single-institution review, we compare our oncologic outcome and toxicity between salvage prostatectomy and cryotherapy treatments.

**Methods:** From January 2004 to June 2013, a total of 23 salvage procedures were performed. Six of those patients underwent salvage prostatectomy while 17 underwent salvage cryotherapy by two high-volume fellowship-trained urologists.

Patients being considered for salvage therapy had localized disease at presentation, a prostate-specific antigen (PSA) < 10 ng/mL at recurrence, life expectancy > 10 years at recurrence, and a negative metastatic workup. Patients were followed to observe cancer progression and toxicity of treatment.

**Results:** Patients who underwent salvage cryotherapy were statistically older with a higher incidence of hypertension than our salvage prostatectomy cohort. With a mean follow up of 14.1 months and 7.2 months, the incidence of disease progression was 23.5% and 16.7% after salvage cryotherapy and prostatectomy, respectively. The overall complication rate was also 23.5% versus 16.7%, with the most frequent complication after salvage cryotherapy being urethral stricture and after salvage prostatectomy being severe urinary incontinence. There were no rectal injuries with salvage prostatectomy and one rectourethral fistula in the cohort after salvage cryotherapy.

**Conclusion:** While recurrences from primary radiotherapy for prostate cancer do occur, there is no consensus on its management. In our experience, salvage procedures were generally safe and effective. Both salvage cryotherapy and salvage prostatectomy allow for adequate cancer control with minimal toxicity.

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## 1. Introduction

Prostate cancer is the most common cancer in males with an estimated 230,000 patients diagnosed annually in the United States.<sup>1</sup> The therapeutic approach for clinically localized prostate carcinoma is either surgery or radiation therapy, with approximately 25% newly diagnosed cases treated with radiotherapy with active surveillance under therapeutic approaches.<sup>2</sup>

Although primary treatment of localized prostate cancer provides oncologic control, some men who choose radiotherapy experience a recurrence of disease. It has been estimated that up to one third of patients will have local failure at 10 years with the biochemical recurrence rate of approximately 63%.<sup>3</sup>

Patients who present with prostate cancer recurrence confined to the prostate may benefit from salvage therapy. Current recognized treatment options for recurrent prostate cancer include prostatectomy, brachytherapy, high-intensity focused ultrasound, and cryotherapy.<sup>1,4,5</sup> However, because no official protocol exists regarding optimal salvage therapy, there is no consensus on the most appropriate management of these patients after radiotherapy

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failure. Previous studies within literature have investigated open prostatectomy and robotic prostatectomy as options for salvage therapy. Cryotherapy is considered a minimally-invasive salvage procedure; however, our study considers robotic prostatectomy as an appropriate option for a minimally-invasive approach for salvage therapy. While many studies have proven both techniques to be safe and effective, there are few studies which compare both. In this single-institution review, we compare our oncologic outcome and toxicity between salvage prostatectomy and cryotherapy treatments.

## 2. Materials and methods

From January 2004 to June 2013, a total of 23 salvage procedures were performed. From this group, we identified six men who underwent salvage prostatectomy, while 17 underwent salvage cryotherapy by two high-volume fellowship-trained urologists. Both options were presented to the patients and their preference was used as the deciding factor. All patients underwent primary local treatment for curative purposes for localized prostate cancer. All surgeries were performed at Cleveland Clinic Florida. Preoperative evaluation and postoperative follow-up were performed according to institutional protocol. Patients being considered for salvage therapy had localized disease at presentation, a prostate-specific antigen (PSA) < 10 ng/mL at recurrence, life expectancy > 10 years at recurrence, and a negative metastatic workup. Both salvage cryotherapy and salvage prostatectomy were offered to patients and choice of treatment was decided by the patient. Patients that underwent salvage procedures had a primary Gleason score average between 6.8 for the cryotherapy group and 7.3 for the prostatectomy group. The cutoff value of biochemical recurrence following primary salvage therapy was two subsequent rises in PSA > 6 months after reaching nadir. All patients had achieved PSA nadir afterwards. We evaluated the following clinical variables: age, race (white vs. nonwhite), and pre-initial treatment variables including PSA and Gleason sum at original diagnosis. We observed for a history of hypertension, coronary heart disease, or diabetes. The primary outcome measure was biochemical failure. In addition, patients were subsequently followed to observe rate of urethral stricture or urinary fistula formation, and severity of urinary incontinence. Patient data was performed retrospectively after Institutional Review Board approval and analyzed with statistical software. All tests were considered statistically significant at  $P < 0.05$ . Following the salvage treatment, disease progression was based on PSA > 0.2 ng/mL.

### 2.1. Analysis

Statistical analysis used to conduct the tests was the two-tailed  $t$  test and Chi-square test with SPSS statistical software, Armonk, NY, USA.

## 3. Results

Within the cryotherapy group, 70.6% were Caucasian, 23.5% were African American, and 5.9% was other. Within the prostatectomy group, 50% were Caucasian and African American. With a mean follow up of 14.1 months and 7.2 months, the incidence of disease progression was 23.5% and 16.7% after salvage cryotherapy and prostatectomy, respectively. The preoperative PSA value for the cryotherapy group was 5.27 ng/mL and postoperatively PSA values had a mean value of 1.42 ng/mL. The preoperative PSA value for the prostatectomy group was 6.08 ng/mL and postoperatively PSA values had a mean value of 1.92 ng/mL. The overall complication rate was also 23.5% versus 16.7%, with the most frequent

complication after salvage cryotherapy being urethral stricture (11.8%) and after salvage prostatectomy being severe urinary incontinence (16.7%). There were no rectal injuries with salvage prostatectomy and one incidence of rectourethral fistula in the cohort after salvage cryotherapy (Table 1). Patients who underwent salvage cryotherapy were statistically older with a higher incidence of hypertension than our salvage prostatectomy cohort.

## 4. Discussion

The goal of salvage therapy for radioresistant prostate cancer is to provide freedom from biochemical recurrence and avoid or delay treatment with hormonal therapy. It is estimated that up to 63% of men will experience biochemical recurrence within 10 years of radiotherapy for localized prostate cancer.<sup>3</sup> Possible mechanisms include radiotherapy resistance of disease, failure to administer a cytotoxic dose, and limitations in the ability to increase the dose to limit side effects.<sup>6</sup> Biochemical recurrence is defined as a rise of 2 ng/mL or more above the nadir PSA.<sup>7</sup> In addition, clinical suspicion for reoccurrence is warranted when the patient presents with new onset bladder outlet obstruction, hematuria, or palpable mass on digital rectal exam.

Among the options for salvage therapy, radical prostatectomy is attractive as it provides better staging information and assessment and allows the opportunity to remove damaged radiated tissue.<sup>4,8</sup> Despite this fact, salvage prostatectomy is not routinely performed due to increased technical difficulty and increased risk of urinary incontinence, rectal injury, and erectile dysfunction. When robotic salvage prostatectomy was first described by Jamal et al,<sup>9</sup> it was noted that the lateral and posterior anatomic planes were obliterated from prior radiotherapy. Additional reports have noted frequently encountering brachytherapy seeds outside the prostate further obscuring dissection planes.<sup>10</sup>

Large series report the major complications from salvage prostatectomy as bladder neck contractures (22%), urinary incontinence (48%), and rectal injury (5%).<sup>11</sup> Robotic salvage prostatectomy has been demonstrated in one series with functional outcomes that are comparable to a contemporary open Salvage Radical Prostatectomy (SRP) series.<sup>11</sup> A minimally invasive approach allows improved visualization that allows an easier and safer dissection of the posterior plane, which is often obliterated in patients with prior local therapy. Finally, patients experienced low amounts of estimated blood loss and one study reported no patients required perioperative transfusion and endured a shorter length of stay.<sup>11</sup> However,

**Table 1**  
Perioperative Characteristics, Oncologic Outcomes, and Toxicities of Salvage Cryotherapy Versus Salvage Prostatectomy

	Salvage cryotherapy (n = 17)	Salvage prostatectomy (n = 6)	P
Age (y)	71.6 ± 5.2	64.7 ± 8.4	0.03
% Caucasian	70.6% (12/17)	50.0% (3/6)	0.39
% African American	23.5% (4/17)	50.0% (3/6)	0.13
Preoperative PSA	5.27 ± 2.38	6.08 ± 3.43	0.55
Gleason score at diagnosis	6.8 ± 0.86	7.3 ± 0.52	0.18
Incidence of hypertension	70.6% (12/17)	16.7% (1/6)	0.02
Incidence of diabetes	23.5% (4/17)	16.7% (1/6)	0.74
Incidence of coronary heart disease	23.5% (4/17)	16.7% (1/6)	0.74
Biochemical recurrence	23.5% (4/17)	16.7% (1/6)	0.74
Follow up PSA	1.92 ± 2.6	1.42 ± 14.3	0.25
Total complication rate	23.5% (4/17)	16.7% (1/6)	0.74
Rate of urethral stricture	11.8% (2/17)	0.0% (0/6)	
Rate of severe urinary incontinence	5.9% (1/17)	16.7% (1/6)	
Rate of urethral fistula	5.9% (1/17)	0.0% (0/6)	
Rate of intraoperative rectal injury	0.0% (0/17)	0.0% (0/6)	

PSA, prostate-specific antigen.

**Table 2**  
Comparison of Perioperative Complications From Salvage Therapy

Series	No. of patients	Salvage modality	% Urethral stricture	% Urinary incontinence	% Urethral fistula	% Rectal injury
Ward et al <sup>11</sup>	89	Prostatectomy	23	56	NR	3
Stephenson et al <sup>4</sup>	60	Prostatectomy	32	68	NR	2
Our series	6	Prostatectomy	0	16.7	0	0
Pisters et al <sup>19</sup>	279	Cryoablation	NR	10.2	1.2	NR
Donnelly et al <sup>16</sup>	46	Cryoablation	0	6.5	2.2	NR
De la Taille et al <sup>18</sup>	43	Cryoablation	5	9.0	NR	NR
Our series	17	Cryoablation	11.8	5.9	5.9	0

NR, not recorded.

robotic salvage surgery of the prostate requires prior experience in radical prostatectomy due to the technically demanding nature of the operation. A comparison of the complications among reviewed studies is detailed in Table 2. In the small number of reported studies, oncologic outcomes of salvage prostatectomy were a 10-year PSA progression-free survival of 30–43% and a 10-year cancer-specific survival rate of 70–77%.<sup>4,11,12</sup> The overall positive surgical margin rate over all studies reviewed was 24.7% (21/89) and the biochemical recurrence rate was 24.7% (21/85).<sup>13</sup>

Cryotherapy has been employed as a salvage intervention due to comparable oncologic outcomes and complication rates and less challenging technical components than salvage prostatectomy.<sup>14</sup> In particular, third generation technology has allowed better evaluation of the prostate and the surrounding structures, and permitted accurate placement of the percutaneous catheters to allow safer surgery with better oncologic outcomes.<sup>15</sup> Donnelly et al<sup>16</sup> demonstrated that patients can achieve biochemical disease-free status after salvage cryotherapy which is durable at 12 months and 24 months. Complications from cryotherapy are more prevalent in patients undergoing salvage therapy, with reported rates of 73% and 72% for urinary incontinence and erectile dysfunction, respectively.<sup>17–19</sup> Other reported complications include rectal pain, intractable dysuria, recurrent urinary tract infections, and urethral fistulae.<sup>16</sup>

A recent analysis compared the effectiveness of salvage cryotherapy and prostatectomy. In an analysis of > 345,000 patients in the Surveillance, Epidemiology, and End Results (SEER) database, 341 underwent salvage cryoablation and 99 patients underwent salvage prostatectomy. The results showed a trend towards increased overall and cancer specific mortality in the prostatectomy cohort when compared to those who had cryoablation.<sup>14</sup> This differs from a retrospective single-center study published in 2009 which showed better overall survival with salvage prostatectomy but comparable cancer specific survival.<sup>20</sup>

Our study is the first which compares salvage cryotherapy with salvage robotic prostatectomy at a single institution. Our results are similar to those published in 2009 in that salvage prostatectomy offered a lower rate of biochemical recurrence than cryotherapy.

Additionally, perioperative complications were lower in the prostatectomy cohort. Limitations of our study include our small sample size and short length of follow up. Our single-institution study and our data may not be generalizable. However, this series provides important information in support of a robotic prostatectomy minimally invasive approach for recurrent prostate cancer after failed primary therapy. In addition, our study provides supporting evidence for a minimally invasive approach for salvage therapy compared to standard open prostatectomy. Additional studies will be needed to validate our findings.

While recurrences from primary radiotherapy for prostate cancer do occur, there is no consensus on its management. In our experience, salvage procedures were generally safe and effective. Both salvage cryotherapy and salvage robotic prostatectomy allow for adequate cancer control with minimal toxicity, which a trend

towards better oncologic and functional outcomes with robotic salvage prostatectomy. Limitations of our study include the limited length of follow up and conclusions derived from such. Despite this, we found that tolerability is better with robotic procedures. With the nature of the operation being technically challenging, we recommended they be performed by surgeons with prior high volume experience with radical prostatectomy. When mastered, it can be as tolerable to patients as outpatient cryoablation.

Our single institution study compares the effects of two types of minimally invasive salvage procedures: robotic prostatectomy versus cryotherapy. We observed safe and favorable outcomes of robotic prostatectomy with outcomes comparable to open salvage radical prostatectomy. Observed benefits of a robotic approach include improved visualization of the posterior dissection plane, low complication rates, reported low blood loss, and decreased hospital stay. We recommend further follow up and studies to determine the usefulness of this approach.

## Conflicts of interest

All contributing authors declare no conflicts of interest.

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