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Original Article

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

Anup Vora [1, *], Vidhi Agarwal [2], Prabhjot Singh [2], Rupen Patel [3], Rodolfo Rivas [2], Josh Nething [2], Nic Muruve [2]

[1] Chesapeake Urology Associates, Silver Spring, MD, USA
[2] Cleveland Clinic Florida, Department of Urology, Weston, FL, USA
[3] Eastern Carolina University, Greenville, NC, USA

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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.



## 1. Introduction

Prostate cancer is the most common cancer in males with an estimated 230,000 patients diagnosed annually in the United States.[1] 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.[2]

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%.[3]

Patients who present with prostate cancer reoccurrence 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.[1,4,5] However, because no official protocol exists regarding optimal salvage therapy, there is no consensus on the most appropriate management of these patients after radiotherapy

* Corresponding author. Chesapeake Urology Associates, 3801 International Dr, Suite 310, Silver Spring, MD, USA.
*E-mail address:* aurology@cua.md (A. Vora).

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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.[3] 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.[6] Biochemical recurrence is defined as a rise of 2 ng/mL or more above the nadir PSA.[7] 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.[4,8] 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,[9] 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.[10]

Large series report the major complications from salvage prostatectomy as bladder neck contractures (22%), urinary incontinence (48%), and rectal injury (5%).[11] Robotic salvage prostatectomy has been demonstrated in one series with functional outcomes that are comparable to a contemporary open Salvage Radical Prostatectomy (SRP) series.[11] 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.[11] 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.