

# Salvage open radical prostatectomy after failed radiation therapy: a single center experience

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## KEY WORDS

biochemical recurrence ▶ prostate cancer ▶  
salvage radical prostatectomy ▶ radiation therapy

## ABSTRACT

**Introduction.** Currently there is no universally accepted approach for the management of radiation-recurrent prostate cancer. The aim of this study was to detail our experience performing salvage radical prostatectomy for patients who failed primary treatment of prostate cancer with radiation therapy.

**Material and methods.** We retrospectively queried our institutional database of radical prostatectomy cases for patients who underwent salvage surgery for radiation-recurrent prostate cancer. Patients were assessed for the risk of complications and oncologic outcomes following salvage surgery.

**Results.** Twenty-four patients with a mean age of 65 years (range 51-74) underwent salvage radical prostatectomy. Fourteen of these patients (58%) received androgen deprivation therapy prior to surgery. Intraoperatively, mean blood loss was estimated at 415 mL (range 100-1000) and 19 (79%) patients received autologous blood. No patient required an allogeneic transfusion or experienced a rectal injury. Postoperative bladder neck contracture and urinary incontinence developed in 17% and 39% of men, respectively. Two (29%) of seven patients remained potent after salvage surgery. No patient developed a fistula. Overall and recurrence-free survival at 5-years was 90% and 39%, respectively. On multivariate analysis, extracapsular extension was the only significant predictor of biochemical recurrence (HR 6.9, 95% CI 1.9-25.3  $p = 0.003$ ).

**Conclusion.** In carefully selected patients, salvage radical prostatectomy for radiation-recurrent prostate cancer is a treatment option with acceptable oncologic outcomes and a moderate complication rate.

## INTRODUCTION

Among newly diagnosed cases of clinically localized prostate cancer (PCa), approximately 35% of patients undergo primary treatment with radiation therapy (RT) [1]. Up to 30% of these patients will develop biochemical recurrence (BCR) and be considered for some form of salvage therapy [2, 3]. Local treatment options for RT-recurrent PCa (RR-PCa) include salvage radical prostatectomy (SRP), additional RT, cryotherapy, and high intensity focused ultrasound [4, 5, 6, 8, 9]. To date, there is no universally accepted approach for the management of RR-PCa. Historically, SRP was felt to be a technically challenging procedure with a high risk of

complications such as rectal injury, fistula formation and the development of bladder neck contracture (BNC) [7, 8]. Accordingly, only a minority of patients with RR-PCa are treated with SRP. The aim of this study was to review our outcomes of patients who underwent SRP over the last 19 years with an emphasis on postoperative morbidity.

## MATERIAL AND METHODS

Between January 1992 and January 2011, 2,166 men underwent open radical prostatectomy by a single surgeon (M.S.S.). We retrospectively reviewed our comprehensive Institutional Review Board approved database of prostatectomy cases for men who underwent SRP for RR-PCa. From among the 2,166 cases, 24 (1.1%) underwent SRP. Clinical, pathological, functional and oncological data was obtained for these patients.

Data was analyzed with PASW 18.0 (IBM Corporation, Somers, NY). Biochemical recurrence (BCR) after SRP was defined as a PSA  $\geq 0.2$  ng/mL, continence as using no pads, and potency as ability to have sexual intercourse with or without use of phosphodiesterase type-5 inhibitors on  $>50\%$  of attempts [9]. BCR-free and overall survival were estimated with Kaplan-Meier analysis. Uni- and multivariate Cox proportional hazards analyses were performed to identify parameters associated with BCR after SRP. Any parameter with a  $p$  value of  $<0.20$  was entered into the multivariate analysis. A  $p$  value of  $<0.05$  was considered statistically significant.

## RESULTS

Twenty-four patients with a mean age of 65 years (range 51-74) underwent SRP with curative intent for biopsy-proven RR-PCa. Of these patients, 13 (54%) had a history of external beam radiation therapy and 11 brachytherapy (46%). Patients had a mean preoperative PSA of 9 ng/mL (range 4-20). Prior to surgery, all patients had a projected life expectancy of at least 10 years and a negative metastatic workup with bone scan and contrast enhanced computed tomography of the abdomen and pelvis. Fourteen patients (58%) received androgen deprivation therapy prior to surgery. Patient characteristics, including preoperative and final pathology data, are detailed in Table 1.

Intraoperatively, patients experienced a mean blood loss of 415 mL (range 100-1000). This volume of blood loss was not statistically different than those patients in our database who underwent a primary radical prostatectomy (mean 506 mL;  $p = 0.133$ ). Autologous blood was given to 19 (79%) patients and none received an allogeneic transfusion. Five (21%) patients underwent a nerve sparing procedure and 15 (63%) a pelvic lymph node dissection (Table 1). No patient had a rectal injury.

Patients were followed for a mean of 63 (range 4-176) months. Postoperatively, four (17%) patients developed a BNC and were successfully managed endoscopically. Prior to surgery, 23 of 24 patients were fully continent. Following SRP, eight (35%) patients developed some degree of incontinence and were initially managed with pads. One patient ultimately required the placement of an ar-

**Table 1.** Patient characteristics

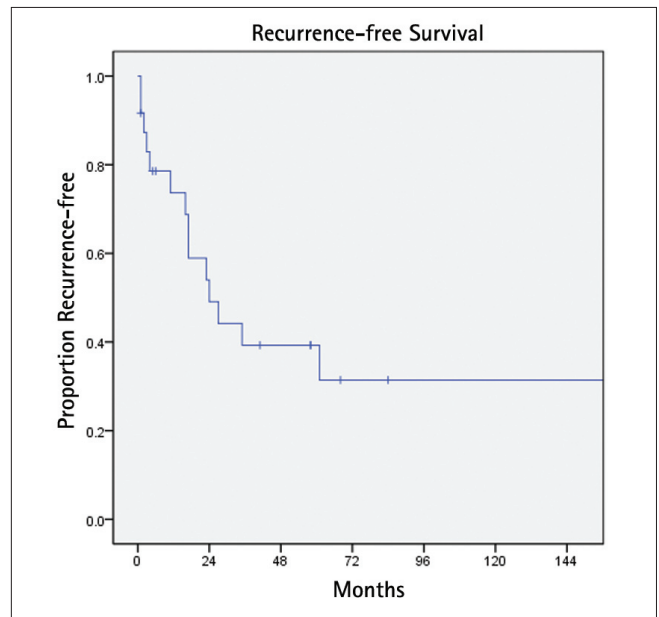
Parameter	n = 24
Age, mean (range)	64.5 (51-74)
Preoperative PSA, mean (range)	8.7 (3.5-19.47)
Biopsy Gleason sum, n (%)	
≤6	10 (41.7)
=7	5 (20.8)
≥8	9 (37.5)
Pathologic Gleason sum, n (%)	
≤6	6 (25.0)
=7	9 (37.5)
≥8	9 (37.5)
Neoadjuvant androgen deprivation	
Yes	14 (58.3)
No	10 (41.7)
Nerve sparing, n (%)	
Bilateral	3 (12.3)
Unilateral	2 (8.3)
None	19 (79.2)
Pelvic lymph node dissection, n (%)	
Bilateral	13 (54.3)
Unilateral	2 (8.3)
None	9 (37.5)
Pathologic T stage, n (%)	
T2	11 (45.8)
T3a	5 (20.8)
T3b	8 (33.3)
Margin status, n (%)	
Positive	11 (45.8)
Negative	13 (54.2)
Positive lymph nodes	
Yes	2 (13.3)
No	13 (86.7)

tifical sphincter. Only seven patients were potent prior to surgery and two (29%) developed erectile dysfunction after surgery. No patient developed a fistula.

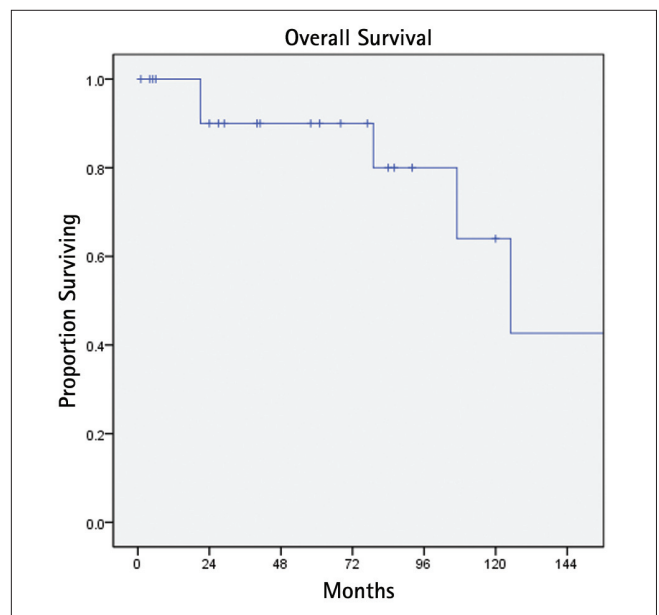
BCR was detected in 14 patients (58%) at a median interval of 24 months (Fig. 1). Eight of these patients were treated with androgen deprivation. On univariate Cox proportional hazards analysis (Table 2), extracapsular extension was the only significant predictor of BCR (HR 6.9, 95% CI 1.9-25.3 p = 0.003). This result was unchanged on multivariate analysis. During follow-up, six (25%) patients died, two (8%) due to PCa (Fig. 2). One patient died with metastatic PCa at 18 months after SRP with a pathologic Gleason score of 9 and positive lymph nodes. The other died nine years after surgery with Gleason 7 PCa and extraprostatic extension.

## DISCUSSION

Although the result of salvage RT following failed radical prostatectomy has been extensively studied [10-12], SRP for RR-PCa is limited to relatively few reports. To date, SRP has been the most

**Fig. 1.** Biochemical recurrence-free survival.**Table 2.** Univariate analysis of parameters associated with recurrence after SRP

Parameter	Hazard ratio (95% CI)	p value
Extracapsular extension	6.9 (1.9-25.3)	0.003
Gleason score	-	0.806
Neoadjuvant androgen deprivation	-	0.845
Node metastasis	-	0.441
Positive margin	-	0.263
Radiotherapy type	-	0.433
Seminal vesicle invasion	-	0.147
Total PSA	-	0.980

**Fig. 2.** Overall survival.

reported treatment approach with the longest follow-up. In a large single center series by Ward and coworkers, the authors studied their experience treating 138 men with SRP between the years of

1967 to 2000 [4]. At a median follow-up of seven years, patients had a 10-year disease-specific survival of 77% and median progression-free survival of 8.7 years. In a more contemporary multi-institutional report of 404 open SRP cases (1985 to 2009), 10-year BCR-free, metastasis-free, and cancer-specific survival probabilities were 37%, 77%, and 83%, respectively [5]. In our series, we found a 10-year BCR-free and overall survival of 31% and 64%, respectively.

On multivariate analysis, we found extracapsular extension to be the only parameter associated with BCR following SRP (HR 6.9, 95% CI 1.9-25.3,  $p = 0.003$ ). In contrast, Chade and coworkers [5] found PSA and Gleason sum to be predictors of BCR. This difference is likely the result of our study's small sample size as evident by the large confidence interval. Of note, Chade et al. also evaluated the risk of progressing to metastatic disease. These authors reported that PSA, Gleason sum, and positive lymph nodes predicted metastases. Their report is the first to specifically evaluate metastatic disease as others have focused only on BCR, disease-specific, and overall survival.

With regard to complications, a review of contemporary SRP series cited an incidence of urinary incontinence, BNC and rectal injury at 24 – 67%, 12 – 30%, and 0 – 15%, respectively [7]. Our data is consistent with these reports as we observed incidences of 39%, 17%, and 0%, respectively. We believe our relatively low complication rate is the result of careful patient selection. An important component of patient selection was the digital rectal exam. Any patient with a flat prostate resulting from radiation changes was excluded from surgery. Only those with a relatively normal prostate size and shape were selected for SRP. In addition to careful patient selection, we believe our modified surgical approach in which the prostate was mobilized lateral to medial with sharp dissection was also responsible for the low complication rate. This differs from the standard dissection that proceeds medial to lateral. Using our modified approach, no patient had a rectal injury. Moreover, in the postoperative period no patient developed a fistula.

Taken together, our data, as well as that of others, suggests a reasonable oncologic outcome of SRP with an acceptable complication rate. The complications of urinary incontinence and BNC can be successfully managed conservatively or endoscopically as was the case for all of our patients with BNC.

In addition to SRP, recent reports have focused on novel ablative technologies for the treatment of RR-PCa. Cryotherapy is the best studied ablative approach with reports ranging in size from 18 to 279 patients [8]. In a retrospective comparative study, SRP proved to offer superior oncologic outcomes to that of cryotherapy [13]. Using a PSA of greater than 0.4 ng/mL as the definition of BCR, the authors found a 5-year BCR-free survival of 21% for patients treated with cryotherapy as compared to 61% for those treated with SRP ( $p < 0.001$ ). However, no significant difference was observed for 5-year disease specific survival. This report did not offer any comparison of procedure-related complications.

High-intensity focused ultrasound is another ablative technology, which has gained attention for the treatment of prostate cancer [14, 15]. While it remains too early to judge the oncologic efficacy of this approach in the setting of salvage treatment, current data suggests a high complication rate related to this procedure. In one study, three of 46 (6.5%) patients developed a post-treatment urinary fistula [16]. In contrast, none of the patients in our study developed this complication.

While less extensively reported on than cryotherapy, salvage RT for RR-PCa has also been studied. The 5-year disease-free survival of case series on salvage brachytherapy ranges from 20–70% [8]. This wide range is the result of the many varied definitions of treatment failure used in these reports. Thus it is difficult to in-

terpret these data. In a feasibility study, Vavassori and coworkers treated six patients with RR-PCa with the CyberKnife image-guided radiosurgical system (Accuray Incorporated, Sunnyvale, CA) [6]. At a median follow-up of 11.2 months, all patients were alive without evidence of urinary or rectal morbidity. Four patients (67%), however, had disease recurrence.

One limitation common to reports on salvage treatment for RR-PCa is the lack of diagnostic tests with sufficient sensitivity to a detect treatment failure. At present no studies have validated the use of PSA as a marker for recurrence following salvage treatment. This is in contrast to the well established use of a PSA  $\geq 0.2$  ng/mL in the setting of primary prostatectomy or the Phoenix criteria for primary RT [9, 17]. Future work must focus on defining failure following salvage treatment. This is of particular concern when studying non-surgical approaches such as cryotherapy or salvage-RT. Other limitations of this report include its retrospective design and small sample size. In the future urologists should consider a collaborative randomized trial comparing SRP to other well-established management strategies.

## CONCLUSION

For men with RR-PCa, SRP is a reasonable treatment option with reproducible oncologic outcomes. Common complications of SRP include urinary incontinence, BNC, and erectile dysfunction. Careful patient selection is crucial for minimizing the risk of these complications.

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