

## Salvage Robotic-assisted Laparoscopic Radical Prostatectomy: Experience with 14 Cases

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**Abstract.** Aim: To report the outcomes of salvage robot-assisted radical prostatectomy (S-RaRP). Patients and Methods: Fourteen patients underwent S-RaRP. The mean initial prostatic-specific antigen level was 14.3 ng/ml and mean Gleason score was 6.93. Initial definitive treatment was external irradiation in 11 cases, cyberknife in two, and high-intensity focused ultrasound in one. Time from definitive treatment to S-RaRP was a mean of 36.5 months. Results: The mean console time was 134.9 min and blood loss was 99.6 ml. Stage pT2N0, T3N0, and T3N1 were found in eight, four, and two cases, respectively. A positive surgical margin was found in 21.4% (3/14) of the patients. The continence rate was 71.4% (10/14). Mild stress urinary incontinence (one or two pads/day) was noted in 28.6% (4/14) of patients. Biochemical recurrence-free status was noted in 11 (78.5%) patients with a mean follow-up of 32.4 months. Conclusion: S-RaRP is feasible with a low complication rate, good continence rate, and an acceptable potency rate. The short-term oncological outcomes are encouraging.

Reportedly up to two out of three men (34.2-63%) who receive external-beam radiation therapy (EBRT) for prostate cancer will experience biochemical recurrence (BCR) in the first 3-5 years after treatment (1, 2). The options for patients with biochemical recurrence after EBRT for prostate cancer include androgen-deprivation therapy (ADT), salvage radical prostatectomy (SRP), salvage cryotherapy, salvage high-

intensity focused ultrasound (HIFU), and salvage brachytherapy; however, these modalities are non-curative, with the exception of SRP. Theoretically, SRP provides the possibility of a curative outcome and it is the best management for radiation-failure prostate cancer in young patients. A survey of practice patterns among urologists and radiation oncologists in the United States revealed 25% would recommend SRP to a patient aged 45-65 years, but only 4% would recommend it to a 65- to 75-year-old patient with biochemical or local failure after definitive irradiation therapy (3). In real-world clinical practice, only four (0.9%) out of 430 patients received SRP after EBRT in the CaPSURE database (2). Thus, it appears that patients rarely undergo SRP. A number of factors may explain why SRP is not recommended by the majority of doctors. SRP is more technically demanding than standard open radical prostatectomy due to loss of dissection planes between the prostate and rectum, and the difficulty in differentiating between local and distant recurrence. However, no significant differences in operative time, blood loss or transfusion rate were found between SRP and open radical prostatectomy at one medical center (4). It is worth noting that the SRP group had a higher rate of surgical complications, including urinary tract infection in 20.4%, bladder neck contracture in 47%, urinary retention in 25.3%, urinary fistula in 4.1%, abscess in 3.2%, and rectal injury in 9.2% (4). Moreover, recovery of continence was achieved in 30% at year 3 (4).

Currently, improved patient selection, improved surgical technique, and more experience at centers with greater volume of patients with prostate cancer may have reduced the rates of surgical complications and enhanced outcomes. Robotic-assisted radical prostatectomy is a near gold standard for localized prostate cancer (5). In this study, we evaluated the benefits and drawbacks of salvage robotic-assisted radical prostatectomy (S-RaRP) after definitive EBRT, HIFU, or cryotherapy failure in patients with prostate

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cancer. We herein report our experience with 14 cases of S-RaRP failure after definitive treatment for prostate cancer. The patients' postoperative functional and oncological outcomes were analyzed.

## Patients and Methods

From December 2005 to June 2016, 1230 cases underwent RaRP performed by a single surgeon (YC Ou). Among them, 14 (1.13%) underwent S-RaRP and were enrolled into this study. After the protocol was approved by our Institutional Review Board (IRB CE15215B), the prospective database was collected. BCR following EBRT, HIFU, or cryotherapy was defined according to the original American Society for Therapeutic Radiation and Oncology (ASTRO) definition with the demonstration of three consecutive increases in serum prostatic-specific antigen (PSA) from a post-treatment (irradiation, HIFU, or cryotherapy) nadir PSA (6).

Patient characteristics are described in Table I. Initial definitive treatment was external irradiation in 11 cases, cyberknife in 2, and HIFU in one. Seven (50%) patients also received ADT during definitive treatment. The duration of ADT ranged from 2 to 24 months. The nadir PSA level after definitive treatment ranged from 0.014-8.8 ng/ml with a mean value of 1.21 ng/ml. A case with a nadir PSA of 8.8 ng/ml occurred at 13 months after external irradiation only. The mean PSA level at S-RaRP was 6.69 ng/ml with a range from 0.558 to 25 ng/ml. The mean period from definitive treatment to S-RaRP was 36.5 months.

With respect to the surgical technique employed in our series, the steps of S-RaRP procedure were largely the same as those previously described for RaRP (7-9). In the preoperative evaluation, digital rectal examination was the most important method of detecting the mobile prostate from the rectal wall, not fixed prostate or frozen pelvis due to previous irradiation. 3-Tesla multiparametric magnetic resonance imaging is an important modality for detecting the tumor location, amount, involvement, or pelvic lymph node metastasis, while computed tomography and bone scan are valuable for detecting metastatic lymph nodes beyond the pelvic rim, visceral metastasis, and bone metastasis.

The loss of dissection planes from extensive scarring and adhesion after radiation may deter the surgeon from performing S-RaRP. The key procedures to overcoming this challenge are dedicated posterior dissection of the prostate, endopelvic fascia dissection, and apical dissection. The dissection of Denonvillier's fascia from the posterior prostate is paramount to preventing rectal injury. Sometimes this plane may be obliterated due to scarring or neovascularization, but with sufficient traction and countertraction, the dissection route to a position near the prostate apex may be recognized. Similarly, the plane of the endopelvic fascia and pelvic side wall may also be hard to recognize. After a well-performed and detailed dissection of the bilateral and posterior aspect, the prostate is freely movable and the risk of unnecessary injury can be avoided.

Neurovascular bundle (NVB) preservation should only be performed in low-risk and young patients, and not only antegrade but also retrograde dissection should be attempted, due to vascularization and bleeding which may obliterate the plane from maximal preservation.

After preservation of anterior and posterior urethral continence components, healthy bladder neck and a long urethral stump would be crucial for early continence. Vesicourethral anastomosis can be performed with barbed continuous suture (3-o V-Loc™, Covidien)

and 200 ml saline irrigation test to secure the anastomosis (10). Foley catheter should be kept for 10 days and postoperative cystourethrogram should not be routinely performed.

Parameters recorded for each surgery included surgeon's console time, estimated blood loss, specimen volume, and complication rate. Specimens were fixed, coated with Indian ink, and cut into systematic stepwise sections at 3-mm intervals (7). The tumor volume, tumor percentage, Gleason score, pathological stage, positive surgical margin rate, angiolymphatic invasion, and node-positive rate were recorded.

Patient follow-up at 6 weeks after S-RaRP included evaluation of PSA. Continence was defined as having no pad use. Potency was defined as the ability to achieve and maintain satisfactory erections firm enough for sexual intercourse with or without the use of oral phosphodiesterase type 5 inhibitors. Continence and potency were subjectively estimated by the patients at postoperative visits by interview with the treating surgeon. BCR was defined as two consecutive PSA levels of >0.2 ng/ml after S-RARP.

## Results

The results of S-RARP are presented in Table II. The characteristics of the three patients with BCR are described in Table III and the outcomes are shown in Table IV. Regarding the D'Amico risk factor before focal treatment, patient 4 was intermediate-risk and both patient 7 and 13 were high-risk. Pathological upstaging was observed in one case, from cT3a to pT3b after S-RaRP. Positive surgical margin was noted in two out of the three patients. All three of these patients received ADT later and one patient developed multiple lung metastases (patient 4) and one developed bone combined with lymph node metastases (patient 13) (Table IV).

Four out of the 14 patients suffered from complications. Intra-operative bladder tear occurred in one patient and repair was carried out immediately without urine leakage. One patient suffered from penile ecchymosis after sexual intercourse on post-operative day 28. Two patients suffered from anastomosis stricture and one received urethral sounding once, while another patient needed urethral sounding every 2 to 3 months due to severe scarring and urethral injury during re-insertion of Foley catheter when it became dislodged on post-operative day 6 at a local hospital.

## Discussion

Several studies have demonstrated salvage local treatment for prostate such as SRP could lead to considerably improved BCR-free and metastasis-free survival (11, 12). Although some factors such as poorly differentiated tumor and high Gleason score, rapidly rising PSA with short doubling time, or undetectable nadir PSA have been shown to be associated with BCR, no individual factors have definitively excluded the possibility that local salvage therapy may be beneficial (13, 14). Several studies on the use of SRP after definitive radiation

Table I. Patient characteristics of salvage robotic-assisted radical prostatectomy (n=14) (S-RaRP).

Parameter	Mean/number
Age (years)	67.8 (51-84)
Initial PSA (ng/ml)	14.3 (3.4-51.3)
PSA group	
10 ng/ml	7 (50.0%)
10-20 ng/ml	5 (35.7%)
≥20 ng/ml	2 (14.3%)
Initial stage	
cT1	6 (42.9%)
cT2	7 (50.0%)
cT3	1 (7.1%)
Tumor amount at biopsy (%)	19.14% (4-80%)
Biopsy Gleason score	6,93
Biopsy Gleason score group	
6	5 (35.7%)
7	6 (42.9%)
8	2 (14.3%)
9	1 (7.1%)
D'Amico risk	
Low	4 (28.6%)
Intermediate	3 (21.4%)
High	7 (50.0%)
ADT during RT (n)	7 (50.0%)
ADT duration (months)	14.6
Nadir PSA (ng/ml)	1.21 (0.014-8.8)
Nadir PSA <0.5 ng/ml	6 (42.3%)
PSA (ng/ml) at S-RaRP	6.69 (0.558-25)
RT to S-RaRP (months)	36.5 (13-103)

ADT: Androgen deprivation therapy, RT: radiation therapy, SD: standard deviation, ADT duration 3 months (two patients), 6 months (one patient), 18 months (one patient), 24 months (three patients).

therapy reported that surgical complications and functional outcomes were the major concerns (4, 15). Salvage ADT may be the first consideration for patients with BCR after local treatment due to fewer comorbidities; however, despite its systemic treatment effect, it is still not a curative treatment option (16). SRP may provide the possibility of disease-free status with a 5-year BCR-free survival rate of approximately 64% and a one-year continence rate of 80% (11).

In the era of robotic surgery, the benefits of 3-dimensional vision and endowrist instruments for deep pelvic surgery have yielded excellent outcomes worldwide over the past 10 years (17). At our Institute, more than 1,200 prostatic surgeries have been carried out with excellent oncology and functional outcomes (18, 19). Maintenance of the pneumoperitoneum can reduce bleeding from the venous plexus. High resolution 3-dimensional imaging allows fine dissection, especially when developing the plane of Denonvilliers' fascia, which helps prevent rectal injury and enables maximal preservation of functional urethra. A water-tight anastomosis reduces the incidence of postoperative leakage.

Table II. Peri-operative and result of salvage robotic-assisted radical prostatectomy (S-RaRP).

Parameter	Mean/number
Clinical stage at S-RaRP	
T2N0	10 (71.4%)
T3N0	3 (21.4%)
T3N1	1 (7.2%)
Console time (min)	134.9 (105-170)
EBL (ml)	99.6 (30-160)
Pathology stage	
T2N0	8 (57.1%)
T3N0	4 (28.6%)
T3N1	2 (14.3%)
Lymph node number	9.8 (7-13)
Specimen volume (ml)	38 (25-80)
Pathology tumor amount (%)	14.36% (1-40%)
PSM (n)	21.4% (3/14)
Continence rate*	71.4% (10/14)
Time to continence (months)	4.4 (2 week-12 months)
Potency after bilateral NVB preservation	66.7% (2/3)
Follow up duration (months)	32.4
BCR-free survival	78.5% (11/14)

EBL: Estimated blood loss, PSM: positive surgical margin, NVB: neurovascular bundle, BCR: biochemical recurrence. \*Four patients suffered from stress urinary incontinence needing 1-2 pads per day.

The most notable difference between S-RaRP and RaRP may be the risk of severe adhesion and obscure plane after radiation therapy (20). Surgery begins from the posterior aspect of the prostate, with sharp dissection at Denonvilliers' fascia, which provides early protection of the rectum. After dropping the bladder later, the endopelvic fascia can be opened with sharp dissection and in most situations, this plane may be obliterated and hard to recognize (21). Performing dissection of bladder neck and full mobilization will improve the visualization of prostatic apex, which may be the most adherent after radiation therapy and easily lead to rectal injury (22, 23).

Table V lists the surgical variables of S-RaRP in our series and in the literature. In our perioperative outcomes, the operation time was about 34.9 minutes and the estimated blood loss was 99.6 ml, which were similar to values reported in other studies: operative time ranged from 130 to 183 minutes and the estimated blood loss ranged from 75 to 381 ml. This indicates that despite the greater difficulty of the surgery, we were still able to achieve an acceptable operative time and limited blood loss. Rectal injury is another risk of concern, but fortunately it was not observed in our series. The only patient who suffered from rectal injury reported by Kaffenberger *et al.* had an unrecognized pT4 disease (23), and the overall incidence was still low. This may be due to the advantage provided by high-resolution imaging in S-RaRP. The incidence

Table III. *Characteristics of patients with biochemical failure after salvage robotic-assisted radical prostatectomy (S-RaRP).*

Parameter	No. 4	No. 7	No. 13
Age (years)	73	70	66
Initial PSA (ng/ml)	3,4	12,03	51,3
Initial clinical stage	T1b	T2c	T2c
Biopsy tumor amount (%)	10%	25%	40%
Biopsy Gleason score	3+4=7	4+3=7	4+3=7
D'Amico risk	Intermediate	High	High
Primary treatment	RT	RT	RT
ADT during RT, duration (months)	Nil	24	18
Nadir PSA (ng/ml)	2,1	0,9	0,3
PSA at S-RaRP (ng/ml)	7,3	15,2	18,8
Time from RT to S-RaRP (months)	27	24	65

RT: Radiation therapy, ADT: androgen deprivation therapy, PSA: prostatic-specific antigen.

Table IV. *Outcomes of biochemical failure after salvage robotic-assisted radical prostatectomy (S-RaRP).*

Parameter	No. 4	No. 7	No. 13
Clinical stage at S-RaRP	T2c	T3a	T3aN1
Pathology stage	T2cN0	T3bN0	T3aN1
Lymph node (positive/yield number)	0/9	0/7	3/12
Specimen volume (ml)	30	40	45
Tumor amount (%)	25%	15%	45%
PSM	Negative	Positive	Positive
Continence (months)	2	3	*SUI
NVB preservation	Nil	Nil	Nil
BCR (months)	5	4	8
Comment	Multiple lung metastases under ADT	No definite local recurrence or metastases under ADT	Right iliac bone and left external iliac lymph node metastases, under ADT, RT for bone lesion

NVB: Neurovascular bundle, BCR: biochemical recurrence, ADT: androgen deprivation therapy. \*Patient had Parkinsonism with medication.

Table V. *Current functional outcomes and cancer control after salvage robotic-assisted radical prostatectomy for radiation-recurrent prostate cancer.*

Author	Year	Number	Op time (min)	EBL (ml)	Rectal injury (%)	Anastomosis stricture (%)	Continence (%)	Potency (%)	Follow up (month)	PSM (%)	BCR-free rate (%)
Boris et al. (20)	2009	11	183	113	9	9	80	18	20	27	73
Eandi et al. (21)	2010	18	160	150	0	17	33	0	18	28	67
Chauhan et al. (22)	2011	15	140	75	0	NA	71	0	5	13	72
Kaffenberger et al. (23)	2013	34	179	175	2,9	8,8	44	29	16	26	82
Yuh et al. (24)*	2014	51	179	175	2,9	22,9	45	23	36	31,4	57% at 3-year
Bates et al. (25)	2015	53	130	120,4	0	0	76,9	31,5	36	18,9	67% at 3-year
Kenny et al. (26)	2016	20	NA	381	0	Anastomosis leak 40%	NA	NA	NA	17	78
Current study*	2017	14	134,9	99,6	0	14,3	71,4	66(2/3)	32,4	21,4	78,5

Op time: Operative time, EBL: estimated blood loss, PSM: positive surgical margin, BCR: biochemical recurrence, NA: not assessed. \*Positive lymph nodes in 5.9% in Yuh *et al.*'s series and 14.3% in our series.

of rectal injury in SRP was more common with a prevalence rate of 0-28% (12).

Anastomosis stricture was another complication with a prevalence rate of 14.3% in our series. Radiation-induced cell apoptosis, inflammation, vascular injury, and atrophy lead to poorly-oxygenated tissue and eventual tissue scarring, which results in a greater frequency of anastomosis stricture than in normal prostate tissue (24, 25). In contrast, continence outcome with pad-free status or only one safety pad was good in our series (71.4%) and ranged from 33-80% in the literature. Potency was hard to assess as only three patients were potent before surgery. Bate *et al.* reported an overall continence rate of 76.9% and a potency rate of 31.5% in a series of 53 patients who underwent S-RaRP, which provided the advantage of NVB sparing (25).

In our series, we achieved a relatively low positive surgical margin rate (21.4%). Most patients who underwent salvage local treatment had more advanced disease. Greater tissue density, obscure plane, and advance tumor behavior may lead to a higher incidence of positive surgical margin, which ranged from 13 to 31.4% in the literature. Most positive surgical margins occurred at the prostatic apex with an overall rate of 78% (23). Consistent with previous studies, our findings showed that S-RaRP provided patients with the possibility of becoming disease-free, with a BCR-free survival rate of 78.5% at a mean follow-up of 32.4 months.

Although S-RaRP achieved an excellent oncology outcome and an acceptable functional outcome, it is important to note that this surgical modality should be applied on an individual basis after the patient has undergone a thorough evaluation to avoid unnecessary surgery.

In order to attain the benefits of a reduced complication rate and a better surgical outcome provided by S-RaRP, the clinician must perform patient selection according to certain criteria. Several previous studies have demonstrated a number of important prognostic variables that appear to predict oncology outcome. Kaffenberger *et al.* reported PSA doubling time and Gleason score at original diagnosis were two major independent risk factors for BCR (23). Yuh *et al.* reported that high PSA and extracapsular extension may be related to early BCR, with an estimated 3-year BCR rate of 43% (24). In summary, most patients who underwent S-RaRP had a relatively advanced disease status with potential distant metastasis and therefore patient selection is of paramount importance. Preoperative bone scan and computed tomography is crucial for detecting distal metastatic lesions to prevent unnecessary surgery.

In our single-institute experience, our findings indicate that S-RaRP was capable of achieving good oncological control with an excellent BCR free-rate, as well as satisfactory symptomatic control. Most of the patients that received radiation suffered from low urinary tract symptoms

related to chronic obstruction which were resolved after surgical intervention. Although some patients suffered from incontinence, an experienced surgeon can expect to achieve excellent overall functional outcome. Our outcomes showed that S-RaRP resulted in fewer surgical complications such as low estimated blood loss and no rectal injury and thus we propose that this modality may offer suitable candidate patients the possibility of becoming cancer-free.

There were some limitations to our study. This was a retrospective investigation with a limited number of patients and thus these findings should be interpreted with caution in clinical practice. Moreover, because prostate cancer is relatively slow-growing, further long-term follow-up may be needed to further clarify the beneficial effect of S-RaRP on survival rates.

## Conclusion

S-RaRP is a technically feasible operation with a low complication rate. Operative time was increased but there was no significant increase in blood loss. Continence rate was good and potency rate was acceptable. Short-term oncological outcomes are encouraging; however, longer follow-up is necessary to determine the long-term survival benefits.

## Conflicts of Interest

None of the contributing Authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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