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Early Experience with Salvage Robotic-Assisted Radical Prostatectomy in Proton Beam Radiotherapy Failures

Yaşar Bozkurt[1], Murat Atar[2], Louis L. Pisters[3]

[1]Department of Urology, İstinye University, İstanbul, Turkey
[2]Department of Urology, Bower Hospital, Diyarbakır, Turkey
[3]Department of Urology, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA

Aims: To assess the perioperative and short-term functional and oncologic outcomes of the salvage robot-assisted radical prostatectomy (sRARP), after recurrence following primary proton beam therapy for clinically localized prostate cancer.

Methods: Ten patients undergoing sRARP after failure of the prior definitive proton beam therapy for localized prostate cancer were included. BCR is defined as a prostate-specific antigen (PSA) value of 2.0 ng/mL greater than the absolute nadir. All of the individuals had a diagnosis of prostate cancer via biopsy after proton beam therapy, with negative findings on magnetic resonance imaging/computer tomography of the pelvis and abdomen, and a bone scan. The sRARP procedure with pelvic lymph node dissection was performed by a single surgeon in all patients.

Results: The median age of the cohort at sRARP was 66.8 years, and the mean BMI was 29.2 kg/m^2. The mean duration from proton beam therapy to sRARP was 58.4 months; the mean preoperative PSA level was 5.5 ng/mL, the mean operative time was 230 minutes, and the approximate blood loss was 745 mL. Anastomotic leakage occurred in half of the individuals, and bladder neck contracture developed in 6 patients. For 8 patients, the continence results within 6 months follow-up were available. Overall, 24 complications occurred in 9 patients. At follow-up in the 32nd month, the overall survival rate was 80%, and the BCR-free survival rate was 90%.

Conclusion: sRARP after proton beam therapy is an applicable procedure, but has a high risk of serious complications.

INTRODUCTION

For patients suffering from localized prostate cancer (PCA), there are various options for curative treatment, such as brachytherapy (BT), external-beam radiotherapy (EBRT), and radical prostatectomy (RP). Indeed, radiation therapy (RT) is widely used to treat localized PCA.[1,2] Following RT, 72% of the patients who had biochemical relapse and were clinically metastasis-free had biopsy-proven local recurrence.[3] High PSA levels and cancer, detected on biopsy 2 years subsequent to the RT, were defined as the true local recurrence of the disease. Patients who experience this situation can be candidates for salvage RP. The options for salvage treatment include cryotherapy, high-intensity focused ultrasound (HIFU), salvage brachytherapy, and salvage radical prostatectomy (sRP). On the other hand, salvage therapies lack an ideal treatment protocol due to the shortage of high-quality data, undesirable side effects of treatments, and inadequate contribution to survival rates.[4,5]

Robot-assisted radical prostatectomy (RARP) makes difficult urological surgeries easier, safer, and more acceptable to both the surgeon and the patients. RARP provides the most improved visualization of the surgical area and improved instrument control, when compared with other techniques. Thus, it can theoretically overcome the major constrictions of sRP surgery, and improve the oncologic and functional outcomes.[6] Until now, there have been few salvage robot-assisted laparoscopic prostatectomy (sRARP) series.[7-10] The studies above suggest that sRARP is applicable for patients with recurrent PCA. However, previously performed RT makes sRP a technically challenging procedure, and the complication rate depends on the previously achieved radiation dose.

Currently, three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and proton beam therapy (PBT) are the 3 kinds of RT that are commonly used for localized PCA.[11] With their minimal toxicity to surrounding healthy tissues, IMRT and PBT are enhanced forms of RT which can

Corresponding author: Yaşar Bozkurt, Department of Urology, İstinye University, İstanbul, Turkey
e-mail: dryasarbozkurt@hotmail.com

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ORCID iDs of the authors: Y.B. 0000-0003-3916-6625; M.A. 0000-0003-1659-8134; L.L.P. 0000-0002-9226-6062.

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achieve radiation dose escalation.[12] It has been proven by several studies that an increased dosage of RT has a positive impact on the biochemical recurrence (BCR) rates, distant metastasis, and local disease progression. However, a great number of these patients may ultimately encounter a BCR and recurrence.[5, 13]

In a retrospective study, the authors suggest that PBT is effective and well-tolerated for PCA.[14] Some studies comparing PBT with IMRT have demonstrated conflicting results; one study suggests that both are equal in terms of rectal dose sparing; however, IMRT is actually superior in terms of bladder sparing.[15] On the other hand, the other study states a clear advantage of PBT.[16] Two other reports have asserted that PBT is associated with greater intestine toxicity than IMRT.[12, 17] Owing to its higher toxicity, increased complication rates after sRARP are probable.

The aim of this study is to report the short-term oncological and functional outcomes of sRARP after PBT failure. To our knowledge, this is the first study that discloses the results of patients who solely received PBT before sRARP.

MATERIAL AND METHODS

After approval by the Institution Review Boards (RCR03-0847), the study was carried out at The University of Texas MD Anderson Cancer Center (MDACC). The study included 10 men undergoing sRARP after failure of prior definitive PBT for localized PCA. For every patient, the following variables were noted: age, race, BMI, total PSA level before PBT and before sRARP, clinical stage, pathological stage, and Gleason scores on biopsy and on sRARP. The inclusion criteria were clinically organ-confined PCA disease after failure of PBT, and having followed-up at least 6 months after sRARP treatment. The exclusion criteria for the study were previous RT for PCA other than PBT, and previous pelvic surgery.

Biochemical failure after PBT has been defined as a PSA value of 2.0 ng/mL greater than the absolute nadir, according to the American Society for Therapeutic Radiation and Oncology criteria. Every patient underwent a physical examination, serum PSA testing, magnetic resonance imaging (MRI) or computed tomography (CT), and bone scan to exclude distant metastases prior to the surgery. In order to confirm the recurrence of the disease, every patient underwent a prostate biopsy. After the biopsy procedure, patients whose recurrence was proven were considered as candidates for sRARP.

Surgical Technique

All sRARP operations were carried out by a single surgeon using the six-port Da Vinci® surgical system with either SI or XI platforms. An initial posterior dissection of the seminal vesicles and vas deferens was carried out with a trans-peritoneal approach.

Subsequently, an extended template bilateral pelvic lymph node dissection was performed in all cases. The bladder was then dropped, and the sRARP was completed with sharp dissection along the rectum from both the right and left sides and from base to apex. A 2-0 polydioxanone posterior Rocco suture was placed to anchor the bladder to the sub-urethral tissues. Vesicourethral anastomosis was performed using a combination of 2 or 3 interrupted 4-0 polydioxanone posterior anastomotic sutures followed by a running 2-0 polydioxanone suture for the lateral and anterior aspects of the anastomosis. An anterior bladder closure was carried out in those cases with a wider bladder neck, and this anterior closure performed with a combination of figure of eight 4-0 polydioxanone suture and a running 2-0 polydioxanone suture secured with Lapra-Ty® clips.

According to the Clavien–Dindo classification, post-operative complications were assessed by categorization as early (within 90 days) or late (occurring after 90 days).[18]

Pathologic Analysis

All biopsies conducted by other institutions were re-read by a single experienced genitourinary pathologist of our hospital. Before sRARP, cancer diagnosis was histologically proven by a TRUS-guided needle biopsy. The pathologic staging of the sRARP specimen was performed by the same pathologist.

RESULTS

One patient was African American, one patient was Asian, and the others were white. Prior to the operation, every patient was continent, and all patients underwent sRARP. The median age of the cohort at sRARP was 66.8 years (57-74), and mean BMI was 29.2 kg/m^2. After PBT, PCA was proven in all patients via a biopsy procedure. The mean PSA level prior to surgery was 5.5 ng/ml, and the mean time elapsed from PBT to sRARP was 58.4 months. The final report of histopathology demonstrated a tumor stage of T2 in 2, T3a in 3, T3b in 3, and T4 in 2 patients. Extended pelvic lymph node dissection was carried out in every patient at the time of the operation, and 2 patients were confirmed to have positive lymph node results. Table 1 displays characteristic data of the patients.

There was no rectal injury or other major intra operative complication. The operation took 230 minutes, and the blood loss was 745 mL. The median length of hospital stay after sRARP was 3.9 (1-10) days. The median follow-up of patients after sRARP was 31.8 (17-65) months (Table 2). Anastomotic leaks were observed in 5 patients (50%). Even though they were managed with prolonged catheterization, a bladder neck contracture eventually occurred in most patients. Bladder neck contractures developed in 6 patients and were managed with direct-vision internal urethrotomy and/or transurethral resection of the bladder neck in 5 patients. Vesicopubic fistula with breakdown of the vesicourethral anastomosis plus bladder neck contracture were observed in 1 patient, and managed with robotic salvage radical cystectomy-ileal conduit plus urethrectomy at the sixth month. All post-operative complications, stricture details, and treatments are listed in Table 3.

According to a preoperative assessment of erectile dysfunction (ED), 7 patients reported that they did not have ED. After the surgery, 5 patients reported about their erectile functions. Unfortunately,

TABLE 1. Patient Characteristics

Patients	Pre-PBT PSA (ng/mL)	Pre-PBT Gleason sum	Pre-PBT T-stage	PSA Nadir After PBT	Time Elapsed from PBT to sRARP (Months)	Age at sRARP (Years)	Pre-sRARP, BMI (kg/m^2)	PSA Prior to sRARP	Pre-sRARP Gleason Sum	Gleason Sum at Specimen	Pathologic T-Stage	PSM	Total/Positive Nodes
1	3.6	6	T1c	0.70	34	64	31.86	3.9	8	9	PT3bN0	Negative	16/0
2	5.5	7	T1c	0.90	58	69	26.13	4.0	7	9	PT2N0	Negative	20/0
3	3.6	6	T1c	0.60	35	64	30.92	3.9	8	9	PT3aN0	Negative	16/0
4	7.0	7	T2b	0.40	60	73	34.54	9.0	9	NA	PT4N1	**Positive**	**23/2**
5	5.1	7	T2b	0.20	71	57	26.14	2.5	7	7	PT3bN0	Negative	25/0
6	5.0	7	T1c	0.90	60	69	25.32	4.0	8	9	PT2N0	Negative	18/0
7	6.9	7	T2b	0.40	62	75	34.34	9.0	9	NA	PT4N1	**Positive**	**23/3**
8	8.0	7	T1c	0.90	70	74	26.87	5.2	8	9	PT3aN0	Negative	14/0
9	5.4	6	T1c	1.20	60	66	29.19	5.4	8	9	PT3aN0	Negative	7/0
10	5.4	7	T2a	0.20	74	57	26.14	2.5	7	9	PT3bN0	Negative	16/0
Mean	5.55			0.64	58.4	66.8	29.2	4.94					18/0.5

BMI, body mass index; PBT, proton beam therapy; sRARP, salvage robot-assisted laparoscopic prostatectomy; PSA, prostate-specific antigen (ng/mL); ED, erectile dysfunction; NA, Not Available; PSM, positive surgical margin. The bold parts indicate the patients who have both PSM and positive lymph node results.

none of them were potent at the sixth month. Tables 2 and 3 demonstrate continence results at a minimum 6 months follow-up for 8 patients. Of these 8 patients, 2 were using 0-1 pads per day, and 6 of them were using 4 pads per day. When 16 months had passed after the operation, 1 individual had an artificial urethral sphincter implantation surgery. Totally, 24 complications were observed in 9 patients, with 80% of the patients experiencing multiple complications. Major complications (Clavien Grade 3-4) were seen in 3 patients (Table 3). During the follow-up period, 2 individuals died due to random and natural reasons. At the 32nd month, the BCR-free survival rate was 90% and the overall survival rate was 80%.

DISCUSSION

RT causes a wide spectrum of transformations, such as neo-angiogenesis and necrosis in the prostate and the tissues surrounding it. Consequently, tissues decay, and more complications occur after the surgery. Therefore, a locally recurrent PCA after RT can have an aggressive natural history, with poor prognosis. Numerous perioperative, oncologic, and functional outcomes of larger sRARP series after RT modalities have been published.[4,5,8,9,19,20] When compared to primary RP, an increased risk of complications, such as short-term post-operative events, anastomotic stricture, urinary retention, urinary fistula, rectal injury, abscess, fibrosis, poor wound healing, ED, and urinary incontinence (UI), is related with salvage RP.[21-23]

The number of pads used daily after the surgery was used as a measurement for UI, which is a functional result of salvage therapy after the operation. UI rates at 12 months after salvage surgery were reported to vary from 48% to 85%. Severe UI rates were estimated as 23% on average in all articles about salvage surgery, while some studies have even estimated it as 85%.[5,24,25] Moreover, urinary continence was evaluated as 21-90% on longer follow ups after salvage surgery. As surgical techniques improve, and patient selection increases, these complications have been seen less frequently in recent studies.[5,8,20] In the present study, Tables 2and 3 show continence results at a minimum 6 months follow-up for 8 patients. At the end of 6 months, the severe UI rate was higher than 75%.

According to the recent studies, the rate of rectal wall injury has decreased significantly as a result of increased surgical experience and increased quality of vision provided by laparoscopic and robotic cameras.[20] Another common complication is the occurrence of an anastomotic leak, which is detected in up to 33% of patients in some studies.[20,22] The delayed healing process of the anastomosis can be attributed to poor vascularization of the bladder neck and urethral stump, caused by RT. In the present study, there was no rectal injury or other major intraoperative complication, but anastomotic leaks occurred in 5 patients (50%). In our study, the anastomotic stricture rate was higher than the literature. This situation may be explained by impaired wound healing after PBT, and the higher toxicity rate of PBT compared with other modalities of RT.

TABLE 2. Surgical and Pathological Outcomes After Salvage Radical Prostatectomy

Patients	Blood Loss (mL)	Duration of Surgery (Minutes)	Length of Stay (Days)	# Clavien 1-2	# Clavien 3-4	Anastomotic Leakage	Follow-Up (Months)	Incontinence at 6 Months (Pads/Day)	Pre/Post-sRARP ED
1	2100	268	10	2	0	No	64	4	No/Yes
2	850	220	2	2	2	Yes	23	0	No/NA
3	2100	263	1	1	0	No	64	4	Yes/Yes
4	300	235	6	2	0	No	23	4	Yes/NA
5	300	243	2	3	0	Yes	65	1	No/NA
6	850	187	10	3	1	Yes	18	NA	No/NA
7	300	183	2	3	0	No	23	4	Yes/Yes
8	150	247	2	0	0	No	20	4	No/Yes
9	200	218	3	1	2	Yes	17	4	No/Yes
10	300	243	1	2	0	Yes	65	NA	No/NA
Mean	745	230.7	3.9	1.9	0.5		31.8		

Mohler et al. and Seabra et al.[24] revealed ED rates of 78% and 74% at 6 months and 18 months, respectively, after sRP. Recently, Abufarj et al.[5] found that at least 50% of men report ED after salvage RP. In a systematic review, Chade et al. disclosed that 50-91% of patients had ED before salvage treatment, and 80-100% reported ED after the salvage procedure.[4] According to preoperative assessment, 70% of our patients reported that they did not have ED. Unfortunately, after the surgery, none of them were potent at the sixth month.

Salvage treatment for recurrent PCA exposes the previously treated tissues of the urethra and bladder neck to additional forces, compounding the risk for stricture formation. Anastomotic strictures also vary considerably, ranging from 0% to 55%,[5,21,26] because strictures might occur several months after the procedure. This situation indeed requires further investigation, as the majority of the series have a mean follow-up of less than 2 years. In this study, bladder neck contracture developed in 6 patients and was managed with direct-vision internal urethrotomy and/or transurethral resection of the bladder neck.

While oncologic results were considered, a Gleason score of 8 and an extra-capsular extension rate of 50% have been observed at final pathology in most studies. This shows that radio-recurrent PCA has poor prognosis.[20, 22] Positive surgical margin (PSM) rates are variable, and can be observed in approximately half of the patients in some multicenter series. No evidence of metastatic disease, a post-radiation biopsy confirming PCA, and a sufficiently long life expectancy (≥10 years) are the specifications of a good candidate who will benefit from sRP. The preoperative value of PSA (<10 ng/mL) and Gleason score of the biopsy specimen (≤7) should be defined while deciding whether a patient is appropriate for salvage therapy.[4] In this study, there was no evidence of metastatic disease. The post-radiation biopsy confirmed PCA,

TABLE 3. List of Post-Operative Complications, Stricture Details, and Performed Treatments

Patients	List of Complications Within 90 Days	Stricture/BNC	Stricture Detail/Procedures
1	Wound infection opened (G1). Ileus (G1).	YES	BNC with bladder stones/DVIU at 11 and 15 months
2	Anastomotic leak, pelvic hematoma, sepsis, rectovesical fistula, and colostomy	NO	-
3	Surgical wound infection	YES	Bladder stones/TUR-BN
4	Dysuria, suprapubic pain, stress, incontinence	NO	-
5	Anastomotic leak at 2 months, pelvic pain, dermatitis in bilateral groin area	NO	-
6	Hematuria, drop in hemoglobin, abdominal pain, anastomotic leakage, sepsis	NA	-
7	Pain, hematuria, dysuria, urgency with bacteriuria	YES	BNC/TUR-BN at 16 months
8	None	YES	BNC/DVIU at 12 months, artificial urinary sphincter at 16 months
9	Anastomotic leak, pelvic pain, vesico-pubic fistula with breakdown of the vesicourethral anastomosis	YES	Fistula Plus BNC/robotic salvage radical cystectomy-ileal conduit, urethrectomy at sixth months
10	Anastomotic leak about 40 days post-op, dermatitis in groin and scrotum skin	NA	-

BNC, bladder neck contracture; DVIU, direct-vision internal urethrotomy; TUR, trans urethral resection; BN, bladder neck; G1, grade 1.

TABLE 4. Perioperative, Oncologic, and Functional Outcomes in Some Salvage Robot-Assisted Laparoscopic Prostatectomy Series After Radiation Therapy Modalities and Present Study

Series	No.	Type of Radiation	Mean EBL	Follow-up (Months)	ORT, min	Overall Comp, *n*	PSM, *n*	LNI, *n*	Continence	Potenc, *n*	BCR During, Follow-up, *n*
Onol et al.[9]	94	54 XRT, 23 BT, 3 PBT, 14 XRT+BT	106	24	128	24	16/94	10	45/94	33/94	16
Bates et al.[22]	53		120	26	130	NA	10/53	14	34/53	14/44	8
Eandi et al.[27]	18	8 BT, 8 XRT, 2 PBT	150	18	156	7	5/18	1	6/18	0/18	6
Yuh et al.[28]	51	22BT, 18XRT, 6PBT, 3Cryo, 1HIFU, 1XRT+BT	175	36	179	24	16/51	3	23/51	6/13	10
Kaffenberger et al.[30]	34	13 BT, 11 XRT, 6 BT+XRT, 4 HIFU	NA	16.1	176	13	9/34	0	12/33	5/33	6
Present study	10	10 PBT	745	31.8	231	24	2/10	2	7/8	0/3	1

BT, brachytherapy; PBT, proton beam therapy; HIFU, high-intensity focused ultrasound; Cryo, cryotherapy; XRT, external-beam radiation therapy; sRARP, salvage robot-assisted laparoscopic prostatectomy; EBL, estimated blood loss, (mL); ORT, operative time; LNI, Lymph node involvement; PSM, positive surgical margin; BCR, biochemical recurrence; NA, not available.

and pre-surgical PSA was <10 ng/mL in all patients. The Gleason sum score of the post-radiation biopsy was 7 in 3 patients, 8 in 5 patients, and 9 in 2 patients. The surgical margin was negative in 8 patients, while 2 patients had PSM and positive lymph nodes. The Gleason score of patients who had PSM was 9 before sRARP. Therefore, the Gleason score can be considered as an important prognostic factor for outcomes of sRARP after RT.

The perioperative, oncologic, and functional outcomes of some large sRARP series after RT modalities are listed in Table 4. Eandi et al.[27] have published their study about sRARP including 18 patients, in which the median operative time, EBL, and length of stay were, respectively, 2.6 hours, 150 mL, and 2 days. Yuh et al.[28] described their series of sRARP in 51 patients. In this study, the median age of individuals was 68, while the median time from first therapy to sRARP was 68 months. The estimated amount of blood loss was 175 mL, and the mean duration of the operation was 179 minutes. According to the final pathology results, 50% of the patients had extra-capsular involvement, and 31% of the patients had the PSMs. The writers also reported that the BCR rate or progression-free survival rate was 57%, after a median follow-up of 36 months. In this series, significant complications (47%) were reported, including incontinence and ED. The potency rate was reported, and it shows that only 23% of the patients were potent preoperatively. Moreover, the rate of spontaneous return of urinary continence was reported in 23 patients (45%) with a median time of 6 months. In the present study, the mean EBL was 745 mL, and the rate of the overall number of complications was higher than in previous studies. Major complications (Grade 3-4) occurred in 3 patients.

The relative efficiency of PBT was raised to 1.1 in a study[29] in which the biological efficiency is estimated to be a little higher than that of high-voltage X-ray/Cobalt-60. Although it may increase toxicity level, this 10% increase of biological effectiveness might result in better tumor control. Thus, the higher complication rates in our results, including urine leakage, bladder neck contracture, and incontinence, may be explained by the higher toxicity rate of PBT prior to surgery. However, in order to make this precise conclusion, a randomized control study is necessary. In contrast to other studies in which different RT modalities were conducted before salvage surgery, our study consists of patients who received only PBT before the surgery.

This study has several limitations. Firstly, the study is retrospective. Secondly, the sample size is limited. Thirdly, it is not a comparative study including patients who received other types of RT. Lastly, the short follow-up period impairs our ability to assess precise final oncological and functional results. Despite these limitations, our study is valuable for providing the results of sRARP in isolated groups of patients receiving PBT before surgery.

sRARP after PBT has a high complication rate. Although our sample size is small, it can be said that the higher rate of complications in our results may be explained by the higher toxicity rate of PBT prior to surgery. Additionally, further prospective and randomized controlled studies are required to validate our findings.

Ethics Committee Approval: This study was approved by the Institutional Review Board (RCR03-0847) of MD Anderson Cancer Center.

Patient Consent for Publication: This is a retrospective cross-sectional study for which no formal consent is required.

Data-sharing Statement: The authors confirm that all data supporting the findings of this study are available within the article.

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