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Comparison of outcomes of salvage robot-assisted laparoscopic prostatectomy for post-primary radiation vs focal therapy

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Objectives

To compare salvage robot-assisted laparoscopic prostatectomy (RALP) outcomes in patients who underwent radiation and those who underwent focal ablation as primary therapies.

Patients and Methods

We evaluated 126 patients who underwent salvage RALPbetween 2008 and 2018. Of these, 94 (74.6%) received radiation and 32 focal ablation (25.4%) as primary therapy. These groups were compared with regard to clinical, oncological and functional outcomes. Kaplan–Meier curves and regression models were used to identify survival estimations and their predictors.

Results

Before surgery, more patients were potent in the focal ablation group compared to the radiation group (46.9% vs 22.6%; $P = 0.013$). Peri-operative characteristics and complication rates were not significantly different between the two groups. Postoperative catheterization duration was shorter in the focal ablation group (mean 10 vs 16 days; $P = 0.018$). At final pathology, the focal ablation group had higher non-organ-confined disease (71% vs 50%; $P = 0.042$) and positive surgical margin (PSM) rates (43.8% vs 17%; $P = 0.004$) as compared to the radiation group; however, 5-year biochemical recurrence (BCR)-free survival rates were similar (59% vs 56%; $P = 0.761$). Postoperative 1-year full (no pads/day) and social (0–1 pad/day) continence rates were significantly higher in the focal ablation as compared to the radiation group (77.3% vs 39.2%, $P = 0.002$, and 87.5% vs 51.3%, $P = 0.002$, respectively). Multivariate analyses showed primary focal ablation and nerve-sparing to be predictors of postoperative continence. Erectile function was preserved in 13% and 27% of preoperatively potent patients in the radiation and focal ablation groups, respectively ($P = 0.435$). No predictors were identified for postoperative potency.

Conclusions

Radiation was associated with inferior functional outcomes after salvage RALP. Focal therapies were associated with higher non-organ-confined disease and PSMrates, with no significant difference in short-term BCR-free survival.

Keywords

salvage prostatectomy, robot-assisted laparoscopic prostatectomy, radiation, focal ablation, outcomes

Introduction

Primary treatment of prostate cancer varies from surgery to less invasive treatments, including external beam radiation therapy (EBRT), brachytherapy, high-intensity focused ultrasonography (HIFU) and cryotherapy. In the USA, 12.7%, 41.5% and 45.8% of men diagnosed with localized prostate cancer between 2010 and 2015 received active surveillance, radiotherapy and surgery as initial management, respectively [1]. Although non-surgical therapies seem attractive to many patients, 22–69% of men who receive radiotherapy experience biochemical recurrence (BCR) during follow-up [2,3] and 5–83% of men require further treatment for local recurrence after focal therapy [4,5].

Options for salvage treatment for local failure include radical prostatectomy (RP), cryotherapy, HIFU, brachytherapy and androgen deprivation. Among them, salvage RP provides high long-term cancer control rates (77.5% overall and 88.6% cancer-specific survival at 10 years) [6]. However, salvage RP is underutilized (< 3% of men with local recurrence undergo salvage RP) because of inherent technical challenges and high complication rates [7]. Salvage robot-assisted laparoscopic prostatectomy (RALP) has emerged as a minimally invasive alternative to open salvage RP that is associated with less peri-operative morbidity and equivalent oncological outcomes [8,9]. It has been considered that all salvage RALP cases are the same and that patients have been consented in a similar way, however, over the course of our experience we have

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realized that surgical outcomes can be significantly affected by the type of primary prostate cancer therapy. Because of the scarcity of literature directly comparing salvage RALP outcomes depending on different primary therapies, we decided to investigate the differences in clinical and oncological outcomes between post-primary radiation and focal ablation therapies by examining our series of patients who underwent salvage RALP.

Patients and Methods

We reviewed our institutional review board-approved database that includes >11 500 RALP cases performed by a single surgeon (V.P.). Data were prospectively collected and retrospectively analysed. From this group, we identified 135 patients who underwent salvage RALP between 2008 and 2018 for failed primary treatment. Of these, nine had missing data and were excluded. Overall, the study included 126 patients, of whom 94 (74.6%) and 32 (25.4%) had received radiation and focal ablation treatments, respectively. The radiation group included EBRT (n = 39), intensity-modulated radiation (n = 15), proton beam radiation (n = 3), brachytherapy (n = 23), and combined EBRT and brachytherapy (n = 14). The focal ablation group included patients with focal lesion or partial gland ablation using HIFU (n = 9), cryoablation (n = 20) and other (electroporation, microwave, n = 3) therapies. All patients had biopsy-proven local recurrence without evidence of metastatic prostate cancer.

Surgical Technique

All salvage RALP cases were performed using a transperitoneal six-port technique, as described by our group previously [10]. Bilateral retrograde, athermal nerve-sparing [11] was performed whenever oncologically and technically feasible and if the patient had some degree of preoperative sexual function (Sexual Health Inventory for Men [SHIIM] score >12). The quality of neurovascular bundle (NVB) preservation was graded by the surgeon on each side using a five-point scoring system (1: 0%; 2: <50%; 3: 50%; 4: 75%; and 5: ≥95%), which takes the landmark prostatic/capsular artery as the anatomical reference [12]. A modified posterior rhabdosphincteric reconstruction was performed after prostatectomy [13], followed by vesico-urethral anastomosis using a modified van Velthoven technique. Pelvic lymphadenectomy was performed as previously described [14].

Postoperative Follow-up

We obtained cystograms within 10 days of surgery. The catheter was removed if no contrast extravasation was seen, otherwise it was kept until the next imaging obtained 1 week later. Postoperative complications were documented and classified according to the modified Clavien–Dindo system [15].

Patients were followed with PSA, SHIM score and AUA symptom score questionnaires at 6 weeks, then at 3, 6, 9, 12, 18 and 24 months after surgery. Patient-reported outcomes were obtained by chart review or telephone survey of all patients at the time of analysis. BCR was defined as PSA ≥0.2 ng/mL after salvage RALP. Full continence was defined as use of no pads and social continence was defined as use of 0–1 pad/day. Potency was defined as the ability to achieve and maintain satisfactory erections firm enough for sexual intercourse, with or without the use of phosphodiesterase-5 inhibitors [16].

Statistical Analysis

Continuous variables were reported as mean ± SD or median and range values. Categorical variables were reported as frequencies and proportions.

The data on overall NVB preservation were calculated using the mean of both side's nerve-sparing percentage, and categorized into two groups: 'good' (>50% of total) and 'poor' (≤50% of total) nerve-sparing [17]. We compared the differences in outcomes between radiation and focal ablation groups using Student's t-test, chi-squared and Fisher's exact tests, as appropriate. Kaplan–Meier curves and regression models were used to identify survival estimations and predictors of postoperative complications, biochemical failure, continence, and potency. A point-biserial correlation test was used to determine the relationship between continuous and categorical variables. Statistical analyses were performed using SPSSv25 (IBM Corp., Armonk, NY, USA). A two-tailed test with P value < 0.05 was considered statistically significant.

Results

Baseline Patient Characteristics

Mean age, body mass index and Charlson comorbidity score were not different between the radiation and focal ablation groups (Table 1). Preoperatively, LUTS bother scores were similar between the two groups and 9.7% patients in the radiation and 9.4% patients in the focal ablation group reported severe LUTS (Table 1); however, no patients reported using pads for LUTS or urinary incontinence. Patients in the focal ablation group had significantly better erectile function before surgery. The percentage of patients with SHIM score ≥21 was 46.9% in the focal ablation vs 22.6% in the radiation group (P = 0.007 [Table 1]).

The time between primary prostate cancer treatment and salvage RALP was significantly longer in the radiation group (82.2 ± 51.1 vs 61.1 ± 30.2 months; P = 0.039 [Table 1]). Preoperative cancer characteristics also showed differences

Table 1 Comparison of clinical demographics and preoperative cancer characteristics between post-radiation and post-focal ablation groups treated with salvage robot-assisted laparoscopic prostatectomy.

Characteristic	Radiation group, *n* = 94	Focal ablation group, *n* = 32	*P*
Age, years	65.36 ± 6.53	66.16 ± 6.61	0.555
BMI	29.04 ± 4.03	28.47 ± 4.84	0.514
Charlson comorbidity score	2.66 ± 1.26	2.66 ± 1.23	0.99
Preoperative sexual function, *n* (%)			
No ED (SHIM ≥ 21)	21 (22.6)	15 (46.9)	**0.007***
Mild ED (SHIM score 17–20)	17 (18.3)	3 (9.4)	
Mild-moderate ED (SHIM score 12–16)	16 (17.2)	0 (0)	
Moderate ED (SHIM score 8–11)	11 (11.8)	1 (3.1)	
Severe ED (SHIM score 0–7)	28 (30.1)	13 (40.6)	
Preoperative AUA symptom score, *n* (%)			
Mild LUTS (score 0–7)	43 (46.2)	16 (50)	0.933
Moderate LUTS (score 8–19)	41 (44.1)	13 (40.6)	
Severe LUTS (score 20–35)	9 (9.7)	3 (9.4)	
First treatment to salvage RALP, months	82.2 ± 51.15	61.12 ± 30.22	**0.039***
Adjuvant/salvage ADT before salvage RALP, *n* (%)	24 (25.5%)	4 (12.5%)	0.147
Preoperative PSA (mean ± SD)	4.53 ± 3.28	5.77 ± 10.47	0.314
Clinical stage, *n* (%)			
≤cT2c	91 (96.8)	31 (96.8)	0.194
cT3a	3 (3.2)	0 (0)	
cT3b	0 (0)	0 (0)	
cT4	0 (0)	1 (3.2)	
Biopsy Gleason score, *n* (%)			
Gleason score 6	18 (19.1)	6 (18.8)	**0.012***
Gleason score 7	31 (33)	20 (62.5)	
Gleason score ≥8	36 (38.3)	6 (18.8)	
Deferred	9 (9.6)	0 (0)	
D'Amico class, *n* (%)			
Low risk	24 (25.8)	4 (12.5)	**0.006***
Intermediate risk	31 (33.3)	21 (65.6)	
High risk	38 (40.9)	7 (21.9)	

*ADT, androgen deprivation therapy; BMI, body mass index; ED, erectile dysfunction; RALP, robot-assisted laparoscopic prostatectomy; SHIM, Sexual Health Inventory for Men. Values are mean ± SD, unless otherwise indicated. *P < 0.05.*

between the two groups, with the focal ablation group including more D'Amico intermediate-risk patients and Gleason 7 disease, and the radiation group having more high-risk patients and Gleason ≥8 disease (Table 1).

Operative Characteristics and Postoperative Outcomes

All cases were completed with robotic assistance. There were no differences in mean operating time, console time, estimated blood loss, and degree of nerve-sparing between the two groups (Table 2). Good nerve-sparing was performed in 43% of patients in the radiation group and 34% patients in the focal ablation group. Peri-operative outcomes with respect to treatment subtypes are presented in Table S1.

Table 2 Comparison of peri-operative outcomes and complication rates between post-radiation and post-focal ablation groups

	Radiation group, *n* = 94	Focal ablation group, *n* = 32	*P*
Total operating time, min	128.95 ± 19.33	122.38 ± 16.26	0.087
Total console time, min	83.94 ± 11.38	84.06 ± 12.4	0.958
Estimated blood loss, mL	106.65 ± 60.48	92.5 ± 56.09	0.247
Nerve-sparing degree, *n* (%)			
Poor nerve-sparing (≤50% of total)	53 (56.4)	21 (65.6)	0.410
Good nerve-sparing (>50% of total)	41 (43.6)	11 (34.4)	
Hospital stay, days	1.37 ± 1.44	1.09 ± 0.53	0.289
Postoperative catheter time, days	16.14 ± 13.95	10.16 ± 3.7	**0.018***
Cystographic leak, *n* (%)			
Leak at 10 days	25 (26.6)	5 (15.6)	0.239
Leak at 20 days	14 (14.9)	2 (6.2)	0.355
Postoperative complications, *n* (%)			
None	69 (74.2)	29 (90.6)	0.446
Clavien I	9 (9.7)	1 (3.1)	
Clavien II	11 (11.8)	1 (3.1)	
Clavien IIIa	2 (2.2)	1 (3.1)	
Clavien IIIb	1 (1.1)	0 (0)	
Clavien IVa	1 (1.1)	0 (0)	
Clavien V	0 (0)	0 (0)	
Postoperative 30-day readmission, *n* (%)	6 (6.4)	1 (3.1)	0.678

*Values are mean ± SD, unless otherwise indicated. *P < 0.05.*

There were no intra-operative complications and no rectal injuries. Overall, postoperative complications were encountered in 27 patients (21.4%). Most of these complications were minor grade (Clavien grades I and II [Table 2]) and included UTI (6.9%) and urinary retention after catheter removal (7.8%). Cystographic leak rates within 10 and 20 days after salvage RALP tended to be higher in the radiation as compared to the focal ablation group (26% vs 15% in the first and 14% vs 6% in the subsequent imaging, respectively); however, these differences did not reach statistical significance ($P > 0.05$ [Table 2]). The mean postoperative catheterization time was significantly longer in the radiation group (16 vs 10 days; $P = 0.018$ [Table 2]). Postoperative 30-day readmission rates were not significantly different between the two groups (6.4% vs 3.1%; $P = 0.678$). On multivariable analysis (Table 3), previous androgen deprivation therapy (ADT) was related to an increased risk of postoperative complications, nearing statistical significance (odds ratio 2.670 [CI 0.981–7.269]; $P = 0.055$).

Histopathological Characteristics and Oncological Outcomes

Pathological outcomes with respect to study groups and treatment subtypes are presented in Tables 4 and S2,

Table 3 Multivariable analysis of factors influencing postoperative complication risk, biochemical failure, continence, and potency after salvage robot-assisted laparoscopic radical prostatectomy

	OR (95% CI)	*P*
Postoperative any complication		
Age	1.015 (0.922–1.118)	0.760
BMI, <30 vs ≥30 kg/m^2	0.478 (0.170–1.345)	0.162
Charlson comorbidity index	0.679 (0.390–1.181)	0.171
Serum PSA	0.960 (0.833–1.105)	0.568
Clinical stage, ≤cT2b vs ≥cT3a	0.690 (0.113–4.227)	0.688
Primary therapy, ablation vs radiation	3.238 (0.854–12.273)	0.084
Previous adjuvant/salvage ADT	2.670 (0.981–7.269)	**0.055***
Biochemical failure		
Age	0.97 (0.903–1.042)	0.402
Serum PSA	1.061 (0.951–1.184)	0.292
Primary therapy, radiation vs ablation	1.194 (0.397–3.595)	0.752
Degree of nerve-sparing, ≤50% vs >50% of total	1.085 (0.429–2.742)	0.863
EPE on pathology	1.722 (0.614–4.832)	0.302
Pathological Gleason score, ≥8 vs <8	4.013 (1.549–10.395)	**0.004***
PSM on pathology	2.145 (0.686–6.706)	0.19
Full continence recovery		
Age, <65 vs ≥65 years	2.058 (0.834–5.077)	0.117
BMI, <30 vs ≥30 kg/m^2	1.413 (0.598–3.337)	0.431
Preoperative AUA symptom score, <8 vs ≥8	1.732 (0.765–3.920)	0.188
Primary therapy, ablation vs radiation	2.601 (1.040–6.507)	**0.041***
Previous adjuvant/salvage ADT	0.880 (0.325–2.380)	0.801
Degree of nerve sparing, >50% vs ≤50% of total	2.467 (0.996–6.108)	**0.051***
Cystographic leak at 10 days	0.610 (0.224–1.656)	0.332
Potency recovery		
Age, <65 vs ≥65 years	1.308 (0.329–5.206)	0.703
BMI, <30 vs ≥30 kg/m^2	1.488 (0.452–4.902)	0.514
Charlson comorbidity index, ≤2 vs >2	3.131 (0.784–12.502)	0.106
Preoperative SHIM score, <21 vs ≥21	0.504 (0.138–1.840)	0.300
Primary therapy, ablation vs radiation	1.151 (0.323–4.103)	0.828
Previous adjuvant/salvage ADT	0.154 (0.018–1.329)	0.089
Degree of nerve-sparing, >50% vs ≤50% of total	2.006 (0.521–7.722)	0.312

*ADT, androgen deprivation therapy; BMI, body mass index; EPE, extraprostatic extension; OR, odds ratio; PSM, positive surgical margin; SHIM, Sexual Health Inventory for Men. *P < 0.05.*

respectively. The pathological Gleason score 7 rate was significantly higher in the focal ablation group and Gleason score ≥8 was significantly higher in the radiation group (Table 4). The proportion of patients with pathologically non-organ-confined disease (≥pT3) was 71% in the focal ablation vs 50% in the radiation group (P = 0.042). There was a significantly higher positive surgical margin (PSM) rate in the focal ablation group (43.8% vs 17%, respectively; P = 0.004 [Table 4]). In both groups, the rate of good nerve-sparing was not significantly different between patients who did and did not have PSMs (Table 4); however, the incidence of extraprostatic extension (EPE) was significantly higher in patients with PSMs than in patients without (P < 0.001 for radiation group and P = 0.015 for focal ablation group [Table 4]).

In the whole cohort, there was no correlation between the time from primary treatment until salvage surgery and the presence of EPE or PSMs (data not shown). When data were examined with respect to each study group, time to salvage RALP was significantly shorter in patients with EPE in the focal ablation group (54 ± 30.6 vs 81.3 ± 21.3 months; P = 0.03 [Table 4]) with a significant negative correlation between time and EPE (r_{pb} = −0.411, P = 0.03). In the radiation group, time to salvage RALP was significantly longer in patients with PSMs (110.7 ± 47.7 vs 75.5 ± 49.9 months; P = 0.01 [Table 4]), with a statistically significant positive correlation (r_{pb} = 0.271, P = 0.016).

Eighteen and twelve percent of patients in the radiation and focal ablation groups had postoperative PSA persistence (≥0.2 ng/mL), respectively. During follow-up, 17% of patients in the radiation and 18.8% of patients in the focal ablation group developed BCR (Table 4). The 5-year estimated BCR-free survival rates were 56% and 59% in the radiation and focal ablation groups, respectively (P = 0.761 [Fig. 1]). In multivariable analysis, only Gleason score ≥8 at pathology was predictive of biochemical failure (Table 3).

Functional Outcomes

Overall full (no pads) and social (0–1 pad/day) continence rates at 1 year were 77.3% vs 39.2% (P = 0.002) and 87.5% vs 51.3% (P = 0.002), respectively, for the focal ablation and radiation groups. In patients who were continent preoperatively, 47.9% in the radiation group had severe loss of continence (≥3 pad use/day) at the last postoperative follow-up as compared to 9.4% patients in the focal ablation group (P = 0.001 [Table 4]). Kaplan–Meier analysis reporting the probability of postoperative continence showed significantly higher and faster recovery in the focal ablation group (P = 0.001 [Fig. 2]). In multivariable analysis, focal ablation therapy and good nerve-sparing were predictive of full continence recovery (Table 3).

In patients with no or mild erectile dysfunction (SHIM score ≥17) before surgery, five of 38 patients (13.1%) in the radiation and five of 18 patients (27.7%) in the focal ablation group had preserved erectile function at the last postoperative follow-up (Table 4). Although there was a trend towards higher postoperative potency probability in the focal ablation group (Fig. 3), the difference did not reach statistical significance (P = 0.179). Multivariable analysis did not reveal any independent predictors for postoperative potency (Table 3).

Discussion

In the last decade, salvage RALP has emerged as a minimally invasive alternative for recurrent prostate cancer after primary non-surgical treatment [8,9]. We previously described our salvage RALP technique and published our outcomes [10,14,18]. In the course of our growing experience, we have noticed differences in clinical presentation and outcomes

Table 4 Comparison of pathological, oncological and functional outcomes between post-radiation and post-focal ablation groups

	Radiation group, *n* = 94	Focal ablation group, *n* = 32	*P*
Prostate weight, g	44.27 ± 11.85	35.31 ± 15.58	**0.001***
Tumour volume, %	18.53 ± 16.71	21.38 ± 16.48	0.407
Pathological stage, *n* (%)			
≤pT2c	47 (50)	9 (29)	0.069
pT3a	21 (22.3)	14 (45.2)	
pT3b	26 (27.8)	8 (25.8)	
pT4	0 (0)	0 (0)	
Nodal stage, *n* (%)			
pN0	76 (80.9)	25 (78.1)	0.714
pN1	10 (10.6)	5 (15.6)	
pNx	8 (8.5)	2 (6.2)	
Pathological Gleason score, *n* (%)			
6	2 (2.1)	0 (0)	**0.011***
7	36 (38.3)	23 (71.9)	
≥8	40 (42.6)	6 (18.8)	
Deferred	16 (17)	3 (9.4)	
EPE, *n* (%)	47 (50)	22 (71)	**0.042***
PSM, *n* (%)	16 (17)	14 (43.8)	**0.004***
EPE in positive vs negative PSM	16 (100) vs 31 (39.7)*	13 (92.9) vs 9 (52.9)*	
Good nerve-sparing in positive vs negative PSM	6 (37.5) vs 35 (44.8)	5 (35.7) vs 6 (33.2)	
First treatment to salvage RALP, months			
EPE positive vs negative	88.07 ± 43.21 vs 75.85 ± 58.46	53.99 ± 30.58 vs 81.27 ± 21.36*	n.a
PSM positive vs negative	110.67 ± 47.68 vs 75.52 ± 49.96*	61.79 ± 33.71 vs 60.48 ± 27.76	
Follow-up, months	32 ± 24.21	29.24 ± 26.57	0.592
Cancer status at last follow-up, *n* (%)			
Biochemical recurrence-free	61 (64.9)	22 (68.8)	0.763
Biochemical persistence	17 (18.1)	4 (12.5)	
Biochemical recurrence	16 (17)	6 (18.8)	
Continence change at last follow-up, *n* (%)			
No continence loss	35 (37.2)	20 (62.5)	**0.001***
Mild continence loss (0–1 pad/day)	8 (8.5)	7 (21.9)	
Moderate continence loss (2 pads/day)	6 (6.4)	2 (6.2)	
Severe continence loss (≥3 pads/day)	45 (47.9)	3 (9.4)	
Potency change at last follow-up, *n* (%)			
Patients with good baseline EF (SHIM score 17–25)			
EF unchanged	5 (5.3)	5 (15.6)	0.435
EF deteriorated	33 (35.1)	13 (40.6)	
Patients with poor baseline EF (SHIM score 0–16)			
EF decreased/unchanged	56 (59.5)	14 (43.7)	

*EF, erectile function; EPE, extraprostatic extension; PSM, positive surgical margin; RALP, robot-assisted laparoscopic prostatectomy; SHIM, Sexual Health Inventory for Men. Values are mean ± SD, unless otherwise indicated. *P < 0.05.*

between patients who received different primary therapies. In the present study, we investigated these differences by analysing our contemporary salvage RALP series which represents one of the largest salvage prostatectomy series in the world.

This study included 94 patients (74.6%) with radiation and 32 (25.4%) with focal therapy as the primary treatment. We noted significant differences in clinical presentation and pathological characteristics between these two groups. For example, patients who underwent focal ablation had better erectile function before surgery. This was an expected finding as focal therapies aim to spare at least one NVB to preserve erectile function [19,5].

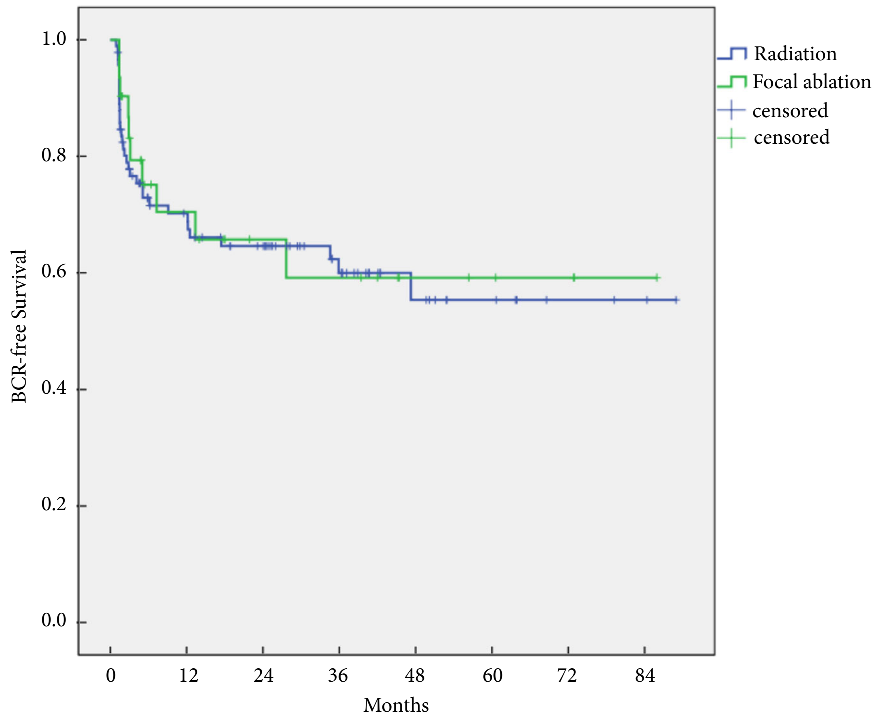
The time from first treatment to salvage RALP was significantly shorter in the focal ablation compared to the radiation group (mean 61 vs 82 months; $P = 0.039$), and it was further reduced in patients with EPE in the focal ablation group. Compared to the radiation group, the focal ablation group also had a higher incidence of extraprostatic disease (71% vs 50%; $P = 0.042$) and PSMs (43% vs 17%; $P = 0.004$). The reason for faster recurrence and higher rate of adverse pathological features after focal therapy is probably multifactorial. First, inadequate staging before primary ablation may have led to wrong patient selection for focal therapy, resulting in prostate cancer persistence or early recurrence with more aggressive disease. Multiparametric MRI is used to stage and identify patients for focal therapy [20]. Despite recent advances in technology, multiparametric MRI has negative and positive predictive values that range from 63% to 98% and 34% to 68% for detecting aggressive prostate tumours, respectively, and presents only moderate inter-reader reproducibility, currently limiting its use to experienced centres [20,21].

Second, prostate cancer persistence and/or recurrence after focal therapy is generally associated with more aggressive features compared to pre-first-line treatment [22]. In a recent series of 35 men treated with salvage RALP for post-HIFU recurrence, Thompson et al. [23] reported upstaging or upgrading features in 80% of their patients. Furthermore, prostate cancer recurrences were in the intended field of treatment in 94% of patients with significant bilateral disease in 80%. This may be attributable to incomplete tissue necrosis in the intention-to-treat field, theoretically resulting in the development of 'ablation-resistant' clones that repopulate the ablated field and metastasize locoregionally [23,24].

Third, patient selection bias for salvage prostatectomy after post-focal ablation recurrence may have resulted in a higher incidence of aggressive features in this cohort [25]. Most recurrences after focal therapy undergo other salvage ablative therapies and salvage RP is generally reserved for men with bilateral significant or high-risk disease, or in whom re-ablation is not technically feasible [23,26]. Thus, our focal ablation cohort may not be representative of all men experiencing recurrence after focal therapies. It is difficult to determine which factor(s) mentioned above played a major role in our outcomes since all our patients were referred from other centres and we did not have complete pre-treatment records.

The high post-focal ablation PSM rate (43.8%) in the present study may raise concerns about the safety of nerve-sparing in these patients. Other studies reported the feasibility of nerve-

Fig. 1 Biochemical recurrence (BCR)-free survival after salvage robot-assisted laparoscopic prostatectomy for the post-radiation and post-focal ablation groups (number of patients in the study groups at each time point is shown at the bottom of the figure).



Radiation	94	78	65	42	22	14	8	4
Focal ablation	32	23	16	14	7	6	4	1

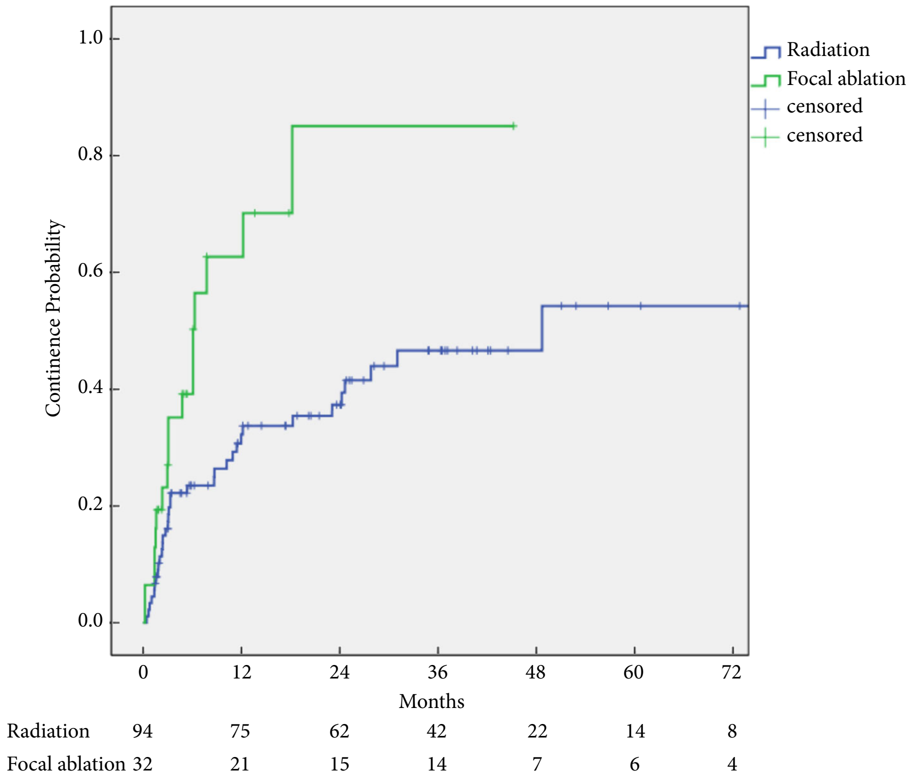
sparing during salvage RALP [17,25,27]. Nunes-Silva et al. [25] performed bilateral nerve-sparing in 54% and unilateral nerve-sparing in 36% of 22 men treated with salvage RALP after focal therapy and reported an overall PSM rate of only 4.5%. Marconi et al. [24] performed nerve-sparing in 76% of their 82 post-ablation salvage RALP patients and reported a 13% overall PSM rate. These lower PSM rates may be related to the lower incidence of EPE in these studies (between 27% and 50%) as compared to our study (71%). Extraprostatic disease was found to be the most important predictor of PSMs after robot-assisted RP [28] and it was present in almost all patients with PSMs in the present study. This underscores the importance of careful preoperative staging and suggests that patients demonstrating signs of extraprostatic disease may not be suitable for nerve-sparing during salvage RALP.

Despite the difference in EPE and PSM rates, estimated BCR-free survival was not significantly different between the focal ablation and radiation groups in the present study. This was in line with a study that compared minimally invasive salvage RP outcomes after whole-gland vs focal therapies over a median follow-up of 62 months [27]. The follow-up in the present study was similarly short, and our long-term results are awaited to better evaluate the BCR differences between the post-radiation and focal ablation groups. We found pathological Gleason score ≥8 to be predictive of BCR, which was consistent with our previous data [17].

In the present series, postoperative complication and 30-day readmission rates were not significantly different between the radiation and focal ablation groups. Postoperative complications occurred in 21% of our patients and the majority of these were low grade (Clavien grades I and II). The total complication rate in other contemporary salvage RALP series ranged between 6% and 47%, with a 0–35% major complication rate [24,25,27,29,30]. Our relatively low complication rate is probably related to the single-surgeon characteristic of our series and the great experience of our surgeon, who has performed >11 500 RALPs.

Interestingly, we found history of previous adjuvant or salvage ADT to be a potential predictor of postoperative complications in multivariable analysis (odds ratio 2.67; P = 0.055). Similarly, in a recent multicentre study of 395 patients who underwent salvage RP, Gontero et al. [29] found a 60% increased probability of experiencing at least one postoperative complication in patients with a history of ADT. They attributed this increased risk to local and systemic consequences of ADT, which may result in a poorer response to stress and more difficult surgical recovery. Nevertheless, it

Fig. 2 Cumulative probability of full continence (no pads/day) after salvage robot-assisted laparoscopic prostatectomy by study group (number of patients in the study groups at each time point is shown at the bottom of the figure).



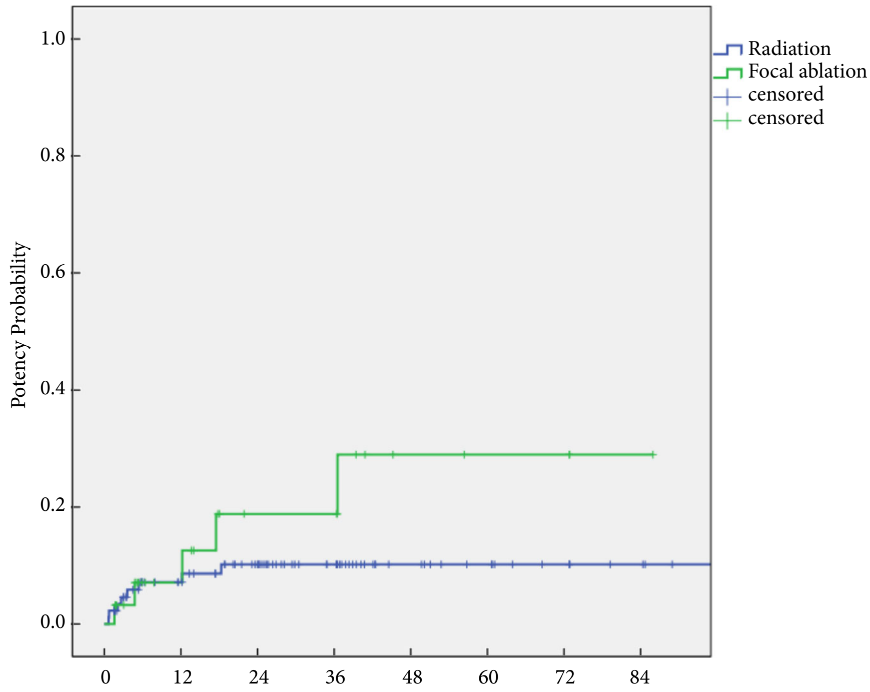
is difficult to fully explain the association between previous ADT and salvage prostatectomy outcomes, and this should be addressed by further studies.

In the present study, salvage RALP resulted in better functional outcomes after focal ablation than after radiation therapies. Postoperative full and social continence rates at 1 year were significantly higher in the focal ablation group. This may be related to the more extensive peri-urethral tissue damage after radiation, which is suggested by the higher postoperative cystographic leak rates and prolonged catheterization in the radiation group. In other studies, continence (0–1 pad/day) rates were reported as 39–64% for salvage RALP after radiation [29–31] and 52–84% after focal ablation failure [24,25,27], which is consistent with our results. In a recent report, primary ablation compared to radiation/brachytherapy showed a positive trend for post-salvage RP continence preservation with a near statistical significance ($P = 0.06$) [29]. This is in line with our multivariate analysis which confirmed primary focal ablation treatment as an independent predictor of continence after salvage RALP.

In patients with preoperative erectile function (SHIM score ≥17), potency was preserved in 13% in the radiation and 27% in the focal ablation group in the present study. Potency rates after salvage RALP ranged between 8% and 31.5% in other studies [24,25,27,29–31]; however, none of these studies analysed the impact of primary therapy on post-salvage RALP potency recovery. Although the focal ablation group showed a higher postoperative potency trend in the present study, the difference did not reach statistical significance, possibly because of the small number of potent patients in both groups.

The present study has several limitations. First, this is a retrospective study like other salvage RALP series; however, our institutional review board-approved and prospectively maintained database ensured the quality of peri-operative clinical and pathological data. Second, there is in-group heterogeneity in both study groups and it is difficult to examine the influence of other possible confounding factors on our outcomes. Third, our results come from a highly experienced single surgeon; thus, these outcomes may not be generalizable to other centres with less experience. Fourth, our follow-up is not long enough to draw final conclusions regarding oncological survival differences between radiation and focal ablation failures. Fifth, we did not have complete pre-first-line treatment records; therefore, the reasons for higher incidence of adverse pathological findings at salvage RALP after focal therapy recurrence could not be elucidated. Despite these limitations, this study adds to the current

Fig. 3 Cumulative probability of potency after salvage robot-assisted laparoscopic prostatectomy by study group (number of patients in the study groups at each time point is shown at the bottom of the figure).



	0	12	24	36	48	60	72	84
Radiation	94	72	62	40	22	14	8	4
Focal ablation	32	20	15	14	7	6	4	1

literature by systematically analysing the differences in outcomes between post-radiation and post-ablation salvage RALP.

In conclusion, all salvage RALPs are not the same. Patients who had focal therapy as primary treatment had better erectile function before surgery than patients who had radiation. Nerve-sparing can be performed in both settings depending on technical feasibility and is a predictor for postoperative continence recovery. However, patients with signs of extracapsular disease may not be suitable for nerve-sparing as there is an increased risk of PSMs in this group. Salvage RALP was associated with inferior functional outcomes after radiation and higher adverse pathology rates after focal ablation, with similar short-term BCR-free survival.

Conflicts of interest

None declared.

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Abbreviations: RALP, robot-assisted laparoscopic prostatectomy; PSM, positive surgical margin; BCR, biochemical recurrence; EBRT, external beam radiation therapy; HIFU, high-intensity focused ultrasonography; RP, radical prostatectomy; SHIM, Sexual Health Inventory for Men; NVB, neurovascular bundle; ADT, androgen deprivation therapy; EPE, extraprostatic extension.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Peri-operative characteristics in each subgroup of post-radiation (RAD) and post-focal ablation (fABL) groups (EBRT, external beam radiation therapy; HIFU, high-intensity focused ultrasonography; MW, microwave; NS, nerve-sparing).

Table S2. Pathological and oncological outcomes in each subgroup of the post-radiation (RAD) and the post-focal ablation (fABL) groups (EBRT, external beam radiation therapy; HIFU, high-intensity focused ultrasonography; MW, microwave).