Comparative effectiveness analyses of salvage prostatectomy and salvage radiotherapy outcomes following focal or whole-gland ablative therapy (High Intensity Focused Ultrasound (HIFU), cryotherapy or electroporation) for localised prostate cancer

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Abstract

Background

Ablative therapy, such as focal therapy, cryotherapy or electroporation, aims to treat clinically significant prostate cancer with reduced treatment-related toxicity. Up to a third of patients may require further local salvage treatment after ablative therapy failure. Limited descriptive, but no comparative, evidence exists between different salvage treatments. We compare oncological and functional outcomes after salvage robot-assisted radical prostatectomy (SRARP) and salvage radiotherapy (SRT).

Methods

Data were collected prospectively and retrospectively on 100 consecutive SRARP cases and 100 consecutive SRT cases, after ablative therapy failure, in a high-volume tertiary centre.

Results

High-risk patients were over-represented in the SRARP group (66.0%) compared to the SRT group (48.0%) (p=0.013). Median (IQR) follow-up after SRARP was 16.5 (10.0-30.0) months and 37.0 (18.5-64.0) months after SRT.

SRT appeared to confer greater biochemical recurrence (BCR)-free survival at one, two and three years compared to SRARP in high-risk patients (year 3: 86.3% vs 66.0%), but BCR-free survival was similar for intermediate-risk patients (year 3: 90.0% vs 75.6%).

There was no statistical difference in pad-free continence at 12- and 24-months between SRARP (77.2% and 84.7%) and SRT (75.0% and 74.0%) (p=0.724,0.114). Erectile function was more likely to be preserved in men who underwent SRT. After SRT, cumulative bowel and urinary Radiation Therapy Oncology Group toxicity grade I were 25.0% and 45.0%, grade II were 11.0% and 11.0%, and grade III or IV complications were 4.0% and 5.0%, respectively.

Conclusion

We report the first comparative analyses of salvage prostatectomy and radiotherapy following ablative therapy. Men with high-risk disease appear to have superior oncological outcomes after SRT; however, treatment allocation does not appear to influence oncological outcomes for men with intermediate-risk disease. Treatment allocation was associated with a different spectrum of toxicity profile. Our data may inform shared decision-making when considering salvage treatment following focal or whole-gland ablative therapy.

Keywords:

ablation, focal therapy, prostate cancer, prostatectomy, radiotherapy, salvage

Introduction

Tissue preserving approaches to prostate cancer (PCa), such as High Intensity Focused Ultrasound (HIFU), cryotherapy or electroporation, aim to mitigate the adverse effects of over-treatment. Previous literature has reported medium-term clinically significant biochemical recurrence (BCR) rates up to 43% after focal therapy with up to 33% of patients requiring further additional local treatment[1, 2]. A large, prospective, multi-centre study showed failure rates of 18% after focal therapy in high-risk patients at five-year follow-up[3].

Currently, there is an unmet need to determine optimal management of local recurrence after ablative therapy of the prostate. However, data for radical salvage treatment options such as prostatectomy and radiotherapy are emerging. Recent studies undertaken in the United Kingdom showed acceptable oncological and functional outcomes following salvage robot-assisted radical prostatectomy (SRARP)[4, 5]. However, matched comparative studies have shown that oncological and erectile function outcomes after SRARP are inferior compared to primary RARP[6, 7]. Salvage radiotherapy (SRT) has shown satisfactory medium-term oncological control with an acceptable side-effect profile albeit from a single-centre case series[8].

However, it remains very challenging for patients and clinicians to make an informed decision between pursuing different salvage treatments after ablative therapy failure as there are no published data comparing outcomes between SRARP and SRT.

We therefore conducted a comparative analysis of men undergoing either SRARP or SRT in our institution to describe oncological and functional outcomes for these patients.

Patients and Methods

Patient population

We identified 100 consecutive men who underwent SRARP and another 100 consecutive men who underwent SRT for locally recurrent prostate cancer after ablative therapy failure from September 2010-2020. All patients received treatment at a high-volume tertiary referral centre with a minimum of six months follow-up. Ablative therapies included HIFU, cryotherapy and electroporation. HIFU included focal and whole-gland ablation, however whole-gland ablation is no longer carried out in our centre. No recognised criteria were available to define primary ablative therapy failure. Instead, a combination of biochemical, histological and image-based parameters as well as referral for further radical salvage treatment was used to identify the study cohort[9]. All men had appropriate staging investigations, including MRI, CT-scan, bone scan, Choline/PSMA PET scans and prostate biopsy for risk stratification and treatment planning before salvage treatment. All men were considered and counselled for both salvage options and the final decision was made based on the multi-disciplinary team recommendation and patient choice. In our centre, salvage radiotherapy was the common historical salvage treatment modality of choice, due to the poor outcomes associated with open prostatectomy. The recent development and use of robot-assistance has made prostatectomy a more feasible procedure. Therefore, longer follow-up is available for the SRT cohort compared to the SRARP cohort. SRARP was carried out by experienced surgeons who had performed at least 500 primary RARP cases. SRT was delivered using the Intensity modulated radiation therapy technique from 2012 onwards with 3D conformal radiotherapy being used previously. Patients were treated with a radical dose

to the prostate, seminal vesicles and pelvic lymph nodes depending on lymph node involvement on staging and risk score.

Data collection

Data were analysed from prospectively and retrospectively populated databases using local cancer registry databases, electronic medical records and patient reported questionnaires. Demographic data, pre-primary and post-primary oncological data, salvage treatment data and post-salvage treatment oncological and functional data were collected. The National Comprehensive Cancer Network (NCCN) risk stratification was amended to combine very low and low risk to 'low risk', favourable and unfavourable intermediate risk to 'intermediate risk' and high and very high risk to 'high risk' [10]. This was to allow for better powered comparisons between risk groups during data analyses. Salvage treatment data included 30-day post-operative complication rates as defined by Clavien-Dindo grade for surgery. For SRT, medium to late cumulative follow-up Radiation Therapy Oncology Group (RTOG) urinary and bowel toxicity scores were used[11, 12]. Cumulative medium to late toxicity was measured from three months after the end of radiotherapy treatment to the end of follow-up.

Post-salvage treatment oncological data collected included time to BCR, further secondary salvage treatment initiated including the use of salvage hormone therapy, cancer-specific and overall mortality. BCR was defined as PSA greater than 0.2ng/ml after SRARP and PSA nadir plus 2ng/ml after SRT as per current practice and the ASTRO-Phoenix guidelines[13, 14]. Time to BCR was defined from the operation date for SRARP and from the date concomitant hormone therapy was completed for SRT[15].

Functional outcomes were measured using patient reported outcome questionnaire data. Urinary continence was defined as pad-free continence as per question 5 of The Expanded Prostate Cancer Index Composite-26 (EPIC-26) urinary assessment[16]. Erectile function was defined as erections sufficient for penetration 50% or more of the time with or without phosphodiesterase inhibitors as per question 2 of the International Index of Erectile Function (IIEF) score[17]. Functional outcomes were collected at three-, six-, 12- and 24-months after salvage treatment. Quality of life was measured at last follow-up using the EQ-5D measure of health status: the best possible score achievable was five out of 25 and the worst possible score was 25 out of 25[18].

Statistical analysis

All patients identified had a minimum data set to qualify for analysis. Valid percentages were used to mitigate for missing data within patient records. Non-parametric comparative tests were used to compare outcomes between SRARP and SRT. Kaplan-Meier curves were plotted to assess time to BCR, and cumulative incidence curves were plotted for urinary continence and erectile function.

Results

Patient demographics and ablative therapy

The median (IQR) age was 69.0 (64.0-72.0) years in the SRARP group and 71.0 (66.0-75.0) years in the SRT group (p=0.003). According to the NCCN risk stratification, 25.0% of patients in the SRARP group had high-risk cancer at the time of initial treatment with ablative therapy compared to 10.4% in the SRT group (=0.001). 92.0% and 94.0% in the SRARP and SRT cohort had HIFU as their primary ablative therapy, of which 84.0% and 74.0% had unilateral treatment only. The median (IQR) time to failure after ablative therapy was 32.0 (16.0-57.0) months in the SRARP group and 49.0 (27.0-81.0) months in the SRT group (p=0.002). Complete demographic and ablative therapy data are presented in Table 1.

Salvage therapy

Post-ablative therapy failure NCCN risk stratification was 34.0% intermediate risk and 66.0% high-risk in the SRARP group and 51.0% intermediate risk and 48.0% high-risk in the SRT group (p=0.013).

The perioperative transfusion rate for SRARP was 0.0% and the median (IQR) length of stay was one (1-2) day. One patient (1.0%) had a grade III or greater Clavien-Dindo complication, a post-operative haematoma that required a washout under general anaesthetic.

All patients received concomitant hormone therapy in combination with radiotherapy. The median (IQR) duration of hormone therapy was 3.0 (2.0-10.0) months in the intermediate-risk patients and 17.0 (4.0-24.0) months in the high-risk patients. Most (97.0%) SRT patients received a radical dose of 74-78Gy in 2Gy per fraction to the prostate and seminal vesicles whilst three patients received a lower dose due to previous bowel disease or due to historical

practice when toxicity outcomes for SRT were not known. 55Gy was used to treat the pelvic lymph nodes, if indicated.

Cumulative bowel RTOG grade I was 25.0%, grade II was 11.0%, grade III was 3.0% and there was one grade IV complication, a rectourethral fistula requiring surgical repair. Cumulative urinary RTOG grade I was 45.0%, grade II was 11.0%, grade III was 5.0% and there were no grade IV complications. Complete salvage treatment data are presented in Table 2.

Oncological outcomes

Overall positive surgical margin (PSM) rates were 38.0% after SRARP. 28.0% had significant margins, defined as multifocal or greater than 3mm in pT2 disease or any positive margin in the presence of pT3 disease [19]. 23.0% and 15.0% had BCR after SRARP and SRT, respectively (p=0.260). Overall, cumulative BCR-free survival was greater after SRT compared to SRARP (Figure 1). For intermediate-risk patients, cumulative BCR-free survival at one-, two- and three-years was 88.0%, 88.0% and 76.0% after SRARP, respectively and 100.0%, 94.0% and 91.0% after SRT, respectively (Figure 2). For high-risk, cumulative BCR-free survival at one-, two- and three-years was 80.0%, 72.0% and 69.0% after SRARP, respectively and 99.0%, 92.0% and 89.0% after SRT, respectively (Figure 3). Median (IQR) follow-up after salvage treatment was 16.5 (10.0-30.0) months after SRARP and 37.0 (19.0-64.0) months after SRT (p<0.001). After SRARP, 13.0% had further hormone therapy and 10.0% had further secondary salvage radiotherapy (SSRT) and hormone therapy due to BCR, nodal or metastatic recurrence. After SRT, 13.0% had further hormone therapy, 1.0% had secondary salvage robot assisted radical prostatectomy (SSRARP) and 1.0% had observation only due to BCR. Cancer specific mortality was 0% (n=0) after SRARP and 4% (n=4) after SRT (p=0.121). Overall

mortality was 1% (n=1) after SRARP and 6% (n=6) after SRT (p=0.118). Complete oncological outcome data are presented in Table 3.

Functional outcomes

Pad-free, continence was 28.0%, 64.0%, 77.2% and 84.7% at three-, six-, 12-, and 24-months in the SRARP group, respectively and 72.0%, 72.0%, 75.0% and 74.0% in the SRT group, respectively (p=<0.001, 0.225, 0.724, 0.114, respectively) (Figure 4). Erectile function was 0.0%, 8.0%, 13.8% and 21.2% at three-, six-, 12-, and 24-months in the SRARP group, respectively and 63.0%, 66.0%, 70.0% and 73.0% in the SRT group, respectively (all p=<0.001) (Figure 4). Median EQ5D quality of life scores were greater after SRARP than SRT, but these were not statistically significant differences. Full functional outcome data are presented in Table 4.

Discussion

Summary

SRARP and SRT are both feasible treatment options with acceptable oncological control and functional outcomes. Cumulative BCR-free survival was greater after SRT compared to SRARP at early- to medium-term follow-up in high-risk patients but similar in intermediate-risk patients. Urinary continence rates after six-months were similar for both salvage strategies though erectile function was superior after SRT. SRT results in high rates of medium to late low-grade (I-II) radiation-related bowel and urinary toxicity, but there is minimal high-grade (III-IV) toxicity.

Implications

Perioperative parameters such as the complication rate, transfusion rate and length of stay are comparable to primary RARP[20] and suggest that SRARP after ablative therapy is a feasible procedure in high-volume centres with experienced surgeons[20, 21]. Our rates of toxicity after SRT were higher than the late toxicity rates for primary radiotherapy treatment of 2-4%, reported in the literature[22]. Due to the retrospective nature of our study, we do not know the baseline toxicity or functional status of men before commencing salvage treatment, having already undergone at least one ablative treatment and further biopsies. It is therefore difficult to conclude the relative toxicity of SRT in this setting and the extent to which these patients developed new-onset toxicity after salvage treatment.

Overall BCR was not statistically significant between SRARP and SRT. However, early- to medium-term cumulative BCR-free survival was significantly greater after SRT. This may be

due to the significantly greater number of high-risk cancer patients in the SRARP group compared to the SRT group. Additionally, SRT patients received concomitant hormone therapy, which may have a prolonged effect on biochemical suppression, even after hormone therapy has been completed, due to potential ongoing testosterone suppression[23]. When accounting for pre-salvage treatment cancer risk, cumulative BCR-free survival is similar in intermediate-risk patients but worse in high-risk patients for SRARP compared to SRT. This may be due to the median duration of concomitant hormone therapy with SRT being longer in high-risk patients resulting in a longer 'lag-time' before BCR can occur.

In the previous large study of SRT after HIFU by Riviere et al in 2010, the BCR rates were 33.0% and 45.0% in intermediate- and high-risk cancer, at five-year follow-up. However only 17.0% of patients received concomitant hormone therapy[8]. In our study, the BCR was considerably lower at 15.0%, at a similar follow-up interval. This may be due to multiple factors including greater adjuvant hormone use with SRT in our cohort with all patients receiving hormones with duration determined as per their clinical risk. BCR rates for SRARP have been shown to be greater compared to primary RARP owing to either a more aggressive cancer genotype or the primary treatment increasing the rate of positive surgical margins due to technical challenges[7].

Secondary salvage hormone therapy, defined as hormone therapy initiated after recurrence following salvage treatment, was used in patients from both cohorts who had biochemical, nodal, or metastatic recurrence after salvage therapy. 10.0% of the SRARP cohort had further SRT after BCR. At last follow-up they had a cumulative RTOG grade II or greater bowel and urinary toxicity rate of 20.0% and 20.0%, respectively. Therefore, SSRT may be a viable further

treatment option available for SRARP patients, allowing them a further step in their treatment pathway, but a future analysis with a greater sample size will be required to confirm this. Cancer-specific mortality and overall mortality were similar in both groups; however, follow-up was longer, and more patients had associated co-morbidities in the SRT group.

Pad-free urinary continence rates were comparable between both groups from six-month follow-up onwards. Social continence, defined as the use of one-pad or less per day, was statistically significantly greater at all follow-up intervals after SRT compared to SRARP. This may be due to the urinary toxicity experienced by men undergoing SRT which may necessitate the use of a single, safety-pad. Patients should be aware that erectile function was significantly worse after SRARP compared to SRT possibly due to technical difficulty in nerve sparing during surgery. SRARP has been shown to have inferior erectile function outcomes compared to primary RARP from a wide range of studies[6]. Our SRT data shows a considerable improvement in erectile function rates of 73.0% at two-years compared to historical literature which has described erectile function rates as low as 17.7%[8].

Limitations

Our study included retrospectively collected data and is thus subject to the inherent biases of such analyses. Medium-term follow-up in our study precludes us from assessment of long-term functional and oncological outcomes. There were more high-risk patients treated in the SRARP group compared to the SRT group and a larger sample size would allow for multivariable analysis or matching of covariates between groups. Nonetheless, in our study, age and co-morbidity parameters were clinically similar between groups. Lack of baseline functional scores at the time of initiating salvage treatment and lack of longitudinal follow-up

time-points for toxicity are a weakness of our analyses. Further prospective, large cohort, multi-centre work is required to better compare these salvage treatments. Notwithstanding these limitations, our study represents a unique analysis of comparative effectiveness of oncological and functional outcomes between salvage surgery and salvage radiotherapy after primary ablative therapy in a high volume PCa treatment centre.

Conclusions

We report the first comparative study of salvage treatment options for men with recurrent prostate cancer after ablative therapy. We demonstrate that oncological and functional outcomes of SRARP and SRT are acceptable, though appear inferior compared to primary radical outcomes. SRT may provide better medium-term oncological control in high-risk disease but requires concomitant hormone therapy and carries more treatment-related bowel and urinary toxicity. SRARP can provide similar urinary continence, but erectile function is inferior to SRT. We recommend that patients and clinicians should consider these comparative outcomes before selecting their choice of salvage treatment and they should be used to better counsel and consider patients selected for primary ablative therapy.

Tables and Figures

Table 1. Demographics and pre-salvage therapy

	SRARP	SRT	P-value
n	100	100	
Median age, years (IQR)	69 (64-72)	71 (66-75)	.003
CCI Score, n (%)			.085
0	77 (77.0)	66 (66.0)	
1	18 (18.0)	20 (20.0)	
2	5 (5.0)	10 (10.0)	
>=3	0 (0.0)	4 (4.0)	
Pre-Ablative therapy			
Median PSA, ng/ml (IQR)	5.8 (3.5-10.1)	6.5 (4.7-10.1)	.040
Gleason Grade Group, n (%)			
1	7 (7.1)	20 (21.1)	<.001
2	51 (51.5)	58 (61.1)	
3	31 (31.3)	16 (16.8)	
4	9 (9.1)	1 (1.1)	
5	1 (1.0)	0 (0.0)	
T-stage, n (%)			
1	3 (3.0)	3 (3.2)	.113
2	80 (80.0)	83 (88.3)	
3	17 (17.0)	8 (8.5)	
NCCN, n (%)			
Low (Very low or low)	5 (5.0)	14 (14.6)	.001
Intermediate (unfavourable or favourable)	70 (70.0)	72 (75.0)	
High (high or very high)	25 (25.0)	10 (10.4)	
Ablative therapy			
HIFU, n (%)	92 (92.0)	94 (94.0)	.847
Cryotherapy, n (%)	5 (5.0)	4 (4.0)	
Electroporation, n (%)	3 (3.0)	2 (2.0)	
Number of treatments			
= 1	58 (58.0)	53 (54.1)	.330
= 2	42 (42.0)	45 (45.9)	
Unilateral, n (%)	84 (84.0)	74 (74.0)	
= 1	50 (59.5)	43 (59.7)	
= 2	34 (40.5)	29 (40.3)	
Bilateral, n (%)	16 (16.0)	26 (26.0)	
= 1	8 (50.0)	10 (38.5)	
= 2	8 (50.0)	16 (61.5)	
Median time to failure, months (IQR)	32 (16-57)	49 (27-81)	.002
Pre-Salvage therapy			
Median PSA, ng/ml (IQR)	5.8 (3.5-10.5)	4.6 (2.2-7.3)	.051
Gleason Grade Group, n (%)			
1	6 (6.0)	1 (1.0)	.845
2	49 (49.0)	56 (56.0)	

3	26 (26.0)	20 (20.0)	
4	10 (10.0)	11 (11.0)	
5	9 (9.0)	10 (10.0)	
T-stage, n (%)			
1	2 (2.0)	0 (0.0)	.987
2	61 (61.0)	63 (64.9)	
3	37 (37.0)	32 (33.0)	
4	0 (0.0)	2 (2.1)	
N-stage, n (%)			
0	98 (98.0)	86 (86.0)	
1	2 (2.0)	14 (14.0)	
M-stage, n (%)			
0	100 (100.0)	96 (96.0)	
1	0 (0.0)	4 (4.0)	
NCCN, n (%)			
Low (Very low or low)	0 (0.0)	1 (1.0)	.013
Intermediate (unfavourable or favourable)	34 (34.0)	51 (51.0)	
High (high or very high)	66 (66.0)	48 (48.0)	

SRARP = Salvage Robot-assisted Radical Prostatectomy, SRT = Salvage radiotherapy, n = numbers, CCI = Charlson co-morbidity index

Table 2. Salvage treatment

	SRARP	SRT	P-value
Modality related treatment			
SRARP-related			
Median Operation time, mins (IQR)	170 (135-180)		
Median EBL, mls (IQR)	200 (100-300)		
Nerve sparing n (%)			
- *Unilateral*	32 (32.0)		
- *Bilateral*	4 (4.0)		
Transfusion	0 (0.0)		
Median Length of stay, days (IQR)	1 (1-2)		
SRT-related			
Site			
Hormone therapy completed		90 (90.0)	
Median hormone therapy duration, months (IQR)		19 (4-24.3)	
- *Intermediate*		3 (2-10)	
- *High*		17 (4-24)	
Dose, n (%)			
74-78Gy / 37-39 #		97 (97.0)	
60-64Gy / 32 #		3 (3.0)	
Complications and toxicity			
Clavien-Dindo grade, n (%)			
I	6 (6.0)		
II	2 (2.0)		
III	1 (1.0)		
IV	0 (0.0)		
V	0 (0.0)		
Cumulative bowel RTOG, n (%)		25 (25.0)	
I		11 (11.0)	
II		3 (3.0)	
III		1 (1.0)	
IV			
Cumulative urinary RTOG, n (%)			
I		45 (45.0)	
II		11 (11.0)	
III		5 (5.0)	
IV		0 (0.0)	

SRARP = Salvage Robot-assisted Radical Prostatectomy, SRT = Salvage radiotherapy, n = numbers, EBL = estimated blood loss, RTOG = radiation therapy oncology group score

Table 3. Salvage treatment oncological outcomes

	SRARP	SRT	P-value
Histology			
PSM, n (%)			
<3mm or focal	25 (25.0)		
- T1-T2 (non-significant)	10 (10.0)		
- T3 (significant)	15 (15.0)		
>3mm or multifocal	13 (13.0)		
Gleason Grade Group, n (%)			
1	1 (1.0)		
2	50 (50.0)		
3	37 (37.0)		
4	3 (3.0)		
5	9 (9.0)		
T-Stage n (%)			
1	0 (0.0)		
2	49 (49.0)		
3a	35 (35.0)		
3b	16 (16.0)		
Recurrence			
Median follow-up, months (IQR)	16.5 (10-30)	37 (18.5-64)	<.001
Post-salvage recurrence, n (%)	23 (23.0)	15 (15.0)	.260
- Intermediate	4 (11.8)	7 (14.3)	.685
- High	19 (28.8)	8 (17.4)	.205
Biochemical recurrence only, n (%)	17 (17.0)	12 (12.0)	.142
- Intermediate	3 (8.8)	7 (13.7)	.835
- High	14 (21.2)	5 (10.4)	.156
Nodal recurrence, n (%)	5 (5.0)	0 (0.0)	<.001
- Intermediate	1 (2.9)	0 (0.0)	
- High	4 (7.6)	0 (0.0)	
Metastatic recurrence, n (%)	1 (1.0)	3 (3.0)	<.001
- Intermediate	0 (0.0)	0 (0.0)	
- High	1 (1.5)	3 (6.3)	
Cumulative recurrence-free survival, % (SE)			
Overall			<.001
Year 1	.802 (.044)	.988 (.012)	
Year 2	.721 (.055)	.923 (.030)	
Year 3	.690 (.061)	.889 (.038)	
Intermediate			.322
Year 1	.882 (.065)	1.00 (1.00)	
Year 2	.882 (.065)	.944 (.039)	

Year 3	.756 (.129)	.909 (.051)	
High			.004
Year 1	.770 (.055)	.974 (.025)	
Year 2	.660 (.069)	.897 (.049)	
Year 3	.660 (.069)	.863 (.058)	
Further treatment			
Salvage hormone therapy only	13 (13.0)	13 (11.0)	.272
- *Intermediate*	2 (5.9)	7 (13.7)	.123
- *High*	11 (16.7)	6 (12.5)	.313
SRARP	-	1 (1.0)	
- *Intermediate*	-	0 (0.0)	
- *High*	-	1 (2.1)	
SRT and salvage hormone therapy	10 (10.0)	-	
- *Intermediate*	1 (3.0)	-	
- *High*	9 (13.6)	-	
Mortality			
Cancer specific mortality	0 (0.0)	4 (4.0)	.121
Overall mortality	1 (1.0)	6 (6.0)	.118

SRARP = Salvage Robot-assisted Radical Prostatectomy, SRT = Salvage radiotherapy, n = numbers, PSM = positive surgical margins

Table 4. Salvage treatment functional outcomes

	SRARP	SRT	P-value
Median follow-up, months (IQR)	16.5 (10-30)	37 (18.5-64)	<.001
Urinary Continence			
Pad-free continence			
3-months (n=100, 100)	28 (28.0)	72 (72.0)	<.001
6-months (n=100, 100)	64 (64.0)	72 (72.0)	.225
12-months (n=92, 100)	71 (77.2)	75 (75.0)	.724
24-months (n=59, 100)	50 (84.7)	74 (74.0)	.114
1-pad / day			
3-months (n=100, 100)	49 (49.0)	91 (91.0)	<.001
6-months (n=100, 100)	83 (83.0)	92 (92.0)	.054
12-months (n=92, 100)	83 (90.2)	93 (93.0)	.486
24-months (n=59, 100)	53 (89.8)	93 (93.0)	.481
Erectile Function			
3-months (n=100, 100)	0 (0.0)	63 (63.0)	<.001
6-months (n=100, 100)	8 (8.0)	66 (66.0)	<.001
12-months (n=65, 100)	9 (13.8)	70 (70.0)	<.001
24-months (n=33, 100)	7 (21.2)	73 (73.0)	<.001
EQ5D Quality of Life*			
Median score, (out of 25) (IQR)	7 (6-9)	9 (6-12)	0.278

SRARP = Salvage Robot-assisted Radical Prostatectomy, SRT = Salvage radiotherapy, n = numbers

*EQ5D scores were measure at median follow-up 22 (17-25) months for SRARP and 44 (28-52) for SRT

References

[1] Valerio M, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol. 2014;66:732-51.10.1016/j.eururo.2013.05.048

[2] Oishi M, Gill IS, Tafuri A, Shakir A, Cacciamani GE, Iwata T, et al. Hemigland Cryoablation of Localized Low, Intermediate and High Risk Prostate Cancer: Oncologic and Functional Outcomes at 5 Years. J Urol. 2019;202:1188-98.10.1097/ju.0000000000000456

[3] Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol. 2018;74:422-9.10.1016/j.eururo.2018.06.006

[4] De Groote R, Nathan A, De Bleser E, Pavan N, Sridhar A, Kelly J, et al. Techniques and Outcomes of Salvage Robot-Assisted Radical Prostatectomy (sRARP). Eur Urol. 2020;78:885-92.10.1016/j.eururo.2020.05.003

[5] Cathcart P, Ribeiro L, Moore C, Ahmed HU, Leslie T, Arya M, et al. Outcomes of the RAFT trial: robotic surgery after focal therapy. BJU Int. 2021.10.1111/bju.15432

[6] Bates AS, Samavedi S, Kumar A, Mouraviev V, Rocco B, Coelho R, et al. Salvage robot assisted radical prostatectomy: A propensity matched study of perioperative, oncological and functional outcomes. Eur J Surg Oncol. 2015;41:1540-6.10.1016/j.ejso.2015.06.002

[7] Nathan A, Fricker M, De Groote R, Arora A, Phuah Y, Flora K, et al. Salvage Versus Primary Robot-assisted Radical Prostatectomy: A Propensity-matched Comparative Effectiveness Study from a High-volume Tertiary Centre. Eur Urol Open Sci. 2021;27:43-52.10.1016/j.euros.2021.03.003

[8] Riviere J, Bernhard JC, Robert G, Wallerand H, Deti E, Maurice-Tison S, et al. Salvage radiotherapy after high-intensity focussed ultrasound for recurrent localised prostate cancer. Eur Urol. 2010;58:567-73.10.1016/j.eururo.2010.06.003

[9] Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clin Oncol (R Coll Radiol). 2013;25:461-73.10.1016/j.clon.2013.05.002

[10] Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17:479-505.10.6004/jnccn.2019.0023

[11] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187-96.10.1097/SLA.0b013e3181b13ca2

[12] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341-6.10.1016/0360-3016(95)00060-c

[13] Roach M, 3rd, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006;65:965-74.10.1016/j.ijrobp.2006.04.029

[14] Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ, Lilja H, et al. Defining Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy: A Proposal for a Standardized Definition. Journal of Clinical Oncology. 2006;24:3973-8.10.1200/JCO.2005.04.0756

[15] Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011;378:2104-11.10.1016/s0140-6736(11)61095-7
[16] Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56:899-905.10.1016/s0090-4295(00)00858-x
[17] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49:822-30.10.1016/s0090-4295(97)00238-0
[18] Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33:337-43.10.3109/07853890109002087
[19] Sooriakumaran P, Ploumidis A, Nyberg T, Olsson M, Akre O, Haendler L, et al. The impact of length and location of positive margins in predicting biochemical recurrence after robot-assisted radical prostatectomy with a minimum follow-up of 5 years. BJU Int. 2015;115:106-13.10.1111/bju.12483
[20] Marconi L, Stonier T, Tourinho-Barbosa R, Moore C, Ahmed HU, Cathelineau X, et al. Robot-assisted Radical Prostatectomy After Focal Therapy: Oncological, Functional Outcomes and Predictors of Recurrence. Eur Urol. 2019;76:27-30.10.1016/j.eururo.2019.03.007
[21] Tewari A, Sooriakumaran P, Bloch DA, Seshadri-Kreaden U, Hebert AE, Wiklund P. Positive Surgical Margin and Perioperative Complication Rates of Primary Surgical Treatments for Prostate Cancer: A Systematic Review and Meta-Analysis Comparing Retropubic, Laparoscopic, and Robotic Prostatectomy. Eur Urol. 2012;62:1-15.10.1016/j.eururo.2012.02.029
[22] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016;17:1047-60.10.1016/s1470-2045(16)30102-4
[23] Sasaki T, Sugimura Y. The Importance of Time to Prostate-Specific Antigen (PSA) Nadir after Primary Androgen Deprivation Therapy in Hormone-Naïve Prostate Cancer Patients. J Clin Med. 2018;7.10.3390/jcm7120565