Brief Correspondence

ROBOTIC ASSISTED RADICAL PROSTATECTOMY AFTER FOCAL THERAPY:ONCOLOGICAL, FUNCTIONAL OUTCOMES AND PREDICTORS OF RECURRENCE

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Abstract word Count:
Full Text Word Count:1035

Number of Tables:1
Number of Figures:1

Number of Supplementary Tables: 2
Number of SupplementaryFigures: 1

Abstract

There are few data on the outcomes and toxicity of radical prostatectomy (RP) among men experiencing local recurrence of prostate cancer (PC) following focal therapy (FT). To characterise perioperative, oncological, and functional outcomes after salvage robot- assisted RP (S-RALP) and determine the risk factors for S-RALP failure, we conducted a multicentre cohort study of 82 patients undergoing S-RALP after FT. All had histological confirmation of PC recurrence, with metastatic disease excluded using pelvic magnetic resonance imaging, a bone scan, and/or positron emission tomography/computed tomography. Progression-free survival was 74%, 48%, and 36% at 12, 24, and 36 mo after surgery, respectively. The 12-mo continence rate was 83%. There were no intraoperative complications and no major postoperative complications. On multivariable analysis, only infield recurrence (hazard ratio [HR] 3.77, 95% confidence interval [CI] 1.11–12.85; p = 0.03) and pT3b stage (HR 5.0, 95% CI 1.53–16.39; p = 0.008) were independent predictors of recurrence. This study represents the largest series of salvage surgery after FT and shows that this approach is safe with no increase in toxicity when compared to primary RALP. Men identified as having infield recurrence after FT appear to have phenotypically aggressive disease and should be counselled regarding the potential need for a multimodal therapeutic approach.

Patient summary:
Robotic surgery after focal therapy for prostate cancer is safe and
achieves postoperative continence results similar to those for robotic radical prostatectomy in treatment-naïve patients. However, if the cancer recurrence is within the previously treated field, the oncological prognosis seems to be worse.

Following focal therapy (FT) for prostate cancer (PC), a proportion of men will develop recurrent disease [1,2]. There is currently no consensus on optimal management for these patients. One option is surgery in the form of radical prostatectomy (RP). However, there are limited data on the outcomes and toxicity of RP after FT [3,4]. Before widespread adoption of FT, it is imperative to characterize radical prostatectomy (RP). However, there are limited data on the outcomes and toxicity of RP after FT [3,4]. Before widespread adoption of FT, it is imperative to characterize the toxicity of secondary treatments after FT to counsel patients, inform clinicians, and underpin guideline recommendations [5]. In the current study we characterised perioperative, oncological, and functional outcomes in the largest international multicentre salvage robot-assisted RP (S-RALP) series among men experiencing PC recurrence after FT.

Patients with localised PC who had received at least one FT (defined as ablation of the index or dominant PC lesion [6]) with subsequent local recurrence were eligible for the study. We included in the analysis consecutive patients with histological confirmation of residual or recurrent PC after FT who then underwent S-RALP. Patients who previously received androgen deprivation therapy or radiotherapy were excluded.

S-RALPs were performed by two surgeons (P.C. and R.S.- S.) across three institutions using a standardised technique. Before surgery, metastatic disease was excluded in all patients using pelvic magnetic resonance imaging, bone scans, and/or positron emission tomography/computed tomography. All patients had life expectancy of at least 10 yr.

The primary outcome was progression-free survival (PFS), which was defined as no biochemical relapse (prostate-specific antigen [PSA] <0.2 ng/ml) and no need for additional treatment. Survival time was calculated from the time of S-RALP to biochemical relapse or the last available follow-up. Urinary continence was strictly defined according to self-reported lack of need for continence pads (0 pad usage). Patients were considered potent when they self-reported erections hard enough for penetration with or without the use of a phosphodiesterase type 5 inhibitor.

Surgical complications within 30 d of surgery are reported using the Clavien-Dindo classification [7]. RP specimens were assessed to identify whether the recurrence was infield (within the previous FT area of ablation) or out of field (exclusively outside the previous FT area of ablation). A multivariable Cox regression model was constructed to determine the impact of risk factors on biochemical recurrence after S-RALP.

Between September 2010 and June 2018, 82 patients underwent S-RALP. Supplementary Table 1 lists patient and tumour characteristics for the study cohort. The mean age at surgery was 65 yr (interquartile range [IQR] 61–69). Before S-RALP, 6.3%, 76% and 18% of patients were considered to have D'Amico low-, intermediate-, and high-risk PC, respectively [8]. The median blood loss was 400 ml (IQR 200–500) and median length of stay was 1 d (IQR 1–3). No intraoperative complications were observed. There were five (6.1%) postoperative complications: four grade 1 and one grade 3b (vesicourethral anastomotic leakage). The positive margin rate was 13% (11/82).

Supplementary Table 2 shows pathological and periop- erative outcomes. During the study period, 34 patients experienced biochemical recurrence following S-RALP. For the overall population, the Kaplan-Meier estimate of median PFS is 24 mo (95% confidence interval [CI] 18.8–29.2; Supplementary Fig. 1A), with PFS of 74%, 48%, and 36% at 12, 24 and 36 mo, respectively. For the intermediate-risk group, PFS at 12, 24, and 36 mo was 82%, 65%, and 39%, respectively (Supplementary Fig. 1B). According to univari- ate analysis, pT3b stage and positive surgical margins (Supplementary Table 3) were associated with worse PFS. On multivariable analysis, only infield recurrence (hazard ratio [HR] 3.77, 95% CI 1.11–12.85; p = 0.03; Fig. 1) and pT3b, stage (HR 5.0, 95% CI 1.53–16.39; p = 0.008) were indepen- dent predictors of recurrence after S-RALP (Table 1).

The continence rate at 12 mo was 83% (64/77). Overall, nerve-sparing surgery was performed in 76% of the patients (bilateral 33%, unilateral 37%, incremental bilateral 4%, and incremental unilateral 2%). The preoperative erectile dysfunction rate in this study cohort was 33%. The absolute potency rate at 12 mo after surgery was 14% (10/72).

The present report provides the best available evidence on functional and oncological outcomes of salvage RP after FT. To date, the literature on surgery after FT is limited and characterised by small series of heterogeneous populations, including patients undergoing whole-gland ablation and focal ablation. Furthermore, studies include a number of different RP techniques (open, laparoscopic, and robotic) [4,9,10].

The first clinical implication of the current study is that we have demonstrated that S-RALP for men experiencing recur- rent disease after FT is safe and feasible with a relatively low toxicity profile. The postoperative continence rates, periopera- tive outcomes, positive margin rate, and complications observed are comparable to those previously reported for series of patients undergoing primary RALP [11,12]. As expected, S-RALP confers worse erectile function results compared to RALP in treatment-naïve patients [13]. Overall, perioperative and functional outcomes after S-RALP are much better after FT than after whole-gland treatment [14].

Second, the relatively high biochemical recurrence rate observed (compared to previous primary RALP cohorts [13]) suggests that men undergoing S-RALP for recurrent disease after FT should be counselled regarding the potential need for multimodal treatment of their disease. Specifically, we identified that men experiencing an infield recurrence had almost four times the risk of developing biochemical failure after S-RALP, independent of margin status, Gleason grade group, PSA, or pT stage. This suggests that those experiencing infield recurrence might have a more aggressive cancer phenotype and are thus more likely to need multimodal therapy with or without systemic therapy. One hypothesis for this finding is that an initial incomplete ablation might result in the development of “ablation-resistant” clones that repopulate the ablation field and metastasise locoregionally. The biological mechanism of this phenomenon is yet to be described and further research exploring the role of genetic and epigenetic alterations in these tumours is ongoing.

The retrospective, noncomparative design of this study is an important limitation. Despite having included all consecutive patients undergoing S-RALP after FT, we could not eliminate selection bias. In fact, the study patients were selected for surgery instead of further FT or surveillance as they were identified as harbouring more aggressive recurrence. Thus, patients in the current study are unlikely to be representative of all men experiencing recurrent disease after FT. The absence of a comparative arm with competitor management strategies, such as radiotherapy, does not allow us to draw conclusions on the comparative effectiveness of both treatments.

In conclusion, RALP for men experiencing recurrent disease after FT is safe and urinary continence outcomes are consistent with documented primary RALP outcomes. Men identified as having infield recurrence after FT appear to have phenotypically aggressive disease and should be counselled regarding the potential need for a multimodal therapeutic approach.

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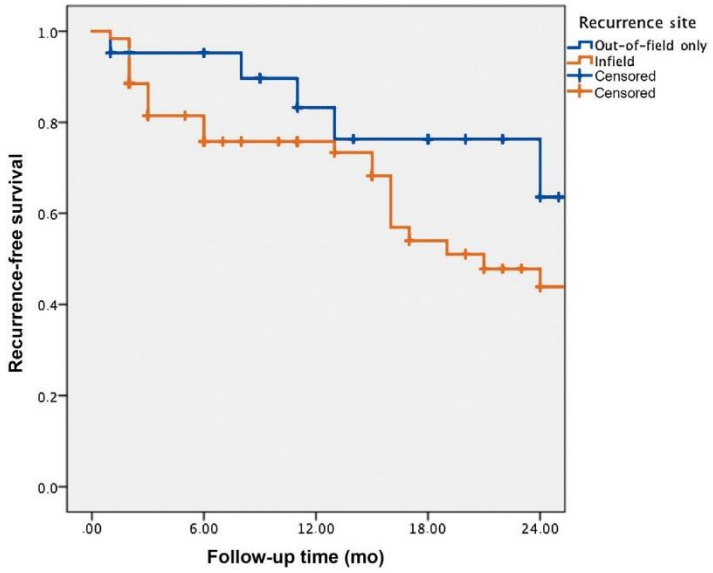
Figures:

Fig. 1 – Kaplan-Meier curves of recurrence free survival after Salvage Robotssisted radical prostatectomy for the groups with infield recurrence and out-of-field recurrence only after focal therapy. Log-rank test: p = 0.16.



Number at risk

	0 mo	6 mo	12 mo	18 mo	24 mo
Infield	61	42	31	18	11
Out-of-field only	21	17	12	9	5

Table 1 – Multivariable analysis of risk factors for biochemical recurrence among men undergoing S-RALP after FT

Risk factor	HR (95% CI)	p value
Age at S-RALP	0.95 (0.88–1.02)	0.2
Pre S-RALP prostate-specific antigen	1.05 (0.96–1.15)	0.3
.08		
ISUP grade (3–5 vs 1–2)	1.38 (0.54–3.51)	0.5
pT stage		
	1.76 (0.62–4.99)	0.3
T3b vs T2	5.0 (1.53–16.39)	0.008
Time from FT to S-RALP	0.98 (0.96–1)	0.1

S-RALP = salvage robot-assisted radical prostatectomy; FT = focal therapy; ISUP = International Society of Urological Pathology; HR = hazard ratio

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