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

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ABSTRACT

Background: Following prostate Focal Therapy(FT), a proportion of patients will develop recurrent disease and, some of them will ultimately require salvage treatment. The toxicity of salvage radical treatments after FT is not clearly understood. Salvage Robotic Assisted Radical Prostatectomy(S-RALP) is one of the options for the management of recurrent disease after FT however very scarce data exists concerning the perioperative, oncological and functional outcomes of this procedure

Objective: Describe the surgical technique and characterize the perioperative, oncologic and functional outcomes after S-RALP. Determine the risk factors for S-RALP failure.

Design, Setting, and Participants: Multi-centre cohort study of 82 patients submitted to S-RALP post FT. We included patients with a life expectancy of at least 10 years, prostate specific antigen (PSA) <30ng/ml and histological confirmation of residual/recurrent prostate cancer (after FT) within the six months previous to radical prostatectomy. In all patients metastatic disease was excluded with a pelvic MRI, bone scan and/or PET-CT.

Intervention(s): S-RALP

Outcome Measurements and Statistical Analysis: The primary outcome was Progression Free Survival (PFS). Secondary outcomes were perioperative and functional outcomes.

Results and Limitations: PFS was 73.9%, 48% and 36.2% at 12, 24 and 36 months, respectively. The recurrence rate in the high and intermediate risk groups was 64.3% and 34.4%, respectively. The continence rate - defined by the use of no pads - at most recent follow up was 83.1%. On multivariate analysis, only Infield Recurrence (HR[95%CI]=4.88[1.3-18.34]; p=0.019) and pT3b stage (HR[95%CI]=3.96 [1.22-12.82]; p=0.02) were independent predictors of recurrence. Major limitations are the retrospective design and absence of a comparative arm.

Conclusions: S-RARP post FT is safe with arguably excellent urinary continence outcomes. Men identified as having infield recurrence after FT appear to have phenoypically aggressive disease should be counselled accordingly regarding the potential need for a multimodal therapeutic approach.

Patient summary: Robotic Surgery after Focal Therapy for prostate cancer is safe and presents excellent post-operative continence results. However, if the cancer recurrence is within the previously treated field the oncological prognosis is worse.

1. INTRODUCTION

Focal therapy (FT) of prostate cancer is defined by the treatment of specific area(s) within the prostate deemed to harbour prostate cancer lesions or more specifically the treatment of the index lesion (i.e. the largest lesion with the highest Gleason grade in the prostate). [1] This emerging tissue-preserving strategy has the main goal of reducing whole gland treatment-related toxicity by minimising damage caused to the prostate and adjacent structures.

Following ablation treatment, a proportion of patients will develop recurrent disease. Local recurrence and rates of salvage local treatments after FT have been reported in 3.6–40% and 0-33% [2, 3], respectively. Studies with systematic post-therapy biopsy after FT have demonstrated recurrent/residual significant cancer in 0-17% of men.[3] Currently, there is no consensus on the optimal management of patients experiencing local recurrence after FT. Options include Active Surveillance, repeat focal ablation, transition to whole-gland Salvage Treatment – be that surgery or radiation – or alternatively systemic therapy using hormone treatment.

To date, few data exist concerning the outcome and toxicity of any of the above treatment strategies on men experiencing recurrence following FT.. [4-6]. Before widespread clinical adoption of FT, it is imperative to characterize the toxicity of secondary treatments after FT in order to counsel patients, inform clinicians and underpin guideline recommendations.

In the current study, we describe the surgical technique of Robotic Robotic Assisted Laparoscopic Prostatectomy for the treatment of men experiencing recurrence disease after FT (Salvage-RALP or S-RALP) and characterize the perioperative, oncologic and functional outcomes of the largest multicentre, international series of S-RARP in men experiencing recurrence disease after FT.

2. PATIENTS AND METHODS

2.1 Study Population

We performed a multi-centre cohort study of patients submitted to S-RALP post FT performed across Guy's and St. Thomas' Hospital and Princess Grace Hospital (London UK), and Institut Mutualiste Montsouris (Paris, France). Patients with localized prostate cancer who had received at least one focal therapy (defined as the ablation of the index or dominant prostate cancer lesion using different energy sources) with subsequent local recurrence were eligible for the study. We included patients with a life expectancy of at least 10 years, prostate specific antigen (PSA) <30ng/ml and histological confirmation of residual/recurrent prostate cancer (after FT) within the six months previous to radical prostatectomy. In all patients metastatic disease was excluded with a pelvic MRI, bone scan and/or PET-CT. Patients with metastatic prostate cancer, serious co-existing medical illness/other active malignancy and less than 2 months of follow up were excluded.

2.2 Pre-operative planning

As part of the pre-operative work-up, all patients booked for S-RALP were reviewed in a weekly image-based surgical planning meeting attended by the surgical team and a uroradiologist. A surgical planning form was completed for each patient including details concerning: 1. Site of prior ablation 2. Detailed mapping of mpMRI and systematic transperineal prostate biopsy histology; 3. Preoperative sexual and urinary function and 4. Comorbidities & prior surgical history. The location of tumour within the prostate gland, derived from a review of the patient's imaging and histology report, was registered in diagrammatic form on the surgical planning proforma, together with individual variations in prostate anatomy. This planning aids in tailoring dissection at several steps of the surgical procedure, including the selection of nerve spare technique(full nerve spare, incremental nerve spare or non nerve spare). Furthermore, the region of the prostate previously ablated was reviewed in order to predict "*focal*" technical difficulties during some of the different steps of the procedure described bellow[e.g. basal ablation (rectum/ureter/bladder neck), anterior ablation (endopelvic fascia), apical ablation (spincter), posterior ablation (recto-prostatic plane)] (please see 2.2 points a to i). These difficulties are mainly due to anatomical asymmetries, thickened tissues and fibrotic and adherent planes caused by prior FT.

2.3 Salvage RALP post FT technique

S-RALP with curative intent was performed on eligible candidates by two surgeons (PJC at Guys Hospital, London and RSS at IMM, Paris) from September 2010 to June 2018. All procedures were performed through a six-port transperitoneal approach using the four-arm Da Vinci Si. The core operative principles do not significantly depart from those of standard RALP described elsewhere[7]. However there are several specific technical intricacies to this procedure:

a. *Initial catheterization*: a cystoscope and guidewire is always ready as initial catheterisation prior to S-RARP can be difficult due to the presence of prostatic cavities and urethral strictures secondary to the previous ablation(s); we have found that more extensive ablations (i.e. hemiablation and extended hemiablation) put patients at higher risk of presenting iatrogenic lesions of the prostatic urethra.
b. *Step 1: Transperitoneal release of the bladder*: patients often have SPC at time of FT and secondary fibrosis may be found in the space of Retzius, making dissection more complex. The peritoneal incision is transverse, extending from the left to the right medial umbilical ligament; this incision is initially extended until the pubic bone is found; then, the extraperinoneal space is developed on each side of the bladder until the endopelvic fascia using contralateral retraction by the 4th arm. A bladder stich is always used for bladder retraction during the case.
c. Step 2: *Incision of the endopelvic fascia*: the effects of prior FT are often readily apparent at the level of the endopelvic fascia of the treated-side (especially in prior anterior treatments), which is frequently thickened, fibrotic and adherent to the underlying tissues. The endopelvic fascia is incised initially on the non-treated side, leaving the treated-side

dissection to a later stage in the operation – usually before the homolateral nerve spare.

d. *Step 3: Anterior bladder-neck transection*: The antero-basal aspect of the prostate is usually asymmetric. The catheter is moved inside out and its diversion to one of the sides of the bladder is used to predict the prostate base asymmetry. Continuous cephalic retraction of the bladder with the Maryland Bipolar Forceps is applied during monopolar dissection of the plane between the prostate and the bladder. As a bladder sparing approach is not used, lateral bladder neck reconstruction is often needed.

e. Step 4: *Posterior bladder neck and Seminal Vesicle Dissection*: During posterior bladder neck dissection the ureteric orifices should always be identified because prior ablation can distort the trigone drawing the ureteric orifice forwards on the ablated side, increasing the risk of iatrogenic injury. FT often distorts the anatomy of the seminal vesicles, which may be smaller due to fibrosis or very large if stenosis of the ejaculatory ducts occurred.

f. *Step 5: Development of the recto-prostatic space*: the inter-fascial plane above the Denonvillier's fascia is adherent to the prostate and the rectum can be tented up at this stage. This phenomenon can often be seen on pre-operative MRI. The perirectal fat plane posterior to Denonvillier's fascia, medially, which is generally well preserved, is developed instead, using sharp dissection. A 0 or 30 up degree scope improves visualization of this plane with the robotic platform and greatly facilitates this dissection. Blunt dissection at this stage is avoided as this could result in rectum tearing.

g. *Step 6: Nerve spare/ Lateral pedicles:* The non-ablated side nerve spare is performed first in order to gain space and obtain better posterior and lateral visualization of the more adherent contra-lateral side. The rectum is used as a point of reference and needs to be kept horizontal in the screen. In fact the prostate often rotates or appear rotated as the ablated side can be retracted. The lateral pedicles can be extremely adherent (especially in the treated side) – diathermy is not used and cold cut is preferred. For haemostasis the pedicles are oversewn after the prostate is removed from the field.

h. *Step 7: Dorsal venous complex:* DVC is cold cut without previous ligation to allow for improved mobility during dissection of the prostatic apex tissue and provide ample urethral length
i. *Step 8: Rocco suture and anastomosis vesicourethral anastomosis*: We use a two-layer Rocco suture which can be used safely in the remaining Denonvillier's fascia fibrous scar tissue. The vesicourethral anastomosis is then performed in the standard fashion however the urethral stump can be exceptionally thickened (especially after apical FT) and difficult to pass the needle through.

2.3 Covariates analysed and follow up

Data was prospectively collected on pre-FT variables (e.g. age, PSA at diagnosis, Gleason Score, staging, Energy modality, area of ablation), pre-S-RARP variables (age, PSA, number of previous FT treatments, post-FT Biopsy characteristics, staging) and S-RALP variables (type of nerve spare, pTNM staging, margin status). Prostate cancer was categorized has low, intermediate and high risk according to the D'Amico definition. [8, 9] All radical prostatectomy specimens were then assessed to identify whether recurrence was "in-field" (within the previous FT area of ablation), "out-of-field" (outside the area of ablation of previous FT) or both. After surgery, patients were followed up at 8 weeks post surgery and every 3 months thereafter.

2.4 Study Outcomes

We analysed Oncological, Perioperative and Functional Outcomes. The primary outcome was Progression Free Survival (PFS), which was defined on the basis of no biochemical relapse (PSA<0.2ng/mL) and no need for additional treatment. Urinary continence was defined very strictly as the use of no pads. A patient was considered potent when there was the self-report of erections hard enough for penetration with or without the use of iPDE5. Surgical complications were also accessed intra operatively and 30 day post-operative using the Clavien-Dindo Classification.[10]

2.5 Statistical analysis

Medians and interquartile ranges were reported for non-normally distributed continuous variables. Frequencies and proportions were reported for categorical variables. Biochemical recurrence free survival was estimated using the Kaplan-Meier method. Survival curves among groups were compared using the log-rank test. A Cox Regression multivariate model was constructed to determine the impact of risk factors for biochemical recurrence after salvage surgery. To adjust for inherent baseline differences among patients, we included age, number of FT treatments, preoperative PSA, pathological tumour stage (pT2 vs. pT3a vs. Pt3b), ISUP grade (3,4 and 5 vs 1 and 2), positive margin status and site of recurrence post FT (infield vs. outfield only) as covariates.

3. RESULTS

3.1 Baseline Patient Characteristics

Between September 2010 and June 2018, 82 patients were submitted to S-RALP after failed FT for prostate cancer(54 at Guy's Hospital/Princess Grace Hospital and 28 at Institute Mutualiste Montsuris). The median[IQR] follow up was 13 [5-22] months. **Table 1** depicts demographics, previous FT and tumour characteristics of the study cohort. Before focal therapy, 36.6%, 54.9% and 8.5% of the patients were categorized as low, intermediate and high risk, respectively. Sixty per cent of the patients had local ablation, 30% hemi-ablation and 10% extended hemi-ablation. The most common source of energy used was HIFU (69.5%) followed by Cryotherapy(19.5%), IRE(4.9%), VTP(3.7%) and PRX302(2.4%). 17 patients had a second FT treatment before S-RALP.

Mean age at surgery was 65 [61-69]years. Median time from FT to S-RALP was 26.5[16-57]months.(**Table 1**) Most patients submitted to S-RALP were considered to have intermediate risk prostate cancer (76.3%). Low and high risk prostate cancer were present in 6.3 and 17.5% of the patients.

3.2 Perioperative outcomes

No intraoperative complications were observed.(**Table 2**) There were 5(6.1%) postoperative complications, which were classified according to the Clavien-Dindo System as Grade I (4 complications: ileus managed with a nasogastric tube, constipation managed with laxatives, haematoma managed conservatively and diarrhoea managed conservatively) and Grade 3b (One patient with vesico-urethral anastomotic leakage). Median[IQR] blood loss was 400[200-500]mL. None of the patients included in the study received postoperative transfusions. No perioperative mortality was observed. Median[IQR] length of stay was 1[1-3] day.

3.3 Pathological results

Table 2 depicts the pathological characteristics of the surgical specimen. Overall, 52.4% of the patients had pT3 disease (25 and 18 patients had pT3a and pT3b, respectively). Lymph node dissection was performed in 12 patients and was positive in one. The positive margin rate was 13.4%. The majority of prostatectomy specimens (51.2%) presented evidence of recurrence simultaneously in the previously treated and untreated areas. Exclusive infield and outfield recurrences were detected in 23.2% and 25.6% of the patients, respectively. (**Table 2**)

3.4 Functional Outcomes

The continence rate - defined by the use of no pads - at most recent follow up(median 13 months) was 83.1%. Overall, nerve spare was performed in 75.5% of the patients (bilateral-32.7%; unilateral-36.7%; incremental bilateral-4.1% and; incremental unilateral-2%). The preoperative erectile dysfunction rate in this study cohort was 32.8%. The postoperative potency rate was 13.9%.

3.5 Oncological Outcomes

Thirty-four patients (41.5%) presented biochemical recurrence post S-RALP. Kaplan Meyer estimate of median biochemical recurrence free survival is 24[95%CI:18.8-29.2]months in the overall population (**Figure 1a**). PFS was 73.9%, 48% and 36.2% at 12, 24 and 36 months, respectively. The recurrence rate in the high and intermediate risk groups was 64.3% and 34.4%, respectively. (**Figure 1b**) Biochemical recurrences were treated with hormone monotherapy (5[14.7%] patients), pelvic salvage radiotherapy with or without hormone therapy (18[52.9%] and 7[20.6%] patients, respectively), hormone and chemotherapy (1[2.9%] patient). One patient is under observation and 2 were lost to follow up. There were no cancer specific deaths.

3.6 Analysis of risk factors for biochemical recurrence

According to univariate analysis, patients who presented an infield recurrence presented with a shorter Biochemical RFS when compared to patients who presented outfield recurrence exclusively (28 vs. 40 months). (**Figure 2a**) Furthermore, patients with pT3b stage (Log Rank p=0.008), a positive surgical margin (Log Rank p=0.003), previously submitted to Local Ablation(vs. Hemiablation) (Log Rank=0.049), with early recurrences(Log Rank p=0.038) present a statistically significant worse median RFS (**Figures 2b, c, d and e**). Age, number of previous FT treatments, pre S-RALP PSA, Positive margin and ISUP grade(**Figure 2f**) were not statistically significant predictors of Biochemical Recurrence post S-RALP.

On multivariate analysis, only Infield Recurrence (HR[95%CI]=4.88[1.3-18.34]; p=0.019) and pT3b stage (HR[95%CI]=3.96 [1.22-12.82]; p=0.02) were independent predictors of recurrence. (**Table 3** – Multivariate analysis). A patient with a recurrence within the previously treated FT field had almost 5 times more chance of developing recurrence post S-RALP.

4. DISCUSSION

Summary

In this multi-institutional study, we present the largest published series of S-RARP in men experiencing recurrent disease after FT for prostate cancer. Furthermore, we have described a standardized and contemporaneous surgical technique (RALP), which is reproducible. We have demonstrated that S-RARP post FT is safe and has arguably excellent urinary continence outcomes (83.1%), even when using a very strict continence definition (i.e. the use of no pads). In this cohort we observed a high rate of biochemical recurrence post surgery, leading to a multimodal treatment approach in a considerable number of patients (41.1%).

Methodological Limitations

This study supports the safety and efficacy of S-RALP after FT. However there are some limitations. The short follow-up time jeopardizes the report on long-term oncologic efficacy. The retrospective design of this study is also a major limitation. Despite having included all consecutive patients submitted to S-RALP after FT in two institutions, we could not eliminate selection bias. In fact these patients were selected for surgery, instead of further focal treatment or surveillance, as they presented with more aggressive recurrences. As such patients in the current study may not be representative of all men experiencing recurrent disease after FT. We are currently running a prospective trial looking at the toxicity and oncological outcomes of RALP after Focal Ablation Therapy (RAFT trial NCT03011606). Finally, 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.

Comparison with other studies

The evidence base on Salvage Radical Prostatectomy post FT is very limited and characterized by small series, the report of heterogeneous populations including patients submitted to whole gland ablation and focal ablation. Furthermore, the reported literature concerns a number of very different radical prostatectomy techniques (i.e. open, laparoscopic and robotic)[5, 11-13].

In a retrospective matched pair analysis, the outcomes of 22 S-RALPs, following recurrent disease after FT (mostly HIFU and Cryotherapy), were compared with men undergoing surgery as a primary treatment.[4] In this analysis, 53% of the patients submitted to S-RALP were continent, using the “no pad” definition while 7 men experienced biochemical recurrence following surgery (31.8%). When S-RALP patients were matched with 44 patients undergoing primary RARP, no difference in urinary continence, perioperative outcomes and complication rates were found. However patients undergoing S-RALP demonstrated a 4.8 fold increased risk of biochemical recurrence when compared to primary RALP, a finding not dissimilar to that reported in the current study.[4] More recently, an international consortium has reported a series of 42 patients undergoing salvage radical prostatectomy using different approaches (20 open, 16 robot-assisted and 6 laparoscopic) after failed Vascular-targeted photodynamic therapy (TOOKAD).[11] The patients were recruited from previous Phase II[14, 15] and Phase III[16] trials where they had been submitted to hemi-ablation(74%) or whole-gland ablation(26%). [11] The reported post-operative continence rate at 12 months was 64%. Sixty-four and 11% of the patients recovered potency with or without treatment (including intra-cavernous injections). Interestingly, authors raise concerns on the oncological outcomes as this cohort presents a relatively high positive lymph node rate (7%) and a considerable number of patients (21%) treated with adjuvant/salvage radiotherapy post salvage radical prostatectomy, a finding again not dissimilar to the current study cohort.

We emphasise that our population should be clearly distinguished from the one submitted to salvage surgery post whole-gland treatment (either using ablation[17] or radiotherapy[18]) as the later is at much higher risk of morbidity and worse functional outcomes.

There are no studies reporting on Salvage External Beam Radiotherapy (S-EBRT) after FT, however data are available concerning S-ERBT for recurrent disease after whole-gland ablative treatment [19, 20]. In the largest series, 100 patients received S-EBRT after whole-gland HIFU therapy.[19] For the 83 patients treated with exclusive radiation therapy, PFS was 72.5% at five years and 93%, 67% and 55% for the low-, intermediate- and high-risk groups, respectively. Early and late Grade>3 urinary AEs occurred in 3.5% and 7% of the patients, including one death. Proton therapy was also used to treat local recurrences after whole-gland cryosurgery or HIFU. The 3-year biochemical PFS rate was 77%.[21]

Clinical implications

The first clinical implication of the current study is that while we have demonstrated that robotic prostate surgery for men experiencing recurrent disease after focal therapy is safe and feasible with a relatively low toxicity profile, especially with regards urinary continence outcomes, the relatively high observed biochemical recurrence rate after S-RALP suggests men undergoing S-RALP for recurrent disease after FT should be counselled regarding the potential need for them to undergo subsequent radiation therapy as a multimodal approach for the treatment of their disease.

There are a number of reasons why surgery, at least as an initial treatment, opposed to radiation alone, may be the optimal approach for the management of men experiencing recurrent disease after FT. First, patients choosing FT are often younger and therefore at higher risk of developing long term complications post radiotherapy. Second, given that men experiencing recurrent disease after FT often have high risk disease, these men have a high chance of experiencing local failure following radiation therapy. If surgery were to be performed following both FT and radiation, the toxicity of surgery would likely far-exceed that reported in the current cohort of men undergoing surgery after FT alone. As such, by surgery being the first initial step in the treatment of recurrence after FT, men have in reserve another local treatment option - namely radiation, whereas if they opt for radiation upfront, their salvage local treatment options are limited. Third, there is a theoretical rationale why radiation may not be the best initial step in treating men with recurrent disease after FT Reactive oxygen species(ROS) generated from oxygen are essential to the cytotoxic effect from radiation together with other free radicals.[22] After FT, prostate cancer cells may be found in islands within fibrotic tissue which has a poor blood supply and as such, the post-ablation may represent a relatively radio-resistant environement for prostate cancer cells.

The second clinical implication of the current study concerns how our data can help define the conduct of focal therapy for men having the treatment approach for the management of primary prostate cancer. We identified that men experiencing an infield recurrence post-FT had almost 5 times more chance of developing recurrence post S-RALP, independently of the margin status, Gleason score or pT stage. This implies that those experiencing infield recurrence have an aggressive cancer phenotype and as such should probably transition early to whole gland radical therapy and arguably utilising surgery as part of a multimodal approach to their disease, rather than having a further attempt at FT in the in-field recurrence.

The biological mechanism for this phenomenon is yet to be described, however we hypothesise that the "ablation-resistant" clones represent a more aggressive phenotype of prostate cancer with the ability to early metastasise loco-regionally. An initial incomplete ablation could arguably result in the development of ablation-resistance and allow such resistant cells to repopulate causing the infield recurrences. This could explain our observation of worse post S-RALP RFS in patients previously submitted to limited local ablation instead of hemi-ablation. In contrast to the above, patients with exclusive out-of-field recurrences or late recurrences appeared to have lower rates of failure following surgey and so appear to represent a group with phenotypically less aggressive disease and as such could represent good candidates for further focal treatment.

5. CONCLUSION

Robotic Assisted laparoscopic Radical Prostatectomy for men experiencing disease recurrence after Focal Therapy is safe with arguably excellent urinary continence outcomes. Men identified as having infield recurrence after FT appear to have phenoypically aggressive disease should be counselled accordingly regarding the potential need for a multimodal therapeutic approach.

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