Topic Article: Current Role of Salvage Robotic Assisted Laparoscopic Prostatectomy

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Introduction

Radiotherapy (RT) for the treatment of localised prostate cancer (PCa) is an accepted treatment modality and is used in up to one-third of patients (1). It is estimated that up to 60% of these patients may experience biochemical recurrence of disease(BCR) following treatment (2). Other non-surgical treatments for localised PCa include cryotherapy and high-intensity focused ultrasound (HIFU), which also are being trialled in focal therapy approaches (3).

Traditionally patients with BCR following non-surgical treatments for localised PCa have been managed with androgen-deprivation therapy (ADT). Alternative treatment options for BCR prostate cancer include salvage brachytherapy (BT), HIFU, salvage cryotherapy, active surveillance (AS) and salvage prostatectomy, the latter as the only option for long-term disease free survival (2, 4, 5).

Salvage radical prostatectomy (sRP) for recurrent PCa following RT was first shown by Carson et al. (6) in the 1980s to be a modality of treatment with acceptable surgical morbidity. It remains an option in BCR with the absence of systemic or metastatic disease, although it has not been widely practised (7). The Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database identified 63% of men developing recurrent disease after RT at a median 38-month follow-up (8). Primary salvage treatment was ADT in 93% of cases (8). Only 2% of men with BCR underwent potentially curative sRP (9).

Salvage radical prostatectomy historically has been associated with significant morbidity (10) but recent large series for open sRP suggest an improvement in surgical morbidity and oncological outcomes (7). It is a challenging surgical procedure which is technically demanding and recommended for experienced, high-volume surgeons (5). In some studies the overall 5-year progression-free probability for sRP is 55-88% and 10-year cancer-specific survival is 77% (11, 12). Despite these improvements sRP performed either open, laparoscopically or robotically, remains a surgically challenging operation and is associated with higher complication rates compared to traditional retro-pubic radical prostatectomy (RRP) (10). Robotic assisted laparoscopic prostatectomy (RALP) is a well established technique for localised PCa with equivocal oncological outcomes and reduced adverse events compared to open (ORP) and laparoscopic radical prostatectomy (LRP) (13). In 2008 the first salvage robotic-assisted laparoscopic prostatectomy (sRALP) was reported by Jamal et al (4) in 2008. Oncological and technical advances has given birth to this new minimally invasive technique for sRP.

The aim of this topic paper is to summarise the published series on sRALP, specifically addressing patient selection criteria for salvage therapy, peri-operative considerations, complications, and functional and oncological outcomes.

Materials and Methods

PubMed and MEDLINE databases were searched in October 2012 using the key words: radical prostatectomy, salvage, robotic, open, radiotherapy, brachytherapy and

high-intensity focused ultrasound. Only English language articles were included. All publications were critically reviewed for relevance, patient selection, operative outcomes, complications and oncological control with regards to sRALP technique.

Results

Patient Selection Criteria for Robotic Salvage Therapy

Localised PCa can be managed with a variety of treatment options including: AS, primary radical prostatectomy, radiotherapy as EBRT or low-dose brachytherapy (BT), cryotherapy and HIFU (5). Recurrence of PCa following RT can be indicated by BCR or clinical evidence of disease progression.

Biochemical recurrence after radiotherapy for localised PCa occurs in 40 – 50% of treated patients (10) and can either represent either localised or systemic disease progression. The definition of BCR as stated by the American Society for Therapeutic Radiology and Oncology (ASTRO) is three consecutive rises in serum PSA from a post-RT established nadir separated by ≥3 months (7, 9, 14). The date of failure is considered to be halfway between the nadir date and the first of three consecutive rises or a rise high enough to initiate salvage therapy (15). The 'Phoneix' definition was determined at an ASTRO meeting in 2005 to redefine BCR after RT as a rise in serum PSA by ≥2 ng/mL from a nadir PSA (14, 15). Both of these consider BCR in the setting following RT, and specifically the Phoenix definition was not recommended for evaluating cryotherapy, radical prostatectomy, thermal or ablative therapies (15).

To be considered for salvage therapy a patient must have confirmed or suspected organ confined disease. The 5-year progression free probability of organ confined, seminal vesicle invading and positive lymph node disease is 77%, 28% and 22% respectively (11). In the setting of BCR and consideration for salvage therapy it is strongly recommend that a repeat prostate biopsy is performed prior to surgery to confirm recurrence of disease (7). To note radiation atypia in normal prostate tissue can often be difficult to distinguish from carcinoma (4).

Evaluation for evidence metastatic disease is essential for potential candidates of sRALP, as would be the case for any potential candidates for salvage therapy. Recommendations are to perform bone scintigraphy, computer-tomography (CT) and magnetic resonance imaging (MRI) imaging and for the latter endorectal MRI in conjunction with spectroscopic imaging significantly enhances the differentiation between localised and systemic disease progression (7).

It is highly recommended that sRALP should only be performed in patients with surgically curable disease prior to primary localised treatment (RT, HIFU or crythotherapy), a positive prostate biopsy, negative evidence for metastatic disease and a life expectancy suitable to justify radical treatment (7). Ideally patients should have minimal comorbidities (4) and a life-expectancy exceeding 10-years (5). Kaffenberger et al (16) suggest that patients with a slow PSA doubling-time (8-12 months) and low Gleason grade (≤ 6) disease at original diagnosis are more likely to benefit from sRALP. In general low-risk patients with the above mentioned features or PSA velocity <2.0ng/mL per year, time to PSA failure > 3 years or a PSA < 10 ng/mL immediately before salvage therapy are expected to have better outcomes following sRP (5).

Surgical Technique

Peri-operative considerations for sRALP are similar to open and laparoscopic sRP. The population of patients suitable for sRALP often create more a more challenging and technically difficult operation compared to traditional RRP performed as first-line treatment for patients with PCa. Anatomical planes and dissection, particularly on the posterior aspect of the prostate is a concern during any sRP procedure (7). During the first case of sRALP described by Jamal et al (4) they experienced difficulty in identifying the anatomical planes lateral and posterior to the prostate in their patient who had previous EBRT. Prior BT anecdotally causes increased adhesions compared to EBRT, although there is no statistical evidence that supports this difference (7). During sRALP Boris et al (17) frequently encountered BT seeds outside the prostate and in the perineum. Kaffenberger et al (16) completely mobilised the lateral margins of the prostate which enhances the dissection and visualisation for the posterior apical dissection, an area noticeably adherent post-radiation. Chauhan et al (2) described transilluminating technique for detecting rectal injuries whereby a sigmoidoscope was inserted rectally and the robotic camera light dimmed to allow illumination of thin and potentially damaged rectal wall. Any positive transillumination tests were sutured in three-layers (2). The only significant rectal injury in a single patient was reported in the largest series by Kaffenberger et al (16) whereby a rectal laceration required repair and diversion. Management of rectal injury is varied but most frequently a two-layered closure is advised (7). In the series by Eandi et al (18) one patient experienced an enterotomy during adhesiolysis which was repaired intraoperatively.

In the study by Kaouk et al (10) two initial patients (not included in the sample size of 4 patients) with a history of PCa and BT underwent robotic cystoprostatectomy for bladder cancer. Both procedures were uncomplicated and surgical technique was unaltered therefore sRALP was performed on four patients sub sequentially (10).

Advantages of the robotic 3D magnification included tissue-plane recognition, especially between prostate and rectum (10) and pneumoperitoneum reducing significant blood loss. Kaouk et al (10) described easier tissue dissection with the robotic technique compared to traditional open sRP. Estimated blood loss for sRALP varied from 75 – 280 ml (2, 10, 17-19) [Table 1], which is substantially less compared to a mean of 690mls calculated from four large open sRP series over the last 10 years (20-23).

A non-nerve sparing approach was adopted by Eandi et al (18) with the goal of curative treatment over preservation of erectile function. However, it must be taken into consideration that their cohort only 22% of patients had adequate non-medicated erections and a median age of 67 years (18). Some robotic surgeons may argue that the technical difficulty in salvage surgery of tissue-plane recognition and dissection alongside the primary aim for curative treatment disfavours a nerve sparing approach. Two patients underwent unilateral nerve sparing procedures in the series by Chauhan et al (2), one with severe ED and the other mild ED. Despite this approach both patients were impotent post-operatively (2).

Lymph node dissection (LND) was performed inconsistently across all series [Table 1], with some studies performing obturator LND on all patients (10, 18), the majority of patients (2) and one performing mixed pelvic node and extended LND (17). This could be attributed to LND in sRP not offering any benefit or danger to the clinical scenario (2).

Oncological Outcomes

Since sRALP is a rare, technically challenging procedure the long-term oncological outcome data is limited and the follow-up periods are varied from the few small studies in the literature [Table 2]. Kaffenberger et al (16) have published the largest series of sRALP with some patient follow-up of up to 5-years. Their study

demonstrated that on univariable analysis PSA doubling-time and original Gleason score at diagnosis had statistically significant association with biochemical failure (p=0.049 and p=0.023 respectively) (16). Biochemical failure in this study was defined as PSA 'persistence' as an initial post-sRALP PSA≥0.1 ng/mL and PSA 'recurrence' of PSA ≥0.2 ng/mL with subsequent confirmatory PSA >0.2ng/mL (16). Apical margin status was also significant (p=0.079) but overall margin status was not associated with biochemical failure (p=0.162). Positive margin rates in all series of sRALP ranged from 13 – 50%, but when low-patient numbers are taken into account these rates are consistent with open sRP which quote rates of 11 - 33% (2, 7, 10, 16-19, 21).

In the study by Kaouk et al (10) which included four patients, three had extra-prostatic extension (EPE), one of which had positive surgical margins (PSM). One patient from the study had rise in PSA post sRALP, which was attributed metastatic disease (10). Boris et al (17) treated 11 patients with sRALP of which PSM rate for organ-confined disease (≤T2) was 0% (0/3) and for extra-prostatic disease (≥T3) was 37.5% (3/8) [Table. 2] (17). There was BCF in 27% (3/11) of patients up to 43-months post sRALP (17). In a retrospective review by Eandi et al (18) of 18 patients, 33% (6/18) developed BCR at a median follow-up of 18-months. Of these 6 patients: 2 had PSA > 10ng/mL preoperatively, 2 had multifocal PSM and 2 had unifocal PSM, all of which were treated with ADT (18) . At a relatively short median follow-up time of 4.6 months Chauhan et al (2) reported 28.6% (4/15) patients with BCR, of which all had negative surgical margins (NSM) and went on to have negative pelvic LND. Strope et al (19) found two out of six patients with BCR at a median of 12-months follow-up.

Considering all the published data in the recent studies following sRALP the overall PSM is 24.7% (22/89) and BCR rate is 24.7% (21/85). However, this rate may not reflect of the true BCR rate, as there was a difference or absence of the definition of BCR between studies, and a median length of follow-up ranging from 5 to 20 months [Table. 2] (2, 10, 16-19).

Boris and Eandi reported similar oncologic outcomes and characteristics compared to open series (7). Salvage radical prostatectomy has been shown to have 5 and 10-year PSA progression-free probability of 47 % to 69% and 25% to 45% respectively (18). When adjusted for pre-operative PSA levels of <4 , 4 to 10 and >10 the 5-year progression free probability after sRP are 86%, 55% and 28% respectively (11). Pre-operative PSA levels > 10 and PSM status are strong predictors of progression-free survival (11, 12). In a laparoscopic series of sRP Vallancien et al (24) reported a BCR rate of 27% at median follow-up of 11.2 months.

From all the studies one single mortality associated with disease progression after sRALP was reported 14-months post-operation (16), with two patients in the same study exhibiting clinical recurrence on bone-scan at the same follow-up point. Eandi et al (18) described one mortality at 18 months post-surgery unrelated to PCa.

Post-operative Complications

In the 11 case series by Boris et al (17) one patient required prolonged pelvic drainage, one extended Foley catheterisation for a anastomotic leak and one anastomotic stricture requiring urethrotomy. Eandi et al (18) reported an anastomotic urine leak rate of 39% diagnosed by routine post-operative cystogram, which might explain this higher figure compared to lower figures in other series (3, 10, 17, 19) [Table 2]. Kaffenberger et al (16) experienced five anastomotic leaks from 34 patients (14.7%). These leaks were all managed conservatively with prolonged catheterisation. A bladder neck contracture (BNC) rate of 18% for sRALP according to Eandi et al (18) is comparable to open sRP. Additional late complications following sRALP included one patient from the study by Strope et al (19) with posterior urethral distraction (Clavien

IIIb). Kaffenberger et al (16) experienced a BNC of 9%, all of which were managed successfully with cystoscopy and dilation.

Blood transfusion rate was zero in all series and there were no major (Clavien ≥4) complications (2, 3, 10, 17-19). Non-urological complications were minimal; Kaffenberger et al (16) had one patient develop a pulmonary embolus (Clavien II), Chauhan et al (2) experienced one patient with deep vein thrombosis treated with anti-coagulation and another patients with a port-site would infection managed with antibiotics (both Clavien grade II).

Functional outcomes

There is no published evidence to suggest variations in continence rates following robot-assisted salvage radical prostatectomy as compared to after open retropubic salvage radical prostatectomy. The continence rate following sRALP as reported by Boris et al (17) was 80% at 12-months follow-up with one patient out of 11 requiring an artificial urethral sphincter (AUS) (17). Of the 18 patients in the Eandi et al series (18) 33% were continent at a mean time of 7 months, whilst two required AUS. Chauhan et al (2) reported a continence rate of 71% at median time of 3 months [Table 2]. The follow-up time for continence data was limited with median of 15.5 months in all sRALP studies compared to conventional open SRP with lengths up to 5 years (18).

Information on outcomes regarding erectile dysfunction (ED) from these studies is varied but generally potency outcomes were poor (2, 10, 16-19) [Table 2]. Strope et al (19) issued quality of life questionnaires to assess continence of ED pre and post-operatively. These included: Expanded Prostate Index Composite (EPIC) and Sexual Health Inventory for Men (SHIM) instruments. Pre-operative sexual and urinary function was compromised in all patients, and continued post-operatively (19). At 1-year SHIM questionnaire follow-up demonstrated three patients who completed the questionnaire had ED and at this point two patients underwent sub-urethral slings procedures with resolution of urinary symptoms (19). Eandi et al (18) reported an adequate erection function pre-operatively in 44% of patients, with all men reporting ED post sRALP. In the study by Chauhan (2) no patients were potent following sRALP but 93% of their patients had mild to severe ED, pre-operatively as defined by the SHIM questionnaire. Kaffenberger et al (16) described 29% of patients were potent post-operatively, with the aid of additional therapy beyond phosphodiesterase-5-inhibitors. Short term follow-up in these series may account for a generally poor potency outcome but in the contemporary open sRP series with long-term follow-up, potency rates remain low with one study quoting 28% at 5-years (7, 21, 25).

Alternatives to sRP

Salvage cryotherapy is an option in recurrent PCa but is associated with significant morbidity including urinary incontinence, obstructive uropathy, erectile dysfunction and perineal pain (26). A prospective study by Ismail et al (27) of 100-patients post salvage cryotherapy after radio-recurrent PCa reported biochemical recurrence free survival at 5-years to be 73%, 45% and 11% for low, intermediate and high risk groups respectively. Through the use of rectal-wall protective techniques the incidence of rectourethral fistulas from this treatment has reduced to 0 – 0.1% (5). However, salvage cryotherapy has been reported to have worse quality of life outcomes (28). These treatment modalities are non-curative as compared to sRP, therefore patients with longer life-expectancy and those favouring less morbidity associated treatment options such be strongly considered for sRP. Following salvage cryotherapy between 14% and 33% of patients will go onto to have a positive biopsy (29, 30).

HIFU is another alternative to sRP. The largest salvage HIFU study was by Murat et al (31) of 167 patients and reported a 3-year progression free survival of low, intermediate and high risk groups as 53%, 42% and 25% respectively. Salvage HIFU is associated with a high incidence of complications; rectiuretheral fistula (3-16%), ED (66-100%) and urethral stricture (11-17.6%) (5). Published studies report that salvage BT offers a wide range of 20-70% for 5-year biochemical recurrence free-survival(5).

Conclusions

From the few publish of series regarding sRALP it has been showed to be a technically feasible operation with decreased operative morbidity, and functional and oncological outcomes comparable to open sRP series. Operative time, intraoperative complications and estimated blood loss is similar to RALP. The 3D-magnification and dexterity of robotic instruments may be an advantage over traditional open sRP in often challenging and traumatised peri-prostatic tissue. The low number of cases in each series restricts the interpretation and analysis of the data for statistically significant results. The functional outcomes of continence and ED following this procedure are variable. However, the population suitable for sRP are more likely to have pre-existing dysfunction in these areas compared to traditional RRP patients and the primary aim of salvage treatment is curative. Larger series with longer follow-up periods are necessary to draw significant conclusions about the functional outcomes and long-term oncological efficacy of sRALP.

Table 1 – Salvage Robotic-Assisted Laparoscopic Prostatectomy series: demographic and perioperative outcomes

First Author	Year	Patients, *n*	Primary Treatment	Mean pre-op PSA *ng/ml* (range)	Median operating time, *min*	Mean EBL, *mL* (range)	NS	LND, *%* (location)	Mean Hospital Stay, *d*
Rodriguez (32)	2007	1*	1 CRYO	23	210	50	Nil	100% (pelvic)	1
Jamal (4)	2008	1*	1 EBRT	0.7	150	100	1 x unilateral	0%	1
Murphy (33)	2008	1*	1 HIFU	2	159	NA	NA	NA	2
Kaouk (10)	2008	4	2 BT, 2 EBRT+BT	3.85 (0.74-8.01)	125	117 (50-250)	Nil	100% (pelvic)	2.7
Boris (17)	2009	11	4 EBRT, 6 BT, 1 EBRT+BT	5.2 (2.5-11.8)	183	113 (50-300)	NA	64% (pelvic) 36% (extended)	1.4
Eandi (18)	2010	18	8 EBRT, 8 BT, 2 PBT	6.8 (1 - 28.9)	160	150 (50-350)	Nil	100% (pelvic)	2
Strope (19)	2010	6	4 EBRT, 2 BT	9.3 (2.9-30)	356	280 (50-800)	1 x partial NS	NA	2
Chauhan (2)	2011	15	5 EBRT, 5 BT, 3 EBRT+BT, 2 PBT	6.9 **	140	75 ** (50-100)	2 x unilateral	80% (pelvic)	1**
Kaffenberger (16)	2012	34	11 EBRT, 13 BT, 5 EBRT+BT, 4 PBT	3.86	176	NA	Nil	85% (pelvic)	1

CRYO cryotherapy, *EBRT* external beam radiotherapy, *HIFU* high-intensity focussed ultrasound, *BT* brachytherapy, *PBT* proton beam therapy, *EBL* estimated blood loss, *PSA* prostate specific antigen, *NS* nerve sparing, NA not available, *LND* lymph node dissection
***** single case reports, ** median value

Table 2 – Salvage Robotic-Assisted Laparoscopic Prostatectomy series: complications, oncological and functional outcomes

First Author	Year	Patients, *n*	Rectal injury, *%*	Clavien III - V complications, %	Anastomotic leak, %	Anastomotic stricture, %	Blood transfusion , %	Overall PSM rate, %	PSM rate for ≤pT2, %	PSM rate for ≤pT3, %	Median follow-up, *mo*	Potency rate, %	Continence rate, %	BCR, %
Rodriguez (32)	2007	1*	0	0	0	0	0	100*	0	100 (1/1)*	10**	0	100	0
Jamal (4)	2008	1*	0	0	0	0	0	0	0	0	3**	NA	100	0
Murphy (33)	2008	1*	0	0	0	0	0	NA	NA	NA	6**	NA	100	0
Kaouk (10)	2008	4	0	0	NA	NA	0	50	0	66 (2/3)	5 ***	NA	75	NA
Boris (17)	2009	11	0	9	9	9	0	27	0	37.5 (3/8)	20	18	80	27
Eandi (18)	2010	18	0	17	33	17	0	28	0	56 (5/9)	18	0	33	33
Strope (19)	2010	6	0	33	33	33	0	17	NA	NA	15 ***	0	0	33
Chauhan (2)	2011	15	0	7	7	7	0	13	0	20% (2/10)	5	0	71	28
Kaffenberger (16)	2012	34	3	3	14.7	9	0	26	NA	NA	16	15	44	18

NA not available, PSM positive surgical margin, *BCR* biochemical recurrence
***** Single case reports, ** true value, *** mean value

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