

Original Article

Salvage robot-assisted radical prostatectomy (sRARP) for radiation resistant prostate cancer in a group of initially high risk patients

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ABSTRACT

Introduction: Salvage robot-assisted radical prostatectomy (sRARP) is seen as an attractive option for salvage treatment of radiation therapy -recurrent prostate cancer (PC), thanks in part to the good visualisation that is possible using this modality. However, the results of fewer than 200 salvage sRARPs have been published in the literature. We report the outcomes in a cohort of initially high risk patients of robot-assisted radical prostatectomy as salvage local therapy for radiation-resistant PC in a Scandinavian healthcare setting.

Materials and methods: A retrospective review of the charts of all patients who underwent sRARP for biochemical failure (BCF) after primary radiation treatment for localised PC at a single institution was performed.

Results: Twenty-two patients, median age 67 years (range 57 to 72), had sRARP performed between June 2008 to July 2013. A median follow-up of 26 months (range 2 to 63) was observed. Perioperative complications occurred in 4 patients (18%), with one patient sustaining a rectal injury. Histo-pathological diagnosis was pT2 in three, pT3a in five, pT3b in twelve and pTx in one patient. Ten patients (45%) had a positive surgical margin (PSM). At follow-up, 54 % of patients were free of biochemical progression and 41% were continent.

Conclusions: We showed that salvage RARP is technically feasible in a cohort of patients with predominantly high risk disease. This study adds to the limited data already in the literature, demonstrating the high frequency of locally advanced (pT3b) PC, a patient group that is usually not included in salvage treatments, as e.g. high frequency ultrasound or salvage brachytherapy. Further, given that the historical barriers to salvage RP with higher rates of rectal injury and poor urinary control no longer seem to be applicable in the modern era, we think that more patients should be considered candidates for this potentially curative salvage treatment of radiation-resistant PC. However, long-term follow-up is needed to confirm if the additional burden on these patients confers to oncological control following the procedure.

Keywords: Prostate cancer, salvage surgery, robot-assisted radical prostatectomy, radiation therapy

INTRODUCTION

Prostate cancer has the highest incidence and is the second leading cause of death due to cancer in men.^{1,2} According to the SEER-Medicare database in the United States, over fifty per cent of patients with clinically localised PC receive radiotherapy (RT) as the primary treatment modality.³ Rates of reported recurrence of PC following primary radiation treatment vary greatly, ranging from 20% to as high as 63%, depending on the specific initial treatment received, the length of follow-up and the year of treatment.^{4,5} Treatment options

for men with local recurrence after primary radiotherapy include androgen deprivation therapy (ADT), or local salvage procedures such as radical prostatectomy (RP), cryotherapy, brachytherapy, or high-intensity focused ultrasound (HIFU).^{6,7} Of the local treatment options, only salvage RP has demonstrated 10-year survival in a reasonable proportion of patients.^{8,9} However, salvage RP is performed relatively infrequently,¹⁰ likely thanks in part to the perceived technical difficulty and the historically reported high morbidity of the procedure, particularly with regard to rectal injury and urinary function.¹¹ The

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introduction and rapid uptake of robot-assisted radical prostatectomy (RARP), with its benefits of improved visualisation and reduced bleeding, is seen as an attractive option for salvage treatment of radio-recurrent prostate cancer.¹² Several centres have reported the results of their salvage robot-assisted radical prostatectomy (sRARP) in small cohorts of patient.^{4,12-19} In total, the results of fewer than 200 sRARP procedures have been published in the literature.²⁰

Data has shown that Norwegian patients tend to present with higher risk disease than in other countries.²¹ The Norwegian Radium Hospital is a center where majority of RARP procedures were performed in Norway, with more than 2,000 procedures having been completed so far. Here we summarise our five-year experience of sRARP in a cohort of patients with predominantly high-risk disease with regards to selection of patients, complications experienced and short-term oncological outcomes.

MATERIALS AND METHODS

Following ethical approval from the regional ethical committee, we reviewed our database of RARP patients and identified twenty-two patients who had undergone sRARP for recurrent PC after primary RT. The operations were performed in the period between June 2008 and July 2013. The American Society for Therapeutic Radiology and Oncology (ASTRO) criteria were applied to define biochemical recurrence (BCR) after radiotherapy.²² All recurrences were diagnosed based on three consecutive increases in PSA above the nadir PSA level taken three months apart. In most cases (68%), transrectal or transperineal transrectal ultrasound guided prostatic biopsies were obtained.

All patients underwent a preoperative evaluation with multiparametric-MRI of the pelvis and a bone scan to rule out presence of metastases. Preoperative evaluation and postoperative care were performed according to the standard institutional protocol. There were no routine differences in preoperative preparation for patients undergoing sRARP compared to standard RARP. All sRARPs were performed transperitoneally with our institutional modifications to the Vattikutti technique.²³ A three or a four-arm daVinci robotic system (Intuitive

Surgical, Mountainview, CA, USA) were used in all cases. Nineteen of the patients (86%) underwent standard bilateral pelvic lymph node dissection, either before primary RT or in conjunction with the sRARP procedure. All the surgeries in this series were performed by the senior authors (KA and BB) who were beyond the learning curve for RARP. As cancer control was our main concern, little emphasis was given to nerve sparing and a wide resections were performed.

An expert uropathologist (UA) re-evaluated all the surgical pathology specimens. Pathological stagings were assigned according to the 2010 AJCC guidelines and Gleason scores were determined.²⁴ The primary outcome measure was biochemical failure (BCF), which included both PSA persistence (PSA > 0.1 ng/ml in initial post sRARP PSA) and PSA recurrence (PSA increase to > 0.2 ng/ml during follow-up). Duration of follow-up was from the time of surgery to the date of last visit to the clinic. Data were collected on all aspects of care including patients' pre-radiotherapy PSA, Gleason score and stage. Radiotherapy treatment features like type of RT, dose, and mode of delivery were also documented. Prior to sRARP, preoperative PSA, Gleason score, clinical stage, and hormone therapy status were recorded. We also evaluated operative parameters including peri- and postoperative complications, surgical specimen characteristics, pathological stage and Gleason score. Functional outcome with regard to continence was defined as number of pads used per day. Potency data are not reported.

RESULTS

Clinical characteristics and documentation of the radiotherapy treatment delivered to the patients is given in Table 1. Primary treatment was high dose rate external beam radiation therapy (EBRT) in 19 patients, intensity-modulated radiotherapy (IMRT) in two patients and high-dose brachytherapy along with EBRT in one patient. Median time to post-radiotherapy biochemical failure (BCF) was 30 months (range 0-91 months). After PSA relapse, eight patients received adjuvant hormonal treatment (androgen deprivation therapy (ADT) = 3, anti androgens (AA)= 5). Median time from radiotherapy to salvage prostatectomy was 62 months (range 36-104 months).

Table 1: Initial diagnostic clinical characteristics and radiotherapy treatment delivered to patients.

Variable	Patients (n (%))
PSA at time of diagnosis (ng/dl)	
< 4	1 (5)
4.0 – 10	7 (32)
> 10	13 (59)
missing	1 (4)
Gleason score at diagnosis,	
≤ 6	7 (32)
7a (3+4)	3 (14)
7b (4+3)	5 (23)
8	4 (18)
9	2 (9)
missing	1 (4)
TNM stage	
T1	4 (18)
T2	8 (36)
T3a	6 (27)
T3b	3 (14)
T4	0
missing	1 (5)
Node status	
pNx	4 (18)
pN0	13 (59)
pN1	3 (14)
missing	2 (9)
Total dose of radiotherapy	
≤ 70 Gy	6 (27)
> 70 Gy	16 (73)
Time to PSA relapse	
≤ 12 months	2 (9)
> 12and ≤ 24 months	5 (23)
> 24and ≤ 36 months	5 (23)
> 36and ≤ 48 months	3 (14)
> 48 months	4 (18)
missing	3 (13)

PSA = prostate-specific antigen; TNM = TNM classification of malignant tumours; EBRT = external beam radiotherapy; IMRT = intensity-modulated radiotherapy; Gy = gray

Table 2: Clinical characteristics and pathological data associated with the sRARP.

Variable	Patients n (%)
Age (years)	
< 60	1 (5)
≥ 60	21 (95)
PSA (ng/dl)	
< 4	14 (64)
4.0 – 10	5 (23)
> 10	2 (9)
missing	1 (4)
TNM stage	
pT1	0
pT2	4 (18)
pT3a	5 (23)
pT3b	12 (54)
pT4	0
pTx	1 (5)
Node status	
pNx	17 (77)
pN0	1 (5)
pN1	3 (14)
missing	1 (4)
Margin status	
positive	10 (45)
negative	12 (55)
Approximate Gleason score	
≤ 6	0
7a (3+4)	2 (9)
7b (4+3)	3 (14)
8	9 (41)
9	8 (36)
Prostate size (grams)	
≤ 50	13 (59)
50-60	8 (36)
60-70	0
> 70	1 (5)
Complications	1
Rectal injury	2
Urinary tract infection	1
Haemorrhage	0
Anastomotic leak	0
Bladder neck contracture	0
Myocardial infarction	0
Pulmonary embolism	0



Patients' median age at the time of sRARP was 67 years (range 57 to 72) and the median preoperative PSA was 2.7 ng/ml (range 0.0 to 38.0). Operative duration was calculated as the time from placing the first laparoscopic port until skin closure. Details of perioperative data are shown in Table 2. Median operative time was 129 minutes (94-230 mins) and the length of hospital stay was two days in the majority of cases (range 1-7 days). No patient required conversion to open surgery or a blood transfusion. Postoperative complications occurred in four patients (18%), of which the most common was urinary tract infection. One patient sustained a rectal injury, which was primarily repaired and loop colostomy performed. This patient did not experience any long-term sequelae and had a colostomy reversal three months later. There was no perioperative mortality and serious morbidity such as myocardial infarction or pulmonary embolism. Ten patients (45%) had a positive surgical margin (PSM) as shown in final pathology. Details of histopathological characteristics of the specimens are shown also shown in Table 2

A median follow-up of 26 months (range 2 to 63 months) was observed after sRARP. Of those who responded to the question on pad use, 41% were continent requiring zero or one pad per day. Five patients had an artificial urethral sphincter (AUS) implanted for severe incontinence. Within the median follow-up of 26 months, 54% of patients were free of BCF. Of the patients who developed BCF after surgery, 50% had positive surgical margins. One patient required a cystectomy for severe haemorrhagic cystitis in the follow-up period.

DISCUSSION

Although BCF develops in a large number of patients after radiation therapy for localised prostate cancer, few undergo local salvage treatment.⁵ Salvage RP represents an established option for patients with curative potential and is the only modality that has demonstrated 10-year survival in a substantial proportion of patients.⁷ The main challenge with salvage RP procedure is the extensive post-RT fibrosis and the obliteration of plane of dissection.¹⁷ The cohort of patients we analysed are predominantly of high-risk disease at the time of initial diagnosis. Despite this sRARP is technically feasible when performed by experienced robotic surgeons with a low complication rate. This study adds to the growing body of literature supporting sRARP as a valid technique

for the management of patients with radio-recurrent PC. With the outcomes of less than 200 cases described in the literature, more data is needed to help surgeons accurately counsel patients as to the possible outcomes following sRARP for radio-recurrent PC.

Salvage RP has been shown to provide effective local control for radio-recurrent prostate cancer with a 10-year cancer-specific survival rate of up to 77%.⁹ Whilst good oncological control has been consistently demonstrated, enthusiasm for the surgical approach was criticized for the historically reported very high incidences of intraoperative rectal injuries in up to 19%, urinary incontinence in up to 73% and bladder neck contracture rates up to 30%.²⁵ However, great improvements in complication rates and morbidity following salvage RP have been observed since the early 1990s.²⁶ This has been attributed to greater surgeon and hospital experience, improvements in technique, better patient selection and advances in RT methodology.¹³ Since the first case of sRARP was published in 2008, improvements in complications and morbidity have progressed such that they at least match contemporary open salvage RP outcomes.¹⁶ In our series we observed two major complications requiring intervention. One case of rectal injury was primarily repaired and colostomy reversed three months later without sequelae, and one case of severe haemorrhagic cystitis underwent cystectomy. The antegrade dissection of the prostate during sRARP is advantageous in minimising rectal injury as it allows for the early separation of the denonvilliers fascia of anterior wall of rectum from the prostate, thereby establishing a well-defined surgical plane. In addition, in the hands of experienced robotic surgeons by the improved visualisation and wristed instrumentation offered by the daVinci system, the disadvantage of a lack of tactile feedback with the robotic technique is thought to be superseded.^{4, 17} No patients in this sRARP series required blood transfusion or conversion to open surgery. Operative times and hospital stay are similar to standard RARP. With increasing experience at high volume specialist centers the outcomes of sRARP are likely to continue to improve.

Continence outcomes at a minimum of two months were available for 17 patients. At the median follow-up of 26-months (range, 2 – 63), 41% of our patients were continent, defined as the use of zero or one pad. This compares favourably with a 33% continence rate

at a median of 18-months (range, 4.5-40) in the report of Eandi et al. study¹⁶, but is below that seen in other studies using the same definition.^{14,15,17} The rates and time to acquire acceptable level of continence are slower than that for standard RARP cohorts. This is likely due to effects of the radiotherapy on the urinary sphincters (internal and external urethral sphincters). For this, the rates of artificial urinary sphincter implantation are higher in sRARP than standard RARP patients. Further research is required to investigate whether these patients are bothered by the deficits of urinary and sexual functions observed after sRARP or they are more concerned for the oncological control of the disease. In addition, to the best of our knowledge, no research has been done on the anxiety levels of patients having salvage RP. It is likely that patients and their families would have had an expectation of cure during the initial radiotherapy. Therefore, it is possible that the need for additional treatment is unexpected and leads to feelings of anxiety, uncertainty, and decisional regret, which should be considered when deciding on additional salvage treatment.

Concerns over the utility of the commonly used American Society for Therapeutic Radiology and Oncology (ASTRO) definition of radio-recurrent prostate cancer have been raised.^{7,11} The main concern is the inherent delay in declaring recurrent prostate cancer when using this definition as the patients' PSA must first reach a nadir and then have three consecutive rises taken three months apart. Given the median time to PSA nadir after RT is 18 to 36 months or longer (depending on the modality of RT treatment)⁷, this means that patients are diagnosed with radio-recurrent prostate cancer some years later and the chances of progression to high risk disease is likely. It has been suggested that salvage RP should be performed at the earliest possible sign of post-RT BCF.¹⁴ However, given the controversy with the commonly used ASTRO definition and the inherent delay in declaring the presence of radio-recurrent prostate cancer, many of the series describing outcomes of sRARP involve a high proportion of patients with high risk disease (PSA > 20 or Gleason score \geq 8 or clinical stage T2c-T3 disease).²⁷ On pathological specimen review, 50% of the patients in the Eandi study had pT3 disease and 33% of those who were able to have a pathological Gleason score assigned had a grading of 8.¹⁶ Seventy-seven per cent of the Chauhan et al. cohort had pT3 disease¹⁷, whilst 26% of the patients in Kaffenberger et al's study were found

to have a pathological Gleason score of eight and T2c disease or greater in 79% of patients.⁴ This compares with our rates of p T3 and p T4 in 77%. Gleason score of 8 in 41% and GS of 9 in 36% of patients. These findings point to the inherent problem of not only the limitations of the ASTRO definition, but also that of accurately identifying organ-confined, low risk prostate cancer using currently available diagnostic tests and imaging. The presumption that the rising PSA following primary RT for prostate cancer is a result of persistent local disease and not locally advanced disease or micrometastasis is the foundation of local salvage procedures, such as sRARP.¹⁵ However, the results of studies, including ours, with patients with high pathological Gleason grade and pT3 disease support the use of sRARP in a high risk patient group. Further, the results suggest that salvage RP should be the preferred treatment over other modalities (for example, cryotherapy or HIFU) that are not able to treat T3b disease.

One concerning aspect of our study is the high rate of PSM observed (45%), even in the setting of wide surgical resections sacrificing neurovascular bundles. This compares with the range of 13% to 31% PSM seen in other sRARP studies.^{4,12,15-17} Of the patients that showed BCF during the short follow-up period of our study, 50% had PSM. The 5-year progression-free probability has been shown to be 38% for those with positive surgical margins.⁸ This compares with 77% in patients with organ-confined disease, 28% in patients with seminal vesicle involvement, and 22% in those with positive lymph nodes.⁸ The combined poor BCF free probability in both patients with pT3 disease and those with positive surgical margins means that it will be important for us to continue to follow up this group of patients to ensure that biochemical and progression free survival rates are satisfactory.

This study is limited by its small patient numbers, retrospective design and the short length of follow-up. However, with such little data available regarding outcomes following sRARP, our study adds to that currently in the literature that supports the feasibility of sRARP for radio-recurrent prostate cancer. Further, longer-term follow-up is required to ensure that oncological control is achieved by the procedure. This study was conducted at a high-volume centre in Norway, therefore, the results may not be applicable to smaller volume community hospitals or those in other health



systems. With the current deficits in staging modalities, identification of the ideal patient and refinement of patient selection for this procedure is limited. Therefore, studies such as these which demonstrate few operative complications and good urinary outcomes are valuable.

CONCLUSION

Although BCF develops in a large number of patients after radiation therapy for localised prostate cancer, only few patients undergo local salvage treatment. Salvage RP represents an established option for patients with curative potential. With this 5 years series, we showed that salvage RARP is technically feasible in a cohort of patients with predominantly high risk disease. Given that the historical barriers to salvage RP of high rates of rectal injury and poor urinary outcomes no longer seem to be applicable in the modern era. We think that more patients should be considered candidates for this potentially curative salvage treatment of radiation-resistant prostate cancer. However, further long-term follow-up is needed to confirm that the additional burden on patients confers oncological control following the procedure.

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