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Oncological and Functional Outcomes of Robot-Assisted Radical Prostatectomy in Kidney Transplant Recipients

Mohammed Shahait, MBBS, Fawaz Al Majali, MD, Ryan W. Dobbs, MD, Alex Sandberg, BS, Adnan El-Achkar, MD, Ayah El-Fahmawi, BS, Philip Mucksavage, MD, David I. Lee, MD

ABSTRACT

Objective: Management of prostate cancer in kidney transplant recipients presents a unique surgical challenge due to the risk of direct or indirect injury to the transplanted kidney. Herein, we report the largest single center study of Robot-assisted Radical prostatectomy (RARP) in kidney transplant recipients.

Methods: Between Jan 2014–2019, 14 kidney transplant recipients with prostate cancer underwent RARP. Clinical and pathological features, perioperative and postoperative complications were retrospectively evaluated. Continence was defined as by patient utilization of zero urinary pads postoperatively.

Results: The median (IQR) age at RARP was 60.2 (57.8–61.3) years, the interval between kidney transplant and RARP was 8.1 ± 7.5 years. The median (IQR) PSA was 6.9 (4–8.6); 10 of 14 patients had intermediate or high-risk prostate cancer. The median ASA score was 3, the mean (SD) operative time was 129.7 (26.3) minutes, and mean (SD) blood loss was 110 (44.6) ml. All cases were completed robotically, there was no graft loss or injury to transplanted ureter, and the mean length of stay was 1 (0.26) day.

Final pathology demonstrated that 42.8% (6/14) of the patients had nonorgan confined disease (pT3a/T3b). 50% (7/14) of the patients were upgraded to higher risk Gleason disease on final surgical pathology. Post-RARP continence rate at 3 months, and 12 months were 45.5% (5/11) and 87.5% (7/8), respectively.

Conclusion: RARP following kidney transplantation represents a safe and feasible operation which does not appear to compromise oncological or transplant outcomes.

Key Words: Prostatic Neoplasms, Robotics, Prostatectomy, Kidney Transplantation.

Department of Surgery, King Hussein Cancer Center, Amman, Jordan (Dr. Shahait).

Department of Surgery, Saint Louis University, St Louis, MO, USA (Dr. Majali).

Section of Urology, University of Pennsylvania (Drs. Dobbs, Sandberg, El-Fahmawi, Mucksavage).

Department of Surgery, Division of Urology, American University of Beirut, Beirut, Lebanon (Dr. Achkar).

Department of Urology, University of California Irvine (Dr. Lee).

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Address correspondence to: Mohammed Shahait, MD, King Hussein Cancer Center, Department of Surgery, Queen Rania street, Amman, Amman 11180, Jordan. E-mail: mshahait@yahoo.com

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INTRODUCTION

Since the first successful kidney transplant between identical twins in 1954, advances in immunology and surgical technique have transformed end stage renal disease (ESRD) from a condition with a generally poor prognosis requiring lifelong hemodialysis to a more chronic condition where many patients may anticipate years or decades of survival following renal transplantation.[1] With this improvement in graft survival and life expectancy during the last decades, there has been a shifting perspective regarding cancer care and screening for these patients.[2] The utility of prostate cancer screening remains controversial in the general population and is particularly contentious for kidney transplant candidates and recipients. Vitiello et al. found that Prostate Specific Antigen (PSA) screening did not affect the survival of kidney transplant recipients and concluded that it might do more harm than good in candidates for kidney transplant by delaying listing for an organ and decreasing transplantation rates.[1,3]

Following transplantation, post-transplant malignancy represents a common cause for post-transplant morbidity and mortality as transplant recipients have unique risk factors including chronic immunosuppression, exposure to oncogenic viruses and underlying medical conditions which are common in the ESRD population. The overall incidence of malignancy in solid organ of transplant recipients within the first five years of transplantation is around 4%, although it varies depending on age and the transplanted organ.[4] Among kidney transplant recipients, the most common malignancies are nonmelanoma skin cancers, lymphoproliferative disorders (mainly non-Hodgkin lymphoma), and genitourinary malignancies, respectively.[5] Prostate cancer is the most common genitourinary malignancy.[6] The incidence of prostate cancer in transplant population was found to be similar to that of the general population.[3]

Treatment of prostate cancer in kidney transplant recipients poses a challenging clinical scenario because of the anatomical position of the graft in the iliac fossa, its proximity to the surgical or radiation field, and immunosuppressive state of these patients. Different treatment options have been proposed to treat prostate cancer in kidney transplant recipient including surgery, radiation, brachytherapy, proton beam therapy, cryotherapy, hormonal therapy and active surveillance.[7] However, surgical resection remains the favored approach, as radiation carries the risk of allograft damage and ureteral stricture. Some experts consider renal transplantation as a contraindication to prostate radiotherapy.[8] On the other hand, brachytherapy is considered less harmful on the allograft and transplanted ureter.[9] One study showed similar cancer control rate for brachytherapy in immunosuppressed prostate cancer patient versus nonimmunosuppressed patients.[9] Presently, there is a paucity of data to support the use of other prostate cancer treatment modalities such as proton beam therapy, cryotherapy, hormonal therapy and active surveillance in the kidney transplant population.

Radical retropubic prostatectomy (RRP) was first demonstrated in a kidney transplant recipient in 1989.[10] Pure laparoscopic radical prostatectomy has been performed successfully in kidney transplant recipients although surgeons identified several technical challenges including difficulty in dissecting and ligating the dorsal venous plexus and an increased risk of rectal injury.[11] Jhaveri et al. reported the first case of the robot-assisted radical prostatectomy in kidney transplant patient in 2008.[12] Increasing availability and surgeon experience with the da Vinci surgical platform (Intuitive Surgical, Sunnyvale CA) has led to the more frequent utilization of the robotic assisted approach, which has improved upon the technical limitations of the pure laparoscopic approach and has been shown to result in less blood loss and shorter hospital stay as compared to the other surgical approaches.[2,4,5,8,13]

Many prior reports have been published emphasizing on the advantages of utilization of robot-assisted approach for post-transplant prostatectomy. However, these studies either consisted of case reports or small case series.[3,6,14,15] Herein, we report the largest single center study of the perioperative, functional, and oncological outcomes of robotic assisted radical prostatectomy (RARP) in kidney transplant recipients.

METHODS

Between 2014 and 2019, a total of 14 kidney transplant recipients with prostate cancer underwent RARP at a single center. Data were prospectively collected in comprehensive IRB-approved institutional database. The decision to perform surgery was based on patient comorbidities, patients' treatment expectations, and consensus of the prostate cancer multidisciplinary and transplant teams.

Baseline clinical characteristics, preoperative PSA, biopsy Gleason score, clinical stage, baseline international prostate symptom score [IPSS] were retrospectively abstracted from prospectively collected institutional databases. Anesthetic risk was assessed and graded according to the American Society of Anesthesiologists Physical Status Classification System [ASA score].[16] Clinical tumor characteristics were assessed via stratification by D'Amico risk groups for disease progression.[17]

Functional outcomes were assessed with the American Urological Association Symptom Score (AUASS) questionnaire with patient reported continence rates at 3- and 12-months following surgery. Continence was defined as the use of zero or one safety pad per day.

Perioperative outcomes of interest including operative time, intraoperative blood loss, intraoperative complications, final pathology, hospital length of stay, readmission, conversion to open technique, and 30-day and 90-day postoperative complications were collected. Complications were classified according to the Clavien-Dindo-classification.[18] Biochemical recurrence [BCR] was defined as a PSA-value of ≥ 0.2 ng/mL.

STATISTICAL ANALYSIS

Baseline characteristics, intraoperative, and postoperative clinical variables were abstracted from the

institutional database. Categorical variables are presented as frequencies and percentages, while continuous variables are presented as median with interquartile range or mean with standard deviation. Statistical significance was established at α-value of 0.05 which was selected a priori.

TECHNIQUE

The procedure was performed using both da Vinci Xi and Si surgical systems (Intuitive Surgical, Sunnyvale, CA, USA). The patient is placed in low lithotomy position and steep 30° Trendelenburg position. Intraperitoneal insufflation was achieved via the Veress needle. Once the pneumoperitoneum was established, the camera trocar was placed cranial to the umbilicus in the midline. The remaining 8 mm robotic trocars were placed, as previously described - except the lower quadrant trocar ipsilateral to the transplanted kidney was shifted cranially few centimeters-, under direct vision across the lower abdomen. In addition, a 5 mm assistant port and a 12 mm valve-less trocar system were placed in the contralateral upper quadrant and lower quadrant respectively.[19,20]

The procedure commenced by development of the space of Retzius where special precautions not to mobilize the allograft are undertaken. The peritoneum is incised just lateral to the median umbilical bilaterally. The incision is carried caudally, ending just medial and superior to the allograft while on the other side the incision is carried caudally ending just lateral and superior to the internal inguinal rings. Once the bladder has been dropped, the periprostatic fat is dissected off the endopelvic fascia, puboprostatic ligament, as well as the prostate gland. The superficial venous complex is isolated and cauterized with Maryland bipolar forceps and transected. The periprostatic fat pad is rolled back toward the prostate-vesical junction, then it is excised.

At that point, the endopelvic fascia is incised on both sides. Afterward, a 3-0 V-loc suture is used to ligate the deep dorsal vein.

Bladder neck dissection is similar to previously described graded bladder neck preservation for robot-assisted radical prostatectomy.[21] Then the seminal vesicle as well as vas deferens are exposed and dissected with caution on both sides. After that, the posterior dissection plan between the prostate and the Denonvilliers' fascia is developed using sharp and blunt dissection and carried distally toward the apex. Then, further lateral dissection of the posterior plane is carried to delineate the prostate pedicles and facilitate the antegrade-nerve sparing of the prostate. The prostate pedicles are controlled using Hem-o-lock, and Antegrade nerve sparing is performed based on the preop erectile patient function, preop MRI results, as well as the biopsy core involvement.

A circumferential 360° anastomosis closure as described by Van Velthoven, using a running, double-armed 3-0 bidirectional barbed suture (Quill™, Angiotech Pharmaceutics) is performed.

Table 1.
Kidney Transplant Patients' Demographics, and Baseline Characteristics Who Underwent RARP

Preoperative Characteristics and Demographics	
Race (White and African American)	12 and 2
Median Age at RARP (IQR) years	60.2 (57.8–61.3)
Median Age at transplant, (IQR) years	51.2 (49.2–56)
Median Charlson comorbidity index (CCI)	6
Median ASA score (IQR)	3 (3–4)
Median IPSS score (IQR)	4 (2–11.75)
Median PSA ng/dl (IQR)	6.9 (4–8.6)
Median SHIM score (IQR)	16 (5–21)
Biopsy Gleason score (%)	
G6	4
G7	9
G8-10	1
D'Amico Risk	
Low- risk	4
Intermediate- risk	9
High risk	1

Table 2.
Peri-Operative Outcomes in Kidney Transplant Recipient Who Underwent RARP

Peri-Operative Outcome	
Mean Operative time (SD) min	129.7 (26.3)
Mean Estimated blood loss (SD), ml	110 (44.6)
Conversion to open, n (%)	0
Postoperative complications, n (%)	
Clavien-Dindo <III	0
Clavien-Dindo ≥ IIII	0
Mean Length of stay (SD) days	1 (0.26)

Table 3.
Pathological Grade, Margins and Extra Prostatic Invasion Post RARP

Pathological Gleason score	N = 14
7 (3 + 4)	8
7 (4 + 3)	4
9 (4 + 5)	2
Invasion of Cancer	
Extra prostatic invasion	6
Seminal vesicle invasion	2
Positive surgical margin	4
Lymph node involvement	0

Pelvic lymph node dissection was omitted on the site of the allograft and was performed on the other side.[22]

RESULTS

The median (IQR) age at RARP was 60.2 (57.8–61.3) years. The mean interval between kidney transplant and RARP was 8.1 ± 7.5 years. The median (IQR) PSA was 6.9 (4–8.6); and 10 of the 14 patients had intermediate or high-risk prostate cancer (**Table 1**). The median ASA score was 3, the mean (SD) operative time was 129.7 (26.3) minutes, and mean (SD) blood loss was 110 (44.6) ml. No blood transfusion was required in any case. All cases were completed robotically, no intra-operative or postoperative complications were encountered, there was no graft loss or transplant ureteral injury, no drain was used in any patient, and the mean length of stay was 1 (0.26) day (**Table 2**).

Final pathology demonstrated that 42.8% (6/14) of the patients had nonorgan confined disease (pT3a/T3b) (**Table 3**). 50% (7/14) of the patients were upgraded to higher Gleason disease on final surgical pathology, while 2 were downgraded. Three of 14 (21.4%) of patients developed biochemical recurrence, 2 of these patients were treated with hormone treatment only, and one patient received concomitant hormonal treatment and adjuvant radiotherapy. Post-RARP continence rate at 3-month, and 12-month were 45.5% (5/11) and 87.5% (7/8), respectively.

DISCUSSION

Treatment of localized prostate cancer following renal transplantation poses many challenges. More than 82% of patients are treated with RP, 12% with EBR and 6% with brachytherapy.[23] Radical prostatectomy remains the favored approach with similar oncological outcomes to that of the general population in terms of OS and CSS. While EBR and brachytherapy remain as valid treatment options, both approaches are associated with higher rates of early and late complications (24.3% and 25% respectively) including graft ureteral strictures, radiation nephropathy and severe LUTS.[24,25]

This represents the largest case series of RARP following renal transplantation. Our population age at diagnosis was younger than the typical of PCa which might be due to the strict and close follow up that the patient with kidney transplant undergoes including routine PSA. Our patients have similar median age, median time from transplant to RARP compared to other series (refer to **Table 4**). African American patients were underrepresented in this cohort, and this might be related to the referral pattern. Within our cohort, most our patients had intermediate or high-risk malignancy, with a significant proportion had Gleason score ≥7 and nonorgan defined disease (pT3a/T3b). The patients had favorable peri-operative and

Table 4.
Summary of Previous Reports of RARP in Kidney Transplant Including Cohort Characteristics and Outcomes

Studies	Number of Patients	Median Age	Median Time from T to RARP	PSA (ng/ml)	Biopsy Gleason Score			pT3	Biochemical Recurrence
					6	7	8–10		
Mistrett et al.	N = 9	60 (56–63)	9 (6–22)	5.6 (5–15)	5	3	1	2 (22%)	2 (22.2%)
Leclerc et al.	N = 12	61.9 (55–73)	6.64 (1.41–20.1)	7.34 (4.9–11)	8	4	0	2 (18%)	2 (16.6%)
Polcari et al.	N = 7	63.3 (55–72)	8.3 (0.5–12.9)	6.2 (3.5–12.8)	2	4	1	4 (57%)	1 (14%)
Iwamot et al.	N = 13	61 ± 6.24	11.3 (3.2–14.8)	8.79 (6.34–12.51)	0	10	3	3 (23%)	4 (30.7%)
Current study	N = 14	60.2 (57.8–61.3)	8.1 (2.19–18) years	6.9 (4–8.6)	4	9	1	6 (42.8%)	3 (21.4%)

postoperative outcomes. Continence rate was 45% and 87% at 3 and 12 months postoperatively, respectively.

We observed in our cohort high rate of upstaging to pT3 disease compared to the literature. Given the low cohort number it is difficult to draw conclusion on the risk factors of upstaging in this population group nor the effect of immunosuppression on risk of upstaging. Polcari et al. 2012 had higher pT3 stage with similar distribution of Gleason score post biopsy. Our cohort has similar median age at RARP and similar median time from transplant to RARP compared to other studies (**Table 4**) making them less likely to be contributing factors to a higher pT3.

The variation in the rate of T3 disease cohorts could be explained by several factors, such as specimen processing (step-wise vs whole-mount examination), interobserver variability in calling EPE.[26] As such, in our center all RP specimens are being read by GU fellowship trained pathologist. Also, most of the biopsies were done outside our institution, and this might explain the high rate of final upgrading at the final pathology in this cohort.

There are no current practice guidelines to address prostate cancer within this specific patient population and current management strategies parallels those of the general population. Most these patients are treated with radical prostatectomy, with the open retropubic approach being the standard of care.[7,8,23,27] Recently, minimally invasive approaches, such as laparoscopic and robot-associated RP, have become more broadly utilized. In renal transplant recipients, RP is more challenging due the distorted anatomy with the presence of the renal graft in the iliac fossa, higher prevalence of intraperitoneal adhesions due to prior peritoneal dialysis, prior surgery and immunocompromised status.[7,27] There is a particularly high risk of graft or ureter and vascular injury. Therefore, an ipsilateral lymph node dissection is usually avoided.[27]

Hevia et al conducted a systematic review of curative treatments of localized prostate cancer in kidney transplant patients, and included 319 patients in the final analysis.[23] Most these patients had a biopsy Gleason score ≤ 7, cT1-T2, and low to intermediate D'Amico risk group. Most patients were treated surgically (71% open RP, 9% LRP and 14% RARP), and postoperative complications were reported in 17% of patients. At 5 years of follow up, 12% of patients had biochemical recurrence; while the 5-year overall survival rate of 850.3%.[23]

RARP is associated with a shorter operative time, lower perioperative and postoperative complication rates, lower blood loss and need for transfusions, less postoperative pain and earlier hospital discharge compared to RRP.[2,5] Nevertheless, functional outcomes, such as urinary and sexual function, are generally comparable in the two approaches.[28] While

Table 5.
Summary of Previous Reports of RARP in Renal Transplant Patients

Study	Years	Number of Patients	Mean Operative Time (Min)	EBL (ml); Transfusion (%)	Complications (%)	LOS (Days)	BCR (%)	Continence Rate (%)	F/U (Months)
Jhaveri et al.	2008	1	200	400; 100	0	3	-	100	1.5
Smith et al.	2005–2008	3[a]	322	75; -	0	2.3	0	100	13
Polcari et al.	2004–2010	7	186	-	43 (3/7)	1.8	14 (1/7)	-	16
Wagener et al.	2012	1	220	300; -	0	-	0	100	9
Ghazi et al.	2012	1	130	125; -	0	2	-	-	-
Le Clerc et al.	2009–2013	12	241	647; 8	42 (5)	-	18 (2/12)	-	31
Iizuka et al.	2013–2014	3	162	52; 0	33 (1/3)	8	33 (1/3)		18
Mistretta et al.	2012–2016	9	160	100; 0	11 (1/9)	4	22 (2/9)	78 (7/9)	42
Iwamoto et al.	2008–2017©	9[b]	153	50; 0	0	6	11 (1/9)	-	27
Moreno Sierra et al.	2015	4	196	-	-	3.2	25% (1/4)	-	-
Current study	2014–2019	14	130	110; 0	0	1	21 (3/14)	88 (7/8)	12

Abbreviations: EBL: estimated blood loss; LOS: length of stay; BCR: biochemical recurrence; F/U: follow up.
[a]The study included three renal transplant recipients and 225 non transplant patients and compared their outcomes.
[b]The study included a total of thirteen renal transplant recipients, nine of which underwent RARP, three underwent LRP and one underwent open retropubic RP; it also included 78 nontransplant patients who underwent RARP. It compared the outcomes of the patients undergoing the robotic associated approach to the laparoscopic approach as well as to the nontransplant patient population.

the data mentioned above pertain mostly to nontransplant patients, evidence is scarce in kidney transplant patients, consistent mostly of small case series. However, these studies report similar outcomes across the two patient populations.[29–32]

In this cohort, we found shorter intra-operative times, less blood loss and a shorter hospital stay compared to other published reports of RARP in renal transplant patients (**Table 5**).[12,14,15,32–37] Interestingly, No postoperative complications were encountered in this cohort which is less than the rate reported in a systematic review of RARP studies in 35 kidney transplant patients.[37] This could be explained by careful patient selection, and surgeons' experience as well as a publication bias in reported series.

Patient reported continence rate in our series is in line with previously published data.[14] Notably, functional and oncological outcomes should be interpreted with caution, as the studies have different follow-up periods (range: 8–42 months) as well as the small patient populations.

There are several strengths and limitation to this study. It is the largest report of RARP in kidney transplant recipients in the literature, however this remains a rare clinical scenario even at a center with a large volume of kidney transplants performed at our institution, and careful patient follow-up. As such, it is limited by the small number of patients, the absence of a comparative arm, and short follow-up.

CONCLUSION

Our study provides further support to the safety of RARP in renal transplant patients. It offers a shorter operative time, lower complication rate and an earlier hospital discharge as compared to RRP, as well as similar favorable functional and oncological outcomes. Larger prospective studies across multiple centers are warranted to further confirm our findings. Emerging surgical technology such as the da Vinci Single Port platform may continue to advance the treatment of these patients in the future.

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