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Radical Cystectomy and Orthotopic Urinary Reconstruction in Patients with Bladder Cancer following Renal Transplantation: Clinical Outcomes and Description of Technique

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Abstract

Objectives—Radical cystectomy (RC) with pelvic lymph node dissection and urinary diversion is the gold-standard treatment for muscle-invasive bladder cancer. In the setting of prior renal transplantation, surgical treatment remains the mainstay but is technically challenging. We report our patient outcomes in this unique population with a description of the technique.

Methods—We identified five patients with a prior history of renal transplantation who underwent RC and orthotopic urinary diversion. Preoperative clinical and demographic features were compiled and disease-specific and functional outcomes were assessed. Intraoperative technical challenges and maneuvers for avoiding complications are highlighted.

Results—Four patients were male and 1 was female, with a median age of 64 years. Gross hematuria was the most common sign at presentation. Clinical staging was T2, T2 with CIS, HG Ta with CIS, T2 with squamous differentiation, and HG T1, and pathologic tumor stage was pTisN1, pT3N0, pTisN0, pT3N0 and pT0N0, respectively. One patient received a Studer-type diversion and 4 underwent Hautmann diversion. Median followup after cystectomy was 12.9 months. Graft ureteral identification was aided by the use of intravenous dye in all patients. Ipsilateral pelvic lymph node dissection was not possible in any patient. All patients are alive at followup, with two experiencing recurrence at 7.2 months and 66.8 months. No patient experienced a significant decrease in estimated creatinine clearance (eCrCl) post-operatively. Postoperative daytime control was reported by all patients while 2 noted complete nighttime control.

Conclusions—RC with orthotopic diversion is a technically demanding procedure in patients with a history of prior renal transplantation. Meticulous technique and careful attention to the altered anatomy are required for successful outcomes.

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Keywords

bladder cancer; renal transplantation; urinary diversion

Introduction

Renal transplantation is the optimal treatment for patients with end stage renal disease. A number of studies suggest that there is an increased incidence of malignancy in the renal transplant population.¹⁻⁵ Though rare, bladder cancer may occur in renal transplant recipients with some evidence suggesting that the disease may progress more rapidly and aggressively in the transplant population.¹ Radical cystectomy (RC) is the gold standard for patients with muscle invasive bladder cancer or for patients with non-muscle invasive bladder cancer who have progressed after non-extirpative therapy. Various methods of urinary diversion in patients with prior renal transplantation have been reported in the literature.⁶⁻⁸ More recent literature on urinary diversion in the renal transplant population have focused on orthotopic diversion as the method of choice due to improved aesthetics, ability to preserve renal function, and ability to provide normal voiding function.^{2,9-14}

We review our experience in this unique patient population, with particular emphasis on operative technique, intraoperative challenges and functional outcomes.

Materials and Methods

Selection of Patients

After obtaining Institutional Review Board approval, we retrospectively queried our electronic medical record database from January 2000 to April 2012 by cross-referencing the ICD-9 bladder cancer code (188) with ICD-9 codes for renal transplantation, chronic kidney disease, and renal failure unspecified (V42.0, 585, 586). The medical record was then reviewed to include only those patients who developed bladder cancer after renal transplantation. In total, we identified five patients with a history of renal transplantation who underwent RC and orthotopic urinary diversion for bladder cancer.

Demographic and Perioperative Data Collection

We examined demographic data including age, gender, smoking history, type of immunosuppression, age at transplantation, and preoperative estimated creatinine clearance (eCrCl) as calculated by the Cockcroft-Gault equation. All patients underwent complete medical evaluation and cardiac risk stratification prior to surgery. Cancer specific data included presentation, time from transplantation to bladder cancer diagnosis, original pathologic staging, time from transplantation to extirpative surgery, type of urinary tract reconstruction, final pathologic stage, adjuvant therapy (chemotherapy or radiation therapy), functional outcomes, perioperative morbidity and overall disease outcome. Intraoperative variables included estimated blood loss, intraoperative blood transfusion, operative time, and intraoperative technical difficulties. The choice of urinary diversion (Hautmann vs Studer) was according to surgeon preference. Complications were assessed using the Clavien-Dindo

classification of surgical complications. Postoperative outcome variables included eCrCl, continence, and status at followup.

Surgical Technique

Early Identification of the Graft—Preoperative imaging in the form of abdominal and pelvic CT or MRI will provide localization of the graft, usually within the right pelvis, although other locations are possible. It is important to note in the patient history any prior grafts that have been removed or are non-functioning and where it is located. After making the initial incision and separating the rectus bellies, entry into the space of Retzius is facilitated by focusing on the side opposite the graft. Cooper's ligament is then identified and this landmark is used to free the bladder from the scarring on the side of the graft. Then attention should be directed to identifying the graft within the pelvis. This allows the surgeon to approximate the location of the vessels and ureter within the pelvis and make a safe incision along the line of Toldt lateral to the cecum for bowel mobilization. Once the retractor is placed into position, care must be taken so that the retractor blades are not resting on the graft. Mobilization on the side of the graft, where there are likely to be dense adhesions, is facilitated by dissection in a distal to proximal fashion, beginning under the pubis. Alternatively, establishing location of the aortic bifurcation and proximal common iliac will allow for proximal vascular control. Using a combination of sharp and blunt dissection allows for careful mobilization, while avoiding the possibility of cautery injury prior to identification of the ureter. Once the bowel has been mobilized and the peritoneum has been incised, the native ureters can be identified just above the level of the bifurcation of the common iliac vessels. The ureters can be isolated with soft vessel loops or Penrose drains, and further proximal and distal dissection can be performed if a native nephroureterectomy is planned.

Localizing the Graft Ureter and Vascular Pedicles—The graft ureter is likely to be surrounded by dense peri-transplant fibrosis, thus it is very important to avoid excessive dissection and manipulation of the ureter to avoid trauma to the tenuous blood supply. The ureter is likely to be found adhered to the lateral portion of the bladder but may be adherent along the pelvic sidewall along with a laterally displaced bladder. Dense scarring should be expected all along the ipsilateral side of the bladder making visual identification of the transplant ureter-bladder anastomosis difficult. Administration of intravenous indigo carmine or methylene blue can facilitate identification within pelvic scar tissue. Free flow of dye or urine can be identified from the transected ureteral end. Once the ureter has been identified, excision of the distal ureter at its entry to the bladder maximizes length on what is otherwise a short ureter. The use of cautery and staples should be avoided until the ureter and vas have been ligated. Once this is completed, the superior vesicle pedicle should be identifiable and can be ligated in the standard fashion. The vascular pedicle to the graft can then be more readily identified, which may be anastomosed to the external or hypogastric vessels.

Posterior Dissection and Lymph Node Dissection—Incision of the peritoneum in the pouch of Douglas and dissection of Denonvillier's fascia is best approached starting on the side opposite the graft. The posterior dissection should be relatively spared of adhesions.

Careful sharp dissection under direct vision will minimize the risk of a rectotomy. The posterior bladder pedicles can be ligated in the usual fashion, and one can proceed with the cystectomy as in a standard case. Ipsilateral lymph node dissection was not performed in any of the patients due to the location of the graft over the vessels and the significant peri-transplant fibrosis. This finding is consistent with previously published series.^{9, 12} Palpation of the lymph node basin should be performed, with selective biopsy and/or excision of suspicious tissue taking care not to injure the graft or its blood supply.

Preparation of the Urethral Remnant and Ureteral Anastomosis—The bladder neck in a female or the apex of the prostate is typically spared of the dense fibrosis found more proximally along the bladder. This allows for careful preparation of the prostatic apex for urethral transection. It may be more challenging in the female to free the ipsilateral bladder neck-urethral junction due to scarring, however minimizing dissection of the endopelvic fascia should be attempted to avoid injury to the urethral/rhabdosphincteric neural innervation. Cavernous nerve sparing can be performed on the contralateral side if nerve preservation is required, however it will be significantly more difficult to successfully preserve the ipsilateral nerve bundle. The graft ureter may be quite short, so the surgeon must ensure that the ureter has adequate length to attach to the neobladder while maintaining the potentially tenuous blood supply to prevent ureteral tension or stricture. This can be accomplished by performing the urethral anastomosis followed by the uretero-neobladder anastomosis. If native nephroureterectomy is not being performed, it is critical to preserve as much length as possible, as the position of the neobladder will be more dependent on the length of the graft ureter.

Results

Demographic data for the cohort are summarized in Table 1. Median follow-up time after surgery was 12.9 months (mean 24.9 months, range 3.2–67.8 months). Median age at the time of radical cystectomy (RC) was 64y (mean 58.4y) (range 27–74). Mean time from transplantation to RC was 83.9 months. Bladder cancer diagnosis was made histologically at a mean of 71.5 months after renal transplant (range 19–127 months). Gross hematuria was the most common presentation, with one patient presenting with microscopic hematuria and irritative voiding symptoms. Each patient was staged by CT of the abdomen/pelvis or MRI and chest X-ray to confirm absence of metastatic disease prior to RC.

Intraoperative and post-operative data are summarized in Table 2. Patient 1 was treated with neoadjuvant gemcitabine and cisplatin prior to RC with unilateral pelvic lymph node dissection (PLND) Hautmann orthotopic diversion, bilateral native nephroureterectomy and sacrocolpopexy. Patient 2 had a RC, unilateral PLND, Studer ileal orthotopic diversion and native left ureterectomy due to a history of left nephrectomy for renal cell carcinoma. Patient 3 had RC, unilateral PLND, Hautmann orthotopic diversion and native bilateral nephroureterectomy after prior intravesical therapy with Mitomycin-C and gemcitabine. Patient 4 was initially treated with 6 weeks of intravesical bacillus Calmette-Guerin (BCG), however the patient progressed to muscle invasive disease and received neoadjuvant gemcitabine and cisplatin, followed by RC, unilateral PLND, Hautmann orthotopic diversion, bilateral native nephroureterectomy, left adrenalectomy, and left PLND. Patient 5

was initially treated with 6 weeks of intravesical BCG, however was found to have persistent HG T1 disease at re-resection. The patient went on to have RC, unilateral PLND, bilateral native nephroureterectomy, and Hautmann orthotopic diversion. Mean operative time was 396 minutes (range 289–495 minutes). Mean operative blood loss was 1480 ml (range 500–3500 ml). Three patients required intraoperative blood transfusion. Complete right pelvic lymph node dissection was not possible in any of the patients due to dense adhesions at the pelvic side wall.

Initial transurethral resection pathology was T2 (micropapillary variant) in patient 1, T2 with CIS in patient 2, HG Ta with CIS in patient 3, T2 with squamous differentiation in patient 4, and HG T1 in patient 5. Final pathology was pTisN1 in Patient 1, pT3N0 in Patient 2, pTisN0 in Patient 3, pT3N0 in Patient 4, and pT0N0 in patient 5. All patients are alive at followup. Patient 2 had pelvic recurrence at 7.2 mo which caused mild hydronephrosis of the graft kidney. A percutaneous nephrostomy tube was placed and the patient subsequently had gemcitabine and cisplatin. The pelvic mass and hydronephrosis resolved after chemotherapy and the percutaneous nephrostomy has subsequently been removed. Patient 3 experienced pelvic recurrence, occurring 66.8 months after surgery, which has been managed conservatively.

All of the patients report complete daytime continence and 2 have nighttime continence, while 3 patients report mild nighttime stress urinary incontinence. No patient has required intermittent catheterization to empty the orthotopic neobladder. Additionally, no patient experienced a significant decrease in eCrCl after surgery and all have remained off dialysis.

Postoperative complications are summarized in Table 2. Patient 1 required readmission for E.coli urinary tract infection requiring intravenous antibiotics on POD#11 (Clavien grade 2). Patient 2 had an arterial thrombus requiring thrombectomy (Clavien grade 3b) and pulmonary embolus requiring initiation of oral anticoagulation on POD#60 (Clavien grade 2), and retroperitoneal hematoma after starting warfarin on POD#76 (Clavien grade 1). This patient subsequently developed a distal graft ureteral stricture diagnosed on POD#157 related to a pelvic recurrence of disease. Patient 3 had no perioperative complications. Patient 4 was readmitted POD#12 with an E.coli urinary tract infection requiring intravenous antibiotics (Clavien grade 2). Patient 5 had an E.coli UTI that was treated on POD#49 with intravenous antibiotics (Clavien grade 2).

Discussion

Improved immunosuppressive drugs and regimens have allowed for longer allograft and patient survival. With the prolonged natural history of these patients, secondary diseases may exert a stronger influence on overall morbidity and mortality. It is likely that transplant recipients are at increased risk for developing malignancies.⁵ Bladder cancer and other urologic malignancies have been shown to have a more aggressive course in patients on immunosuppression.¹ Radical cystectomy (RC) with pelvic lymph node dissection and urinary diversion remains the gold standard treatment for patients with muscle invasive bladder cancer and for those who develop non-muscle invasive bladder cancer refractory to

non extirpative surgical treatment. In the setting of prior renal transplantation, this is technically demanding, requiring knowledge of anatomical variation and altered physiology.

There have been approximately 30 patients described in the literature with several series reporting satisfactory oncological and functional outcomes after neobladder substitution.^{12,13,15} Kamal et al reported 5 patients who underwent either urethral hemi-Kock pouch formation or Hautmann-type neobladder diversion with serous lined extramural tunnels.¹² Two patients with pT3 disease died of metastasis at 3 and 14 months, one died of cerebrovascular accident at 14 months, and the remaining two were alive without disease at 28 and 12 months. They reported that all patients were able to spontaneously void without the need for intermittent catheterization, however rates of daytime or nighttime continence rates were not described. Manassero et al identified four patients who had Studer neobladder formation after RC for bladder cancer.¹³ Two patients died of disease at 14 and 20 months, while the remaining two patients are alive without disease at 36 and 56 months followup. They reported satisfactory day and nighttime continence in all patients. Lang et al described 4 patients who had RC and Hautmann neobladder from 1986 to 2003.⁹ One patient died of disease at 15 months, and two patients were alive at 62 and 118 months. All patients had satisfactory daytime continence and 3 patients with mild intermittent nocturnal incontinence were controlled with a nightly alarm clock reminder to void.

In three of the patients in our cohort, we performed orthotopic diversion in the setting of an estimated creatinine clearance (eCrCl) of <60 ml/min. None of the patients experienced a decline in renal function requiring dialysis or medical management of metabolic acidosis. The decision to perform orthotopic diversion in the setting of renal insufficiency should be made carefully and requires preparation for potential complications. Olsson et al reported performing ileal orthotopic diversion in a young patient with creatinine clearance of 23.6 ml/min due to bilateral obstruction by a bladder mass.¹⁶ The patient's creatinine improved to 3.7 mg/dl from 3.2 mg/dl and was managed with protein restriction and sodium bicarbonate. Patients being considered for ileal orthotopic urinary diversion should be evaluated for adequate renal function due to the predisposition for development of hyperchloremic metabolic acidosis. A creatinine of <2mg/dl has been advocated prior to urinary diversion, with formal measurement of glomerular filtration being performed in patients with borderline function.¹⁷ Sodium bicarbonate is an important adjunct to offset the increased resorption of urinary metabolites by the intestinal surface.¹⁸

The role of bilateral native nephroureterectomy remains controversial. In our series, four of the five patients underwent bilateral native nephroureterectomy. Kao et al reported the highest rate of upper tract urothelial carcinoma in patients with a history of renal transplant.¹⁹ However, confounding factors that increase the risk of developing upper tract urothelial carcinoma, such as Chinese herb nephropathy and black foot disease, could not be assessed. Other centers argue against prophylactic nephroureterectomy as they have not found any asynchronous development of upper tract urothelial carcinoma to date.¹³ Though the true risk of upper tract disease is unknown, the immunosuppressed state of the patient in conjunction with the presence of potentially malignant non-functional urothelium leads us to advocate performance of native nephroureterectomy.

In conclusion, we report our series of RC and orthotopic urinary diversion after renal transplantation. Special consideration should be given to patients with prior renal transplantation who will undergo RC and urinary diversion. First, renal allograft function must be preserved without compromising oncologic outcome. Second, surgeons should expect significant technical challenges in the dissection of the transplant unit and ipsilateral pelvic lymph nodes. Third, chronic immunosuppression may alter the natural history of bladder cancer, necessitating an aggressive surveillance regimen. Given these challenges, RC with orthotopic urinary diversion in these patients should be performed in centers with extensive experience in performing RC. This approach is technically feasible and allows patients to enjoy maximum functional ability and quality of life without compromising oncologic outcome.

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Table 1

Patient demographics

Patient	1	2	3	4	5
Age (y)	27	74	69	64	58
Age at time of transplantation (y)	15	71	65	60	47
CCI	3	3	2	4	4
Time from transplantation to bladder cancer diagnosis (mos)	127.0	39.0	18.9	45.0	127.5
Gender	Female	Male	Male	Male	Male
BMI (kg/m ²)	14.7	25.2	21.4	25.3	26.8
Ethnicity	Asian	Caucasian	African-American	Caucasian	Caucasian
Smoking hx (packs per year)	0	40	0	0	1
Preoperative eCrCl (ml/min)	34	73	61	47	30
eCrCl at followup	32	54	59	55	24
Immunosuppressive regimen	mycophenolate mofetil, tacrolimus, prednisone	mycophenolate mofetil, tacrolimus, prednisone	tacrolimus, prednisone	mycophenolate mofetil, tacrolimus, prednisone	tacrolimus, prednisone
Mode of presentation	Gross hematuria	Lower urinary tract symptoms, microhematuria	Gross hematuria	Gross hematuria	Gross hematuria

BMI- body mass index; CCI, Charlson comorbidity index; eCrCl- estimated creatinine clearance

Table 2

Perioperative and post-operative data

Patient	1	2	3	4	5
Age at time of cystectomy (y)	27	74	69	64	58
Time to followup after surgery (mos)	37.9	12.9	67.8	3.2	4.3
Surgery	Cystectomy, Left PLND, bilateral native nephroureterectomy, Hautmann neobladder, sacrocolpopexy	Cystoprostatectomy, Left PLND, Studer neobladder, left partial ureterectomy	Cystoprostatectomy, Left PLND, bilateral native nephroureterectomy, appendectomy, Hautmann neobladder	Cystoprostatectomy, Left PLND, bilateral native nephroureterectomy, left adrenalectomy, Hautmann neobladder	Cystoprostatectomy, Left PLND, bilateral native nephroureterectomy, Hautmann neobladder
Intraoperative time (min)	362	383	495	451	289
Estimated blood loss (ml)	1000	800	1600	3500	500
Initial pathology	T2 (micropapillary variant)	T2 with CIS	HG Ta with CIS	T2 with squamous differentiation	HG T1
Intravesical therapy	None	None	Mitomycin × 6 weeks Gemcitabine	BCG x6 weeks	BCG x6 weeks
Neoadjuvant chemotherapy	Gemcitabine Cisplatin	None	None	Gemcitabine Cisplatin (partial due to declining renal function)	None
Adjuvant chemotherapy	None	Gemcitabine Cisplatin	None	None	None
Final Pathology	pTisN1	pT3N0	pTisN0	pT3N0	pT0N0
Intraoperative transfusion	2 units pRBC	None	2 units pRBC, 2 units FFP	4 unit pRBC, 2 units FFP	None
Intraoperative findings	No Right PLND, transplant ureter identified using indigo carmine	No Right PLND, transplant ureter identified using indigo carmine	No Right PLND, transplant ureter identified by indigo carmine and frozen section	No Right PLND, transplant ureter identified by indigo carmine and frozen section	No Right PLND, transplant ureter identified by indigo carmine and frozen section
Hospital Days	6	7	8	7	5
Postoperative complications	Readmitted for E.coli urosepsis, IV antibiotic treatment	Arterial thrombus s/p thrombectomy, pulmonary embolus,	None	Readmitted for E.coli UTI, IV antibiotic treatment	Readmitted for E.coli UTI, IV antibiotic treatment

Patient	1	2	3	4	5
		retroperitoneal hematoma on coumadin			
Postoperative imaging	Normal	Retroperitoneal hematoma	Metabolically active pelvic mass on PET- CT	Normal	Normal
Continence	Continent	Complete daytime continence, mild nighttime stress urinary incontinence	Continent	Complete daytime continence, mild nighttime stress urinary incontinence	Complete daytime continence, mild nighttime stress urinary incontinence
Disease status at followup	No evidence of disease	Metastasis to pelvis consistent with urothelial cancer (7.2mo)	Metastasis to pelvis consistent with urothelial cancer (66.8mo)	No evidence of disease	No evidence of disease

BCG- bacillus Calmette-Guerin; CIS- carcinoma in-situ; HG- high grade; PLND- pelvic lymph node dissection; pRBC- packed red blood cells; UTI- urinary tract infection