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ORIGINAL ARTICLE

Orthotopic bladder substitute in renal transplant recipients: experience with Studer technique and literature review

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Summary

Renal transplant recipients with high-risk bladder cancer following cystectomy need a urinary diversion preserving the renal function and possibly maintaining body image, while still offering the best oncological outcome. The aim of this report is to describe our experience of radical cystectomy and orthotopic ileal neobladder with Studer technique in this population, and to review the literature. We performed radical cystectomy and Studer ileal neobladder in four male patients (median age 67 years) after median time of 9.5 years following renal transplantation. Pathology revealed pT1HGN+ transitional cell carcinoma in one case, pT1HGN0 in two and pT3aHGN0 in one. Two patients presenting aggressive disease (N+ and pT3a) died of tumour progression after 20 and 14 months, respectively, while the other two are alive after 56 and 36 months of follow-up with no evidence of disease, stable serum creatinine (2.29 and 1.6 mg/dl) and mild metabolic acidosis. Day and night-time urinary continence were satisfactory in all patients. Good functional outcomes have been reported in the 20 cases of ileal orthotopic neobladder with different techniques published so far and the global experience of 24 cases with a median follow-up of 39 months documents a cancer specific survival of 62.5%.

Introduction

Bladder cancer following renal transplantation is relatively uncommon, but it usually follows an aggressive course and radical cystectomy may be often required. Ileal orthotopic bladder substitute has been proposed to preserve renal function, as external urinary diversion presents an increased risk of infection.

The aim of the present study is to describe our experience with radical cystectomy and ileal orthotopic bladder substitute with Studer technique in four patients who developed aggressive bladder cancer following renal transplantation, analysing the clinical outcomes and functional results [1].

We also review the literature of this form of urinary diversion in kidney transplant recipients, since the two largest single-centre series of ileal neobladders in this setting consist of only five and four cases, respectively, and the remaining are case reports [2,3].

Materials and methods

We performed radical cystectomy with ileal orthotopic bladder substitute according to Studer technique in four male patients (median age 67 years) after a median time of 9.5 years following deceased donor renal transplantation. During the same time interval of 5 years, 417 renal transplantations were performed at our Institution. Transitional cell carcinoma was pathologically demonstrated by transurethral bladder resection in all cases (clinical recurrent high grade T1 in the first case and clin-

ical high grade T1 with positive re-trans urethral resection (re-TUR) in the other three). Preoperative staging was completed by chest x-ray, abdominal CT scan and total body bone scan. Radical cystectomy and Studer orthotopic ileal neobladder were performed as previously described (Fig. 1) [4].

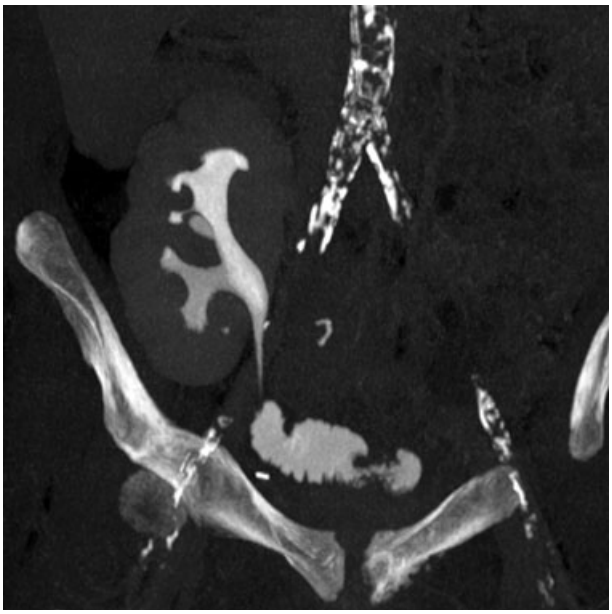

Figure 1 CT-urography of patient 4, who had previously undergone renal transplantation to the right iliac vessels and subsequent radical cystectomy with Studer orthotopic neobladder, revealing normal appearance of the pyelocalyceal system, a short ureter and opacification of the afferent nondetubularised ileal loop.

We used 55 cm of terminal ileum, which was detubularized and folded twice, leaving a 15 cm proximal ileal loop, to which was anastomosed the graft ureter by means of a modified split cuff technique, consisting in simple eversion of the last 5 mm of the ureter without incision. A ureteral stent was left in all patients for 14 days. Pelvic lymphadenectomy was limited to the opposite side of the graft to prevent damage of its vascular supply. Two patients underwent synchronous transperitoneal bilateral nephrectomy of native kidneys. All the relevant demographic and oncological data are summarized in detail in Table 1.

For immunosuppression Cyclosporin A and Azathioprine were originally used in two patients and Cyclosporine A and Mycophenolate in the other two, all in conjunction with Prednisone. Treatment was modified to Cyclosporine A (in the first patient), to Cyclosporine A and Mycophenolate (in the third), to Mycophenolate and Sirolimus in the other two after cancer diagnosis. Further immunosuppression therapy modifications are reported in detail in Table 2. Oncological and functional follow-up included abdominal sonography, CT scan and chest x-ray every 6 months, and serum creatinine and arterial gas analysis every 3 months during the first 2 years.

Results

Pathology revealed high grade pT1 pN+ transitional cell carcinoma in one case, high grade pT1 pN0 in two and high grade pT3a pN0 in one. Ten months after surgery the first patient (pT1 pN+) had periaortic nodal recur-

Table 1. Demographics, treatment and oncological results of Pisa University experience with radical cystectomy and ileal orthotopic bladder substitute with Studer technique in renal transplant recipients. Histopathological grade is expressed according to 2004 WHO classification.

Patient	1	2	3	4
Age at transplantation	58	37	61	63
Age at diagnosis	70	49	68	66
Time to cancer (years)	12	12	7	3
Pathology				
TURB-T	T1 G3 recurrent	T1 G3 + re-TUR	T1 G3 + re-TUR	T1 G3 + re-TUR
Stage after cystectomy	pT1N1	pT1N0	pT3aN0	pT1N0
Histology	TCC	TCC	TCC	TCC
Grade	high	high	high	high
Comorbidities	–	Gallstones	Prostate cancer	Ischemic cardiophaty
Treatment and outcomes				
Treatment	RC, neobladder	RC, neobladder, bilateral nephrectomy, colecistectomy	RC, neobladder, bilateral nephrectomy	RC, neobladder, appendicectomy
Months of follow-up	20	56	14	36
Metastases/recurrences	Lymph nodes	–	Lymph nodes	–
Months to metastases	10	–	9	–
Survival status	DOD	ANED	DOD	ANED

TURB-T, trans urethral bladder resection tumour; re-TUR, re-trans urethral resection; TCC, transitional cell carcinoma; RC, radical cystectomy; DOD, dead of disease; ANED, alive with no evidence of disease.

Table 2. Immunosuppression dosages (mg/day).

Patient	1	2	3	4
Originally	Prednisone 15 mg Aza 50 mg CsA 230 mg	Prednisone 5 mg Aza 50 mg CsA 225 mg	Prednisone 15 mg MMF 1500 mg CsA 225 mg	Prednisone 15(10) mg MMF 1000 mg CsA 125 mg
After cancer diagnosis	Prednisone 5 mg CsA 200 mg	Prednisone 5 mg SMF 360 mg Sirolimus 5 mg	Prednisone 15 mg MMF 1500 mg CsA 225 mg	Prednisone 10 mg MMF 1000 mg Sirolimus 5 mg
After surgery	Prednisone 5 mg CsA 150 mg	Prednisone 5 mg SMF 360 mg Sirolimus 3(4) mg	Prednisone 5 mg MMF 1500 mg CsA 125 mg Prednisone 5 mg MMF 1000 mg Sirolimus 2 mg	Prednisone 10 mg SMF 720 mg CsA 125 mg

Aza, azathioprine; CsA, cyclosporine A; MMF, mycophenolate mofetil; SMF, mycophenolate sodium.

rences necessitating chemotherapy with Epidoxorubicyn and Gemcytabine but he died of tumour progression 10 months later, although his serum creatinine level was normal and well functioning neobladder without either hydronephrosis or severe acidosis.

Another patient had nodal disease progression 9 months after surgery and he died 5 months later despite chemotherapy and radiotherapy. The return to dialytic therapy 1 year after cystectomy was related to diffuse oedema more than kidney failure.

The remaining two patients are alive after 56 and 36 months, respectively, with stable serum creatinine (2.29 and 1.6 mg/dl, respectively). They present a mild metabolic acidosis (base excess −3.2 mmol/l and −2.3 mmol/l, respectively), requiring 2 g oral sodium bicarbonate substitution each.

We did not record major postoperative complications and only two moderate postoperative complications occurring both in the same patient. He developed ureteral anastomosis stenosis, corrected with endourological antegrade balloon dilatation 2 months later, and neovesical-urethral anastomosis stricture 13 months after cystectomy, caused by migration of nonabsorbable sutures originally placed for retropubic hemostasis, and successfully treated endoscopically.

Day and night-time urinary continence are satisfactory and no voiding problems were recorded. Continent bladder function during daytime was achieved in all cases and two presented night incontinence, a fairly common event after orthotopic neobladder. Mean bladder capacity was 450 ml. The urinary flow was satisfactory with not significant residual urine, no urinary tract infections were recorded and intermittent self-catheterization was not needed. A 49-year-old man treated with nerve sparing cystoprostatectomy has preserved sexual potency, while the remaining three patients (two dead and one 66 years old, with low IIEF Index (International Index of Erectile Function Index) (16 points) and ischemic cardiopathy, were not sexually active after the procedure). The clinical outcome details are reported in Table 1.

Discussion

Treatment of bladder cancer in renal transplant recipients is a challenge because not only the best oncological care, but also preservation of renal function and satisfactory urinary diversion must be achieved. The main problems for the surgeon are the unusual pelvic anatomy, altered by the graft, and the increased risk of complications attributable to chronic immunosuppression. In transplant recipients most reports document the rapid progression of neoplasms, including bladder cancer [5]. Therefore, early radical cystectomy combined with standard pelvic lymphadenectomy and urinary diversion is highly recommended.

The published series of radical cystectomy with orthotopic neobladder in kidney transplant recipients together with our experience are reported in Table 3 [2,3,6–13].

The long-term survival rates observed so far in 24 patients appear similar to those observed in non-transplant recipients of comparable stage and grade, although the vast majority of the reported cases present a relatively short follow-up (median 39 months with a cancer specific survival of 62.5%). The observed poor outcomes are presumably related to the advanced tumour stage found in this population, as a result of chronic immunosuppression, and perhaps a result of the lack of lymph node dissection on the graft side, where the iliac vessels had already been stripped at the moment of transplantation. Comparative data on cystectomy series suggest that extended lymphadenectomy is improving the overall survival [14], but we prefer to avoid the pelvic node dissection

Table 3. Published series of orthotopic ileal neobladder following renal transplantation. Histopathological grade is expressed according to 1973 WHO classification for uniformity criteria.

Reference	Year	*n*	Neobladder technique	Follow-up time, months (median)	Pathological stage and grade	Follow-up status	Kidney function
Shokeir [6]	1994	1	Kock	24	pT3G2N0	ANED	Stable
Colombo [7]	1997	1	Ileal not specified	8	pT3bG2-3N0	ANED	Stable
Perabo [8]	1998	1	Hautmann	8	pT2G2N0	ANED	Stable
Matzkies [9]	2000	1	Ileal	48	advanced	DOD	Dialysis
Giessing [10]	2001	1	Vescica ileale padovana	20	pT1G1-2 (multifocal)	ANED	Stable
Master [11]	2004	2	Ileal not specified	31, 105 (m 68)	pT3aN1 pT3aN0	AWD ANED	Stable (2)
Lang [3]	2005	4	Hautmann, (2) afferent loop	11 15 62 118 (m 38.5)	pT3bG3N0 pT3aG3N0 (+ pT2N0 pelvis) pT2aG3N0 pTaG2N0	DOC (1) DOD (1) ANED (2)	Stable (3), Mild acidosis (3), Dialysis (1)
Kamal [2]	2007	5	1 EmiKock, 4 Ghoneim	3, 14 14 28 12 (m 14)	pT3aG3N0 (2) pT2bG1N0 pT2bG2N0 pT2aG3N0	DOD (2) DOC (1) ANED (2)	Stable (5), Mild acidosis (2)
Cooke [12]	2007	2	Hautmann + aff loop	6, 48 (m 27)	pT2G3N0 (2)	ANED (2)	Stable (2)
Wang [13]	2009	2	T-pouch W-pouch	14 84 (m 49)	pT4G3N1 pT3aG3N0	ANED (2)	Stable (2)
Present series		4	Studer	56 36 20 14 (m 28)	pT1G3N0 pT1G3N0 pT1G3N1 pT3aG3N0	ANED (2) DOD (2)	Stable (4), Mild acidosis (2)
Total		24		(m 39)		ANED(15) AWD (1) DOC (2) DOD (6)	Stable (22), Mild acidosis (7), Dialysis (2)

ANED, alive with no evidence of disease; DOD, dead of disease; AWD, alive with disease; DOC, dead of other cause.

on the side of the graft for the risk of damage to its vascular supply, extending controlateral dissection.

Chemotherapy and external irradiation are often contraindicated for the nephrotoxicity and a recent report failed to show an improvement of survival in muscle invasive bladder cancer treated by radio-chemotherapy [15].

The role of prophylactic bilateral nephroureterectomy is unclear: the potential source of postoperative infective complications or tumour recurrence of the upper tract left behind has to be weighted against the advantage of remnant diuresis. It has been our policy to perform it at the end of the procedure when the duration was maintained within 5 h and the patient was stable.

As for immunosuppression regimen after bladder cancer diagnosis, many reports suggest that conversion to Sirolimus, a mammalian target of rapamycin inhibitor, can reduce cancer progression and even induce complete responses [16,17], particularly in patients who developed Kaposi's sarcoma [18,19]. However, one of the severe adverse effects of Sirolimus is its ability to impair tissue healing. Furthermore, a recent report failed to show difference of urothelial tumours recurrence in renal transplant recipients treated with Sirolimus [20].

So far, twenty cases have been described in the literature and many reports of orthotopic neobladder in renal transplant recipient showed good functional outcomes. The first orthotopic continent diversion in a man has been reported in 1994 by Shokeir *et al.* (urethral Kock pouch) [6], while Colombo *et al.* in 1997 reported the first orthotopic ileal neobladder in a woman [7], 9 and 8 years after kidney transplantation, respectively. Both

patients were continent, graft function was only slightly impaired and electrolyte disorders were minor, without wound healing disorders or severe infections as a result of immunosuppression. Other reports followed and the two largest single-centre series in this setting, consisting of only four and five cases, respectively, were published in 2005 and 2007 [2,3].

When cystectomy is necessary in patients with a transplanted kidney, the form of urinary diversion should be weighted and adapted to the function of renal transplant. Reconstruction ranges from simple cutaneous ureterostomy to an orthotopic neobladder: the latter is recommended only in patients with a stable glomerular filtration rate of 50 ml or more. Intestinal segments in the form of an ileal conduit or continent cutaneous diversion (Kock pouch) have been used in the past when cystectomy was necessary in renal transplant recipients, despite the high risk of renal infection and graft deterioration when these procedures are performed in immunosuppressed individuals [21].

When orthotopic neobladder is performed following renal transplantation, a wide variety of techniques have been used: Hautmann with or without afferent loop, vescica ileale padovana, hemi-Kock pouch, Ghoneim (ileal W with serous-lined extramural tunnels) and T-pouch (Table 3). Their common characteristic is the creation of a spherical detubularized reservoir placed in the centre of the pelvis with low pressure but relatively efficient voiding. The spherical shape ensures the maximum volume with the minimal reabsorptive surface area; moreover, in accord to Laplace's law, it results in a maximum radius that means lower pressure. Detubularization and cross-folding of the bowel prevents peristaltic contractions and reduces high pressure peaks.

Other noncompletely detubularized ileal neobladders (such as Camey II) are presently less in favour even in normal cystectomy patients since they present a less optimal surface to volume ratio, therefore increasing the possibility of metabolic acidosis. This might explain the unfavourable case described by Airoldi *et al.*, who observed severe acidosis in a patient who had a Camey II neobladder for tuberculosis and subsequently received renal transplantation [22].

Studer ileal neobladder, since its first description, previews the preservation of an intact afferent ileal loop which provides a dynamic antireflux mechanism with preserved peristalsis, which proved to be equivalent to ileal intussusception, protecting the upper urinary tract for up to a decade [23].

For this reason authors who have used other techniques (like W shaped neobladder), performed reimplantation of the transplant ureter with a submucosal antireflux technique in the first two cases, but they moved to an afferent not detubularized ileal segment in the last two [3].

Complex antireflux techniques appear to present a relatively high rate of strictures and consequent reduction of the renal function even with normal kidneys, and the risks are obviously higher in renal grafts which are under constant risk of rejection and present a short ureter. The simplified split cuff technique used in the present series is almost equivalent to a direct uretero-ileal anastomosis and our experience with over 100 neobladders presented a low stricture rate.

Another indisputable advantage of the afferent ileal loop consists in its ability to bridge the gap between the relatively short and rigid graft ureter and the neobladder.

Metabolic acidosis occurs in this setting with two independent pathogenetic mechanisms: transplanted kidney and neobladder. A mild metabolic acidosis occurs in 1/3 of grafted kidneys and can be exacerbated by Tacrolimus nephrotoxicity, urinary infection and reduced graft function. Metabolic acidosis can also occur as a result of reabsorption of urinary solutes by the neobladders. There is absorption of urine over a prolonged contact time with the intestinal mucosa and for this reason a spherical, completely detubularized neobladder presents an optimal surface to volume ratio. The potential sequelae of reabsorption of urinary constituents can be compensated if the creatinine clearance is >40 ml/min [24].

In our experience a mild metabolic acidosis was detected in two patients.

Our results as well as the reports of other authors confirm that ileal orthotopic bladder substitute is feasible and followed by good graft functional outcomes. We observed only two moderate postoperative complications, successfully treated with minimally invasive endourological techniques. Two patients were at high risk for their pathological stage (pN+ and pT3a) and died for oncological relapse.

Conclusions

Renal transplant patients with high-risk bladder cancer need a urinary diversion preserving the renal function and possibly maintaining body image, while still offering the best oncological outcome.

Ileal orthotopic bladder substitute translates into good functional results and satisfactory quality of life. Studer technique appears to be particularly suitable for urinary tract reconstruction following renal transplantation, as its afferent ileal loop can be anatomized to the short graft ureter and preserved peristalsis prevents reflux and hydronephrosis.

Our experience confirms the literature data about the feasibility of an orthotopic substitute after radical cystectomy in renal transplant recipients.

Authorship

FM: collected data, analysed data, wrote the article. GDP: collected data. AM: collected data. GG: collected data. UB: designed research/study. CS: designed research/study and wrote the article.

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