Ureteral stricture formation in laparoscopically procured living donor kidney transplantation

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Introduction: *To identify the incidence of and risk factors for ureteral stricture formation in laparoscopically procured living donor kidney transplantation (LLDKT).* ***Materials and methods:*** *An IRB approved retrospective review of our institution's living donor database was performed. Patients were divided into two cohorts, those with ureteral strictures requiring procedural intervention and those without evidence of ureteral strictures. Analysis was limited to those patients with at least one year of follow up.* ***Results:*** *Of the 584 LLDKT's performed at our institution since June 1999, 510 had at least 1 year of follow up. Four hundred and ninety-six patients had no evidence of stricture disease (97.2%) while 14 (2.8%) developed clinically significant ureteral strictures. The incidence of delayed graft function was higher in the stricture group (21% versus 3%, $p < 0.0001$) while the intraoperative placement of a ureteral stent was associated with decreased incidence of ureteral strictures (21% of the stricture group received stents compared to 58% in the no stricture group, $p = 0.006$). In multivariable logistic regression models, delayed graft function was strongly associated with the development of clinically significant ureteral stricture disease (OR 19.3; 95% CI 3.59, 104.2; $p = 0.001$) while the placement of intraoperative ureteral stents was protective against ureteral stricture formation (OR 0.09; 95% CI: 0.02, 0.49; $p = 0.005$).* ***Conclusion:*** *Delayed graft function and nonuse of ureteral stents are associated with the development of ureteral strictures following LLDKT.*

Key Words: ureteral stricture, laparoscopic living donor kidney transplantation

Introduction

Despite the significant advances made in recent years in the area of kidney transplantation, complications that threaten the function of the allograft still remain. Ureteral obstruction is one such complication and is the most common urologic complication following kidney transplantation.[1] Although there are many causes of ureteral obstruction (ureteral calculi, blood clots, pelvic hematomas), the most common cause is ureteral strictures with reported rates between 2.8% and 5.5% following kidney transplantation.[2,3] Early reports of laparoscopic donor nephrectomy revealed a significantly higher rate of ureteral complications with laparoscopic techniques compared to open.[4,5] However, other studies have demonstrated that with refinement of the laparoscopic dissection, the incidence of ureteral complications is reduced to levels comparable to open techniques.[6] In the current study, we investigated the incidence of and factors associated with the development of clinically significant ureteral stricture disease following laparoscopically-procured living donor kidney transplantation (LLDKT) by constructing statistical models that evaluated the full spectrum of donor, recipient, and transplant factors.

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Materials and methods

Five hundred and ten recipients received living donor kidney transplants procured by laparoscopic nephrectomy between June 1999, when our institution adopted this procurement method of choice, and September 2008. The techniques of laparoscopic donor nephrectomy (LDN) have previously been described.[7,8] All surgeons employed the same extravesical technique for the ureteroneocystostomy (Lich-Gregoir).[9,10] All donor-recipient pairs were T- and B-cell cross-matched and ABO blood type compatible. All recipients received immunosuppressant therapy according to protocols at our center, consisting of an induction agent, either anti-thymocyte globulin or alemtuzumab, a calcineurin inhibitor, mycophenolate mofetil, and a rapid steroid taper to off or low dose over 4 days. Delayed graft function (DGF) was defined as any patient requiring postoperative dialysis within the first week, excluding any patient requiring dialysis due to graft nephrectomy in the immediate postoperative period. Slow graft function (SGF) was defined as any patient with a serum creatinine greater than 3 mg/dL on postoperative day 5 but not requiring dialysis while immediate graft function (IGF) was defined by a serum creatinine level < 3 mg/dL on postoperative day 5. Clinically significant stricture disease was defined as any patient with a ureteral stricture requiring any procedural (either surgical or radiographic) intervention. The median follow up was 3.0 years (range 1 mo-10 yrs). Warm ischemia times were estimated intraoperatively and recorded in the donor nephrectomy operative note.

All statistical calculations were computed using Stata/IC v 10.0 (College Station, TX) for Mac OS X. Continuous variables with normal distributions were analyzed using the student t-test with unequal variances. The normality of all continuous variables was examined using histograms, box plots, and kernel density plots. Variables that violated that normality assumption were analyzed using the Mann-Whitney U-test. Analysis of categorical data was performed using the chi-squared test. Odds ratios for donor, recipient and transplant factors were determined using logistic regression analysis. Variables with a p value less than 0.10 in the simple models were included in the multivariable regression models.

Results

Transplant characteristics by group

Of the 584 LLDKT's performed at our institution since June 1999, 510 had at least 1 year follow up. Four hundred and ninety-six (97.2%) patients had no evidence of stricture disease while 14 (2.8%) developed clinically significant ureteral strictures requiring procedural intervention. With regard to nearly all the donor, recipient and transplant characteristics included in Table 1, no significant differences were noted between the groups with two notable exceptions. First, the incidence of delayed graft function was markedly higher in the stricture group (21% versus 3%, $p < 0.0001$). Approximately 17% of all patients who developed DGF subsequently developed strictures. Second, the placement of intraoperative ureteral stents was higher in the control group (58% versus 21%, $p = 0.006$). It is important to note, however, that of the four transplant surgeons whose patients are in this current series, two did not routinely place intraoperative ureteral stents in all patients. Comparison between surgeons did not reveal any statistical differences between the rates of ureteral strictures (surgeon 1 [3.7%], surgeon 2 [2.3%], surgeon 3 [5.6%], and surgeon 4 [0%], $p = 0.06$).

Factors associated with development of ureteral strictures

Simple logistic regression analysis revealed two variables with statistically significant associations with the development of ureteral strictures: delayed graft function (OR 9.51; 95% CI: 2.34, 38.7; $p = 0.002$), and ureteral stent placement at the time of transplant (OR 0.20; 95% CI: 0.05, 0.71; $p = 0.013$), Table 2. In the multivariable models, both variables retained their significant explanatory power for ureteral stricture formation. Even after controlling for the placement of intraoperative ureteral stents and donor BMI, delayed graft function retained its significant association with ureteral stricture formation (OR 19.3; 95% CI 3.59, 104.2; $p = 0.001$). Furthermore, when plotted on a

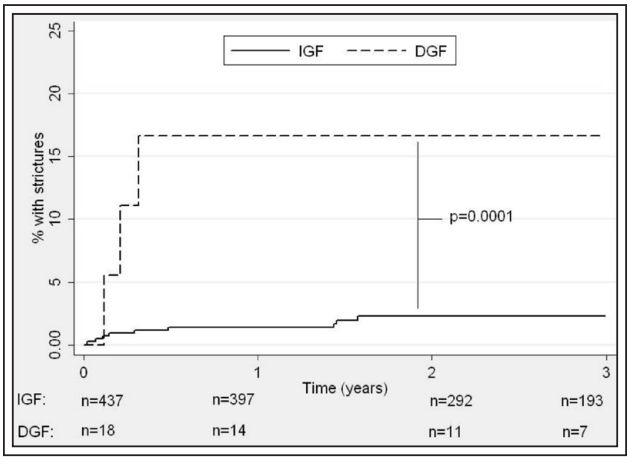

Figure 1. Stricture formation by delayed graft function (DGF) versus immediate graft function (IGF).

TABLE 1. **Donor, recipient, and transplant factors by group**

	No stricture n = 496	**Stricture n = 14**	**p value**
Age at transplantation (yr)	50.0	45.6	0.35
Recipient male/female, no	297/199	8/6	0.84
Race			0.63
Caucasian	355 (72)	9 (64)	
Hispanic	70 (14)	2 (14)	
American Indian	28 (6)	2 (14)	
African American	23 (5)	1 (7)	
Other	20 (4)	0 (0)	
Slow graft function[a]	46 (9)	2 (14)	0.35
Delayed graft function[b]	15 (3)	3 (21)	< 0.0001
Prior kidney transplant	55 (11)	3 (21)	0.22
Ureteral stent placement at Tx			0.006
Stent	288 (58)	3 (21)	
No stent	208 (42)	11 (79)	
Pretransplant dialysis	338 (68)	12 (86)	0.16
Pretransplant diabetes	117 (24)	5 (36)	0.29
HLA mismatch	3.3	3.9	0.25
Donor age (yr)	41.3	37.3	0.25
Genetically related donor	292 (59)	9 (64)	0.69
Donor male/female, no	194/302	6/8	0.78
Donor right kidney	60 (12)	3 (21)	0.30
Donor body mass index[c]	27.0	29.3	0.065
Multiplicity of renal arteries	114 (23)	3 (21)	0.89
Ligation of small polar artery	16 (3)	1 (7)	0.41
Serum creatinine at Tx	6.7	6.6	0.85
Warm ischemia time (secs)	139.2	136.3	0.74

[a]excludes graft nephrectomy and delayed graft function (n = 485)
[b]excludes graft nephrectomy and slow graft function (n = 455)
[c]variable violated normality assumption.
Mann-Whitney U-test was applied.

Kaplan-Meier failure function curve, patients who develop DGF had a significantly higher incidence of ureteral stricture formation (Figure 1, logrank $p < 0.0001$).

Discussion

Our current series is the first study to demonstrate the association of delayed graft function (DGF) with ureteral stricture formation following LLDKT. Here we show that even after controlling for the placement of intraoperative ureteral stents, DGF is strongly associated with the development of clinically significant ureteral strictures. Several studies have demonstrated the deleterious effect of DGF in both cadaveric and living donor renal transplantation, especially with regard to graft rejection and survival. Our data suggest that efforts to reduce DGF in this setting may also be beneficial in terms of reducing the formation of clinically significant ureteral strictures.

Few other studies have evaluated the risk factors associated with the development of posttransplant urologic complications. In a retrospective analysis of 1698 patients, multivariable Cox regression models

TABLE 2. **Regression models for the development of ureteral strictures**

	Odds ratio	95% CI	p value
Simple model			
Delayed graft function	9.51	2.34, 38.7	0.002
Ureteral stent placement at Tx	0.20	0.05, 0.71	0.013
Age at transplantation (yr)	0.98	0.94, 1.02	0.25
Recipient male gender	0.89	0.31, 2.61	0.84
Donor right kidney	1.98	0.54, 7.31	0.30
> 1 renal artery	0.91	0.25, 3.33	0.89
Donor age (per yr)	0.97	0.93, 1.02	0.22
Pretransplant dialysis	2.80	0.62, 12.7	0.18
Donor body mass index (kg/m^2)[a]	15.1	0.77, 299.3	0.07
HLA mismatch	1.24	0.86, 1.82	0.25
Recipient age (per yr)	0.98	0.94, 1.02	0.25
Donor male gender	1.17	0.40, 3.42	0.78
Related D-R pair	1.26	0.42, 3.81	0.69
Serum creatinine at Tx	0.98	0.81, 1.20	0.86
Recipient African American race	0.68	0.35, 1.35	0.28
Recipient Hispanic race	1.01	0.22, 4.63	0.99
Recipient Caucasian race	0.71	0.24, 2.17	0.55
Recipient American Indian race	2.79	0.59, 13.1	0.19
Slow graft function	2.07	0.43, 9.86	0.36
Warm ischemia time (secs)	1.00	0.98, 1.01	0.77
Prior kidney transplant	2.19	0.59, 8.08	0.24
Pretransplant diabetes	1.80	0.59, 5.48	0.30
Multivariable models			
Delayed graft function	19.3	3.59, 104.2	0.001
Stent placement at Tx	0.09	0.02, 0.49	0.005
Donor body mass index (kg/m^2)[a]	8.49	0.26, 281.12	0.231

[a]variable violated normality assumption and was therefore transformed in a logarithmic fashion

identified recipient African American ethnicity, recipient male gender, and the U-stitch technique as significant independent predictors of all-cause urologic complications.[2] Notably, poor early graft function, such as delayed or slow graft function, and the placement of ureteral stents were not included in these models. In a separate retrospective analysis of 1787 renal transplants, donor age > 65 years, multiplicity of renal arteries, and recipients with an anti-HLA immunization less than 25% were identified as independent risk factors for ureteral stricture formation.[11] Notably, early graft function and ureteral stent placement were included in the analysis but were not statistically associated with the development of ureteral stricture formation. Taken together, these data suggest that African American male recipients of grafts from older, genetically dissimilar donors are at a higher risk of developing ureteral stricture disease.

Only one other study has comprehensively reviewed the donor, recipient and perioperative characteristics that are independently associated with ureteral stricture development. In a retrospective review of 1787 cadaveric renal transplantations, multiplicity of renal arteries and DGF were independently associated with the development of

clinically significant ureteral strictures.[12] Based on the results of the current analysis, DGF is likewise associated with the development of ureteral stricture disease following LLDKT. While statistical association was highly significant in our current study, a causal relationship is difficult to prove. Ureteral strictures may instead be more common in patients with DGF because they share a common pathophysiologic mechanism. Alternatively, DGF may simply be a statistical marker for the future development of a ureteral stricture without biologic correlation. Since DGF is by definition a clinical entity that occurs early in the posttransplant course, it may be more useful as a pattern for early recognition of recipients with dramatically increased risk of ureteral strictures. It is likewise notable that SGF was not associated with a statistically significant stricture rate. DGF and SGF likely exist on a spectrum on increasing severity and threat to both the patient and the allograft, which may account for the observed differences.

With respect to the apparent protective effect of intraoperative ureteral stents, we interpret these results with caution. Our current analysis is not equipped to answer the question of whether the placement of ureteral stents reduces the likelihood of clinically significant ureteral strictures for multiple reasons. First, two of the four surgeons in the current series do not routinely use intraoperative stents in all patients and only do so when risk factors for ureteral stricture formation are identified (e.g. sacrifice of lower pole artery), which may have introduced a selection bias. Alternatively, this practice may have surreptitiously undermined our appreciation of the full extent to which ureteral stents protect against strictures. Second, our series is not a randomized prospective study. As a retrospective chart review, our study is inherently inadequate to conclusively endorse or reject the intraoperative use of ureteral stents. There are, however, several prospective, randomized controlled trials evaluating the use of intraoperative ureteral stents in kidney transplantation.[13-16] Furthermore, a recent meta-analysis found that the prophylactic use of ureteral stents reduces the incidence of major urologic complications.[17] Therefore, the placement of intraoperative ureteral stents, while appropriate in many instances, may not be universally endorsed by our current results. Thirdly, since our institution serves as a major referral center for our region, many of our patients elect to receive posttransplant follow up care from providers closer to their place of residence. This may have influenced our ability to detect poor outcomes, and in that respect may have influenced our results.

Conclusion

This comprehensive analysis is the first to show that delayed graft function is associated with the development of ureteral strictures following LLDKT. Knowledge of this association may help clinicians to better inform and manage patients with DGF. □

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