Title: SINGLE CENTER EXPERIENCE WITH ROBOTIC KIDNEY TRANSPLANTATION FOR RECIPIENTS WITH BMI ≥40 kg/m²: A COMPARISON WITH THE UNOS REGISTRY.

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Abbreviations:

ANOVA: analysis of variance

BMI: body mass index

CV: cardiovascular
DGF: delayed graft function

SD: standard deviation

ILUI: University of Illinois Transplant Center.

LD: Living donor

NS: not statistically significant.

UNOS: United Network of Organ Sharing
ABSTRACT PAGE

INTRODUCTION

Obesity represents a barrier to kidney transplantation, but the increasing prevalence amongst renal failure patients has forced some centers to carefully consider such candidates. Morbidly obese patients may be at increased risk of DGF, higher postoperative complications and inferior graft outcomes. Nevertheless, mortality on the waiting list remains significantly higher than after transplant. We have applied minimally invasive surgery to perform kidney transplant in individuals with BMI ≥ 40 kg/m². We compared our results to the national UNOS database.

METHODS

The UNOS registry was reviewed for adult LD kidney transplant recipients with BMI ≥ 40 kg/m² performed from September 2009 to December 2014. We compared transplants performed with robotic technique (RKT) versus patients performed with open surgery at all US centers including our own (OKT). Subgroup analysis in patients with BMI ≥ 45 kg/m² was conducted. We compared outcomes including patient and graft survival, renal function and technical complications.

RESULTS

RKT group had a significantly higher mean BMI overall. The 1-year patient and graft survival rates were similar between groups. Renal function was also similar at 6, 12 and 36 months. Thrombosis caused 1.3% of the graft losses in OKT and 0% in the RKT group. Interestingly, 52.8% of the overall experience in patients with BMI ≥ 45 kg/m² was performed with the robotic technique.
CONCLUSIONS

Robotic surgery offers similar patient and graft survival with comparable renal function to open technique. RKT permits transplantation in extreme BMI categories without additional technical complications. Further studies are required to establish the role of RKT for obese candidates but preliminary data is encouraging.
INTRODUCTION

In the past three decades, obesity has become a common comorbid condition afflicting over 30% of the population in some States(1). Obesity is also a limiting condition for patients with Stage V renal disease to access the opportunity of transplantation(2). The majority of transplant centers consider \( \text{BMI} \geq 40 \text{ kg/m}^2 \) a contraindication for transplant. The possible explanation to restrict access may be due to the perception of increased risk of complications associated with obesity and other comorbidities usually present in this patient population(3). The only definitive recipient risk factor shown to negatively impact the outcomes of the graft is the occurrence of wound infection, which is 40% more likely to occur in patients with a body mass index (BMI) superior to 40Kg/m\(^2\) (4). Obese patients that do not develop a wound infection have similar outcomes to those with normal BMI.

Minimally invasive surgery offers several advantages and recently our group reported the initial outcomes using robotic assisted laparoscopic kidney transplantation in obese patients(5). The occurrence of wound infection was significantly lower in the robotic kidney transplant group than in patients undergoing conventional open kidney transplantation. We wanted to analyze the outcomes of living donor recipients with morbid obesity (defined as BMI \( \geq 40\text{Kg/m}^2 \)) performed with minimally invasive surgery at the University of Illinois compared conventional open approach.
MATERIAL AND METHODS

Retrospective data collection was conducted from the electronic medical records at our institution and obtained from the United Network of Organ Sharing (UNOS) database. We included all adult living donor (LD) kidney transplant recipients performed from September 1st 2009 to December 31st 2014. Recipients with BMI below 40kg/m² were excluded from the analysis. The University of Illinois (ILUI) is the only center in the US performing robotic kidney transplantation (RKT) in obese candidates. Since the majority of the RKT at ILUI were from a living donor, we excluded deceased donor transplants from the analysis. The data collected included: patient and donor demographic information, dialysis status and duration, dialysis in the first week from transplant, induction and maintenance immunosuppression, hospital readmissions, graft function at 6 months, 1 year, 2 and 3 years, technical complications and causes of graft failure and patient death.

We divided the sample into two groups: patients that had their kidney transplant performed using the DaVinci robotic technique at the University of Illinois (RKT), and patients that had conventional open kidney transplant procedure (OKT), including the 9 patients performed at the University of Illinois. We compared the renal function between the groups at 6 months, one, two and three years after transplant. Patient and graft survival rates were compared between the two groups.

Furthermore, we conducted a subgroup analysis of patients with BMI <45Kg/m² and patients with BMI ≥45Kg/m². We compared the renal function as described above and analyzed the patient and graft survival rates in the two subcategories with and without the robotic technique.
Statistical analysis was conducted using SPSS v.21 (IBM, Chicago). Continuous variables were expressed by mean and standard deviation (SD). Categorical variables were expressed by percentage. Continuous variables were compared using the analysis of variance (ANOVA) and categorical variables are compared using t-test. Statistical significance is considered with p<0.05. Kaplan-Meier survival curves were used to express graft and patient survivals. To test for differences between the two groups the log-rank test was utilized.

The Institutional Review Board approved the retrospective review and data collection at our institution with protocol number 2011-1104. UNOS data is deidentified and does not required approval.

RESULTS

From September 2009 to December 2014 a total of 32,356 living donor kidney transplants were performed in United States. Of those, 612 were performed in adult recipients with a BMI $\geq$40Kg/m$^2$, representing 1.9% of the National LD kidney transplant activity in that period of time. Out of 331 transplant centers, 127 centers (38.6%) performed at least one kidney transplant in a patient with BMI $\geq$40 kg/m$^2$, 14 of those accumulated at least 10 procedures in the time period described. The University of Illinois is the transplant center with the most experience in morbidly obese recipients with 76 patients (12.7%), followed by centers with 36 (5.7%) and 32 (5.3%) cases (Table 1). At ILUI, RKT was performed in 67 patients and 9 underwent OKT due to documented severe vascular disease affecting the iliac arteries or presumed hostile abdomen from previous surgery.
Donor Characteristics:

Donor demographic information is represented in Table 2. Donors were significantly younger in RKT group, with a higher mean BMI compared to the OKT donors. The gender distribution was similar in both groups. The RKT group comprised a significantly higher proportion of African American patients, whereas OKT were mainly performed in Caucasian patients. The donor and recipient were predominantly blood related in both groups with no difference between them.

Recipient characteristics:

The recipient’s age at the time of transplant and the gender distribution were similar in both groups. RKT had significantly larger size patients as shown in Table 3. Subgroup analysis of the patients with BMI ≥45kg/m² presented higher mean BMI in RKT than OKT group. The ethnicity distribution was predominantly African American in the RKT group compared to Caucasian in the OKT. The prevalence of Diabetes prior to transplantation was 52.4% in the RKT group compared to 40.2% in OKT (p=NS). Preemptive transplantation was more frequent in RKT but the difference was not significative. The mean waiting time was significantly shorter for patients in RKT group. The length of hospital stay similar for the RKT and OKT groups, it was slightly increased in the subgroup of patients with higher BMI but no difference was found between the two groups.

Induction therapy included steroids in all the patients in the RKT group, compared to 73.8% of patients in OKT (p<0.0001). RKT group received predominantly Thymoglobulin (55.2%) and basiliximab (41.8%) for induction. The OKT group had more
diverse induction therapy, including thymoglobulin (40.7%), Campath® (26.1%), basiliximab (15.8%) or other combinations including rituximab and OKT3 (p<0.0001). Maintenance immunosuppression was mostly steroid-free in RKT (74.6%) compared to OKT that was predominantly using steroid for maintenance therapy (50.8%) (p<0.0001). The majority of patients (88.9%) had a maintenance immunosuppression based on a calcineurin inhibitor in combination with an antimetabolite, generally mycophenolate mofetil or mycophenolic acid, there were no significant differences between the groups in the type of maintenance immunosuppression utilized. Acute rejection during the transplant hospital event was reported in six patients from RKT (9%) versus 12 patients in OKT (2.2%)(p<0.009).

Survival rates:

Patient survival at one year was 96.8% and 98% in RKT and OKT, respectively. At three years, the patient survival for RKT was 96.8% compared to 94.6% in OKT (p=NS). The overall main cause of death was due to infection (2.4%). Cardiovascular death was the second most common reason (1.9%), but none of the patients in RKT group expired due to cardiovascular disease. Other reasons included hemorrhage, malignancy, anoxic brain injury and cerebrovascular disease. There were no significant differences between both groups.

The 1-year crude graft survival was 95.2% and 94.6% for RKT and OKT respectively. The 3 years graft survival was 89.7% for RKT and 90% for the OKT patients, these differences were not found statistically significant (p=0.466). Further
subanalysis did not show a difference comparing each subgroup by the recipient’s BMI category.

Acute rejection was the most frequent cause of graft failure in RKT (4.5%) versus 1.9% in the OKT group. Chronic rejection accounted for 1.5% of graft loses in each group. Primary non-function occurred in one patient in the RKT and 3 patients in the OKT. Furthermore, in the OKT group there were 7 grafts lost due to graft thrombosis, 4 to infection and one to urological complications. None of those complications presented in RKT (Table 4).

*Renal Function:*

The renal function was similar at 6 months; one year, two years and three years follow up (Table 5). Furthermore, analysis was conducted comparing the two BMI subgroups, the renal function at the same intervals was not significantly different. The renal function and the same intervals showed no difference between the BMI subcategories (Figure 1).

The incidence of delayed graft function (DGF), defined by the need of dialysis in the first week, was 3% in RKT group (two patients) compared to 5.7% in OKT (p=0.504). In the first six months after transplant, the readmission rates were 44.8% and 31.7% in both groups respectively (p=NS). The reasons for readmission were not indicated in UNOS.
DISCUSSION

Obesity has become a frequent comorbidity afflicting over 30% of the population in some State in USA(1). The prevalence amongst renal failure patients is also increasing(6), at the end of 2012 the mean BMI of patients in renal replacement therapy was 31.2 Kg/m² compared to 28.5 Kg/m² just ten years prior(7). As of December 2014, a total of 53,717 (7.6%) renal failure patients on dialysis had a BMI ≥40 kg/m²; of note only 17.4% of those patients were listed for kidney transplant(2, 8). There is also a discrepancy of access to transplantation based on gender and ethnicity(2, 8). Women with BMI ≥40 kg/m² are 50% less likely to be listed for transplant than women with normal range BMI, whereas obese males have only 25% decreased chances of getting listed (8). Once on the transplant list, the likelihood of transplantation within 3 years of listing for women with BMI ≥40 kg/m² is 35%, compared to the males at 56%.

Additionally, African American patients have a have half the possibility to living donor kidney transplantation compared to Caucasian patients (9). Considering that in 2012, more than 30% of the dialysis patients were African American and the females in this group have the highest mean BMI at 33.25 Kg/m², they are the most disadvantaged group of patients to access transplantation(7).

Furthermore, obese candidates being listed are frequently made inactive with request of losing weight. Only half of those patients are reactivated after reaching the requested target in weight loss; the other half never become active on the list again(10). Most transplant centers do not consider obese patients with BMI higher than 40 Kg/m² for renal transplant due to the increased morbidity and mortality observed(2).
Other possible argument against transplantation of obese candidate may have to do with the observed association between obesity and the development of proteinuria and focal segmental glomerulosclerosis in non-renal failure patients(11). Factors such as prolonged ischemia time, delayed graft function (DGF), as well as longer warm ischemia time and hyperfiltration injury may potentially contribute to further renal dysfunction and accelerated graft loss in obese recipients. There are controversial opinions exist regarding the association between obesity and acute rejection episodes(12-16). Furthermore, obesity has been associated with increased incidence of delayed graft function(14, 17-19). Recently, a meta-analysis including over nine thousand patients concluded that the relative risk of DGF in obese patients was 1.41 (95% CI 1.27-1.57) but there was no association to increased risk of rejection(14). The incidence of DGF in living donation is significantly lower compared to deceased kidney transplantation, in our cohort of patients the rate of DGF in both of our study groups was similar to the reported in non-obese patients (20).

Despite this possible explanations for accelerated graft loss, obese candidates have a survival benefit compared to waiting on the list for a deceased kidney transplant while on dialysis(21, 22). This may have contributed to a paradigm change since most recent reports support kidney transplantation in obese candidates(18, 22-25), while prior to year 2000 most publications found that obesity was associated with increased mortality and graft loss(14). The realization that transplantation offers a survival advantage compared to renal replacement therapy, justify the risk in this patient population(8). To reduce the mortality risk, patients should undergo a scrupulous cardiovascular (CV) assessment, especially since obesity has been linked to increased
Risk for CV death (14). Morbidities associated with surgical procedures in obese individuals include: prolonged hospital stay, thromboembolic events, respiratory complications and wound complications (26, 27). However, in multivariable analysis including most common known factors to affect the graft outcomes, the development of wound infection was found to negatively affect the graft function regardless of the recipient’s BMI (4). On that note, morbid obese patients have 40% risk to develop a wound infection and consequently higher risk of worse graft outcomes.

The ILUI center has very wide experience in complex surgical procedures performed with the Da vinci robot platform, which facilitated the application in kidney transplantation. We introduced in our center robotic kidney transplantation for obese recipients in the attempt to minimize the risk of wound infections. In our initial experience, the rate of wound infection was significantly reduced in obese patients with RKT compared to OKT (5).

Historically, we do not refuse to list candidates based solely on high BMI. However since the successful application of robotic surgery to kidney transplantation, we have accumulated 12.7% of the country’s experience with high BMI recipients, notably we have performed more than half of the US volume of patients with BMI $\geq45\text{kg/m}^2$ with no impact in the outcomes compared to the UNOS registry.

There are some controversial opinions regarding the utilization of scarce resources in obese candidates but the argument is irrelevant in the presence of a living donor. Some practitioners argue that obesity is considered a reversible condition and patients should lose weight to optimize their chances for better outcomes (3). Unfortunately, obese renal failure patients have difficulty in achieving weight loss not
unlike general population, which may significantly prolong their waiting time or excluded from transplant.

Several centers have proposed bariatric surgery prior to transplantation to optimize the candidates and reduce their waiting time (28, 29). We do offer the procedure to candidates if they do not have a living donor but would not delay transplant surgery otherwise. RKB can be done as soon as the donor and recipient are medically cleared, weight loss may be encouraged after the transplant. Weight gain after transplant has been associated with worse CV and metabolic profiles (16); bariatric surgery may be beneficial to address the issues after transplant (30, 31). Additionally, we are presently conducting a randomized trial comparing RKT and simultaneous Sleeve gastrectomy to RKT alone, with good preliminary results.

Thanks to the successful application of the RKT in obese candidates. BMI alone is not considered a limit to accept a patient at our institution. This strategy opens the opportunity for transplantation to candidates previously rejected due to obesity and could improve the observed discrepancy for minorities in access to kidney transplantation.

**CONCLUSION**

Robotic kidney transplantation for morbidly obese candidates offers similar results to the conventional open approach. RKT opens the opportunity for transplantation to increasing numbers of obese renal failure patients often denied transplant regardless BMI, race and gender.
REFERENCES