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CASE REPORT

Living donor renal transplantation with incidental renal cell carcinoma from donor allograft

Jose A. Lugo-Baruqui,[1,2] Giselle Guerra,[1,3] Linda Chen,[1,2] George W. Burke,[1,2] Judith A. Gaite[1] and Gaetano Ciancio[1,2]

1 The Lillian Jean Kaplan Renal Transplant Center of the Division of Transplantation, Miami, FL, USA
2 Department of Surgery, University of Miami Miller School of Medicine and Miami Transplant Institute at the Jackson Memorial Hospital, Miami, FL, USA
3 Department of Medicine, Division of Nephrology of the University of Miami Miller School of Medicine, Miami, FL, USA

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Correspondence
Gaetano Ciancio MD, Department of Surgery, Division of Transplantation, University of Miami Miller School of Medicine, P.O. Box 012440 (R-440), Miami, FL 33101, USA.
Tel.: 305 355 5111;
fax: 305 355 5134;
e-mail: gciancio@med.miami.edu

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Summary

To report our series of cases with living donor kidney transplant by laparoscopic nephrectomy with incidental renal cell carcinomas (RCC) at the time of transplant. We performed a search of cases of renal allografts from living donors with incidental tumors which were confirmed as RCC in final pathology. The graft nephrectomy was performed via hand-assisted laparoscopic procedure. All cases underwent partial nephrectomy of the tumor during the back-table preparation of the graft and sent for pathological analysis. We performed 435 living donor kidney transplants at our Institution and identified four cases consistent with the diagnosis of RCC. Two of them were clear cell type, one papillary and one multilocular RCC. All the tumors presented at stage I of TNM classification. After a median follow-up of 36 months, three patients remain free of dialysis with good allograft function. One noncompliant patient presented with a glomerular filtration rate (GFr) below 15 ml/min after a BK viral infection. At the end of follow-up period, all patients had remained free of tumor. Donors with suspicious renal masses might be accepted for living donation. Partial nephrectomy before transplantation could offer a cure for the disease without risks for the recipient with therapeutic benefit for the donor.

Introduction

The waiting list for patients with end-stage renal disease (ESRD) is growing constantly, and the gap between the number of patients awaiting kidney transplants and those actually receiving have increased. The latest UNOS registered number of patients for kidney transplant is 107 563 with a total of 16 892 donations in 2013 (5731 living donors) [1]. This disparity has fomented the search for alternatives to increase the donor pool including nonrelated living donors, expanded criteria donors (ECD), and donors after cardiac death (DCD). It is important to identify potential donors who could expand the organ pool without compromising the outcome of the transplant and survival of recipient.

Over the years, the experience of kidney grafts that are transplanted with tumors has been increasing. The widespread availability of imaging studies and thoughtful examination of living kidney donors in the pretransplant evaluation has elevated the finding of incidental neoplasms in these patients. Among these lesions, renal cell carcinoma (RCC) is the most common solid lesion in the kidney and accounts for approximately 90% of all kidney malignancies. Some of the risk factors consistent with increased risk for RCC are male sex, the age of the donor (older than 60 years), obesity, and history of smoking and hypertension [2].

Objective

The aim of this study was to report our series of cases and discuss follow-up of patients with living donor kidney

transplant by laparoscopic nephrectomy in which incidental renal cell carcinomas were diagnosed after transplantation.

Patients and methods

We performed a search of cases of renal allografts from living donors with incidental tumors which were confirmed as RCC in final pathology. The graft nephrectomy was performed via hand-assisted laparoscopic procedure in all of the patients. Informed consent was obtained from every donor and recipient in whom an incidental mass was identified during donor workup (Fig. 1). Also, recipients were informed about the potential risk for malignancy spread, technical considerations, and probable requirement of partial graft nephrectomy with reduced renal mass. All the donors underwent laparoscopic hand-assisted donor nephrectomy. After the nephrectomy was completed, the organs were flushed with cold preservation solution with Ringer lactate and mannitol. Tumors were resected with partial nephrectomy on the back-table preparation of the graft (Fig. 2a), procuring adequate resection with approximately 5 mm margin from macroscopic edge of the tumor. After resection of the tumor, the renal graft was repaired in two layers: first layer with running PDS 4-0 and second layer with hemostatic horizontal mattress with PDS 3-0 suture with oxidized regenerated cellulose pledgets (Surgicel ®, Ethicon INC Somerville, NJ). Finally, fibrin sealant (Evicel ®, OMRIX Biopharmaceuticals Ltd, Israel) was applied on the surface of the repair site to add hemostatic strength to the reconstruction. As the repair was done in back table, this added in average 15 min to the cold ischemia time of the graft (Fig. 2b and c). All the samples were sent for frozen-section pathological exam. After confirmation of margin-free resection of the tumor, the transplantation process in the recipient proceeded at the discretion of the surgeons.

After transplant, all patients presented immediate graft function and began standard immunosuppression by institution protocol (references). All patients received dual induction therapy with thymoglobulin (1 mg/kg/× 3 daily doses) and basiliximab (20 mg × 2 doses) as well as low-dose maintenance tacrolimus (target trough level: 4-6 ng/mL) and corticosteroids (500 mg methylprednisolone for 3 days). As soon as patients tolerated the oral medication, enteric-coated mycophenolate sodium (EC-MPS, Myfortic, Novartis Pharmaceuticals) was started at 720 g twice daily. The postoperative course of donors and recipients was

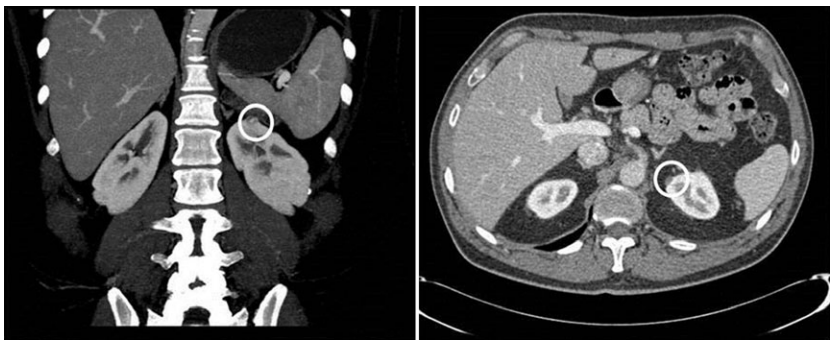

Figure 1 CT scan of the abdomen of a donor which demonstrated a left renal tumor in upper pole of about 0.9 cm diameter (white circle). This kidney was decided to be used for donation.

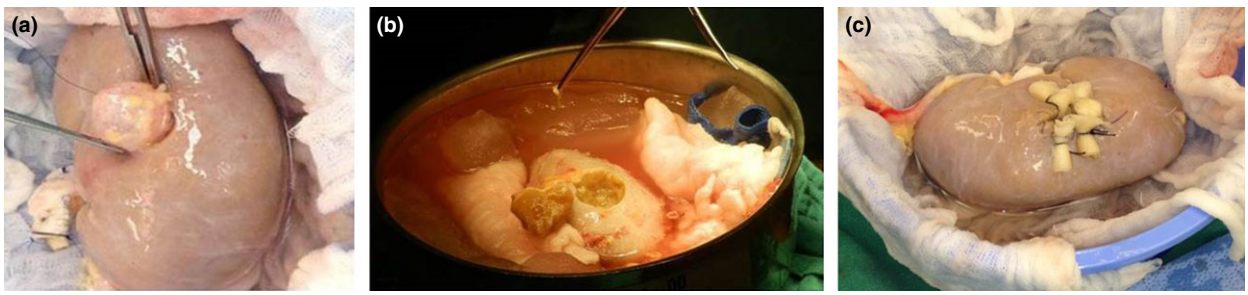

Figure 2 Back-table preparation of renal graft with tumor excision and reconstruction. Renal tumor excision with 5 mm margins (a, b). Reconstruction of renal graft in two layers with pledgets for hemostasis (c).

uneventful. Donors were discharged after a mean stay of 2.1 days and recipients after a mean stay of 4.5 days.

Results

In the period comprised from 2009 to 2013, we performed 435 living donor kidney transplants at the Miami Transplant Institute. Among these cases, we identified four cases of renal allografts from living donors with incidental tumors. The mean age of donors was 49 years (range from 41 to 54 years old) and that of recipients was 57.1 years (range from 20 to 79 years old). Two donors were women. For the recipients, the causes of end-stage renal disease (ESRD) were diabetes mellitus (DM) nephropathy in two of them, and focal-segmental glomerulosclerosis in one case, and nephritis due to chronic nonsteroidal anti-inflammatory drugs diagnosed in the last case. In only one case, the donor was nonrelated. Immunological compatibility was tested in all patients, all of them ABO compatible, with 4 HLA matches in two cases, 2 antigen matches in one case, and only one without matches.

All tumors were consistent with diagnosis of RCC in final pathology. Two of them were clear cell type, one papillary and one multilocular renal cell carcinoma. The mean tumor diameter was 1.4 cm (range from 0.9 to 2.5 cm). For three of them, Fuhrman grade I was reported and only one was Fuhrman grade II. All the tumors presented at stage I of TNM classification (T1aN0M0). All specimens were reported with negative margins in final histologic reports.

After median follow-up of 36 months follow-up, the mean recorded nadir serum creatinine was 1.4 mg/dl. After this period, all patients remained free of hemodialysis. Three patients remain with adequate graft function with mean serum creatinine level of 1.4 mg/dl. One patient was noncompliant with maintenance immunosuppression after a BK virus infection and presented with a GFR less than 15 ml/h. At the end of follow-up, all patients (donors and recipients) had remained free of tumoral recurrence as evidenced by control renal ultrasound studies.

Discussion

The gap between patients with ESRD on the waiting list and those who receive a kidney transplant is increasing. The use of marginal kidneys may help patients become hemodialysis independent and improve quality of life. Although there is no classification that defines "marginal" kidneys, many grafts that were disposed in the past are being transplanted nowadays with good results [3]. Traditionally, grafts coming from older donors, those with complex anatomical variants, untreated metabolic diseases of donors, and of potentially transmissible diseases such as infections or malignancies were discarded in consideration of recipient outcome [4].

The use of renal grafts from donors with extra-renal malignancies diagnosed at the time of organ procurement has been extensively reviewed before [5]. Desai *et al.* updated the risk of cancer transmission from donors characterized as high or unacceptable risk from the cancer registry data. The donors and recipients were identified from the UK Transplant Registry (1990–2008). Of 17 639 donors, 202 (1.1%) had a history of cancer, including 61 donors with cancers considered as unacceptable high risk for transmission. No cancer transmission was noted in 133 recipients of organs from these 61 donors. Ten years after transplantation, the additional survival benefit gained by transplanting organs from donors with unacceptable high-risk cancer was 944 life years (confidence index 851–1037), with a mean survival of 7.1 years per recipient (CI 6.4–7.8) [6].

Musquera *et al.* [7] reported their experience with donors with incidental masses in living and deceased kidney donors including seven patients with clear cell carcinoma (all stage I/IV) with no local recurrence or metastasis after 32 months follow-up. In another study by Nicol *et al.*, they reported their results with 43 kidneys transplants with incidental renal masses from cadaveric and living donors, which were resected with clear margins in back table. The main difference between our protocol and theirs was that for their recipients they chose only elderly patients or those with comorbidities that rendered significant risk of death without prompt transplantation. After 9 years of follow-up, they report only one recurrence in same kidney graft at a distant site from the original resection [8]. Previous reports of transplanted kidneys with proven RCC of low grade (Fuhrman I and II) have shown that the risk of transmission to recipient is low after 5 years when they were resected with negative margins [9]. More recently, the research conducted by the Disease Transmission Advisory Committee (DTAC) Malignancy Subcommittee stated that solitary RCC that is well differentiated (Fuhrman grade I-II) and <1 cm in diameter was considered as minimal risk, while lesions between 1.0 cm and 3.5 cm in diameter were considered as low risk (0.1–1% transmission) if they were completely resected prior to transplant [10].

Flechner and Campbell also reviewed the use of kidneys with small renal tumors for transplantation [5]. They considered that live donors create a potential ethical conflict between those treating patients with renal masses and those with an interest in renal donation. The best available treatment for patients with small renal tumor consists in nephron-sparing tumor excision, as this approach provides for the maximum amount of residual kidney function and enhances survival. In the case of an individual undergoing a live donor evaluation in which a small renal tumor is

detected, a careful analysis of risk and benefit for the potential donor and the recipient is indicated. At this point, the decision is complex and should involve a multidisciplinary approach. Rabbani *et al.* reported a risk of 0.4% of metachronous contralateral kidney after 10 years of observation [11]. Patients who are highly motivated to donate who are newly diagnosed with small renal tumors should be treated like a nondonor patient. We do not recommend biopsy of the renal mass due to its limitations and overtreatment of the incidental tumors that may be found. Patients with renal mass who are undergoing living donor evaluation should be referred to centers with expertise in nephron-sparing techniques, not transplant centers [5].

In our series of patients, tumor resection was successful without any kind of complications for the donor. At current follow-up, all donor and recipient patients are free of tumor, with only one patient with loss of graft function due to noncompliance after transplant. Donor and recipient follow-up is protocol based on abdominal ultrasound. In case, a suspicious mass is found proper imaging studies are taken. Current OPTN/UNOS living donor policy demands transplant programs to provide living donor follow-up data up to 2 years after donation [12]. Long-term care after donation is directed to the primary care physician. In these special situations, PCP should be informed to maintain strict observation in donors for any signs of malignancy recurrence.

Another point to discuss would be the type of maintenance immunosuppression for this type of cases. It has been suggested that mammalian target of rapamycin (mTor) inhibitors has antineoplastic properties. Drugs in this class such as everolimus and sirolimus are used in some maintenance immunosuppressant protocols after kidney transplant. These drugs possess well-known immunosuppressant and antiproliferative characteristics. Their antineoplastic properties have been studied in transplantation in specific malignancies, with apparent risk reduction for *de novo* cutaneous and noncutaneous carcinomas [13]. Everolimus has been approved by the FDA for the treatment of patients with advanced RCC since 2009. Motzer *et al.* reported the results of 416 patients with advanced RCC in the classic RECORD-1 study. In this study, authors conclude that treatment with everolimus prolongs progression-free survival in patients with RCC treated with placebo or with other vascular endothelial growth factor-targeted (VEGF) therapy like sunitinib or sorafenib [14]. As stated in the immunosuppressive protocol, none of the patients in this study were converted to mTor inhibitors during follow-up. There are reports in which patients with renal transplants have been switched to mTOR-based regimes after diagnosis of other solid malignancy with anecdotical regression of the tumor [15,16]. To our knowledge, there is no single prospective study that compares mTor inhibitors to other immunosuppression protocols as primary end point for the evaluation of RCC prevention after kidney transplant. Further research is needed before recommendations in maintenance immunosuppression can be made for these types of patients.

Conclusion

As we expand the candidate pool for living kidney donation, donors with suspicious renal masses might be accepted for donations. From the oncologic point of view, a partial nephrectomy with free margins before transplantation could offer a cure for the disease without risks for the recipient; furthermore, there is therapeutic benefit for the donor. Close follow-up protocol for monitoring of tumor recurrence is advised for both the donor and recipient. Prior to making any recommendations for using renal grafts with suspicious masses or which immunosuppression therapy to use in these patients, we require a longer follow-up period to observe the risk of recurrence.

Authorship

JAL-B: participated in writing of the manuscript, research design, performance of research and data analysis. GG: participated in performance of research. LC: participated in performance of research. GWB: participated in performance of research. JG: participated in writing of the manuscript. GC: participated in writing of the manuscript, research design, performance of research and data analysis.

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References

1. Organ Procurement and Transplantation Network (OPTN), U.S. Transplants performed January 1988 - January 2014, Health Resources and Services Administration, http://optn.transplant.hrsa.gov/, Last access April 12th, 2014.
2. Ljungberg B, Bensalah K, Bex A, *et al. Guidelines on renal cell carcinoma*. Arnhem (The Netherlands): European Association of Urology (EAU), 2013: 56 pp.
3. Friedersdorff F, Roller C, Manus P, *et al.* Fate of finally transplanted deceased donor kidneys initially rejected at other kidney transplantation centers. *Urol Int* 2014; **93**: 474.
4. Maggiore U, Cravedi P. The marginal kidney donor. *Curr Opin Organ Transplant* 2014; **19**: 372.
5. Flechner SM, Campbell SC. The use of kidneys with small renal tumors for transplantation: who is taking the risk? *Am J Transplant* 2012; **12**: 48.

6. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg* 2014; **101**: 768.
7. Musquera M, Pérez M, Peri L, *et al.* Kidneys from donors with incidental renal tumors: should they be considered acceptable option for transplantation? *Transplantation* 2013; **95**: 1129.
8. Nicol D, Fujita S. Kidneys from patients with small renal tumours used for transplantation: outcomes and results. *Curr Opin Urol* 2011; **21**: 380.
9. Buell JF, Hanaway MJ, Thomas M, *et al.* Donor kidneys with small renal cell cancers: can they be transplanted? *Transplant Proc* 2005; **37**: 581.
10. Nalesnik MA, Woodle ES, Dimaio JM, *et al.* Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. *Am J Transplant* 2011; **11**: 1140.
11. Rabbani F, Herr HW, Almahmeed T, Russo P. Temporal change in risk of metachronous contralateral renal cell carcinoma: influence of tumor characteristics and demographic factors. *J Clin Oncol* 2002; **20**: 2370.
12. Guidance for Developing and Implementing Procedures to Collect Post-Donation Follow-up Data from Living Donors, Developed by the OPTN/UNOS Living Donor Committee, Revised and Updated 2013
13. Hernández D, Martínez D, Gutiérrez E, *et al.* Clinical evidence on the use of anti-mTOR drugs in renal transplantation. *Nefrologia* 2011; **31**: 27.
14. Motzer RJ, Escudier B, Oudard S, *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**: 449.
15. Monaco AP. The role of mTOR inhibitors in the management of posttransplant malignancy. *Transplantation* 2009; **87**: 157.
16. Manuelli M, De Luca L, Iaria G, *et al.* Conversion to rapamycin immunosuppression for malignancy after kidney transplantation. *Transplant Proc* 2010; **42**: 1314.