Kidneys With Small Renal Cell Carcinoma Used in Transplantation After Ex Vivo Partial Nephrectomy

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ABSTRACT

Background. The increase in the prevalence of end-stage renal disease in developed countries and the shortage of deceased donors have made it necessary to increase the graft pool by means of several strategies, such as living donation, non–heart-beating organ donors, and expanded-criteria donors. This study aimed to assess the short-term outcomes of donor kidneys with small ($\leq$3.5 cm) renal cell carcinoma (sRCC) and to evaluate the possibility of using marginal kidneys in renal transplantation.

Methods. Patients undergoing nephrectomy for sRCC who agreed to donate their kidneys were enrolled in the study. Seven dialysis patients aged 27-54 years agreed to undergo transplantation with sRCC kidneys. All of the transplantations were performed in Shandong Province Qianfoshan Hospital from May 2012 to March 2017. The function of transplanted kidneys was evaluated after surgery by testing and comparing parameters such as creatinine clearance rate, delayed graft function, and tumor recurrence.

Results. The graft function of the transplanted kidneys was recovered to normal in all of the 7 patients who received sRCC kidneys. The latest serum creatinine levels before publication ranged from 59 to 102 μmol/L in the 7 recipients (normal range of serum creatinine: men, 54-106 μmol/L; women, 44-97 μmol/L). No tumor recurrence was noted 31-58 months after surgery in the recipients.

Conclusions. According to short-term follow up (3-5 years), kidney transplantation in selected patients can be considered for kidneys having small incidental tumors. The use of marginal organs, such as those with sRCC, can increase the donor pool for kidney transplantation.

A large number of patients suffer from end-stage renal disease (ESRD). The midyear 2001 global estimates showed the total population with diabetes to be >1.1 million, and if current trends in ESRD prevalence continue, the size of this population will expand at a rate of 7% per year [1]. Patients who receive renal replacement therapy (RRT) commonly experience considerable physical and psychologic distress. Transplantation increases life expectancy by 3-15 years compared with patients remaining on dialysis, depending on the age and comorbidities of the recipients [2]. Renal transplantation has increased in frequency, but a shortage of donor kidneys exists. Therefore, attempts have been made to take advantage of various marginal kidneys in renal transplantation, eg, the leftover organ after partial nephrectomy due to cancer [3]. Unfortunately, the transplant community broadly deems that the presence of most cancers, including renal cancer, is a contraindication for organ donation [4]. However, a kidney diagnosed with small renal cell carcinoma (sRCC) undergoing nephron-sparing surgery usually has a low recurrence rate (<3%), and the leftover organ has increasingly been accepted as a donor option for renal transplantation [5].

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Table 1. The Size and Pathology of Small RCCs

Case	Tumor Diameter	Donor	Pathology	Pathology Grade	Pathology Stage
1	2.1 cm	F (42 y)	Clear cell carcinoma	I	pT1a
2	3.5 cm	F (53 y)	Clear cell carcinoma	II	pT1a
3	2.5 cm	M (45 y)	Clear cell carcinoma	II	pT1a
4	3.2 cm	M (48 y)	Clear cell carcinoma	II	pT1a
5	3.0 cm	M (50 y)	Clear cell carcinoma	III	pT1a
6	2.8 cm	F (47 y)	Clear cell carcinoma	II	pT1a
7	2.3 cm	F (45 y)	Clear cell carcinoma	II	pT1a

Abbreviation: RCC, renal cell carcinoma.

Based on the current evidence, the transmission of malignancy with the transplanted kidney has been shown to be rare (0.015%-1%) in recent clinical practice [6].

With the shortage of donor kidneys, living-donor marginal renal transplantation has been used in some cases [4]. On the one hand, patients having sRCC generally request a complete nephrectomy. Furthermore, these patients are very willing to donate their discarded kidneys if needed. On the other hand, patients who are diagnosed with kidney failure and can not tolerate the pain of dialysis may desire to undergo transplantation with a marginal organ. In the present study, we report our experience of using marginal kidneys after ex vivo surgical removal of sRCC as the donor organs for renal transplantation in 7 cases. Our short-term observation demonstrated that using marginal organ is a feasible and beneficial option for renal transplantation.

METHODS

The study protocol was approved by the Ethics Committees of Shandong Province Qianfoshan Hospital and Shandong University. Potential donors were recruited among patients who were diagnosed as having a single sRCC (2.1-3.5 cm in diameter based on imaging approach [7]; the preoperative diagnosis was pT1a disease in all 7 patients [Table 1]) in the Department of Urinary Surgery of Shandong Province Qianfoshan Hospital from May 2012 to October 2014. Although each potential donor was informed about the magnitude of undergoing a radical nephrectomy for such a mass, all patients insisted on undergoing the nephrectomy because recurrence in the contralateral kidney and risk for future renal dysfunction is always possible. After confirming the surgery type, potential donors understood that their discarded kidneys might be used in kidney transplantation to save patients with end-stage renal failure if they chose to donate. After much consideration and discussion with their family, they all consented to the resection and possible donation of their donor kidneys if deemed to be medically usable (Fig 1).

All reasonable risks and benefits of using a transplanted kidney with a renal mass, including tumor recurrence and multiplicity, were outlined and discussed with the recipients [8]. After both parties were informed, written consent was obtained for the procedure. They were also informed that the donor kidneys had sRCC. They agreed to undergo the transplantation and understood the possibility of tumor relapse. The procedures were performed as follows.

Each patient was transported to the operating room where general anesthesia was induced and an indwelling Foley catheter inserted. Then the patient was positioned on the contralateral side, and laparoscopic ports were established according to standard procedure [9]. The kidney was dissected under laparoscopic vision in the working space, which was maintained by the insufflation of carbon dioxide at a pressure of 12-14 mm Hg [10]. After exposing and isolating the Gerota fascia to the level of the iliac vessel, an incision was made in the Gerota fascia and the ureter was separated [8]. The renal artery and vein were isolated in a retrograde fashion to the renal hilus along the track of the ureter. The kidney artery and vein were clamped with the use of a Hem-o-Lock clamp. The renal artery and vein were dissected freely. Electrocautery was used to divide the adrenal arteries, and the gland was freed from the tail of the pancreas. The dissected mass was retracted downward and its upper margin dissected from the peritoneum. Finally, the original trocar was removed from the original incision when the laparoscopy sacks were introduced, and the isolated kidney was put into a specimen bag that had been introduced into the working space from the original incision. The trocar's incision was opened and the extended kidney was removed.

After finishing the radical nephrectomy, the kidney was immediately placed into an ice preservation solution and moved to the recipient operation room. At the same time, the surface of the kidney was further closely inspected to ensure that no tumor mass remained. The renal tumor specimen was sent to the pathology laboratory, and histologically examined. The 7 renal masses revealed clear cell carcinoma of the following grades: grade I, pT1; grade II, pT1; grade II pT1; grade II pT1; grade III, pT1; grade II, pT1; and grade II, pT1. A portion of the marginal tissue was sent for frozen-section analysis to confirm the absence of any residual tumor [8]. Once the pathologist confirmed the absence of tumor in the resected margin, the renal

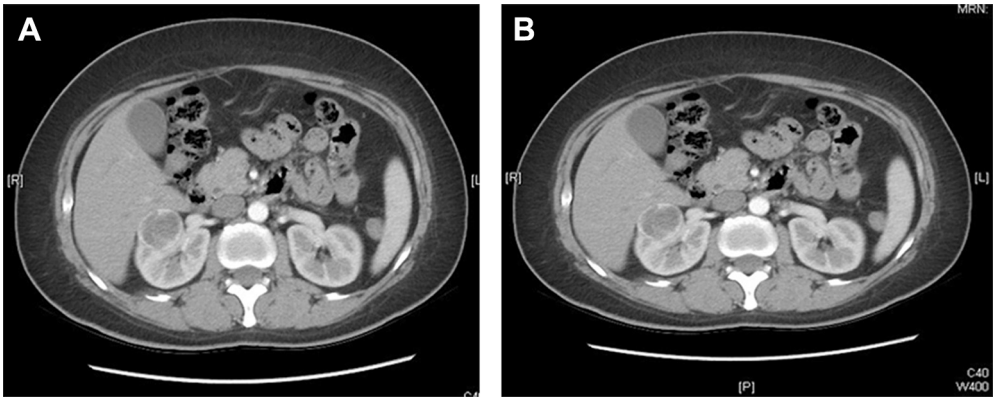

Fig 1. Computerized tomographic scan with renal carcinoma in one of the donor patients.

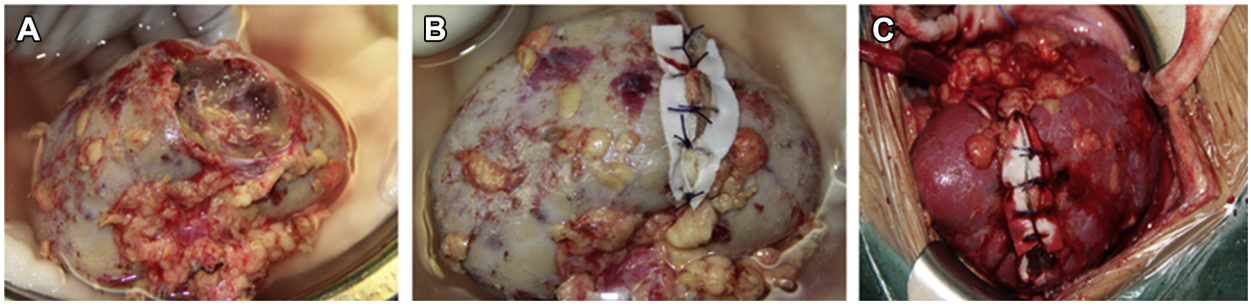

Fig 2. Back-table preparation of kidney graft with identification of the tumor. (**A**) Partial nephrectomy discarded with appropriate surgical margins; (**B**) final repair of the graft before transplantation; and (**C**) transplant kidney after blood perfusion.

defect was reconstructed with the use of an interrupted 3-0 polydioxanone suture with surgical bolsters (Fig 2).

All patients received maintenance immunosuppression with the use of tacrolimus and mycophenolate mofetil and rapid steroid withdrawal. Drug levels were closely monitored at regular clinic appointments. Data were collected specifically on any perioperative complications and from regular clinic visit notes, blood evaluation, and regular imaging of the allograft and renal bed to monitor for tumor recurrence, which included an annual chest x-ray, ultrasonography of the renal bed, and surveillance computerized tomography as necessary. Serum creatinine data from the recipient were collected before the transplantation and at 30 days, 1 year, and the last follow-up. All data reported are expressed as the mean.

RESULTS

Table 2 presents the data from the 7 cases of sRCC kidney transplantation. After renal transplantation, all 7 donors had a good recovery. Relevant laboratory reports indicated that serum creatinine levels were restored. After a short-term follow-up (31-58 mo), no tumor recurrence was evident on imaging in the 7 donors (Fig 3). Regarding the recipients, 5 patients had no delayed graft function, whereas 2 had delayed graft function immediately after transplantation. However, the delayed graft function of those 2 patients was temporary, and the graft function began to recover after 1 week. The latest serum creatinine levels ranged from 59 to 102 μmol/L in the 7 recipients. No tumor recurrence was noted at 31-58 months after surgery in the recipients. Based on these short-term follow-up outcomes and current evidence, the immunosuppressive condition after renal transplantation did not lead to the onset of tumor recurrence. Moreover, the use of marginal organs, such as these with sRCC, could increase the donor pool.

DISCUSSION

Despite the substantial increase in renal transplantation, a significant deficit in donor kidneys is still evident, because various other RRTs can not provide patients with ESRD optimal quality of life. Furthermore, many patients die each year while waiting for a transplant [11]. Renal transplantation is a better method compared with other forms of RRTs available for the growing population of patients with ESRD, because it offers better survival and quality of life for the recipient. However, despite the shortage of donor kidneys, many patients with ESRD can not wait to undergo renal transplantation. Fortunately, various marginal kidneys are used in renal transplantation. Historically, these organs have been discarded for transplantation, and minimal information is available on the isolated cases. The Israel Penn International Transplant Tumor Registry, a voluntary registry collecting data on malignancies in transplant patients since 1968, reported only 14 cases of kidneys (11 from living and 3 from cadaveric donors) in which sRCCs were unexpectedly discovered at the time of donor kidney procurement; after excising the tumor, the kidney was transplanted [12]. Cases of allograft RCC have been reported in the medical literature [12]. The mean duration between transplantation and development of RCC was reported to be ~3.5 years in one case series [13]. In the present case series, all of the potential donors who were diagnosed with sRCC opted to undergo radical nephrectomy before receiving the

Table 2. Relevant Data of 7 Cases of Small RCC Transplantation

Case	HLA Mismatches	Recipient	DGF	Complications	Serum Creatinine Before Transplantation	Most Recent Serum Creatinine After Kidney Transplant	Follow-up Time
1	3	F (35 y)	Yes	No	1,033.54 μmol/L	82 μmol/L	36 mo
2	4	M (57 y)	No	No	897 μmol/L	84.6 μmol/L	42 mo
3	3	M (29 y)	Yes	No	1,123.4 μmol/L	82.10 μmol/L	39 mo
4	4	M (49 y)	No	No	953.1 μmol/L	84.9 μmol/L	40 mo
5	3	M (57 y)	No	No	864 μmol/L	102 μmol/L	58 mo
6	3	M (50 y)	No	No	1,128.6 μmol/L	83 μmol/L	31 mo
7	3	F (51 y)	No	No	924 μmol/L	59 μmol/L	33 mo

Abbreviations: RCC, renal cell carcinoma; DGF, delayed graft function.

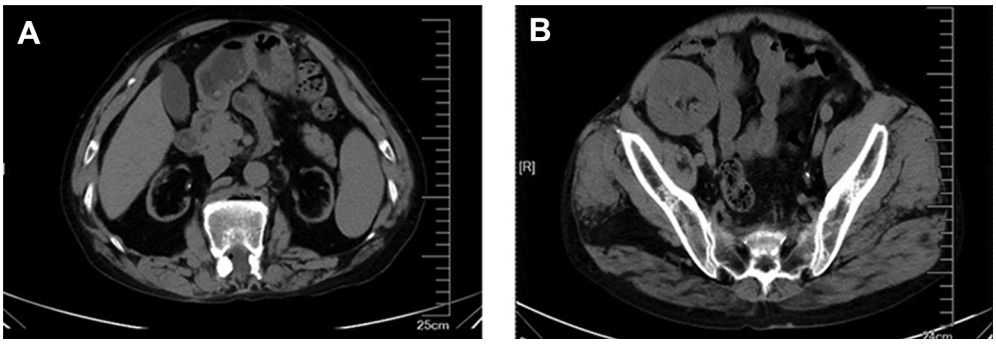

Fig 3. Computerized tomographic scan in one of the recipients after renal transplantation in 2017.

donor kidney. All potential donors understood and agreed to donate their discarded kidneys before undergoing surgery. As a result, 7 dialysis patients would benefit from renal transplantation.

The present results suggested that living donors discovered with incidental renal malignancies should not be prohibited from donating their kidneys, which might be a potential solution to the broad global shortage of donor kidneys worldwide. Although previous authors have suggested alternate solutions, none have reported a series in a previously matched living donor population [8].

Both donors and recipients in this series were followed for up to 40 months, with no tumor recurrence or metastasis in either group. Kidney function after renal transplantation returned to normal in all patients. It is well known that RCC is an immunogenic tumor capable of inducing an immune response [14]. In transplantation settings, the possibility that the recipient's immune system does not target tumors that arise in the donor organ has been suggested. Moreover, much speculation exists about immunosuppressive regimens and differences among cancers [15].

This study had some limitations. First, although the patients remained tumor free at follow-up, the follow-up was relatively short in managing RCC, and thus the results are somewhat limited. This limitation stresses the importance of maintaining a routine follow-up of living donors with incidentally discovered renal masses, including scheduled chest x-rays and ultrasonography of the renal bed to ensure no tumor recurrence, as well as periodic computerized tomography to exclude systemic metastasis. Moreover, consideration should be given to altering immunosuppression regimens to sirolimus-based protocols, which could minimize tumor resurgence in these allografts, although this was not intentionally done in the present recipients [16,17].

Long-term follow-up is not yet available for the present cases [18]. It is anticipated that the patients will have a good long-term outcome without recurrence, based on similar reports in the literature [19].

CONCLUSION

In a relatively short-term follow-up period (31-58 mo), kidney transplantation with the use of marginal kidneys derived from sRCC nephrectomy in selected patients can be considered as a feasible and beneficial strategy for renal transplantation. This may at least in part ameliorate the significant shortage in donor organs.

REFERENCES

[1] Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol 2002;13(Suppl 1):S37–40.

[2] Lugo-Baruqui A, Guerra G, Arocha A, Burke GW, Ciancio G. Use of kidneys with small renal tumors for transplantation. Curr Urol Rep 2016;17:3.

[3] Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation 2002;74:1281–6.

[4] Davis CL, Delmonico FL. Living-donor kidney transplantation: a review of the current practices for the live donor. J Am Soc Nephrol 2005;16:2098–110.

[5] Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. Mayo Clin Proc 2000;75:1236–42.

[6] Nalesnik MA, Woodle ES, Dimaio JM, Vasudev B, Teperman LW, Covington S, et al. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. Am J Transplant 2011;11:1140–7.

[7] Thuroff JW, Abrams P, Andersson KE, Artibani W, Chapple CR, Drake MJ, et al. [EAU guidelines on urinary incontinence]. Actas Urol Esp 2011;35:373–88. Spanish.

[8] Sener A, Uberoi V, Bartlett ST, Kramer AC, Phelan MW. Living-donor renal transplantation of grafts with incidental renal masses after ex-vivo partial nephrectomy. BJU Int 2009;104:1655–60.

[9] Ju X, Li P, Shao P, Lv Q, Wang Z, Qin C, et al. Retroperitoneal laparoscopic nephrectomy combined with bench surgery and autotransplantation for renal cell carcinoma in the solitary kidney or tumor involving bilateral kidneys: experience at a single center and technical considerations. Urol Int 2016;97:473–9.

[10] Ono Y, Kinukawa T, Hattori R, Yamada S, Nishiyama N, Mizutani K, et al. Laparoscopic radical nephrectomy for renal cell carcinoma: a five-year experience. Urology 1999;53:280–6.

[11] Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for End-Stage Liver Disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–6.

[12] Trofe J, Buell JF, Beebe TM, Hanaway MJ, First MR, Alloway RR, et al. Analysis of factors that influence survival with post-transplant lymphoproliferative disorder in renal transplant

recipients: the Israel Penn International Transplant Tumor Registry experience. Am J Transplant 2005;5:775–80.

[13] DeLong MJ, Schmitt D, Scott KM, Ramakumar S, Lien YH. Multicentric papillary renal carcinoma in renal allograft. Am J Kidney Dis 2003;42:381–4.

[14] Bukur J, Malenica B, Huber C, Seliger B. Altered expression of nonclassical HLA class Ib antigens in human renal cell carcinoma and its association with impaired immune response. Hum Immunol 2003;64:1081–92.

[15] Barama A, St-Louis G, Nicolet V, Hadjeres R, Daloze P. Renal cell carcinoma in kidney allografts: a case series from a single center. Am J Transplant 2005;5:3015–8.

[16] Wong G, Chapman JR. Cancers after renal transplantation. Transplant Rev (Orlando) 2008;22:141–9.

[17] Boratynska M, Watorek E, Smolska D, Patrzalek D, Klinger M. Anticancer effect of sirolimus in renal allograft recipients with de novo malignancies. Transplant Proc 2007;39:2736–9.

[18] McHayleh W, Morcos JP, Wu T, Shapiro R, Yousem S, Appleman L, et al. Renal cell carcinoma from a transplanted allograft: two case reports and a review of the literature. Clin Genitourin Cancer 2008;6:53–5.

[19] Thomalla JV. Renal cell carcinoma in a renal allograft successful treatment with 5 year follow-up. Clin Med Res 2004;2:151–3.