Multiorgan Transplant From a Donor With Solid Renal Masses: An Initial Experience and Clinical Considerations

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ABSTRACT

Background. Patients with early-stage renal cell carcinoma (RCC) are considered to be eligible donors. Although preliminary experience in using kidneys of specific pathologic types, mainly those with small renal masses (SRMs), have been established, multiorgan utilization of the same donor with SRMs is limited.

Methods. One deceased donor whose left-side kidney was diagnosed with Fuhrman grade I RCC was included. The tumor mass in the kidney was removed through partial nephrectomy according to the gold standard. Then, 3 transplant surgeries were performed, in which 1 recipient accepted kidney transplant after tumor exeresis, 1 simultaneous heart-kidney (the contralateral one) transplant, and 1 liver transplant. Recipients were followed up according to our standard protocol for renal cancers. (All allografts were allocated in compliance with the Declaration of Helsinki and the Declaration of Istanbul.)

Results. After 32 months, no radiographic findings showed any morphologic changes of the lesion, and all patients were in good condition, with neither tumor recurrence nor allograft rejection or infection. No complaints such as pain, oliguria, dyspnea, nausea, or fatigue were recorded.

Conclusions. To the best of knowledge, this initial work takes the lead in elaborating the organ utilization of multiorgan donors with SRMs. We hope the experience will provide support for cross discussion concerned with multiorgan transplant from tumor-affected donors in clinical practices, further expand the donor pool and address the donor shortage problem.

KIDNEY transplantation is the treatment of choice for patients with end-stage renal disease (ESRD) [1]. The use of marginal organs such as kidneys with small renal masses (SRMs) has been suggested for kidney transplantation as a new allograft source [2-6]. However, the use of most cancer-affected organs, including those affected by renal cancer, was limited as donor-transmitted cancers were found in many cases [7]. However, over decades, different centers have reported successful renal transplantation cases, among which few recurrence cases occurred [8-11]. This achievement was attributed to the clinical application of partial nephrectomy (PN). PN is the gold standard treatment for SRMs (<4 cm) in the general population [3,12], yielding low renal cell carcinoma (RCC) recurrence rates (nearly 1.47%) [6,13]. Additionally, reasonable active surveillance follow-up strategy is important to control the recurrence of RCC, which helps detect metastasis as early as possible and reduce the risk for donor-transmitted cancer to 0.05% [14-16] as well. Based on these literatures, nowadays, with rare compromising oncologic outcomes and similar outcomes in renal function, kidneys with SRMs excised are acceptable sources for transplantation [17]. The widely accepted pathologic types are mainly RCC in pathologic stage of pT1

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(predominantly the clear-cell subtype, followed by chromophobe type, lipoma, and oncocytoma) [5,18-19].

Progress has been made in using kidneys with SRMs excised. Some articles suggest that contralateral kidney use should also be considered [20]. Although views are different on discussion of RCC metastasis risk to contralateral renal, the risk is relatively low based on the existing literature. On the one hand, immunosuppression would not significantly increase the recurrence of RCC after renal transplantation [21-22]. On the other hand, using affected kidneys with tumor removed would neither increase the risk for recurrence significantly [6,20]. Given the low risk for progression of the aforementioned tumors, if we can combine with active surveillance, which is a potential alternative to surgery to the selected patients, it is possible to further expand the use of donor organs. In this work, we aim to implemented multiorgan transplant (MOT) protocol derived from a donor with SRMs, and discussed the potential feasibility and ethical pitfalls, which may further give evidence to solve the shortage of donor organs in the current situation.

MATERIALS AND METHODS

After obtaining approval from the Ethics Committee of Changhai Hospital, School of Medicine, Second Military Medical University and patients' informed consents, we selected the donor kidney by first gaining overall understanding of tumor characteristics based on collected follow-up information, determining benign or malignant tumors; then SRMs (<4 cm) were removed by PN, with TNM (tumor, node, metastasis) staging confirmed by intraoperative frozen section. Only stage I tumors (T1N0M0) were included. After retrieval of the 3 organs, 3 surgeries were performed by experienced surgeons who had >10 years of experience in the liver, heart, and kidney transplantation field, respectively. To determine the effects of MOT after SRM excision, the recipients were followed up over 2 years immediately after the surgeries. The 4 allografts were actively monitored through ultrasonography every 6 months until now and magnetic resonance imaging every year.

Patient characteristics including age, sex, and tumor size in pathologic specimens, data of surgery type and immunosuppressant regimen, and specific laboratory data during follow-up were extracted from the medical records and are shown in Table 1. The process is shown in Fig 1.

RESULTS

All recipients were fully informed about tumor transmission risk, after which both the first-degree relatives of the deceased donor and the correspondent recipients provided surgical consents. After approval issued by the ethics committee, the donor underwent nephrectomy with mass excised in bench surgery. The mass was immediately analyzed in frozen section, so as to assess histology and negative surgical margins, followed by implantation of the affected kidney. The contralateral kidney, heart, and liver were then transplanted to the other 2 recipients. All allografts were allocated by the Organ Procurement Organization. All follow-up data of the 3 cases were included in the analysis.

Tumor characteristics are shown in Fig 2. The tumor was 14 mm in diameter, had a clear margin, was pT1a stage, and was low grade (Furhmann I/IV). Histologic results revealed that predominant cell type was clear cell renal carcinoma with all margins were negative.

The donor was 51 years old, male, and dying of cerebrovascular disease (ie, hypertensive intracerebral hemorrhage and secondary brain herniation). Three recipients underwent surgery. The recipient who received an affected kidney was 52 years old, female, and diagnosed with ESRD. The other 2 recipients received the remaining organs. Among these recipients, 1 was 35 years old, female, diagnosed with ESRD and dilated cardiomyopathy, and received the contralateral kidney and the heart, whereas the other was aged 56 years, male, diagnosed with hepatocellular carcinoma and received the liver. The characteristics and immunologic matching of donors and recipients are shown in Table 1.

Transplantations were performed by department of organ transplantation from the same institution, applying the conventional surgical technique. No complications such as bleeding, infection, pain, oliguria, dyspnea, nausea, or fatigue were reported.

The immunosuppressant treatments after transplantation were a conventional regimen including thymoglobulin, mycophenolic acid, and steroids, with tacrolimus + mizoribine for the affected kidney recipient (with SRM excision), tacrolimus + mycophenolate mofetil+ prednisone for the simultaneous heart-kidney recipient (the contralateral kidney), and tacrolimus + rapamycin for the liver recipient.

All recipients were followed up regularly for 32 months and all had proper organ (kidney, heart, liver) function with normal results in creatinine range, type B-natriuretic peptide and alanine transaminase. Nadir data of all patients were collected 1 week after the surgical procedures. No tumoral recurrence occurred.

DISCUSSION

According to Chinese National Renal Data System, the number of patients with ESRD in China has reached 0.67 million. Although 10% of these patients need kidney transplantation, only 10,000 on the waiting list actually receive kidney transplantation per year [5]. Actually, organ shortage is a worldwide problem. Only a minority of patients with ESRD ultimately receive a transplant. Organ demand continues to outstrip supply in most developed nations [23,24].

To increase the pool of organs available, grafts using kidneys with SRMs and the contralateral ones are now considered as suitable options for transplantation [25,26]. RCC accounts for 2% to 3% of all cancers and is the most common type among those incidentally found in donors aged 60 years or older [25,27]. The American Urological Association and European Association of Urology updated their guidelines and recommended PN for T1a renal tumors as the standard treatment choice [28-30]. PN appears to be a good alternative to radical nephrectomy [31], even for tumors ≤7 cm in diameter, although better patient survival rates are observed in those with tumors <4 cm [12,32]. The low risk for recurrence and progression strongly supports use of these grafts. Currently, many transplantation centers are accepting contralateral kidneys as eligible

Table 1. Donor and Recipient Characteristics

						Blood Biochemical Parameters			
	Sex	Age at Surgery	Clinical Diagnosis	Graft	HLA	Nadir	End of Follow-Up (2020-2011)	Complications	Immunosuppressant (Dose)
Donor (deceased)	M	51	Cerebral vascular accident (HICH and cerebral hernia)		A2, A24, B15, B55, C1, C1, DR8, DR9, DQ3, DQ4, DP5, DP5	eGFR: 63.72 mL/min			
Recipient 1	F	52	ESRD	Kidney (left, affected)	A11, A31, B60, B60, C7, C10, DR8, DR11, DQ4, DQ7	eGFR: 96.78 mL/min	eGFR: 91.48 mL/min	No	FK506: 1 mg q12h MRZ: 50 mg twice a day
Recipient 2	F	35	ESRD, DCM	Heart-kidney (right,	contralateral)	A2, A11, B39, B46, C1, C7, DR8, DR9, DQ3, DQ6, DP2, DP13	eGFR:		97.35 mL/min BNP: 16 pg/mL
eGFR: 97.35 mL/min BNP: 88 pg/mL	No	FK506: 1 mg q12h	MMF: 360 mg q12h Prednisone: 2.5 mg QD						
Recipient 3	M	56	HCC	Liver	N/A	ALT: 17 U/L TBil: 13 mmol/L	ALT: 19 U/L TBil: 11 mmol/L	No	FK506: 0.5 mg (q12h) Rapa: 1 mg QD

ALT, alanine transaminase; BNP, type B-natriuretic peptide; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female; FK506, tacrolimus; HCC, hepatocellular carcinoma; HICH, hypertensive intracerebral hemorrhage; M, male; MMF, mycophenolate mofetil; MRZ, mizoribine; RAPA, rapamycin; TBil, total bilirubin

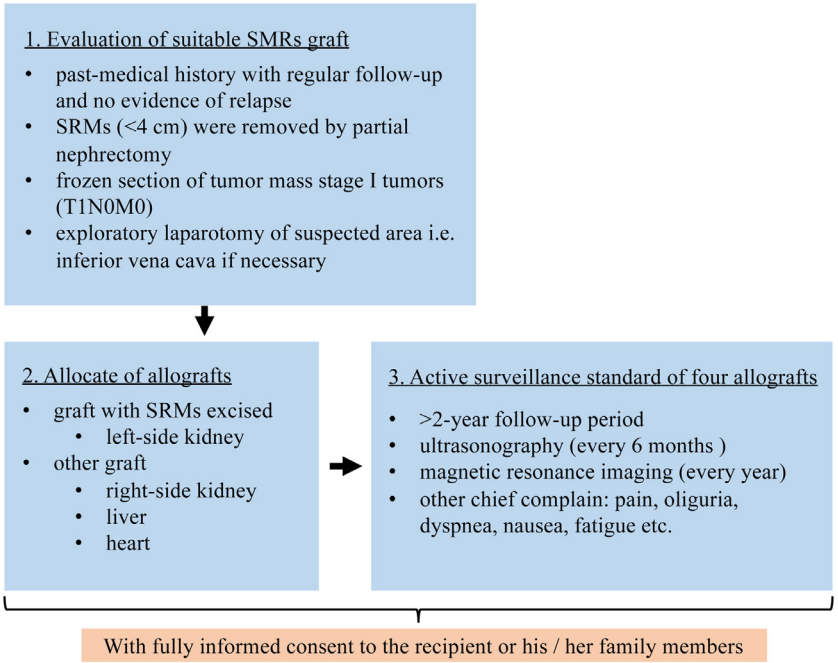

Fig 1. Scheme of work process. 1. Evaluation of suitable graft with SMRs. 2. Allocation of allografts by OPO, IRB, and in compliance with the Declaration of Helsinki and the Declaration of Istanbul. 3. Active surveillance standard of 4 allografts. IRB, Institutional Review Board; OPO, Organ Procurement Organization; SMR, small renal mass.

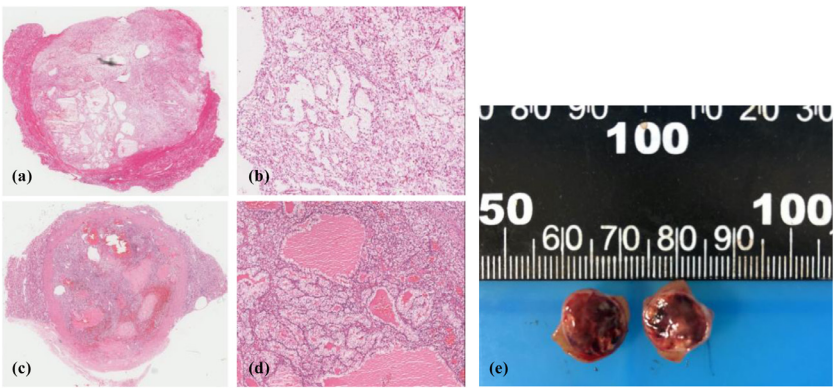

Fig 2. Tumor characteristic. The paradigm shows the gross and microscopic finding of the tumor mass on inferior pole of the left-side kidney: (**A, B**) frozen section; (**C, D**) paraffin section; and (**E**) tumor mass on gross, with scale above. The histological result: clear cell carcinoma, Fuhrman grade I.

grafts [33,34] and the European Committee updated its guidelines for choosing kidneys with T1a renal tumors as a donor choice [35]. In some cases, grafts cannot be used when tumors are very close to the hilum or >3 cm. Although related cases were rarely reported, these conditions were regarded as ineligible for transplantation. One study reported a rare case of tumor-to-tumor systematic metastasis, in which they found an intratumoral cancer by frozen section analysis but did not pay attention to it [36]. Therefore, in addition to strictly restricting pathologic types, to find qualified tumor grafts, one must also consider tumor location and have a standard procedure for use, such as analysis of intraoperative frozen section, which is also a routine requirement.

In an era where the demand for organs far outweighs the supply, maximizing the utility of deceased donor organs with SRMs is reasonable, although the utilization of the remaining organs of patients with cancer may be questioned for lack of ample evidence to justify a clear benefit for recipients. But in some cases, there is a need to make use of other organs from the same donor. As we know, the number of MOTs has increased considerably over the past 2 decades, and ≤90% included kidney transplantation [37]. Renal dysfunction is common among patients awaiting heart transplantation and may lead to irreversible renal failure that requires renal replacement therapy. In this respect, patients with adult congenital heart disease are facing higher risk for unique physiology imposed by the disease [38]. This population is always present on lists for MOT, in particular heart/lung and heart/liver transplants. Thus, simultaneously receiving a kidney and a heart or liver transplant may improve outcomes in patients with multiorgan failure and advanced kidney disease [39]. As we did with recipient 2 (Table 1), the simultaneous heart-kidney transplant would be a better choice for this patient.

Another problem in this study was the immunosuppression states of recipients, which could lead to different outcomes of these patients. Still, there is no evidence suggesting that

immunosuppression has a negative effect on the natural history of localized RCC [40]. Still, we should be aware of the possibility of tumor transmission, as known or unknown malignancies in organ donors can be transmitted to immunosuppressed recipients [41]. At present, if ethical issues are not a concern, the evidence shows relatively low recurrence rates of small RCC after renal transplantation, leading to good outcomes. Kidneys with SRMs should not be a taboo for organ transplant and are worthy of further research and application.

As mentioned previously, our work is based on relevant literatures including high-level clinical trials and case reports or series of medical records. Although tumor-affected organ transplantation has gradually matured, and extended to contralateral kidney use, research reports on multiple organ utilization besides the affected organ itself are still in short supply. In this study, we discussed the use of the remaining organs and comprehensively considered the tumor recurrence as well as follow-up strategies, providing supplementary research for organ utilization of affected donors.

Limitations

In interpreting the results of this study, certain limitations must be considered. Most importantly, only a small population was enrolled in our study. Limited by the principle of organ allocation, we cannot obtain all the organs of the same donor, so only 1 "pair (1 deceased donor + all allografts from him or her)" were completed in a short time. The relatively low number of donors and large variety of allografts precluded us from performing multivariate analysis to identify the effect of SRMs on allograft outcomes. But we insist on the paired SRM kidney analysis design when examining the outcomes of remaining allografts from the same donor, because the approach would control donor factors and temporal effects, strengthening the results. Furthermore, a registration and reporting system should be established so that every kidney with SRMs from deceased donors and remaining "paired" allografts can be reported publicly.

CONCLUSIONS

By using the affected graft and remaining organs from the same deceased donor, we achieved the use of multiorgan from one affected donor. The risk for recurrence was low with close follow-up to detect it in an early stage. For now, none of the recipients experienced recurrence. This work would complement the evidence for affected graft transplant and maximize organ use of deceased donors with SRMs.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.transproceed.2021.08.006.

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