Transplantation of Restored Kidneys From Unrelated Donors After Resection of Renal Cell Carcinoma: Results From 10 Patients

Y. Ogawa[a,*], K. Kojima[b], R. Mannami[b], M. Mannami[b], K. Kitajima[c], M. Nishi[d], S. Ito[e], N. Mitsuhata[e], and H. Afuso[f]

[a]Department of Urology, Tokyo-West Tokushukai Hospital, Akishima-city, Tokyo-to, Japan; [b]Department of Urology, Uwajima Tokushukai Hospital, Uwajima-city, Japan; [c]Department of Urology, Kagoshima Tokushukai Hospital, Kagoshima-city, Japan; [d]Department of Urology, Saint Martin's Hospital, Sakaide-city, Japan; [e]Department of Urology, Kure-Kyosai Hospital, Kure-city, Japan; and [f]Department of Urology, Okinawa Chubu Tokushukai Hospital, Okinawa-city, Japan

ABSTRACT

Purpose. To relieve the chronic shortage of donor kidneys, we conducted a prospective kidney transplantation trial using kidneys removed from 10 unrelated patients (51 to 79 years of age) who had undergone nephrectomy for small renal cell carcinoma (1.5 to 3.9 cm) of low-to-moderate complexity based on RENAL (radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior location relative to polar lines) nephrometry (objective description helpful for operative indication and planning).

Methods. Donors were selected from among 15 patients who opted to undergo nephrectomy for small renal cell carcinoma. A total of 76 dialysis patients 34 to 85 years of age who agreed to undergo restored kidney transplantation were recruited as transplant candidates.

Results. In stage 1 (5 cases), high-risk patients were selected without human leukocyte antigen testing, and accelerated acute rejection occurred in 4 of 5 recipients. This trial was subsequently extended with human leukocyte antigen testing, and an additional 5 patients were enrolled in stage 2. Eight recipients, including 4 recipients with a history of renal transplantation, experienced rejection; 1 patient resumed dialysis 35 months after transplantation. The most recent serum creatinine levels ranged from 1.10 to 3.19 mg/dL in the 9 recipients with functioning grafts and from 0.84 to 4.68 mg/dL in the 10 donors. No tumor recurrence was noted at 32 to 58 months after surgery in either the recipients or the donors.

Conclusions. Restored kidney transplantation using kidneys with a small renal tumor seems suitable for carefully selected high-risk recipients and, in particular, elderly kidneys can also function well. Avoiding cancer transmission, fair recipient selection, close follow-up, and a well-organized tracking system warrant further study.

THE LONGSTANDING shortage of donor kidneys is a challenging problem in many countries worldwide. In 1995, the transplantation of kidneys following ex vivo resection of small tumors was first reported in 14 recipients without any recurrence (Penn I) [1]. Based on that experience, Buell et al. concluded that kidneys with small (0.5 to 4 cm in diameter), incidental renal cell carcinomas (RCCs) of low histological grade could be used for transplantation after

This trial was financially supported by the Tokushukai Medical Group (the procedure and follow-up cost was approximately $100,000 for each case).

*Address correspondence to Yoshihide Ogawa, Department of Urology, Tokyo-West Tokushukai Hospital, 3chome-1-1 Matsubara-cho, Akishima-city, Tokyo-to, #196-0003 Japan. E-mail: yoshihide.ogawa@tokushukai.jp

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360 Park Avenue South, New York, NY 10010-1710

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tumor excision with a low risk of recurrence in the recipient [2]. Mannami et al. reported the results of restored kidney transplantation in 42 patients, including 8 kidneys obtained after nephrectomy for RCC, among a variety of efforts to expand the donor kidney pool for high-risk recipients [3]. In 2008, Nicol et al. reported an additional 43 cases of restored kidney transplantation after nephrectomy for renal tumors, including 31 cases of RCC (diameter <3 cm) [4]. The transplantation of kidneys removed to treat small RCCs has been reported by several investigators and performed in a total of 97 patients to date [5]. The transmission of malignancy with the transplanted kidney has been rare (0.015% to 1%) in recent clinical practice given stringent donor criteria [6–8]. Meticulous surgical techniques and careful pathological examinations are also essential [9]. According to a report by the Amsterdam Forum, a history of malignancy (including RCC) typically excludes living-related kidney donation [10]. To optimize organ usage, Nalesnik et al. recently evaluated the risk of transmitting certain cancers, such as solitary, well-differentiated (Fuhrman nuclear grade I-II) RCCs [11–13]. The suggested risk categories (1 cm in diameter for minimal risk, 1 to 2.5 cm for low risk, and 4 to 7 cm for intermediate risk) have been incorporated with clinical considerations into several guidelines [14], including the European Association of Urology guidelines for renal transplantation [15], UK guidelines [16], the World Health Organization Notify project [17], the ATOS group in Spain [18], and the Kidney Health Australia Caring for Australasians with Renal Impairment [19]. The Notify project also warned of special cases of unusual transmission and recurrence; thus, the risks associated with specific case series should be reported. Despite differences in the interpretation of the risk categories, all of these guidelines unanimously accept that renal tumors <4 cm in diameter (stage pT1a) with a Fuhrman grade of I to II pose either a nonstandard or a standard risk [17].

Although the risk of transmitting malignancy is low with careful assessment of donor kidneys, all recipients must be informed of this risk [20,21]. Based on a comparison of the risk of death while on dialysis with the risk of developing cancer from a transplanted kidney [22,23], high-risk patients may be the most appropriate candidates for the transplantation of kidneys removed to treat small RCCs [24–26]. More than 80% of small renal tumors (<4 cm) are treated by nephrectomy in Japan, and approximately 2000 kidneys are discarded after this process every year [27]. Deceased kidney donors are scarce in Japan, with only 150 to 200 deceased renal allografts available annually. Living-related kidney transplantation is primarily performed, with kidneys from 1389 donors used in 2011 [28,29]. A total of 13,389 of 309,946 dialysis patients are registered with the Japan Organ Transplant Network as seeking renal transplantation [28,30]. The mean waiting time for kidney transplantation is 14 years and 6 months, leading to an increase in transplant tourism in Japan [31–34]. Altruistic donation and paired kidney exchange programs are not currently accepted in Japan. In addition, the transplantation of kidneys with benign or malignant diseases was banned by the Japanese government in 2007 with the exception of transplants conducted as part of clinical trials (the medical fee must be paid by the hospital).

After carefully examining the literature on the suitability of discarded kidneys for transplantation [2–4,24,25,35,36], we focused on the use of kidneys with small RCCs (<4 cm in diameter on imaging studies) out of various disease kidneys, that is different from the previous study [3]. No prospective outcome data were available; thus, we conducted a prospective, open clinical trial utilizing 5 kidneys with small RCCs that were restored and transplanted into 5 unrelated recipients (stage 1) [37]. This trial was subsequently extended to enroll an additional 5 patients (stage 2). Here, we report the first prospective clinical trial of restored kidney transplantation using kidneys with small RCCs guided by the nephrometry scoring system.

PATIENTS AND METHODS

This clinical trial of restored kidney transplantation in unrelated recipients with a planned enrollment of 5 patients (stage 1) was approved by the Tokushukai Joint Ethics Committee in July 2009 (registration at US ClinicalTrials.gov: NCT00980317). The trial was financially supported by the Tokushukai Medical Group (the procedure and follow-up cost was approximately $100,000 for each case). The primary trial end points included graft function and tumor transmission up to 1 year after transplantation. The 1-year glomerular filtration rate is a good predictor of long-term graft function [38–40]. There is no general consensus about monitoring patients after treatment for RCC [41]. Tumors typically recur within 2 to 3 years after surgery [42,43]. Secondary end points, including morbidity and adverse events, also were evaluated up to 1 year after transplantation. Serious adverse events (SAEs), including postoperative complications, infections, and rejection, were reported to the Transplant Office and then immediately to the Ministry of Health, Labor, and Welfare. Two trial committees were organized and approved by the Tokushukai Joint Ethics Committee: the Restored Kidney Transplant Committee (composed of 5 members unconnected to the Tokushukai group) and the nonprofit organization Recipient Selection Committee (composed of 5 third-party members). The Restored Kidney Transplant Committee determined whether the kidney donors and recipients met the study inclusion criteria. The first restored kidney transplant procedure was successfully performed on December 30, 2009. After the fifth transplant was performed in August 2010, an extension of the trial was approved after careful review of the 5 patients treated in stage 1. An additional 5 patients were enrolled because of requests from dialysis patients on the waiting list. The tenth transplant was performed in February 2012.

Donor Enrollment

Potential donors were recruited among patients who were diagnosed as having a single, small RCC (<4 cm in diameter on imaging studies) at any of the 7 hospitals approved by the Tokushukai Joint Ethics Committee. Imaging studies were performed to measure the tumor size and location, and the anatomical tumor features were classified according to the RENAL (radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior location relative to polar lines)

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nephrometry score [44], the PADUA (preoperative aspects and dimensions used for an anatomical) classification [45], and the centrality (C) index [46]. The patients were provided information regarding the nature, size, and location of the renal tumor; the possibility of recurrence after surgery; the function of their opposite kidney; possible morbidities; the experience of the surgical team; and treatment options, including nephron-sparing procedures [47]. If the patient opted to undergo total nephrectomy for a small RCC after extensive discussion of other possible treatment modalities, written, informed consent for nephrectomy was obtained. The possibility of donating the removed kidney for transplantation was only presented after the patient elected to undergo a nephrectomy. The potential donors were subsequently approved by the committee.

From December 2009 to February 2012, 15 patients with renal tumors gave permission for their resected kidneys to be transplanted, and 10 patients were ultimately approved by the committee. After the patients provided written consent to donate their kidneys, the possibility of nephron-sparing surgery (NSS) was re-explained. All of the patients chose to undergo a nephrectomy despite the potential merit of NSS. To confirm their intentions and to eliminate coercion, the patients were re-interviewed before surgery by a member of the ethics committee. The patients were informed by the ethics committee member that they had the right to refuse nephrectomy at any time before surgery.

The ethics committee at each donor hospital reviewed the patient criteria according to our checklist and determined their suitability for surgery. The potential donors were then registered with the Transplant Office at Tokyo-West Tokushukai Hospital. The Restored Kidney Transplant Committee held a meeting for each patient to review all of the necessary documents and records and to discuss the donor's eligibility for inclusion.

Recipient Registration and Selection

Dialysis patients throughout Japan who agreed to undergo restored kidney transplantation visited Uwajima Tokushukai Hospital for clinical evaluation. The patients were fully informed about the risk of cancer transmission and surgical morbidity, and the patients who accepted the risks and signed a consent form were subsequently registered with the Tokyo-West Tokushukai Hospital Transplant Office as transplant candidates. A total of 56 dialysis patients ages 31 to 83 years (mean: 58.7 years; 24 in blood group A, 6 in blood group B, 20 in blood group O, and 6 in blood group AB) and 76 patients ages 34 to 85 years (mean: 61.1 years; 30 in blood group A, 12 in blood group B, 26 in blood group O, and 8 in blood group AB) were enrolled as transplant candidates for stages 1 and 2, respectively. Each time a potential donor was registered and enrolled in the trial, the 5 most suitable transplant candidates with the same blood group were selected by the Recipient Selection Committee based on the results of the clinical evaluations using our selection criteria, which included medical and psychosocial risk factors [48,49]. The selection of recipients was primarily based on ABO compatibility and stage 1 clinical scores. Immunological risk factors (panel reactive antibody and human leukocyte antigen mismatch) and a history of previous kidney transplantation and blood transfusion were added as selection criteria for the extended trial (stage 2) [48]. Cross-matching between the 5 transplant candidates and the potential donors was also important for selection because many patients were highly sensitized, including patients with a history of transplantation or blood transfusion.

The Restored Kidney Transplant Committee examined the medical records and consent forms of the 5 transplant candidates for each selection and discussed the cases to prioritize transplant candidates based on the report by the Selection Committee and the immunological test results. All of the selected candidates were again informed about donor disease and the possibility of cancer transmission. After again agreeing to undergo restored kidney transplantation, the candidate with the highest priority was called to the hospital to prepare for surgery. The ethics committee of Uwajima Tokushukai Hospital provided the final approval for the procedures after reviewing all data concerning both the potential donor and the recipient and the minutes from all committee meetings.

RESULTS

A total of 8 male and 2 female patients 51 to 79 years of age (mean ± SD: 65.3 ± 10.2 years) with small renal tumors were judged to be suitable kidney donors by the Restored Kidney Transplant Committee. In addition to these 10 donors, 5 additional potential donors were registered with the Transplant Office. These additional potential donors were rejected by the committee because of the following protocol violations: tumor diameter >4 cm in 3 patients, participation in another clinical trial by 1 patient, and insufficient renal function because of diabetic nephropathy in 1 patient. Four donor kidneys were harvested at Uwajima Tokushukai Hospital, 4 at Kure-Kyosai Hospital, and 1 kidney each at Kagoshima and Okinawa Chubu Tokushukai Hospitals. The surgical technique, either laparoscopic or open nephrectomy [41,50], was based on the surgeon experience and personal preference. Open nephrectomy was chosen for all patients. Of the 10 donors, 3 were blood group type A, 3 were type B, and 4 were type O. All kidneys had a single tumor that ranged from 1.5 to 3.9 cm in diameter (Table 1). The renal tumor was a clear cell carcinoma in 9 patients and a granular cell carcinoma in 1 patient. All tumors were stage pT1a in all donors. The RENAL tumor scores ranged from 6 to 9, indicating low-to-moderate complexity [44] (Fig 1). Blood loss during nephrectomy ranged from 100 to 1000 mL (433 ± 316 mL). The operating time ranged from 1 hour and 40 minutes to 5 hours and 15 minutes, and the total ischemic time ranged from 1 hour and 46 minutes to 9 hours and 56 minutes, comparable with the results of the EORTC intergroup phase 3 study [51]. The tumor was excised with an adequate border (1 cm) of healthy parenchyma [52]. Upon arrival at the transplanting hospital, the kidney was confirmed to be cancer-free according to the pathological report of the cut surface provided by the donor hospital. As soon as the kidney arrived at Uwajima Tokushukai Hospital, the cut surface was sutured and repaired on the second table, which required 5 to 53 minutes. The fifth kidney had a positive margin, requiring additional resection to be cancer-free. The frozen sections were similar to the final pathology in all cases. The restored kidneys were transplanted into 10 unrelated recipients ages 46 to 66 years (Table 2). The transplantation procedure lasted between 1 hour and 56 minutes and 3 hours and 39 minutes (Table 3). The donor kidney from a blood group B patient was transplanted into an AB recipient in the seventh case because no suitable

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Table 1. Characteristics of Donor Patients and Tumors, including Blood Type, Renal Function, Latest Most Recent Serum Creatinine, Tumor Size, and RENAL Nephrometry Score

Case Number, Age, Sex	ABO, Rh	eGFR/DTPA-GFR of Donor Kidney (mL/min)	Latest Serum Creatinine (mg/dL)	Tumor Diameter (cm)	RENAL Nephrometry Score	PADUA Score	C Index
1. 51 y, M	B Rh(+)	76/30.32	1.30	3.9	6	6	2.7
2. 57 y, M	O Rh(+)	88/44.69	1.17	3.5	6	8	2.4
3. 79 y, M	O Rh(+)	40/27.84	4.68	2.0	6	9	2.1
4. 61 y, M	B Rh(+)	64/34.62	1.65	3.5	7	9	1.6
5. 69 y, M	A Rh(+)	62/22.80	1.45	3.8	7	10	1.9
6. 71 y, M	A Rh(+)	68/36.62	1.02	3.8	8	10	2.0
7. 77 y, F	B Rh(+)	55/26.92	1.11	2.4	6	9	3.9
8. 64 y, M	O Rh(+)	103/45.85	0.84	3.5	8	9	2.3
9. 73 y, M	A Rh(+)	73/42.00	1.21	3.7	9	11	2.5
10. 51 y, F	O Rh(+)	66/35.86	0.98	1.5	6	7	4.5

RENAL, radius, exophytic/endophytic properties, nearness to a collecting system or sinus, anterior/posterior, location relative to polar lines; eGFR, estimated glomerular filtration rate; DTPA, diethylene triamine pentaacetic acid; M, male; F, female.

group B recipient patient was available. Transplantation was performed in the right iliac fossa in 6 recipients. In 4 recipients who previously underwent transplantation, transplantation was performed in the left iliac fossa (Table 3). Four recipients required blood transfusion (4 to 6 units) during transplantation. A retroperitoneal hematoma developed in the sixth recipient, but no other major perioperative complications (hematoma or urinoma) were noted. All 10 recipients received triple-agent immunosuppression that was gradually tapered. In stage 1, 4 recipients survived an accelerated acute rejection that required plasma exchange and hemodialysis. Some of these patients subsequently experienced more rejection episodes. Three patients experienced multiple SAEs. One patient (no. 4) survived 6 SAEs, and the graft functioned well until 35 months after surgery. However, this patient died of cardiac failure because of arrhythmia and chronic renal failure 40 months after surgery. Among stage 2 patients, 4 recipients experienced rejection episodes but did not require hemodialysis. The most recent serum creatinine levels ranged from 1.10 to 3.19 mg/dL in the 9 surviving recipients and from 0.84 to 4.68 mg/dL in the 10 donor patients (Tables 1 and 4). RCC recurrence was not noted during the follow-up period (32 to 58 months) in either the recipients or the donor patients (Table 4).

In the third donor (79 years of age), kidney function worsened, and the serum creatinine level was 4.68 mg/dL 4 years and 5 months after nephrectomy. In the recipient (62 years of age), kidney function improved, and the serum creatinine level was 2.04 mg/dL 4 years and 5 months after transplantation. The restored kidneys from donors ages 71 to 79 years continue to function well in recipients ages 46 to 62 years. In these recipients, the serum creatinine levels ranged from 1.10 to 2.37 mg/dL at 36 to 53 months after transplantation, suggesting that kidneys from donors over 70 years old are not necessarily of poor quality.

DISCUSSION

Kidney transplantation is generally regarded as the treatment of choice for end-stage renal disease with respect to survival, quality of life, and cost [53–56]. Graft survival rates and other long-term outcomes are similar for elderly patients and patients younger than 60 years. Thus, the presence of comorbidities should be the only clinical criterion for excluding elderly patients as kidney transplant candidates [57]. The projected life expectancy after transplantation is 17 to 19 years, compared with only 5.84 years for patients on dialysis [58–61]. On average, recipients of marginal kidney transplants live 5 years longer than dialysis patients on the transplant waiting list, whereas ideal deceased kidney recipients gain a 13-year survival benefit [62].

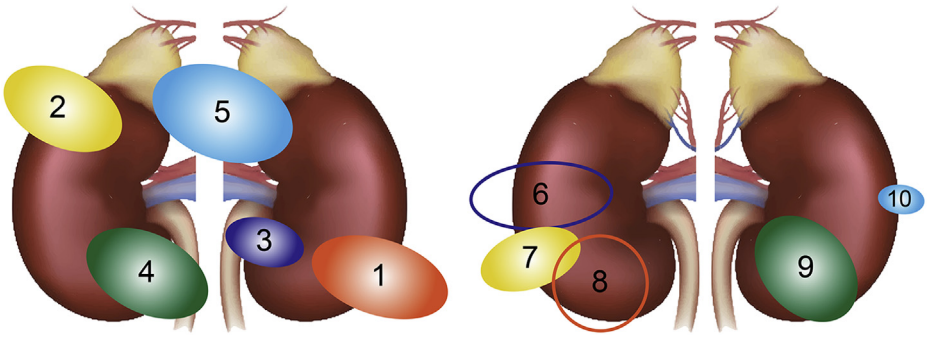

Fig 1. Sizes and locations of the 10 renal tumors.

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Table 2. Recipient Demographic Factors, Including Blood Type, Renal Pathology, Duration of Hemodialysis/Peritoneal Dialysis, Transplant History, and Duration of Graft Function

Case Number, Age, Sex	ABO, Rh	Renal Pathology	HD/PD Duration	Transplantation History	Graft Survival (Transplantation Date)
1. 47 y, F	B Rh(+)	Immunoglobulin A nephropathy	10 mo	None	4y, 10 mo (Dec. 30, 2009)
2. 54 y, F	O Rh(+)	CGN	1 y, 9 mo	None	4 y, 6 mo (Apr. 6, 2010)
3. 62 y, F	O Rh(+)	PKD	1 y, 4 mo	8 y	4 y, 5 mo (Apr. 27, 2010)
4. 66 y, M	B Rh(+)	DM nephropathy	3 y, 10 mo	3 y	4 y, 2 mo (Jul. 24, 2010)
5. 55 y, F	A Rh(+)	CGN	3 y, 7 mo	None	4 y, 1 mo (Aug. 24, 2010)
6. 46 y, M	A Rh(+)	RPGN	9 y, 11 mo	None	3 y, 9 mo (Jan. 12, 2011)
7. 56 y, F	AB Rh(+)	CGN	1 y, 9 mo	None	3 y, 8 mo (Jan. 30, 2011)
8. 65 y, F	O Rh(+)	PKD	14 y	None	3 y, 4 mo (Jun. 1, 2011)
9. 54 y, M	A Rh(+)	CGN	9 y, 5 mo	1 mo	3 y, 0 mo (Sept. 14, 2011)
10. 56 y, F	O Rh(+)	CGN	8 y, 5 mo	2 y, 10 mo	2 y, 8 mo (Feb. 13, 2012)

HD, hemodialysis; PD, peritoneal dialysis; CGN, chronic glomerulonephritis; PKD, polycystic kidney disease; DM, diabetes melitis; RPGN, rapidly progressive glomerulonephritis.

Mannami et al. used restored kidney allografts for "unrescuable" dialysis patients waiting for transplantation, thus only 14 of 42 patients (33.3%) received a primary transplantation in their series [3]. Urologists manage not only patients in need of renal transplantation but also patients who require nephrectomy for various diseases. Thus, Mannami et al. chose to transplant kidneys that would otherwise have been discarded into dialysis patients in need of renal transplantation [3]. Our prospective trial was designed based on this concept for rescuing high-risk patients, eg, patients in whom arteriovenous fistulas are difficult to create and who require a second or third transplantation.

Restored kidney transplantation involves a nephrectomy, an ex vivo partial nephrectomy with restoration, and transplantation. The entire procedure is demanding and complicated; an understanding of and experience with these specialized procedures is required. Donor nephrectomy may be associated with bleeding requiring blood transfusion, and restored kidney transplantation complications include perinephric hematoma, calyceal fistula, and arteriovenous fistula [4].

Transplant surgeons often inform their patients that living donor transplants are typically safe and provide an extended better quality of life for the recipient. However, the use of living donors raises an ethical dilemma because organ donation has the potential to cause harm to the healthy living donor. The perioperative mortality rate after living donor nephrectomy is 0.03%. The morbidity rate, including minor complications, is approximately 10% [63]. The consequences of being a living donor have proven to be excellent, and living donors can have better outcomes than their population counterparts [64–67]. The 30-day mortality rate after nephrectomy for RCC was 0.9% in an entire cohort of 24,535 patients (Surveillance, Epidemiology, and End Results [SEER] database), and the foremost determinants of mortality were age and tumor stage [68]. Despite the increase in morbidity and mortality typically observed in elderly patients [69], we found that restored kidneys from donors over 70 years old continued to function properly in 4 recipients, demonstrating encouraging results for the utility of transplanted kidneys from elderly donors. In the United States, 219 living kidney donors over 70 years old had an excellent 10-year overall survival rate (56.2%) [70], suggesting that transplantation from live donors over 70 years old can be beneficial with appropriately selected donor-recipient pairs [71–78]. The risk of transmitting a small RCC by restored kidney transplantation (0.015% to

Table 3. Details of Donor Nephrectomy and Transplantation Surgery, Including Tumor Histopathology, Operating Time, Blood Loss, and Transfusion

Case Number	Histopathology	Donor Nephrectomy	Blood Loss (mL)	Ischemic Time	Restoration	Transplant Time	Blood Transfusion
1.	Clear cell RCC, G2	5h 15 min	800	6 h 24 min	10 min	1 h 56 min	None
2.	Clear cell RCC, G1	3 h 0 min	153	1 h 46 min	20 min	3 h 12 min	None
3.	Clear cell RCC, G2	3 h 43 min	237	3 h 4 min	53 min	3 h 39 min	4 units
4.	Clear cell RCC, G2	1 h 52 min	230	3 h 8 min	33 min	2 h 38 min	None
5.	Granular RCC, G3	2 h 8 min	800	8 h 26 min	45 min	2 h 25 min	4 units
6.	Clear cell RCC, G2	4 h 45 min	1000	7 h 53 min	29 min	3 h 26 min	4 units + albuminate 7
7.	Clear cell RCC, G2	1 h 59 min	419	2 h 8 min	21 min	2 h 17 min	albuminate 2
8.	Clear cell RCC, G2	4 h 55 min	100	7 h 19 min	23 min	1 h 57 min	6 units + FFP 4 units
9.	Clear cell RCC, G2	4 h 20 min	300	6 h 46 min	9 min	2 h 50 min	None
10.	Clear cell RCC, G1	1 h 40 min	290	9 h 56 min	5 min	3 h 14 min	None

RCC, renal cell carcinoma.

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Table 4. Transplantation Outcomes, Including Baseline Clinical Scores, Cross-Matching and HLA Compatibility, Latest Immunosuppression, Latest Serum Creatinine, Acute Rejection, and Serious Adverse Events

Case Number, Age, Sex	Clinical Score	HLA Compatibility Cross-Match Tw/Tc/Bw/Bc	Latest Immunosuppression	Latest Serum Creatinine	Acute Rejection	SAE Excluding AR
1. 47 y, F	75.16/104	0/5/0/0	MMF 1000 mg TAC 4 mg	1.34	1	2 (FUO, CMV)
2. 54 y, F	76.37/104	0/0/0/0	MMF 500 mg TAC 5 mg	1.22	0	0
3. 62 y, F	75.35/104	5/0/0/5	MMF 500 mg TAC 2 mg	2.04	1	0
4. 66 y, M	78.15/104	0/0/0/0	HD at 35 m	Died at 40 m	3	6 (pneumonia, leucopenia, nephrosis, anemia, CMV) died of MI on Jan. 28, 2014
5. 55 y, F	79.71/104	5/5/0/0	MMF 500 mg TAC 4 mg PSL 10 mg	3.19	3	4 (UTI, abscess, leucopenia)
6. 46 y, M	66/76	Tw/Tc/Bw/Bc/PRA/ Mismatch 0/0/0/0/ Class I-class II -/4	MMF 1000 mg TAC 6 mg PSL 10 mg	2.37	1	1 (CMV)
7. 56 y, F	71/76	0/0/0/0/+ -/6	MMF 500 mg TAC 5 mg PSL 10 mg	2.04	1	2 (leucopenia, proteinuria)
8. 65 y, F	64/76	0/0/0/0/- -/3	MMF 500 mg TAC 2 mg	1.12	0	2 (FUO)
9. 54 y, M	66/76	5/5/0/0/+ +/6	MMF 500 mg TAC 2 mg	1.10	2	1 (CMV+BKV)
10. 56 y, F	66/76	5/0/5/15/- -/4	MMF 1000 mg TAC 5 mg	1.75	2	0

HLA, human leukocyte antigen; Tw, T warm; Tc, T cold; Bw, B warm; Bc, B cold; MMF, mycophenolate mofetil; TAC, tacrolimus; PSL, prednisolone; AR, acute rejection; SAE, serious adverse event; FUO, fever of unknown origin; CMV, cytomegalovirus infection; MI, myocardial infarction; BKV, BK virus infection.

1%) seems insignificant compared with the perioperative mortality rates for nephrectomy (0.03% for living donor nephrectomy and 0.3% to 1.7% for nephrectomy to remove RCC) and transplantation (1.7%).

A systematic review indicated that NSS results in significantly enhanced preservation of renal function compared with radical nephrectomy (RN). This evidence cannot be considered conclusive because of the inclusion of low-quality studies with a high risk of bias [79–81]. Only 1 prospective randomized study, conducted by the European Organisation for Research and Treatment of Cancer group, compared RN and NSS for RCC in 541 patients with tumors <5 cm in diameter and a normal contralateral kidney. This study provided the first level 1 evidence that both surgical procedures achieve excellent oncological results. Furthermore, the 10-year overall survival rate was significantly enhanced after RN compared with NSS [82]. The potential protective effect of NSS on noncancer mortality remains controversial [51,83–87]. Whether NSS is a suitable technique for older patients with T1 renal tumors in a general urology practice remains to be determined [88,89].

If a patient has renal cancer, the risk of harm from the operation is typically outweighed by the benefit of removing the tumor, which might otherwise spread and kill the patient. A kidney restored by resection of a small RCC could be considered a marginal organ because its volume is reduced by tumor resection. Thus, kidneys with satisfactory function that are removed because of other diseases might also warrant consideration for selected patients. Tsutsumi (2009) estimated that 2000 kidneys are discarded in Japan each year, and the use of these organs raises fewer ethical issues than using kidneys from healthy living donors [27]. Questionnaire surveys conducted by the Japan Urological Association in 2010 and by the Japanese Ministry of Health, Labor, and Welfare in 2012 confirmed that the estimate by Tsutsumi seems reasonable [90]. In the USA, nearly 3000 kidneys could be made available for transplantation annually [21,91]. Cooperberg et al. reported that the number of patients with stage I disease in the United States increased to 14,176 in 2007. Among these patients, 57.7% received a total nephrectomy, and 1809 kidneys with RCCs <2.5 cm were removed [92]. In the UK, approximately 7000 new RCC cases are diagnosed each year, and more than half are stage T1a tumors treated by radical nephrectomy [93]. Urologic oncologists should have discussions with transplant surgeons about kidney transplantation in selected recipients after ex vivo excision of small masses from selected donors [25].

We used the RENAL nephrometry system, which is useful for surgeons for both preoperative and intraoperative decision making. The nephrometry score provides a useful tool for objectively describing renal mass characteristics and enhancing operative planning regarding renal masses. Our ninth donor had a small renal tumor (3.7 cm), and the surgeons cut superficially 1 cm around the tumor. However,

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re-excision because of a positive surgical margin was performed three times because the tumor capsule was not well developed. The tumor was entirely endophytic, and its texture was similar to the normal parenchyma. This endophytic tumor without a clear capsule illustrates the possible difficulty of identifying the tumor margin within a short time period at the time of partial nephrectomy. Positive surgical margins are present in 0% to 7% of patients after open NSS, 0.7% to 4% of patients with positive surgical margins after NSS remain disease-free, and surveillance is preferable to surgical re-intervention [94–100].

Nicol et al. suggested that transplant units should establish connections with their urologist colleagues [4]. Meng et al. proposed a system of utilizing a multidisciplinary team approach for planned transplantations of restored kidneys after tumor excision [91]. The Western Australia Group initiated a new program in which local urologists are encouraged to contact the transplantation service when considering RN, and recipients are selected according to strict criteria [101]. Equal access criteria (UNOS 2001) include wait time, age, organ type, blood type, organ size, distance from donor to patient, and medical urgency [102]. In addition, organs should be distributed on the basis of maximum benefit despite bias, lying, favoritism, and other unfair practices. Maximizing years of life should be the most important criterion for the distribution of organs [103].

In conclusion, carefully selected patients can tolerate restored kidney transplantation, and good renal function can be achieved without tumor recurrence. Various lessons were learned from our prospective trial, which implies a national project necessary to organize transplant surgeons and urologists to work together for restored kidney transplantation. The use of living donors seems to offer the best solution to the organ shortage problem [104]. Therefore, kidneys with a small renal tumor in potential living donors should be used for transplantation [105], most likely leading to better understanding this kind of procedure. Restored kidneys from donors over 70 years old can function well, providing another source of donor kidneys, especially between an elderly couple. High-risk recipients tend to have immunological risk factors because of long-term hemodialysis, previous transplantation, and/or blood transfusion. The inclusion of high-risk patients may be associated with the high incidence of rejection episodes, which needs further study. Therefore, further studies defining the most suitable high-risk recipients for this procedure and using new immunosuppressants to prevent cancer transmission and reduce rejection episodes are warranted [9]. Importantly, care must be taken to avoid cancer transmission and to ensure fair recipient selection, close follow-up, and a well-organized tracking system.

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