



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

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### 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.

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**T**HE 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

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

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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](http://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 post-operative 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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