Journal of Clinical and Experimental Transplantation

Ogawa et al., J Clin Exp Transplant 2016, 1:1

Review Article Open Access

What Disease Conditions could be Considered for Potential Therapeutic Kidney Donations?

Yoshihide Ogawa*[1], Rensuke Mannami[2], Makoto Mannami[2], Mitsuo Nishi[3] and Naoki Mitsuhata[4]

[1]*Department of Urology, Tokyo-West Tokushukai Hospital, Akishima, Tokyo, Japan*
[2]*Department of Urology, Uwajima Tokushukai Hospital, Uwajima, Japan*
[3]*Department of Urology, Saint Martin's Hospital, Sakaide, Japan*
[4]*Department of Urology, Kure-Kyosai Hospital, Kure, Japan*

Abstract

We coined the term "therapeutic kidney donation" specifically in reference to donatable kidneys that have been nephrectomized due to urologic diseases and reviewed various series of reports and empirical sporadic reports. Kidneys with small renal tumors and distal ureter tumors in addition to benign kidney pathologies have historically been used for transplantation. Some ethical problems exist in cases in which therapeutic donor kidneys are used for unrelated living transplantation but not for related transplantation. Therefore, a well-organized national project, such as the OPTN policy, is awaited. Kidneys with small renal masses are an attractive source for donation, but these organs have several unsolved problems, including locally advanced stages, high histological grades, multifocality, and distant metastasis. Further clinical studies are warranted to organize and recruit proper therapeutic kidney donation for restored kidney transplantation.

Keywords: Therapeutic donor kidney; Urologic disease; Restored kidney transplantation; High-risk recipient

The OPTN/UNOS Living Donor Committee, UNOS Policy Department, coined the term "therapeutic organ donor" to describe an individual who has an organ removed as a component of their treatment for a medical problem, and their removed organ is suitable for transplantation into a transplant candidate. The committee suggested that potential therapeutic donors may have conditions, such as renal cell carcinoma (with the tumor removed after recovery and before transplantation), ureteral trauma (a transected ureter), or maple syrup urine disease (which is the most common type of domino liver donor) [1]. Many chronic kidney disease (CKD) patients on a transplant waiting list are eagerly anticipating this new OPTN policy proposal. In this manuscript, we would like to concentrate on the kidney as a therapeutic organ and propose a list of renal conditions associated with "therapeutic donatable kidneys" which include "donatable kidneys that are nephrectomized due to urologic diseases".

The shortage of donor kidneys is a serious problem in Japan, and this trend has become worse partly because altruistic donations and paired kidney exchange programs are not currently accepted in Japan, while ABO-incompatible living kidney transplantation has increased to 30%. In addition, restored kidney transplantation by "therapeutic kidney donation" was banned by the Japanese government in 2007, with the exception of transplantations conducted as part of clinical trials. This donor shortage crisis prompts dialysis-intolerant patients to seek transplantation and donor kidneys in foreign countries, leading to an increase in transplant tourism. To reverse this situation, the Tokushukai group launched two clinical trials of therapeutic kidney donation (TKD) in 2009, which are still ongoing, to transplant restored kidney allografts in patients without appropriate donors among their family members or who have used all of the possible living donors in their family. Therefore, the Tokushukai group is attempting to save "unrescuable" dialysis patients using restored kidney transplantations conducted as part of clinical trials [2,3]. These restored kidney transplantations include living renal transplantations conducted in clinical studies between family members using restored kidneys with small renal tumors, renal stones, ureteral tumors, ureteral strictures, or renal cysts and a clinical study of living renal transplantations between third parties using restored kidneys (partial resection and renorrhaphy) with a solitary small renal tumor. Therefore, in cases of living related or altruistically donated renal transplantation using therapeutic donatable kidneys, the surgical indication for a therapeutic donor nephrectomy could be elective, while in cases of living unrelated renal transplantations, the surgical indication for a therapeutic donor nephrectomy should be relatively imperative (depending on the decision of an expert urologist regarding whether to perform nephron-sparing surgery or discard the kidney, considering that renal salvage is always a primary goal for the urologist). It is necessary to determine and discuss which conditions could be clinically implicated for potential therapeutic kidney donation (elective or imperative) and transplantation into a transplant candidate. Therefore, in this communication, the relevant literature on "therapeutic kidney donors" was reviewed to identify potential disease conditions and clarify their contextual clues.

The first organ transplant in Japan occurred at Niigata University in 1956 (T. Kusunoki) when a living kidney obtained from a patient with idiopathic renal bleeding was temporarily transplanted to a patient with acute renal failure. In 1964, a living kidney was transplanted into a patient with chronic renal failure at the University of Tokyo, which was the first full-scale transplant intended for permanent grafting [4]. Some empirical experiences with unrelated kidney transplantation have been conducted using therapeutic kidneys that were removed due to kidney diseases, including kidney stones and hydronephrosis; however, most of these sporadic cases were semi-confidentially managed, accepted

***Corresponding author:** Yoshihide Ogawa, Department of Urology, Tokyo-West Tokushukai Hospital, 3chome-1-1 Matsubara-cho, Akishima, Tokyo, 196-0003 Japan, Tel: +81-42-500-4433; Fax: +81-42-500-6632; E-mail: yoshihide.ogawa@tokushukai.jp

Received March 31, 2016; **Accepted** July 18, 2016; **Published** July 25, 2016

Citation: Ogawa Y, Mannami R, Mannami M, Nishi M, Mitsuhata N (2016) What Disease Conditions could be Considered for Potential Therapeutic Kidney Donations? J Clin Exp Transplant 1: 106.

locally without ethical approval, or not actually reported to the general public. Therefore, only a few people were aware of the data. Mannami et al. reported their clinical experiences using a new source of 42 kidneys, which included eight cases of benign pathologies, eight of small renal cancer, eight cases of ureteral cancer, six cases of aneurysms, four cases of severe nephrotic syndrome, and four cases of ureteral stenosis, that were restored to transplant into "unrescuable" dialysis patient [5]. Kidneys that were removed due to various diseases and used for renal transplantation, according to the Japanese literature, are shown in Table 1. In Australian and Spanish reports, restored kidneys with complex cysts, benign tumors, or complicated ureteric injuries were transplanted after nephrectomy (Table 2) [6,7]. The transplantation of kidneys removed to treat small RCCs has been reported by several investigators and performed in more than 97 patients [8]. Despite differences in the interpretation of the risk categories of tumor transmission by Nalesnik et al. [9] several guidelines for renal transplantation unanimously accept that small renal tumors pose some risk [10,11] and encourage further expansion of the living-donor pool. The renal transplantation procedure is demanding, similar to the living kidney transplantation procedure, and has the advantages of allowing sufficient time for preoperative immunological screening, short ischemic time, and potential immediate renal function; the renal transplantation procedure is also similar to deceased kidney transplantation in terms of providing benefits to unrelated high risk recipients and also expanding the donor pool. The spirit of "Reduce, Reuse, and Recycle" or the "Mottainai campaign" (Prof. Wangari Maathai) should be encouraged to solve the organ shortage crisis by utilizing therapeutic kidneys donated for transplantation. Regarding the discussion about the cancer transmission risk, the perioperative mortality rates for nephrectomy (0.03% of living donor nephrectomies and 0.3-1.7% of RCC nephrectomies) and of transplantation (1.7%) and the transmission risk of small RCCs from the restored kidney (0.015-1%) in clinical settings should be noted [3].

Ex vivo restoration of therapeutic kidney donation is expected to expand the supply of available organs for renal transplantation in the future. However, some problems are still unanswered. Pahernik and colleagues proposed that clinical staging underestimates pathological staging for small RCCs (up to 4 cm) with respect to stage pT3. The rate of multifocality was 2.0%, 5.1%, and 7.05% of cases in the 2, 3, and 4 cm groups, respectively. Advanced tumor stage (pT3) was found in

Year	Donor kidney	Transplant Institution
1956	Idiopathic renal bleeding	Niigata University (T. Kusunoki)
1965	Floating kidney	Tokyo University (T. Inou)
1983	Idiopathic renal bleeding *	Uwajima City Hospital (M. Mannami)
1985	Renal aneurysm	Sendai Hoken Hospital (S. Ohtsuki)
1987	Renal aneurysm	Hokkaido University (M. Togashi)
1989	Renal aneurysm	Kyoto Prefectual University(N. Yoshimura)
1989	Renal aneurysm	Fukuoka Red Cross Hospital (K. Anan)
1990	Renal aneurysm	Hokkaido University (M. Kanekawa)
1991	Renal aneurysm *	Kure Kyosai Hospital (N. Mitsuhata)
1991	Renal aneurysm × 2 cases	Hiroshima University (T Okimoto)
1992	Renal aneurysm	Tachikawa General Hospital (T Kawano)
1992	Renal aneurysm	Sendai Shakaihoken Hospital (H Murakami)
1993	Renal aneurysm × 2 cases	Kyoto Prefectual University (T Hamashima)
1993	Renal aneurysm	Fujita Health University (K. Hoshinaga)
1994	Free kidney	Kitasato University (T. Endou)
1994	Renal aneurysm	Hamamatsu University (A. Ishikawa)
1998	Renal aneurysm × 8 cases	Tokyo Women's Medical University (F Toda)
2000	Renal aneurysm × 3 cases	Tokyo Women's Medical University (S Koga)
2001	Renal aneurysm	Toda Central General Hospital (T Nozaki)
2003	Renal aneurysm	Sapporo City University (H Harada)
2007	Small renal tumor	Akita University (T. Habuchi)
2009	Renal aneurysm	Kumamoto Red Cross Hospital (S I)
2009-2016	Small RCCs and AMLs**	Uwajima Tokushukai Hospital (M. Mannami)
2015	Small renal cell carcinoma	Ehime Prefectural Hospital (K. Okamoto)

* Benign pathologies (8 cases), ureter cancer (8), aneurysm (6), severe nephrotic syndrome (4), ureter stenosis (4), small renal cell carcinoma (8)
**17 cases to date in 2016

Table 1: Therapeutic donor Kidneys transplanted in Japan

Mannami et al.[5]	Eight benign pathologies (two angiomyolipoma, 1 cavernous angioma, 1 necrosis of ureter, 1 pelvic kidney, 1 retroperitoneal chronic infection, one renal abscess, one renal cyst with calcification), eight small renal cell carcinomas, eight ureteral cancers, six aneurysms, eight severe nephrotic syndrome from 4 patients and four ureteral stenoses.
Nicol et al. [6]	Small (<3 cm) incidentally detected renal lesions, consisting of clear cell carcinoma (25), papillary carcinoma (5), chromophobe carcinoma (1), oncocytoma (4), angiomyolipoma (3), and complex/multiloculated cysts (3)
Musquera et al.[7]	Incidental renal masses, including clear renal cell carcinoma (5), chromophobe type (2), and lipoma (1)
He et al. [16]	21 kidneys with small RCCs and 3 kidneys with complicated ureteric injuries

Table 2: Therapeutics donor kidneys retrieved due to urologic disease transplanted in large series.

3.0%, 5.1%, and 12.1%; grade 3 was noted in 7.1%, 9.0% and 14.0%; and metastases at diagnosis were identified in 3.0%, 2.6%, and 6.0% of cases in the 2, 3, and 4 cm groups, respectively [12]. Another study [13] also confirmed similar results and concluded that the aggressive potential of small RCC increases steeply beyond a tumor diameter of 3 cm, suggesting that the threshold for selecting patients for a surveillance strategy should be set well below a tumor size of 3 cm. Smaldone et al. [14] reported a systematic review and pooled analysis of small renal masses under active surveillance (18 retrospective studies comprising 880 patients and 936 SRMs) and revealed that eighteen lesions progressed to metastases with growth rates more than double (0.8 cm/year) those of non-progressors (0.3 cm/year), but these were generally late events (mean time to metastases 40.2 months) [14]. They also discussed one reported case of a 73-year-old male with a 2.4 cm renal mass progressing to bony metastases at 5 months with no increase in tumor size [15]. In consideration of these provocative results, the increased accuracy of diagnosis of frozen section histology performed immediately after tumor removal or biopsy may provide insight into the inherent biology of small renal tumors.

In conclusion, further studies are warranted regarding the following two points: 1) imperative therapeutic kidney donation could include selected cases of small renal cell carcinoma, renal aneurysm, complicated ureter injury, or distal ureteral tumor and 2) elective therapeutic kidney donation may include cases of benign renal tumors (AML), renal stones, renal injury, idiopathic renal bleeding, ureteric stenosis, complex renal cysts. A large-scale national project is necessary to organize transplant surgeons and urologists to work together to recruit therapeutic kidney donations for restored kidney transplantation. This will primarily rescue "dialysis-intolerant" patients who may benefit from renal transplantation. We welcome the therapeutic organ donation policy of the United States and anticipate utilizing living donors with therapeutic kidneys to provide a solution to the worldwide organ shortage problem in the future.

References

1. OPTN/UNOS Living Donor Committee (Bolton L.). OPTN/UNOS public comment proposal: Proposal to Establish and Clarify Policy Requirements for Therapeutic Organ Donation. Available at: https://optn.transplant.hrsa.gov/media/1185/0815-05_Therapeutic_Donor.pdf
2. Ogawa Y, Mitsuhata N, Nishi M, Mannami R, Mannami M (2012) One proposal to solve the organ shortage crisis in full understanding of donor-transmitted malignancies in kidney transplantation. Am J Transplant 12: 259-260.
3. Ogawa Y, Kojima K, Mannami R, Mannami M, Kitajima K, et al. (2015) Transplantation of Restored Kidneys from Unrelated Donors after Resection of Renal Cell Carcinoma: Results from 10 Patients. Transplant Proc 47(6):1711-1719.
4. Unrelated living renal transplantation (in Japanese) Available at: http://www6.plala.or.jp/brainx/reserved2.htm
5. Mannami M, Mannami R, Mitsuhata N, Nishi M, Tsutsumi Y, et al. (2008) Last resort for renal transplant recipients, 'restored kidneys' from living donors/patients. Am J Transplant 8: 811-818.
6. Nicol DL, Preston JM, Wall DR, Griffin AD, Campbell SB, et al. (2008) Kidneys from patients with small renal tumours: A novel source of kidneys for transplantation. BJU Int 102:188-192.
7. Musquera M, Pérez M, Peri L, Esforzado N, Sebastià MC, et al. (2013) Kidneys from donors with incidental renal tumors: should they be considered acceptable option for transplantation? Transplantation 95: 1129-1133.
8. Yu N, Fu S, Fu Z, Meng J, Xu Z, et al. (2014) Allotransplanting donor kidneys after resection of a small renal cancer or contralateral healthy kidneys from cadaveric donors with unilateral renal cancer: a systematic review. Clin Transplant. 28: 8-15.
9. Nalesnik MA, Woodle ES, DiMaio JM, Vasudev B, Teperman LW, et al. (2011) Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. Am J Transplant 11: 1140-1147.
10. A Global Consultation Organised by CNT with the co-sponsorship of WHO and the participation of the EU-funded SOHO V&S Project NOTIFY Exploring Vigilance Notification for Organs, Tissues and Cells. Available at: www.eatb.org/media/uploads/NOTIFYBolognaReport.pdf
11. Giessing M (2012) Donors with malignancies-risk or chance? Transplant Proc. 44: 1782-1785.
12. Pahernik S, Ziegler S, Roos F, Melchior SW, Thüroff JW (2007) Small renal tumors: correlation of clinical and pathological features with tumor size. J Urol 178: 414-417.
13. Remzi M, Ozsoy M, Klingler HC, Susani M, Waldert M, et al. (2006) Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. J Urol 176: 896-899.
14. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, et al. (2012) Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer 118: 997-1006.
15. Jewett MA, Finelli A, Morash C, Chin JL, Siemens R, et al. (2009) Active Surveillance of Small Renal Masses: A Prospective Multi-Center Canadian Uro-Oncology Group Trial. J Urol 181: 320.
16. He B, Mitchell A, Lim W, Delriviere L (2013) Restored kidney graft from urologist referrals for renal transplantation. Transplant Proc 45:1343-1346.

Citation: Ogawa Y, Mannami R, Mannami M, Nishi M, Mitsuhata N (2016) What Disease Conditions could be Considered for Potential Therapeutic Kidney Donations? J Clin Exp Transplant 1: 106.