Transplanting kidneys from donors with small renal masses — a strategy to expand the donor pool

Octav Cristea, MD[1,2]; Jeff Warren, MD[1,2], Brian Blew, MD[1,2], Neal Rowe, MD[1,2]

[1]Division of Urology, Department of Surgery, The Ottawa Hospital, Ottawa, ON, Canada; [2]University of Ottawa, Ottawa, ON, Canada

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Abstract

Introduction: Renal transplantation is the optimal treatment for end-stage renal disease, but organ demand continues to outstrip supply. The transplantation of kidneys from donors with small renal masses (SRMs) represents a potential avenue to expand the donor pool. We reviewed all published cases of transplants from donors with SRMs and we present followup data, best practices, and outline an actionable series of steps to guide the implementation of such transplants at individual centers.

Methods: A detailed literature search of the MEDLINE/PubMed and SCOPUS databases was performed. Thirty unique data sets met inclusion criteria and described the transplantation of tumorectomized kidneys; nine data sets described the transplantation of contralateral kidneys from donors with SRMs.

Results: A total of 147 tumorectomized kidneys have been transplanted. Pathology revealed 120 to be renal cell carcinomas (RCCs), of which 116 were stage T1a (0.3–4 cm). The mean followup time was 44.2 months (1–200). A single suspected tumor recurrence occurred in one patient nine years post-transplantation and it was managed with active surveillance. Twenty-seven kidneys have been transplanted from deceased donors with contralateral renal masses. Pathology revealed 25 to be RCCs, of which 19 were confirmed to be stage T1 (<7 cm). The mean followup time was 46.7 months (0.5–155). One recipient developed an RCC and underwent curative allograft nephrectomy.

Conclusions: Careful use of kidneys from donors with SRMs is feasible and safe, with an overall recurrence rate of less than 1.5%. The use of such kidneys could help alleviate the organ shortage crisis.

Introduction

Renal transplantation is considered the gold standard of care for end-stage renal disease (ESRD) and offers significant survival, quality of life, and economic benefits.[1-3] Despite this, only a minority of patients with ESRD ultimately receive a transplant and organ demand continues to outstrip supply in most developed nations.[4-7]

Multiple strategies have been implemented to increase organ donation and utilization, including increasing living kidney donation, donations after cardiac death (DCD), the use of expanded criteria donor (ECD) kidneys, and national programs to facilitate kidney-paired donations and transplants for highly sensitized patients.[8-10] In certain regions, system-wide rescue allocation schemes have been implemented in an effort to minimize the discard rate of deceased donor kidneys.[11] Despite such efforts, more than 15% of all deceased donor kidneys are discarded.[4,6] The reasons for discarding a kidney are complex and may include donor, recipient, and organ factors. One potential factor is the incidental discovery of a renal mass at the time of organ procurement or during donor workup in the case of living donation. The prevalence of incidental renal cell carcinoma (RCC) among cadaveric donors has previously been measured at 0.9%.[12] While uncommon, this nevertheless represents the annual loss of hundreds of potentially transplantable kidneys in North America alone.

The oncological management of small renal masses (SRMs) continues to evolve; nephron-sparing surgery, in the form of partial nephrectomy, is considered to be the standard of care for T1a (≤4 cm, organ-confined) renal masses, when technically feasible.[13-15] A recent U.S. nationwide analysis assessing the uptake of partial nephrectomy for the treatment of SRMs between 2009 and 2012 demonstrated rates of 48% and 33% in teaching and non-teaching institutions, respectively.[16] In Canada, a survey of academic centers revealed a partial nephrectomy rate of 78% for T1a tumors from 1988–2014, with an increasing trend over time.[17] Some SRMs, therefore, continue to be treated with radical nephrectomy. Often, this may be due to technical factors related to the tumor itself, but a proportion of cases result from patient preference for radical nephrectomy. Such kidneys may represent potentially transplantable organs that would otherwise be discarded.

The potential for safely transplanting kidneys with SRMs was recognized as early as 1982, when Stubenbord et al published a case report describing the transplantation of an allograft following removal of a small calcified renal

mass, later confirmed to be an RCC.[18] A number of groups have since published multiple case series describing the transplantation of tumorectomized kidneys from living or deceased donors, as well as kidneys from donors with contralateral renal malignancies. Here, we review and summarize all known cases, to date, of kidneys transplanted from donors with SRMs complete with followup data. We conclude by outlining a framework for the implementation of a transplant protocol for kidneys recovered from donors with SRMs, and discuss the potential ethical and logistical pitfalls that may be encountered.

Methods

Two authors (NR and OC) performed a detailed literature search of the MEDLINE/PubMed and SCOPUS databases to identify all published literature describing the transplantation of kidneys from donors with SRMs. A review of abstracts yielded 39 original studies and case reports, as well as 11 review papers; all of these were individually reviewed. Thirty original publications described the transplantation of tumorectomized kidneys only, five described the transplantation of both tumorectomized and contralateral kidneys, and four described the transplantation of contralatral kidneys only. Three publications were excluded from our summary due to insufficient data. Two pairs of studies presented data from the same patient cohorts; in these instances, the more recently published and complete data set was used for analysis. Thus, a total of 30 unique data sets describing the transplantation of tumorectomized kidneys were included in our analysis (Table 1), alongside nine unique data sets describing the transplantation of contralateral kidneys from deceased donors with SRMs (Table 2). Data was extracted using prespecified parameters and included donor type, donor and recipient age, tumor size and pathology, followup time and recurrence, followup protocol, iummonosuppresion regimen, postoperative graft function, and surgical complications. Any discrepancies or disagreements that arose during the review and data collection process were resolved by the senior reviewer (NR).

Results

A total of 147 tumorectomized kidneys have been transplanted and are included in our summary. Final pathology revealed 120 to be RCCs, 18 to be angiomyolipomas (AMLs), and nine to be of other benign etiologies. One hundred and thirty (88%) kidneys came from living donors, the majority of which came from patients undergoing radical nephrectomy for treatment of a renal mass, with the largest such series published by Brook et al.[19] All of the tumors in the deceased donor kidneys were incidentally discovered. All of the 120 RCCs were stage T1: 116 were T1a (0.3–4 cm), one was T1b (4.3 cm), and three were identified only as T1 (≤7 cm). Pathological subtype was reported as clear cell for 66 (55%), papillary for 11 (9%), multilocular/cystic for three (3%), chromophobe for two (2%), and was unspecified or could not be determined for 38 (31%). Followup time was specified for 119 of the RCCs and ranged from 1–200 months, with a mean of 44.2 months. A single tumor recurrence was documented in a 71-year-old male nine years post-transplant and was characterized by a 1 cm lesion in the allograft, remote from the original tumor site. The patient opted for active surveillance and, at the time of study publication, the lesion had increased by 0.2 cm over an 18-month observation period.[19]

The presence or absence of postoperative complications was specifically commented on in 22 of the 30 data sets, accounting for 112 of the tumorectomized kidneys. Among these, there were five (4.5%) instances of urine leak, all of which were successfully managed conservatively; two (1.8%) instances of bleeding requiring re-operation; and two (1.8%) instances of an arteriovenous fistula or pseudoaneurysm requiring angioembolization.[18-21] One-year graft survival could be determined for 129 of the tumorectomized kidneys and was 95%.

A total of 27 kidneys have been transplanted from deceased donors with contralateral renal masses; of these, final pathology confirmed 25 as RCCs, one as a tubulo-papillary adenoma, and one as an oncocytoma. Amongst the RCCs, 19 were stage T1, while the stage was unspecified in six cases. Followup time was reported for 24 of the RCCs and ranged from 0.5–155 months, with a mean of 46.7 months. One kidney in this group was removed three months post-transplant due to non-salvageable acute rejection. This patient subsequently died 75 months after the original transplant from a confirmed de novo renal cancer of his native kidneys, which was deemed unrelated to the transplanted kidney.[22] The patient who received a kidney from a donor with a contralateral 1.7 cm tubulo-papillary adenoma underwent a biopsy at four months to rule out rejection; this demonstrated diffuse and poorly differentiated RCC and imaging revealed enlarged adjacent lymph nodes. He subsequently underwent allograft nephrectomy and was monitored for two years before receiving a second transplant; three years after his second transplant, he remained free of disease.[23] Of note, in this particular case, the recipient of the original donor heart succumbed to metastatic RCC seven months post-transplant, suggesting circulating cancer cells at the time of organ procurement.

Discussion

It is well-known that solid organ transplantation increases the overall risk of malignancy in transplant recipients, most likely as a consequence of the post-transplant immunosuppressed state.[24,25] However, there is no evidence to sug-

Table 1. Summary of published data sets describing the transplantation of tumorectomized kidneys

Publication	Location	Donor type	Pathology	Tumor size, cm (mean)	Recipient age, yr (mean)	Followup, mo. (mean)	Recurrence
Wang, 2018[41]	China	Living	7 RCC	2.1–3.5 (2.8)	29–57 (46.9)	31–58 (39.9)	None
Lim, 2017[40]	South Korea	Living	2 RCC	0.9, 0.7	52, 34	>32	None
Nyame, 2017[42]	U.S.	Living	1 AML	2.6	Not specified	24	None
Pandanaboyana, 2016[32]	U.K.	Deceased	3 RCC	<7	3–63 (40)	12–51 (33)	None
McGregor, 2016[43]	Canada	Living	1 AML	2.2 cm	Not specified	12	None
Ogawa, 2015[44]	Japan	Living	10 RCC	1.5–3.9 (3.1)	46-66 (56.1)	32–58 (46.1)	None
Lugo-Baruqui, 2015[45]	U.S.	Living	4 RCC	0.9–2.5 (1.4)	20–79 (57.1)	36	None
*Musquera, 2013[20]	Spain	Living & deceased (4; 4)	7 RCC 1 lipoma	0.3–4.3 (1.5) 1.4	38–73 (53.4)	1–57 (32.3)	None
He, 2013[21]	Australia	Living	20 RCC 1 AML	1.7–3.3 (2.5)	49–80 (66.3)	6–55 (28.3)[ε]	None
Khurana, 2013[46]	U.S.	Deceased	1 RCC	0.7	58	8	None
Singh, 2013[47]	India	Living	1 AML	4.3	Not specified	1	None
Valente, 2012[48]	Italy	Deceased	1 RCC	0.8	39	52	None
Abboudi, 2012[49]	Netherlands	Living	1 AML	7	54	36	None
Ali, 2012[50]	U.K.	Living	2 RCC	0.5, 1.4	57, 51	48, 72	None
Melgosa Hijosa, 2012[39]	Spain	Living	1 RCC	2.5	3	96	None
Meyyappan, 2012[51]	India	Deceased	1 RMICT	2	36	3	None
[δ]Brook, 2010[19] & Nicoll, 2008[52]	Australia	Living & deceased (38; 3)	31 RCC 5 AML 3 complex cysts 2 oncocytomas	1–2.9 (2.2)	(60.9)	(32)	1 suspected (108 mo.)
Bycroft, 2010[53]	U.K.	Living	1 RCC	0.7	49	Not specified	Not specified
Sener, 2009[54]	U.S.	Living	3 RCC 2 AML	1.0–2.2 (1.6) 1.1, 2.3	47–56 (51) 58, 61	9–31 (18.3) 1, 41	None None
Manami, 2008[55]	Japan	Living	8 RCC 2 AML 1 cavernous angioma 1 calcified cyst	1.2–3.5 (2.4) 3.5, – 2.5	28–69 (50.8) 56, 47 48 67	3–145 (52.3) 107, 16 90 13	None None None None
Johannes, 2008[56]	U.S.	Living	1 AML	1.5	55	18	None
Ghafari, 2007[57]	Iran	Living	1 RCC	0.5	12	15	None
Dainys, 2007[38]	Lithuania	Living	1 RCC	2	38	>72	None
Buell, 2005[58] & Penn, 1995[22]	U.S.	Living & deceased (11; 3)	14 RCC	0.5–4 (2.1)[ε]	(40.8)	14–200 (88)[ε]	None
Hetet, 2004[59]	France	Living	1 AML	0.7	29	24	None
Lasaponara 2000[60]	Italy	Living	1 RCC	1	Not specified	138	None
Chen, 2000[61]	U.S.	Living	1 AML	7	62	Not specified	None
Weiss, 1998[62]	U.S.	Living	1 RCC	1	45	120	None
Bissada, 1993[63]	U.S.	Living	1 AML	3	44	2	None
Stubenbord, 1982[18]	U.S.	Deceased	1 RCC	3	Not specified	96	None

*Tumor size and followup time provided for entire cohort of 10 patients as a whole, which includes two patients who received contralateral kidneys from Table 2. [δ]Average recipient age and followup time provided for entire cohort of 43 patients as a whole, which includes two patients who received contralateral kidneys from Table 2. [ε]In these instances medians, accompanied by minimum and maximum values, were reported by the authors. We provide here an estimated mean for the cohort in question, calculated using techniques available in the published literature, in order to allow for a comparison across studies.[67] AML: angiomyolipoma; RCC: renal cell carcinoma.

gest that immunosuppression has a negative impact on the natural history of localized RCC. Reflecting this, multiple existing clinical guidelines suggest that patients with small (<5 cm), incidentally discovered RCCs need not delay renal transplantation after undergoing surgical treatment, given the low risk of recurrence.[26,27]

The results of the aforementioned studies suggest that transplantation of tumorectomized kidneys is similarly safe and feasible, with only one suspected tumor recurrence demonstrated to date. The data supporting the transplantation of contralateral kidneys is more limited. However, the risk of concomitant metastatic disease for T1a renal masses

Table 2. Summary of published data sets describing the transplantation of contralateral kidneys from donors with small renal masses

Publication	Location	Donor type	Pathology	Tumor size, cm (mean)	Recipient age, yr (mean)	Followup, mo. (mean)	Recurrence
Pandanaboyana, 2016[18]	U.K.	Deceased	2 RCC 1 oncocytoma	<7	41, 56 48	24, 25 64	None –
Morris, 2015[64]	Greece	Deceased	1 RCC	2.5	Not specified	48	None
*Musquera, 2013[20]	Spain	Deceased	2 RCC	0.3–4.3 (1.5)	54, 57	1–57 (32.3)	None
Valente, 2012[48]	Italy	Deceased	2 RCC	0.2, 1.5	45, 50	22, 56	None
δBrook, 2010[19] & Nicoll, 2008[52]	Australia	Deceased	2 RCC	1–2.9 (2.2)	(60.9)	(32)	None
Barrou, 2001[23]	France	Deceased	1 tubulo-papillary adenoma	1.7	63	4	1 confirmed (4 mo.)
Carver, 2001[65]	U.S.	Deceased	1 RCC	1.0	65	48	None
Penn, 1995[22]	U.S.	Deceased	14 RCC	≤4 cm in 7 unknown in 7	Not specified	0.5–155 (55)	None
Pliskin, 1998[66]	U.S.	Deceased	1 RCC	2.7	46	Not specified	Not specified

*Tumor size and followup time provided for entire cohort of 10 patients as a whole, which includes 8 patients who received tumorectomized kidneys from Table 1. δAverage recipient age and followup time provided for entire cohort of 43 patients as a whole, which includes 41 patients who received tumorectomized kidneys from Table 1. RCC: renal cell carcinoma.

is <2% and contralateral kidneys in this setting are, therefore, expected to be low risk for disease transmission with transplantation. To date, one case of recurrence has been described and occurred in a manner suggesting the presence of circulating cancer cells and/or micrometastases at the time of organ procurement. Taken together, the entire data set presented herein demonstrates a 1.4% recurrence rate among recipients of tumorectomized and contralateral kidneys from donors with confirmed small RCCs. This rate is comparable to that described in the literature for SRMs treated with partial nephrectomy.[28]

While not without risk, the small risk of RCC recurrence needs to be weighed against the risk of remaining on dialysis. In their analysis of 43 patients who received tumorectomized kidneys, Brook et al demonstrated an increased four-year survival rate over dialysis patients remaining on the waiting list; survival was comparable to recipients of living, unrelated kidneys matched for age, gender, and HLA mismatch.[19] Not all kidney transplant candidates would be willing to receive a kidney from a donor with a SRMS and, indeed, only a subset of patients would be suitable recipients. One survey of patients on a transplant list in northern England, however, revealed that 59% would support the use of such kidneys.[29]

We propose that judicious use of such kidneys in carefully selected patients is warranted and may serve as a reasonable and readily implementable strategy for combating the growing organ shortage crisis. To guide the implementation of such an effort, we outline a number of key considerations based on best practices from the studies hitherto published in the literature. A robust discussion of the ethical implications of transplanting kidneys with SRMs is presented by Flechner and Campbell[30] and serves as a valuable adjunct to the considerations presented herein.

Ethical and legal approval

For any institution interested in transplanting kidneys from donors with SRMs, we recommend an initial consultation with their respective Ethics and Legal departments. The objective is to review proposed protocols and supporting evidence, such that no transplant program risks running afoul of the ethical and legal criteria pertinent to their particular center.

Recipient selection and counselling

Patients being newly listed or currently on the transplant wait list should receive counselling about the potential of receiving a kidney from a donor with a SRM. The consent discussion must clearly outline the risk of cancer recurrence and transmission, including the possibility of death from metastatic disease, as well as the risk of surgical complications related to the tumor excision. Specific surgical risks, such as bleeding, urine leak, and arteriovenous fistula should be discussed. Patients should be informed about the need for ongoing post-transplant surveillance for RCC recurrence, in addition to the standard post-transplant followup. We propose that this informed process be conducted in a similar fashion and time as that performed for consideration of ECD and DCD kidneys. Consideration should also be given to establishing a well-defined set of eligibility criteria. In their series, Brook et al limited potential recipients to those older than 60 years of age, with significant comorbidities, difficulties with vascular access, and/or an expected mortality rate of >50% within 3–4 years.[19] While there is insufficient data to determine an optimal set of recipient criteria, we recommend that both patient life expectancy, as well as expected wait list time be taken into consideration when formulating such criteria. We also recognize that these criteria will, and likely should, differ between individual transplant centers.

Donor counselling

In all patients found to harbor an incidentally discovered SRM, a referral should be sent to a urologist for consideration of nephron-sparing surgery. The patient should be counselled about all currently accepted management options, including active surveillance, ablative therapies, nephron-sparing surgery, and radical nephrectomy. It is imperative that these patients be counselled primarily from the standpoint of oncological control and preservation of renal function and not as potential kidney donors. Failure to adopt this mindset may jeopardize patient care, compromise trust in the transplant community, and expose those involved in their care to ethical and legal ramifications. It is our recommendation that the subject of kidney donation not be raised until the decision to proceed with radical nephrectomy has been independently made and well-documented. Furthermore, it is important that the process be expedited so as not to cause any unnecessary delay in definitive treatment of the tumor. We recommend that the transplant surgeon not be involved in the final decision about tumor management so as to avoid any potential conflict of interest. Likewise, patients being evaluated for living kidney donation who are found to have an incidental renal mass should be referred to a urologist for a full discussion about the appropriate oncological management of SRMs. Only once this discussion has been completed should living donation be entertained, provided both donor and recipient still wish to pursue this course of action.

Donor workup and investigations

All potential living donors found to have a SRM should undergo full clinical and radiographical evaluation, including history, physical exam, abdominal computed tomography (CT), chest x-ray, and laboratory investigations. It is important that such patients be counselled about the risk of metachronous tumors of the contralateral kidney, which can occur in up to 0.8% of cases.[31] This figure may be higher if a papillary subtype of RCC is confirmed on final pathology. When appropriate, clinicians should screen patients for genetic syndromes that are associated with an increased risk of renal tumors, such as Von Hippel-Lindau or Tuberous Sclerosis Complex. Genetic testing should be offered to these patients and their families when indicated. Finally, a differential renal scan should be considered in all donors to ensure adequate nephron function in the contralateral kidney prior to undergoing radical nephrectomy.

Deceased donors with incidentally discovered renal tumors should undergo careful intraoperative assessment to rule out the presence of metastatic disease, including sternotomy and inspection of the thoracic organs. In their series, Pandanaboyana et al used back-table ultrasound to inspected all contralateral kidneys and rule out the presence of a synchronous or metastatic tumor.[32] The families of deceased donors with small incidentally discovered masses should be informed about the findings, and potential recipients of other organs from the same donor should be counselled accordingly.

We recommend that only kidneys from donors with T1a tumors (≤4 cm, organ-confined) be considered for transplantation. At the time of organ procurement, a sample of tissue can be sent for frozen section analysis at the discretion of the transplant surgeon; while this should reliably confirm the diagnosis, recently published data casts doubt on its utility in accurately predicting surgical margins and changing management.[33]

Immunosuppression

Contemporary immunosuppression in kidney transplant recipients most commonly consists of a calcineurin inhibitor (CNI), an anti-proliferative agent, and a systemic corticosteroid. Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus, are alternate maintenance agents for CNIs and are used most commonly in the setting of refractory CNI toxicity.[34] These drugs have well-characterized antineoplastic properties; everolimus, for example, is currently approved for treatment of metastatic RCC.[35] In the transplant setting, the use of sirolimus has been associated with a decreased incidence of renal and cutaneous malignancies, but an increased risk of prostate cancer.[36] Instances of tumor regression after conversion to mTOR inhibitors have also been reported in some de novo post-transplant malignancies; however, data for the regression of solid tumors is limited.[37] In the reviewed data series presented, five studies used an mTOR inhibitor in their maintenance immunosuppression regimen as a matter of course, accounting for 34 patients.[20,21,38-40] Based on the published literature, it is unclear if the use of mTOR inhibitors would reduce the risk of RCC recurrence, and a definitive recommendation cannot be made at this time.

Followup protocol

There is no universally established followup regimen for patients with small, localized renal malignancies.[28] Among the studies reviewed herein, eight specified a followup protocol. The frequency of imaging ranged from every 3–12 months and included a combination of ultrasound, chest x-ray, and CT scans. In the absence of definitive guidelines, we recommend a conservative approach comprised of ultrasound, chest x-ray, abdominal CT, and laboratory investigations (complete blood count, basic metabolic panel, liver function test including alkaline phosphatase and calcium), as outlined in Table 3.

Table 3. Suggested cancer-specific followup protocol for patients receiving a transplant kidney from a donor with a small renal mass

Time frame post-transplantation	Suggested investigations
0–2 years	Ultrasound every 3 months alternating with abdominal CT every 6 months Chest x-ray every 3 months Laboratory investigations every 3 months
2–5 years	Ultrasound every 6 months alternating with abdominal CT every 12 months Chest x-ray every 6 months Laboratory investigations every 6 months
5+ years	Ultrasound every 12 months Chest x-ray every 12 months Laboratory investigations every 12 months

CT: computed tomography.

Data collection and monitoring

At centers instituting a practice of transplanting kidneys from donors with SRMs, we recommend a well-defined patient roster for the purposes of tracking patient outcomes. Patients discharged back to the care of their primary care physicians should be instructed to report any suspected tumor recurrence to the original transplant center.

Limitations

Our review has several limitations. Much of the available data has been published in the form of case reports or small case series, and there exists a risk of publication bias. There is some heterogeneity of the data, making detailed comparisons or statistical analysis difficult. The followup data presented was generally limited to the medium-term, with only a few long-term cases. Nevertheless, the very low rate of recurrence in this setting is still reassuring and suggests that the oncological risk is not significantly affected by the immunosuppressed state.

Conclusions

Kidneys recovered and restored from donors with SRMs are often suitable for subsequent transplantation. Post-transplant immunosuppression does not appear to alter the natural history of localized RCC; observed recurrence rates are minimal and in keeping with those expected from SRMs in non-transplant patients. To the best of our knowledge, this review represents the most comprehensive summary of such cases to date. Potential recipients should be carefully selected and extensively counselled about the potential use of such kidneys; a rigorous informed consent process is necessary for both living donors and any intended recipients. We argue that the existing data supports judicious use of such kidneys to expand the donor pool and help alleviate the current organ shortage. Centers that implement the use of these transplants should do so in a structured and protocolized manner, and long-term followup should be instituted to monitor for recurrence.

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Correspondence: Dr. Octav Cristea, Division of Urology, Department of Surgery, The Ottawa Hospital, Ottawa, ON, Canada; octavcristea@gmail.com