

# Living-donor renal transplantation of grafts with incidental renal masses after ex-vivo partial nephrectomy

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## OBJECTIVES

To assess transplantation of high-risk kidneys with incidental renal masses (found occasionally during the routine evaluation of a living kidney donor) into recipients with limited life-expectancy on haemodialysis, as this offers a potential solution to the current organ deficit.

## PATIENTS AND METHODS

We detected five small (<2.3 cm), incidental, enhancing renal masses during donor evaluation. All patients had a standard

metastatic evaluation. After laparoscopic donor nephrectomy a back-table partial nephrectomy was performed and frozen-section analysis was used to confirm both the diagnosis and negative surgical margins before transplantation.

## RESULTS

Renal cell carcinoma was found in three of the five masses (one each cystic, clear cell and papillary; Fuhrman grades II, II and III, respectively) and the other two patients had angiomyolipoma. There were no long-term complications in the transplanted kidneys. One patient developed delayed acute humoral rejection after transplantation and was treated appropriately. Both donor and recipient were followed with periodic

imaging. At a median (range) last follow-up of 15 (1–41) months, four patients were alive and one had died from complications after a fall. The cancer-specific survival was 100%. There was no evidence of local recurrence in any patient at the last follow-up.

## CONCLUSION

Live donor kidneys with incidental small renal masses might be acceptable for transplantation in high-risk recipients after careful back-table partial nephrectomy.

## KEYWORDS

kidney, transplant, renal cell carcinoma, living donor, nephrectomy

## INTRODUCTION

The number of patients requiring renal transplantation increases each year, primarily due to the increasing incidence of hypertension and diabetes mellitus (DM) in North America [1]. Although attempts continue to be made to match the expanding shortage of organs, including the use of deceased and expanded-criteria donor kidneys, as well as the introduction of laparoscopic donor nephrectomy, there has only been a slight improvement in the availability of transplantable kidneys [2]. Numerous studies have shown that early renal transplantation improves the life-expectancy of dialysis-dependent recipients by significantly reducing their cardiovascular morbidity [3,4]. Compounded with the added evidence that long-term allograft function of

live-donor allografts is significantly better than those organs obtained from deceased donors, this has induced transplant centres to encourage and educate patients with end-stage renal disease (ESRD) to consider potential living donors [5,6]. The transplant community has embraced the increasing numbers of potential living donors and continues to be very diligent in ensuring the safety of these generous individuals. However, occasionally the routine evaluation of potential kidney donors reveals incidental renal masses arising from the donor kidney.

Solid, enhancing renal masses are generally considered to be Renal Cell Carcinoma (RCC) until proven otherwise [7]. Although the more contemporary management options for treating small renal masses is debatable, there is a wide range of options depending upon

the size and location of the tumour, patient preference, and the pre-existing comorbidities of the patient [8]. However, there is agreement that despite its associated potential complications, including peri-operative bleeding, urine leak from the repair and wound infection, partial nephrectomy is curative for most T1aN0M0 lesions, and is the accepted treatment of choice in otherwise healthy individuals [9], and carries a small risk of metastasis [10]. Despite this evidence, we observed that potential kidney donors with incidentally identified small renal masses during the evaluation for donation insisted on pursuing kidney donation after being presented with the option of a partial nephrectomy. Many patients on the transplant waiting list are challenged by the decreasing availability of dialysis access for renal-replacement therapy

(RRT), and a gradual decline in general health making them potentially unfit for transplantation, which inevitably leads to death from comorbidities, so the potential for receiving a living-donor kidney can be life-saving and timely.

The transplantation of a living donor kidney with an enhancing renal mass is controversial and considered a high risk. However, in light of the ongoing shortage of available deceased organs, and considering that the alternative of waiting will lead to certain death in a high mortality-risk recipient, several donor/recipient pairs decided to undertake the donation and transplantation of kidneys with incidentally identified renal masses. In the present study we report the oncological and graft function outcomes in a series of living donor kidneys with incidentally discovered renal masses of <2.3 cm that were transplanted following ex-vivo partial nephrectomy.

## PATIENTS AND METHODS

Between July 1996 and July 2008, 1164 patients had a laparoscopic donor nephrectomy for transplantation at the University of Maryland Medical Center, Baltimore, Maryland, USA. A retrospective analysis showed that five of these donor kidneys underwent back-table partial nephrectomy and reconstruction for incidentally found renal masses on preoperative donor evaluation. All reconstructed kidneys were transplanted into their intended recipients. Ethical approval was obtained through our Institutional Review Board for this retrospective analysis, and data collection and storage was in compliance with our institutional protocols.

Although these five potential recipients were evaluated according to current guidelines, and were found to be fit for transplantation, they all had significant comorbidities that precluded long waiting times on the waiting list and thus presented to us with a voluntary living donor. Recipient patient comorbidities at the time of presentation for transplant evaluation were: patient 1, severe hypertension, recurrent UTIs and kidney stones, severe proteinuria from focal segmental glomerular sclerosis (FSGS); patient 2, hypertension, DM and loss of available dialysis access for haemodialysis; patient 3, severe hypertension requiring

multiple antihypertensives, anaemia and recurrent UTIs due to VUR; patient 4, severe hypertension and loss of available dialysis access for haemodialysis; and patient 5, severe hypertension, previous RCC requiring nephrectomy, multiple vascular surgery including coarctation of the aorta, abdominal aortic aneurysm repair and aortic valve replacement.

As part of our routine donor evaluation, each potential donor met individually with our team of social workers, psychologists and clinicians, where they underwent a review of their medical history and a thorough physical examination followed by blood evaluation and urine analysis. All potential donors also had contrast-enhanced CT with delayed imaging to evaluate any potential anatomical anomalies that might pose obstacles during the donor operation. All images were reviewed by the donor and recipient surgeons, and by a radiologist. Once an incidental renal mass was identified, confirmatory imaging and a metastatic evaluation was carried out, and the case was then discussed at the weekly multidisciplinary transplant evaluation meeting, and with the recipient/donor pair. All reasonable risks and benefits to using a kidney with an incidental renal mass for transplantation, including tumour recurrence and multiplicity, and the increased risk of future cardiovascular events after radical nephrectomy [11], were outlined and clearly discussed with both the recipient and donor. In particular, we stressed to the donor that a partial nephrectomy would be the treatment of choice for such a mass, as recurrence in the contralateral kidney and the risk for future renal dysfunction were always possible. After both parties were informed, written consent was obtained for the procedure.

Using a transperitoneal laparoscopic approach, all kidneys were meticulously dissected free from their surrounding tissues, taking care not to disturb the area around the renal mass. The ureter, renal artery and vein were then stapled using a 30-mm endovascular stapler and the kidney carefully removed through a Pfannenstiel incision. The kidneys were immediately placed on ice and taken to the recipient operating room. There, the kidney was flushed with cold renal preservation solution (Custodiol HTK Solution, Odyssey Pharmaceuticals Inc., Florham Park, NJ, USA) and the renal mass exposed and resected sharply with adequate margins. Care was taken not to enter the renal collecting

system. A portion of the marginal tissue was sent for frozen-section analysis to confirm the absence of any residual tumour. Once the pathologist confirmed the absence of tumour in the resected margin, the renal defect was reconstructed using an interrupted 3-0 polydioxanone suture with Surgicel (Johnson & Johnson Gateway, Inc, Langhorne, PA, USA) bolsters. The tumour specimen was sent for permanent pathological evaluation. All kidneys were heterotopically transplanted into the recipient iliac fossa in an extraperitoneal fashion. All patients received maintenance immunosuppression with a tacrolimus and mycophenolate mofetil, and rapid steroid withdrawal. One patient was unable to tolerate the effects of tacrolimus and was placed on rapamune instead. Drug levels were closely monitored at regular clinic appointments.

Data were collected specifically on any perioperative complications, and on information obtained from regular clinic visit notes, blood evaluation and regular imaging of the allograft and of the renal bed, to monitor for tumour recurrence, which included an annual chest X-ray, ultrasonography (US) of the renal bed and surveillance CT as necessary. Serum creatinine data from the recipient were collected before the transplantation and at 30 days, 1 year and at the last follow-up. Creatinine clearance was calculated using the Modification of Diet in Renal Disease Study equation, as it has been shown to be the most accurate for estimating GFR from serum creatinine [12]. All data reported are expressed as the mean (SD).

## RESULTS

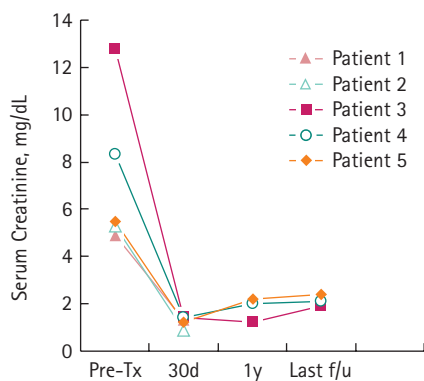
As listed in Table 1, the mean (SD, range) age of the transplant recipients was 54 (6, 47-61) years; the donors were all healthy individuals with no comorbidities and aged 56 (12, 38-72) years at the time of donation. Of the five donor pairs, two of them were unrelated whereas three were genetically related; all pairs were at least one human leukocyte antigen mismatched. Causes of ESRD ranged from hypertension and diabetes to VUR and FSGS. There were no intraoperative complications or conversions from laparoscopic to open donor nephrectomy. Only one patient had a minor complication of a wound infection after surgery, which was treated appropriately with antibiotics and wound packing. There were no

TABLE 1 The demographics of the transplant recipients and estimated creatinine clearance using Modification of Diet in Renal Disease Study formula

| Variable   | Patient |              |             |              |                  | Mean (SD)   |
|--|---------|--------------|-------------|--------------|------------------|-------------|
|  | 1       | 2            | 3           | 4            | 5                |             |
| Age, years                                       | 58      | 56           | 47          | 50           | 61               |             |
| Cause of ESRD                                    | FSGS    | HTN, DM      | VUR         | HTN          | Severe HTN & PVD |             |
| Periop complications                             | None    | None         | None        | None         | Wound infection  |             |
| Tumour size, cm                                  | 1.1     | 1.0          | 2.2         | 1.5          | 2.3              |             |
| Pathology  | AML     | pRCC, FG III | cRCC, FG II | ccRCC, FG II | AML              |             |
| Follow-up, months                                | 1       | 9            | 15          | 31           | 41               |             |
| Recurrence or metastasis                         | No      | No           | No          | No           | No               |             |
| Creatinine clearance, mL/min/1.73 m <sup>2</sup> |         |              |             |              |                  |             |
| Before transplant                                | 17      | 15           | 5           | 9            | 14               | 12.0 (4.9)  |
| 30 days  | 72      | 112          | 70          | 69           | 79               | 80.4 (18.1) |
| 1 year   | n/a     | n/a          | 84          | 46           | 39               | 56.3 (24.1) |
| Last follow-up                                   | n/a     | n/a          | 49          | 43           | 46               | 46.0 (3.0)  |

HTN, hypertension; pRCC, papillary RCC; cRCC, cystic RCC; ccRCC, clear cell RCC; FG Fuhrman grade; PVD, peripheral vascular disease.

FIG. 1. Serum creatinine measured before (Pre-Tx) and at various time points after (30 days, 1 year and at the last follow-up) living renal transplantation of allografts undergoing back-table partial nephrectomy.



reports of postoperative bleeding or urine leakage from the allograft, and the median (range) hospital stay was 7 (7–20) days.

Four of five patients had immediate graft function, whereas patient no. 5 developed delayed graft function (DGF) secondary to acute tubular necrosis diagnosed by allograft biopsy. Patient no. 2 developed acute humoral rejection, which was treated with three cycles of i.v. hyperimmune globulin and plasmapheresis. This graft never recovered, as confirmed by subsequent biopsies, and required RRT with haemodialysis; the allograft was left *in situ* and continued to be monitored with periodic imaging for tumour recurrence,

as the final pathology on the resection was papillary RCC, Fuhrman grade III. Final pathological analysis showed RCC in three of the five incidental masses (one papillary Fuhrman grade III, one cystic Fuhrman grade II and one clear cell Fuhrman grade II). The other two resections showed benign angiomyolipoma (AML). All surgical margins were free of tumour. The mean (SD, range) size of the incidental renal masses was 1.7 (0.5, 1.0–2.3) cm on the gross specimen (Table 1).

As expected, renal transplantation resulted in a significant increase in estimated creatinine clearance, from 12.0 (4.9) to 80.4 (18.1) mL/min (at 30 days after transplant) which remained elevated at 46.0 (3.0) mL/min at the last follow-up (Table 1). The trend was similar in serum creatinine (Fig. 1); a slight decline in creatinine clearance at 1 year can be attributable to patient no. 5, who had DGF and acute tubular necrosis before the transplant.

At a median (range) follow-up of 15 (1–41) months, four of the patients were alive with functioning renal grafts. One patient (no. 2) died from complications of a fall completely unrelated to her ESRD at almost 1 year after transplantation. The cancer-specific survival was thus 100%. There was no evidence of local tumour recurrence or metastasis in both the donors and recipients at the last follow-up, based on annual chest X-rays and US of the allograft and nephrectomy bed.

## DISCUSSION

Although there are several forms of RRT available for the growing population of patients with ESRD, renal transplantation is the optimum method as it offers better survival and quality of life to the recipient, while at the same time reducing the overall burden to reimbursement systems [6,13]. Fortunately, there has been an increase in the number of transplants over the past decade, which is attributable to both an increase in deceased donor transplants by 16% and a 68% increase in living-related transplants through the generosity of friends, spouses, partners and anonymous donors [1,14]. Despite this substantial increase there continues to be a significant deficit, as the increase in the donor population is insufficient to match the rate of expansion of the ESRD population, and thus many patients die each year while waiting for a transplant.

The present results suggest that organs obtained from living donors who were discovered to have incidental renal masses should not prohibit transplantation, and might be one potential solution to the ongoing global shortage of kidneys. Although previous authors have also suggested analogous solutions, none have reported a series in a previously matched living donor population. Whitson *et al.* [15] described the transplantation of a kidney from a 22-year-old man who had undergone a laparoscopic radical nephrectomy for a 2-cm central lesion into an unrelated 62-year-old man on the

waiting list. Similarly, Nicol *et al.* [16] showed that when radical nephrectomy is used to treat small, localized, incidentally discovered renal masses, the discarded kidney can be used to transplant into high-risk individuals who would benefit from renal transplantation but would probably not survive the waiting period for a deceased donor allograft. In the latter study, the authors found that at 9 years after surgery, only one of the 38 allografts showed possible tumour recurrence. The remainder of the allografts continued to function at a mean of 32 months, despite seven separate episodes of acute rejection that were treated adequately. Most recently, Mannami *et al.* [17] reported that of 42 'restored kidneys' from unrelated individuals undergoing nephrectomy for a range of diseases and that the authors transplanted after ex-vivo repair, eight contained small renal masses. Both the donors and recipients were followed for up to 135 months, with no tumour recurrence or metastasis in either group over that period. Only three grafts continued to function at the follow-up in that series.

Although the mortality rate has remained stable, the incidence of RCC has increased over the past decade [18,19]. This is probably attributable to the increased use of US and CT in early detection, as most of these lesions are discovered as incidental, small masses during imaging for unrelated conditions [20]. However, RCC continues to be the fifth leading malignant condition in men and the 10th in women, and accounts for 3% of all malignancies in North America [21]. Therapeutic options available for small renal masses include observation, partial nephrectomy, radical nephrectomy and minimally invasive therapies, including radiofrequency ablation and cryotherapy [8,22]. The donors in the present study had elected to undergo laparoscopic donor nephrectomy before the incidental diagnosis of their renal masses. Although the incidence of multiplicity and metastasis from these small renal tumours is <3%, full evaluation of the donor showed no suspicious lesions. After the risk of future recurrence on the contralateral side, as well as the potential risk of developing chronic renal disease, which might require excisional therapy and potential dialysis, were considered, all of our donors elected to proceed with donor nephrectomy as planned.

Although donor informed consent in these cases is extremely important, equally valuable

is the recipient's understanding of the risks of accepting an allograft containing a tumour. Immunosuppressive therapy is well known to increase the incidence of malignancy after transplantation [23]. Primary RCC in transplant recipients represent  $\approx$ 4.6% of all malignancies in the transplant population [24]. The study by Nicol *et al.* [16] exemplifies the possibility of tumour recurrence after partial nephrectomy in an allograft, but in this case the origin of the tumour could not be confirmed, as the patient elected to undergo observational therapy. In addition, the inadvertent transmission of RCC from a donor kidney to the recipient is an inherent risk of transplantation despite concerted efforts to minimize the transfer of any obvious lesions; however, reports suggest that cure is achievable through excision of the tumour alone. In a large series reported by Penn [25] over a decade ago, of 30 patients who received back-table partial nephrectomy for renal masses discovered at the time of organ procurement, only 14 (47%) had no further recurrence or metastasis. In addition, Penn reported that in another cohort of 17 patients who received kidneys containing unrecognized renal masses, 10 had an allograft nephrectomy at the time of diagnosis with no further complications, whereas the remaining seven developed metastases at 12 months after transplantation. Half of these patients were cured by reduction of immunosuppression and allograft nephrectomy. Most recently, McHayle *et al.* [26] reported two cases of RCC arising from the allograft. In one patient, the tumour had metastasized, and fluorescence *in situ* hybridization analysis of the biopsy material showed a female karyotype, consistent with the female donor. The second recipient presented with renal failure 22 years after transplantation and was found to have multifocal RCC on allograft nephrectomy [16,26–28]. Given the reported incidences of tumour recurrence in the allograft, it is a calculated risk undertaken by the recipients to accept these organs. However, in the case of high-risk patients, as in our five recipients, this risk was acceptable.

Tumour recurrence in a previously resected tumour bed in a renal allograft has been approached using options ranging from radical allograft nephrectomy to nephron-sparing surgery, by either a standard partial nephrectomy [29] or, more recently, via enucleation using a harmonic scalpel [27]. Although a nephron-sparing approach is ideal

for preserving allograft function, it can be a daunting undertaking, as vascular control is difficult. Recently, Aron *et al.* [30] described the use of radiofrequency ablation of a tumour in a transplanted kidney. This method shows promise in this population, as it is associated with less morbidity and a shorter hospital stay than the more conventional nephron-sparing approaches [24,30]. In the rare case of metastasis from RCC on a renal allograft, reports are limited as to the availability of options. Although the use of vascular endothelial growth factor inhibitors in addition to metastatic resection is an option, the long-term outcomes are unknown in face of concurrent immunosuppression [31].

Interestingly, we found that two of the five incidentally discovered enhancing renal masses were AML. Although the diagnosis of AML is made radiologically, based upon the degree of attenuation caused by fat within an enhancing renal lesion, it is not uncommon to have fat-poor AML masquerading as RCC [32]. In fact, Milner *et al.* [32] reported that in 15 patients who were operated on for suspected RCC, 11 had a final pathological diagnosis of AML; these authors concluded that fat-poor AML should be defined as lesions containing <25% fat on high-power field microscopy; this definition then raises the issue of a need for preoperative diagnostic biopsy. The finding that two of the present five suspicious donor kidney lesions were AML (this is consistent with the reported rate of 40–50% of benign lesions of <2 cm) suggests that incidental renal masses in a potential donor should be investigated rather than automatically rejected. Incidental renal masses should be considered useable, especially with the shortage of available grafts.

Although the present patients remained tumour-free at the follow-up, the follow-up was relatively short in the management of RCC, and hence these results are somewhat limited. This limitation stresses the importance of maintaining a routine follow-up of living donors with incidentally discovered renal masses, with scheduled chest X-rays and US of the renal bed to ensure no tumour recurrence, as well as periodic CT to exclude systemic metastasis. Similarly, recipients of these organs need to be diligently surveyed for both recurrence and metastasis. Although the rate of growth of low-grade and -stage RCC is slow, the absolute risk of tumour progression cannot be

discounted, especially in the face of concurrent immunosuppression. In addition, consideration should be given to altering immunosuppression regimens to rapamune-based protocols, that could theoretically minimize tumour resurgence in these allografts, although this was not intentionally done in the present recipients [33,34].

The global increase in the ESRD population highlights the importance of identifying novel means to increase the donor pool. The current study provides evidence to suggest that kidneys from donors with incidentally discovered renal masses offer a minor yet feasible solution to the current organ shortage, and can be transplanted into recipients with limited life-expectancy on haemodialysis after careful back-table partial nephrectomy. Diligent follow-up of not only the donor but also of the recipient is imperative in these cases.

#### CONFLICT OF INTEREST

None declared.

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**Abbreviations:** ESRD, end-stage renal disease; DM, diabetes mellitus; AML, angiomyolipoma; DGF, delayed graft function; FSGS, focal segmental glomerular sclerosis; US, ultrasonography; RRT, renal-replacement therapy.

#### EDITORIAL COMMENT

This report from a large transplant centre describes an approach to a dilemma which, albeit infrequent, is likely to confront many other institutions performing living-donor transplantation. Based on autopsy studies [1] and observed epidemiology [2] it is expected that a few patients being assessed as potential live donors will have a small tumour detected on US and CT as part of this process. The donor, their potential recipient and clinicians involved with the care of both, are then confronted with a difficult dilemma. First, the donor who has indicated a desire or willingness to undergo nephrectomy and its associated risk on an altruistic basis for the benefit of the potential recipient needs to reassess their position and decision, based on the radiological findings. Issues they need to confront must incorporate the management options of all patients who have small renal masses detected as incidental findings. Nephron-sparing surgery (NSS), minimally invasive ablative procedures, nephrectomy and in selected cases observation, are the treatment options to be considered in this

situation. NSS is frequently the preferred option over nephrectomy, offering equivalent cancer-specific survival to nephrectomy whilst preserving overall renal function [3]. The latter advantage needs to be balanced against the additional surgical risks of bleeding, urinary leakage and wound-related complications. By contrast with other patients, the potential live donor has resolved the issue of nephrectomy and its risks, for the benefit of their potential recipient. In many cases the additional information might not alter their motivation to undergo nephrectomy if this would provide a better outcome for their recipient than remaining on dialysis, and if there was suitable consideration of a deceased donor transplant. The recipient might find the diagnosis of a possible cancer challenging, as a consequence of the risks of local recurrence and metastatic disease. These risks need to be balanced against those associated with continued dialysis and the possibility of subsequent deceased-donor transplantation, which in some cases might not be possible as a consequence of waiting times and that in many centres comorbidities influence eligibility for the latter. Overall, the risks of tumour recurrence after NSS are substantially less than ongoing dialysis, particularly in the elderly or in the context of tenuous access to dialysis[4]. Clinicians dealing with the donor and recipient need to recognise the dilemma confronting both individuals, and assist with the final decision by providing a balanced perspective of the risks, acting as advocates for both, as well as respecting their autonomy of choice. The age and individual circumstances obviously will influence the advice provided.

The strategy used by Sener *et al.*, coupled with other recent publications [5,6], highlights an issue of broader urological significance. Whilst NSS might be the preferred option for patients with small incidentally detected tumours it must be recognised that nephrectomy is the commonest procedure in this clinical scenario. Data from several registry sources in the USA indicate that NSS is only performed in 20–30% of such cases [7,8]. Concerns have been expressed about this statistic [3], highlighting the availability of expertise to perform NSS as a factor which might change over time. However, patient

preference must be recognised as a legitimate influence on treatment choice, with concerns about local recurrence, risk of operative and postoperative complications and emotional factors all being legitimate considerations. In the context of appropriate informed consent for treatment options, urologists need to recognise that with patients who elect to undergo nephrectomy, they are dealing with a valuable resource to society that is squandered once placed in formalin.

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