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ORIGINAL ARTICLE

Outcomes of transplants from patients with small renal tumours, live unrelated donors and dialysis wait-listed patients

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Summary

We report the outcomes of renal transplant patients ($n = 43$) who received grafts from donors ($n = 41$) with small (<3 cm) renal tumours removed before transplantation covering the period from May 1996 to September 2007. Patient and graft survival were compared with the outcomes of conventional live unrelated transplants (LURTs) ($n = 120$) and to patient survival on the transplant waiting list for those who did not receive a kidney during this period ($n = 153$). Patient survival at 1, 3 and 5 years were 92%, 88% and 88% for recipients of tumourectomized kidneys (TKs), 99%, 97% and 97% for LURTs, and 98%, 92% and 74% for dialysis patients waiting for a deceased donor kidney (log rank score 10.4, $P = 0.005$). One patient experienced a local tumour recurrence at 9 years following transplantation. This patient declined intervention and is currently under active surveillance. Transplantation of tumourectomized kidneys from patients with small, localized, incidentally detected renal tumours results in similar outcomes to conventional LURTs and confers a significant survival advantage for patients who would otherwise be unable to receive a transplant.

Introduction

The mismatch between the number of patients with end-stage renal failure (ESRF) and available organs is a challenge for renal transplant programmes. Kidneys obtained from older donors and non heart-beating donors are now used to complement cadaveric and live donor numbers, but a shortfall in availability of organs remains [1,2]. This shortage means that many ESRF patients (excluded on medical grounds) do not qualify for the cadaveric transplant waiting list [3–5], although they may benefit from transplantation. This quandary has led us to explore the use of what may be considered high-risk organs for these high-risk recipients.

Many patients under the care of the discipline of urology are undergoing radical nephrectomy for small renal tumours, and our group felt it would be worthwhile exploring the use of these organs, which would otherwise be discarded, for transplantation [6].

The kidneys are removed as per a live donor operation, the small renal tumour is excised on the back-table after perfusion with preservation fluid, and the (tumourectomized, TK) kidney transplanted into a recipient.

Our rationale is that the risk of tumour recurrence is small, and the benefits of a functioning organ to these high-risk patients, who would otherwise not receive a transplant, are great.

This study aimed to compare graft and patient outcomes for TK recipients and conventional live unrelated renal transplant recipients (LURTs). Patient survival in these groups was also compared with that of dialysis patients accepted onto our deceased donor waiting list who did not receive a transplant because of lack of organ availability.

Methods

The outcomes of patients at our institution who were transplanted with kidneys removed from patients with small (<3 cm), incidentally detected renal lesions with a presumed diagnosis of renal cell carcinoma (RCC) were reviewed. These outcomes were compared with outcomes of conventional LURT ($n = 120$) and dialysis patients who were on the deceased donor transplant waiting list but who did not receive a donor kidney during this period ($n = 153$) (see Table 2).

Data were retrieved from our unit's prospective database of all dialysis patients and renal transplants, encompassing the period between May 1996 and Sept 2007. This information was cross referenced with the Australian and New Zealand Dialysis and Transplant Registry [2]. This is a national centrally maintained database that captures data on all patients in these two countries with ESRF, receiving dialysis or undergoing renal transplantation.

Patients on the deceased donor waiting list are referred from multiple dialysis centres based on medical suitability. The Princess Alexandra Hospital is the sole provider of renal transplantation in Queensland, which has a population of approximately 4.2 million. Allocation of deceased donor grafts is based on a national computer-based system with an algorithm incorporating waiting time from commencement of dialysis and HLA matching for 0, 1 and 2 mismatches. For patients who qualify for this waiting list, age and co-morbidities do not influence time to organ allocation.

All patients receiving TK kidney transplants from genetically unrelated live donors and deceased donors who had a small tumour detected at the time of organ retrieval or from patients referred by urologists with a radiologically detected renal lesion suspicious of RCC, were identified. The flow diagram below (Fig. 1) illustrates the protocol for donor and recipient selection in TK kidneys. Renal tumour size and position were measured either directly at the time of organ retrieval in the case of deceased donors or by estimation on preoperative CT scan in the case of live unrelated donors. With the latter, standard work-up included abdominal and chest CT scans for staging. The referring urologist discussed the options of active surveillance, partial or radical nephrectomy with the patient and a decision was reached. This was prior to any reference to the patient of possible utilization of the kidney for transplantation. Those patients who elected to have a radical nephrectomy were approached only after making their treatment decision and asked whether the kidney could be used for transplantation. The referring urologist would then contact the transplant team to discuss suitability of the kidney for transplantation. Radical nephrectomy was performed at their local hospital or at our institution by their referring

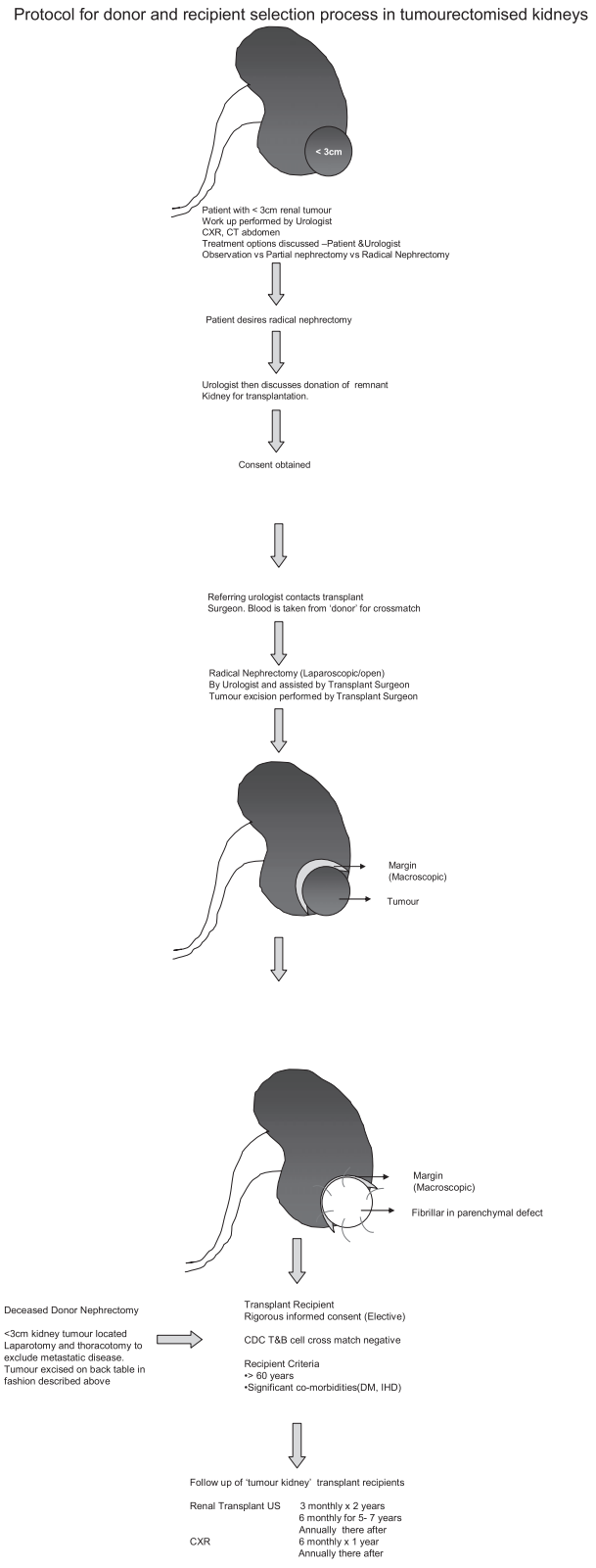

Figure 1 Flow diagram illustrating protocol for donor and recipient selection for kidneys with excised tumours.

urologist and transported to the Princess Alexandra Hospital.

After perfusion with University of Wisconsin (UW) preservation solution, bench tumour excision was undertaken, incorporating a margin of renal parenchyma based on macroscopic assessment. Vessels and collecting system were oversewn or repaired using interrupted 3/0 PDS. Perinephric fat was used to plug the defect and sutured circumferentially with interrupted 3/0 PDS.

Potential recipients of TK kidneys were identified from our deceased donor transplant waiting list using the selection criteria:

1 Patients older than 60 years of age.

2 Patients with significant co-morbidities (access problems, cardiovascular disease or multi-organ effects of diabetes) and a significant prospect of death (>50%) within 3–4 years without transplantation.

For the transplants described in this article, the Hospital Ethics Committee was approached who advised that the matter was not an ethical issue for their consideration and that it was a legal issue pertaining to informed consent. Health Department legal opinion was sought with the recommendation that it was an acceptable practice if appropriate informed consent was obtained from recipients outlining the potential risks of tumour recurrence, complications related to bench surgery and the consequences of the alternative option of continued dialysis. The standard consent form signed by all renal transplant patients was modified to include these additional considerations. The recipients underwent a rigorous informed consent process highlighting the possibilities of tumour recurrence and/or death resulting from metastatic disease. Specific surgical complications related to excision of the tumour (bleeding, urinary leakage, urinary fistula and arteriovenous malformation) were discussed. Immunosuppression comprised cyclosporine, azathioprine 2 mg/kg and prednisolone 3 mg/kg reducing to a maintenance dose of 5 mg per day. More recently, we have used a combination of tacrolimus, mycophenolate 1 gm b.i.d. reducing to 500 mg b.i.d., and prednisolone.

Prospective follow-up was maintained for all recipients. For those with malignant pathology from the resected specimen, follow-up was intensified to include 3-monthly transplant ultrasound for 2 years, 6-monthly ultrasound for 5–7 years and yearly thereafter to screen for tumour recurrence. Chest X-rays were performed once every 6 months for the first year and then annually.

Results

Tumorectomised kidney recipient group

From May 1996 to September 2007, 43 renal failure patients received a transplant from a patient with a small renal tumour. Kidneys were obtained from 38 patients undergoing elective radical nephrectomy for presumed RCC. In 37 cases, donors were patients who had small (3 cm) solid or complex lesions detected as incidental findings when they underwent imaging for unrelated symptoms. The final case was a potential living donor in whom a 1-cm diameter renal tumour was detected during assessment imaging. Radical nephrectomy was performed as an open procedure in 12 cases and laparoscopically in 26. To date, all 38 'donors' are alive with no biochemical or radiological evidence of local, contralateral or distant recurrence of tumour.

Three cadaveric kidney donors were found to have small renal tumours at the time of retrieval. Five of the possible six kidneys from these donors were used for tumorectomised kidney transplantation.

In two cadaveric pairs, the contralateral kidney was also transplanted into another recipient. In one deceased donor pair, the tumour was detected at the time of the transplant and felt to be a benign cyst. Subsequent paraffin section reported a focus of malignancy in the cyst wall. The transplant recipient was advised of the result and elected to undergo transplant nephrectomy. The contralateral donor kidney was transplanted into the same recipient.

Tumours ranged from 1 to 2.9 cm (mean = 2.2 cm). Nineteen of the tumours were located in the lower pole of the kidney, 11 in the upper pole and 13 in the midpole but not extending into the collecting system. Histologically, the resected tumours were clear cell carcinoma (n = 25), papillary carcinoma (n = 5), chromophobe carcinoma (n = 1) oncocytoma (n = 2), angiomyolipoma (n = 5) and complex/multiloculated cysts (n = 3) (Table 1). The remaining organs transplanted were the contralateral kidneys from the deceased donor pairs containing a clear cell carcinoma.

Intra-operative blood transfusion attributable to haemorrhage from the site of tumour excision was required in one case. Transfusion was required in the postoperative period in further five patients. Mean total ischaemic time for these kidneys was 8.80 h compared to a mean of 1.72 h for the conventional live unrelated donors reported in the study.

Postoperative complications in tumorectomised kidneys in transplant recipients

Four transplant recipients experienced early complications. One patient underwent exploration of a perinephric haematoma although no specific bleeding site was identified. Another developed a calyceal fistula at the site of tumour resection. The urinary leakage was controlled by placement of a nephrostomy tube into the renal pelvis through the defect, and insertion of a ureteric stent. This

Table 1. Histological analysis of tumours removed from transplanted kidneys.

Tumourectomized kidneys (n = 41)	Histology	Grade	Margins	Vascular invasion
25	Clear cell RCC	n = 14 G1 n = 7 G2 n = 4 G3	Negative	None
5	Papillary Ca	n = 2 G1 n = 3 G2	Negative	None
1	Chromophobe Ca	n = 1 G2	Negative	None
2	Oncocytoma		Negative	None
5	Angiomyolipoma		Negative	None
3	Complex cyst		Negative	None

nephrostomy was left in place for 3 weeks and the stent removed at 5 weeks; no further problems were encountered. One recipient represented 4 weeks post-transplantation with macroscopic haematuria. Doppler ultrasound revealed an arteriovenous fistula at the site of tumour resection. This was confirmed on angiography and closed with selective angioembolization. A laparotomy was required in a morbidly obese patient 3 weeks following transplantation for intra-abdominal sepsis related to a bowel perforation.

There were eight episodes of acute rejection; all but one were steroid-sensitive, and one required OKT3 treatment.

Mean and median follow-up times were 32 and 25 months respectively. One patient returned to dialysis 30 months post-transplant after developing recurrent focal sclerosing glomerulonephritis. Four transplant recipients have died with functioning grafts. All deaths were attributable to nonrenal causes – carcinoma of the pancreas (6 months) and of breast (27 months), systemic sepsis (5 months) and myocardial infarction (2 months). All other grafts in the surviving transplant recipients have maintained function with a mean serum creatinine of 146 μM at 12 months.

Follow-up of the 43 transplant recipients with 3-monthly ultrasound scans of the allograft and chest X-rays in addition to standard medical review and investigations, had demonstrated one tumour recurrence. This occurred 9 years post-transplantation when a small lesion was noted in the graft remote from the initial tumour resection site. The patient, a 71-year-old man, has refused both nephrectomy or treatment with radiofrequency ablation of the tumour. The lesion has been monitored for 18 months and increased in size from 1.0 to 1.2 cm during this time on serial ultrasound.

Live unrelated transplant group

During the same time period, 120 LURTs were performed at our institution. Patient survival from the time of kidney transplantation was evaluated by Kaplan–Meier analysis.

Deceased donor waiting list group

For the purposes of comparison, survival was also evaluated in patients who were accepted onto the renal transplant waiting list during the period from May 1996 until September 2007. During this period, a total of 788 potential recipients were placed on the list. Of those, 474 patients received renal transplants leaving 314 patients on the waiting list who did not receive a donor kidney. Of the 314 patients, 109 patients were removed permanently from the list for a variety of reasons including – malignancy, significant medical problems, smoking, worsening cardiac disease, noncompliance, relocation and patient request. Sixteen of the 109 patients were removed because they underwent a live related transplant. A further 34 patients were removed because up-to-date investigations were not forthcoming. Eighteen patients died while on the waiting list of a variety of causes including cardiac arrest (n = 5), myocardial infarction (n = 2), malignancy (n = 1), septicaemia (n = 2), liver disease (n = 1), mesenteric infarction (n = 1) and dialysis withdrawal (n = 2). The other causes of death were unknown. Therefore, out of the 314 patients, 153 patients remained active on the transplant waiting list but did not receive a renal transplant. Survival was calculated from the time of acceptance onto the deceased donor transplant list. Data were censored for renal transplantation and 20 September 2007. If the patient was withdrawn from the transplant list, they were included in the survival analysis on an intention-to-treat basis.

The Kaplan–Meier survival analysis demonstrated that the recipients of kidneys from donors with excised renal tumours experienced an early increase in mortality compared with the other groups. By approximately 4 years post-transplant, survival of recipients of kidneys with excised renal tumours was superior to that of dialysis patients who were accepted onto the renal transplant list

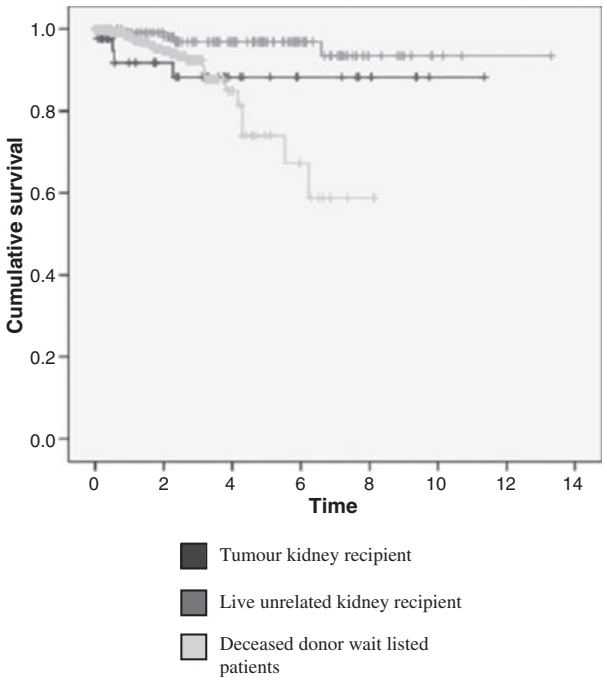

Figure 2 Survival of recipients of tumorectomised kidneys was significantly superior to that of dialysis patients who were accepted onto the renal transplant list but inferior to that of LURT at 4 years. (log rank score 10.4, $P = 0.005$).

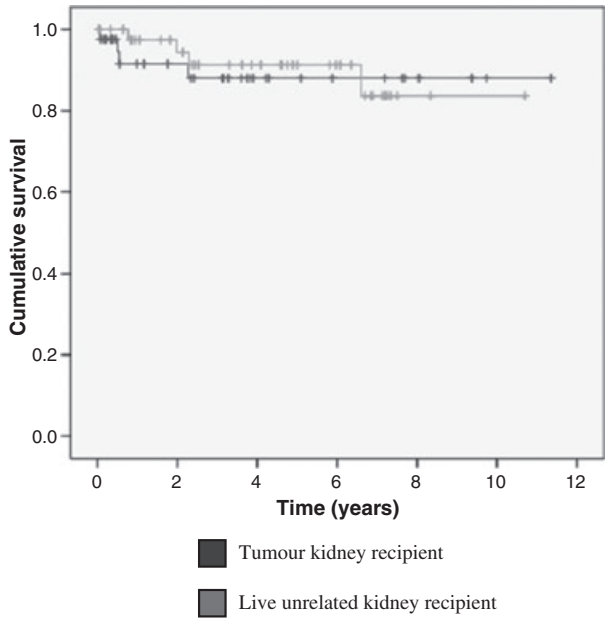

Figure 3 Comparison of patient survival between transplant recipients of kidneys with excised tumours ($n = 43$) and LURT ($n = 43$) matched for age, gender and HLA mismatch.

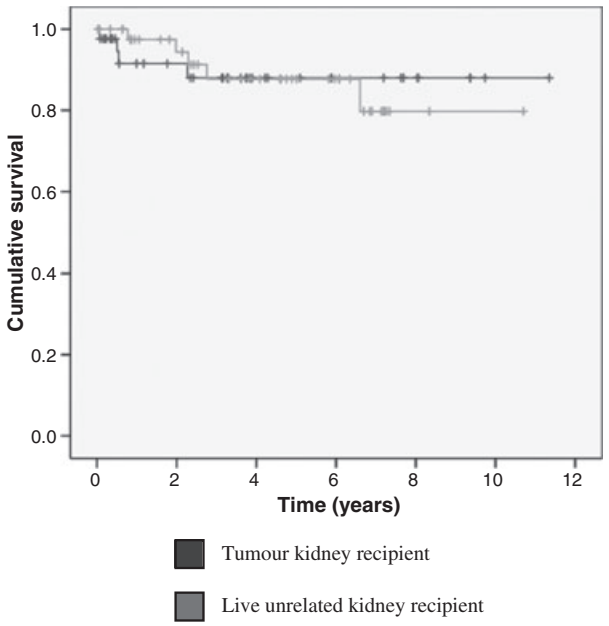

Figure 4 Comparison of graft survival between recipients of kidneys with excised tumours and LURT matched for age, gender and HLA mismatch (log rank 0.003, $P = 0.96$).

but inferior to that of LURTs (Fig. 2). Respective 1-, 3- and 5-year survival rates were 92%, 88% and 88% for TK recipients, 99%, 97% and 97% for LURT, and 98%, 92% and 74% for dialysis patients accepted onto the deceased donor kidney transplant list (log rank score 10.4, $P = 0.005$).

In a subsequent matched cohort analysis, recipients of kidneys from donors with excised renal tumours and LURTs were matched for age (within 2 years), gender and HLA mismatch. There was no observed difference in the overall survival between the two groups (log rank score 0.09, $P = 0.77$) (Fig. 3). Similarly, graft survival (not censored for death) was not significantly different between the two matched groups (log rank 0.003, $P = 0.96$) (Fig. 4).

Discussion

To date, we have used 43 kidneys from donors with small renal tumours for transplantation. The basis on which we have pursued this programme is our belief that the probability of tumour-related mortality is lower than the probability of dialysis-related mortality whilst waiting for a deceased donor transplant.

Although dialysis is a life-sustaining intervention, it still carries a significant mortality risk. We have previously reviewed our experience in elderly transplant recipients compared with similar patients who were on our active transplant waiting list [3].Amongst patients considered

Table 2. Baseline characteristics of the three groups.

Parameter	Tumour	LURT	Wait-listed	*P*-value
Age (years)	60.9 ± 10.2	50.0 ± 12.3	46.9 ± 13.2	<0.001
Female (%)	20 (47%)	49 (41%)	315 (40%)	NS
Caucasian (%)	35 (81%)	110 (92%)	671 (85%)	NS
Diabetes (%)	8 (19%)	9 (8%)	56 (7%)	<0.05
Coronary artery disease (%)	11 (26%)	13 (11%)	80 (10%)	<0.01
HLA mismatch	4 [3–5]	4 [4,5]	NA	NS

LURT, live unrelated renal transplant recipient.

suitable for inclusion in the waiting list, patients with co-morbidities or greater than 60 years of age, transplantation is associated with a substantial survival advantage compared with dialysis [3]. ESRF patients over this age awaiting transplantation have an annual mortality risk of 25% despite aggressive screening to exclude patients at high risk of cardiovascular complications [3]. Several other studies have also demonstrated a significant survival advantage with transplantation over dialysis – particularly in elderly patients and those with co-morbidities [4,5]. In Australia, the average waiting time for a deceased donor transplant is now approximately 4 years [2]. During this period, many elderly patients or those with significant co-morbidities that are accelerated by the effects of ESRF will die without ever receiving a transplant [3,4].

The widespread use of cross-sectional imaging has altered the incidence and presentation of patients with renal tumours [9]. Registry data has shown a dramatic increase in the incidence of RCC, independent of the ageing population [7,8]. These incidentally detected tumours are frequently small and localized and it is likely that many of these tumours will not prove clinically significant in the course of the patients' lives [9]. The very slow growth pattern with a low risk of metastatic spread in most tumours <3 cm in diameter has been documented [10,11]. With RCC, prognosis is closely linked to tumour stage and size. Recurrence or metastases occur or are present in 1–4% of pT1 tumours [16,17] Radiological and biopsy features of small renal tumours however can not reliably distinguish clinically significant from indolent tumours [12].

Patients presenting with small localized tumours are usually advised to undergo surgical excision of the lesion with either a radical nephrectomy or partial nephrectomy, if they are fit for surgery. Partial nephrectomy, originally reserved for patients with a solitary or functionally compromised contralateral kidney, is now increasingly utilized for patients with a small tumour and a normal contralateral kidney. Excellent results have been reported, with cancer-specific survival comparable to radical nephrectomy [13,14]. However, partial nephrectomy is associated with a higher risk of complications including bleeding, urine leakage and wound-related problems [14]. Local recurrence rates are low and reported in 0–4% of patients undergoing elective partial nephrectomy for pT1 tumours [13,15]. Despite these excellent results for partial nephrectomy (generally reported from major teaching institutions), population-based studies indicate that radical nephrectomy remains the commonest procedure for T1 tumours. Currently in the United States, where the majority of renal cell carcinomas are detected as T1 tumours, partial nephrectomy is still undertaken in only 12.3–15.5% of patients with renal tumours [16,17]. Based on Medicare data (http://www.medicareaustralia.gov.au/statistics) partial nephrectomy was performed for 23% of cases undergoing surgery for renal tumours in Australia in 2006. In contrast, whilst laparoscopic partial nephrectomy has been reported, it represents a much greater technical challenge than radical nephrectomy for small tumours Even in units with substantial experience complication rates appear significantly higher than those seen with laparoscopic nephrectomy [18,19]. It would therefore appear likely that whilst many patients with small renal tumours may elect partial nephrectomy a significant number will still prefer radical nephrectomy based on these considerations. Prior work using the population-based Surveillance Epidemiology and End Results registry in the United States has demonstrated that, as recently as 2001, 58–80% of patients with renal tumours less than 2 cm and 2–4 cm respectively were preferentially treated with radical nephrectomy giving an estimation that there may be as many as 7000 usable kidneys per year in the US, which are currently discarded post radical nephrectomy [16,20].

Transmission of RCC from the donor has been reported in the past [21]. This would appear related to the inadvertent use of kidney containing an unrecognized tumour that subsequently progressed. On occasions, RCC of donor origin may arise many years following transplantation suggesting that the tumour may not have been present at the time of retrieval [22,23]. In cases with localized RCC diagnosed in an allograft, patients have been successfully managed with excision of the tumour alone [23–25]. Percutaneous minimally invasive techniques

using radiofrequency ablation are now also employed as an alternative to surgical excision of small renal tumours and have also been described in the context of a tumour within a renal allograft [26]. When metastatic disease has presented, treatment can be undertaken by withdrawal of immunosuppression and removal of the allograft [21]. With this approach, complete regression of the tumour occurs in 50% of cases.

Our results suggest that radical nephrectomy specimens containing small (<3 cm) tumours may be safely transplanted, enhancing the length and quality of life of marginal transplant recipients who would otherwise have a significant risk of not receiving a renal allograft. Patient and graft survival in this group is comparable to that of standard LURT. Survival is also significantly better in this group than a comparable cohort who did not receive a transplant.

Although the utilization of kidneys following removal of a tumour conferred significant benefits for patients in our study, these need to be balanced against the potential risks, based on data related to radical nephrectomy and partial nephrectomy with metastasis or local recurrence in <4% of T1 tumours [13,15]. Our experience would not suggest any excess risk in this pattern of recurrence in immunosuppressed recipients in the intermediate term. We acknowledge that the data presented are not long-term results and that continued follow-up may reveal more tumour recurrences.

Underpinning the strategy that we have employed has been a vigorous informed consent process. In the majority of cases, the nephrectomy has been an elective procedure allowing time for identification of potential recipients and the opportunity for discussions with one or more of these. Information discussed with potential recipients has included the risk of recurrent malignancy with stated estimations of tumour recurrence of approximately 5% and that with this, metastases could occur and prove fatal despite withdrawal of immunosuppression. Patients were also made aware of technical considerations including reduced renal mass, increased risk of haemorrhage and haematoma formation, as well as the possibility of urinoma/urinary fistula. In one of our cases, a calyceal fistula developed at the site of tumour excision but was successfully managed by re-exploration, nephrostomy drainage and ureteric stenting. Arteriovenous fistula formation is a potentially serious complication although to date we have only experienced this in a single case within weeks of transplantation. Regular routine ultrasound monitoring of the graft to identify this during this period in addition to the standard follow-up protocol we have employed warrants consideration.

As our experience has increased, we have begun to discuss the possible availability of such marginal kidneys with some patients at the time they are placed on the transplant waiting list. These are patients who by virtue of their age or co-morbidities are felt to have a significant risk of becoming unfit for transplantation, during the anticipated 3- to 4-year waiting time for a kidney. This allows them to be well informed ahead of time and improves their capacity to make the difficult decision related to consent.

From this study it appears that kidneys with small renal tumours can be safely transplanted after bench surgery into elderly patients or those with significant co-morbidities who may not otherwise be able to receive a transplant. A substantial survival advantage is seen when compared with similar patients who remain on dialysis even with intermediate follow-up. Graft survival in this group appears comparable to that seen with conventional LURT. Although this is a novel source of donation, we believe it is potentially a very valuable resource for patients with ESRF who otherwise would not receive a kidney.

Authorship

NRB: study design, data collection, wrote paper, involved in procedures. NG: data collection, involved in procedures. DWJ: data analysis, study design. DLN: Departmental head, initiator of TK transplantation idea, study design.

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