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REVIEW

# Transplantation of kidneys with tumors

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**Abstract** The shortage of donors in the face of the increasing number of patients wait-listed for renal transplantation has prompted several strategies including the use of kidneys with a tumor, whether found by chance on harvesting from a deceased donor or intentionally removed from a living donor and transplanted after excision of the lesion. Current evidence suggests that a solitary well-differentiated renal cell carcinoma, Fuhrman nuclear grade I-II, less than 1 cm in diameter and resected before grafting may be considered at minimal risk of recurrence in the recipient who, however, should be informed of the possible risk and consent to receive such a graft.

**Keywords** Renal cancer · Renal transplantation · Kidney donation · Tumor transmission · Safety of donation

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## Introduction

At present, renal transplantation is the best treatment available for patients with end-stage renal disease (ESRD) and is current practice in industrialized countries thanks to the significant improvements in immunosuppressive and supportive therapy that have occurred in recent years. However, while the number of patients listed to receive a kidney from a deceased donor is progressively increasing, donor numbers have remained stable in the last few years, leading to larger waiting lists and longer waiting time to receive a kidney.

Several strategies have been proposed to face the shortage of donors, including transplantation of kidneys from 'extended criteria' donors, transplantation from living donors whether related or not, paired living donation from exchanging donors to overcome donor-recipient incompatibility, sometimes within a chain of 'domino transplantation' starting from an altruistic donation [1]. In this setting, with the aim of transplanting the largest number possible of available kidneys, even organs with a renal mass have been considered for grafting.

## Safety of grafting kidneys with a tumor

Whether a kidney with a tumor should be transplanted is still a matter for discussion. While the Kidney Disease—Improving Global Outcomes (KDIGO) guidelines do not address the issue of evaluation of kidney donors [2], the European Best Practice Guidelines (EBPG) discourage the acceptance of donors with malignancies [3]. On the other hand, the European Association of Urology (EAU) guidelines suggest that kidneys with a small renal cell carcinoma (RCC) may be transplanted after excision of the lesion [4].

Transplantation of kidneys with a tumor includes the possibility of transplanting organs with a small lesion found during the donation procedure or even kidneys removed due to the presence of a renal mass. This latter option has been proposed for patients at higher risk who accept these grafts, provided that surgery spares enough renal tissue to allow the recipient good renal function [5–9]. This proposal rests on the observation that RCCs show great variability in their biological aggressiveness and only 20 % of small tumors, i.e., less than 2 cm in diameter, are potentially aggressive [10] with a 1–2 % incidence of metastatic progression within 2–3 years from diagnosis [11]. The proposal is further supported by the good oncological outcome reported in patients who underwent partial nephrectomy for a solitary, small renal mass, generally smaller than 4 cm in major axis, compared to patients who underwent radical nephrectomy [12–14].

Although complications such as perinephric hematoma or calyceal fistula have been reported more frequently after partial nephrectomy, nowadays this last procedure is largely used with a view to preserving renal function, particularly when one considers that patients tend to be older and have several co-morbidities so that at diagnosis approximately one-third of them already have a reduced renal function [15]. Since this approach has brought oncologic outcomes equivalent to radical nephrectomy when treating small and limited RCCs [16], the American Urologic Association Guidelines strongly recommend the approach as the reference standard of care [17].

Clearly, transplantation of kidneys discarded because of a renal tumor raises some ethical concerns: many believe it unethical to refer subjects with small renal tumors to a transplant center where the removed kidney may be transplanted after excision of the lesion [9]. Such treatment is not optimal for the patient and entails a clear conflict of interest, unless the subject had already decided to donate a kidney and the renal cancer was incidentally discovered during medical evaluation for donation.

For both options considered, the discussion focuses on safety for the recipients, given the increased incidence of cancer in transplanted patients, as well as on the kidney's residual function. It is known that renal cancer occurs more frequently in renal transplanted patients than in the general population, with a 4.9 standardized incidence ratio (SIR), accounting for the third most frequent solid tumor observed in the series reported by Piselli et al. [18]. The large majority of renal cancers observed in transplanted patients arise in the native kidneys, while only about 10 % of cases occur in the graft, rarely due to donor-recipient transmission [19]. Prolonged immunosuppressive therapy has been regarded as the most important factor in increasing the tumor risk in renal transplant recipients although other factors have emerged [20].

The progressive increase in donor age implies a higher risk of unintended transmission of malignancies and a prominent role of RCCs. This tumor was the donor-derived malignancy most frequently reported to the Organ Procurement and Transplantation Network (OPTN) between 2005 and 2009, accounting for 43.8 % of all malignancy reports [21]. Seven out of 64 potential donor-derived RCCs reported to the OPTN were confirmed as being transmitted along with the transplanted kidney, and one recipient died as a result of the transmitted malignancy [21]. Similar results were reported by the Spanish National Transplant Organization Tumor registry [22] where again kidney tumors were the most frequently observed in donors, accounting for 47 % of cases with cancer, subsequently transmitted to two recipients. However, the cases reported (Table 1) indicate that, despite prolonged immunosuppressive therapy to prevent rejection, the recurrence rate of small renal cancer is low, provided the lesion is completely removed.

Several years ago Penn first focused attention on the problem by reporting a series of 30 patients transplanted from donors with a renal mass. In 14 cases the mass, found upon harvesting, was radically removed without any recurrence in the recipient; in 2 cases where the lesion was only partially removed (R1 margins) the recipients experienced tumor recurrence and metastasis, thus underlining the importance of radical excision of the lesion before grafting. The remaining 14 patients received a kidney from donors in whom the opposite kidney had a malignancy: only one possible tumor recurrence occurred when a carcinoma was found during histological examination of the graft removed for rejection [23].

However, in a more recent paper Buell et al. reported that 43 out of 70 (61 %) donors with RCC recorded in the Israel Penn International Transplant Tumor Registry (IPITTR) resulted in malignancy transmission to the recipients, with a 15 % patient mortality [24].

Nicol et al. described a series of 43 patients intentionally transplanted with kidneys discarded because of a mass during a 13-year period, where a new tumor developed in only one patient, 9 years after grafting, leaving it open to question whether this was a real recurrence or a *de novo* cancer, not only due to the length of time from grafting but also because the new lesion was far from the previous resection [9].

These results suggest that, with due caution, kidneys with small tumors may be used for transplantation into patients who accept the risk, offering them a chance to improve their quality of life and, hopefully, survive longer than on dialysis treatment [25].

As far as immunosuppressive therapy is concerned, there has been mounting evidence in recent years that mammalian target of rapamycin (mTOR) inhibitors may

**Table 1** Reported cases of transplantation of kidneys with a tumor

| References | Cases (*n*) | Tumor transmission to recipient (n) | Recipient death due to transmission | Notes |
|---|---|---|---|---|
| Ison et al. [21] | 64 | 7 | 1 | Data from OPTN/UNOS registry |
| Sener et al. [5] | 5 | 0 | 0 | 3 RCC, 2 AML; all LD |
| Garrido et al. [22] | 55 | 2 | 0 | Data from Spanish National Transplant Organization Tumor registry |
| Mannami et al. [6] | 8 | 0 | 0 | All RCC, transplanted from LD |
| Nicol et al. [9] | 43 | 1 | 0 | 38 LD; 3 AML; 4 ONC; 31 KC; 3 CC |
| Buell et al. [24] | 70 | 43 | 15 % | Data from Israel Penn International Transplant Tumor Registry |
| Penn [23] | 30 | 3 | 2 | Recurrence in 2 cases with partial removal of tumor and in 1 out of 14 pts who received a contralateral kidney from a RCC donor |

*OPTN/UNOS* Organ Procurement and Transplantation Network/United Network for Organ Sharing, *RCC* renal cell carcinoma, *AML* angiomyolipoma, *LD* living donor, *ONC* oncocytoma, *KC* kidney cancer, *CC* complex cyst

reduce the cancer risk of renal transplant recipients. Since several studies have reported a lower malignancy rate in patients converting to mTOR inhibitors than those who continue to take calcineurin inhibitors [26–28] it seems advisable to use these drugs to prevent rejection in patients who receive a kidney with a small tumor, although there is no evidence at present that such approach can affect positively their outcome.

## Importance of pathological diagnosis

Accurate pathological diagnosis of the lesion is of the utmost importance when deciding whether to transplant a kidney from a donor with a renal mass, as suggested by the observation that in the Penn series 7 out of 17 patients who received kidneys with a non-diagnosed renal mass developed metastases 12 months after transplantation [23].

Although clear cell carcinoma accounts for the majority of renal tumors, several other entities have recently been added to the traditional classification [29, 30] or are under discussion (Table 2), further emphasizing the need for a proper diagnosis in order to assess the risk of tumor transmission and recurrence in the recipient.

In this setting, tissue processing and the techniques used are, of course, important. The value of frozen section examination to evaluate the margins of the renal mass during surgery is debatable. While Penn [31] stressed its utility, Algaba et al. [32] reported 20–37 % false negative results due to incorrect sampling of the lesion, particularly when only some fragments are sent to the pathologist who cannot carry out a gross examination of the whole lesion which is often crucial for diagnosis.

Necrosis, fibrosis and/or a cystic tumor component raise the percentage of false negative results in fragmentary samples [33–35]. Moreover, in frozen tissue the cytology and sometimes the architecture too may not be well preserved so that a specific diagnostic feature, clearly appreciable on paraffin sections, may not be evident on frozen sections. Thus, for example, the classic RCC in a frozen section appears as a lesion with large eosinophilic cytoplasm, because the well-known 'clear cell cytology' is an artifact of routine processing dissolving the glycogen contained in the cytoplasm. A variable percentage of false positive cases, ranging from null to 34 % [33], have also been reported primarily due to misinterpretation of crushed renal tubules as a renal neoplasm [36]. Again, the exact cytological nucleolar grade may be puzzling, due to the nuclear/nucleolar artifacts. However, intraoperative frozen section examination may be useful in determining the status of the margins in partial nephrectomies [32], provided the pathologist receives the entire lesion and not only small fragments, avoiding crush artifacts due to diathermocoagulation. When appropriate, immunohistochemistry should be used to define the diagnosis, as indeed for the differential diagnosis between oncocytoma and chromophobe renal cell carcinoma.

Recent observations suggest that even kidneys with multiple low-grade tumors may be suitable for transplantation, provided this condition does not influence the functionality of the residual parenchyma. The presence of multiple/miliary nodules may in fact compress the parenchyma, creating extensive fibrosis and global glomerular sclerosis, or multifocality may herald a hereditary renal neoplastic syndrome [37].

**Table 2** Classification of renal neoplasms

| | |
|---|---|
| *Historical classification* [29] | |
| Clear cell renal carcinoma (CCR) | 70 % of renal tumors; multifocal 4 %; bilateral 0.5–3 % |
| Papillary cell renal carcinoma (PRCC) | |
| Renal cell carcinoma chromophobe cell type | 5 % of renal tumors |
| Oncocytoma | Benign; differential diagnosis with the eosinophilic variant of chromophobe RCC or CCR |
| Collecting duct carcinoma | <1 % renal carcinoma |
| Renal medullary carcinoma | Children and patients with sickle-cell disease |
| Mucinous tubular spindle cell RCC | Female preponderance |
| Angiomyolipoma | Benign lesion, multifocal in 20 % of cases; the epithelioid variant is malignant |
| *New proposed entities* [30] | |
| Tubulo-cystic RCC | Rare |
| Acquired cystic disease RCC | Patients with ESRD; multifocal (50 %); bilateral (20 %) |
| Clear cell tubulo-papillary RCC | 1 % of renal cancers |
| MiT family translocation RCC | |
| Hereditary leiomyomatosis RCC | Autosomal dominant syndrome |
| *Rare entities under discussion* [30] | |
| Thyroid-like follicular neoplasia | |
| Succinate-dehydrogenase B mutation-associated RCC | |
| ALK translocation RCC | |

*ESRD* end-stage renal disease, *RCC* renal cell carcinoma, *MiT* microphthalmia-associated transcription, *ALK* anaplastic lymphoma kinase

## Current opinion

The Disease Transmission Advisory Committee (DTAC) of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) of the United States suggests that solitary well-differentiated RCCs, Fuhrman nuclear grade I–II, less than 1 cm in diameter and resected before grafting, may be considered at minimal risk of recurrence in recipients [38]. Solitary well-differentiated RCCs 1–2.5 cm in diameter should be considered at low risk and still usable for transplantation, although only in selected patients whose clinical risk while on dialysis treatment outweighs that of being transplanted with such a graft (Table 3).

However, extreme caution should be used when examining data on renal transplantation from donors with renal tumors, since most of the cases reported (Table 1) were transplanted from living donors, thus presumably investigated more accurately than is usually possible when transplanting a graft from a deceased donor, where only a short time is available for the donation procedure. In addition, all cases included in the registries were voluntarily reported, raising the possibility that they may not represent the real risk of tumor transmission. Finally, the small dimension of a RCC does not always make it risk-free, since small tumors may be multifocal [39], nor is it a guarantee of good prognosis, considering that 7 % may

**Table 3** Risk of donor transmission of renal neoplasms to graft recipients (modified from Ref. 38)

| Tumor | Risk of transmission | Transplant |
|---|---|---|
| Solitary RCC <1 cm, well differentiated (Fuhrman 1–2) | Minimal (<0.1 %) | Yes with informed consent |
| Solitary RCC 1–2.5 cm, well differentiated (Fuhrman 1–2) | Low (0.1–1 %) | Only in patients at risk if not transplanted—informed consent required |
| Solitary RCC T1b 4-7 cm, well differentiated (Fuhrman 1–2) | Intermediate (1–10 %) | Not recommended |
| RCC > 7 cm or stage II-IV | High (>10 %) | To avoid |

*RCC* renal cell carcinoma

cause metastases despite the small dimension of the tumor [40] and need to be checked for in a potential donor.

With all these caveats in mind, a donor with a low-grade renal cell cancer may be considered at standard risk of disease transmission to the recipient [41], who should be informed of the possible risk and should consent to receive the graft. There is no specific recommendation as far as the follow-up of these patients is concerned, but an ultrasound study of the graft every 6 months is advisable and already carried out in all renal transplant recipients in most centers.

Finally, although renal transplantation has been proved to be a better treatment than dialysis, the pros and cons of the two treatment modalities should be carefully weighed up when making decisions carrying even slightly increased risks, and the clinical situation of each single patient needs to be thoroughly assessed.

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