

## Renal cancer in kidney transplanted patients

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**Abstract** Renal cancer occurs more frequently in renal transplanted patients than in the general population, affecting native kidneys in 90 % of cases and the graft in 10 %. In addition to general risk factors, malignancy susceptibility may be influenced by immunosuppressive therapy, the use of calcineurin inhibitors (CNI) as compared with mammalian target of rapamycin inhibitors, and the length of dialysis treatment. Acquired cystic kidney disease may increase the risk for renal cancer after transplantation, while autosomal dominant polycystic kidney disease does

not seem to predispose to cancer development. Annual ultrasound evaluation seems appropriate in patients with congenital or acquired cystic disease or even a single cyst in native kidneys, and every 2 years in patients older than 60 years if they were on dialysis for more than 5 years before transplantation. Immunosuppression should be lowered in patients who develop renal cancer, by reduction or withdrawal of CNI. Although more evidence is still needed, it seems reasonable to shift patients from CNI to everolimus or sirolimus if not already treated with one of these drugs, with due caution in subjects with chronic allograft nephropathy.

**Keywords** Renal cancer · Renal transplantation · Immunosuppressive therapy · Calcineurin inhibitors · mTOR inhibitors

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### Introduction

Cancer is a major cause of morbidity and mortality in renal graft recipients.

When compared to the general population, kidney transplanted patients have an increased risk of developing various malignancies. There are several factors, including prolonged immunosuppressive therapy, both before and after transplantation, viral infections and duration of dialysis treatment, interacting with traditional risk factors such as sun exposure, smoking and age. In accordance with the various series reported, the risk of developing solid-organ tumors is 3- to 6-fold higher than among the general population, but 7- to 10-fold increased where renal cancers are concerned, although the majority of these last consist in incidental low-stage and low-grade tumors with a good prognosis [1, 2].

## Incidence and mortality of renal cancer after kidney transplantation

Of course, the length of follow-up is relevant when assessing the risk of malignancy after transplantation. In a cohort of 7217 patients who received a renal graft between 1997 and 2007, Piselli et al. found that the cumulative risk for all cancer was 4.8 and 9.9 % at 5 and 10 years respectively, with an overall 1.7-fold higher risk compared to the general population [3]. In their series, renal cancer showed a 4.9 standardized incidence ratio (SIR), accounting for the third most frequent solid tumor observed.

In addition, patients with kidney transplants exhibit an increased mortality for any given stage and grade of malignancy compared with the non-immunosuppressed population [4]. Farrugia et al. investigated the overall and site-specific risk of cancer death among kidney transplant recipients. The most common sites of malignancy-related death were lymphoma (18.4 %) and lung (17.6 %), followed by kidney (9.8 %). At univariate and multivariate analysis, age, pre-transplant history of malignancy and deceased-donor kidney transplantation were significantly associated with the risk of post-transplant cancer-related death, which was 10-fold higher in patients with kidney transplants than cancer patients in the general population [5]. Interestingly, more than half of all malignancy-related deaths in recipients with a pre-transplant cancer history were renal in origin, although the authors were unable to verify the site of the pre-transplant cancer.

The large majority of renal cancers observed in transplanted patients arise in the native kidneys, while about 10 % of cases occur in the graft, rarely due to donor-recipient transmission [6]. Analysis of a large series of transplanted patients found that graft cancer affected 12 out of 2396 patients (0.5 %), occurring on average 13 years after surgery, thus ruling out the possibility of a pre-existing lesion in the donor [7].

## Pathogenesis of posttransplant malignancy

The number of cases reported to date is not large enough to allow us to identify any specific risk factor or assess the growth rate of such tumors; likewise, the mechanisms leading to the increased cancer susceptibility of transplanted patients have not been fully elucidated.

Prolonged immunosuppressive therapy is regarded as the most important factor in increasing the tumor risk in renal transplant recipients, particularly after the introduction of more effective drugs affecting various steps of the immune response and used in combination to prevent graft rejection. However, this relationship may appear fairly loose if we consider that recipients of ABO-incompatible

living-donor kidney transplants, who receive intense immunosuppression, do not exhibit any increased cancer risk when compared with their ABO-compatible counterparts [8]. In addition, the observation that the standardized incidence ratio of cancer in transplanted patients is higher than that observed in subjects with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [9] seems to suggest that immunosuppression by itself is not enough to increase cancer susceptibility. Thus, probably not only the degree of immunosuppression but also other factors such as the drugs used and the length of treatment may play a more important role in determining susceptibility to cancer.

Calcineurin inhibitors (CNI), which have greatly contributed to reducing acute rejection and led to a significant improvement in graft survival, are known to be associated with biological changes that may promote tumor growth, such as increase in transforming growth factor (TGF)- $\beta$  and vascular endothelial growth factor (VEGF) [10].

Again, the relationship between individual immunosuppressive agents and cancer risk is far from clear. Bustami et al. showed a significantly lower incidence of de novo tumors among patients with kidney transplants treated with tacrolimus than those on cyclosporine [11]. Otherwise, no significant differences in terms of cancer risk were found in a retrospective study including 481 patients treated with azathioprine and prednisolone, cyclosporine monotherapy, or cyclosporine monotherapy followed by a switch to azathioprine and prednisolone after 3 months [12].

There has been mounting evidence in recent years that mammalian target of rapamycin (mTOR) inhibitors may reduce the cancer risk of renal transplant recipients, possibly though their effect on the hypoxia-inducible factor (HIF)/VEGF axis. Thus, in the series of renal transplant recipients studied by Piselli et al. a 46 % reduction in cancer risk was observed in patients treated with mTOR inhibitors for both Kaposi sarcoma and overall solid tumors, although the study had not been designed to assess the effect of anti-rejection drugs [3]. In addition, several studies have reported a lower malignancy rate in patients converting to mTOR inhibitors than those who continue to take calcineurin inhibitors [13–15].

Regulatory T cells (Tregs), a subpopulation of T cells involved in suppressing cellular rejection and inducing tolerance, have been shown to play a crucial role in cancer development in these patients [16]. Thus, for example, the number of Tregs found in renal transplanted patients who developed solid tumors seems higher than among patients without cancer [16]. In addition, conversion from CNI to mTOR inhibitors seems less effective in patients with increased Tregs [17, 18]. Interestingly, infiltrating Tregs are associated with the pro-angiogenic phenotype of renal

cell carcinoma (RCC), and an increased percentage of Tregs correlates with the stage and grade of RCC [19] although a direct association between the level of Treg and the risk of renal cancer in patients with kidney transplants has not yet been documented.

The importance of factors other than immunosuppression has been underlined by a recent study that confirmed previous observations suggesting subjects who received a kidney from a living donor had a lower risk of post-transplant malignancies. The study analyzed the clinical course of 7040 patients, 468 of whom (6.6 %) developed cancer during follow-up [20]. In this cohort, people who received a kidney from a deceased donor had a higher risk of cancer [hazard ratio (HR) 1.52,  $p = 0.004$ ] than did recipients of living-donor kidneys, a finding which proved even higher for genitourinary cancer (HR 1.79,  $p = 0.038$ ) and post-transplant lymphoproliferative disease (HR 2.72,  $p = 0.004$ ).

Since there is no substantial difference in immunosuppressive schedules between patients receiving a graft from a living or a deceased donor, it has been suggested that the time spent on dialysis, which is significantly shorter in patients transplanted from a living donor, could be relevant to the risk of malignancies.

Registry data show that the risk of kidney cancer development in the dialysis population progressively increases with time, reaching a sevenfold excess risk after 10 years of treatment [21] due to several factors including endothelial damage, cellular immunity deficiency and exposure to potential carcinogens related to the procedure. Uremia by itself increases the risk of cancer even in people who are not on dialysis, as suggested by the observation that older subjects with reduced renal function have a 1.4-increased risk of cancer than those without chronic kidney disease [22]. More recently, a linear relationship between duration of dialysis and cancer risk after transplantation has been found in a large cohort of patients who received a renal graft between 1997 and 2009 [23], correlating with a significantly increased risk of cancer of the urinary tract.

### Cystic kidney diseases and the risk of development of renal cancer

Cystic kidney diseases have been suggested as another potential pre-transplant factor which might contribute to cancer susceptibility. They can be categorized as inheritable, developmental, or acquired. The most common are acquired cystic kidney disease (ACKD), where no inheritable or developmental etiology is known or suspected, and autosomal dominant polycystic kidney disease (ADPKD) caused by a mutation in gene PKD1 or PKD2.

### Acquired cystic kidney disease and renal cancer

Historically, the definition of ACKD has varied. But there is now general agreement that such cysts need to be bilateral, with four or more cysts identified [24–27]. Ultrasound, CT scanning, and magnetic resonance imaging (MRI) are all acceptable imaging modalities to make the diagnosis. Unlike polycystic kidney disease (PKD) where the kidneys are markedly enlarged and lose their normal reniform contour, ACKD kidneys are generally of normal size with a largely preserved morphology.

While the incidence of ACKD rises as the time on dialysis increases, onset often predates progression to end-stage renal disease (ESRD). It is estimated that approximately 20 % of patients have ACKD when they first begin renal replacement therapy. This figure increases to 60–80 % for patients on dialysis for 4 years, and to 90 % for patients on dialysis for 8 years. Other studies have shown that approximately 7 % of patients with chronic kidney disease have multiple renal cysts, while another 30–50 % have cysts, but less than the four cysts required for ACKD diagnosis. While the prevalence of ACKD increases the longer a patient is on dialysis, it is the patient's renal failure rather than exposure to dialysis that leads to this condition. Interestingly, the etiology of the renal failure does not seem significantly to affect the rate of ACKD development [24].

Acquired cystic kidney disease is generally a clinically silent condition, but the cysts can predispose to development of infection, and may also bleed resulting in gross hematuria or retroperitoneal hematoma, or else progress toward development of a malignancy, which is the most feared complication of ACKD [28, 29].

Conflicting results have been reported in the past as far as the association between RCC after transplantation and renal cysts is concerned [30–32]. However, a more recent, though retrospective, study carried out in 1036 renal transplant recipients observed from 1995 to 2007 found a strong association between renal cancer development after grafting and native renal cysts, with a 1.7-fold higher risk [33]. This underlines the importance of considering even a single native kidney cyst as a risk for malignant evolution after transplantation.

In this setting, it would be advisable to do a follow-up on cystic lesions using ultrasound, CT scanning or MRI, taking into account that this last can detect substructural features within cysts (such as thin septations, small calcifications, etc.) that may be missed by CT scanning. The intervals between check-ups should be adjusted according to the risk of malignant evolution which may be assessed by means of the Bosniak classification, originally developed to interpret renal cystic lesions identified by CT

**Table 1** The Bosniak classification of renal cysts

Bosniak stage	Features	% Malignant
Bosniak 1	Simple cyst	<1
Bosniak 2	Minimally complex, a few thin (<1 mm) septa, thin calcifications; non-enhancing high-attenuation	1–3
Bosniak 2F	Increased number of septa, minimally thickened or enhancing septa or wall thick calcifications Hyperdense cyst >3 cm diameter	5–15
Bosniak 3	Indeterminate, thick or multiple septations, mural nodule, hyperdense on CT	40–60
Bosniak 4	Clearly malignant, solid mass with large cystic or necrotic component	100

CT computed tomography

scanning and later extrapolated to ultrasound and MRI images (Table 1).

Bosniak class 1 lesions are simple cysts and are associated with an approximately 1 % risk of malignant transformation. As this risk of progression to malignancy is extremely low, interval imaging reassessment is not strictly required. Bosniak class 2 lesions have minimally abnormal radiographic features, such as very thin septations and tiny microcalcification in a fairly small cyst. These lesions are also known to have a low risk of becoming malignant, approximately 3 % progressing to cancer. Bosniak class 2F (“F” to designate and draw attention to the need for interval “follow up”) was added to the classification system in 1993 to include a subset of class 2 lesions which appeared slightly more complex, but not sufficiently complex to justify being graded as class 3 (i.e. they do not clearly meet either the Bosniak class 2 or 3 definitions). These cysts have a risk of progressing to malignancy in 5–15 % of cases. Bosniak class 3 and class 4 lesions have a 40–60 and >80 % risk of being cancerous, respectively.

Unfortunately, there is still no consensus as to the frequency of reassessment with repeated imaging of Bosniak class 2F lesions. Again, some authors draw attention to the potential risk of repeated radiation exposure if serial CT scanning is the mode utilized for follow-up, so they recommend rotating ultrasound and MRI imaging to reduce exposure.

### Autosomal dominant polycystic kidney disease and RCC after transplantation

Autosomal dominant polycystic kidney disease is the most common genetic renal disease, affecting 1–3 per 1000 individuals. It accounts for 6–11 % of ESRD in Europe and is the fourth most common cause of ESRD in the United States. Currently, there are more than 16,000 ADPKD patients living with a renal transplant in the US [34, 35].

Autosomal dominant polycystic kidney disease derives from a mutation in one of two genes: PKD1 and PKD2. Each cyst in kidneys with ADPKD derives from proliferation of a single cell driven by upregulation of proto-

oncogenes, akin to a neoplastic process [34]. Development of a cyst requires a “second hit” inactivating the remaining normal PKD allele in a cell that already harbors a mutated allele of the PKD gene. The occurrence of the “second hit”, the nature of which may vary from cyst to cyst in the same kidney, recalls the “loss of heterozygosis” hypothesis as to neoplastic transformation in general [36].

The literature on the subject has been quite sparse, consisting of no more than 50 case reports and few systematic analyses.

A review of 38 cases published in 1994 found that, compared to the general population, ADPKD-associated RCCs are characterized by younger patient age (45 vs. 61 years), higher frequency of fever, night sweats and weight loss at presentation, no sex preference, frequent bilaterality (12 vs. 2–6 %), frequent multifocality (30 vs. 5 %), and a preference for the sarcomatoid type [37]. Subsequent published cases have been consistent with these results. The presence of these distinctive features might suggest a specific role for ADPKD in RCC; and indeed, some authors have found a high prevalence of renal cancers in nephrectomies from ADPKD patients [35, 38, 39].

However, these findings may also have a different explanation. First, it frequently occurs that radiology studies and nephrectomies performed for other reasons can result in incidentally-found small tumors [35]. In addition, cancers arising in ADPKD are more likely to be reported because of their rarity. Moreover, Perrone et al. analyzed the relative risk and causes of death after ESRD in ADPKD vs. non-diabetic control patients using data from the United States Renal Data System (USRDS), and concluded there was no significant difference in cancer-related mortality [40]. Thus, there is no current evidence that the risk of RCC is higher in ADPKD patients than in the general population.

Hajj et al. retrospectively reviewed a series of 89 nephrectomies performed in 79 patients with ADPKD, demonstrating a prevalence rate of RCC of 8.3 % in patients with ADPKD and chronic renal failure. This value increased to 12 % in the subgroup of patients receiving more than 1 year of dialysis or kidney transplantation. Specifically, there were only two transplanted patients with

**Table 2** Reported cases of RCC in ADPKD transplanted patients

Reference	Number of cases	Age (years)	Sex	Immunosuppressive regimen	Years from transplantation	Outcome
Regan et al. [41]	1	N/A	N/A	N/A	N/A	N/A
Ng and Suki [42]	1	N/A	N/A	N/A	N/A	N/A
Hadimeri et al. [43]	1	N/A	N/A	N/A	N/A	N/A
Errasti et al. [44]	1	N/A	N/A	N/A	N/A	N/A
DeLong et al. [45]	1	59	M	Thymo+ster, CsA	13	Hemodialysis
Hajj et al. [46]	2	62	M	N/A	7	N/A
		58, 64	M	N/A	5, 11	N/A
Patel et al. [47]	2	N/A	N/A	N/A	4	N/A
		N/A	N/A	N/A	6	N/A

RCC renal cell carcinoma, ADPKD autosomal dominant polycystic kidney disease, N/A not applicable, CsA cyclosporine A

RCC in this series, one of whom had bilateral cancer [35]. In addition, we found only seven other cases of RCC arising after kidney transplantation in ADPKD patients previously reported, as described in Table 2.

A recent study by Wetmore et al. compared the incidence of cancer between patients with ADPKD and patients with other kidney diseases, linking data from the Scientific Registry of Transplant Recipients (SRTR) with 15 population-based cancer registries in the United States. After adjustment for age and other factors, PKD recipients were actually 16 % less likely to develop cancer. In particular, there was a significant decrease in the risk of kidney cancer among PKD recipients, with 49 kidney cancers (45 RCC) in 101,660 kidney recipients with PKD versus 610 kidney cancers (505 RCC) in 107,339 non-PKD recipients, though the association remained non-significant for RCC. These results may be explained by the higher prevalence of nephrectomy in ADPKD patients, which has been estimated at about 20–30 % during lifetime; unfortunately, these data were not available in the SRTR [34].

Alternatively, it is also possible that PKD mutations play a role in preventing cells from undergoing malignant transformation. In a recent population study by Ward et al. [48], germline mutations in PKHD1 (the gene responsible for autosomal recessive PKD) proved protective against colorectal cancer. The authors speculated that a reduction in fibrocystin activity might increase mitotic instability, “paradoxically” inhibiting carcinogenesis [34].

## Screening and treatment of renal cancer in renal transplant recipients

### Screening

Since neoplastic disorders are a major cause of morbidity and mortality after renal transplantation, early detection and treatment of malignancies, as well as specific cancer

surveillance protocols, are needed to improve long-term survival of transplant recipients.

However, it is still a matter of discussion whether systematic screening to detect early RCC lesions is appropriate, given the lack of randomized controlled trials proving the benefit of such an approach in transplant recipients.

Likewise, regarding suggestions for the general population, the American Society of Transplantation and the Kidney Disease—Improving Global Outcomes (KDIGO) guidelines for kidney transplant recipients do not recommend screening for renal cancer [49–51]. By contrast, others have suggested regular investigation although at different time intervals, ranging from annual [52] to 3-yearly [32], including the European Association of Urology which recommends annual ultrasound screening in high-risk patients [53].

Ultrasonography is a relatively inexpensive and non-invasive tool for screening, but, on the other hand, its sensitivity in detecting small lesions or cancer arising in patients with multi-cystic disease is questionable. By using analytical modelling in a cohort of transplanted patients, Wong et al. concluded that annual or biennial ultrasound screening achieves only a small gain in life expectancy, suggesting that it should be limited to patients at higher risk, such as those with acquired cystic diseases, a family history of renal cancer, or von Hippel–Lindau syndrome [54]. Goh et al., who observed a close relationship between native renal cysts and RCC development after transplantation [55], suggested initial screening within 1 month of grafting followed by a 2-yearly ultrasound examination in patients with even a single cyst, or 5-yearly in the remainder.

Pending more conclusive data and taking into consideration the low cost of ultrasonography, our personal recommendation is to follow the suggestions of the European Association of Urology: an annual check in patients at risk, i.e. those with congenital or acquired cystic diseases, or even a single cyst in a native kidney, and every 2 years in

patients older than 60 years treated with dialysis for more than 5 years before transplantation.

## Treatment

Surgical management remains the most effective form of treatment for renal cancer: RCC arising in native kidneys, no longer functioning, of transplanted patients are best treated by nephrectomy, while there is no consensus on treatment of malignancies arising in the graft.

The American Urological Association guidelines recommend that nephron-sparing surgery is the procedure of choice for T1a and most T1b lesions (i.e. lesions confined to the kidney that are no larger than 4 or 7 cm, respectively) [56]. Data derived from the Surveillance, Epidemiology, and End Results (SEER) database confirm that management of T1b lesions by partial nephrectomy is associated with a survival that is similar to that of patients treated by radical nephrectomy [57]. Again, an earlier report describing the single-center experience at the Cleveland Clinic found that partial nephrectomy offered an equivalent cancer control to radical nephrectomy, but that overall patient survival was superior with partial nephrectomy. This survival benefit appeared, in part, to be related to better residual renal function in the latter group [58]. In the series reported by Ploussard et al. the allograft was removed in cases with RCC exceeding 40 mm, while the others were treated by means of nephron-sparing surgery or cryoablation provided that the graft function was good, the tumor was peripheral and the patient gave informed consent [7].

An open partial nephrectomy is usually performed for lesions arising in transplanted kidneys, but more recently a robot-assisted, transperitoneal, laparoscopic procedure has also been reported in selected cases [59].

In recent years, three systems have been proposed as categorizing renal tumors according to their radiographic characteristics. They are: the Radius, exophytic/endophytic nearness, anterior/posterior, location (RENAL) nephrometry score (NS) [60], the Preoperative aspects and dimensions used for anatomic (PADUA) classification [61], and the centrality indexing (C-index) score [62]. The concepts behind these three systems are similar, and they all perform quite well from the perspective of inter-observer variability and prediction of warm ischemia times and percent creatinine increase following partial nephrectomy [63]. Of the three methods, NS is currently emerging as the preferred system and, when it is used to compare tumor outcomes, tumors with higher nephrometry scores are associated with higher peri-operative complication rates [64–66].

This tool could help surgeons to identify patients with a kidney transplant tumor where a nephron-sparing procedure may be appropriate, although to date it has not been validated.

## Targeted agents for kidney cancer

In recent years, several agents, mainly but not exclusively interfering with tumor-associated angiogenesis, have been introduced into clinical practice. These include the pure anti-VEGF monoclonal antibody bevacizumab (which is used in combination with interferon), the multikinase inhibitors sorafenib, sunitinib, pazopanib and axitinib (mainly targeting the receptors for VEGF), and the two mTOR inhibitors everolimus and temsirolimus, these latter after the observation that mTOR activity is increased in RCC and that the mTOR and HIF/VEGF pathways are strictly connected [67].

Since the natural history of RCC is variable, the European Society of Medical Oncology (ESMO) guidelines recommend no systemic treatment other than partial or radical nephrectomy for patients without metastatic disease [68]. Subjects with metastases are treated according to risk stratification: for those with good or intermediate prognosis sunitinib, bevacizumab + interferon-alpha, or pazopanib are standard treatment options, while sorafenib and interleukin-2 are alternative options; patients with poor prognosis usually receive temsirolimus as a first-line treatment, while tyrosine kinase inhibitors (TKIs) and everolimus are used as second-line options.

Arterial hypertension and proteinuria are major side effects of drugs targeting VEGF (Table 3). Hypertension occurs in almost 80 % of patients receiving these treatments and is the consequence of endothelial dysfunction induced by VEGF blockade with impairment of vasodilatory pathways, such as nitric oxide and prostacyclin. Inadequate sodium excretion due to resetting of the pressure-natriuresis mechanism contributes to increasing blood pressure by circulating volume expansion. In this clinical setting, the majority of renal transplanted patients, who are already hypertensive, require increasing dosages of blood pressure lowering medication [69].

VEGF signaling in the glomerulus is essential to maintain the integrity of endothelial cells and the glomerular filtration barrier, in that VEGF, produced by the podocytes, binds to VEGF-receptors located on the podocytes, endothelial cells, mesangium and peritubular capillaries [70].

Proteinuria to some degree has been observed in up to 60 % of subjects treated with anti-angiogenic drugs in a dose-related manner; on the contrary, nephrotic range proteinuria has been reported in 1–7 % of patients included in early trials, which excluded patients with renal function impairment [71].

Nephrotic syndrome occurs in 7–8 % of RCC patients treated with bevacizumab [72] suggesting the possibility that patients with a single kidney, with a compensatory increased filtration fraction, may be at higher risk of developing high-grade proteinuria during treatment. Thus, renal transplanted

**Table 3** Toxicity of drugs currently used to treat metastatic RCC

Drug	Renal toxicity	Dose adjustment
Bevacizumab	Proteinuria, AH	None
Sunitinib	Proteinuria, NS, TMA, Hypokalemia; hypocalcemia	None
Sorafenib	Proteinuria, NS, TMA,	GFR <40 ml/min; 50 % of dose; GFR <15 ml/min; 25 %
Pazopanib	AH, hyponatremia, hyperkalemia	None
Axitinib	Proteinuria, bicarbonate loss, hyper-hyponatremia, hyperkalemia	None
Everolimus	AH, proteinuria, hyponatremia, hyperkalemia, hypophosphatemia,	None
Temsirolimus	creatinine increase	

RCC renal cell carcinoma, AH arterial hypertension, NS nephrotic syndrome, TMA thrombotic microangiopathy, GFR glomerular filtration rate

patients may be more susceptible to developing proteinuria while being treated with anti-angiogenic drugs.

TKIs seem associated with a lower risk of proteinuria than VEGF-inhibitors [73] although no head-to-head comparisons between the two classes of drugs have been carried out. The combination of different anti-VEGF drugs increases the risk of endothelial damage leading to severe endothelial swelling similar to that observed in women with pre-eclampsia, followed by proteinuria and, in more severe cases, to thrombotic microangiopathy (TMA) [74].

Renal transplanted patients have lower than normal renal function, but dose adjustment of the drugs reported above is not required, with the exception of sorafenib, which should be reduced to 50 % when glomerular filtration rate (GFR) is below 40 ml/min and to 25 % in subjects with GFR lower than 20 ml/min.

To the best of our knowledge, there is no metabolic interaction between these drugs and the immunosuppressive medications currently used in renal transplanted patients.

Inhibitors of mTOR, a ubiquitous serine/threonine protein kinase, are well known to nephrologists since sirolimus and everolimus have been used as immunosuppressants for many years. The most common side-effects of these drugs include dyslipidemia, stomatitis, arthralgia, edema and proteinuria, usually below the nephrotic range. Biopsy-proven acute tubular necrosis has recently been reported as an adverse effect of mTOR inhibitors [75] and, although rare, it calls for prompt withdrawal of the drug to allow recovery from renal failure, as in patients with delayed graft function after transplantation, due to the anti-proliferative effect of rapamycin-derived drugs.

### Modification of immunosuppressive therapy in transplanted patients who develop RCC

Given the possible contribution of immunosuppressive treatment in cancer development after renal transplantation, in accordance with the KDIGO guidelines [51], it seems advisable to reduce immunosuppression in patients

who develop RCC, although there is no randomized controlled trial supporting the benefit of withdrawal or reduction of immunosuppressive medications.

Taking into account experimental studies which demonstrate that CNIs may increase tumor growth and metastasis [76] through their effect on TGF- $\beta$  and VEGF [10], these drugs should be reduced or completely withdrawn when a renal cancer is detected.

There has been increasing evidence in recent years that mTOR inhibitors may reduce the cancer risk of renal transplant recipients through their effect on VEGF. In a prospective, randomized, controlled trial, conversion to sirolimus in the case of transplanted patients who developed non-melanoma skin cancer resulted in regression of lesions and lower onset of new carcinomas as compared to patients who continued to assume CNIs [13], an observation subsequently confirmed in more recent controlled trials [14, 15]. At present, there is not enough evidence as to the benefit of converting transplanted patients who develop non-skin tumors to mTOR inhibitors, but several studies have reported a lower incidence of malignant disease in subjects treated with mTOR inhibitors at some stage after surgery [3, 77].

Since mTOR inhibitors are currently used in RCC patients as a third-line therapy, it seems reasonable to shift to everolimus or sirolimus patients who are not already being treated with one of these drugs; caution is required, however, in subjects with chronic allograft nephropathy, particularly if their proteinuria is above 1 g/day and/or GFR below 40 ml/min, since they may experience worsening of graft function [78].

To summarize, renal cancer is the third most frequent solid tumor observed in renal graft recipients and accounts for approximately 10 % of cancer-related deaths. The risk of developing renal malignancies is related to several factors including prolonged immunosuppressive therapy, pre-transplant cancer history, duration of dialysis treatment and age. Thus patients at risk, i.e. those with congenital or acquired cystic diseases, or even a single cyst in a native

kidney, should undergo an annual ultrasound check while subjects older than 60 years treated with dialysis for more than 5 years before transplantation should be examined every 2 years. It seems advisable to reduce immunosuppression in patients who develop RCC. In addition, since there is mounting evidence that mTOR inhibitors may reduce the cancer risk of renal transplant recipients and since these drugs are currently used in RCC patients as a third-line therapy, it seems reasonable to shift to everolimus or sirolimus patients with renal cancer who are not already being treated with one of these drugs.

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#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** For this type of study formal consent is not required.

**Research involving human participants and/or animals** This article does not contain any studies with human participants or animals performed by any of the authors.

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