***De Novo* Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-center Experience**

DEMETRIOS MORIS, KIRIAKI KAKAVIA, CHRYSOULA ARGYROU, NIKOLAOS GARBIS,
JOHN BOKOS, SPYRIDON VERNADAKIS, KONSTANTINOS DILES,
GEORGIOS SOTIRCHOS, JOHN BOLETIS and GEORGIOS ZAVOS

Transplantation Unit, Laikon General Hospital, Athens, Greece

Abstract. *Background: The risk of renal cell carcinoma (RCC) development in renal transplant recipients is 15-100 times higher than in the general population. The majority of RCCs found in renal transplant recipients develop in the recipient's native kidneys, only 9% of tumors develop in the allograft itself. The mechanisms of development of RCC in native kidneys and renal allografts are not completely understood. We present our experience in renal transplant recipients with RCC of native kidneys providing valuable and clinically applicable treatment and follow-up data. Patients and Methods: The records of 2,173 patients who underwent renal transplantation in our Department between March 1983 and December 2015 were retrospectively reviewed. Using these data, we analyzed the incidence and types of post-transplant RCCs, as well as their clinical courses, focusing on native malignancies. Results: We found 11 RCCs (0.5%) during the observation period in native kidneys. The mean ($\pm$ SD) follow-up period was 50.54 ± 32.80 months. Four patients died during this period (36.4%). Conclusion: Most RCCs in renal transplant recipients are low-stage, low-grade tumors with a favorable prognosis. Their diagnosis is usually incidental. RCC development in the native kidney of renal transplant recipients is an early event, frequently observed within 4 to 5 years after transplantation. The different natural history of these tumors is still undefined. Further research is needed to determine whether these differences are due to particular molecular pathways or to biases in relation to the mode of diagnosis.*

Currently, renal transplantation (KTx) is the primary therapeutic option in patients with end-stage renal disease

(ESRD) due to its superiority in terms of cost, efficacy and quality of life compared to dialysis (1). In order to achieve long-term allograft function, the use of highly potent immunosuppressive agents is compulsory to impede acute and chronic allograft rejection (2). The concomitant price to be paid, however, is the markedly increased incidence of malignancy in the post-transplantation period (3-6). Even if the incidence of malignancy is difficult to accurately calculate, a proportion of 6% to 11% of *de novo* malignancies has been reported among transplant recipients in Western countries (4-8); but it may be higher as there is a steady increase in graft survival, reflecting a risk of approximately 100 times greater than a normal age-matched population (5, 6, 8).

Native kidney and renal allograft are affected by both benign (9), and malignant or metastatic tumors more frequently than previously thought. The risk of renal cell carcinoma (RCC) development in renal transplant recipients is 15-100 times higher than in the general population (10-12) and the rate among all malignancies is less than 5% (11, 13-16). The majority of RCCs found in transplant recipients develop in the recipient's native kidneys, with only 9% of tumors developing in the allograft itself. Tumors transmitted by donors represent only 0.02% to 0.2% of cases (17, 18). Most *de novo* allograft RCCs are single tumors.

The mechanisms of development of RCC in native kidneys and renal allografts are not completely understood. Moreover, the different natural history of these tumors is still undefined. Several risk factors have been suggested, including duration and type of immunosuppression, native kidney disease, recipient/donor age, pre-transplant dialysis time and microscopic hematuria (13). Because of the current lack of prospective multicenter series with clearly defined treatment and follow-up protocols of RCC in renal transplant recipients, particularly concerning metastatic disease and allograft tumors, which challenge the delicate balance between oncological safety and renal function, a broad variety of therapeutic and surveillance strategies exists.

Correspondence to: Demetrios Moris, MD, Ph.D., Transplantation Unit, Laikon General Hospital, Agiou Thoma 17 Street, Athens, Greece. E-mail: dimmoris@yahoo.com

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We present our experience on renal transplant recipients with RCC in native kidneys of the largest Greek Transplant Program, providing valuable and clinically applicable follow-up data.

Patients and Methods

The records of 2,173 patients who underwent KTx at our Department between March 1983 and December 2015 were retrospectively reviewed. Of these patients, 1072 received their transplants from living first-, second-, or third-degree relatives, 1101 from deceased donors and seven were combined kidney and pancreatic transplantations. Recipients presenting RCC were evaluated regarding histological type of neoplasm, presence of cysts, age, gender, time from KTx to RCC diagnosis, time from RCC diagnosis to endpoint (death or end of follow-up), use of immunosuppressive regimens, graft functional status and rejection-return to dialysis episodes. This study was carried out by our Department with the contribution of the Departments of Pathology and Nephrology. Using these data, we retrospectively analyzed the incidence and types of post-transplant RCCs, as well as their clinical courses, focusing on native kidney malignancies.

All patients under care of our Department received meticulous preoperative evaluations according to currently valid urological and nephrological guidelines on KTx. Post-transplant check-ups were performed at Laikon General Hospital by nephrologists at least twice a year and included semiyearly sonography of the graft and native kidneys.

For the present study, clinical, histopathological and surveillance data were collected of renal transplant recipients who developed a *de novo* RCC of native kidney after KTx. Study endpoints were defined as patient death or last follow-up before 31st December 2015. No patient was lost during the follow-up period.

Descriptive values were recorded as the mean, median and standard deviation. Tumors were staged according to the currently valid TNM classification of the Union Internationale Contre le Cancer (19) and graded according to the Fuhrman system (20).

Immunosuppression protocol. Immunosuppression (IS) regimens, at the time of KTx, were available for all participants. We typically use induction treatment with basiliximab or daclizumab, in all patients who undergo KTx. Recipients of kidneys from expanded criteria donors or any case with a cold ischemia time significantly longer than the mean time of our center (more than 16 h), or in the case of established delayed graft function, receive induction therapy with antithymocyte globulin (ATG). During treatment with ATG, calcineurin inhibitors are discontinued and are reinstituted 1-2 days before cessation of ATG. All patients receive treatment with corticosteroids at the time of KTx, administered as 500-1000 mg of methylprednisolone during surgery, followed by 20-40 mg/day (depending on the immunological risk) orally, and a gradual steroid taper in the absence of rejection. Maintenance immunosuppression consists of a calcineurin inhibitor, cyclosporine or tacrolimus (TAC), with mycophenolate acid (MPA) formulations and methylprednisolone. Patients at high immunological risk are preferentially treated with TAC and an MPA formulation in full dose, while those with a history of cancer are treated with an inhibitor of the mammalian target of rapamycin (mTOR), aiming at a goal of 6-8 ng/ml if combined with MPA, and 4-6 ng/ml if combined with a calcineurin inhibitor (21-24).

Statistical analysis. Results were statistically analyzed using the Fisher and chi-square tests for categorical data and *t*-test for continuous data. All statistical analyses were performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

General analysis. In the group of 2,173 kidney transplanted patients, we found 11 RCCs during the observation period, resulting in a cancer detection rate of 0.5%. No patient had a pre-transplant history of malignancy. One patient developed papillary thyroid cancer and another developed non-Hodgkin skin lymphoma during the follow-up period. No case of RCC in renal allografts was found in our series. Different nephropathies caused ESRD requiring replacement therapy: four cases of chronic glomerulonephritis, two of polycystic kidney disease, and one each of hypertension, diabetes, congenital renal dysplasia, obstructive nephropathy and unknown cause, respectively.

Among the 2,173 patients who received renal transplants at our center during the past 30 years, post-transplant RCC developed in 11 patients (0.5%), including six men (54.5%) and five women (45.5%). Seven patients (63.6%) received a graft from a deceased donor and four (36.4%) from a living one. The mean±SD age at KTx was 44.82±13.51 years (range=18-62 years) and the mean age at RCC diagnosis was 57.45±11.91 years (range=33-75 years). The mean time from KTx to RCC diagnosis was 151.45±92.15 months and the mean time from RCC diagnosis to an endpoint was 50.54±32.80 months. Four patients died during the follow-up period, indicating a disease-specific mortality rate of 36.4%. All patients who died did so with a functioning graft. The most common cause of death was metastatic disease-generalized carcinomatosis (4/4 cases, 100%). The mean serum creatinine concentration at cancer diagnosis was 1.68±0.9 mg/dl (median=1.72 mg/dl, range=0.7-4.28 mg/dl). The average time on dialysis was 74.25±32.50 months. Three patients presented with clinical symptoms at diagnosis. These symptoms were fever and weight loss. In all patients, tumors were detected during post-transplant follow-up examinations as incidental findings on ultrasound (10 cases) and computed tomographic scan (one case).

Histologically, all malignant neoplasias of kidneys were RCC. Histological subtypes comprised conventional clear cell (n=6, 54.5%) and papillary (n=5, 45.5%) tumors. Of the papillary subtype, three were with chromophilic cytoplasm (=type 1) and two with eosinophilic cytoplasm (=type 2). There were two grade 1 (18.2%), seven grade 2 (63.6%) and two grade 3 (18.2%) RCCs. Seven tumors were classified as pT2 (63.7%), two as pT3a (18.1%), one as pT3b (9.1%) and one as pT4 (9.1%). Histologically, positive lymph node status was detected in two patients with renal tumors with carcinoma infiltration of a peri-renal lymph node.

Table I. Summary of the general findings of the study.

Gender	Age, years		Time, months		IS	Donor	Cause of ESRD	TNM	Histology	Fuhrman grade
	At KTx	At RCC diagnosis	KTx to RCC diagnosis	Diagnosis to endpoint						
M	55	63	97	49	TAC,MMF, steroids	D	Renal Dysplasia	pT3	CC	II
F	62	64	31	58	AZA, steroids, CYA	D	Obstructive	pT3	P	II
F	35	58	278	52	AZA, steroids, CYA	L	GTN	pT2	CC	III
M	40	42	20	102	AZA, steroids, CYA	D	GTN	pT2	CC	II
M	52	56	55	10	MMF, steroids	D	PCKD	pT2	P	III
F	35	58	277	51	AZA, steroids, CYA	L	GTN	pT2	P	III
M	41	61	239	109	AZA, steroids, CYA	D	GTN	pT4	CC	I
F	60	75	170	21	Sirolimus, TAC	D	Unknown	pT2	CC	I
M	57	70	152	14	MMF, TAC, steroids	D	PCKD	pT3	P	II
F	18	33	180	26	Sirolimus, TAC	L	GTN	pT2	P	II
M	38	52	168	64	TAC, MMF, steroids	L	DM	pT2	CC	II

KTx: Renal transplantation, M: male, F: female, TAC: tacrolimus, MMF: mycophenolate mofetil, CYA: cyclosporine, AZA: azathioprine, PCKD: polycystic Kidney Disease, GTN: glomerulonephritis, DM: diabetes mellitus, ESRD: end-stage renal disease, CC: clear cell, P: papillary, D: deceased, L: living, IS: immunosuppression, RCC: renal cell carcinoma.

Table II. Analysis of the most common malignancies in our population.

Cancer type	Incidence, % (number)	Disease-related mortality (%)	Time from KTx to diagnosis (months)*	Time from diagnosis to endpoint (months)*	TAC regimen, n (%)	CYA regimen, n (%)
Gastric AC	0.32 (7)	85.7	101.86±49.06	9.28±10.24	3/7 (42.9%)	4/7 (57.1%)
Lung	0.78 (17)	82.4	91.08±59.4	10.3±8.6	6/17 (35.3%)	11/17 (64.7%)
Colorectal AC	0.41 (9)	88.9	97.14±53.23	20.5±11.04	7/9 (77.8%)	2/9 (22.2%)
Breast	0.41 (9)	22.2%	71.38±55.50	71±30.42	5/9 (55.6%)	4/9 (44.4%)
Prostate AC	0.28 (6)	50%	98.5±74.78	45.67±11.67	5/6 (83.3%)	1/6 (16.7%)
RCC	0.5 (11)	36.4%	151.45±92.15	50.54±32.80	5/11 (45.5%)	5/11 (45.5%)

KTx: Renal transplantation, AC: adenocarcinoma, RCC: renal cell carcinoma, TAC: tacrolimus, CYA: cyclosporine. *Mean±standard deviation.

Native kidney cancer was removed by 11 open radical nephrectomies, including two with extended lymph node dissection without major perioperative complications. The mean tumor size in the surgical specimens was 38±36 mm (median=28 mm, range=3-120 mm). Modification of immunosuppressive regimen due to tumor was carried out for only one patient after diagnosis of systemic metastases by changing to rapamycin and steroid.

Table I summarizes the patient data of this study.

Analysis among malignancies. We also analyzed and compared the data of the subgroup of patients with RCC with those of the patients suffering from the most frequent *de novo* visceral malignancies in our total population of renal transplant recipients (8). We included patients with prostate adenocarcinoma, breast cancer, lung cancer, gastric adenocarcinoma and colorectal cancer.

We compared the incidence, the time from KTx to diagnosis of malignancy, the time of diagnosis of malignancy to the end-point, the immunosuppression and the disease-related mortality of each malignancy group with the group of patients with RCC. According to this analysis, patients with RCC seem to be diagnosed later than those with other types of malignancy ($p=0.0001$) as well as demonstrating better outcomes in terms of disease-related mortality and survival during the follow-up period compared with all the other malignancies ($p=0.0001$), with the exception of the patients with breast cancer, whose results were better ($p=0.0001$). No correlation was found between the RCC group and any of the other groups of malignancy as far as immunosuppression and incidence are concerned.

Table II summarizes the data of the groups of the most frequent visceral malignancies in our population.

Discussion

It is well-established that the estimated rate of RCC development in native kidney is 10- to 100-times the incidence in the general, immunocompetent population (0.04%) (25, 26), while RCC occurrence in the graft has been reported to be less frequent, accounting for approximately 10% of cases (5, 27). Our series demonstrates one of the lowest incidences of RCC in native kidneys (0.5%) (11-16, 28-34). Moreover, our results confirm those of a recent study and current literature findings, where the vast majority of renal malignancies were detected in the native kidneys of the recipients (85%) (33). The incidence of RCC in native kidneys mostly varies from 0.35% (35) to 1.5% (11), whereas the incidence of RCC in renal allograft is generally far less frequent (0.25%) (11-16, 28-34, 36). Studies with similar design to ours demonstrated an incidence of 1.3% RCC in the native kidney (11-16, 28-31, 33, 34). These findings of high incidence of RCC in the native kidney of renal transplant recipients are consistent with previous observations (32, 37), although they were of prospective design.

The median time from KTx to development of any RCC is reportedly 4.5 years (3, 5, 27), with median times for development of RCC in the native kidney being much shorter than those in the allograft (33). In contrast to these findings, other studies have shown a longer median time of 3.9 to 7.4 years for development of RCC after KTx (38-40). The time for RCC detection also varied from as early as 1 month to as late as 12.2 years after KTx (33).

Many risk factors have been identified as contributing to RCC development in renal transplant recipients. The duration of ESRD is suspected to be a primary determinant of risk for RCC development in the native kidney (41). Some reports indicate that patients with ESRD have approximately 100-times greater risk of RCC than age-matched healthy controls (42). Cigarette smoking, hypertension, obesity and family history are also well-established risk factors for RCC. Male gender and African American race were also independently associated with RCC (31).

Patients with ESRD are more prone to developing RCC, either by congenital predisposition (von Hippel-Lindau syndrome), or acquired cystic kidney disease, with an overall incidence of RCC in the native kidney of hemodialysis patients reported to be approximately 2% (43, 44). Acquired cystic kidney disease has been identified as a strong risk factor for RCC development, with a standardized incidence ratio of RCC ranging from 3.6 to 24.1 (45). Therefore, improvements in allograft and recipient outcomes, with longer survival after reaching ESRD, are likely to be associated with further increases in the occurrence of RCC (46). RCC occurring in ESRD is characterized by a younger age at diagnosis and higher incidence rate of males to females compared with the general population (47).

Multifocality in up to 40% and bilateral occurrence in up to 20% are other clinical characteristics, which distinguishes RCC in renal transplant recipients from sporadic tumors in non-transplanted patients (13). Clear cell RCC is the most common subtype, although papillary RCC more frequently occurs than in non-transplanted patients.

The survival rate of patients diagnosed with malignancy after transplant, including RCC, also appears to be lower than that of the general population (36). Of interest, native kidney RCCs arising in patients with ESRD are of lower stage and lower grade compared to RCCs diagnosed in the general population, and these tumors exhibit favorable clinical and outcome features (29, 40). Incidental RCC can be diagnosed early in the natural history and at a curable stage through implementation of a surveillance program. In general, RCC in native kidneys is thought to be more fatal (39, 40). In a recent series, it was found that no cancer-specific deaths occurred from allograft tumors; however, 23.3% of cancer-specific deaths occurred in patients with cancer in the native kidney (33), with 5- and 10-year cancer-specific survival rates of 71.2% and 58.5% respectively (33).

Because of its low incidence, most transplant units worldwide do not apply any specific approach to early detection of RCC in native kidneys or renal allografts of renal transplant recipients. Moreover, no trials assessing the role of screening for RCC in this population have been conducted as far as we are aware, and previous attempts to model the performance of screening by ultrasound were shown not to be cost effective (48). Compared to a previous study that used the Australia and New Zealand Dialysis and Transplant Registry in 2008, which demonstrated a cumulative incidence of 46 per 100,000 per year, the updated extension until 2012 showed a 17.8% increase in kidney-related tumors (33). Although this is a small change in the incidence of RCCs after KTx, this increase, along with the poor survival rates, suggests a possible benefit in the use of screening in this population.

The current recommendations of the European Association of Urologists for screening of RCC in renal transplant recipients suggest annual screening of the allografts and native kidneys to detect renal tumors (49). However, the American Society of Transplantation and the Kidney Disease Improving Global Outcomes Clinical Practice Guidelines for the Care of the Kidney Transplant Recipient do not recommend routine screening for renal cancer after KTx (50). Although routine annual ultrasonographic screening for RCC may improve survival by up to 25%, it has not been shown to be cost effective for renal transplant recipients, even for those at high risk of disease (48). Some of the underlying limitations in the use of ultrasonography as a screening tool are user dependence, lower sensitivity and specificity in detecting small tumors (<3 cm), and uncertain performance in the presence of cystic

Table III. Summary of current literature on renal cell carcinoma (RCC) in native kidneys and renal allografts in renal transplant recipients. All studies were retrospective except that of Neuzillet *et al.* (32).

Author	Year	Number of patients	Incidence of RCC		Follow-up (months)*	5-Year survival		Disease-related mortality (%)
			Native kidney (%)	Renal allograft (%)		Native kidney RCC (%)	Renal allograft RCC (%)	
Tsaur <i>et al.</i> (11)	2011	2001 in 30 years	1.24	0.26	58.6±62.3	75.1	83.5	15.4
Sun <i>et al.</i> (35)	2013	1457 in 20 years	0.35	N/A	34.8**	80	N/A	20
Goh and Vathsala (30)	2011	1036 in 22 years	0.97	N/A	69.6**	100	N/A	0
Gigante <i>et al.</i> (53)	2012	215 in 25 years	N/A	N/A	N/A	97	N/A	3
Kato <i>et al.</i> (54)	2016	750 in 42 years	1.33	0.26	15.1±8.2	N/A	N/A	N/A
Barama <i>et al.</i> (28)	2005	1073 in 33 years	N/A	0.46	N/A	N/A	80	0
Breda <i>et al.</i> (29)	2015	2690	1.26	N/A	90.2±5.7	>85	N/A	N/A
Moon <i>et al.</i> (16)	2015	1386 in 12 years	1.22	0.14	31.08**	N/A	N/A	15.8
Filocamo <i>et al.</i> (14)	2009	694 in 16 years	1.6	N/A	41	70	N/A	0
Leveridge <i>et al.</i> (15)	2011	3568 in 42 years	1.1	0.2	Native: 79.2 Allograft: 43.2	82	87.5	Native:18 Allograft: 12.5
Tillou <i>et al.</i> (34)	2009	800 in 18 years	2.75	N/A	34.8	93.3	N/A	3.6
Karczewski <i>et al.</i> (12)	2012	836 in 18 years	1.3	0.2	120±38.4	N/A	N/A	9.1
Ranasinghe <i>et al.</i> (33)	2016	8850 in 12 years	0.53	0.09	110.4	71.2	88.75	23.3
Neuzillet <i>et al.</i> (32)	2005	933 in 16 years	1.29	N/A	39±41	82	N/A	18
Current study	2016	2173 in 32 years	0.50	N/A	50.54±32.80	63.6	N/A	36.4

N/A: Not available. *Data are mean values±SD, except for **which are median values.

kidney disease and small scarred kidneys, which are commonly present in patients with ESRD (48). Contrast-enhanced computer tomographic scans have risks of contrast-induced nephropathy and acute kidney injury (48, 51, 52).

The majority of RCCs in native kidney and renal allografts have been treated by organ removal (radical nephrectomy) and discontinuation of immunosuppressive therapy (5, 27, 32). Good results can be obtained this way because radical nephrectomy achieves local control of the disease, while discontinuation of immunosuppression allows the immune system to recover and reject residual tumor cells. However, poor outcomes also have been reported in patients dying of hepatic metastases or febrile paraneoplastic syndrome soon after transplant removal.

Table III summarizes the data of current literature on the incidence of RCC in native kidneys and renal allografts in renal transplant recipients.

We are aware of the limitations of our study due to its retrospective nature. Long-term prospective studies and large registries should provide a better understanding of the different natural behavior of RCC in native kidneys.

Conclusion

In conclusion, most RCCs in renal transplant recipients are low-stage, low-grade tumors with a favorable prognosis; however, the prognosis of metastatic RCC is poor. These

tumors are generally small and asymptotic and their diagnosis is usually incidental. It also seems that RCC development in the native kidney of renal transplant recipients is an early event, frequently observed within 4 to 5 years after transplantation, but it is usually diagnosed later than other malignancies in renal transplant recipients.

We believe that kidneys of renal transplant recipients should be routinely screened by ultrasound during the first 5 years after transplantation for early-stage diagnosis. This cost-effective and minimally-invasive method still provides the best predictive value in screening and diagnosing of RCC and could substantially improve patient outcomes. We advocate annual surveillance ultrasound for RCC in the pre-transplant population awaiting transplant.

The mechanisms of development of RCC in native kidneys and renal allografts are not completely understood. Moreover, the different natural history of these tumors is still undefined. Further research is needed to determine whether these differences are due to particular molecular pathways or to biases in relation to the mode of diagnosis.

Conflicts of Interest

None.

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