

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

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Abstract

Objectives: Our study aimed to determine the incidence of de novo renal cell carcinoma in the native kidneys of patients transplanted at our center and to identify possible risk factors.

Materials and Methods: We performed a retrospective, single-center cohort study, which included patients transplanted at the District Hospital in Poznan, Poland, during 1994-2011, among whom 836 were selected. Sixty-three patients with confirmed de novo cancer were found. Of those, 11 had renal cell carcinoma in the native kidney (1.3%) and 2 in the transplanted kidney (0.2%).

Results: Mean follow-up was 10 ± 3.2 years. Mean age at renal cell carcinoma diagnosis was 52 ± 9.4 years, and mean time from transplant was 3 ± 2.6 years. A statistical analysis showed no significant differences in demographic or clinical characteristics between renal cell carcinoma and noncancer group, except for the prevalence of male sex and smoking in the cancer group ($P < .05$).

Conclusions: Renal cell carcinoma development in the native kidney seems to be an early event, frequently observed within 4 to 5 years after transplant. We believe that kidneys in renal transplant recipients should be routinely screened by ultrasound for early diagnosis.

Key words: Native kidney, Posttransplant malignancy, Renal cell carcinoma, Renal transplant, Urologic oncology

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Introduction

Renal transplant is the treatment of choice for the end-stage renal disease. The development of new and potent immunosuppressants has led to prolonged long-term graft survival; however, adverse effects associated with the use of immunosuppression often result in several complications. Renal transplant recipients are known to be at a higher risk for de novo cancer than the general population.¹ The data suggest the prevalence of renal cell carcinoma (RCC) in the native kidney of renal transplant recipients.²⁻⁵ The reported incidence of de novo RCC in native kidney varies between 0.3% to 4.8%.⁶ Several risk factors have been suggested including duration and type of immunosuppression, native kidney disease, recipient/donor age, pretransplant dialysis time, and microscopic hematuria.⁶ This study sought to determine the incidence of de novo renal cell carcinoma in the native kidney of patients transplanted at our center and to identify possible risk factors.

Materials and Methods

We performed a retrospective, single-center cohort study, which included patients transplanted at the District Hospital in Poznan, Poland, during 1994-2011, among whom 836 were selected. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines with the 1975 Helsinki Declaration. Written, informed consent was obtained from all patients. All transplanted patients were white and received deceased-donor kidneys. Sixty-three patients with confirmed de novo cancer were found; of those, 11 had RCC in the native kidney (1.3%) and 2 in the transplanted kidney (0.2%). The patients did not have a prior history of malignancy, and all

reviewed cases were de novo malignancies. Their diagnoses were based on routine ultrasound during the follow-up and confirmed by computed tomography. Tumor staging and grading were present according to current tumor, node, metastases (TNM) and histopathologic grading classifications. Patients' data were analyzed including donor and recipient age, sex, underlying renal disease, time on pretransplant dialysis, number of transplants, age at tumor diagnosis, cold and warm ischemia time, degree of HLA match, percentage of panel-reaction antibodies, type of immunosuppressive therapy, and outcome of the patient. Continuous variables expressed as mean values \pm standard deviation were compared using the *t* test or the Mann-Whitney *U* test. Categorical variables were analyzed by a chi square test. Also, the Kaplan-Meier survival analysis was performed with comparison by the log rank test. Values were considered to be significant when $P < .05$.

Results

Eight patients with RCC in the native kidney were men, comprising 81.8% of the group (Table 1). The mean time of pretransplant hemodialysis was 25 ± 22.6 months. The mean age at RCC diagnosis was 52 ± 9.4 years, and the mean time from transplant was 3 ± 2.6 years. The initial nephropathy in the group included 8 cases of chronic glomerulonephritis, 2 cases of polycystic kidney disease, and 1 case of hypertensive nephropathy. Histologically, surgical specimens revealed 6 clear cells, 2 papillary, 2 tubulopapillary, and 1 tubulopapillary/clear cell carcinomas, and were staged to pT1 in 9 cases, pT2 in 1 case, and pT3 in 1 case. The grading was G1 in 1 case, G2 in 5 cases, and G3 in 4 cases (1 type, staging, and grade was unknown). In addition, 2 patients with RCC developed multiple lesions of squamous-cell carcinoma located on the head and upper extremities.

Treatment of RCC included nephrectomy, reduction of immunosuppression, or conversion to mTOR inhibitor (6 cases). One patient failed to respond to the treatment and died. Of the remaining 10 patients, 8 patients had stable allograft functions, whereas 2 patients were on hemodialysis. None of them showed any evidence of tumor recurrence. The mean follow-up for the group was 10 ± 3.2 years. A

statistical analysis did not show significant differences in demographic or clinical characteristics between RCC and noncancer group, except for the prevalence of male sex and smoking in the cancer group ($P < .05$). No significant differences in other suspected risk factors, including immunosuppressive protocols, time on pretransplant dialysis, or donor/recipient age, were found between the groups.

Discussion

This study analyzed data of patients transplanted at the District Hospital in Poznan, Poland, during 1994 to 2011, among whom 836 patients were selected. Sixty-three patients with confirmed de novo cancer were found, of those 11 had RCC in the native kidney (1.3%) and 2 in the transplanted kidney (0.2%). Our findings regarding a high incidence of RCC in the native kidney of renal transplant recipients are consistent with previous observations.^{2, 4, 5} The estimated rate of RCC development in native kidney is 10 to 100 times the incidence in the general, immunocompetent population⁷; while RCC occurrence in the graft has been reported to be less frequent, accounting for approximately 10% of cases.⁸

The high incidence of RCC observed in our series seems to be associated with prolonged immunosuppression, smoking, and male sex (the number of estimated age-standardized kidney cancer incidences per 100 000 people in 27 European countries are 15.8 for men and 7.1 for women).⁹ The main cause and duration of end-stage renal disease are also suspected to be a primary determinant of risk for RCC development in the native kidney.^{10, 11} Some reports indicate that end-stage renal disease patients have approximately 100 times greater risk of RCC than age-matched healthy controls.¹² The risk is also expected to increase progressively to the duration of dialysis. Renal cell carcinoma occurring in end-stage renal disease is characterized by a younger age at diagnosis and higher incidence rate of male to female, compared with the general population.¹³ It also is believed that acquired renal cystic disease, which develops in end-stage renal disease patients, is a risk factor for RCC. The incidence of RCC in this group is 3 to 6 times higher than it is in the general population.^{12, 13} Our findings also may reflect the upward trend of kidney cancers observed worldwide, especially in Europe and North America.¹⁴ The causes of this trend are not well

Table 1. Clinical and Pathological Characteristics of Renal Transplant Recipients With RCC in the Native Kidney

Age at Transplant (y)	Sex	ESRF	Time of Diagnosis (y)	Tumor Location	Type of Tumor	Stage	Immunosuppression	Treatment	Outcome
47.3	M	Chronic glomerulonephritis	4.3	Right kidney	Tubulopapillary/clear cell	pT1N0M0, G2	Tac+MMF+P	Open right nephrectomy	Alive
48.2	F	Chronic glomerulonephritis	2.0	Left kidney	Clear cell	pT1bN0M0, G3	CsA+Aza+P	Open left nephrectomy/ conversion to RAPA+P	Alive
37.0	M	Chronic glomerulonephritis	9.0	Right kidney	Clear cell	pT2N1M1, G3 (metastases Th4)	Tac+Aza+P	Open right nephrectomy	Dead
32.4	M	Chronic glomerulonephritis	0.5	Right/left kidney	Clear cell	not known	CsA+Aza+P	Open bilateral nephrectomy/ conversion to RAPA+MMF+P	Alive
64.3	M	Hypertensive nephropathy	2.7	Right/left kidney	Clear cell	pT1bN0M0, G3	CsA+Aza+P	Open bilateral nephrectomy/ conversion to RAPA+P	Alive
50.6	M	Chronic glomerulonephritis	1.0	Right kidney	Papillary	pT1N0M0, G2	Tac+MMF+P	Open right nephrectomy/ conversion to RAPA+MMF+P	Alive
50.5	F	Chronic glomerulonephritis	5.7	Right kidney	Papillary	pT1aN0M0, G2	Tac+Aza+P	Open right nephrectomy/ conversion to RAPA+P	Alive
41.2	M	Polycystic kidney disease	3.3	Left kidney	Tubulopapillary	pT1N0M0, G2	CsA+Aza+P	Open left nephrectomy	Alive
50.2	M	Chronic glomerulonephritis	1.6	Right kidney	Clear cell	pT1N0M0, G3	Tac+MMF+P	Open right nephrectomy/ conversion to RAPA+MMF+P	Alive
60.5	M	Polycystic kidney disease	0.4	Right kidney	Clear cell	pT1bN0M0, G2	Tac+MMF+P	Open right nephrectomy	Alive
60.5	M	Chronic glomerulonephritis	1.3	Left kidney	Tubulopapillary	pT1aN0M0, G1	CsA+Aza+P	Open right nephrectomy	Alive

Abbreviations: AZA, azathioprine; CsA, cyclosporine; ESRF, end-stage renal failure; F, female; M, male; MMF, mycophenolate mofetil; P, prednisolone; RAPA, rapamycin; Tac, tacrolimus

understood and might be associated with specific risk factors including obesity, age, smoking, hypertension, diabetes, and diet.

The statistical analyses did not show significant differences in other suspected risk factors, including immunosuppressive protocols, time on pretransplant dialysis, or donor/recipient age between RCC and noncancer group.^{8, 15} As mentioned before, acquired renal cystic disease is a recognized risk factor for RCC. In our series, however, this correlation was not found. It is also worth mentioning that RCC was found in 1.5% of routine nephrectomies, before transplant. Other reports indicate the incidence rate of RCC 1.8% to 4.2%.^{13, 16} The standard procedure preoperatively in our center involves an abdominal ultrasonography performed every 6 months, followed by computed tomography scan when suspected solid masses are found. In case of confirmation, a nephrectomy and histologic study on the tumor are done.

We are aware of the limitations of our study including a relatively small cohort from a single center, the retrospective nature of the analysis, and the limited clinical data available. Long-term prospective studies and large registries should provide a better understanding of contributing risk factors.

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.¹⁷ These tumors are generally small and asymptomatic, 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 transplant.⁸ We believe that kidneys of renal

transplant recipients should be routinely screened by ultrasound during that period 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.

References

- Stratta P, Morellini V, Musetti C, et al. Malignancy after kidney transplantation: results of 400 patients from a single center. *Clin Transplant*. 2008;22(4):424-427.
- Doublet JD, Peraldi MN, Gattegno B, Thibault P, Sraer JD. Renal cell carcinoma of native kidneys: prospective study of 129 renal transplant patients. *J Urol*. 1997;158(1):42-44.
- Schmidt R, Stippel D, Krings F, Pollok M. Malignancies of the genito-urinary system following renal transplantation. *Br J Urol*. 1995;75(5):572-577.
- Neuzillet Y, Lay F, Luccioni A, et al. De novo renal cell carcinoma of native kidney in renal transplant recipients. *Cancer*. 2005;103(2):251-257.
- Ianhez LE, Lucon M, Nahas WC, et al. Renal cell carcinoma in renal transplant patients. *Urology*. 2007;69(3):462-464.
- Klatte T, Marberger M. Renal cell carcinoma of native kidneys in renal transplant patients. *Curr Opin Urol*. 2011;21(5):376-379.
- Leveridge M, Musquera M, Evans A, et al. Renal cell carcinoma in the native and allograft kidneys of renal transplant recipients. *J Urol*. 2011;186(1):219-223.
- Melchior S, Franzaring L, Shardan A, et al. Urological de novo malignancy after kidney transplantation: a case for the urologist. *J Urol*. 2011;185(2):428-432.
- Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer*. 2008;44(10):1345-1389.
- Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol*. 2003;14(1):197-207.
- Farivar-Mohseni H, Perlmutter AE, Wilson S, Shingleton WB, Bigler SA, Fowler JE Jr. Renal cell carcinoma and end stage renal disease. *J Urol*. 2006;175(6):2018-2020; discussion 2021.
- Nouh MA, Kuroda N, Yamashita M, et al. Renal cell carcinoma in patients with end-stage renal disease: relationship between histological type and duration of dialysis. *BJU Int*. 2010;105(5):620-627.

13. Denton MD, Magee CC, Ovuworie C, et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. *Kidney Int.* 2002;61(6):2201-2209.
14. Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell carcinoma. *Eur Urol.* 2011;60(4):615-621.
15. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. *Transpl Int.* 2006;19(8):607-620.
16. Fischereder M, Jauch KW. Prevalence of cancer history prior to renal transplantation. *Transpl Int.* 2005;18(7):779-784.
17. Neuzillet Y, Tillou X, Mathieu R, et al. Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. *Eur Urol.* 2011;60(2):366-373.