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ORIGINAL PAPER

Renal cell carcinoma in native kidneys before transplantation - When will we stop waiting?

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Summary ***Introduction: Kidney transplantation requires immunosuppression, traditionally regarded as a risk factor for progression in all malignancies. Based on the Cincinnati Registry, a waiting period before transplantation is therefore mandatory. However, recent evidence suggests this increased risk is restricted to particular tumors, whereas others like renal cell carcinoma (RCC) are not negatively affected. We aimed to compare oncological outcomes of RCC in native kidneys of end-stage renal disease (ESRD) patients, according to their transplantation or dialysis status.***

Material and methods: Retrospective analysis of all ESRD patients diagnosed with RCC between 2010 and 2020 in our center. Recurrence-free survival (RFS) and overall survival (OS) were estimated with Kaplan-Meier curves. Multivariable Cox regression model was used to evaluate their association with kidney transplantation.

Results: Clinical and pathological characteristics were similar between groups. Kidney transplant recipients had similar risk of recurrence (hazard ratio [HR] 0.40, 95% confidence interval [CI) 0.04-4.46, p = 0.458) and overall survival (HR 0.34, 95%CI 0.07-1.77, p = 0.202) as dialyzed patients. On multivariable Cox regression model, presence or absence of transplantation was not significantly associated with RFS (p = 0.479) or OS (p = 0.236). Time on dialysis was the only independent predictor of worse survival (HR 1.86, 95%CI 1.18-2.93, p = 0.008).

Conclusions: Most RCC in native kidneys of ESRD patients are low-grade, low-stage and exhibit favourable pathological and outcome features. Immunosuppression does not seem to have an impact on oncological outcomes, but an increased time on dialysis seems to be associated with worse overall survival. Therefore, waiting time for transplantation for these tumors could be reduced.

KEY WORDS: *Kidney transplantation; Immunosuppression; Dialysis; Renal cell carcinoma; Recurrence; Overall survival; Waiting period.*

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INTRODUCTION

Renal transplantation is the most successful treatment for *end-stage renal disease* (ESRD) owing to its superior survival and quality of life compared to other replacement therapies (1). However, it requires immunosuppression, traditionally being regarded as a risk factor for increased tumor incidence and progression. The increased incidence of cancer in this population is a significant cause of death, contributing to their excess mortality in comparison to the general population (2). Therefore, until recently, any form of active neoplasia was regarded as a contraindication to renal transplantation, and a waiting period between cancer treatment and transplantation was mandatory.

The decision on the waiting period for transplantation in patients with a history of treated cancer is mainly based on the *Cincinnati Transplant Tumor Registry* (3), with times varying from two to at least five years, depending on the type of tumor. However, this study published more than twenty years ago has several drawbacks that may not reflect the actual epidemiology of current diagnosed cancers: treatment and staging were not defined, and many diagnostic, therapeutic and prognostic tools have improved over these last years. Therefore, nowadays, there is not enough evidence to support a fixed waiting period before transplantation.

Besides, there is growing recent evidence suggesting that the increased risk of cancer by immunosuppression is restricted to particular subtypes, while others may not be affected. Cancers at highest risk are viral-induced cancers such as lymphomas and Kaposi sarcoma, and those caused by impaired immune surveillance or via direct DNA damage by anti-rejection drugs such as skin and lip cancers (4). Although *renal cell carcinoma* (RCC) of native kidneys is one of the most common tumors in renal transplant recipients, accounting for 8% of malignancies in this population (5), it has been shown that its incidence is lower during transplantation than during graft non-functioning periods without immunosuppression (6). A typical feature of ESRD is a higher incidence of RCC, where it can be up to ten times higher than the general population, being found in 4% of dialyzed or renal transplant patients (7). The main risk factor for RCC is *acquired cystic kidney disease* (ACKD), which increases with duration of dialysis (8), and seems to regress after successful transplantation. Thus, a longer waiting period for transplantation may paradoxically increase the risk of this kidney dysfunction-related cancer.

Since the outcomes of RCC after kidney transplantation and its prognosis under immunosuppressive regimens remain poorly understood with conflicting evidence, we aimed to evaluate clinical and pathological characteristics of RCC of native kidneys in ESRD patients, and to compare the risk of recurrence and survival according to their dialysis or transplantation status at the time of diagnosis.

Materials and methods

Study design and patient selection

In this observational retrospective, single-center, cohort study, we evaluated data on all consecutive patients with ESRD diagnosed with RCC of native kidneys and submitted to radical nephrectomy between 2010 and 2020. Overall, 40 RCC cases were identified in this population based on post-operative histopathological staging. They were subsequently stratified according to their kidney transplantation or dialysis status at the time of diagnosis, and clinical, pathological and oncological outcomes were compared between groups. We excluded from analysis patients diagnosed with RCC while on dialysis who later received a renal transplant, and patients with regional or distant metastatic disease. Renal transplant patients diagnosed with RCC, with later graft failure leading to resuming of dialysis were included in the kidney transplant cohort. Perioperative and socio-demographic data, clinical and histopathological characteristics and survival outcomes were extracted from medical records.

Pre-operative staging and surgical technique

All patents were evaluated preoperatively with *computed tomography* (CT) of the abdomen, pelvis and chest to confirm localized disease, and with biochemical blood work with creatinine.

All patients were treated with radical nephrectomy, performed by either an open approach through flank incision or laparoscopic approach by standard transperitoneal four-trocar technique, based on patient and surgeon preference. Lymph node dissection was not performed in any patient, since there was no nodal involvement suspected based on preoperative imaging or intraoperatively enlarged nodes.

All kidney transplant patients were on standard immunosuppressive regimen, and no modification to this scheme due to oncological concerns was made at the time of RCC diagnosis or during follow-up.

Pathological evaluation

All surgical specimens were processed according to standard pathological procedures. All lesions were confirmed to be malignant renal cell carcinomas. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer TNM classification (9) and the histological subtype was assigned according to the 2016 *World Health Organization* (WHO) classification of kidney tumors (10). Tumors were graded according to the *International Society of Urological Pathology* grading classification (11). Tumor multifocality was defined as the presence of two or more synchronous lesions in the same kidney, pathologically confirmed to be RCC. Tumor bilaterality was defined as the presence of synchronous lesions in both kidneys at the time of diagnosis.

Follow-up

Patients were followed every 6 months during the first year after surgery, yearly until 3 years, and once every 2 years thereafter. Follow-up consisted of medical history and appropriate physical examination, routine blood work and imaging re-evaluation.

Oncological outcomes comprised *recurrence-free survival* (RFS) and *overall survival* (OS). Both survival outcomes were evaluated from the date of surgery to time of event or, when lost to follow-up, the last documented outpatient visit with his physician. Recurrences were treated with surgical excision, and patients continued on regular follow-up.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and *interquartile ranges* (IQR) for variables with skewed distributions. Normal distribution was checked using Shapiro-Wilk test or skewness and kurtosis.

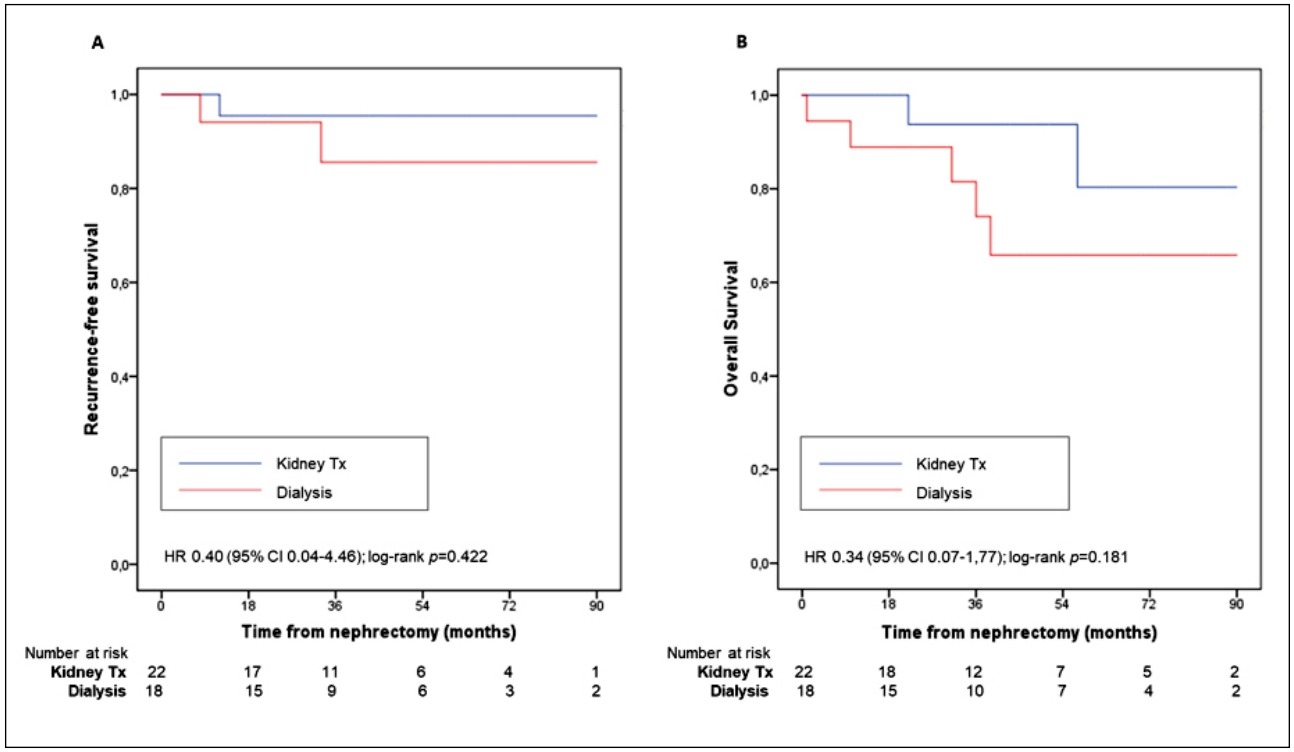
Univariate logistic regression was used to investigate the association between baseline patient and pathological characteristics and the transplantation or dialysis status. Continuous variables were compared with the use of paired Student's t-test or Mann-Whitney test for variables with normal and skewed distribution, respectively. Categorical variables were compared with the use of

Table 1.
PPLA score system for renal papillae (16).

	Kidney transplant (n = 22)	Dialysis (n = 18)	P value
Demographic characteristics			
Age (years)	57.7 ± 11.0	57.7 ± 11.0	0.999
Sex, n (%)			
Male	19 (86%)	18 (100%)	0.238
Female	3 (14%)	0 (0%)	
ASA score, n (%)			
≤ 3	21 (95%)	8 (44%)	< 0.001
> 3	1 (5%)	10 (56%)	
BMI (Kg/m^2)	25.0 ± 3.38	25.9 ± 3.04	0.387
Time on dialysis before diagnosis (months) (IQR)	38.5 (13-60)	28.0 (11-42)	0.430
Time on immunosuppression (months) (IQR)	136.5 (66-182)	-	-
GFR (ml/min/1.73 m^2), n (%)			
< 15	1 (5%)	18 (100%)	< 0.001
15-30	4 (18%)	-	
> 30	17 (77%)	-	
Clinical and pathological characteristics			
Size (mm)	29.27 ± 16.78	38.11 ± 21.14	0.148
T stage, n (%)			
pT1a	18 (82%)	11 (61%)	0.184
pT1b	3 (14%)	5 (28%)	
pT2a	1 (4%)	0 (0%)	
pT2b	0 (0%)	0 (0%)	
pT3a	0 (0%)	2 (11%)	
Histological subtype, n (%)			
Clear cell	12 (55%)	8 (44%)	0.714
Papillary (type 1 and 2)	6 (27%)	8 (44%)	
Clear cell papillary	2 (9%)	1 (6%)	
Other	2 (9%)	1 (6%)	
ISUP grade, n (%)			
Grade 1-2	21 (95%)	11 (61%)	0.014
Grade 3-4	1 (5%)	7 (39%)	
Tumor multifocality, n (%)	3 (14%)	4 (22%)	0.680
Tumor bilaterality, n (%)	1 (5%)	1 (6%)	0.884

ASA = American Society of Anesthesiologists; BMI = Body mass index; GFR = Glomerular filtration rate; IQR = Interquartile range; ISUP = International Society of Urological Pathology.

Figure 1.
Kaplan-Meier estimates of recurrence-free survival (A) and overall survival (B) following radical nephrectomy, comparing kidney transplant (Kidney Tx) and dialysis patients.



Fisher's exact test or the chi-square test, as appropriate.
Kaplan-Meier survival curves were calculated for each group of ESRD patients and log-rank (Mantel-Cox) test calculated for difference or equivalence between treatment groups, censoring patients without the event at their date of last follow-up. A multivariate Cox proportional hazards regression model was fit with time to recurrence and time to death of any cause as the dependent variables, and clinical and pathological characteristics as the independent variables, to identify independent prognostic factors of RFS and OS.
All reported p values are two-sided, with a p value less than 0.05 indicating statistical significance. Statistical analyses were performed using the *Statistical Package for the Social Sciences* (SPSS®), version 24.0 (*IBM Corp., Armonk, NY, USA*).

Results

Demographic and pathological characteristics of the cohort stratified by kidney transplant or dialysis status at the time of diagnosis are shown in Table 1. Kidney transplant recipients and dialysis accounted for 22 (55%) and 18 (45%) patients, respectively. Mean age at the time of diagnosis was 58 years old, and the majority of patients in both groups were male (93% overall). Demographic characteristics were similar between groups, except for a lower ASA score being more common in the kidney transplant cohort (ASA score ≤ 3, 95% kidney transplant vs 44% dialysis, p < 0.001). Median time on dialysis until diagnosis was similar (p = 0.430). Pathological characteristics were homogeneous between populations. Most of the patients had pT1a disease (82% transplant *vs* 61% dialysis, p = 0.184), with median tumor size 3-4 cm. The most frequent histological subtype was clear cell (cc) RCC, closely followed by papillary (pRCC) which was slightly more frequent in the dialysis group, albeit without statistically significant difference (p = 0.714). 3 (7.5%) patients presented with *clear cell papillary RCC* (ccpRCC). Dialyzed patients were more likely to have higher grade disease (5% kidney transplant vs 39% dialysis, p = 0.014). Overall, 7 (18%) and 2 (5%) patients presented with tumor multifocality and bilaterality respectively, similarly distributed between groups.
Over a median follow-up of 41 months (IQR 22-71), 3 recurrences occurred: 1 in kidney transplants (from ccRCC) and 2 in dialyzed patients (1 ccRCC, 1 pRCC). All the 3 recurrences occurred in the contralateral kidney with the same histological subtype, and neither any of these recurrent patients nor from the remaining overall cohort later progressed to regional node or distant metastatic disease.
Figure 1 shows the probability of freedom from recurrence following nephrectomy according to kidney transplant or dialysis status. Median time to recurrence was not reached in any group (NR, 95% *confidence interval* (CI) *not evaluable* (NE) - NE), with 5-year RFS of 96% (95%CI 91-99) and 89% (95%CI 79-98) for kidney transplant and dialyzed patients, respectively (log-rank p = 0.443). Kidney transplant patients did not show an increased risk of recurrence [*hazard ratio* (HR) 0.40, 95%CI 0.04-4.46, p = 0.458]. On multivariable Cox

Table 2.
Multivariable Cox regression model predicting RFS and OS after radical nephrectomy.

	RFS			OS		
	Hazard ratio	**95% CI**	**p value**	**Hazard ratio**	**95% CI**	**p value**
Kidney transplant, yes vs no	0.42	0.04-4.65	0.479	0.04	0.01-7.78	0.236
Age, years	0.92	0.82-1.02	0.098	1.04	0.94-1.15	0.464
ASA score, > 3 vs ≤ 3	5.39	0.49-59.87	0.170	0.31	0.01-8.18	0.487
Time on dialysis, years	1.05	0.61-1.82	0.855	1.86	1.18-2.93	**0.008**
Time on immunosuppression, months	0.98	0.95-1.02	0.322	1.00	0.98-1.02	0.862
Histological subtype, non-clear cell vs clear cell	0.605	0.06-6.70	0.682	0.62	0.08-5.06	0.658
T stage, ≥ T1b *vs* T1a	5.78	0.52-63.78	0.152	0.50	0.01-44.35	0.762
ISUP Grade, G3-4 vs G1-2	2.03	0.18-22.58	0.564	0.55	0.02-14.55	0.718
Size, mm	1.03	0.98-1.08	0.276	1.00	0.92-1.08	0.945

ASA = American Society of Anesthesiologists; CI = confidence interval; ISUP = International Society of Urological Pathology; OS = Overall survival; RFS = Recurrence-free survival. P values < 0.05 are shown in bold type.

regression analysis (Table 2), adjusting for clinical and pathological confounders, presence or absence of kidney transplant (and consequently immunosuppression) was not significantly associated with RFS (HR 0.42, 95%CI 0.04-4.65, p = 0.479). Likewise, the time on immunosuppression was not an independent predictor of RFS (HR 0.98, 95%CI 0.95-1.02, p = 0.322).

There were 7 deaths during follow-up, 2 in kidney transplant and 5 in dialysis patients. No cancer-related deaths were seen. Most deaths were related to cardiovascular disease (71% overall; 100% kidney transplant and 60% dialysis). Median time to death was not reached in any group (HR 0.34, 95%CI 0.07-1.77, p = 0.202). 5-year OS was 91% (95%CI 78-99) for kidney transplant recipients and 72% (95%CI 59-85%) for dialyzed patients (log-rank p = 0.181). On multivariable analysis, neither the presence or absence of transplantation (HR 0.04, 95%CI 0.01-7.78, p = 0.236) nor the time on immunosuppression (HR 1.00, 95%CI 0.98-1.02, p = 0.862) were significantly associated with OS. The only independent predictor of worse survival was time on dialysis (HR 1.86, 95%CI 1.18-2.93, p = 0.008).

Discussion

Considering that malignancy is a major cause of death after transplantation, a systematic screening for the presence of any active/latent cancer or a past history of cancer is mandatory when evaluating candidates for renal transplantation (12). However, previous history of malignancy and the role of immunosuppression as a causative risk factor for recurrence is still controversial, particular in certain subtypes of malignancy such as RCC, making it difficult to decide if the patient is suitable for transplantation and, if so, how long should the waiting period be. Few studies have focused on the oncological outcomes of native kidneys RCC in ESRD patients, all retrospective and most of them noncomparative, providing conflicting results.

Farrugia et al. (2) have shown that previous history of neoplasia was an independent risk factor for post-transplant death from malignancy. In a large Swedish cohort of more than 10000 solid organ transplant recipients, *Brattström et al.* (13) have found a 30% increased mortality risk for patients with a previous history of neoplasia. Nevertheless, this risk was mainly driven by recipients of non-kidney transplants: mortality was increased by 20% in kidney recipients and by 80% among other organs recipients. Besides, after stratification by waiting time between cancer treatment and transplantation, there was no association of increased mortality in kidney recipients, irrespective of waiting period. A two-fold increased risk of cancer-specific death was seen in transplant patients with a history of previous cancer other than kidney compared to RCC, regardless of waiting time. On the contrary, *Viecelli et al.* (14), using data from the *Australian and New Zealand Dialysis and Transplant Registry*, reported no significant association of previous cancer history with *cancer-specific survival* (CSS) or OS in kidney transplant recipients. Similarly, a recent nationwide Norwegian study found that kidney recipients with a history of neoplasia had a similar OS and graft survival as recipients without such cancer, and although cancer mortality was increased, particularly during the first 5 years, a short waiting period was not associated with all-cause or recurrent cancer mortality (15).

In line with the most recent evidence, in our cohort, kidney transplant patients did not have an inferior RFS or OS compared to dialyzed patients. Moreover, on multivariable Cox regression model, the presence or absence of transplant (and consequently immunosuppression) was not significantly associated with the risk of recurrence or increased mortality. In fact, the only independent predictor of an inferior survival was time on dialysis (HR 1.86, p = 0.008), which means that the common policy of a 2-year waiting period before transplantation would translate into a 3-4-fold increased risk of death.

Cardiovascular disease remains a major cause of death in dialyzed patients (16) and since most ESRD patients are elderly, it is possible that a longer waiting period will eventually lead to death, not due to cancer recurrence, but due to the burden of dialysis (17). Reducing unnecessary lengthy waiting times could improve the care of these patients, optimizing timely transplantation.

In accordance with our results, several studies have shown the safety of transplantation and immunosuppression in patients with a history of native kidney RCC. In a multicentric study from 24 centres conducted by the French Urological Association, *Gigante et al.* (18) compared oncological outcomes of RCC in 213 transplanted and 90 dialyzed patients and reported higher 5-year RFS and CSS in the transplanted population. On multivariable analysis, presence of kidney transplant was not associated with CSS, with only T stage remaining an independent predictor of inferior survival. Similarly, in a single-centre study comparing outcomes of native kidneys RCC in renal transplant recipients with a population with RCC without transplant, *Klatte et al.* (19) showed that the presence of transplant did not affect CSS and OS, and that most RCC were low-stage, low-grade with a favourable

outcome. TNM stage and grade were the only predictors of worse survival. A recent systematic review aimed to compare oncological outcomes of urological cancer in patients who subsequently received a kidney transplant or remained on dialysis (20). For RCC of native kidneys, RFS, CSS and OS were similar between groups, with most of recurrences occurring in the contralateral kidney without impact on survival. The main prognostic factors for recurrence were stage, grade and histological subtype, with the authors concluding that immunosuppression didn't modify the natural history of RCC.

In our cohort, no metastasis (apart from recurrences in the contralateral kidney) or cancer-related deaths occurred, precluding any conclusion about these oncological outcomes. This contrasts with most of previous studies and could be related to the fact that only patients with localized disease with more favourable prognosis were included. However, in our opinion, a reduction or even elimination of waiting period would only be feasible in these low-stage cancers, making assumptions more reliable. For high-risk RCC, we believe that a waiting period according to the Cincinnati Registry is still adequate due to the considerable risks of recurrence and progression.

Several studies have highlighted the distinctive clinical and pathological features of RCC in ESRD comparing to sporadic RCC (19, 21, 22). In line with these reports, we have also found that RCC occurred mainly in young male patients, were generally small and had low stage and grade, with a high incidence of multifocality and bilaterality. We found a higher incidence of papillary subtype compared to the general population and a substantial prevalence of ccpRCC. ccpRCC is a new but rare entity, first listed in the WHO 2016 renal tumor classification, that has an indolent course with no cases of metastasis reported to date (23). Although also occurring in non-ESRD patients, it is speculated that its prevalence is increased in dialyzed patients. Although RCC of native kidneys of ESRD patients seem to exhibit more favourable pathological and outcome features, the exact reason for its less aggressive behaviour still has to be determined. Possible reasons for this better prognosis include a specific molecular pathway related to ACKD not yet identified, or an earlier diagnosis due to more frequent imaging than the general population.

There are no high-level evidence-based recommendations regarding screening for RCC in ESRD patients, and no prospective studies on the cost-effectiveness of this approach. Due to the higher incidence of RCC in this population and the fact that this risk increases with duration of dialysis, several authors have advocated regular screening in pretransplant and post-renal transplant recipients (19, 20, 24). In line with these studies, we also believe that regular screening of native kidneys should be part of pretransplant evaluation in order to diagnose RCC at lower stage and grade, allowing the feasibility of a shorter waiting period for renal transplantation.

We acknowledge several limitations in our study. First, in line with previous reports, we recognize that our study is limited by its observational design and that the results should be interpreted within the limits of retrospective data. Although it is unlikely that randomised controlled trials will be conducted in this setting due to ethical and logistical difficulties, well-designed prospective cohort studies are needed to confirm the safety of a reduced waiting period. Second, this was a single-center study with a small sample size, which only included patients with localized disease. However, in order to evaluate the safety of reducing the waiting period for transplantation, we felt that it would be more appropriate to exclude patients with regional nodal or distant metastasis, as these are high-risk patients for recurrence or progressive disease even in the absence of immunosuppression, making comparisons more homogeneous and reliable.

Nevertheless, it precluded any conclusion on the effect of immunosuppression in pN+ and/or M+ patients. Third, the low number of events in our cohort may have hampered our survival estimates and precluded further analysis on CSS. On the other hand, this low number reflects the favourable prognosis that most of these indolent tumors have.

Conclusions

Our study shows that most RCCs in native kidneys of renal transplant and dialyzed patients are incidental low-grade and low-stage cancers. These tumors exhibit many favourable clinical, pathological and outcomes features. Kidney transplant recipients with RCC do not have increased risk of recurrence or death compared to dialyzed patients. Immunosuppression doesn't seem to have an impact on oncological outcomes, but an increased time on dialysis seems to be associated with worse overall survival. Therefore, waiting time for transplantation for these tumors could be reduced. Well-designed prospective studies are needed to confirm our findings.

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