OPEN ACCESS

GAVIN PUBLISHERS

Journal of Urology and Renal Diseases

Namiki S, et al. J Urol Ren Dis: JURD-195.

Research Article

DOI: 10.29011/2575-7903.000095

The Influence of Bilateral Occurrence on the Clinicopathological Features and Prognosis of Renal Cell Carcinoma in End-Stage Renal Disease Patients on Hemodialysis

Shunichi Namiki[1*], Yoshihiro Ikeda[2], Takashi Kudo[1], Juntaro Koyama[1], Masataka Aizawa[1], Naomasa Ioritani[1], Yasuhiro Nakamura[3]

[1]Department of Urology, Japan Community Health Care Organization Sendai Hospital, Sendai, Japan

[2]Department of Urology, Osaki Citizen Hospital, Osaki, Japan

[3]Division of Pathology, Tohoku Medical and Pharmaceutical University, Sendai, Japan

[*]**Corresponding author:** Shunichi Namiki, Department of Urology, Japan Community Health Care Organization Sendai Hospital, 3-16-1 Tsutumi-machi, Aoba-ku, Sendai, Miyagi 980-8501, Japan. Email: namikin@uro.med.tohoku.ac.jp

Citation: Namiki S, Ikeda Y, Kudo T, Koyama J, Aizawa M, et al. (2018) The Influence of Bilateral Occurrence on the Clinicopathological Features and Prognosis of Renal Cell Carcinoma in End-Stage Renal Disease Patients on Hemodialysis. J Urol Ren Dis: JURD-195. DOI: 10.29011/2575-7903.000095

Received Date: 24 May, 2018; **Accepted Date:** 05 June, 2018; **Published Date:** 12 June, 2018

Abstract

Background: This study aimed to investigate the influence of bilateral occurrence on the clinicopathological features and prognosis of Renal Cell Carcinoma (RCC) in End-Stage Renal Disease (ESRD) patients on Hemodialysis (HD).

Methods: We analyzed 262 patients on HD with RCC who underwent radical nephrectomy at our institute between November 1985 and June 2016. Unilateral RCC occurred in 207 patients. Bilateral RCC was observed in 55 patients including synchronous in 31 and metachronous in 24. The median post-surgical follow-up period was 95 months (range 1 - 374 months).

Results: There were no significant differences in median duration of dialysis before surgery, mean tumor size, and pathological tumor stage and tumor grade between the two groups. Patients in the bilateral RCC group were more likely to show more multifocal tumors than patients in the unilateral RCC group (69% vs 26%, $p < 0.001$). Regarding histological subtypes, the bilateral RCC group more frequently had acquired cystic disease-associated RCC and less frequently had clear cell RCC ($p < 0.001$). The 5-year cancer-specific survival rate was more than 90% in both groups with no significant difference between the two groups. Multivariate analysis showed that advanced pathological stage were positively associated with death from cancer.

Conclusions: ESRD patients on HD with bilateral RCC and unilateral RCC had similar prognoses. The significant pathological findings in bilateral RCC are acquired cystic disease-associated RCC and multifocality.

Keywords: End-Stage Renal Disease; Hemodialysis; Renal Cell Carcinoma; Radical Nephrectomy

Introduction

Patients with End-Stage Renal Disease (ESRD) have been recognized to be a high risk for many cancers, including kidney and urinary tract cancers [1]. Previous reports suggested that bilateral renal cell carcinoma (RCC) occurred in 5% to 36% of Hemodialysis (HD) patients [2,3]. In patients undergoing HD, the incidence rates of Acquired Cystic Disease Of The Kidney (ACDK) have ranged from 35% to 79% [4,5]. The main complication of ACDK is frequent development of renal tumors [6]. Patients with bilateral sporadic RCC have a poor prognosis compared to those with unilateral RCC [7]. Although previous reports have suggested that tumor size, performance status, tumor grade, and HD duration before surgery were the prognostic factors for ESRD patients with RCC, bilateral RCC has not been discussed. The purpose of the study was to investigate the influence of bilateral RCC on clinicopathological features and prognosis in hemodialysis patients with ESRD, and to compare the findings with features of patients

treated for unilateral RCC.

Materials and Methods

This retrospective study was approved by our institutional review board and included consecutive patients from November 1985 to June 2016. ESRD patients with renal tumors who underwent surgical therapy at our institution were identified from our surgical database. ESRD was defined as chronic renal failure treated by HD or peritoneal dialysis. Using abdominal Ultrasonography (US) and Computed Tomography (CT), annual screening for RCC was performed in patients on HD. When RCC was suspected in patients with ACDK because of enlarged cysts after the most recent US and CT, dynamic CT or magnetic resonance imaging was also performed. All ESRD patients with RCC were included after the initiation of dialysis. In the present study, paraffin-embedded tumor specimens were histopathologically evaluated by one pathologist at our institution. The criteria used for the diagnosis of ACDK were in accordance with previous reports [8]. The tumors were classified according to the World Health Organization (2004) classification system. Tumor size was defined as the diameter of the largest tumor if there were multiple cancerous lesions in the same kidney. Information was collected on age, sex, symptoms, duration of dialysis therapy, tumor staging and grading, histological subtype and outcome. The median post-surgical follow-up period was 95 months (range 1-374 months). There were 317 radical nephrectomies performed in 207 patients with unilateral RCC and in 55 patients with bilateral RCC including synchronous RCC in 31 patients and metachronous RCC in 24. The median time between the 1st and 2nd RCC diagnoses was 32 months (range 11-130 months). Statistical analysis was performed using Student's t-test and the chi-square test. A p-value of less than 0.05 was considered significant. Patient survival was defined as the time between the date of surgery and the date of death. The 5-year cancer specific survival rate was calculated using the Kaplan-Meier method, and significance was determined by the log-rank test. Patients alive after their last follow-up were censored.

Results

Patients' Characteristics

We identified 262 patients with ESRD who were surgically treated for RCC at a single institution (Table 1).

	Unilateral	Bilateral	Total	P value
Number	207	55	262	
Mean age, years (SD)	57	52		0.001
Median (range)	58 (21-81)	52 (30-78)		
Gender (%)				0.019
Male	169 (82)	52 (95)		
Female	38 (18)	3 (5)		
Dialysis duration months (SD)				0.782
Mean	141	148		
Median (range)	137 (1-400)	149 (1-300)		
Type of surgery (%)				0.022
open	104 (50)	70 (64)		
Laproscopic	103 (50)	40 (36)		
Follow-up period, months	96	132		<0.001
Median (range)	82 (3-374)	126 (19-286)		
T stage (%)				0.393
1	198 (96)	109 (99)		
2	5 (2)	1 (1)		
3	4 (2)	0 (0)		
Grade (%)				0.929
1	44 (21)	21 (19)		
2	140 (68)	77 (70)		
3	23 (11)	12 (11)		
Tumor (%)				<0.001
Unifocal	152 (73)	41 (37)		
Multifocal	55 (27)	69 (63)		
Mean tumor size, cm	2.5	2.2		0.203
Median (range)	2 (0.5-19)	2 (0.5-7)		
Histology (%)				<0.001
Clear cell	130 (63)	45 (41)		
Papillary type 1	17 (8)	4 (4)		
Papillary type 2	23 (11)	18 (16)		
ACDK-associated RCC	31 (15)	34 (31)		
Clear cell-papillary	4 (2)	9 (8)		
Chromophobe	2 (1)	0 (0)		

Table 1: Comparison of clinical characteristics between unilateral and bilateral RCC patients.

Symptomatic RCC was evident in 28 (11%) patients, and gross hematuria was the most frequent complaint (12 patients). RCC was incidentally diagnosed in 237 (91%) patients by US or CT screening. The overall mean age at diagnosis was higher in the unilateral RCC group (57 years vs 52 years, respectively; p=0.001) and the rate of female sex was higher in the unilateral RCC group than in the bilateral RCC group (18% vs 5%; p = 0.019). There were no significant differences with regard to the median duration of dialysis before surgery between the two groups. The median follow-up period was significantly longer in the bilateral RCC group than in the unilateral RCC group (126 months vs 82 months; p<0.001). There were no differences in tumor size between contralateral kidney tumor in bilateral group and primary tumor in unilateral group (2.5 cm vs 2.2 cm; p=0.258).

Pathological Findings and Outcomes

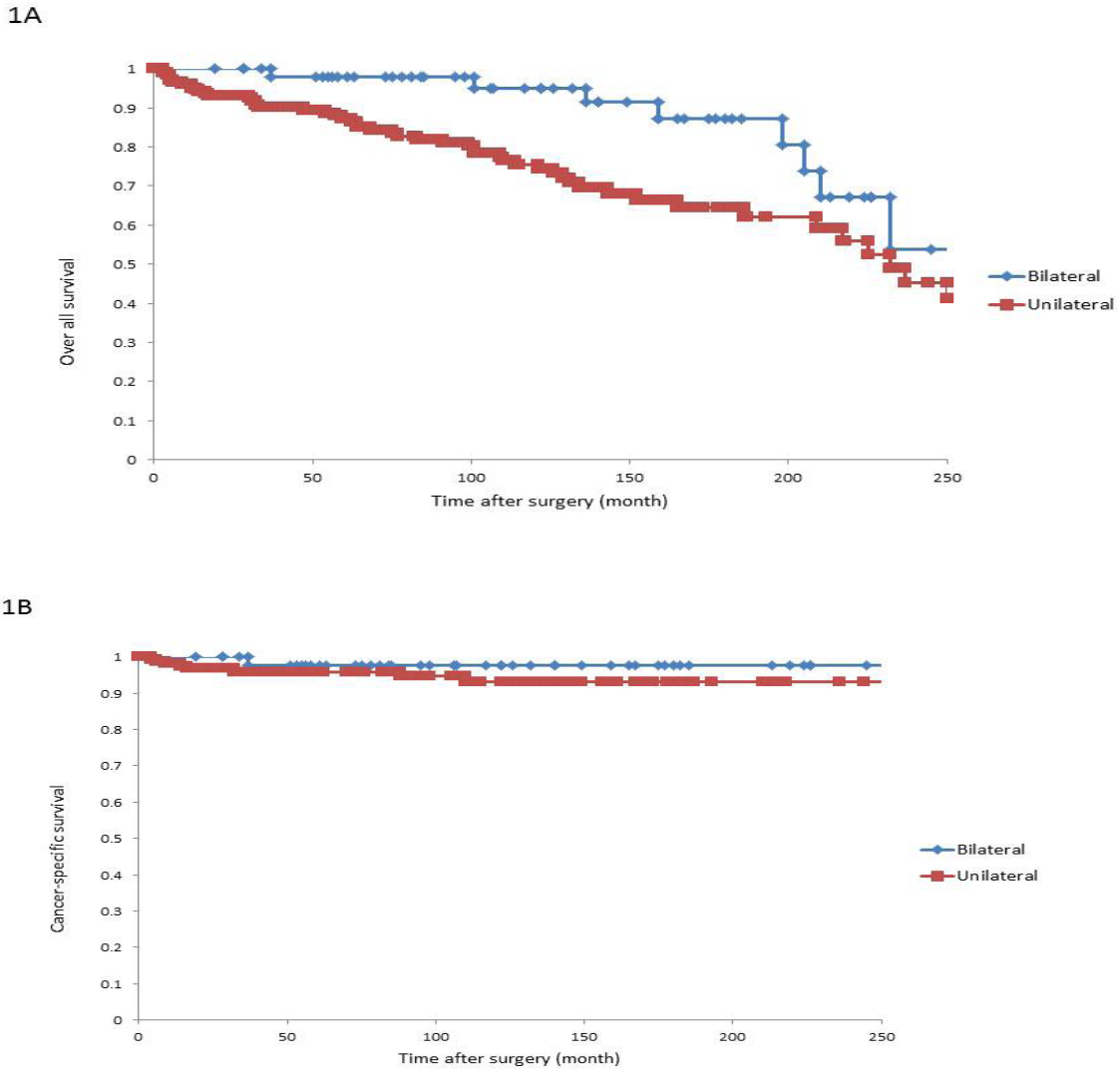
(Table 1) shows the pathological characteristics between the unilateral and bilateral RCC groups. The mean maximum tumor size was 2.45 cm (range 0.5-19 cm). Organ-confined cancer was pathologically proven after radical nephrectomy in 98% of the patients, including 86% of those with pT1 (tumors < 7 cm). Only four patients had advanced RCC (pT3). There were no significant differences between the two groups with regard to mean tumor size, pathological tumor stage, and tumor grade. The patients in the bilateral RCC group were more likely to show more multifocal tumors than the patients in the unilateral RCC group (69% vs 26%, p < 0.001). With regard to the histological subtypes, RCC in the bilateral RCC group was more frequently ACDK-associated RCC (30% vs. 14%), and was comprised less frequently of clear cell RCC than in the unilateral RCC (40% vs 62%, p < 0.001). (Table 2) shows the histology of both kidneys in the patients with bilateral occurrence. Twenty-eight of 55 patients had the same pathological findings in both kidneys.

	The other side				
	Clear cell	Papillary type 1	Papillary type 2	ACDK-associated	
One side					
Clear cell	13				13
Papillary type 1	2				2
Papillary type 2	5	1	5		11
ACDK-associated RCC	9	1		10	20
Clear cell-papillary RCC	4		1	4	9
Total	33	2	6	14	55

Table 2: Clinicopathological characteristics of bilateral RCC patients.

Comparison of Survival Between the Unilateral And Bilateral RCC Cases

In survival analysis, overall survival at 5 years was significantly higher in the bilateral RCC group than in the unilateral RCC group (P=0.011) (Figure 1A). However, the 5-year cancer-specific survival rate was more than 90% in both groups, which was not significantly different between the two groups (P=0.162) (Figure 1B).



Figures 1(A-B): A: Overall survival of 262 RCC patients on hemodilysis who underwent surgery. **B**: Cancer-specific survival of 262 RCC patients on hemodilysis who underwent surgery. RCC, renal cell carcinoma.

Overall ten patients out of 207 (4.8%) with a unilateral occurrence and two patients out of 55 (3.6%) with a bilateral occurrence died from kidney cancer in the follow-up period. On Multivariate Cox Regression Analysis, advanced stage was positively associated with death from cancer. Age, the duration of HD before surgery, tumor size, pathological results, and bilateral occurrence did not affect the likelihood of death from cancer (Table 3).

Variable	p value	Hazard ratio (95% CI)
Duration of HD	0.336	0.993 (0.979 - 1.007)
Age	0.343	1.067 (0.933 - 1.220)
TNM stage	0.025	7.739 (1.295 - 46.263)
Tumor grade	0.230	3.798 (0.430 - 33.567)
Tumor size	0.930	1.039 (0.445 - 2.424)
Pathological features	0.459	0.248 (0.006 - 9.878)
Bilateral/unilateral	0.982	—

Table 3: Predictors of death from cancer in RCC patients on HD on multivariate analysis.

Discussion

Among the study patients, there were a very small proportion of patients with advanced disease (1.5%). The present findings are in line with the report by Gigante, et al. [9], who found that RCC in ESRD patients demonstrated favorable clinical, pathological, and outcome features compared with RCC patients in the general population. Specifically, these investigators found that in the ESRD group, tumors were smaller, clear cell histology occurred less frequently, the tumors were discovered incidentally more frequently, the tumors had less advanced T category (less than T3) and produced less nodal invasion, and the patients experienced less metastatic disease. The risk and pathogenesis of RCC may differ in patients on dialysis compared to the general population. The kidney of ESRD shows tubular atrophy, interstitial inflammation and fibrosis, and arterial, arterior and glomerular sclerosis, resulting in acquired cysts due to the loss of structural integrity [10]. Regular screening of patients on dialysis may increase survival by encouraging radical treatment for kidney cancer at an earlier tumor stage. Moreover, in Japan, most patients with ESRD are treated with long-term dialysis which accelerates the development of ACDK and then RCC [1,3,11]. This might be attributed to the common application of dialysis therapy. Thus, regular screening of patients on dialysis contributes to improving survival rates for RCC at earlier tumor stages.

In the present study, bilateral RCC showed favorable prognosis with a representative 5-year overall survival rate of 97%. Some reports showed that the prognosis of bilateral RCC was comparable to that of unilateral RCC [12-14]. Several factors have been reported to cause RCC occurrence in HD patients with ACDK. In previous ESRD studies, the frequency of ACDK-associated RCC ranged from 23% to 50% [15,16]. This suggests that molecular pathways distinct from the von Hippel-Lindau tumor suppressor protein/hypoxia-inducible factor/ vascular endothelial growth factor pathways are involved in ESRD patients with ACDK. Among the types of histopathological degeneration, ACDK alone has been implicated as the risk factor for malignant transformation [17]. Recent studies have reported that most ESRD-associated RCCs are classic histological types [18]. The first and most common of these is designated ACDK-associated RCC, and the other subtype is clear cell papillary RCC of ESRD [19]. The first subtype occurs only in kidneys with ACDK, while the second subtype occurs in non-cystic ESRD and in patients with ACDK. ACDK has been reported as being associated with a particular histological subtype of RCC: the clear-cell papillary RCC of ESRD. This subtype is known to behave less aggressively than conventional RCC [20]. These features are probably a combination of being on the whole biologically less aggressive biologically as well as the constant medical surveillance of these patients at an early stage. ACDK in patients treated with dialysis is frequently complicated by RCC, either multiple or bilateral [21]. In our study, the patients with bilateral RCC had a higher incidence of ACDK and papillary RCC than the patients with unilateral RCC, indicating favorable overall survival rate.

Papillary RCC had been previously reported as being one of the common histological subtypes found in the background of ACDK in dialysis patients, accounting for 42% to 71% of cases [22]. However, in our study, only 29% of the study patients had papillary RCC. One of the reasons was ethnic differences. The incidence of papillary RCC in Asian countries is thought to be lower than in Western countries [13]. Most RCCs occurring in patients with ESRD, particularly in ESRD with ACDK, have been reported to be papillary RCC [23]. Tickoo et al. suggested that the tumors arising in the setting of ESRD either show morphology similar to that of sporadic cases (clear cell, papillary, and chromophobe RCC) or have features that are unique to ESRD (ACDK-associated RCC, and clear-cell papillary RCC of end-stage kidneys) [24].

Prognostic factors for death from RCC in HD patients have been discussed in previous studies. In the present study, tumor grade and pathological stage were significant prognostic factors for cancer death although bilateral occurrence did not influence cancer-specific survival, as reported by Neuzille,t et al. [25]. Although the oncological mechanism in ESRD RCC tumors was thought to be different from that in sporadic RCC, high grade and tumor stage cancer influence cancer prognosis. The present study had some limitations including the retrospective and single-center design. In addition, because the treatment option was selected by the patient together with the urologist, the results might not be

representative of the overall population of ESRD patients with hemodialysis who undergo surgery. Next, we could not incorporate risk factors for ESRD, such as family history of chronic kidney disease, presence of hyperlipidemia, hypertension, the **Charlson Comorbidity** Index, performance status or body mass index into the analysis. Finally, no molecular analysis has been conducted using our specimens to date. Nevertheless, this large retrospective cohort study at a single institution has yielded information that helps to clarify the nature of, and excess risk for kidney cancer in patients treated by maintenance dialysis for ESDR.

Conclusions

In the present study, the dialysis patients with RCC who underwent nephrectomy had favorable clinical and pathological characteristics and good long-term outcomes. ESRD patients with bilateral RCC and with unilateral RCC had a similar prognosis. The significant pathological findings in bilateral RCC are acquired cystic disease associated RCC and multifocality.

Conflicts of Interest

None.

Acknowledgements

The authors would like to thank Yoshio Terasawa at Japan Community Health care Organization Sendai Hospital, who assisted with data collection and management.

References

1. Satoh S, Tsuchiya N, Habuchi T, Ishiyama T, Seimo K, et al. (2005) Renal cell and transitional cell carcinoma in a Japanese population undergoing maintenance dialysis. J Urol 174: 1749-1753.
2. Kojima Y, Takahara S, Miyake O, Nonomura N, Morimoto A, et al. (2006) Renal cell carcinoma in dialysis patients: a single center experience. Int J Urol 13:1045-1048.
3. Hashimoto Y, Takagi T, Kondo T, Iizuka J, Kobayashi H, et al. (2015) Comparison of prognosis between patients with renal cell carcinoma on hemodialysis and those with renal cell carcinoma in the general population. Int J Clin Oncol 20: 1035-1038.
4. Vaziri ND (1982) Acquired renal cystic disease in dialysis patients. Int J Artif Organs 5: 336-338.
5. Hughson MD, Buchwald D, Fox M (1986) Renal neoplasia and acquired cystic kidney disease in patients receiving long-term dialysis. Arch Pathol Lab Med 110: 592-601.
6. Ishikawa I, Saito Y, Shikura N, Kitada H, Shinoda A, et al. (1990) Ten-year prospective study on the development of renal cell carcinoma in dialysis patients. Am J Kidney Dis 16: 452-458.
7. Haferkamp A, Kurosch M, Pritsch M, Hatiboglu G, Macher-Goeppinger S, et al. (2010) Prognostic factors influencing long-term survival of patients undergoing nephron-sparing surgery for nonmetastatic renal-cell carcinoma (RCC) with imperative indications. Ann Surg Oncol 17: 544-545
8. Ishikawa I (1991) Uremic acquired renal cystic disease. Natural history and complications. Nephron 58: 257-267.
9. Gigante M, Neuzillet Y, Patard JJ, Tillou X, Thuret R, et al. (2012) Renal cell carcinoma (RCC) arising in native kidneys of dialyzed and transplant patients: are they different entities? BJU Int 110: E570-E573.
10. Stewart JH, Buccianti G, Agodoa L, Gellert R, McCredie MR, et al. (2003) 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 14: 197-207.
11. Prasad N, Jha V (2015) Hemodialysis in Asia. Kidney Dis 1: 165-177.
12. Klatte T, Wunderlich H, Patard JJ, Kleid MD, Lam JS, et al. (2007) Clinicopathological features and prognosis of synchronous bilateral renal cell carcinoma: an international multicentre experience. BJU Int 100: 21-25.
13. Takagi T, Kondo T, Izuka J, Kobayashi H, Tomita E, et al. (2011) Prognosis and characteristics of renal cell carcinoma in hemodialysis patients: bilateral occurrence does not influence cancer-specific survival. Int J Urol 18: 806-812.
14. Boorjian SA, Crispen PL, Lohse CM, Leibovich BC, Blute ML (2008) The impact of temporal presentation on clinical and pathological outcomes for patients with sporadic bilateral renal masses. Eur Urol 54: 855-863.
15. Neuzillet Y, Lay F, Luccioni A, Daniel L, Berland Y, et al. (2005) De novo renal cell carcinoma of native kidney in renal transplant recipients. Cancer 103: 251-257
16. Moudouni SM, Lakmichi A, Tligui M, Rafii A, Tchala K, et al. (2006) Renal cell carcinoma of native kidney in renal transplant recipients. BJU Int 98: 298-302.
17. Matson MA, Cohen EP (1990) Acquired cystic kidney disease: occurrence, prevalence, and renal cancers. Medicine (Baltimore) 69: 217-226.
18. Sule N, Yakupoglu U, Shen SS, Krishnan B, Yang G, et al. (2005) Calcium oxalate deposition in renal cell carcinoma associated with acquired cystic kidney disease: a comprehensive study. Am J Surg Pathol 29: 443-451.
19. Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, et al. (2006) Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol 30: 141-153.
20. Bhatnagar R, Alexiev BA (2012) Renal-cell carcinomas in end-stage kidneys: a clinicopathological study with emphasis on clear-cell papillary renal-cell carcinoma and acquired cystic kidney disease-associated carcinoma. Int J Surg Pathol 20: 19-28.
21. Ishikawa I, Hayama S, Morita K, Nakazawa T, Yokoyama H, et al. (2010) Long-term natural history of acquired cystic disease of the kidney. Ther Apher Dial 14: 409-416.
22. Dhillon J, Amin MB, Selbs E, Turi GK, Paner GP, et al. (2009) Mucinous tubular and spindle cell carcinoma of the kidney with sarcomatoid change. Am J Surg Pathol 33: 44-49.
23. Denton MD, Magee CC, Ovuworie C, Mauiyyedi S, Pascual M, et al. (2002) Prevalence of renal cell carcinoma in patients with ESRD pretransplantation: a pathologic analysis. Kidney Int 61: 2201.

24. Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, et al. (2006) Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol 30: 141-153.

25. Neuzillet Y, Tillou X, Mathieu R, Long JA, Gigante M, et al. (2011) 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 60: 366-373.