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## Histopathology in Surgically Treated Renal Cell Carcinoma: Survival Differences by Subtype and Stage

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### Abstract

**Purpose**—Previous studies of the impact of renal cell carcinoma histopathology on survival are conflicting and generally limited to institutional analyses. Thus, we determined the role of renal cell carcinoma histopathology on the stage specific survival rate in a large population based cohort.

**Materials and Methods**—We used the 2000 to 2005 National Cancer Institute SEER (Surveillance, Epidemiology and End Results) database to identify 17,605 patients who underwent surgery for renal cell carcinoma and met study inclusion criteria. Patients were stratified by histological subtype (clear cell, papillary, chromophobe, collecting duct and sarcomatoid differentiation) and pathological stage. We performed Cox proportional hazard modeling and Kaplan-Meier survival analysis to determine overall and cancer specific survival.

**Results**—Patients with papillary and chromophobe pathology were less likely to present with T3 or greater disease (17.6% and 16.9% ,respectively) while patients with collecting duct and sarcomatoid variants were more likely to present with T3 or greater disease (55.7% and 82.8%, respectively) compared to those with clear cell histology ( $p < 0.001$ ). On multivariate analysis histology was significantly associated with overall and cancer specific survival. Patients with chromophobe pathology had improved survival (HR 0.56, 95% CI 0.40–0.78) while those with collecting duct and sarcomatoid variants had worse survival (HR 2.07, 95% CI 1.44–2.97 and 2.26, 95% CI 1.93–2.64, respectively).

**Conclusions**—Renal cell carcinoma histological subtype predicts overall and cancer specific survival. Patients with collecting duct and sarcomatoid variants of renal cell carcinoma have poor survival, even those who present with low stage disease. These data suggest inherent differences in renal cell carcinoma biology and may ultimately form the basis of future histologically targeted therapies.

### Keywords

kidney; carcinoma; renal cell; SEER program; survival analysis; histology

In 1997 the Heidelberg classification identified 4 distinct histological renal cell neoplasm subtypes, including conventional (clear cell), papillary, chromophobe and collecting duct variants. While sarcomatoid variation is noted in all renal cell subtypes it is not considered a discrete subtype but rather a progression of pathological high grade disease.<sup>1</sup> Despite this, sarcomatoid differentiation is a clearly recognized pathological entity with distinct biological activity.<sup>2,3</sup>

Several groups have addressed the role of renal cell histopathology in survival. Initial studies were largely institutional with a sample size of 186 to 2,466 patients.<sup>4-11</sup> On univariate analysis most groups noted that histopathology predicted outcome, specifically citing a survival advantage of the papillary and chromophobe subtypes relative to that of clear cell renal cancer. In a multi-institutional, international study of 4,063 patients Patard et al found that histopathology predicted survival on univariate analysis.<sup>12</sup> However, this influence was not statistically significant on multivariate analysis. Only TNM stage, grade and Eastern Cooperative Oncology Group status were independent variables. While this study was the largest at the time, it was limited by the relatively small sample size of certain stage specific histological categories, higher staged cancers from North American sites and no analysis of sarcomatoid or collecting duct pathology.

Recently Capatano et al used the National Cancer Institute SEER database to evaluate the effect of histology on RCC prognosis.<sup>13</sup> They noted in univariate and multivariate models that histopathology was an independent predictor of cause specific mortality. However, accuracy analysis revealed that histopathology contributed only 0.1% to cause specific mortality. While this represents an important finding on the role of histopathology in cause specific mortality, that study was limited by the inclusion of data before the implementation of consensus histological definitions and the absence of collecting duct and sarcomatoid variants.

Thus, we evaluated all renal cell histopathology in a contemporary, population based cohort with an emphasis on the role of histopathology in stage specific, overall and cancer specific survival.

## **MATERIALS AND METHODS**

### **Subjects**

We used the SEER database, a prospective national cancer registry that captured data on approximately 26% of the American population during 1973 to 2005.<sup>14</sup> Data before 2000 were excluded from analysis due to the lack of pathological consensus on histopathological subtypes and absent chromophobe histology. We also excluded patients younger than 30 years to omit familial renal cell variants and patients with unknown T stage, grade or histology.

### **Population**

All renal cancer cases (ICD-9 code 189.0) between the 2000 and 2005 were identified. Patients were included in study if they underwent partial or radical nephrectomy and final histology on pathological evaluation was clear cell, papillary, chromophobe, collecting duct or sarcomatoid differentiation. Four cases of medullary renal cell carcinoma were categorized as collecting duct renal cell carcinoma.

### **Variables**

For each identified patient we abstracted data on age, race, gender, treatment, lymph node status, cause of death, time from diagnosis to death or last followup, and tumor

histopathology, grade, size, extension and stage. Tumor size, extension, lymph node status and stage were used to construct a final stage scheme (T1N0M0, T2N0M0, T3N0M0, T4N0M0, N+M0, M+). For analysis we used the revised 1997 American Joint Committee on Cancer TNM staging system. We defined treatment as partial or radical nephrectomy.

### Statistical Analysis

The primary outcome measures were the cancer specific and overall survival rates based on histopathological subtype at nephrectomy. Univariate and multivariate Cox proportional hazard modeling and Kaplan-Meier survival analysis were used to evaluate survival based on histopathology. Covariates included in the adjusted models were age, gender, race, grade and stage. The Chi-squared test was used to determine the association between histopathology and each covariate. Statistical analysis was done using R, version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

We identified 17,605 patients with RCC who underwent radical or partial nephrectomy between January 2000 and December 2005, and met our study inclusion criteria (table 1). Of these patients 78.6%, 12.9%, 5.4%, 2.5% and 0.6% had clear cell, papillary, chromophobe, sarcomatoid differentiation and collecting duct pathology, respectively. Median overall survival was 19 months (range 0 to 71). A total of 1,699 patients in our cohort died of RCC. Median survival in those who died of RCC was 10 months (range 0 to 66). Median survival in patients with sarcomatoid and collecting duct RCC was 6 (range 0 to 68) and 13 months (range 0 to 59), respectively, which was significantly less than for the clear cell (19 months, range 0 to 71), papillary (18, range 0 to 71) and chromophobe (19, range 0 to 71) subtypes (Pearson chi-square test  $p < 0.001$ ).

Tumor stage was significantly associated with histopathology ( $p < 0.001$ ). Compared to patients with clear cell histology, of whom 28% had T3, T4, N+ or M+ disease, those with sarcomatoid and collecting duct variants were more likely to present with advanced disease (82.8% and 55.7%, respectively) while patients with papillary and chromophobe variants were less likely to present with advanced disease (17.6% and 16.9%, respectively). Similarly a significant association was found between grade and histopathology with 94.7% of sarcomatoid and 69.1% of collecting duct cases presenting with grade 3 or 4 tumors compared with only 28.5%, 28.8% and 32.7% of clear cell, papillary and chromophobe cases, respectively ( $p < 0.001$ ).

Figures 1 and 2 show Kaplan-Meier survival plots of the impact of histological subtype on cancer specific and overall survival. Univariate Cox proportional hazard models revealed that all variants of histopathology were statistically significant compared with the referent clear cell pathology for cancer specific and overall survival (table 2). Specifically papillary and chromophobe variants were associated with a significantly lower hazard of cancer specific and overall mortality compared with clear cell histology. In contrast, collecting duct and sarcomatoid histologies were associated with a significantly higher hazard of overall and cancer specific survival.

The effects of histopathology on cancer specific and overall survival were then explored using a multivariate Cox proportional hazards regression model adjusted for the covariates patient age, gender, race, grade and stage. Except for patient gender each covariate remained a statistically significant predictor of survival in the multivariate model (table 2). The effects of histopathology were decreased substantially after accounting for the covariates, although the general direction of the relationships was unchanged. Compared with clear cell tumors a lower hazard of cancer specific mortality was identified in patients with chromophobe

variants (HR 0.56, 95% CI 0.40–0.78) while a higher hazard of mortality was found in those with sarcomatoid and collecting duct pathology (HR 2.26, 95% CI 1.93–2.64 and 2.07, 95% CI 1.44–2.97, respectively). It was not statistically significant on multivariate analysis but there was a trend toward a lower hazard of cancer specific mortality in patients with papillary histology (HR 0.85, 95% 0.70–1.02). Notably there was little difference in overall survival between papillary and clear cell pathologies.

## DISCUSSION

These data reveal several important findings regarding the proportion of specific renal cell subtypes and the demographic distribution of renal cell histopathology. Of note, this importantly, this secondary data analysis reflects a population based cohort after the incorporation of consensus pathology definitions and during a contemporary era of increased detection of incidental renal masses. As expected, clear cell and papillary variants are the 2 most common RCC pathologies and their proportions were approximately similar to those in previous series.<sup>4–6,8</sup> All RCCs show a male predominance, although chromophobe tumors are relatively more common in women, a finding noted but not elaborated upon in other series.<sup>11,15,16</sup> Congruent with previous reports<sup>11,15,16</sup> chromophobe variants present at greater size than clear cell variants (22.3% vs 11.1% were T2). Patients with chromophobe RCC remain at lower risk for cancer specific and overall mortality despite this tendency toward higher stage at presentation. Lastly, chromophobe tumors have an increased tendency to present at age extremes relative to other RCC pathologies.

Demographics aside, prior data are conflicting regarding the impact of RCC histopathology on survival. On univariate analysis initial studies showed that histopathology predicts survival. Some groups discovered a survival advantage in patients with papillary and chromophobe variants.<sup>4–6,8</sup> Consistent with these studies our data reveal that patients with chromophobe and papillary RCC had improved cancer specific survival on univariate analysis relative to those with clear cell RCC. This trend persisted in multivariate analysis, although it was not statistically significant. Our data demonstrate that papillary histology is disproportionately represented in black Americans. Furthermore, papillary RCC is associated with end stage and acquired cystic renal disease.<sup>17</sup> While speculative, the increased comorbidities, lower socioeconomic status and health care disparities associated with these groups<sup>18,19</sup> may explain the discrepancy between papillary cancer specific and overall survival.

In contrast to chromophobe and papillary RCC, the collecting duct and sarcomatoid variants have a universally poor outcome relative to that of clear cell RCC. For sarcomatoid differentiation, poor outcomes are statistically significant despite adjusting for stage and grade. Also, sarcomatoid and collecting duct tumors present with a high percent of metastatic disease (55.3% and 34.0%, respectively,  $p < 0.001$ ), showing higher metastatic potential than clear cell RCC (10.0%).

Our data suggest that the most powerful predictor of outcome is tumor stage, as borne out by previous series. Notably, this study was sufficiently powered to detect significant differences in survival by each histological subtype. The conflicting results of variable outcomes by histology in the literature may be due to a substantial co-linear relationship of histopathology with stage and grade.

In the last 25 years there has been an increase in the incidence of renal cell cancer with subsequent stage migration.<sup>20,21</sup> Paradoxically, the increased detection and treatment of RCC is associated with a rise in cancer specific mortality from 1.5 deaths per 100,000 population in 1983 to 6.5/100,000 in 2002.<sup>22</sup> The implications of this are twofold. This not

only bolsters the claim that observation may be warranted for a proportion of small renal masses since surgery for these masses has not improved survival but also indicates that the biological behavior of renal masses is disparate. While some tumors are indolent, others are destined to progress. Furthermore, aggressive tumors, such as sarcomatoid or collecting duct lesions, show diverse gene mutations<sup>23-25</sup> as well as a variable response to chemotherapy and immunotherapy for metastatic disease.<sup>26,27</sup> In sum these data point to inherent differences in RCC tumor biology and call for improved pretreatment diagnostic techniques, ie biopsy and molecular markers, since exploiting these biological differences would likely form the basis of future treatment decision making and targeted therapy.

While this analysis is robust, it is limited in several respects. Our data show that high tumor grade is an independent predictor of cancer specific and overall survival but considerable debate exists on the validity and accuracy of grading for nonclear cell renal cancers.<sup>28-30</sup> Also, SEER data are retrospective in nature with inherent limitations, such as omitted variable bias. Furthermore, the likelihood of undergoing surgery favors patients with resectable disease. Thus, there exists a potential selection bias against patients who present with high stage disease. Moreover, unlinked SEER registry data lack coding for comorbidity, immunotherapy, and as well as performance status and symptom data. The latter parameters were significant determinants of outcome in key institutional series.<sup>6,11</sup> Further limitations that are particularly germane to this analysis are the limitations of SEER data due to the lack of centralized pathological review and the inability to differentiate types I and II papillary RCC. These are shortcomings of many administrative data sets in terms of interrater variability, lack of consistency in grading schema and uniform pathological interpretation.<sup>28</sup>

Despite limitations our findings are notable. To our knowledge this report represents the largest study to date to evaluate the role of all renal cell histopathology on patient survival in the computerized tomography era.

## CONCLUSIONS

Histological subtype in patients with RCC predicts overall and cancer specific survival. Despite adjustment for stage, patients with collecting duct and sarcomatoid RCC variants have poor survival. These findings may inform the role of percutaneous renal biopsy and other pretreatment diagnostic techniques since differences in histology reflect intrinsic biological variance and may ultimately form the basis of future targeted therapy.

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## Abbreviations and Acronyms

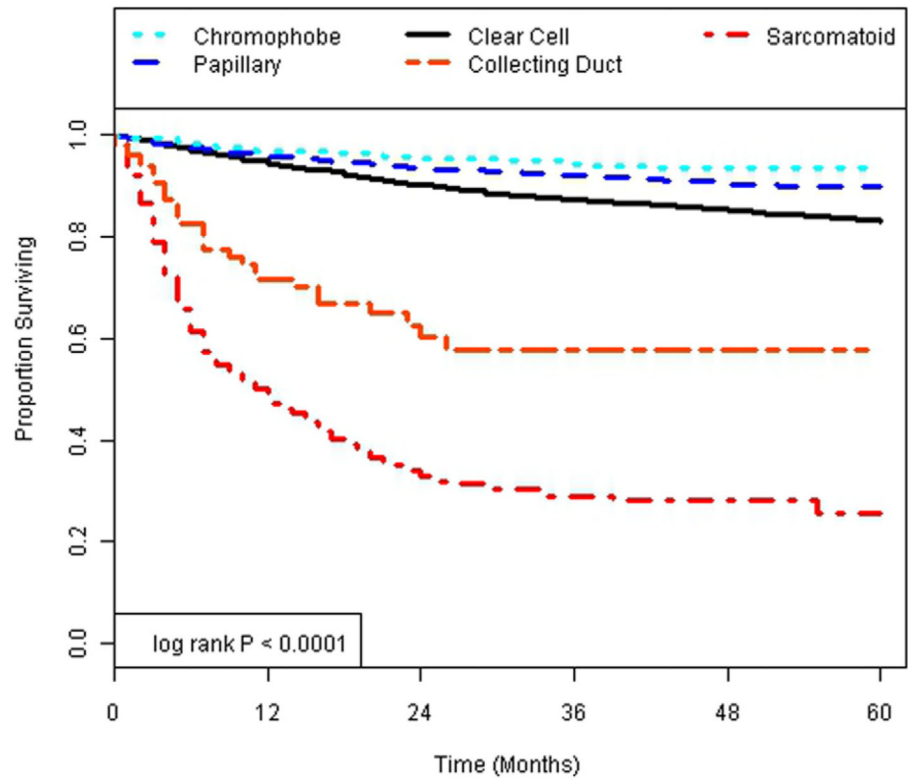
**RCC**      renal cell carcinoma

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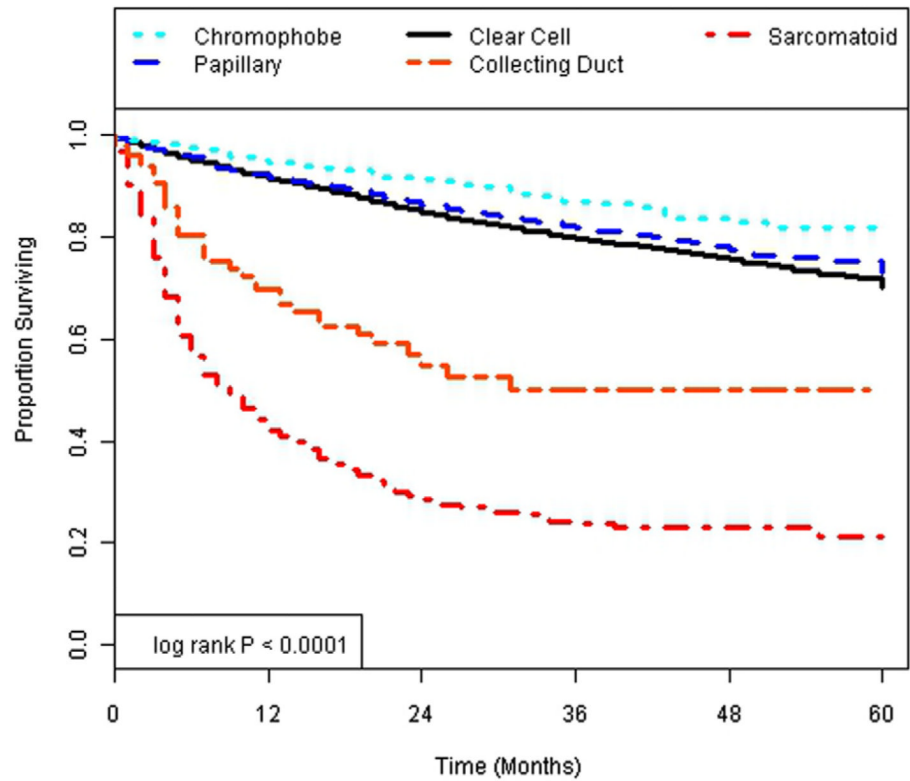
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Chromophobe	949	626	387	229	102	6
Papillary	2278	1461	885	557	254	35
Clear Cell	13841	9249	5779	3716	2082	825
Collecting Duct	97	50	27	14	6	0
Sarcomatoid	440	149	67	39	23	3
	Number at Risk					

**Figure 1.**  
Cancer specific survival.





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	Number at Risk					

**Figure 2.**  
Overall survival.

**Table 1**  
Demographics of 17,605 patients with surgically treated RCC stratified by histopathology (p <0.001)

Variables	No. Clear Cell (%)	No. Papillary (%)	No. Chromophobe (%)	No. Sarcomatoid (%)	No. Collecting Duct (%)	Total No. (%)
Age group: p value						
30-40	658 (4.8)	89 (3.9)	78 (8.2)	20 (4.5)	5 (5.2)	850 (4.8)
40-50	2,064 (14.9)	305 (13.4)	169 (17.8)	61 (13.9)	13 (13.4)	2,612 (14.8)
50-60	3,651 (26.4)	613 (26.9)	213 (22.4)	121 (27.5)	34 (35.1)	4,632 (26.3)
60-70	3,768 (27.2)	636 (27.9)	228 (24.0)	118 (26.8)	20 (20.6)	4,770 (27.1)
70-80	2,923 (21.1)	500 (21.9)	187 (19.7)	93 (21.1)	16 (16.5)	3,719 (21.1)
80+	777 (5.6)	135 (5.9)	74 (7.8)	27 (6.1)	9 (9.3)	1,022 (5.8)
Gender: p value						
M	8,501 (61.4)	1,740 (76.4)	568 (59.9)	300 (68.2)	68 (70.1)	11,177 (63.5)
F	5,340 (38.6)	538 (23.6)	381 (40.1)	140 (31.8)	29 (29.9)	6,428 (36.5)
Race: p value						
White	12,022 (86.9)	1,728 (75.9)	760 (80.1)	374 (85.0)	69 (71.1)	14,953 (84.9)
Black	853 (6.2)	482 (21.2)	137 (14.4)	37 (8.4)	20 (20.6)	1,529 (8.7)
Other	966 (7.0)	68 (3.0)	52 (5.5)	29 (6.6)	8 (8.2)	1,123 (6.4)
Stage: p value						
T1N0M0	8,375 (60.5)	1,592 (69.9)	577 (60.8)	36 (8.2)	35 (36.1)	10,615 (60.3)
T2N0M0	1,579 (11.1)	285 (12.5)	212 (22.3)	40 (9.1)	8 (8.2)	2,124 (12.1)
T3N0M0	2,412 (17.4)	228 (10.0)	107 (11.3)	82 (18.6)	19 (19.6)	2,848 (16.2)
T4N0M0	84 (0.6)	8 (0.4)	6 (0.6)	39 (8.9)	2 (2.1)	139 (0.8)
N+M0	172 (1.2)	67 (2.9)	11 (1.2)	46 (10.5)	7 (7.2)	303 (1.7)
M+	1,219 (8.8)	98 (4.3)	36 (3.8)	197 (44.8)	26 (26.8)	1,576 (9.0)
Grade: p value						
1	2,487 (18.0)	371 (16.3)	81 (8.5)	7 (1.6)	10 (10.3)	2,956 (16.8)
2	7,410 (53.5)	1,251 (54.9)	558 (58.8)	16 (3.6)	20 (20.6)	9,255 (52.6)
3	3,247 (23.5)	577 (25.3)	263 (27.7)	163 (37.0)	48 (49.5)	4,298 (24.4)
4	697 (5.0)	79 (3.5)	47 (5.0)	254 (57.7)	19 (19.6)	1,096 (6.2)
Totals	13,841 (78.6)	2,278 (12.9)	949 (5.4)	440 (2.5)	97 (0.6)	17,605 (100)

**Table 2**

Univariate and multivariate Cox proportional hazards models of cancer specific and overall survival

Histopathology	Survival HR (95% CI)	
	Ca Specific	Overall
<i>Univariate</i>		
Clear cell	Referent	Referent
Chromophobe	0.44 (0.32–0.61)	0.60 (0.48–0.75)
Papillary	0.65 (0.54–0.78)	0.90 (0.80–1.02)
Collecting duct	4.49 (3.14–6.41)	3.29 (2.38–4.55)
Sarcomatoid	10.63 (9.26–12.22)	7.52 (6.63–8.53)
<i>Multivariate</i>		
Histopathology:		
Clear cell	Referent	Referent
Chromophobe	0.56 (0.40, 0.78)	0.67 (0.53, 0.83)
Papillary	0.85 (0.70, 1.02)	0.98 (0.87, 1.12)
Collecting duct	2.07 (1.44, 2.97)	1.81 (1.31, 2.52)
Sarcomatoid	2.26 (1.93, 2.64)	2.21 (1.92, 2.55)
Age group:		
30–40	Referent	Referent
40–50	1.42 (1.02, 1.97)	1.32 (1.01, 1.74)
50–60	1.47 (1.07, 2.01)	1.57 (1.21, 2.03)
60–70	1.75 (1.28, 2.40)	2.14 (1.66, 2.77)
70–80	2.06 (1.50, 2.83)	2.78 (2.15, 3.61)
80+	2.44 (1.71, 3.48)	4.41 (3.35, 5.80)
Gender:		
M	Referent	Referent
F	1.04 (0.94, 1.16)	0.96 (0.89, 1.04)
Race:		
White	Referent	Referent
Black	1.29 (1.08, 1.54)	1.49 (1.31, 1.69)
Other	0.72 (0.58, 0.88)	0.73 (0.62, 0.86)
Stage:		
T1N0M0	Referent	Referent
T2N0M0	2.71 (2.17, 3.39)	1.41 (1.23, 1.63)
T3N0M0	5.20 (4.36, 6.21)	2.10 (1.88, 2.35)
T4N0M0	16.88 (12.40, 22.98)	5.57 (4.30, 7.23)
N+M0	16.33 (12.89, 20.73)	5.50 (4.56, 6.63)
M+	33.23 (28.18, 39.18)	10.74 (9.69, 11.92)
Grade:		
1	Referent	Referent
2	1.16 (0.94, 1.42)	0.99 (0.88, 1.13)
3	1.97 (1.60, 2.43)	1.44 (1.26, 1.64)

Histopathology	Survival HR (95% CI)	
	Ca Specific	Overall
4	2.62 (2.08, 3.31)	1.93 (1.64, 2.27)