Published in final edited form as:

J Urol. 2009 November ; 182(5): 2132–2136. doi:10.1016/j.juro.2009.07.019.

PROGNOSTIC IMPACT OF HISTOLOGICAL SUBTYPE IN PATIENTS WITH SURGICALLY TREATED LOCALIZED RENAL CELL CARCINOMA

Patrick E. Teloken, R. Houston Thompson, Satish K Tickoo, Angel Cronin, Caroline Savage, Victor E. Reuter, and Paul Russo

Department of Surgery- Urology Service, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Purpose—Despite the clear demonstration that different histological subtypes of renal cell carcinoma (RCC) exhibit distinct pathogenesis and genetic alterations, the impact of histology on prognosis remains controversial. We evaluated our experience with tumor histology in patients with localized RCC.

Patients and Methods—We identified 1,863 patients with localized clear cell, papillary, or chromophobe RCC who were treated surgically between 1989 and 2006 at our tertiary care center. Cox proportional hazards regression models were used to evaluate the relationship between tumor histology and outcome—defined as metastasis or death from disease, adjusting for age, sex, operation type, ASA score, TNM stage, and tumor size

Results—Among 1,863 patients, 72% (n=1333) had clear cell histology, 17% (n=310) had papillary RCC, and 12% (n=220) had chromophobe RCC. The median follow-up for patients without an event was 3.4 years. Univariately, patients with clear cell histology had worse clinical outcomes: the 5-year probability of freedom from metastases or death from disease was 86% (95% CI: 84%, 88%), 95% (95% CI: 91%, 97%), and 92% (95% CI: 85%, 96%) for patients with clear cell, papillary, or chromophobe histology, respectively ($p < 0.001$). On multivariate analysis chromophobe and papillary histology were also significantly associated with better outcome (HR chromophobe 0.40 (95% CI 0.20, 0.80); HR papillary 0.62 (95% CI: 0.34, 1.14); $p=0.014$).

Conclusions—Clear cell histology seems to be independently associated with worse outcomes in patients undergoing surgical treatment for RCC even after controlling for widely accepted factors influencing prognosis.

Keywords

renal cell carcinoma; tumor histology; prognosis

INTRODUCTION

In 1997, an international consensus conference on renal cell carcinoma (RCC) sponsored by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) outlined recommendations for the classification of renal cell tumors¹. The UICC/AJCC adopted the classification system originally proposed at the Heidelberg conference in 1996. This classification identified 5 distinct malignant histological subtypes: conventional clear cell, papillary, chromophobe, collecting duct, and unclassified RCC². Despite the clear demonstration that different histological types of RCC exhibit different pathogenesis and genetic alterations³⁻⁵, RCC has routinely been managed surgically as a single entity. This can be, at least partially, explained by the contentious effect of histological subtype on prognosis⁶⁻⁸.

Proper characterization of prognostic factors in malignancy is paramount not only as an aid for clinical decision-making but also for accurate patient counseling. The most widely accepted factors independently affecting prognosis in patients with RCC are TNM stage, Fuhrman grade, tumor size, and patient performance status⁹⁻¹². Tumor necrosis on histology has been cited but its characterization and role are not as established¹³⁻¹⁵. Conversely, the impact of tumor histology remains controversial^{6-8, 16, 17}.

Cheville et al reviewed the Mayo Clinic experience demonstrating that patients with clear cell histology had a lower cancer-specific survival when compared to those with papillary or chromophobe histology⁶. Additionally, we previously reported outcomes with RCC suggesting that chromophobe histology was an independent predictor of greater freedom from disease progression⁷. More recent data from Patard et al suggested that tumor histology loses prognostic significance when factors such as TNM stage, Fuhrman grade and ECOG performance status are incorporated in a multivariate model⁸. These results are also supported by Amin et al who found that histology is not independently associated with disease-free survival among 405 patients after adjusting for TNM stage, necrosis and Fuhrman grade¹⁶. These discordant results suggest that further evaluation of RCC histology is warranted.

This study was undertaken in an effort to define whether RCC histological type has an independent impact on the prognosis in patients who receive surgical treatment.

MATERIALS AND METHODS

After obtaining institutional board review approval, we reviewed the Memorial Sloan-Kettering Cancer Center nephrectomy database. This database is prospectively maintained and includes all patients treated surgically for a renal mass at our institution beginning in 1989. From this database, we identified 1,863 patients with single, localized, clear cell, papillary, or chromophobe RCC who underwent partial or radical nephrectomy at our institution between 1989 and 2006. A lymph node dissection was performed when there was radiographic evidence of lymphadenopathy or palpable lymphadenopathy was identified at time of surgery. Patients with collecting duct and unclassified RCC were excluded from this study, as the small number of patients with these entities would preclude us from performing

robust statistical analysis. Patients with multiple tumors were excluded because it has not been clearly established whether the prognosis of patients with hereditary syndromes is the same of those with sporadic RCC, and being Von Hippel-Lindau the most common of these syndromes, the inclusion of such patients could skew patients with clear cell histology to a worse outcome.

Histological subtype was assigned in accordance with the Heidelberg classification¹. TNM stage was reported in accordance with the 2002 AJCC version of the tumor, node, metastasis staging system¹⁸. Since the application of the Fuhrman grading system for papillary and chromophobe RCCs remains controversial, and as these subtypes are not routinely assigned such a nuclear grade at our institution, nuclear grade was primarily only available for clear cell RCC.

Follow-up was determined in part by the pathologic findings. In general, patients were followed postoperatively at 6 months intervals with a history and physical exam, comprehensive metabolic panel, abdominal CT or ultrasound and a chest x-ray or CT. If a patient remained disease free for 3 years, follow-up frequency was often changed to yearly.

Statistical Methods

Kaplan Meier curves stratified by tumor histology were created and differences in event-free survival between tumor histology were tested using the logrank test. Cox proportional hazards regression was used to evaluate the relationship between tumor histology and event-free survival; defined as the time from surgery to the earlier of metastasis or disease specific death, controlling for: age, sex, operation type and American Society of Anesthesiologists Physical Status Classification System (ASA) score (3/4 vs. 1/2); TNM stage (1–4), and tumor size. Although Fuhrman grading is not routinely assigned for non-clear cell RCC at our institution, our pre-specified analysis was to include it as a covariate. However, simply excluding cases with missing Fuhrman grade would have provided a different distribution of histological subtype than what we experienced, which we decided was unsound since histology was our primary interest. Instead, we decided to exclude Fuhrman grade from the multivariate model, and perform a sensitivity analysis with Fuhrman grade as covariate using a value of “missing” in an effort to not exclude a majority of non-clear cell patients. The results from this analysis (not shown) support the findings presented below where patients with papillary or chromophobe RCC were less likely to experience an event than patients with clear cell histology. Statistical analyses were conducted using Stata 10.0 (StataCorp LP, College Station, TX).

RESULTS

Among the 1,863 patients, 72% (n=1333) had clear cell histology, 12% (n=220) had chromophobe and 17% (n=310) had papillary RCC. Patients with chromophobe histology tended to be younger and have slightly larger tumors (Table 1). Across all histological subtypes most patients were male, had TNM Stage 1 disease, were classified as ASA 2 and lymph node involvement was infrequent.

Overall there were 187 events, defined as the first occurrence of either metastasis or disease specific death; 161, 17, and 9 events occurred among patients with clear cell, papillary, and chromophobe histologies, respectively. The median follow-up time for patients without an event was 3.4 years (interquartile range 1.3–6.5 years). Figure 1 demonstrates event-free probability by tumor histology. Patients with clear cell histology were significantly more likely to experience an event: the 5-year event-free survival probability was 86% (95% CI: 84%, 88%), 95% (95% CI: 91%, 97%), and 92% (95% CI: 85%, 96%) for patients with clear cell, papillary, or chromophobe tumor histology, respectively ($p < 0.001$). In pairwise comparisons, patients with clear cell histology showed significantly worse survival than chromophobe ($p=0.0024$) and papillary ($p=0.0019$). We did not find evidence of a statistically significant difference in the survival of patients with chromophobe as compared to papillary tumors ($p=0.6$).

The results of the multivariable analyses are demonstrated in Table 2. Histology remained significantly associated with having an event (global p -value for difference in histology $p=0.014$). Chromophobe and papillary tumors were associated with a better outcome (HR chromophobe 0.40 (95% CI 0.20, 0.80) $p=0.010$; HR papillary 0.62 (95% CI: 0.34, 1.14; $p=0.12$) than clear cell tumors. Although the difference between clear cell and papillary tumors did not reach statistical significance, these data support the hypothesis that patients with clear cell tumors tend to fare worse than those with papillary tumors.

DISCUSSION

In the current analysis of 1,863 patients, our results suggest that clear cell histology is independently associated with a worse prognosis. Even after controlling for age, sex, ASA score, tumor size and TNM stage, patients with papillary and chromophobe histologies were less likely to experience an adverse outcome, defined as development of new metastases or cancer-specific death, than those with clear cell histology.

Despite the discordant results currently present in the literature regarding prognostic impact of RCC histology, there is little doubt that RCC tumors represent distinct entities, as different genetic alterations, morphological appearances, cells of origin and responses to immunotherapy and targeted therapies have been observed^{3–5, 19}. Therefore, it is tempting to believe that these different subtypes of RCC behave in diverse manners; and this has led us and others to investigate whether histological subtype has any impact on prognosis.

The largest study to date evaluating prognostic impact of RCC histology represents a multi-institutional collaboration by Patard et al, who performed a retrospective study comprising 4063 patients from 8 institutions, and found that tumor histology had prognostic significance in univariate analysis⁸. However, such effect was not observed on a multivariate model including TNM stage, Fuhrman grade and ECOG performance status. Importantly, there was no centralized slide review in this study and therefore misclassifications cannot be excluded. A recent study showed that the correlation between original and reviewed histological classification is suboptimal²⁰. Additionally, nearly 25% of patients in this multi-institutional analysis had distant disease, and therefore this sample is not entirely comparable to ours. Furthermore, it is not representative of the stage in which most patients present currently.

The second largest study evaluating histology is a single institution experience at the Mayo Clinic which encompasses 2528 patients who underwent radical nephrectomy between 1970 and 2000 for unilateral, sporadic RCC⁶. All slides were reviewed by a single urologic pathologist. Patients with clear cell RCC had significantly lower cancer-specific survival when compared with those with papillary or chromophobe histology, even after stratification by pathologic stage and nuclear grading. Despite differences in patient population and outcome used, these results are in accordance with our current findings.

The use of Fuhrman's nuclear grading system is well established for clear cell RCC, but its role in papillary and chromophobe RCC is controversial²¹. While some studies have used original Fuhrman's grading system^{8, 16}, Cheville et al⁶ applied a 4-tiered scheme modeled after Fuhrman's but with standardized definitions, which had been shown to outperform non-standardized nuclear grade on the prediction of disease-specific survival²². We believe that the routine assignment of nuclear grades to non-clear cell RCC is inadequate, and therefore do not practice it at our institution. For that reason, such parameter was not incorporated in the presented multivariable analysis.

This study is not without limitations. Our data represent a retrospective analysis of a database from a single institution and therefore, our results are subject to the inherent biases that accommodate such observations. We were unable to adjust for ECOG performance status, since this variable is not routinely collected in our database; however, we adjusted for ASA score which served as a predetermined correction for comorbidity profile. Histological subtype was assigned at the time of the surgery and was not re-reviewed for this analysis as the urologic pathologists at our institution, a tertiary care cancer center, are accustomed to evaluating malignancy.

CONCLUSIONS

Clear cell histology seems to be independently associated with worse outcomes in patients undergoing surgical treatment for localized RCC, even after controlling for widely accepted factors influencing prognosis.

Key of Definitions for Abbreviations

RCC	renal cell carcinoma
ASA	American Society of Anesthesiologists Physical Status Classification System
HR	hazard ratio

References

1. Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CS, Delahunt B, Eble JN, Fleming S, Ljungberg B, Medeiros LJ, Moch H, Reuter VE, Ritz E, Roos G, Schmidt D, Srigley JR, Storkel S, van den Berg E, Zbar B. The Heidelberg classification of renal cell tumours. *J Pathol.* 1997 Oct; 183(2):131–3. [PubMed: 9390023]
2. Reuter VE. The pathology of renal epithelial neoplasms. *Semin Oncol.* 2006 Oct; 33(5):534–43. [PubMed: 17045082]

3. Schuetz AN, Yin-Goen Q, Amin MB, Moreno CS, Cohen C, Hornsby CD, Yang WL, Petros JA, Issa MM, Pattaras JG, Ogan K, Marshall FF, Young AN. Molecular classification of renal tumors by gene expression profiling. *J Mol Diagn*. 2005 May; 7(2):206–18. [PubMed: 15858144]
4. Furge KA, Lucas KA, Takahashi M, Sugimura J, Kort EJ, Kanayama HO, Kagawa S, Hoekstra P, Curry J, Yang XJ, Teh BT. Robust classification of renal cell carcinoma based on gene expression data and predicted cytogenetic profiles. *Cancer Res*. 2004 Jun 15; 64(12):4117–21. [PubMed: 15205321]
5. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med*. 2005 Dec 8; 353(23):2477–90. [PubMed: 16339096]
6. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol*. 2003 May; 27(5):612–24. [PubMed: 12717246]
7. Beck SD, Patel MI, Snyder ME, Kattan MW, Motzer RJ, Reuter VE, Russo P. Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. *Ann Surg Oncol*. 2004 Jan; 11(1):71–7. [PubMed: 14699037]
8. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman A, De La Taille A, Tostain J, Artibani W, Abbou CC, Lobel B, Guille F, Chopin DK, Mulders PF, Wood CG, Swanson DA, Figlin RA, Belldegrun AS, Pantuck AJ. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol*. 2005 Apr 20; 23(12):2763–71. [PubMed: 15837991]
9. Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognostic nomogram for renal cell carcinoma. *J Urol*. 2001 Jul; 166(1):63–7. [PubMed: 11435824]
10. Patard JJ, Kim HL, Lam JS, Dorey FJ, Pantuck AJ, Zisman A, Ficarra V, Han KR, Cindolo L, De La Taille A, Tostain J, Artibani W, Dinney CP, Wood CG, Swanson DA, Abbou CC, Lobel B, Mulders PF, Chopin DK, Figlin RA, Belldegrun AS. Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *J Clin Oncol*. 2004 Aug 15; 22(16):3316–22. [PubMed: 15310775]
11. Shuch BM, Lam JS, Belldegrun AS, Figlin RA. Prognostic factors in renal cell carcinoma. *Semin Oncol*. 2006 Oct; 33(5):563–75. [PubMed: 17045085]
12. Raj GV, Thompson RH, Leibovich BC, Blute ML, Russo P, Kattan MW. Preoperative nomogram predicting 12-year probability of metastatic renal cancer. *J Urol*. 2008 Jun; 179(6):2146–51. discussion 51. [PubMed: 18423735]
13. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*. 2002 Dec; 168(6):2395–400. [PubMed: 12441925]
14. Sengupta S, Lohse CM, Leibovich BC, Frank I, Thompson RH, Webster WS, Zincke H, Blute ML, Cheville JC, Kwon ED. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. *Cancer*. 2005 Aug 1; 104(3):511–20. [PubMed: 15973740]
15. Lam JS, Shvarts O, Said JW, Pantuck AJ, Seligson DB, Aldridge ME, Bui MH, Liu X, Horvath S, Figlin RA, Belldegrun AS. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. *Cancer*. 2005 Jun 15; 103(12):2517–25. [PubMed: 15880379]
16. Amin MB, Tamboli P, Javidan J, Stricker H, de-Peralta Venturina M, Deshpande A, Menon M. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. *Am J Surg Pathol*. 2002 Mar; 26(3):281–91. [PubMed: 11859199]
17. Delahunt B, Bethwaite PB, Nacey JN. Outcome prediction for renal cell carcinoma: evaluation of prognostic factors for tumours divided according to histological subtype. *Pathology*. 2007 Oct; 39(5):459–65. [PubMed: 17886093]
18. Greene, FL.; Page, DL.; Fleming, ID.; Fritz, AG.; Balch, CM.; Haller, DG.; Morrow, M. *AJCC Cancer Staging Manual*. 6. New York, NY: Springer Press; 2002.
19. Haas NB, Uzzo RG. Targeted therapies for kidney cancer in urologic practice. *Urol Oncol*. 2007 Sep-Oct; 25(5):420–32. [PubMed: 17826664]

20. Ficarra V, Martignoni G, Galfano A, Novara G, Gobbo S, Brunelli M, Pea M, Zattoni F, Artibani W. Prognostic role of the histologic subtypes of renal cell carcinoma after slide revision. *Eur Urol*. 2006 Oct; 50(4):786–93. discussion 93–4. [PubMed: 16697521]
21. Tickoo SK, Gopalan A. Pathologic features of renal cortical tumors. *Urol Clin North Am*. 2008; 35(4):551–61. [PubMed: 18992609]
22. Lohse CM, Blute ML, Zincke H, Weaver AL, Cheville JC. Comparison of standardized and nonstandardized nuclear grade of renal cell carcinoma to predict outcome among 2,042 patients. *Am J Clin Pathol*. 2002; 118(6):877–86. [PubMed: 12472281]

Number at risk				
clear cell 1333	464	130	17	
chromophobe 220	63	16	4	
papillary 310	100	28	6	

Figure 1.

Kaplan-Meier curve for patients with kidney cancer, stratified by tumor histology: clear cell (solid line), papillary (short dash), chromophobe (long dash).

Event-free survival was defined as the time from surgery to the earlier of metastasis or disease specific death

Table 1

Patient characteristics.

	Clear Cell n=1333	Chromophobe n=220	Papillary n=310	P value
Age at surgery (years)	62 (53, 70)	59 (49, 67)	64 (56, 71)	<0.001
Tumor diameter, cm	4.1 (2.7, 6.8)	4.5 (3, 8.5)	3.5 (2.5, 5.3)	
Male	836 (63%)	120 (55%)	236 (76%)	<0.001
Radical nephrectomy (vs. partial)	871 (65%)	121 (55%)	141 (45%)	<0.001
Lymph node involvement	23 (6%)	4 (5%)	7 (11%)	0.3
Year of Surgery				0.003
Before 1995	228 (17%)	23 (10%)	52 (17%)	
1995 – 2000	346 (26%)	47 (21%)	70 (23%)	
2000 – 2006	759 (57%)	150 (68%)	188 (61%)	
TNM Stage				<0.001
1	869 (65%)	133 (60%)	235 (76%)	
2	94 (7%)	42 (19%)	29 (9%)	
3	346 (26%)	43 (20%)	41 (13%)	
4	24 (2%)	2 (1%)	5 (2%)	
ASA Score				0.004
1	76 (6%)	22 (10%)	13 (4%)	
2	667 (50%)	131 (60%)	150 (48%)	
3	437 (33%)	56 (25%)	106 (34%)	
4	8 (1%)	2 (1%)	0 (0%)	
Missing	145 (11%)	9 (4%)	41 (13%)	

All values are median (interquartile range) or frequency (proportion).

Table 2

Multivariable Cox model for outcome of the earlier of metastasis or death from disease. N=1668

Predictor	Hazard Ratio	95% CI	P value
Histological subtype			
Clear Cell	Ref	Ref	
Chromophobe	0.40	0.20, 0.80	0.01
Papillary	0.62	0.34, 1.14	0.12
Age at surgery (per 10 years)	1.04	0.899, 1.21	0.6
Male	1.17	0.826, 1.66	0.4
Nephrectomy type			
Partial	Ref	Ref	
Radical	1.76	0.982, 3.17	0.058
Tumor diameter (mm)	1.14	1.08, 1.20	<0.0005
ASA Score ≥ 3	1.28	0.889, 1.84	0.19
TNM Stage			<0.001
1	Ref	Ref	
2	1.31	0.700, 2.45	
3	1.66	1.05, 2.64	
4	8.39	3.89, 18.1	

CI: confidence interval