VOLUME 23 · NUMBER 12 · APRIL 20 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Value of Histologic Subtypes in Renal Cell Carcinoma: A Multicenter Experience

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Submitted July 12, 2004; accepted January 12, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2312-2763/$20.00

DOI: 10.1200/JCO.2005.07.055

ABSTRACT

Purpose
To analyze to what extent histologic subtype is of prognostic importance in renal cell carcinoma based on a large, international, multicenter experience.

Patients and Methods
Four thousand sixty-three patients from eight international centers were included in this retrospective study. Histologic subtype (1997 International Union Against Cancer [UICC] criteria of tumor response), age, sex, TNM stage, Fuhrman grade, tumor size, Eastern Cooperative Oncology Goup performance status (ECOG PS), and overall survival were determined in all cases. The prognostic values of clear cell, papillary, and chromophobe histologic features were assessed by uni- and multivariate analysis using the Kaplan-Meier method and Cox model, respectively.

Results
Clear cell, papillary, and chromophobe carcinomas accounted for 3,564 (87.7%), 396 (9.7%) and 103 (2.5%) cases, respectively. In univariate analysis, a trend toward a better survival was observed when clear cell, papillary, and chromophobe histologies were considered prognostic categories (log-rank $P = .0007$). However, in multivariate analysis, TNM stage, Fuhrman grade and ECOG PS, but not histology, were retained as independent prognostic variables ($P < .001$).

Conclusion
The stratification in three main renal cell carcinoma histologic subtypes as defined by the 1997 UICC–American Joint Committee on Cancer consensus should not be considered a major prognostic variable comparable to TNM stage, Fuhrman grade and ECOG PS.

J Clin Oncol 23:2763-2771. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of cancers in adults.[1] Although TNM stage, Fuhrman grade, and Eastern Cooperative Oncology Group performance status (ECOG PS) are the most widely recognized prognostic factors in RCC, research continues to determine strong and easily available prognostic parameters that could help to classify patients in groups with different risks of death as a result of renal cancer.

Currently, RCC histologic subtypes are classified according to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) recommendations.[2] This classification is based on the Heidelberg classification system, [3] which categorizes RCCs as clear cell, papillary, chromophobe, collecting duct, and unclassified RCC subtypes. Recent studies[4,5] have suggested that stratification by histologic subtype could lend prognostic value. However, there is a predominance of

clear cell RCCs in most series, and conclusions about a better survival in papillary and chromophobe tumors are questionable due to the small numbers of tumors in the two former groups. Series with small number of papillary and chromophobe tumors are limited in their ability to provide information regarding the potential independent prognostic value of histologic subtype compared with stage and grade. Recently, a large single-center series including 2,385 patients[6] confirmed the prognostic value of a histology-based classification even when adjusted for stage and grade. Our objective was to analyze to what extent these previous results were verified when histologic subtype was stratified by tumor stage, grade and ECOG PS in a large multicenter study including 4,063 patients from eight international centers.

PATIENTS AND METHODS

Patients

The study included patients from eight international academic centers: Rennes University Hospital, Rennes; North Hospital, Centre Hospitalier Universitaire (CHU), Saint Etienne; Créteil, France; Medical School of University Frederico II, Naples; University of Verona, Verona, Italy; University of California, Los Angeles, Los Angeles, CA; The University of Texas M.D. Anderson Cancer Center, Houston, TX; and University Medical Center, Nijmegen, the Netherlands. Patient records were extracted from each institutional database. Data collected from each patient included TNM stage, Fuhrman grade, ECOG PS, survival, and histologic subtype. Other variables analyzed included age, sex, and tumor size. All data were labeled with their respective institution and pooled.

Patients included in the study were staged preoperatively with computed tomography (CT) of the abdomen and pelvis, chest CT or chest x-ray, serum electrolytes, and liver function tests. Postoperative follow-up was according to protocols established at each institution.

Tumor stage was determined according to the 1997 UICC TNM classification of renal tumors.[7] Tumor histology was classified according to the Heidelberg classification,[3] and tumors were graded according to the Fuhrman grading scheme[8] by the pathologists at each of the eight institutions. ECOG PS was assigned for each patient according to the original criteria set forth by Oken et al.[9] Of the 4,204 patient records resulting from the fusion of the eight databases, 16 (0.4%), 31 (0.7%) and 94 (2.2%) histologies were labeled as "collecting duct carcinomas," "unclassified tumors," and "missing values," respectively. Because our objective was to correlate histologic groups to stage, grade, ECOG PS, and survival, we decided to focus on the three main histologic subtypes and to delete other records (141 exclusions). Patients were diagnosed between 1984 and 2001.

Histologic Features

Three subtypes of RCCs were reported in our study: conventional, papillary, and chromophobe.

In conventional clear cell RCCs, the neoplastic cells were characterized by a clear cytoplasm surrounded by a distinct cell membrane, but eosinophilic cells could be predominant. Various architectures were described. Usually tumors had an alveolar or acinar pattern. There was a network of delicate interconnecting capillaries or sinusoidal stroma supported by a network of thin reticulin fibers.

Papillary RCC consisted predominantly of papillary or tubulopapillary architecture. The neoplastic cells were cuboidal or columnar with eosinophilic granular cytoplasm, but foci of clear cells could be observed. Usually fine fibrovascular stalks were present. The stroma contained plasma cells, lymphocytes, neutrophils, and macrophages with focal or diffuse accumulation of foamy macrophages in the stromal spaces. Psammoma bodies were identifiable.

Chromophobe RCCs usually had a solid growth pattern, but could show some foci of tubular, tubuloalveolar, and cribriform areas. Neoplastic cells showed an abundant and pale or eosinophilic cytoplasm. A narrow zone of cytoplasmic condensation was found frequently along the cell periphery. The nuclei were central, and some were binucleated. The cytoplasm was slighty positive for Periodic Acid Schiff and strongly positive for Hale's acid iron colloid stain. In all of these tumors, areas of necrosis, hemorrhage, and fibrosis could be identified.

Statistical Analysis

Survival was determined from the date of surgery to the date of death from cancer or last follow-up. χ^2 (Fisher's exact test) and Student t tests were used to compare the qualitative and quantitative variables, respectively. For the purpose of survival analysis, histologic subtype was considered a single categoric variable. Estimations of the cumulative survival distributions were calculated according to the Kaplan-Meier method, and the log-rank test was used to compare groups. The Cox proportional hazards model was used for multivariate analysis. All P values were two sided, and a $P < .05$ was considered significant. All data analysis was processed through the SPSS statistical software version 10.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient and tumor characteristics are given in Table 1. Three thousand five hundred sixty-four tumors (87.7%), 396 (9.7%) and 103 (2.6%) were classified as conventional clear cell, papillary, and chromophobe carcinoma, respectively. Among centers, clear cell features were observed in 635 (93.4%), 198 (96.1%), 263 (86.5%), 454 (86.1%), 583 (86.4%), 580 (79.6%), 596 (91.7%), and 255 (87.6%) cases, respectively. Papillary tumors were diagnosed in 31 (4.6%), three (1.5%), 24 (7.9%), 57 (10.8%), 75 (11.1%), 124 (17%), 50 (7.7%), and 32 (11%) cases, respectively. Chromophobe carcinoma accounted for 14 (2.1%), five (2.4%), 17 (5.6%), 17 (3.2%), 17 (2.5%), 25 (3.4%), four (0.6%) and four (1.4%) cases, respectively.

Tumors were classified as localized and distant disease in 3,056 (75.2%) and 1,007 (24.8%) cases, respectively. The median survival time was 19 months for 1,398 patients who died during follow-up. The median follow-up for 2,665 surviving patients was 43 months.

An association was found among histologic subtype, tumor size, sex, TNM stage and grade (Table 2). Clear cell,

Table 1. Patient Demographics and Tumor Characteristics

	No.	%
Age, years		
Median	61	
Range	10-93	
Sex, %		
Male	67.1	
Female	32.9	
Tumor size, cm		
Median	6.0	
Range	0.4-25	
TNM stage		
1	1,611	39.7
2	509	12.5
3	1,059	26.1
4	884	21.8
Fuhrman grade		
G1	830	20.5
G2	1,493	36.7
G3	1,398	34.4
G4	342	8.4
ECOG PS		
≥ 1	1,383	34.0
Tumors		
Localized	3,056	75.2
Metastatic	1,007	24.8
Histology		
Clear cell	3,564	87.7
Papillary	396	9.7
Chromophobe	103	2.5
Deaths	1,398	34.4

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

papillary, and chromophobe carcinomas were classified as stage I to II in 50.3%, 62.9%, and 74.8% of the cases, respectively ($P < .001$). The association between stage and histologic subtype was particularly evident when considering distant metastasis that occurred in 765 (21.5%), 59 (14.9%), and 3 (2.9%) patients with clear cell, papillary and chromophobe tumors, respectively ($P < .001$). Similarly, Fuhrman grades 1 and 2 were found in 55.8%, 66.9%, and 68% of the three histologic subtypes, respectively ($P < .001$). Mean tumor size tended to be lower in papillary tumors compared to clear cell and chromophobe tumors. (6.30 ± 3.6 cm *v* 7.1 ± 3.8 and 6.8 ± 4.2 cm; $P < .001$). A male predominance was observed mainly in papillary (75%) and in clear cell tumors (66.5%), whereas it was less pronounced in chromobophe tumors (55.3%). Conversely, no association was found between histologic subtype and ECOG PS.

Five-year survival rates for localized clear cell, papillary, and chromophobe carcinoma were 73.2%, 79.4%, and 87.9% respectively. Among the 3,056 patients with localized disease, patients with chromophobe carcinoma (n = 97; 3.2%) were found to have a better outcome compared with patients with papillary or clear cell tumors (log-rank $P = .03$; Fig 1). Only six patients with chromophobe carcinomas had distant disease (three N1to N2, three M1), and they were not considered for survival analysis in metastatic patients. One thousand one patients with nonlocalized clear cell (n = 919; 91.8%) or papillary carcinomas (n = 82; 8.2%) were available for survival analysis. No survival difference was observed between these two groups (log-rank $P = .6$; Fig 2). Five-year survival rates were 10.5% and 10.3% for the two groups, respectively.

When histologic subtypes were adjusted to TNM stage, no significant survival difference remained among the three histologic groups (log-rank $P = .81$ and .16 for stages I to II and III to IV, respectively; Fig 3). Similarly, when stratifying histology according to tumor grade the three histologic groups had the same outcome for grade 1 and 2 tumors (log-rank $P = .3$; Fig 4), whereas chromophobe carcinoma had a better outcome in grade 3 and 4 tumors (log-rank $P = .02$; Fig 4). When stratifying histology by ECOG PS, a trend toward a better outcome was found for chromophobe carcinoma compared to papillary and clear cell histologies in both PS 0 and PS ≥ 1 groups (log-rank $P = .02$ and .06, respectively; Fig 5). Finally when adjusting histologic subtype to University of California, Los Angeles, Integrated Staging System (UISS) level,[10] which is a prognostic system that simultaneously combines TNM stage, Fuhrman grade, and ECOG PS, no significant survival difference was found among the three main histologic types (Fig 6).

Finally we considered histologic subtype as a single categoric variable for univariate and multivariate analysis. Overall, a trend toward a better outcome was observed when histologies were identified as clear cell, papillary, and chromophobe, respectively. Median survival times were 119 months, 153 months and not reached for the three categories, respectively (log-rank $P = .0007$; Table 3). In both overall and localized disease, only TNM stage, Fuhrman grade, and ECOG PS remained significant for predicting survival in multivariate analysis (Table 4).

DISCUSSION

TNM stage, nuclear grade, and ECOG PS are the three most recognized prognostic factors in RCC. Currently, efforts are being made to identify new prognostic variables that could help stratify patients into risk groups in addition to the usual prognostic parameters. In this large multicenter study including 4,063 patients from eight international centers, we tried to assess whether histologic subtype could be retained as a powerful independent prognostic parameter as well as TNM stage, Fuhrman grade, or ECOG PS in both localized and metastatic RCC tumors. From our study, it is clear that although histologic subtype is correlated to TNM stage and grade and is significant as a single variable, the

Table 2. Relationship Between Clinical and Pathologic Variables and Histologic Subtype in Patients With Renal Tumors (N = 4,063)

	Histologic Subtype			
	Clear Cell Carcinomas	Papillary Carcinomas	Chromophobe Carcinomas	*P*
Patients				
No.	3,564	396	103	
%	87.7	9.7	2.5	
Variable				
Age, years				.81 (NS)
Mean	60.0	59.6	58.4	
SD	12.0	13.3	15.0	
Tumor size, cm				.001
Mean	7.1	6.3	6.8	
SD	3.8	3.6	4.2	
Sex, male				.001
No.	2,371	297	57	
%	66.5	75	55.3	
TNM stage				
1-2				.0001
No.	1,794	249	77	
%	50.3	62.9	74.8	
3-4				
No.	1,770	147	26	
%	49.7	37.1	25.2	
Fuhrman grade				
1-2				.0001
No.	1,988	265	70	
%	55.8	66.9	68	
3-4				
No.	1,576	131	33	
%	44.2	33.1	32	
ECOG PS, ≥ 1				.138 (NS)
No.	1,230	119	36	
%	34.5	29.5	35.0	

Abbreviations: SD, standard deviation; NS, not significant; ECOG PS, Eastern Cooperative Oncology Group performance status.

histologic subtype was removed from the multivariate model by TNM stage, tumor grade, and ECOG PS. Papillary and clear cell tumors were not found to have a significantly different outcome in distant disease. When adjusted to TNM stage and grade, chromophobe carcinoma was found to have a better outcome when compared with other subtypes only in the case of high-grade tumors.

Since the first report[11] suggesting a favorable outcome for patients with papillary tumors compared with clear cell histology, significant advances have been made in morphologic and genetic characterization of papillary tumors, which are now recognized as a well-defined histologic entity.[12] The frequency found in our study (9.7%) is consistent with what is generally reported (10% to 15%).[13] We also confirmed the tendency for papillary tumors to present at an earlier stage and grade when compared with clear cell tumors.[5,12,13] Similar to Cheville et al,[6] we found a close correlation between papillary and clear cell tumors with TNM stage, Fuhrman grade, and tumor size. We did not perform a specific search for prognostic factors in papillary tumors; however, most studies agree on the prognostic value of TNM stage, nuclear grade, and sarcomatoid component but not tumor necrosis[4,6,12] in this subset of patients. Finally, our reported 79.4% overall 5-year survival rate is consistent with the 82% to 90% survival rate that is generally reported.[12] However, some authors have reported less favorable outcomes in papillary tumors.[14] Recently, two distinct papillary histologic profiles have been described (type 1 and 2) which possess distinct clinical behaviors. Mejean et al[15] reported 5-year survival rates of 95% and 66% in type 1 and 2 papillary tumors respectively.

Chromophobe RCC, first described by Thoenes et al,[16] also has distinguishable clinicopathologic and molecular biologic features.[17] Our reported chromophobe carcinoma frequency (2.5%) is slightly less than previously published reports in surgical series (4% to 10%).[4-6,13,18] However we found an 88% 5-year survival rate, which is consistent

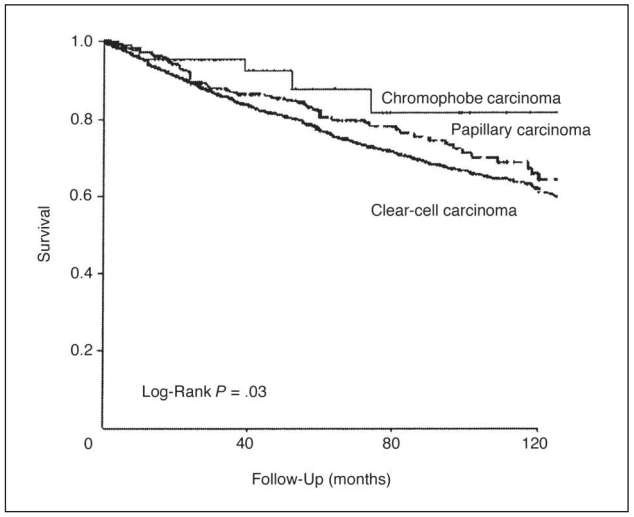

Fig 1. Survival in 3,056 patients with localized renal tumors according to histologic subtype.

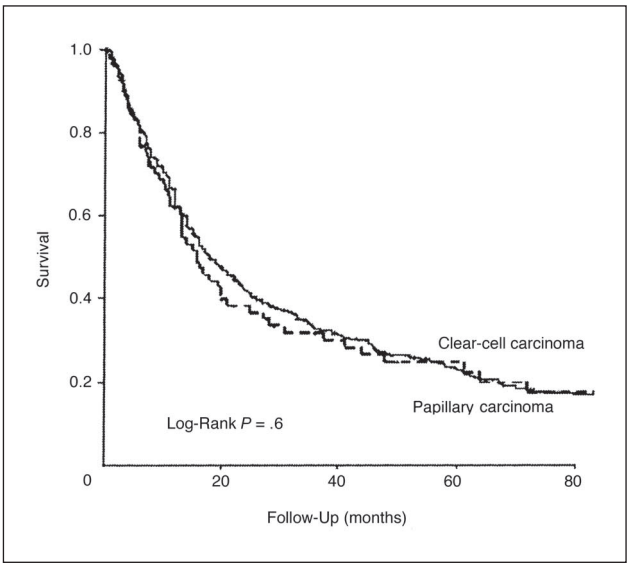

Fig 2. Survival in 1,001 patients with metastatic renal tumors according to histologic subtype.

with the excellent outcome that is generally reported in most series with 5-year survival probability ranging from 80% to 100%.[5,6,13]

Five previous reports including a total of 4,621 patients have focused on the prognostic value of the histologic subtype classification derived from the 1997 UICC/AJCC consensus. Ljungberg et al[14] first reported significantly different outcomes among histologic subtypes for 186 patients including 145 (78%) with conventional clear cell, 25 (13%) with papillary, and 12 (7%) with chromophobe carcinoma. The 5-year cancer-specific survival rates for patients with conventional, papillary, and chromophobe RCC were 43%, 61%, and 91%, respectively. Moch et al[4] reported a better outcome for chromophobe carcinoma compared to clear cell tumors ($P = .05$) in 588 patients including 487 (83%) with clear cell, 64 (11%) with papillary, and 31 (5%) with chromophobe carcinoma, but showed no difference between papillary and chromophobe tumors, as well as no statistical significant stratification among the three groups ($P = .1$). Amin et al[5] reported 76%, 86% and 100% 5-year

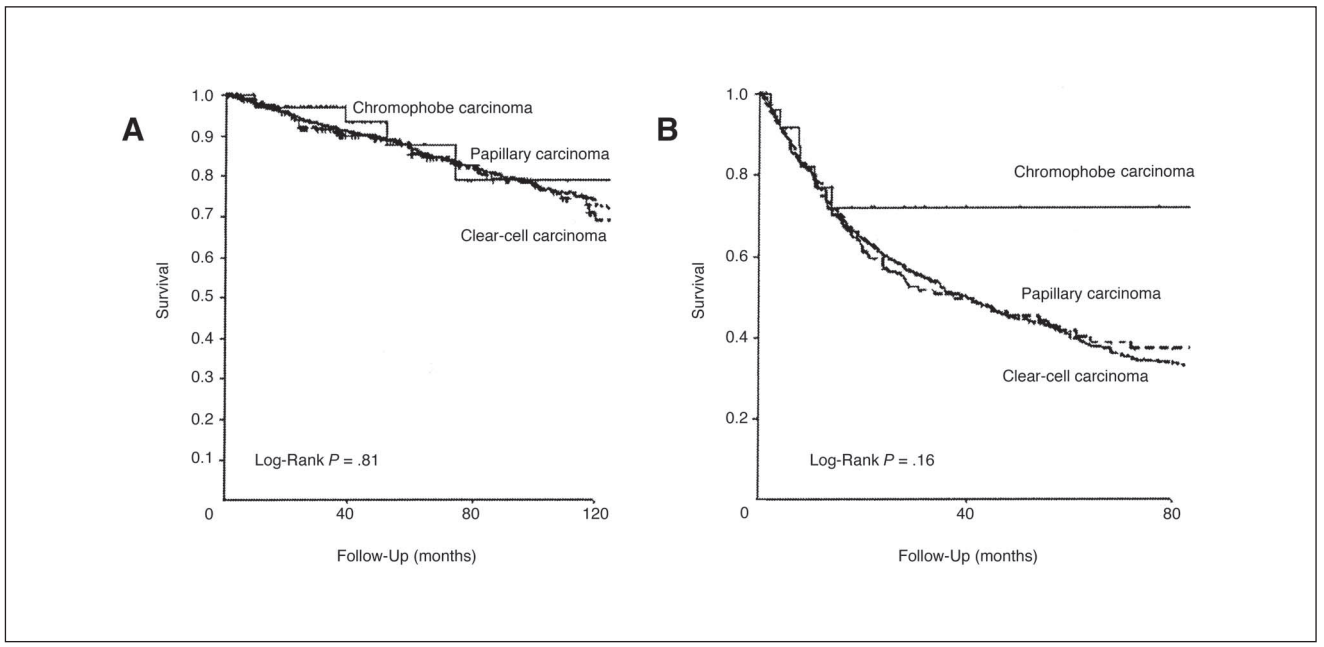

Fig 3. Survival in 4,063 patients with renal tumors according to histologic subtype and TNM stage. (A) TNM stage I to II. (B) TNM stage III to IV.

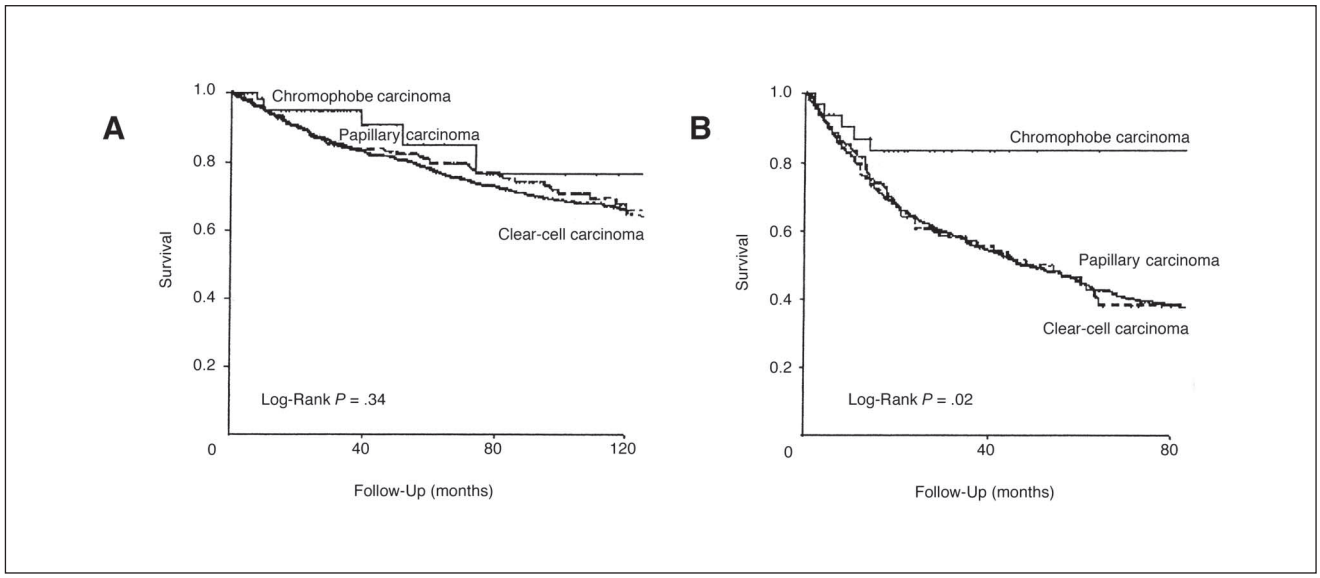

Fig 4. Survival in 4,063 patients with renal tumors according to histologic subtype and Fuhrman grade. (A) Fuhrman grade 1 to 2. (B) Furhman grade 3 to 4.

cancer-specific survival rates, respectively, in 377 patients including 255 (63%) with clear cell, 75 (18.5%) with papillary, and 24 (5.9%) with chromophobe tumors. Although significant in univariate analysis, the histologic subtype was not retained in multivariate analysis. Independent variables that were significantly associated with survival in this study were TNM stage, nuclear grade, and tumor necrosis. Cheville et al[6] found 5-year survival rates of 68.9%, 87.4%, and 86.7%, respectively, in 2,385 patients including 1,985 (83.2%) with clear cell, 270 (11.3%) with papillary, and 102 (4.3%) with chromophobe carcinoma. Patients with clear cell tumors had a significantly poorer outcome compared with patients with tumors of the two other types ($P < .001$) even when adjusted to TNM stage and grade. However, no survival difference was observed between papillary and chromophobe tumors ($P = .9$). Beck et al[13] found 5-year survival rates of 73.3%, 81.7%, and 80.1%, respectively, in a 1,057-patient series with localized disease including 784 (75%) with clear cell, 157 (15%) with papillary, and 106 (10%) with chromophobe tumors. Patients with clear cell tumors had a significantly worse survival compared with patients with papillary ($P = .015$) and chromophobe carcinoma

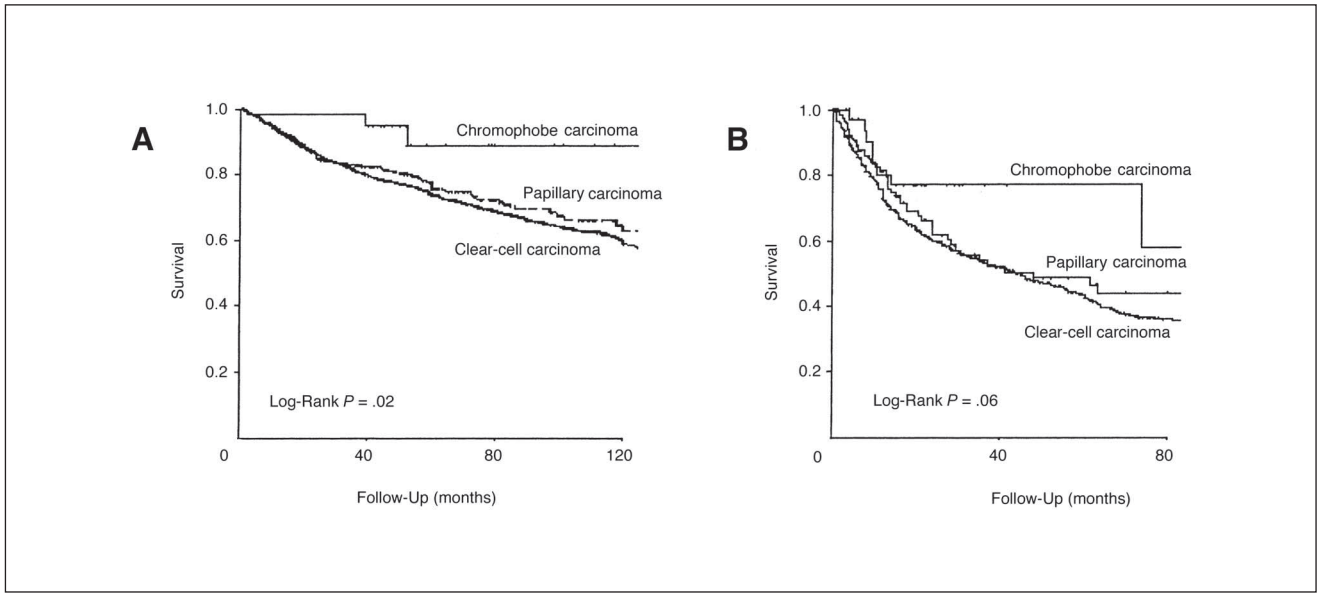

Fig 5. Survival in 4063 patients with renal tumors according to histologic subtype and Eastern Cooperative Oncology Group performance status (ECOG PS). (A) ECOG PS = 0. (B) ECOG PS ≥ 1.

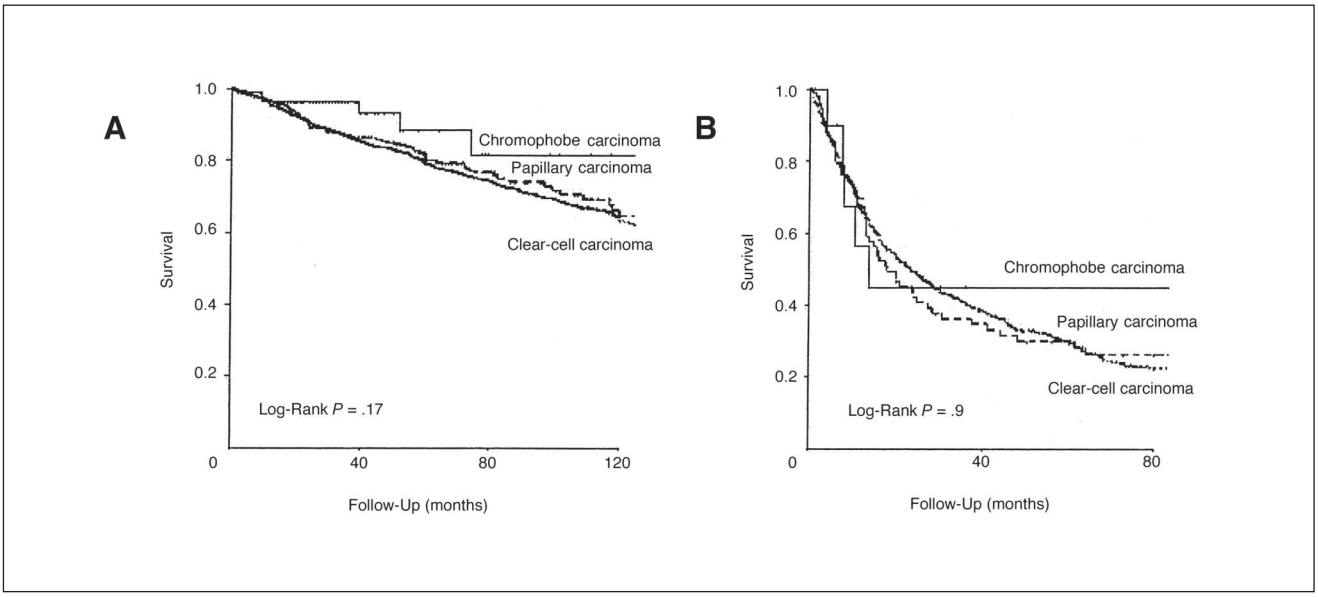

Fig 6. Survival in 4,063 patients with renal tumors according to histologic subtype and University of California, Los Angeles, Integrated Staging System (UISS) classification. (A) UISS 1 to 2. (B) UISS 3 to 5.

($P = .013$). However, patients with papillary and chromophobe carcinoma did not have a significantly different outcome ($P = .6$). In summary, only two previous studies have conducted a multivariate analysis to determine whether histologic subtype could be retained as an independent prognostic variable. Amin et al failed to demonstrate such an independent prognostic value for the histologic type. Beck showed that the only combination that could be retained in the multivariate model was chromophobe versus clear cell histology, whereas papillary feature was not retained. In the former study, it should be noted that nuclear grade was not included in the Cox model. Thus, it is not certain that the chromophobe feature would have been retained as an independent prognostic variable if grade had been included. Although associated in most studies with stage and grade and providing a significant survival stratification in univariate analysis, there is no strong evidence from all these studies that the histologic subtype should be considered an independent prognostic parameter when compared with TNM stage and grade. In our study including 4,063 patients with 3,564 (87.7%) clear cell, 396 (9.7%) with papillary, and 103 (2.5%) with chromophobe tumors, no survival difference was observed between papillary and clear cell histologies in metastatic tumors, and only TNM stage, Fuhrman grade and ECOG PS were retained as independent prognostic variables in the overall population.

There is a need in patients with metastatic RCC to define prognostic factors that enable stratification of patients into risk groups and predict response to therapy. It is noteworthy that none of the prognostic models that have been developed recently in metastatic RCC has integrated histologic subtype as a prognostic variable.[19,20] The only histologic feature that has been retained as a prognostic variable in predicting response to immunotherapy is the presence of a sarcomatoid component.[21] Motzer et al[22] found that patients with chromophobe tumors had a longer survival compared with papillary and collecting duct histology in 64 metastatic patients with non–clear cell histology. However, as shown in our study, the chromophobe feature is extremely rare in metastatic series (0.6%). Thus, this variable has little utility in decision making in metastatic RCC. Additionally, in our series no survival difference was observed between 59 metastatic patients with papillary and 765 patients with clear cell tumors. Thus, we failed to confirm the general belief that metastatic papillary tumors have a more aggressive profile than metastatic clear cell tumors.

The main limitation of our study is the lack of central pathologic review. It is likely that it resulted in misclassifications. However, it is worth noting that, although due to the relative infeasibility of centrally reviewing more than 4,000 RCC cases occurring across eight independent medical centers on two continents, and although cases were not reviewed across centers, within each center cases were often reviewed by a single pathologist, lending a uniformity to the diagnoses of pathologic variables within sites. In other sites, diagnoses were rendered by a small group of pathologists experienced in the classification of RCC using the Heidelberg and Furhman classifications. Nevertheless, it cannot be denied that differences in the relative prevalence of the three histologic subtypes that were found across the eight institutions may be due to histologic misclassification rather than to differences in patient recruitment or cancer

Table 3. Factors Affecting Survival in Univariate Kaplan-Meier Analysis in Patients With Renal Tumors (N = 4,063)

	Survival (months)		5-Year Survival Estimates (%)	10-Year Survival Estimates (%)	*P*
	Median	Range			
Overall population variable	120	108-132	64.8	50.6	—
Sex					
Male	111	100-123	63.0	47.9	.002
Female	157	124-190	68.3	56.4	
Age, years					
< 52	168	122-214	69.7	57.7	.0001
52-61	136	107-164	65.3	53.3	
61-69	108	89-127	62.0	47.7	
≥ 69	87	74-100	61.9	41.1	
Tumor size, cm					
< 4		—	87.4	75.3	.0001
4-6	180	122-288	76.3	63.8	
6-9	101	85-117	63.2	46.9	
≥ 9	43	36-50	43.8	30.0	
TNM stage					
I		—	90.1	79.6	.0001
II	157	123-191	77.9	57.6	
III	71	61-81	55.7	37.7	
IV	17	15-19	21.9	9.6	
Fuhrman grade					
1	240		89.1	81.0	.0001
2	154	136-172	72.1	56.5	
3	59	52-66	49.8	30.1	
4	17	13-21	28	18.8	
ECOG PS					
0	168	146-190	74.8	60.9	.0001
≥ 1	45	38-52	44.0	28.6	
Histologic subtype					
Clear cell	119	106-132	63.8	49.9	.0007
Papillary	153	110-196	69.8	54.1	
Chromophobe		—	83.9	77.9	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

epidemiology in each place. It could also explain why our reported percentages of unclassified renal cell carcinomas (0.7%) and chromophobe cell carcinomas (2.5%) were lower compared to that of the literature and why the overall percentage of clear cell carcinoma was higher than anticipated. It is also conceivable that misclassifying good prognostic tumors together with more aggressive tumors could somewhat "neutralize" the prognostic effect of the histologic type. This issue was recently addressed by a group at Harvard that recently presented relevant data at the American Society of Clinical Oncology. To assess the accuracy and completeness of pathology data contributed to large databases, Carloss et al[23] collected hematoxylin and eosin–stained pathology slides and outside pathology reports of RCC primary tumors from patients with RCC. Central review was performed according to preset criteria by a single pathologist blinded to the outside pathology reading, and the degree of concordance between the two readings was compared. In this study, 99% of those classified as clear cell by local review were confirmed to be the same by central review, while there was an 84% concordance between the two reviews in describing papillary features. Overall, therefore, we don't believe that a centrally performed classification would have significantly modified our results since differences obviously existed in univariate analysis. Nevertheless, it is not surprising that those differences disappeared in multivariate analysis due to strong correlations that exist among stage, grade, and histologic types.

Even though tools for distinguishing histologic features have evolved during recent years, rendering more uniform the evaluation of histology across centers, it is likely that in the oldest cases, pathologists tended to lump all tumors with clear cell features including some papillary renal cell carcinomas and chromophobe renal cell carcinomas into the category of carcinoma with clear cell features. Another limitation of the study due to the lack of central pathologic review is the concern about reliability of the tumor grading. It is known that inter- and intra-observer discrepancies exist concerning Fuhrman grade classification.[24,25] It is likely that such inaccuracies occurred in our study since different pathologists from

Table 4. Factors Affecting Survival in Multivariate Analysis in Patients With Renal Tumors (N = 4,063)

Variable	Hazard Ratio	95% CI	*P*
TNM stage			
1	1		
2	1.4	1.1-1.8	.006
3	2.6	2.1-3.2	< .001
4	6.3	5.0-7.8	< .001
Fuhrman grade			
G1	1		
G2	1.2	1.0-1.5	.04
G3	1.6	1.2-2.0	< .001
G4	2.4	1.9-3.1	< .001
ECOG PS			
≥ 1	1.6	1.4-1.8	< .001

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

different centers evaluated nuclear grade during a long period of time. Conversely, the lack of centralized pathology review perhaps lends a better insight into the prognostic value of histologic type in general practice.

Finally, the prognostic issue is not the only reason that it is important to recognize different histologic subtypes in RCC. As we have demonstrated, different subtypes have different predilections for stage as well as different metastatic profiles; different subtypes have different propensities for multicentricity and renal vein invasion and may respond differently to different therapies. Given the fact that each type of cancer has its own genetic and protein signature and has corresponding syndromic and familial associations, those differences are probably driven at the molecular level. Although substantial progress has been made during the last 10 years, the story of histologic subtyping is not complete. Further understanding of the molecular basis of histologic subtyping may provide us with greater insight into the various tumorigenic pathways of kidney carcinogenesis.

In summary, histologic subtyping of RCC along morphologically and genetically/molecularly well-characterized subtypes has prognosis significance in a univariate setting; however, in an independent analysis including TNM stage, Fuhrman nuclear grade, and ECOG PS, the prognostic significance does not hold true.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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