Histological Subtype is an Independent Predictor of Outcome for Patients With Renal Cell Carcinoma

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Purpose: There are significant differences in clinicopathological features among renal cell carcinoma histological subtypes but controversy exists regarding the independent impact of histological subtype on patient outcome after nephrectomy. We examined the significance of histological subtype on progression to distant metastasis and cancer specific death after nephrectomy.

Materials and Methods: In a retrospective review of our institutional nephrectomy registry we identified 3,062 patients treated surgically for clear cell, papillary or chromophobe renal cell carcinoma between 1970 and 2003.

Results: We identified 2,466 patients (80.5%) with clear cell, 438 (14.3%) with papillary and 158 (5.2%) with chromophobe renal cell carcinoma. There were significant differences in age at surgery, gender, symptoms at presentation, tumor size, stage and grade, tumor necrosis, sarcomatoid differentiation and multifocality among the 3 renal cell carcinoma subtypes ($p < 0.01$ for all). A significant difference in metastasis-free and cancer specific survival existed between patients with clear cell renal cell carcinoma and the 2 other subtypes, although no significant difference in these outcomes was identified between patients with the papillary and chromophobe subtypes. The clear cell renal cell carcinoma subtype remained a significant predictor of metastasis (HR 2.76, 95% CI 2.05–3.73) and cancer specific death (HR 1.77, 95% CI 1.38–2.26, each $p < 0.001$) after multivariate adjustment for the features listed above.

Conclusions: Histological subtype is an independent predictor of progression to distant metastasis and cancer specific death in patients with renal cell carcinoma.

Key Words: kidney; carcinoma, renal cell; neoplasm metastasis; mortality; pathology

Abbreviations and Acronyms

ECOG = Eastern Cooperative Oncology Group

RCC = renal cell carcinoma

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Renal cell carcinoma is composed of multiple distinct histological subtypes. In 1997 the American Joint Committee on Cancer and UICC adopted the modified recommendations of the Heidelberg conference on appropriate histological subclassification for RCC tumors.[1,2] Currently accepted terminology for RCC subtypes includes clear cell (conventional), papillary, chromophobe and collecting duct. RCC tumors that are not in one of these subtypes are classified as RCC not otherwise specified. In addition to easily recognizable morphological differences, these histological variants also have distinct genetic aberrations, are associated with different heritable RCC syndromes[3,4] and show differential responses to systemic therapy.[5,6]

Several groups have explored variability among RCC subtypes in pre-

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sentation, biological aggressiveness and features predicting prognosis.[7–12] Controversy remains regarding the impact of histological subtype on outcome after accounting for tumor stage, grade and size. We report the impact of RCC histological subtype on prognosis after multivariate adjustment for other common prognostic features.

MATERIALS AND METHODS

Patient Selection

Upon approval from our institutional review board we identified 3,062 consecutive patients treated with radical nephrectomy or nephron sparing surgery for unilateral, sporadic clear cell, papillary or chromophobe RCC between 1970 and 2003 in the nephrectomy registry at our institution. Patients with cystic clear cell RCC were excluded from analysis.[13]

Clinicopathological Features

Clinical features studied included age at surgery, gender, symptoms at presentation, ECOG performance status and tumor thrombus level. Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute onset varicocele or constitutional symptoms, including rash, sweats, weight loss, fatigue, early satiety and anorexia, were considered symptomatic. Pathological features studied included histological subtype classified according to American Joint Committee on Cancer, UICC and Heidelberg guidelines,[14] tumor size, 2002 primary tumor classification, regional lymph node involvement, distant metastasis, 2002 TNM stage groups, nuclear grade, coagulative tumor necrosis, sarcomatoid differentiation and multifocality, ie more than 1 ipsilateral tumor of the same histological subtype. To determine these features a single urological pathologist (JCC) reviewed all specimens while blinded to patient outcome.

Statistical Methods

Associations of RCC histological subtype with other clinicopathological features studied were evaluated using the chi-square test. Kaplan-Meier curves were used to determine associations of RCC histological subtype with patient outcome and comparisons among curves were evaluated using the log rank test. Univariate and multivariate Cox proportional hazards regression models were used to estimate the magnitude of the association of RCC histological subtype with patient outcomes, as shown with the HR and 95% CI. Statistical analysis was done with SAS®. All tests were 2-sided with $p < 0.05$ considered statistically significant.

RESULTS

Of the 3,062 study patients 2,466 (80.5%) had clear cell, 438 (14.3%) had papillary and 158 (5.2%) had chromophobe RCC. Table 1 lists clinicopathological features by histological subtype.

Of the 2,466 patients with clear cell RCC 1,621 had died by last followup, including 879 of RCC a median of 1.9 years (range 0 to 26) after surgery. Of the 438 patients with papillary RCC 212 had died by last followup, including only 52 of RCC at a median of 2.7 years (range 0 to 16). Of the 158 patients with chromophobe RCC 73 had died at last followup, including 21 of RCC at a median of 1.4 years (range 0 to 16). In the 1,156 patients with any subtype who were alive at last followup median followup was 8.1 years (range 0 to 36). Only 38 patients (3.3%) had fewer than 2 years of followup.

Part *A* of the figure shows cancer specific survival by RCC histological subtype. Table 2 lists estimated cancer specific survival rates after surgery for clear cell, papillary and chromophobe RCC. While cancer specific survival differed among the 3 subtypes ($p < 0.001$), there was no statistically significant difference in outcome in patients with papillary vs chromophobe RCC ($p = 0.494$). Thus, the papillary and chromophobe RCC subtypes were combined and compared with the clear cell subtype in the multivariate models.

On univariate analysis patients with clear cell RCC were more than 3 times as likely to die of RCC than patients with papillary and chromophobe RCC (HR 3.29, 95% CI 2.59–4.18, $p < 0.001$, table 3). After adjusting for age at surgery, gender, symptoms at presentation, 2002 TNM stage groups, tumor size, nuclear grade, coagulative tumor necrosis, sarcomatoid differentiation and multifocality the clear cell subtype remained independently and significantly associated with death from RCC (HR 1.77, 95% CI 1.38–2.26, $p < 0.001$, table 3). However, there appeared to be significant interactions of histological subtype with tumor stage and grade, ie the association of subtype with death from RCC varied by stage and grade. To explore this further we evaluated the associations of subtype with death from RCC stratified by stage and grade.

Of the 1,393 patients with early stage and low grade RCC, ie TNM stage groups I and II, and grades 1 and 2, those with clear cell RCC were more than twice as likely to die of RCC than those with the papillary and chromophobe subtypes (HR 2.26, 95% CI 1.29–3.96, $p = 0.004$). The clear cell subtype was significantly associated with death from RCC in the 599 patients with early stage, high grade RCC (HR 3.72, 95% CI 2.18–6.35, $p < 0.001$) and in the 255 with late stage, low grade RCC (HR 2.94, 95% CI 1.20–7.19, $p = 0.018$). Of the 815 patients with late stage, high grade RCC those with clear cell RCC were no more likely to die of RCC than those with the papillary and chromophobe subtypes (HR 1.03, 95% CI 0.74–1.42, $p = 0.873$). However, there were only 41 patients with late stage, high grade papillary RCC, of whom 27 died of RCC, and 21 with late stage, high grade chromophobe RCC, of whom 12 died of RCC.

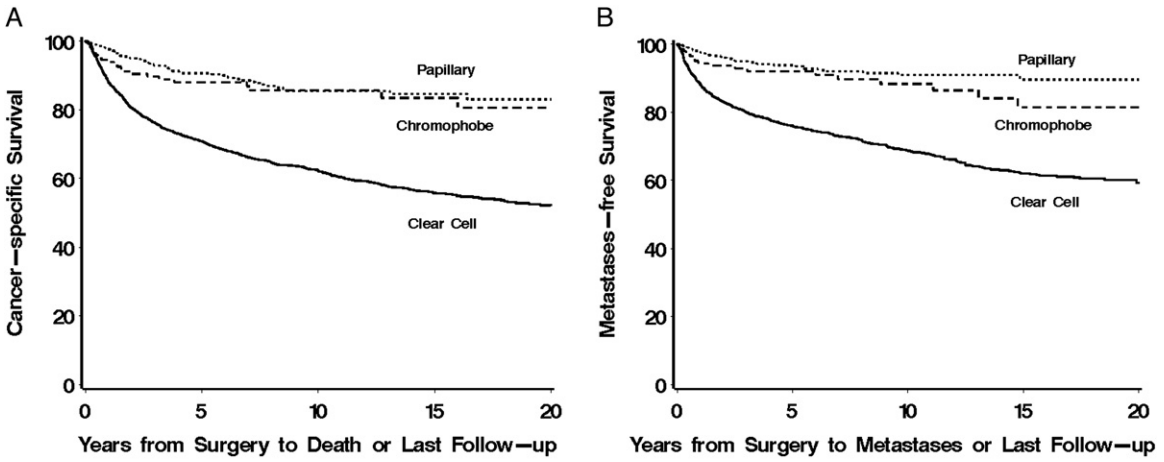
Table 1. *Clinical and pathological features by histological subtype in 3,062 patients with RCC*

Feature	No. Clear Cell (%)	No. Papillary (%)	No. Chromophobe (%)	p Value
Age at surgery:				
Less than 65	1,352 (54.8)	201 (45.9)	91 (57.6)	0.002
65 or Greater	1,114 (45.2)	237 (54.1)	67 (42.4)	
Gender:				
F	854 (34.6)	76 (17.4)	72 (45.6)	<0.001
M	1,612 (65.4)	362 (82.6)	86 (54.4)	
Symptoms at presentation	1,668 (67.6)	229 (52.3)	98 (62.0)	<0.001
Constitutional symptoms at presentation	743 (30.1)	75 (17.1)	32 (20.3)	<0.001
ECOG performance status (2,232 pts):				
0	1,570 (88.2)	309 (92.5)	102 (87.2)	0.059
1 or Greater	211 (11.8)	25 (7.5)	15 (12.8)	
Tumor thrombus:				
None	1,905 (77.3)	419 (95.7)	149 (94.3)	<0.001
Level 0	365 (14.8)	11 (2.5)	7 (4.4)	
Level I–IV	194 (7.9)	8 (1.8)	2 (1.3)	
Primary tumor size (cm):				
Less than 5	803 (32.6)	241 (55.0)	49 (31.0)	<0.001
5–Less than 7	488 (19.8)	82 (18.7)	20 (12.7)	
7–Less than 10	601 (24.4)	57 (13.0)	41 (26.0)	
10 or Greater	574 (23.3)	58 (13.3)	48 (30.3)	
2002 Primary tumor classification:				<0.001
pT1a	616 (25.0)	205 (46.8)	37 (23.4)	
pT1b	580 (23.5)	112 (25.6)	37 (23.4)	
pT2	455 (18.5)	71 (16.2)	60 (38.0)	
pT3a	241 (9.8)	30 (6.9)	14 (8.9)	
pT3b	521 (21.1)	18 (4.1)	8 (5.0)	
pT3c	23 (0.9)	1 (0.2)	0	
pT4	30 (1.2)	1 (0.2)	2 (1.3)	
Regional lymph node involvement:				
pNX + pN0	2,334 (94.7)	417 (95.2)	152 (96.2)	0.640
pN1 + pN2	132 (5.3)	21 (4.8)	6 (3.8)	
Distant metastasis:				
M0	2,088 (84.7)	423 (96.6)	151 (95.6)	<0.001
M1	378 (15.3)	15 (3.4)	7 (4.4)	
2002 TNM stage group:				
I	1,124 (45.6)	313 (71.5)	73 (46.2)	<0.001
II	360 (14.6)	65 (14.8)	57 (36.1)	
III	563 (22.8)	36 (8.2)	18 (11.4)	
IV	419 (17.0)	24 (5.5)	10 (6.3)	
Nuclear grade:				<0.001
1	232 (9.4)	9 (2.0)	2 (1.3)	
2	1,040 (42.2)	261 (59.6)	104 (65.8)	
3	977 (39.6)	161 (36.8)	36 (22.8)	
4	217 (8.8)	7 (1.6)	16 (10.1)	
Coagulative tumor necrosis	743 (30.1)	197 (45.0)	32 (20.3)	<0.001
Sarcomatoid differentiation	126 (5.1)	6 (1.4)	13 (8.2)	<0.001
Multifocality	52 (2.1)	39 (8.9)	2 (1.3)	<0.001

A total of 2,662 patients had clinical M0 disease at nephrectomy (table 1). Of the 2,088 patients with M0 clear cell RCC 612 had progression to distant metastasis at a median of 1.5 years (range 0 to 25) after surgery. Of the 423 patients with M0 papillary RCC 32 had progression to distant metastasis at a median of 2.1 years (range 0 to 15). Of the 151 patients with M0 chromophobe RCC 17 had progression to distant metastasis at a median of 1.3 years (range 0 to 15).

Part *B* of the figure shows distant metastasis-free survival by RCC histological subtype. While distant metastasis-free survival differed among the 3 subtypes ($p < 0.001$) there was no statistically significant difference in outcome between patients with papillary and chromophobe RCC ($p = 0.143$).

On univariate analysis patients with M0 clear cell RCC were almost 4 times as likely to have progression to distant metastasis than those with papillary and chromophobe RCC (HR 3.82, 95% CI 2.86–5.11, $p < 0.001$, table 4). After adjusting for age at surgery, gender, symptoms at presentation, 2002 TNM stage groups, tumor size, nuclear grade, coagulative tumor necrosis, sarcomatoid differentiation and multifocality the clear cell subtype remained independently and significantly associated with progression to distant metastasis (HR 2.76, 95% CI 2.05–



RCC histological subtype and survival. *A*, cancer specific survival in 2,466 patients with clear cell, 438 with papillary and 158 with chromophobe RCC. *B*, distant metastasis-free survival in 2,088 patients with clear cell, 423 with papillary and 151 with chromophobe RCC who underwent nephrectomy for clinical M0 disease.

3.73, p <0.001, table 4). Significant interactions of histological subtype with tumor stage and grade were also apparent in the subset of M0 cases. The strongest associations of histological subtype with progression to distant metastasis were noted in the 1,393 patients with early stage, low grade RCC (clear cell vs papillary and chromophobe HR 2.76, 95% CI 1.59–4.80) and in the 599 with early stage, high grade RCC (HR 6.15, 95% CI 3.34–11.35, each p <0.001).

In contrast, histological subtype was not significantly associated with progression to distant metastasis in the 175 patients with late stage, low grade RCC (HR 1.70, 95% CI 0.68–4.25, p = 0.253) or in the 495 with late stage, high grade RCC (HR 1.45, 95% CI 0.91–2.31, p = 0.116). However, RCC was late stage and low grade in only 16 papillary RCC cases, of which 4 progressed, and in 7 of chromophobe RCC, of which 1 progressed. Similarly RCC was late stage and high grade in only 29 papillary cases, of which 12 progressed, and in 14 of chromophobe RCC, of which 7 progressed. This limited our ability to detect statistically significant differences in outcome among subtypes.

DISCUSSION

Although pathological classification of RCC subtypes based on morphological features is well accepted, controversy exists on the impact of histological subtype on clinical outcome.[15] We noted that the clear cell subtype portends a worse prognosis than papillary and chromophobe RCC after nephrectomy when adjusting for accepted pathological prognostic features, including TNM stage, grade and size.

In a prior report Cheville et al noted that histological subtype was significantly associated with cancer specific survival on univariate analysis and clear cell RCC was associated with decreased survival compared with papillary and chromophobe RCC.[9] Our series represents an extension of that study with additional patients, extended followup and multivariate analysis showing the independent significance of histological subtype in regard to cancer specific and metastasis-free survival. We excluded 90 patients with cystic clear cell RCC from analysis since we previously observed that the cystic variant of clear cell RCC is indolent with 100% cancer specific survival after surgery for localized tu-

Table 2. *Cancer specific and distant metastasis-free survival*

Survival	% Estimated Survival (95% CI)/No. Still at Risk			
	5 Yrs	10 Yrs	15 Yrs	20 Yrs
Ca specific:				
Clear cell	71 (69–73)/1,303	62 (60–64)/700	56 (53–58)/346	52 (49–55)/152
Papillary	91 (88–94)/291	86 (82–89)/156	85 (81–89)/67	83 (78–88)/26
Chromophobe	88 (83–94)/92	86 (80–92)/52	84 (77–91)/32	81 (72–90)/14
Distant metastasis-free:				
Clear cell	76 (74–78)/1,155	69 (67–71)/632	62 (59–65)/304	59 (56–63)/134
Papillary	94 (91–96)/284	91 (88–94)/154	90 (86–94)/65	90 (86–94)/26
Chromophobe	92 (88–97)/92	88 (83–95)/51	82 (73–91)/31	82 (73–91)/14

Table 3. *Univariate and multivariate associations of histological subtype with death from RCC in 3,062 patients with RCC*

Feature	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age at surgery:				
Less than 65	1.0 (referent)	0.11	1.0 (referent)	0.03
65 or Greater	0.90 (0.79–1.02)		1.16 (1.02–1.33)	
Gender:				
F	1.0 (referent)	0.74	1.0 (referent)	0.10
M	0.98 (0.85–1.12)		0.89 (0.78–1.02)	
Symptoms at presentation:				
Absent	1.0 (referent)	<0.001	1.0 (referent)	0.002
Present	2.43 (2.06–2.85)		1.30 (1.10–1.54)	
2002 TNM stage group:				
I	1.0 (referent)	<0.001	1.0 (referent)	<0.001
II	4.05 (3.17–5.18)		2.25 (1.66–3.03)	
III	8.77 (7.08–10.87)		3.76 (2.89–4.89)	
IV	33.74 (27.28–41.73)		13.69 (10.50–17.86)	
Primary tumor size (cm):				
Less than 5	1.0 (referent)	<0.001	1.0 (referent)	<0.001
5–Less than 7	3.53 (2.72–4.57)		1.88 (1.44–2.47)	
7–Less than 10	6.27 (4.96–7.93)		1.67 (1.27–2.21)	
10 or Greater	10.57 (8.42–13.28)		2.02 (1.53–2.67)	
Nuclear grade:				
1 + 2	1.0 (referent)	<0.001	1.0 (referent)	<0.001
3	4.42 (3.79–5.16)		1.63 (1.31–1.78)	
4	15.27 (12.55–18.58)		2.23 (1.64–3.04)	
Coagulative tumor necrosis:				
Absent	1.0 (referent)	<0.001	1.0 (referent)	<0.001
Present	3.91 (3.44–4.44)		1.52 (1.31–1.78)	
Sarcomatoid differentiation:				
Absent	1.0 (referent)	<0.001	1.0 (referent)	<0.001
Present	8.12 (6.67–9.86)		1.78 (1.31–2.40)	
Multifocality:				
Absent	1.0 (referent)	0.03	1.0 (referent)	0.94
Present	0.61 (0.39–0.96)		0.98 (0.62–1.56)	
RCC histological subtype:				
Papillary + chromophobe	1.0 (referent)	<0.001	1.0 (referent)	<0.001
Clear cell	3.29 (2.59–4.18)		1.77 (1.38–2.26)	

mors.[13] The strongest associations of histological subtype with cancer specific outcomes were observed in clinical M0 cases with TNM stage groups I and II, encompassing 75% of cases of M0 disease. In the remaining 25% of patients with late stage RCC histological subtype was not significantly associated with outcome. However, it is critical to note that most patients with papillary and chromophobe RCC present with TNM stage I and II disease.

Although our findings show that histological subtype is an independent predictor of outcome after nephrectomy for RCC, other series examining the association between histological subtype and outcomes did not identify this relationship. Patard et al reported a multicenter experience in 4,063 RCC cases of the impact of histological subtype on survival.[11] On univariate analysis papillary and chromophobe tumors were significantly associated with improved survival compared with clear cell RCC. However, after adjusting for TNM stage, grade and ECOG performance status histological subtype was no longer significantly associated with survival. In another multicenter study in 2,530 patients Karakiewicz et al found no significant association of histological subtype with outcome on multivariate analysis.[16] In those 2 studies data were derived from multiple medical centers without central pathological review.[11,16] The distribution of RCC subtype in the study by Patard et al differed among centers from 79.6% to 96.1% for clear cell RCC, 1.5% to 17% for papillary RCC and 0.6% to 5.6% for chromophobe RCC,[11] indicating possible inconsistencies in the histological subtyping of the tumors among the 8 participating centers. No subtype distribution by center was provided by Karakiewicz et al.[16]

Recently Surveillance, Epidemiology and End Results data from 9 American RCC cancer registries were studied to develop a prognostic model for RCC and determine the significance of RCC histological subtype in regard to cancer specific mortality.[17] This study identified that histological subtype is an independent predictor of outcome but there was no improvement in outcome prediction by adding histological subtype when stage and grade were included in

Table 4. *Univariate and multivariate associations of histological subtype with distant Metastasis in 2,662 patients with clinical M0 RCC*

Feature	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age at surgery:				
Less than 65	1.0 (referent)	0.13	1.0 (referent)	0.15
65 or Greater	0.89 (0.76–1.04)		0.89 (0.76–1.04)	
Gender:				
F	1.0 (referent)	0.54	1.0 (referent)	0.23
M	1.05 (0.89–1.24)		0.90 (0.76–1.07)	
Symptoms at presentation:				
Absent	1.0 (referent)		1.0 (referent)	0.29
Present	2.69 (2.21–3.27)	<0.001	1.12 (0.91–1.38)	
2002 TNM stage group:				
I	1.0 (referent)	<0.001	1.0 (referent)	<0.001
II	4.31 (3.43–5.42)		1.73 (1.26–2.39)	
III	9.31 (7.60–11.40)		2.98 (2.25–3.95)	
IV	21.48 (14.74–31.31)		5.03 (3.23–7.83)	
Primary tumor size (cm):				
Less than 5	1.0 (referent)	<0.001	1.0 (referent)	<0.001
5–Less than 7	3.41 (2.53–4.59)		2.02 (1.48–2.76)	
7–Less than 10	6.77 (5.18–8.84)		2.25 (1.59–3.18)	
10 or Greater	11.22 (8.63–14.59)		3.01 (2.11–4.30)	
Nuclear grade:				
1 + 2	1.0 (referent)	<0.001	1.0 (referent)	<0.001
3	4.36 (3.66–5.19)		1.89 (1.54–2.32)	
4	13.80 (10.75–17.71)		3.00 (2.06–4.38)	
Coagulative tumor necrosis:				
Absent	1.0 (referent)	<0.001	1.0 (referent)	<0.001
Present	3.65 (3.13–4.25)		1.64 (1.37–1.96)	
Sarcomatoid differentiation:				
Absent	1.0 (referent)	<0.001	1.0 (referent)	0.01
Present	7.29 (5.49–9.68)		1.67 (1.11–2.52)	
Multifocality:				
Absent	1.0 (referent)	0.03	1.0 (referent)	0.99
Present	0.51 (0.28–0.92)		1.00 (0.55–1.83)	
RCC histological subtype:				
Papillary + chromophobe	1.0 (referent)	<0.001	1.0 (referent)	<0.001
Clear Cell	3.82 (2.86–5.11)		2.76 (2.05–3.73)	

a prognostic model. The study consisted of 11,618 patients, excluding 18,432 due to insufficient pathological data, without central pathological review. The combined distribution of subtypes in the multiple registries was clear cell RCC in 92% of cases, papillary RCC in 6.2% and chromophobe RCC in 1.6%. This subtype distribution is significantly different compared to that in studies with central pathological review. In the 5 largest RCC series with central pathological review the subtype distribution was relatively constant with clear cell RCC in 72%, 75%, 83%, 83% and 83% of RCC cases, papillary RCC in 15%, 21%, 12%, 11% and 11%, and chromophobe RCC in 10%, 7%, 5%, 5% and 4%, respectively.[8–10,18,19] Also, Ficarra et al reported the impact of central pathological review on RCC histological subtyping and its association with survival outcomes at a single institution.[18] Importantly the impact of histological subtype on cancer specific survival was only noted after central pathological review.

In addition to the lack of central pathological review, the small size of patient cohorts and the rarity of metastatic relapse or cancer specific death in patients with papillary and chromophobe RCC in studies with pathological review have potentially limited the statistical power needed to identify differences in outcome by subtype. For instance, Amin et al reviewed 377 RCC cases and reported a 76%, 86% and 100% 5-year cancer specific survival rate for clear cell, papillary and chromophobe RCC, respectively.[8] Tumor stage, grade and necrosis predicted outcome on multivariate analysis but histological subtype did not. However, only 73 patients had papillary RCC, including 10 who died of the disease, and only 24 with chromophobe RCC, including 1 who died of the disease. This provided limited statistical power to identify a significant association between subtype and cancer specific survival. Even larger studies may be limited by the number of patients with papillary and chromophobe RCC who

experience an adverse event. In a study of 1,057 RCC patients by Beck et al 157 patients had papillary RCC but only 9 had metastatic relapse and 106 had chromophobe RCC but only 6 had relapse.[19] In that series chromophobe but not papillary RCC had a significantly better outcome than clear cell RCC on multivariate analysis but the rate of metastatic relapse in papillary and chromophobe RCC cases was identical at 5.7% vs 11.9% in clear cell RCC cases. In these 2 studies the small number of patients with papillary and chromophobe RCC who experienced an adverse outcome may not have provided sufficient statistical power to identify differences in outcome by histological subtype.

A potential limitation of our data set is that it represents a retrospective review of experience at a single institution. However, several strengths of the registry used to generate these data warrant mention. All cases were reviewed by a urological pathologist blinded to patient outcome and all cases are reviewed yearly for evidence of disease progression and cancer specific death. This central pathological review of a large number of cases using standardized criteria for histological subtype and grade ensures accurate, consistent interpretation of all cases, especially those treated before adoption of the 1997 subtype guidelines. This is especially important when examining the impact of histological features on long-term clinical outcomes.

CONCLUSIONS

Histological subtype is significantly associated with metastatic progression and cancer specific death even after adjusting for traditional prognostic features, including TNM stage, grade and size. Most patients in our series presented with localized RCC. In these patients we identified the strongest association of histological subtype with outcome.

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EDITORIAL COMMENT

Histology as a prognostic marker in RCC cases has been much debated in the literature. These authors from Mayo Clinic weigh in with their single center experience in 3,062 patients treated surgically for unilateral, sporadic RCC. On multivariate analysis clear vs nonclear cell histology was a predictor of

cancer specific and metastasis-free survival even after controlling for stage, grade and other clinical variables. These findings contradict those in several similar or even larger patient cohorts. The authors state that this reflects the importance of central pathological review as the main reason to explain the differences in conclusions among studies. In published series of cases in which central review was done but failed to identify the prognostic significance of histology the authors cite small sample size as the culprit.

While the concept of central pathological review is a laudable one for which the Mayo Clinic group is to be congratulated, is that the only explanation for the contradictory findings reported? Maybe and maybe not. What is clear is that no study is perfect, including this one. In this series ECOG performance status, which in numerous studies has been an important independent predictor of outcome, was not even significant on univariate analysis and not reported in more than 800 patients in this cohort.[1,2] The authors also excluded patients with cystic clear cell RCC from analysis, which was probably included as the clear cell subtype in other studies and may have impacted the results. Had these 90 patients been included in the localized clear cell group, it may have significantly improved the outlook in the clear cell cohort. Finally, they report that the significance of histology for predicting outcome was strongest for localized disease but lost in patients with more advanced stage, higher grade disease. How can this be? If there should be any strong correlation between outcome and histology, it should be in cases of advanced disease. Several studies have demonstrated the poor prognosis in advanced nonclear cell histology cases, be it from an inherent difference in biology or from the lack of effective systemic therapy options (references 5 and 12 in article).

I think that we can all agree that differences in histology probably reflect inherent differences in molecular biology at the cellular level. However, in my opinion whether these differences in biology are more predictive of outcome than traditional clinical parameters, such as stage, grade and performance status, remains an open question.

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REPLY BY AUTHORS

The decision to exclude patients with cystic clear cell RCC was based on our experience, which suggests significant differences in cancer specific survival between cystic clear cell RCC and conventional clear cell RCC (reference 13 in article). However, when these 90 patients were included in analysis, the significant impact of histological subtype (clear cell vs papillary and chromophobe RCC) remained on multivariate analysis for cancer specific death (HR 1.73, 95% CI 1.35–2.22, $p < 0.001$) and distant metastasis (HR 2.70, 95% CI 2.00–3.65, $p < 0.001$). Thus, exclusion of the cystic variant of clear cell RCC had limited influence on our original results.

In regard to the impact of histological subtype on patients with advanced disease, we agree that based on the available literature one would expect a significant association between histology and outcome. We believe that the lack of a significant association in the current series is due to limited statistical power since so few patients presented with advanced papillary or chromophobe RCC.

Regardless of how predictive histological subtype is compared to traditional clinicopathological parameters, it is a known predictor of response to systemic therapy by patients with metastatic RCC and, based on our data, it is a significant predictor of disease specific outcomes of patients with localized disease. Taken together these findings may have implications beyond prognosis alone, such as the need for and response to adjuvant therapy after nephrectomy for pathologically localized disease. Ongoing clinical trials evaluating the efficacy of adjuvant therapy in this patient population will hopefully provide new insight into the disparate biology of RCC histological subtypes.