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Prognostic Relevance of the Histological Subtype of Renal Cell Carcinoma

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ABSTRACT

Objective: According to several studies, when the histological subtype of renal cell carcinoma is established it is possible to attribute a different life expectancy to each patient. We analyzed the prognostic significance of the histological subtype in renal cell carcinoma.
Materials and Methods: The authors retrospectively analyzed the follow-up of 230 patients after radical or conservative renal surgery. The histological characteristics of the different subtypes of tumor were obtained and the disease-free and cancer-specific survival curves for the clear cell, cromophobic, papillary, collecting duct (Bellini) subtypes and those with sarcomatoid differentiation were individualized.
Results: The disease-free and cancer-specific survival rates for clear cell tumors were 76.6% and 68.0% respectively, 71.2% and 82.1% respectively for the cromophobic type, 71.1% and 79.8% respectively for the papillary type, 26.9% and 39.3% respectively for the sarcomatoid type, and 0.0% and 0.0% respectively for the collecting ducts ($p < 0.001$).
Conclusion: The histological subtypes of renal tumors can stratify patients into different prognostic groups only when the sarcomatoid differentiation is present.

***Key words**: renal cell carcinoma; prognosis; histology; survival*
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INTRODUCTION

The distinct histological subtypes of renal cell carcinoma (RCC) have been widely studied as an independent prognostic factor. The histological classification has recently been internationally standardized and accepted (1). However, the aggressive behavior of each biological pattern is still under discussion.

The most common RCC subtypes are: clear cell (75%); papillary (15%); cromophobic (5%) and collecting duct carcinoma (2%) (2). Sarcomatoid degeneration may occur in any of the four RCC subtypes (1) and increases the risk related to the aggressiveness of the disease.

Whether the histological types of RCC present differences regarding the survival rate is still a controversial issue (3-7). The aim of this study was to evaluate the RCC behavior after surgical treatment by histological subtype.

MATERIALS AND METHODS

Two hundred and thirty patients with RCC who had undergone surgical treatment at our institu-

tion between March/1991 and June/2003 were assessed retrospectively. Their ages ranged from 44 to 80 years (median 63 years). The group evaluated was homogeneous and the follow-up occurred between three and two hundred months (median 48 months). The surgeries performed were 168 radical nephrectomies (73%), 44 enucleation (19%), and 18 polar nephrectomies (8%).

The surgical specimen for pathological analysis was fixed in formalin, soaked in paraffin, sectioned and fixed in the usual way with eosin-hematoxylin (EH). Classification by histological subtypes: (clear cell, papillary cromophilic), cromophobic and collecting duct was undertaken. Further, sarcomatoid differentiation, characterized by the stretching of the tumor cells, nuclear grade, pleomorphism, mitotic index and tumor necrosis, was analyzed. Immunohistochemical analysis was performed on eight patients with sarcomatoid differentiation tumors only and confirmed the presence of an epithelial component. The other seven had sarcomatoid differentiation in association with clear cell carcinoma.

All patients were evaluated according to age, gender, symptoms upon presentation, disease stage, pathologic characteristics, administration of adjuvant immunotherapy, time to disease recurrence, and survival. The demographic data is showed in the Table-1.

The follow-up after surgery was based on thorax X-ray, computerized tomography and/or abdominal ultrasound and hematological tests each four months during the first year, once per semester from the second to fifth years and annually thereafter.

The survival curve analysis was carried out by the Kaplan-Meier statistical method and the log Rank test was used to compare data. Statistical significance was considered as a $p < 0.05$.

***Table 1** – Demographic data.*

Patients	**N = 230**
Age	59 ± 12
Mean ± standard deviation	(9.0 - 90.0)
Gender	
Male	168 (73.0%)
Female	62 (27.0%)
Clinical presentation	
Incidental	120 (52%)
Symptomatic	110 (48%)
Surgery	
Radical	180 (79.3%)
Nephron-sparing	47 (20.7%)
Tumor Size	
≤ 7 cm	169 (73.5%)
> 7 cm	61 (26.5%)
Characteristics	
Single	212 (92.2%)
Multiple	18 (7.8%)
Histologic type	
Clear cell	148 (64.3%)
Cromophobe	23 (10.0%)
Papillary	45 (19.6%)
Sarcomatoid	13 (5.7%)
Bellini's cell	1 (0.4%)
Grade	
1 or 2	145 (63.3%)
3 or 4	84 (36.7%)
Lymph nodes	
Negative	216 (93.9%)
Positive	14 (6.1%)
Microvascular invasion	
Negative	171 (74.3%)
Positive	59 (25.7%)

RESULTS

Of the 230 tumors, there were 148 clear cell tumors (64%), 46 cromophilic tumors (20%), 23 cromophobic tumors (10%), 15 sarcomatoid tumors (5.6%) and 1 Bellini's duct tumor (0.4%).

Regarding histological type, there was a 76.6% disease-free survival rate for the clear cell type, 71.2% for the cromophobic type, 71.1% for the papillary type, 26.9% for the sarcomatoid type, and 0.0% for the Bellini duct type (Figure-1). The cancer-specific sur-

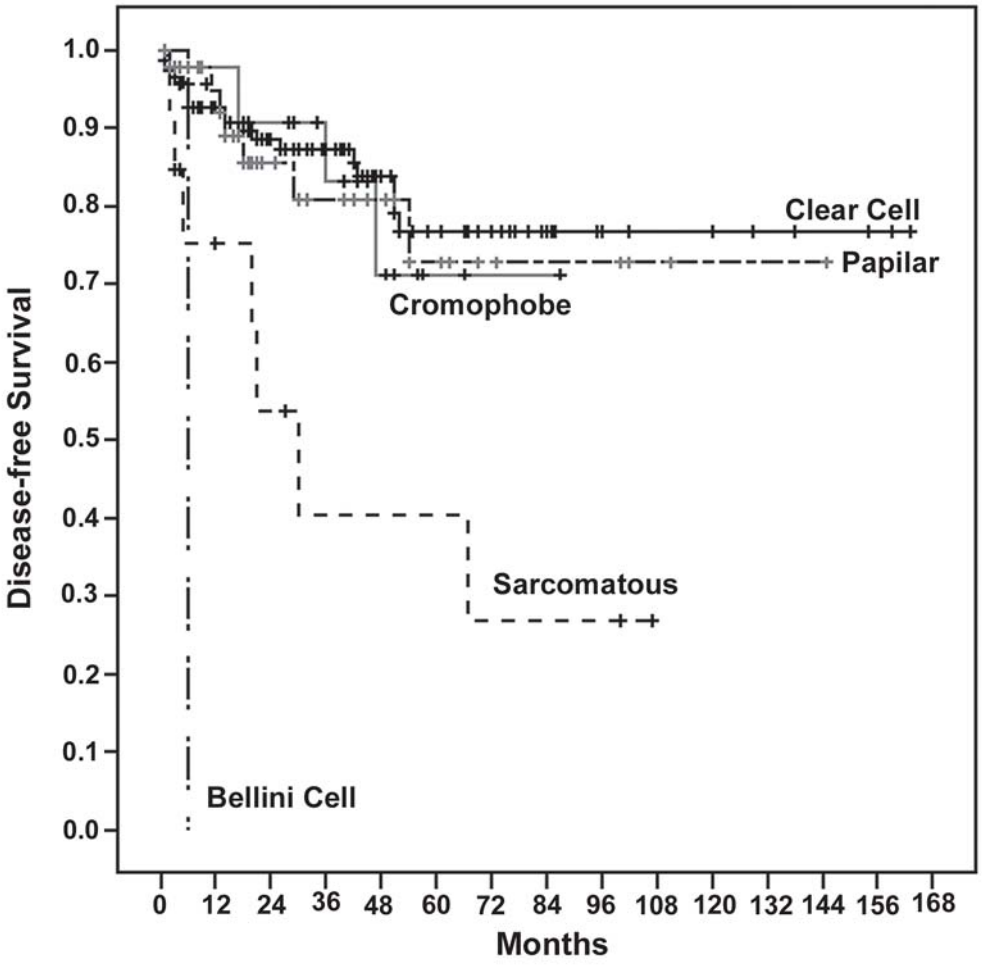

Figure 1 – *Probability disease recurrence curve by histological type (p < 0.001).*

vival rate was 68.0% for the clear cell histological type, 82.1% for the cromophobic, 79.8% for the papillary, 0.0% for the sarcomatoid and the Bellini duct (Figure-2).

For the sarcomatoid pattern, many tumors were medium size 9.5 cm (4 to 24 cm), and 86.6% were high-grade tumors and stage PT3-T4.

However, there was no statistical difference as regards survival rates for the distinct histological subtypes, except when there was an association with the sarcomatoid pattern (Figures-1 and 2). The presence of only one patient with the Bellini duct subtype with extremely aggressive behavior was insufficient for more accurate evaluation. However, every time the different histological types were compared with the common type (clear cell) with the Cox regression model for recurrence (Table-2), the risk was higher only in this single case (Bellini duct) and with the sarcomatoid tumors with a large confidence interval.

COMMENTS

Our study demonstrated that there was no difference regarding tumor behavior among the RCC histological subtypes, nor as regards survival rates related to the clear cell, papillary and cromophobic subtypes. The collecting duct subtype only occurred in one patient and led to premature death. Sarcomatoid degeneration associated with the clear cell sub-

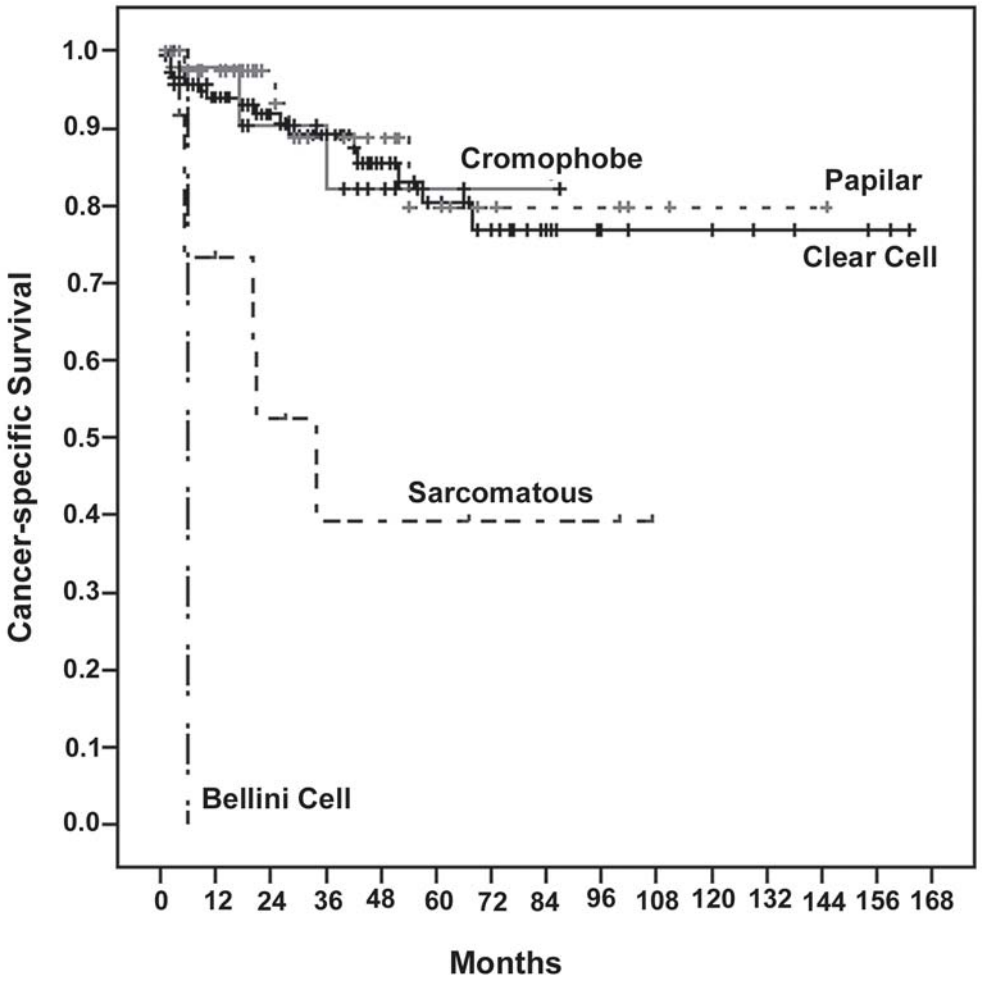

Figure 2 – *Probability curves of death due to the disease by histological type ($p < 0.001$).*

type occurred in half of the cases, and life expectancy dropped in these cases from 71-75% to 39% over five years.

It is believed that the cromophobic subtype has a better prognosis than the conventional clear cell subtype, and that the papillary subtype is of intermediate behavior (8). The renal cromophobic carcinoma seems to have a better prognosis than the clear cell subtype (9), however this is controversial since the series are short, the tumors were low grade, were

Table 2 - *Cox regression model for recurrence.*

Variable	Relative Risk	CI (95%)	p Value
Subtype			
Papillary/ clear cell	1.176	[0.497 ; 2.781]	0.713
Cromophobic/ clear cell	1.154	[0.394 ; 3.381]	0.794
Sarcomatoid/ clear cell	4.475	[1.889 ; 10.603]	0.001
Bellini/ clear cell	16.802	[2.169 ; 130.175]	0.007

discovered in the initial stages, and presented behavior similar to that of the clear cell subtype (10). The cromophobic tumor was more indolent with a tendency to remain organ confined even when it grows (11), and affording a better survival rate than the clear cell subtype (78% versus 50%) (12). Aggressive variants of the cromophobic RCC have been described (13), which justifies further investigation.

Our study showed that all histological subtypes had similar behaviors. However, the survival time was reduced when sarcomatoid degeneration occurred. Another point to be emphasized is the clear cell association with the sarcomatoid pattern in 45% (7/15) of the cases. Among the cases of RCC, the sarcomatoid differentiation occurs within a range of 2% to 5%, frequently associated with the conventional clear cell carcinoma (14).

Usually, the papillary subtype is associated with a better prognosis than the clear cell pattern (15). Thus, the new classification divided it into type 1 (basophilic) and type 2 (eosinophilic), thus its behavior is distinct, type 2 tumors being more aggressive, generally of high grade and at more advanced stages (12). Solid papillary RCC variations identified only by cytogenetic analysis may be responsible for more aggressive behavior (4).

The collecting duct tumors are highly aggressive and develop systemic metastases rapidly (16). In this study, only one patient that presented RCC at the collecting ducts underwent nephrectomy and died six months later. There is a consensus that the collecting duct carcinoma (or Bellini's) is very rare (< 1%) and has a worse prognosis with the development of early metastases (11, 16, 17) and death in 67% (11) of patients during the first two years. However, MacLennan et al. (18) identified collecting duct tumors with lesser aggression in RCC.

The metastatic potential of RCC shows that the aggression seems to be greater in the clear cell subtype (65%), decreases in the papillary (14%; intermediary risk), and is least in the cromophobic subtype (8%; lower risk) (19).

In our series we found no statistical significant differences among the histological types regarding the survival rate or recurrence, except as compared to tumors with sarcomatoid degeneration (mean survival: 5 years - 40%, 10 years - 0%). However, Patard et al. (20) confirm the relative prognostic importance of histological subtype as compared to grade and stage. Our results may reflect the fact that patients in Brazil are presenting with larger (more than a quarter had tumors > 7 cm) and more symptomatic tumors (almost 50%) and survival differences are eliminated across histological subtypes that when occurs.

CONCLUSION

The histological subtypes of renal tumors represent an ominous prognostic factor only when there is associated sarcomatoid degeneration.

CONFLICT OF INTEREST

None declared.

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