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Original Article

Clinical outcomes of papillary renal cell carcinoma: Does the subtyping have a prognostic utility?

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Abstract

Introduction

The prognostic value of the histological subtypes of papillary renal cell carcinoma (pRCC) is debatable as different studies have shown different outcomes. This study describes the clinical characteristics and the survival indices of types 1 and 2 pRCC in a cohort of patients from Sri Lanka.

Methods

This was a cohort study involving a consecutive sample of patients who were diagnosed to have pRCC over a period of eight years (2012-2019) in a tertiary care urology unit in Sri Lanka. Death or the longest period of disease-free survival was considered as the primary end points. Non-parametric tests were employed for the analysis since the sample size was small.

Results

A total of 43 patients with histologically confirmed pRCC were followed up. The mean age of the sample was 56.2 years (range 19-74) and the male to female ratio was 2.7:1. Fifteen patients (36.4%) had type 1 pRCC and 28 (63.6%) had type 2 pRCC. Type 2 tumors were larger in size, advanced in stage and had a higher nuclear grade at the time of diagnosis compared to type 1. The five-year survival of patients with type 1 pRCC was significantly lower (61%) compared to the published data, although that of type 2 tumors was comparable (57.3%). Five-year overall survival was not different between patients with type 1 and type 2 tumors.

Conclusion

Although type 2 pRCC presents with larger, advanced stage and higher-grade tumors, the five-year survival between the two groups was not different. The findings of this study show that the use of histopathological subtype as an independent prognostic factor is questionable.

Key words :Renal cell carcinoma, Type 1 papillary renal cell carcinoma, Type 2 papillary renal cell carcinoma, Overall survival, Disease free survival

Introduction

Papillary renal cell carcinoma (pRCC) is a special type of renal cell carcinoma (RCC) which has distinct genetic, molecular, histological and clinical characteristics (1, 2). It comprises 6% - 18% of RCC according to the published series. The identification of a papillary core sandwiched between one or more layers of malignant epithelial cells is the

pathological hallmark of pRCC, which was first recognized as a specific tumor morphotype of RCC by Mancilla-Jimenz et al in 1976 (3). Two readily recognizable histological patterns within pRCC enabled the subdivision of pRCC into type 1 and type 2. Type 1 pRCC has papillae covered by cuboidal cells with nuclei arranged in a single layer and containing scanty cytoplasm. Type 2 tumors are characterized by the presence of nuclear pseudostratification, the cells of which are often of higher nucleolar grade with abundant eosinophilic cytoplasm (4, 5).

Generally, pRCC is known for having a more favorable prognosis compared to clear cell RCC which is the predominant and well-studied histological type of RCC (6). The difference of clinical outcomes between the two subtypes of pRCC is an ongoing debate. Many studies have observed inferior outcomes in patients with type 2 pRCC compared to type 1 (6-10), while some studies have found no difference in the survival indices of the two types (11, 12). This study was carried out to evaluate clinical characteristics and survival outcomes of type 1 and type 2 pRCC in a cohort of patients from Sri Lanka.

Methods

This was a cohort study involving a consecutive sample of patients who had pRCC, over a period of eight years (2012-2019) in a tertiary care urology unit in Sri Lanka. The decision to offer nephron sparing surgery or radical nephrectomy was taken in multi-disciplinary team meetings, taking the nephrometric score (RENAL score), patient comorbidities and patient preference into consideration. Histopathological evaluation was done according to the World Health Organization (WHO) and International Society of Urological Pathology (ISUP) classification, 2016 (4, 5). Tumor grading was based on the Fuhrman grading system initially and the ISUP grading system subsequently after its development (13). Since the differences between the two grading systems were minimal, comparable grades were used interchangeably. Tumor staging was done using the TNM classification of the Union for International Cancer Control 2009 (14, 15).

Death or the longest period of disease-free survival was considered as the primary end points. Overall survival was calculated from the date of surgery to the last follow up date or death. Disease-free survival was defined as the interval from the date of surgery to the first recurrence, death, or last follow-up visit. Analysis of data was done using SPSS 21 software. Non-parametric tests were employed for the analysis since the sample size was small. Mann-Whitney U test was used to analyze quantitate variables and Fishers exact test and chi square test were used to analyze all qualitative variables. Survival curves were derived from Kaplan-Meier estimates (KM). The log-rank test was used to compare survival distributions between subgroups. Hazard ratios (HR) associated with overall survival and disease-free survival were calculated with their 95% confidence interval.

Results

A total of 43 patients with histologically confirmed pRCC were followed up. The mean age of the sample was 56.2 years (range 19-74) and the male to female ratio was 2.7:1. Out of them 15 (36.4%) had type 1 pRCC and 28 (63.6%) had type 2 pRCC. The details of patients with types 1 and 2 pRCC are given in tables 1 and 2 respectively. The median age of the type 1 pRCC group was 58 years and that for the type 2 pRCC group was 60 years and the difference was statistically not significant

(p=0.93). Male to female ratio between the two groups was also comparable (p=0.48).

The average size of the type 1 tumors was 4.1 cm while the same for type 2 tumors was 7.8 cm. This was statistically significant (p = 0.02) (figure 1). In type 1 tumors 75%, 6.2% and 18.8% were in stage 1, 2 and 3 respectively at the time of diagnosis while no tumor was found to be in stage 4. On the contrary, the percentages of type 2 tumors for stage 1, 2, 3, and 4 were 35.8%, 32.1%, 28.6% and 3.6% respectively. Therefore, type 2 tumors were diagnosed at an advanced stage compared to type 1 tumors (p= 0.04). Most type 1 pRCC tumors were amenable for partial nephrectomy (PN) (68.7%) and only 31.2% of them needed radical nephrectomy (RN) whereas the majority of type 2 pRCC tumors (67.9%) needed RN. This difference was also statistically significant (p=0.02). In type 1 pRCC 30.8%, 53.8%, 7.7%, 7.7% and in type 2 pRCC 4.2%, 45.8%, 29.2%, 20.8% were found to be comprising of ISUP nuclear grades 1, 2, 3 and 4 respectively. This difference was statistically significant (p=0.01); i.e. type 2 pRCC tumors had higher ISUP nuclear grades than type 1 tumors.

Five (11.4%) patients had tumor extension to the renal vein while one of them had the involvement of inferior vena cave. All of them belonged to type 2 pRCC. Five patients had metastases at the time of presentation and all of them belonged to type 2 category (adrenal – 2, lungs – 1, liver – 1, bone - 1). Three (6.8%) patients (two type 2 and one type 1) had multifocal tumors and all three of them were alive at the end of a median follow-up of 36 months. One of them with type 2 pRCC had bilateral, multiple tumors and he is alive six years after undergoing radical nephrectomy on one side and partial nephrectomy on the other side, with a serum creatinine of 1.5 mg/ dL. One patient presented with a perirenal hematoma after spontaneous rupture of the tumor (Wunderlich syndrome).

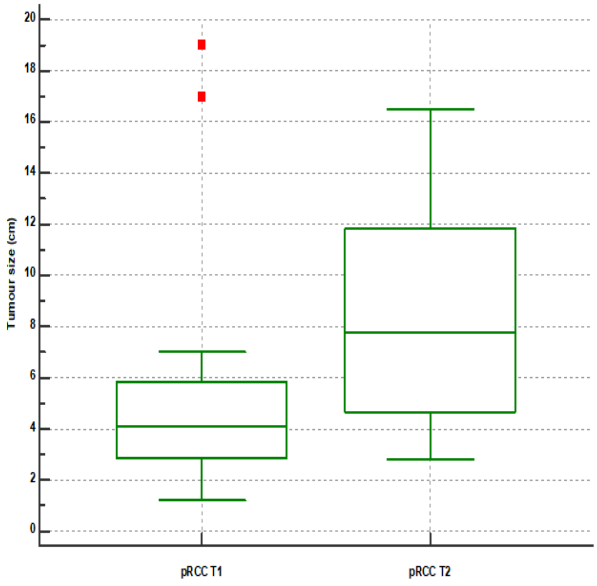

Fig 01.*The difference in tumour size between type 01 and type 02 pRCC*

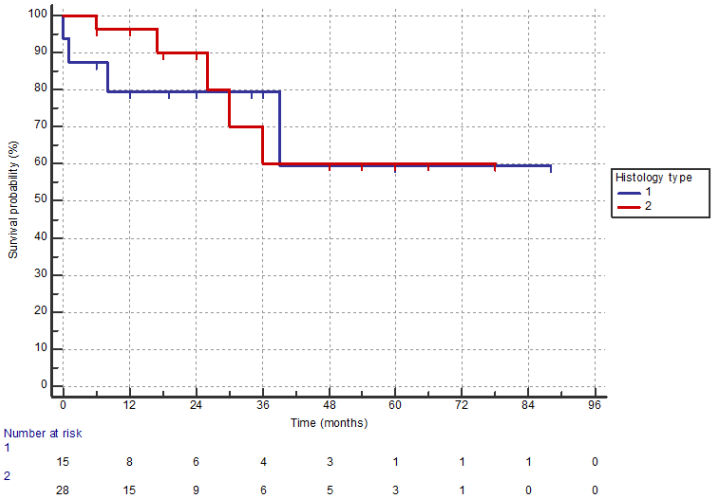

Fig 02. *Survival curve for type 01 and type 02 pRCC patients*

Table 01.*Characteristics of type 01 pRCC tumours*

Index number	Age (years)	Sex	Tumour size (cm)	T Stage	Type of Surgery	Ferman Grade	Follow up (months)	End point	Special features
01	19	F	4.6	1	PN	2	88	L	-
02	58	F	17	2	RN	1	12	L	-
03	55	M	4	1	PN	1	19	L	-
04	58	M	6	1	PN	2	34	L	-
05	62	M	4	1	PN	1	39	D – NR	-
06	63	M	2	3	PN	2	60	L	-
07	63	F	1.2	1	PN	1	60	L	-
08	29	M	19	3	RN	4	8	D – R	-
09	73	M	4.2	1	PN	2	12	L	-
10	73	M	3.5	1	RN	2	36	L	MFT
11	68	M	7	3	RN	2	1	D – NR	-
12	67	M	4	1	PN	1	24	L	-
13	51	M	2	1	PN	2	0	D – NR	-
14	58	M	5.5	1	RN	3	6	L	-
15	50	M	2.2	1	PN	2	6	L	-

The KM curve illustrates the pattern of overall survival for the patients with type 1 and type 2 pRCC (figure 2). The overall five-year survival was 62.5 years. Although the survival rates were inferior for type 1 pRCC in the early periods (up to three years), the trend was not seen with longer follow-up and the difference was not statistically significant (p=0.69). The HR for type 1 pRCC was 0.76 and that for type 2 pRCC was 1.3.

Discussion

Many recent advances in knowledge about the genetic, molecular and histological features of pRCC have strengthened the distinction between the two types of pRCC. The differences in clinical presentation and prognosis between the two types of pRCC, which are clinically more relevant, have attracted the attention of many researchers. Type 2 pRCC is found to possess unfavorable tumor characteristics like larger size, advanced stage and higher nuclear grade at the time of presentation in many studies (7, 9, 10). This observation is further supported by the results of this study, where all these three parameters had statistically significant difference. This difference was translated into the difference observed in the surgical management of patients in the two groups i.e. type 2 tumors needing RN in most occasions compared to type 1 pRCC tumors. Therefore, it is clear that, the histological subtype influences the type of treatment a patient with pRCC would have. Moreover, patients with type 2 pRCC start their oncological journey from an unfavorable position compared to patients with type 1 pRCC,

Table 02.*Characteristics of type 02 pRCC tumours*

Index number	Age (years)	Sex	Tumour size (cm)	T Stage	Type of Surgery	Ferman grade	Follow up (months)	End point	Special features
01	66	M	5.6	1	RN	1	36	D NR	-
02	39	M	9	2	RN	1	6	L	-
03	55	F	13	3	RN	2	66	L	-
04	53	F	5	3	RN	3	26	D – R	-
05	67	M	7.5	2	RN	2	78	L	-
06	39	M	13	3	RN	2	6	L	-
07	65	M	3	1	PN	2	6	L	-
08	71	M	4	1	PN	2	66	L	-
09	53	M	14.2	2	RN	1	48	L	-
10	57	M	3	1	PN	2	6	L	-
11	50	M	9.5	2	PN	2	60	L	MFT
12	40	M	4.8	2	PN	2	17	D – R	-
13	66	F	3	3	PN	2	54	L	-
14	58	M	10	2	RN	3	24	L	B/L MFT
15	62	M	9	2	RN	2	24	L	-
16	65	M	15	3	RN	3	30	D – R	SD
17	64	M	16.5	3	RN	2	6	L	-
18	40	F	11.7	4	RN	3	18	L	SD
19	42	F	6.6	1	RN	3	18	L	-
20	59	M	8.4	3	RN	4	6	L	RD
21	68	M	4	1	PN	4	18	L	-
22	74	F	8	2	RN	4	6	L	SD
23	65	M	4.5	1	PN	4	6	D + R	SD + RD
24	64	M	5.4	1	RN	3	6	L	-
25	38	F	12	3	RN	3	6	L	-
26	61	F	7.4	1	RN	2	12	L	-
27	63	M	13	2	RN	2	12	L	-
28	40	F	2.8	1	PN	4	6	L	SD

F – Female, M – male, PN – Partial Nephrectomy, RN – Radicle Nephrectomy, L – Living, D - Died

Because the parameters mentioned above has a significant prognostic value according to the available evidence. The presence of histopathological variants like sarcomatoid and rhabdoid differentiation is also known to have prognostic implications. In this study, these two histologically unfavorable features were exclusively seen with type 2 pRCC. Sarcomatoid differentiation was found in 15.9% of patients of the study, which is much higher than the reported rate of 5%-6% (8, 9). This may be because the present study cohort having more type 2 cases (63.6%) than in other reported studies (47.7%) (9). There were three (7%) multifocal tumors in this series with all surviving at the end of a median follow-up of 36 months. This is in accordance with the existing knowledge; multifocality is associated with low stage and well differentiated tumors and good prognosis. However, multifocality has been reported in 38.1% of pRCC in one study which was much higher than ours (16). There was one patient with bilateral, multiple type 2 pRCC tumors in this study and this challenges the existing notion that there is no increased

risk of bilateral tumors in patients with pRCC (17).

Five-year overall survival for type 1 and type 2 pRCC in the available literature is 89% and 55% (9). The overall survival of patients with type 1 pRCC is significantly lower in our series (61%) although that of type 2 tumours was comparable (57.3%). The survival of the patients with type 1 pRCC was surprisingly lower than that of patients with type 2 pRCC in the early follow up period of the study. This difference flattened out after three years of follow up and after that the survival of both groups was similar. There was no statistically significant difference of the HR for the two groups which confirms the above.

Survival outcomes were found to be inferior in patients with type 2 pRCC in many series (6, 10). In fact, some studies have paralleled the outcome of type 2 pRCC with that of clear cell RCC which has the worst outcomes out of all RCC types (6). On the contrary, in a small scale study, no difference was observed in pathological stage, nuclear grade, lympho-vascular invasion and disease free and overall survival between these two types (11). Interestingly, a study including only T1 tumors of type 1 and type 2 pRCC, there was no difference in the survival between the two groups although type 2 tumors were larger and of higher nuclear grade (12). The results of our study also emphasize the fact that there is no difference in overall survival in patients with the two types of tumors. There were four deaths in the type 1 pRCC group and five deaths in type 2 pRCC group during the study period which is statistically not significant. However, only one out four deaths was cancer related in type 1 pRCC group whereas four out of five were cancer related deaths in type 2 pRCC group. However, the small sample size of the study limited the opportunity to do multivariate analysis for survival, calculate cancer specific mortality and draw Kaplan-Meir curves for cancer specific survival.

It may be that types 1 and 2 pRCC may not constitute isolated well-defined entities and this heterogeneity may reflect in the different behavior and outcome of pRCC subtypes in different series. Already some believe type 2 tumors with voluminous, finely granular, evenly distributed eosinophilic cytoplasm and oncocytoma-like nuclei and known as oncocytic pRCC, should be renamed as type 3 pRCC (18). Furthermore, the heterogeneity in type 02 pRCC is established by genomic and molecular studies (2). The role played by special histological findings like sarcomatoid and rhabdoid differentiation and the nuclear grade may be more important than the type alone in the prognosis of pRCC and this needs to be studied further. Then a newer reclassification which would reflect the prognosis better can be developed.

Conclusions

Type 2 pRCC presents with larger, advanced stage and higher nuclear grade tumors compared to type 1 tumors. But the overall survival between the two groups is similar which contradicts the findings of many previous publications. Therefore, the role played by the type 1 and 2 histological classification in prognostication of pRCC is debatable. It appears that types 1 and 2 pRCC are heterogenous groups consisting of several subgroups with varying behavior. A more comprehensive histopathological classification correlating with clinical behavior, to identify prognostically important subgroups of already described types of pRCC may solve this controversy.

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