

Original Article

Cystic renal cell carcinoma: a surveillance, epidemiology, and end results database analysis

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Received September 27, 2019; Accepted December 14, 2019; Epub February 15, 2020; Published February 28, 2020

Abstract: Purpose: To explore the risk factors affecting the prognosis of patients with cystic renal cell carcinoma (CRCC). Methods: We identified 1,135 patients diagnosed with CRCC from 1973 to 2015 in the Surveillance, Epidemiology, and End Results (SEER) database and the incidence was calculated. Kaplan-Meier analysis was used to compare the cancer-specific and overall survival rates. COX multivariate regression analysis was used to analyze the relationships between the influencing factors. The factors analyzed included marital status, age at diagnosis, year of diagnosis, sex, race, tumor grade, laterality, TNM stage, AJCC stage, SEER stage, surgery on primary tumor and regional lymph node dissection. Results: According to the data analysis, the 5-year overall survival rate of CRCC patients was 87.3%, and the 5-year cancer-specific survival rate was 94.7%. COX multivariate regression analysis showed that marital status, AJCC stage and surgery on primary tumors had statistical significance in predicting cancer-specific survival, while marital status and surgery on primary tumors had statistical significance in predicting overall survival. Conclusion: Although CRCC has the characteristics of low stage, low grade, low malignancy and good prognosis, early diagnosis and treatment are necessary to improve the prognosis of CRCC. Marital status, AJCC stage and surgery on primary tumor can be used as independent prognostic factors for CRCC and guiding clinical practice.

Keywords: Cystic renal cell carcinoma, survival, prognosis, treatment, surveillance epidemiology and end results database

Introduction

Cystic renal cell carcinoma (CRCC) is a rare clinical subtype of renal cell carcinoma (RCC) originating from the tubular epithelium. CRCC refers to cases of RCC with cystic or cystic-solid mixed changes identified by radiographic evaluation, which occur in approximately 4-15% of RCC cases, with a male-female ratio of 2.4:1. The age at onset was 40-83 years, with a median age of 62.7 years [1]. Due to the rarity of the disease, there is still a lack of systematic research on CRCC. In this study, we collected the clinical data for CRCC patients available in the Surveillance, Epidemiology and End Results (SEER) database. We calculated the incidence of CRCC, and carried out COX multivariate regression analysis after screening important data to explore independent factors affecting

prognosis. We generated Kaplan-Meier survival analysis curves to provide the basis of prognosis predictions for patients.

Materials and methods

Data source

We identified 263,485 American patients with renal (including renal pelvis) malignancies (Site and Morphology. Site recode ICD-O-3/WHO 2008 = "Kidney and Renal Pelvis") included in the SEER database from 1973 to 2015. CRCC (ICD-O-3 His/behavior, malignant: 8316/3 Cyst-associated renal cell carcinoma) accounted for 0.4% of all these patients; a total of 1,135 cases. The SEER database had no records of CRCC patients from before 2001. Analysis of the age-adjusted incidence of CRCC patients in

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Table 1. Age-adjusted incidence rate¹ of CRCC per 1,000,000 population

Time Period and Sex	All (patient, n)	Male (patient, n)	Female (patient, n)
SEER 2001-2005			
All race	1.56	1.87	1.32
White	1.36	1.56	1.21
Black	4.74	6.77	3.65
Other ²	0.40	0.41	
Unknown	-	-	0
SEER 2006-2010			
All race	1.06	1.16	0.96
White	0.90	1.01	0.82
Black	2.97	2.87	2.81
Other ²	0.58	0.52	0.64
Unknown	-	-	-
SEER 2011-2015			
All race	0.75	0.98	0.56
White	0.62	0.79	0.48
Black	2.15	3.03	1.46
Other ²	0.32	0.51	0.17
Unknown	-	-	-

¹Rates are per 1,000,000 population (95% confidence interval) age-adjusted to year 2000 U.S. standard population. Cases were selected by ICD-O-3 histology codes 8316/3 (Cyst-associated renal cell carcinoma). ²RACE (Other): American Indian/AK Native, Asian/Pacific Islander.

the SEER database revealed incidences of 1.56/1,000,000, 1.06/1,000,000 and 0.75/1,000,000 during 2001-2005, 2006-2010 and 2011-2015, respectively. The results of subgroup analysis of patient race and sex are shown in **Table 1**. We screened 1,135 patients with CRCC as primary tumor and obtained their clinical data; 457 patients with incomplete survival time and non-pathological diagnosis were excluded. Finally, 678 patients with CRCC were included in our analysis. The average age of these patients was 55.7±13.3 (17-92) years, with an average survival time of 78.0±50.5 (0-179) months and a median survival time of 78 months.

The following data were extracted for each case: marital status, age at diagnosis, year of diagnosis, sex, race, tumor grade, laterality, TNM stage, AJCC stage, SEER stage, surgery on primary tumors, regional lymph node dissection, cause-specific death classification, survival time and vital status. Among these, TNM stage and AJCC stage refer to the 8th Edition of

the AJCC Cancer Staging Manual [2], and the SEER stage refers to the SEER Summary Stage 2018: Codes and Coding Instructions [3]. Surgery on primary tumor included non-surgical interventions, local tumor resection (including photodynamic therapy, electrocautery, cryosurgery, laser ablation, and laser excision), partial nephrectomy and nephrectomy (including radical nephrectomy). Detailed clinical data are shown in **Table 2**.

Statistical methods

IBM SPSS Statistics 19.0 software (SPSS Inc, Chicago, US) was used for statistical analysis. Kaplan-Meier survival analysis was used to generate cancer-specific survival curves and the overall survival curves of CRCC patients, and the survival rate was calculated. The relevant factors that may affect the prognosis of CRCC in the SEER database were coded as independent variables, and the COX multivariate analysis model was used to obtain the independent factors affecting the prognosis of CRCC patients. Kaplan-Meier survival curves corresponding to independent influencing factors were generated and the corresponding survival rate was calculated. All tests were 2-sided, $P < 0.05$ was considered to indicate statistical significance.

Results

According to Kaplan-Meier survival analysis, the cancer-specific and total survival rates (1, 2, 3, 4, 5 and 10 years) of 678 CRCC patients were calculated (**Table 3**), and the corresponding survival curves were generated (**Figures 1 and 2**). COX multivariate analysis was performed on marital status, age at diagnosis, year of diagnosis, sex, race, tumor grade, laterality, AJCC stage, SEER stage, surgery on primary tumor, and regional lymph node dissection. As shown in **Table 4**, marital status, AJCC stage and surgery on primary tumor had statistical significance in guiding cancer-specific survival prognosis ($P < 0.05$), while only marital status and surgery on primary tumor had statistical significance in guiding overall survival prognosis ($P < 0.05$). The corresponding Kaplan-Meier survival curves are shown in **Figures 3-7**.

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Table 2. Characteristics of 678 CRCC patients

Characteristic	No. of patients (% of total)
Marital status at diagnosis	
Single	114 (16.8)
Married	428 (63.1)
Divorced	58 (8.5)
Widowed	52 (7.7)
Unknown	26 (3.9)
Age at diagnosis	
Age ≤ 30	12 (1.8)
30 < Age ≤ 50	246 (36.2)
50 < Age ≤ 70	314 (46.3)
70 < Age	106 (15.7)
Year of diagnosis	
2001-2005	250 (36.9)
2006-2010	235 (34.7)
2011-2015	193 (28.4)
Sex 0.852	
Male	372 (54.9)
Female	306 (45.1)
Race	
White	497 (73.3)
Black	137 (20.2)
Other ¹	36 (5.3)
Unknown	8 (1.2)
Grade	
Grade I	237 (35.0)
Grade II	202 (29.8)
Grade III-IV	71 (10.5)
Unknown	168 (24.7)
Laterality	
Left	333 (49.1)
Right	340 (50.2)
Bilateral	3 (0.4)
Unknown	2 (0.3)
T Stage	
T1	441 (65.0)
T2	51 (7.5)
T3	26 (3.8)
Unknown	160 (23.7)
N Stage	
N0	517 (76.3)
N1	2 (0.3)
Unknown	159 (23.4)
M Stage	
M0	524 (77.3)
M1	6 (0.9)
Unknown	148 (21.8)

AJCC Stage	
Stage I	430 (63.4)
Stage II	50 (7.4)
Stage III	24 (3.5)
Stage IV	6 (0.9)
Unknown	168 (24.8)
SEER Stage	
Localized	624 (92.0)
Regional	40 (5.9)
Distant	11 (1.6)
Unknown	3 (0.5)
Surg Prim Site	
None	15 (2.2)
Local tumor destruction	10 (1.5)
Partial nephrectomy	279 (41.1)
Any nephrectomy	374 (55.2)
Regional lymph node dissection	
None	570 (84.1)
Yes	30 (4.4)
Unknown	78 (11.5)

¹RACE (Other): American Indian/AK Native, Asian/Pacific Islander.

Table 3. Cancer-specific survival and overall survival rates for the cohort of CRCC of based on the Kaplan-Meier analysis

No. of months	Cancer-specific survival in percentage (SE ¹)	Overall survival in percentage (SE ¹)
12	98.2 (0.005)	95.2 (0.008)
24	97.4 (0.007)	93.5 (0.010)
36	96.8 (0.007)	91.6 (0.011)
48	95.6 (0.009)	89.3 (0.013)
60	94.7 (0.010)	87.3 (0.014)
120	91.4 (0.014)	74.6 (0.022)

¹SE: Standard error.

Regarding the marital status of patients, this study showed significant differences between the average survival times of single, married, divorced and widowed patients, which were 148.6, 170.6, 152.1 and 145.7 months, respectively (P = 0.002). For the same groups categorized according to marital status, the 1-year cancer-specific survival rates were 97.1%, 95.5%, 97.2% and 97%, respectively; the 5-year cancer-specific survival rates were 91.3%, 96.7%, 90.6% and 87.6%, respectively; and the 10-year cancer-specific survival rates were 76.8%, 95% and 82.4%, respectively.

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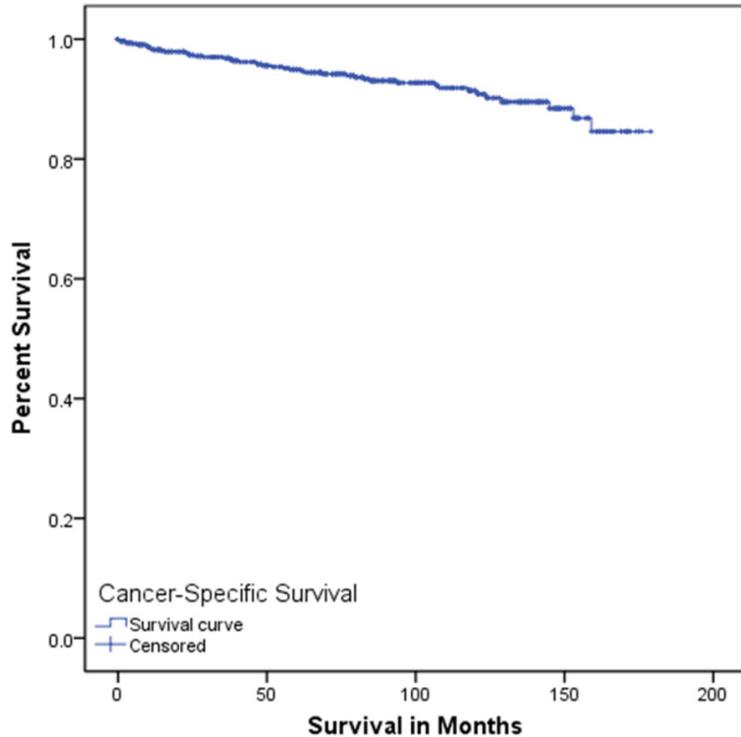


Figure 1. Kaplan-Meier curve of CRCC cancer-specific survival.

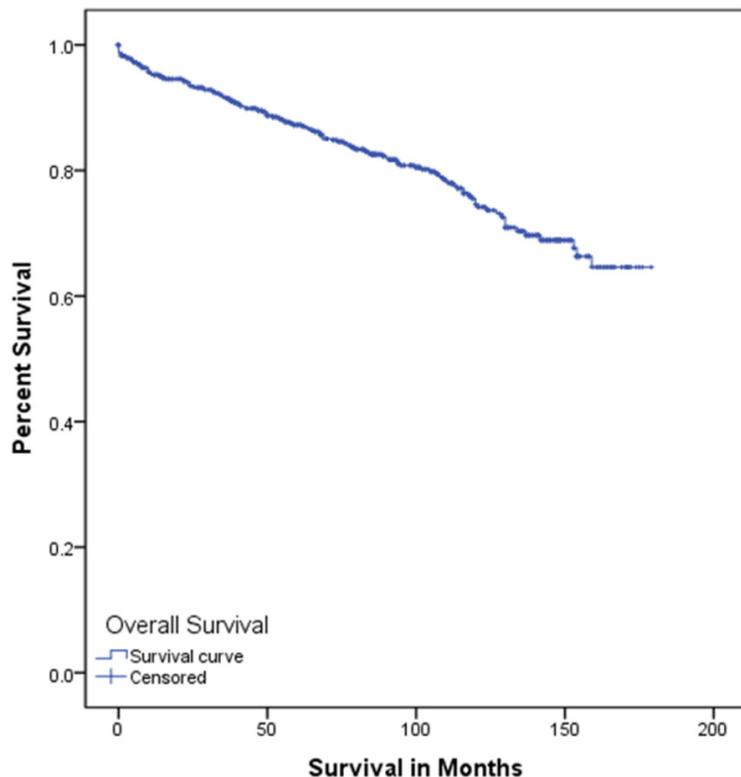


Figure 2. Kaplan-Meier curve of CRCC overall survival.

COX multivariate analysis showed that the relative risk of married, divorced and widowed patients was 0.222, 0.761 and 0.429 times higher, respectively, than that of single patients. For this reason, we conclude that married patients have the best prognosis and single patients have the worst prognosis. For AJCC stage, our study showed significant differences in the average survival times of AJCC stages I, II, III, and IV patients, which were 138.7, 133, 124 and 52.8 months, respectively, ($P < 0.001$). For the same groups categorized according to AJCC stage, the 1-year cancer-specific survival rates were 99.5%, 97.9%, 95.2% and 60%, respectively; and the 5-year cancer-specific survival rates were 96.8%, 91.1%, 84.8% and 20%, respectively. The 10-year cancer-specific survival rate of AJCC stage I patients was 94.8%. COX multivariate analysis showed that the relative risks of AJCC stage II, AJCC stage III and AJCC stage IV disease were 1.275, 2.081 and 39.678 times higher than that of AJCC stage I, respectively. These results showed that AJCC stage I patients had the best prognosis and AJCC stage IV patients had the worst prognosis. For primary tumor surgery in CRCC, there were significant differences in the average survival times of patients without primary surgery, local tumor resection, partial nephrectomy and nephrectomy, which were 48.1, 137, 174.1 and 161.5 months, respectively ($P < 0.001$). The 1-year survival rate of patients without primary surgery was 45.3%, whereas the 10-year cancer-specific survival rate of

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Table 4. Multivariate analysis of CRCC patient cancer-specific survival and overall survival

Characteristic	Cancer-specific survival		Overall survival	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Marital status				
Single	Reference		Reference	
Married	0.222 (0.096, 0.513)	0.000	0.399 (0.245, 0.652)	0.000
Divored	0.761 (0.240, 2.406)	0.641	0.606 (0.281, 1.308)	0.202
Widowed	0.429 (0.114, 1.618)	0.212	0.730 (0.363, 1.468)	0.377
Age at diagnosis				
Age ≤ 30	Reference		Reference	
30 < Age ≤ 50	0.809 (0.127, 5.160)	0.823	0.465 (0.132, 1.639)	0.233
50 < Age ≤ 70	1.961 (0.315, 12.190)	0.470	1.078 (0.308, 3.771)	0.906
70 < Age	3.801 (0.504, 28.690)	0.195	2.951 (0.818, 10.643)	0.098
Year of diagnosis				
2001-2005	Reference		Reference	
2006-2010	0.530 (0.200, 1.399)	0.200	0.729 (0.420, 1.266)	0.262
2011-2015	0.144 (0.016, 1.274)	0.081	0.748 (0.337, 1.662)	0.476
Sex				
Male	Reference		Reference	
Female	0.872 (0.415, 1.832)	0.718	0.859 (0.570, 1.295)	0.469
Race				
White	Reference		Reference	
Balck	1.480 (0.644, 3.400)	0.356	1.139 (0.720, 1.802)	0.578
Other ¹	0.367 (0.044, 3.021)	0.351	0.616 (0.231, 1.638)	0.331
Grade				
Grade I	Reference		Reference	
Grade II	2.238 (0.829, 6.038)	0.112	1.390 (0.824, 2.345)	0.217
Grade III-IV	2.877 (0.937, 8.836)	0.065	1.467 (0.735, 2.927)	0.277
Laterality				
Left	Reference		Reference	
Right	1.386 (0.723, 2.658)	0.325	1.154 (0.798, 1.669)	0.446
Bilateral	1.148 (0.062, 21.162)	0.926	0.586 (0.054, 6.305)	0.659
AJCC Stage				
Stage I	Reference		Reference	
Stage II	1.275 (0.317, 5.124)	0.732	0.715 (0.293, 1.744)	0.461
Stage III	2.081 (0.303, 14.311)	0.456	0.414 (0.099, 1.724)	0.225
Stage IV	39.678 (2.250, 699.730)	0.012	2.021 (0.356, 11.460)	0.427
SEER Stage				
Localized	Reference		Reference	
Regional	2.303 (0.575, 9.222)	0.239	1.788 (0.791, 4.043)	0.163
Distant	0.499 (0.030, 8.201)	0.626	1.684 (0.432, 6.572)	0.453
Surgery of Primary Tumor				
None	Reference		Reference	
Local tumor destruction	0.139 (0.014, 1.361)	0.090	0.291 (0.059, 1.423)	1.127
Partial nephrectomy	0.012 (0.002, 0.069)	0.000	0.068 (0.024, 0.198)	0.000
Any nephrectomy	0.028 (0.006, 0.139)	0.000	0.144 (0.052, 0.396)	0.000
Regional lymph node dissection				
None	Reference		Reference	
Yes	1.058 (0.279, 4.018)	0.934	0.819 (0.281, 2.381)	0.713

¹RACE (Other): American Indian/AK Native, Asian/Pacific Islander.

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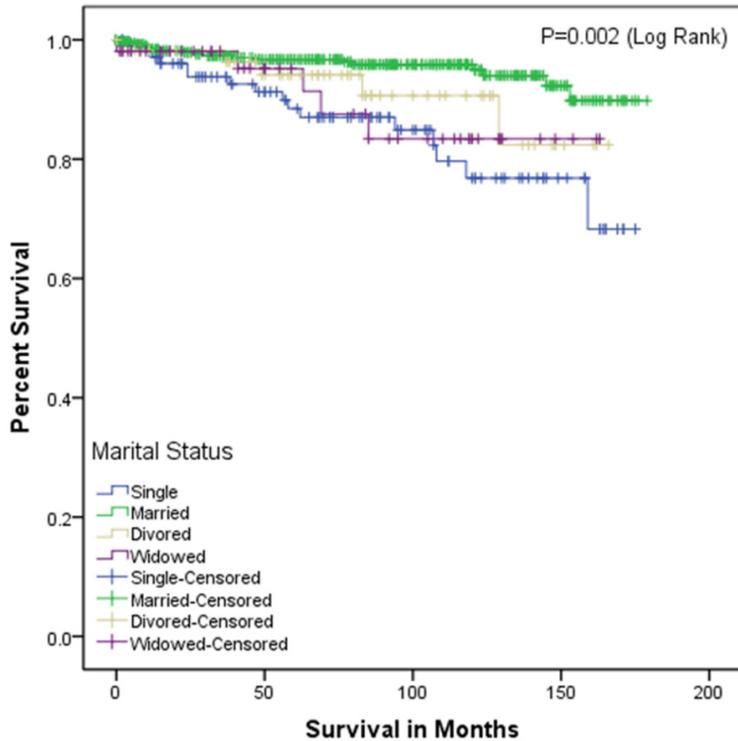


Figure 3. Kaplan-Meier cancer-specific survival curves comparing patient marital status.

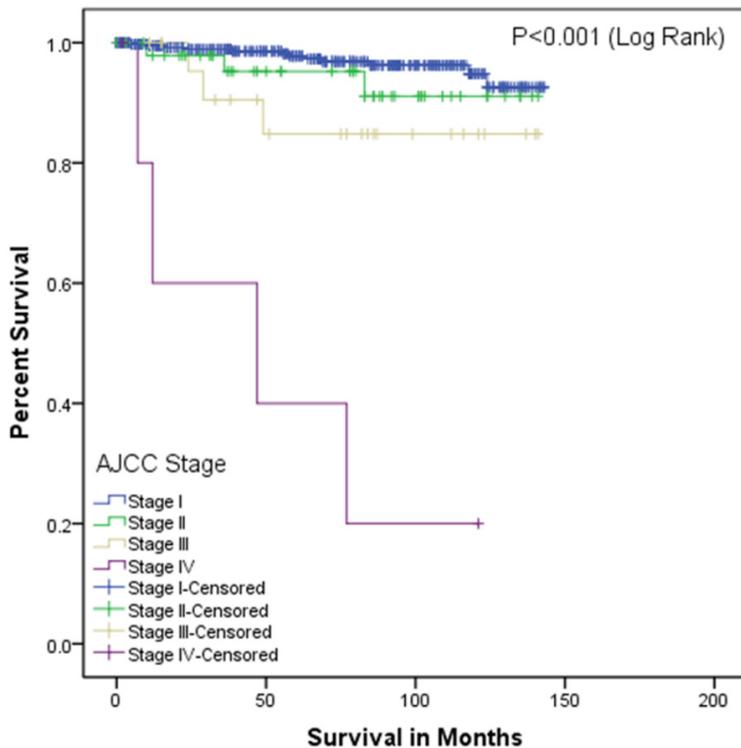


Figure 4. Kaplan-Meier cancer-specific survival curves comparing patient AJCC stage.

patients undergoing local tumor resection was 66.7%. The 1-year, 5-year and 10-year survival rates of patients undergoing partial nephrectomy were 99.2%, 97.9% and 94.6% respectively, whereas the 1-year, 5-year and 10-year cancer-specific survival rates of patients undergoing nephrectomy were 98.6%, 92.6% and 89.2% respectively. COX multivariate analysis showed that the relative risks of local tumor resection, partial nephrectomy and nephrectomy were 0.139, 0.012 and 0.228 times higher than that of patients without primary surgery. The results showed that patients who underwent partial nephrectomy had the best prognosis, while those who did not undergo primary nephrectomy had the worst prognosis.

Discussion

At present, it is believed that CRCC is a type of renal tumor consisting of a large number of cystic masses. The septal tissue between the cysts contains mainly clear cell masses similar to grade I clear cell carcinoma [4]. Hartman divides CRCC into four types according to its basic pathologic mechanisms: intrinsic unilocular growth, intrinsic multiloculated growth, origin from the epithelial lining of a pre-existing simple cyst and cystic necrosis of renal tumor, accounting for 10-33%, 15-40%, 0-18% and 20-33% of all CRCC, respectively [5]. Pathologically, CRCC is characterized by the presence of one or more layers of epithelial cells on the wall and septum of the cyst. The tumor cell can protrude into the cystic cavity or grow on the wall of the cyst and the

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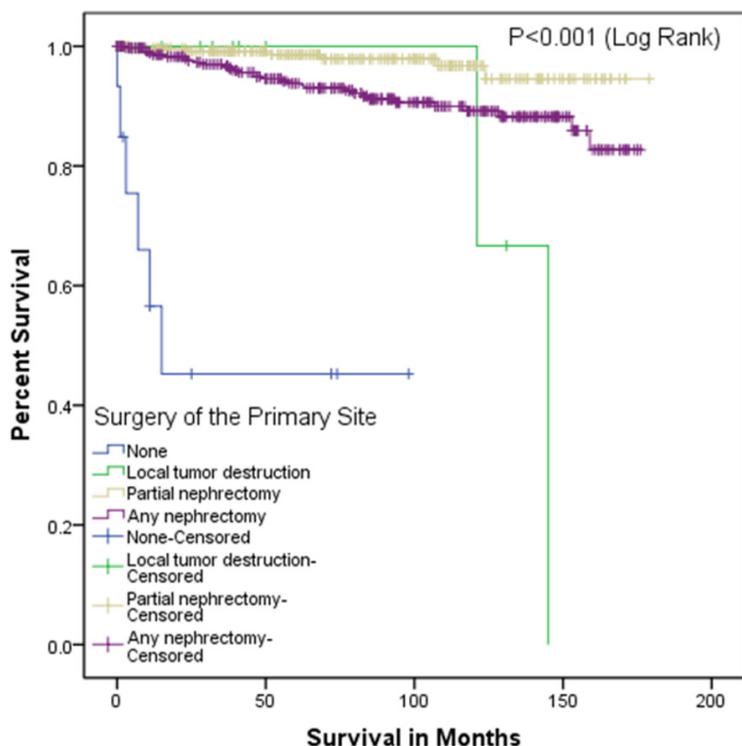


Figure 5. Kaplan-Meier cancer-specific survival curves comparing surgery of primary tumor.

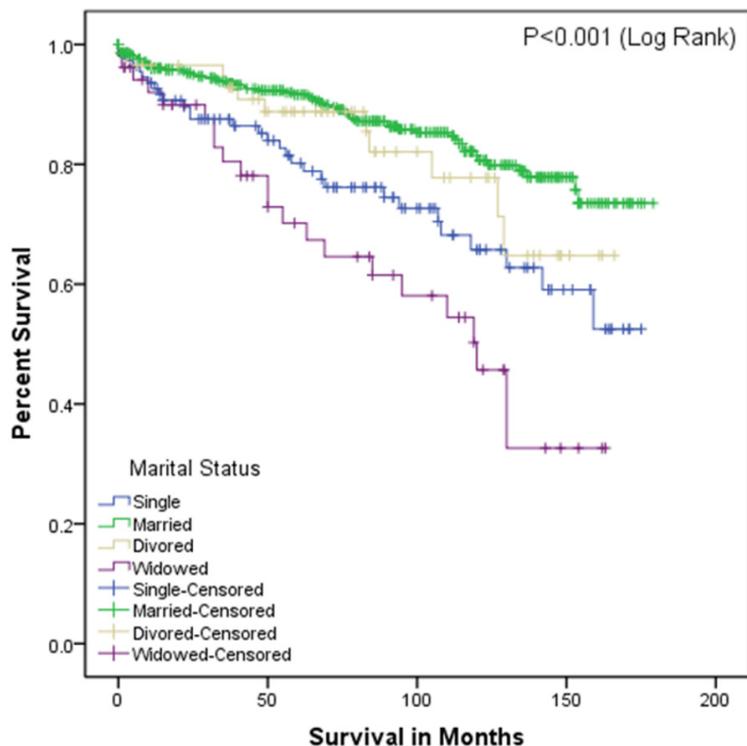


Figure 6. Kaplan-Meier overall survival curves comparing patient marital status.

nuclei of the CRCC cells are World Health Organization/International Society of Urological Pathology (WHO/ISUP) grade 1 or 2 [6, 7]. The immunohistochemistry and molecular pathology of CRCC are similar to that of renal clear cell carcinoma, being PAX8- and CAIX-positive, and most have VHL mutations and 3P deletions, suggesting that there is a correlation with renal clear cell carcinoma at the molecular pathological level [5]. In recent years Fuhrman grading of RCC is no longer applicable to the latest classification of RCC subtypes. The latest WHO/ISUP grading system for renal cell carcinoma was validated only for clear cell and papillary renal cell carcinomas, but has not been validated for other histologic subtypes of renal cell carcinoma. The application of the WHO/ISUP grading system in CRCC remains to be explored [2].

A detailed description of CRCC was not included in the 2004 WHO classification of kidney tumors, although multilocular cystic renal cell carcinoma (MCRCC) is classified as a subtype of RCC and is considered to be a well differentiated clear cell carcinoma, usually classified as Bosniak Classification II-III [8, 9]. Since then, a large amount of clinical data has confirmed that patients with MCRCC have a good prognosis; thus, in the 2016 WHO Classification Of Tumors Of Urinary System And Male Genital Organs, MCRCC was renamed multilocular cystic renal neoplasm of low malignant potential (MCRN-LMP) [7]. Eble postulated that the low malignant potential of MCRN-LMP can be explained from three

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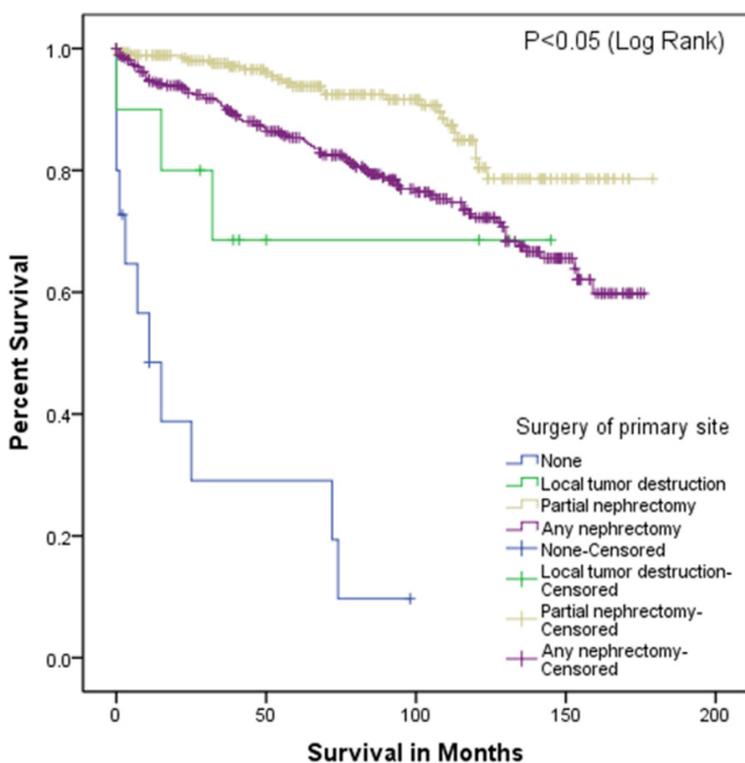


Figure 7. Kaplan-Meier overall survival curves comparing surgery of primary tumor.

aspects: 1. This type of tumor is a fibrous wall-enclosed expansive mass; 2. The tumor is composed entirely of cysts and septal tissues with no growth of solid nodules within them; and 3. The septal tissues between cysts are composed mainly of epithelial cells with clear cytoplasm [10].

The 2016 WHO classification reported a study of more than 200 cases of MCRN-LMP, in which no recurrence or metastasis occurred during more than 5 years of follow-up [7]. In a retrospective study of 76 MCRN-LMP patients conducted in 2016, Li reported that 66 of these patients had no recurrence or metastasis in 55 months after surgery, and only one patient died of primary rectal cancer [11]. In a follow-up of nine CRCC patients after radical nephrectomy for an average of 65 months, Koga found no recurrence or metastasis and the 5-year and 10-year overall survival rates were 100%. These findings suggest that the prognosis of CRCC patients is good, and that surgical treatment can achieve a better survival [12, 13].

In this study, the 5-year cancer-specific survival rate of 678 CRCC patients was 94.7%, and the

5-year cancer-specific survival rate of patients undergoing partial nephrectomy exceeded 97%, which was significantly higher than the survival rate of RCC in previous studies (the 5-year cancer-specific survival rate was 77% after primary tumor surgery) [14]. COX multivariate analysis showed that marital status, AJCC stage and surgery of primary tumor were clinically significant independent prognostic factors for CRCC patients. Some experts also consider that pathological stage, histological grade, histological subtype of RCC, microvascular invasion, tumor necrosis and renal collecting system invasion are important factors that affect the prognosis of CRCC patients [15, 16]. In recent years, numerous studies have confirmed that marital status can be used as a predictor of the prognosis of cancer patients, such as lung cancer,

colorectal cancer, breast cancer, pancreatic cancer, prostate cancer, non-Hodgkin's lymphoma, ovarian cancer, and esophageal cancer. This positive influence on prognosis may be related to more relatives, friends and social support for these patients [17-19]. In 2017, Wang's study of 62,405 RCC patients showed that the 5-year cancer-specific survival rates of married, widowed, single and divorced patients were 80.3%, 69.2%, 78.9%, and 76.5%, respectively, thus, showing a relatively higher cancer-specific mortality in widowed patients [20]. This conclusion was confirmed in our study.

The 8th edition of the AJCC Cancer Staging Manual states that AJCC stage IV includes T4/Any N/M0 and Any T/Any N/M1, which also applies to CRCC staging [2]. In our study, only six CRCC patients were classified as AJCC stage IV (accounting for 0.9% of all patients), which was significantly lower than the corresponding number of RCC patients (total distant metastasis rate was approximately 25% [21]). Of these six patients, four underwent radical nephrectomy with an average survival time of 64.3 months, while the remaining two patients who did not undergo relevant surgical treatment

survived for only 2 and 7 months, respectively. We believe that primary tumor reduction surgery for advanced CRCC patients can improve the prognosis and survival time of these patients. However, for the vast majority of CRCC patients, nephron-sparing surgery is usually the preferred treatment because distant metastasis is rare [8]. We found that CRCC patients with nephron-sparing surgery had the best prognosis, with an average survival time of 174.1 months, which was higher than that of patients who underwent nephrectomy (including radical nephrectomy). However, without primary tumor surgery, the average survival time of CRCC patients was only 48.1 months. Because of the small number of CRCC patients with regional lymph node metastasis and distant metastasis in this study, we were unable to assess whether surgical treatment of metastatic lesions can improve the prognosis of metastatic CRCC patients.

Conclusion

The prognosis of patients with CRCC is good and distant metastasis is rare. The clinical manifestation of CRCC is not specific and similar to that of RCC, and currently, its diagnosis depends mainly on imaging examinations. Based on the survival analysis of patients with CRCC found in the SEER database, we found that marital status, AJCC stage and surgery of primary tumors are closely related to the prognosis of patients with CRCC, and can be used to guide clinical practice. In addition, we believe that, although CRCC has the characteristics of low stage, low grade, low malignancy and good prognosis, early diagnosis and treatment are necessary to improve the prognosis of CRCC.

Acknowledgements

The authors thank all the patients and their families for their cooperation during regular follow-up.

Disclosure of conflict of interest

None.

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