Age is a powerful predictor of survival in pT2N0M0 clear cell renal cell cancer patients: A SEER-based study

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Research article

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Abstract

Background: To elucidate whether age is a prognostic factor in clear cell renal cell cancer (ccRCC) with stage II (pT2N0M0,the American Joint Committee on Cancer 6 th or 7 th staging system) , we analyzed data from the SEER (Surveillance, Epidemiology and End Results) database to evaluate the impact of age on clinicopathological features and survival in pT2N0M0 ccRCC patients.

Methods: A total of 2806 patients with stage II (pT2N0M0) were collected. Patients were categorized into three groups according to age at diagnosis as follows: young age (< 40 years, n = 129), middle-age (40-69 years, n = 2,075), and old age (≥ 70 years, n = 602) groups. Clinicopathological variables and survival rates were compared between the three groups.

Results: 5-year overall survival (OS) rates were 93.0%, 83.9%, 69.3% respectively and 10-year OS rates were 87.6%, 74.5%, 47.0% respectively in the young, middle, and old age groups (P<0.001). 5-year cancer-specific survival (CSS) rates were 94.6%, 88.4%, 84.4% respectively and 10-year CSS rates were 90.7%, 82.1%, 74.6% respectively in the young, middle, and old age groups (P<0.001). Age at diagnosis was the only predictor for both overall survival and cancer-specific survival in multivariate analysis (each P<0.001). Age together with marital status, tumor size and grade were independent prognostic factors for CSS in multivariate analysis (P<0.001,P=0.017, P=0.001, P=0.02 respectively).

Conclusions: Age at diagnosis is a powerful predictor for survival in pT2N0M0 clear cell renal cell cancer patients. Compared to their young counterparts, elder patients have a significantly worse outcome with regard to overall survival and cancer-specific survival.

Background

An estimated 73,820 Americans will be diagnosed with renal cancer and 14,770 will died of this cancer in the United States in 2019 [1]. 3.8% of renal cancer arises from renal parenchyma, named Renal Cell Carcinoma (RCC) which includes all kinds of subtypes. Approximately 80% are clear cell tumors [2].Histological subtype is an independent predictor of patients outcome, and clear cell renal cell cancer (ccRCC) had a worse cancer-specific survival (CSS) when compared to papillary or chromophobe subtype [3]. It is rational to treat patients differently for different subtype, which is based on the awareness of each biological behaviors and prognostic factors.

The role of age at diagnosis in the prognosis of ccRCC has been researched extensively. A early study by Frank I et al presented a prognosis scoring system based tumor stage, size, grade and necrosis in 1,801 adult patients with unilateral clear cell renal cell carcinoma treated with radical nephrectomy, but not including age [4].However, this scoring system cannot be validated by later studies[5–6]. Another study by Gillett et al showed no difference on CSS between young and old patients with ccRCC [7]. But there were only 75 ccRCC patients in the young group in that study. A Korean study with 619 RCC (included 513 ccRCC) by Jung EJ et al revealed that young age was independently associated with a longer cancer-specific survival rate of ccRCC in the American Joint Committee on Cancer(AJCC) stage I/II setting, not in stage III/IV group [8]. Muramaki M et al analyzed 710 Japanese patients with pT1N0M0 RCC (including

625ccRCC), comparing recurrence-free survival between 340 aged ≤60 years and 370 aged >60 years and found that elder patients confers a worse recurrence-free survival [9]. A SEER based study with 8,578 localized RCC (clear cell predominant) patients showed a statistically significant trend toward lower relative survival with increasing age in patients with medium size tumors (4 to 7cm) but no difference for patients with small (less than 4 cm, AJCC T1a) or large (greater than 7 cm, AJCC T2 or more advanced stage) tumors [10]. These studies confirmed that age is a statistics powerful predictor for pT1N0M0 (stage I) ccRCC patients. Considering that above Korean study had only 84 stage II cases, versus 388 stage I cases, the conclusion that young age was a favorable predictor of CSS in stage I/II ccRCC should mainly attribute to stage I cases. Karakiewicz PI et al analysed 3595 patients from 14 European centers who had partial or radical nephrectomy, and showed age at diagnosis is a determinant factor of renal cell carcinoma-specific survival in all stages (from I to IV), with 338 stage II RCC [11]. However, except clear cell subtype, this study also included papillary and chromophobe subtypes. Another study had similar situations when obtaining a significance prognostic different on stage II RCC according to age [12]. So the role of age as a prognostic factor in pT2N0M0 (stage II) ccRCC is not well elucidated.

The aim of this present study was to clarify the prognostic implications of age in stage II (pT2N0M0) ccRCC, using the Surveillance, Epidemiology and End Results (SEER) database.

Methods

2.1 SEER cohort

The dataset we used for this analysis was SEER Program (www.seer.cancer.gov) Research Data (1973–2015), November 2017 Submission. This cohort data were abstracted from the year at diagnosis 2004 to 2010, and the follow-up cutoff date was December 31, 2015. So there was at least 5 years follow-up time. Only patients with microscopically confirmed clear cell renal cell cancer (using the *International Classification of Diseases for Oncology,* Third Edition histology/behavior codes: 8310/3) and stage II (AJCC 6th or 7th TNM staging system) were collected, excluding cases of unknown follow-up and bilaterality. The other variables were obtained from SEER: Sex, Age, Race, Marital Status, Laterality, Tumor Size, Tumor Extension, Grade, Surgery Type. Some variables were regrouped as follow (Table 1):

Age was classified as 3 groups: “<40 years”, “40–69 years”, “≥70 years”.

Race was reclassified into 5 groups: “Caucasian”, “African-American”,”Asian”,”Others”, and “Unknown”.

Marital Status was reclassified into 5 groups: “Single”, “Married”,

“Separated/Divorced”, “Widowed”, “Unknown”.

Tumor size was classified as 3 groups: “7–10cm”, “>10cm”, “Unknown”.

For Tumor Extension, we named “Invasive cancer confined to kidney cortex and/or medulla” as “Kidney Cortex and/or Medulla (KCM)“, and “Renal pelvis or calyces involved /Separate focus of tumor in renal pelvis/calyx” as “Outside KCM”.

Surgery Type was classified as 3 groups: "Nephron-sparing surgery", "Radical nephrectomy", and "Nephrectomy NOS".

2.2 Statistical analysis

Clinical and pathological features were compared between the age groups using the $\chi 2$ test or Fisher's exact test. Kaplan-Meier analyses with log rank tests were then used to compile life tables, and compare survival rates between the different groups. A cox proportional hazards model was used to assess the independent prognostic value of age and other variables. All tests were two-sided with $P < 0.05$ considered to indicate statistical significance. Analyses were performed using SPSS 22.0 software (IBM, NY, USA).

Overall survival (OS) is defined as the months from the date of diagnosis to the date of death or last follow-up. Cancer-specific survival (CSS) was defined as time from diagnosis to death from ccRCC.

Results

3.1Patient and tumor characteristics

A total of 2806 patients with ccRCC of stage II after surgery were identified in the period from the year at diagnosis 2004 to 2010. Patients had a median age of 59 years old (range, 13.0–92.0), other clinical characteristics according to age categories were summarized in Table 1. The male to female ratio was lower in the old age group than in the young and middle-age groups ($P<0.001$). The old age group had more widowed patients than the other age groups (<0.001).No differences in race, laterality, tumor size, extension, grade, or surgery type were observed between the groups.

3.2 Survival analysis according to age at diagnosis and other variables

5-year OS rates were 93.0%, 83.9%, 69.3% respectively and 10-year OS rates were 87.6%, 74.5%, 47.0% respectively in the young, middle, and old age groups ($P<0.001$,Figure 1A). 5-year CSS rates were 94.6%, 88.4%, 84.4% respectively and 10-year CSS rates were 90.7%, 82.1%, 74.6% respectively in the young, middle, and old age groups ($P<0.001$,Figure 1B).

Age at diagnosis was the only predictor of both overall survival and cancer-specific survival in multivariate analysis (each $P<0.001$). Age at diagnosis together with marital status, tumor size, grade, were independent prognostic factors for CSS in multivariate analysis ($P<0.001$, $P = 0.017$, $P = 0.001$, $P = 0.02$ respectively, Table 2).

Discussion

Most previous studies reported the role of age as a prognostic factor in RCC patients with all subtypes and all stages, telling conflicting conclusions [7,11–20]. Of these studies, some have claimed that the prognosis of RCC in younger patients did not differ from that in older patients [13–15]. The most recent multicenter study including 5,178 patients who underwent surgery for RCC showed no significant difference in CSS among three age groups (< 40 years, ≥ 40 and < 60 years, ≥60 years) [15]. However, more studies reported

better CSS rates in young RCC patients than in older ones [16–20]. Although clear cell cancer is the predominant pathological subtype, these studies conclusions can not simply extrapolate to the pT2N0M0 ccRCC setting. Because above studies had limited pT2N0M0 ccRCC cases or no further stratified by stage I and II, or included other subtypes. As we know, because of differences in the prognosis among RCC subtypes, the prognostic implications of age can vary among RCC subtypes. Hence the statistics power is weak.

Several studies exploring the role of age as a prognostic factor in localized RCC (stage I and II) patients suggested that age was a significant predictor of survival [9,12,21–23]. These patient populations also included other subtypes or had relatively few proportion of pT2N0M0 RCC cases (9.7–27%), or no further stratified by stage I and II. So the role of age as a prognostic factor in pT2N0M0 ccRCC is unclear.

In the present SEER-based study, our analysis demonstrated for the first time that age is a powerful independent prognostic factor for OS and CSS in pT2N0M0 ccRCC patient population. Age is the only risk factor for overall survival in multivariable analyses and also the most powerful predictor for CSS (Table 2). We found that old age was associated with worse OS and CSS, especially for≥70 years old patients. There are many possibilities to explain this. First, the elderly patients were more likely to have complications either after radical nephrectomy or after partial nephrectomy, which confers worse survival [24]. Second increasing age companies progressive decline in immune function, which may account for poor survival in elderly RCC patients [25]. Third, majority of pT2N0M0 ccRCC patients received radical nephrectomy (Table 1), which seems to be risk factors associated with a poor outcome if renal function insufficiency happens [26]. Fourth, the old age group had more widowed patients than the other age groups (P<0.001, Table 1), which confers a worse survival [27].

We also found that marital status, tumor size and grade were also independent prognostic factors for CSS in both univariate and multivariate analysis, which is consistent with previous studies [27–29]. With respect to tumor size, our study is not consistent with previous study by Scoll BJ et al who revealed that age was not a significant predictor of relative survival for patients with large (greater than 7 cm) tumors in localized renal cell carcinoma [10]. However, above study sample was from 1988 to 1997, part of the cases with large (greater than 7 cm) tumors was T3 or T4 stage according to modern TNM stage. Besides, its study end point is relative survival instead of CSS.

Our study represents the largest series of pT2N0M0 ccRCC published to date with assessment of the prognostic impact of age in this patient population. Combined with the conclusions from previous studies [8–9], we can confirm that age is a powerful predictor for survival in pT1–2N0M0 ccRCC, so previous conflicting results may be partially explained by the small sample size or the heterogeneity of the study cohort by incorporation of other subtypes and all stages.

Several limitations of the present study should be noted. First, SEER does not collect performance status data, which might be a predictor of CSS in a previous study [35]. Second, SEER does not distinguish sporadic ccRCC from familial cases such as Von Hippel-Lindau disease (VHL). However VHL disease is the most common cause of hereditary renal cell carcinoma and comprises only about 2–3% of the total RCC

incidence. RCCs tend to be multifocal and bilateral in the setting of VHL disease [30]. In this settings, we had excluded cases of bilaterality, so the bias is small.

Conclusions

Our analysis suggests that age at diagnosis is a powerful predictor of survival in pT2N0M0 clear cell renal cell cancer patients. Compared to their young counterparts, elder patients have a significantly worse outcome with regard to overall survival and cancer-specific survival. It is important to determine subtype-specific and stage-specific therapies and follow-up schedule according to age.

Abbreviations

ccRCC:Clear cell renal cell cancer; SEER:Surveillance, Epidemiology and End Results; OS:Overall survival;OS:Overall survival;RCC:Renal cell cancer;AJCC:the American Joint Committee on Cancer; KCM:Kidney cortex and/or medulla; NOS:Not Otherwise Specified;VHL:Von Hippel-Lindau disease

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws. The SEER database is the publicly available cancer dataset. This study was deemed exempt from ethical approval and informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

Dataset of this study will be available from the website: *https://seer.cancer.gov/.*

Competing interests

Neither author has any conflict of interest.

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Not applicable.

Authors' Contributions

Conception of work:Kaiyuan Teng, Lanting Huang;Data collection:Lanting Huang, Wenfang Cheng, Juhui Chen;Data analysis and interpretation:Lanting Huang, Wenfang Cheng. Drafting the manuscript::Lanting Huang, Wenfang Cheng, Juhui Chen. Critical review of the manuscript: Kaiyuan Teng, Lanting Huang, Wenfang Cheng. Final approval of version to be published: Lanting Huang, Wenfang Cheng, Juhui Chen,Kaiyuan Teng. All authors read and approved the final manuscript.

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Tables

Table 1 Patient and tumor characteristics

Variable	Age categories (%)			p Value
	<40 years	40-69 years	≥70 years	
No.pts	129	2075	602	
Sex				<0.001
Male	83 (64.3)	1352 (65.2)	329 (54.7)	
Female	46 (35.7)	723 (34.8)	273 (45.3)	
Race				0.086
Caucasian	100 (77.5)	1767 (85.2)	517 (85.9)	
African-American	16 (12.4)	165 (8.0)	35 (5.8)	
Asian	6 (4.7)	84 (4.0)	34 (5.6)	
Others	4 (3.1)	36 (1.7)	8 (1.3)	
Unknown	3 (2.3)	23 (1.1)	8 (1.3)	
Marital Status				<0.001
Single	48 (37.2)	324 (15.6)	43 (7.1)	
Married	65 (50.4)	1357 (65.4)	360 (59.8)	
Separated/Divorced	9 (7)	232 (11.2)	40 (6.6)	
Widowed	0 (0)	82 (4.0)	144 (23.9)	
Unknown	7 (5.4)	80 (3.9)	15 (2.5)	
Laterality				0.541
Right	58 (45.0)	1020 (49.2)	286 (47.5)	
Left	71 (55.0)	1055 (50.8)	316 (52.5)	
Tumor size				0.148
7-10cm	92 (71.3)	1526 (73.5)	470 (78.1)	
>10cm	37 (28.7)	547 (26.4)	132 (21.9)	
Unknown	0 (0)	2 (0.1)	0 (0)	
Extension				0.812
KCM	101 (78.3)	1612 (77.7)	468 (77.7)	
Outside KCM	23 (17.8)	347 (16.7)	106 (17.6)	
Unknown	5 (3.9)	116 (5.6)	28 (4.7)	
Grade				0.211
Well differentiated	14 (10.9)	172 (8.3)	46 (7.6)	
Moderately differentiated	68 (52.7)	974 (46.9)	281 (46.7)	
Poorly differentiated	29 (22.5)	666 (32.1)	189 (31.4)	
Undifferentiated	6 (4.7)	114 (5.5)	46 (7.6)	
Unknown	12 (9.3)	149 (7.2)	40 (6.6)	
Surgery Type				0.480
Nephron-sparing surgery	4 (3.1)	81 (3.9)	15 (2.5)	
Radical nephrectomy	122 (94.6)	1957 (94.3)	578 (96.0)	
Nephrectomy NOS	3 (2.3)	37 (1.8)	9 (1.5)	

Abbreviations: KCM =Kidney Cortex and/or Medulla; NOS = Not Otherwise Specified.

Table 2 Patient characteristics and survival analysis for pT2N0M0 ccRCC.

Variables	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age		<0.001		<0.001		<0.001		<0.001
<40 years	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
40-69 years	2.16 (1.34-3.51)	0.002	2.16 (1.34-3.51)		1.97 (1.13-3.42)		1.97 (1.13-3.42)	0.017
≥70 years	5.40 (3.32-8.80)	<0.001	5.40 (3.32-8.80)		3.39 (1.93-5.97)		3.35 (1.90-5.90)	<0.001
Sex		0.520				0.692		
Male	1.00 (reference)				1.00 (reference)			
Female	0.96 (0.83-1.10)	0.520			0.97 (0.81-1.15)			
Race		0.697				0.679		
Caucasian	1.00 (reference)				1.00 (reference)			
African-American	0.96 (0.75-1.23)	0.74			0.85 (0.60-1.19)	0.337		
Asian	1.06 (0.77-1.46)	0.74			1.36 (0.94-1.95)	0.352		
Others	0.75 (0.42-1.32)	0.31			0.70 (0.33-1.48)	0.102		
Unknown	0.86 (0.46-1.61)	0.64			0.83 (0.37-1.86)	0.657		
Marital Status		<0.001				0.001		0.017
Single	1.00 (reference)				1.00 (reference)		1.00 (reference)	
Married	1.03 (0.84-1.25)	0.81			1.14 (0.88-1.49)	0.323	1.04 (0.80-1.36)	0.749
Separated/Divorced	1.27 (0.97-1.66)	0.08			1.48 (1.05-2.08)	0.026	1.39 (0.99-1.96)	0.059
Widowed	2.14 (1.66-2.77)	<0.001			2.18 (1.56-3.06)	<0.001	1.58 (1.10-2.26)	0.013
Unknown	0.96 (0.63-1.47)	0.856			1.30 (0.79-2.15)	0.299	1.23 (0.75-2.03)	0.418
Laterality		0.076				0.123		
Right	1.00 (reference)				1.00 (reference)			
Left	1.13 (-)	0.076			1.14 (0.97-1.35)	0.123		
Tumor size		0.803				0.002		0.001
7-10cm	1.00 (reference)				1.00 (reference)		1.00 (reference)	
>10cm	1.02 (0.88-1.19)	0.756			1.33 (1.11-1.59)	0.002	1.35 (1.13-1.62)	0.001
Unknown	-	-			-	-	-	-
Extension		0.650				0.701		
KCM	1.00 (reference)				1.00 (reference)			
Outside KCM	1.29 (1.09-1.52)	0.003			1.32 (1.08-1.63)	0.008		
Unknown	1.02 (0.75-1.39)	0.914			1.02 (0.68-1.51)	0.934		
Grade		0.265				0.029		0.020
Well differentiated	1.00 (reference)				1.00 (reference)		1.00 (reference)	

Moderately differentiated	1.22 (0.92-1.61)	0.161	1.33 (0.90-1.96)	0.149	1.31 (0.89-1.93)	0.172
Poorly differentiated	1.62 (1.22-2.15)	0.001	2.12 (1.44-3.13)	<0.001	2.08 (1.41-3.07)	<0.001
Undifferentiated	2.55 (1.81-3.59)	<0.001	3.83 (2.46-5.96)	<0.001	3.78 (2.43-5.89)	<0.001
Unknown	1.16 (0.80-1.67)	0.439	1.47 (0.91-2.39)	0.119	1.49 (0.92-2.42)	0.108
Surgery Type		0.750		0.376		
Nephron-sparing surgery	1.00 (reference)		1.00 (reference)			
radical nephrectomy	0.96 (0.68-1.37)	0.838	1.07 (0.67-1.71)			
Nephrectomy NOS	1.19 (0.66-2.14)	0.568	1.49 (0.72-3.09)			

Abbreviations: KCM =Kidney Cortex and/or Medulla; NOS = Not Otherwise Specified; HR= Hazard Ratio; CI=confidence interval.

Figures

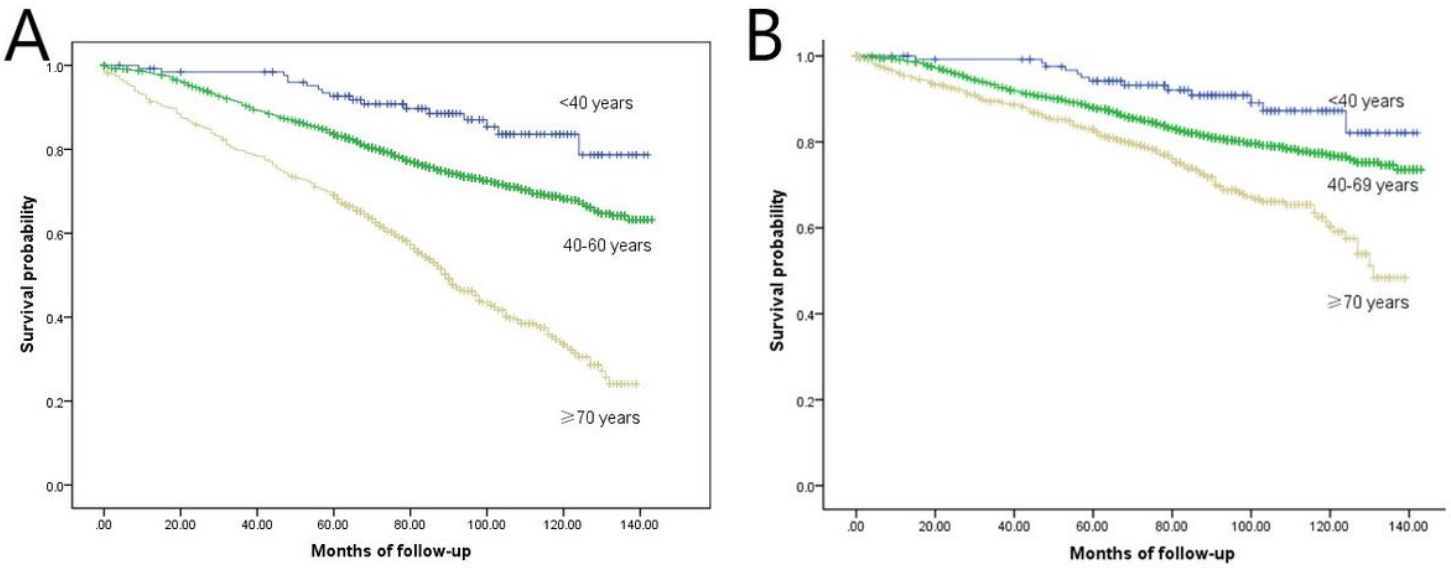

Figure 1

A. Kaplan–Meier curve of overall survival according to age. 5-year OS rates were 93.0%, 83.9%, 69.3% respectively and 10-year OS rates were 87.6%, 74.5%, 47.0% respectively in the young, middle, and old age groups (Log-lank, P<0.001). B. Kaplan–Meier curve of cancer-specific survival according to age. 5-year CSS rates were 94.6%, 88.4%, 84.4% respectively and 10-year CSS rates were 90.7%, 82.1%, 74.6% respectively in the young, middle, and old age groups (Log-lank, P<0.001).