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

Keywords: Renal cell cancer; Clear cell; Age; Survival; SEER Program

Posted Date: September 11th, 2019

DOI: https://doi.org/10.21203/rs.2.14303/v1

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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 6th or 7th 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 7 cm) 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: “7–10 cm”, “>10 cm”, “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”.

Page 3/12
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 χ2 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

3.1 Patient 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; 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/](https://seer.cancer.gov/).

**Competing interests**

Neither author has any conflict of interest.

**Funding**

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. 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.

Acknowledgements

We would like to thank National Cancer Institute in the USA who provided the publicly available cancer dataset and all of the participating patients.

References

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; Jan; 69(1): 7–34.
2. Moch H, Gasser T, Amin MB et al. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors. Cancer Aug. 2000; 1; 89(3): 604–14.
3. Leibovich BC, Lohse CM, Crispen PL et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol. 2010 Apr; 183(4): 1309–15.
4. Frank I, Blute ML, Cheville JC et al. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol. 2002; 168: 2395–400.
5. Waalkes S, Becker F, Schrader AJ et al. Is there a need to further subclassify pT2 renal cell cancers as implemented by the revised 7th TNM version? Eur Urol. 2011; 59: 258–63.
6. Novara G, Ficarra V, Antonelli A et al. Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? Eur Urol. 2010; 58: 588–95.
7. Gillett MD, Cheville JC, Karnes RJ, et al. Comparison of presentation and outcome for patients 18 to 40 and 60 to 70 years old with solid renal masses. J Urol. 2005; 173: 1893–1896.
8. Jung EJ, Lee HJ, Kwak C et al. Young age is independent prognostic factor for cancer-specific survival of low-stage clear cell renal cell carcinoma. Urology. 2009 Jan; 73(1): 137–41.
9. Muramaki M, Miyake H, Sakai I et al. Age at diagnosis as a powerful predictor for disease recurrence after radical nephrectomy in Japanese patients with pT1 renal cell carcinoma. Int J Urol. 2011 Feb; 18(2): 121–5.
10. Scoll BJ, Wong YN, Egleston BL et al. Age, tumor size and relative survival of patients with localized renal cell carcinoma: a surveillance, epidemiology and end results analysis. J Urol. 2009 Feb; 181(2): 506–11.
11. Karakiewicz PI, Jeldres C, Suardi N et al. Age at diagnosis is a determinant factor of renal cell carcinoma-specific survival in patients treated with nephrectomy. Can Urol Assoc J. 2008;2: 610–7.

12. Komai Y, Fujii Y, limura Y et al. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology. 2011 Apr;77(4):842–7.

13. Abou El Fettouh HI, Cherullo EE et al. Sporadic renal cell carcinoma in young adults: Presentation, treatment, and outcome. Urology. 2002;60:806–810.

14. Patard JJ, Leray E, Rioux-Leclercq N et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol. 2005;23:2763.

15. Kang HW, Seo SP, Kim WT et al. Impact of Young Age at Diagnosis on Survival in Patients with Surgically Treated Renal Cell Carcinoma: a Multicenter Study. J Korean Med Sci. 2016 Dec;31(12):1976–1982.

16. Verhoest G, Veillard D, Guillé F et al. Relationship between age at diagnosis and clinicopathologic features of renal cell carcinoma. Eur Urol. 2007 May;51(5):1298–304; discussion 1304–5. Epub 2006 Dec 8.

17. Taccoen X, Valeri A, Descotes JL et al. Renal cell carcinoma in adults 40 years old or less: young age is an independent prognostic factor for cancer-specific survival. Eur Urol. 2007 Apr;51(4):980–7. Epub 2006 Oct 25.

18. Hupe MC, Merseburger AS, Lokeshwar VB et al. Age—an independent prognostic factor of clinical outcome in renal malignancies: results of a large study over two decades. World J Urol. 2014;32: 115–21.

19. Rampersaud EN, Klatte T, Bass G et al. The effect of gender and age on kidney cancer survival: younger age is an independent prognostic factor in women with renal cell carcinoma. Urol Oncol. 2014 Jan;32(1):30.e9–13.

20. Aziz A, May M, Zigeuner R et al. Do young patients with renal cell carcinoma feature a distinct outcome after surgery? A comparative analysis of patient age based on the multinational CORONA database. J Urol. 2014 Feb;191(2):310–5.

21. Ficarra V, Guillè F, Schips L et al. Proposal for revision of the TNM classification system for renal cell carcinoma. Cancer. 2005 Nov 15;104(10):2116–23.

22. Cai M, Wei J, Zhang Z et al. Impact of age on the cancer-specific survival of patients with localized renal cell carcinoma: martingale residual and competing risks analysis. PLoS One. 2012;7(10):e48489.

23. Komai Y, Fujii Y, limura Y et al. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology. 2011 Apr;77(4):842–7.

24. Abouassaly R, Alibhai SM, Tomlinson GA et al. The effect of age on the morbidity of kidney surgery. J Urol. 2011 Sep;186(3):811–6.

25. Hakim FT, Flomerfelt FA, Boyiadzis M et al. Aging, immunity and cancer. Curr Opin Immunol. 2004;16: 151–6.

26. Sejima T, Iwamoto H, Masago T et al. Oncological and functional outcomes after radical nephrectomy for renal cell carcinoma: a comprehensive analysis of prognostic factors. Int J Urol. 2013
27. Marchioni M, Martel T, Bandini M et al. Marital status and gender affect stage, tumor grade, treatment type and cancer specific mortality in T1–2 N0 M0 renal cell carcinoma. World J Urol. 2017 Dec;35(12):1899–1905.

28. Rank I, Blute ML, Cheville JC et al. A multifactorial postoperative surveillance model for patients with surgically treated clear cell renal cell carcinoma. J Urol. 2003;170:2225–32.

29. Klatte T, Patard JJ, Goel RH et al. Prognostic impact of tumor size on pT2 renal cell carcinoma: an international multicenter experience. J Urol. 2007; Jul;178(1):35–40; discussion 40.

30. Meister M, Choyke P, Anderson C et al. Radiological evaluation, management and surveillance of renal masses in von Hippel-Lindau disease. Clinical Radiology. 2009;64:589–600.

Tables

Table 1 Patient and tumor characteristics
### Table 2: Patient characteristics and survival analysis for pT2N0M0 ccRCC.

| Variable                        | <40 years | 40-69 years | ≥70 years | p Value |
|---------------------------------|-----------|-------------|-----------|---------|
| 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.
| Variables       | Overall survival | Cancer-specific survival | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|-----------------|------------------|--------------------------|---------------------|-----------------------|---------------------|-----------------------|
| Age             |                  |                          |                     |                       |                     |                       |
| <40 years       | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)    | 1.00 (reference)      | 1.00 (reference)    | 1.00 (reference)      |
| 40-69 years     | 2.16 (1.34-3.51) | <0.001                   | 1.97 (1.13-3.42)    | 0.017                 | 3.39 (1.93-5.97)    | <0.001                |
| ≥70 years       | 5.40 (3.32-8.80) | <0.001                   | 1.97 (1.13-3.42)    | 0.017                 | 3.39 (1.93-5.97)    | <0.001                |
| Sex             |                  |                          |                     |                       |                     |                       |
| Male            | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)    | 1.00 (reference)      | 1.00 (reference)    | 1.00 (reference)      |
| Female          | 0.96 (0.83-1.10) | 0.520                    | 0.97 (0.81-1.15)    |                       | 0.97 (0.81-1.15)    |                       |
| Race            |                  |                          |                     |                       |                     |                       |
| Caucasian       | 1.00 (reference) | 0.697                    | 1.00 (reference)    | 0.679                 | 1.00 (reference)    | 0.679                 |
| African-American| 0.96 (0.75-1.23) | 0.74                     | 0.85 (0.60-1.19)    | 0.337                 | 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                 | 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                 | 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                 | 0.83 (0.37-1.86)    | 0.657                 |
| Marital Status  |                  |                          |                     |                       |                     |                       |
| Single          | 1.00 (reference) | <0.001                   | 1.00 (reference)    | 0.001                 | 1.00 (reference)    | 0.017                 |
| Married         | 1.03 (0.84-1.25) | 0.81                     | 1.14 (0.88-1.49)    | 0.323                 | 1.14 (0.88-1.49)    | 0.323                 |
| Separated/Divorced | 1.27 (0.97-1.66) | 0.08                     | 1.48 (1.05-2.08)    | 0.026                 | 1.48 (1.05-2.08)    | 0.026                 |
| Widowed         | 2.14 (1.66-2.77) | <0.001                   | 2.18 (1.56-3.06)    | <0.001                | 2.18 (1.56-3.06)    | <0.001                |
| Unknown         | 0.96 (0.63-1.47) | 0.856                    | 1.30 (0.79-2.15)    | 0.299                 | 1.30 (0.79-2.15)    | 0.299                 |
| Laterality      |                  |                          |                     |                       |                     |                       |
| Right           | 1.00 (reference) | 0.076                    | 1.00 (reference)    | 0.123                 | 1.00 (reference)    | 0.123                 |
| Left            | 1.13 (-)         | 0.076                    | 1.14 (0.97-1.35)    | 0.123                 | 1.14 (0.97-1.35)    | 0.123                 |
| Tumor size      |                  |                          |                     |                       |                     |                       |
| 7-10cm          | 1.00 (reference) | 0.803                    | 1.00 (reference)    | 0.002                 | 1.00 (reference)    | 0.001                 |
| >10cm           | 1.02 (0.88-1.19) | 0.756                    | 1.33 (1.11-1.59)    | 0.002                 | 1.33 (1.11-1.59)    | 0.002                 |
| Unknown         |                  | -                        | -                   | -                     | -                   | -                     |
| Extension       |                  |                          |                     |                       |                     |                       |
| KCM             | 1.00 (reference) | 0.650                    | 1.00 (reference)    | 0.701                 | 1.00 (reference)    | 0.701                 |
| Outside KCM     | 1.29 (1.09-1.52) | 0.003                    | 1.32 (1.08-1.63)    | 0.008                 | 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                 | 1.02 (0.68-1.51)    | 0.934                 |
| Grade           |                  |                          |                     |                       |                     |                       |
| Well differentiated | 1.00 (reference) | 0.265                    | 1.00 (reference)    | 0.029                 | 1.00 (reference)    | 0.020                 |
| Grade                | Hazard Ratio (95% CI) | p-value |
|----------------------|-----------------------|---------|
| Moderately differentiated | 1.22 (0.92-1.61)     | 0.161   |
| Poorly differentiated  | 2.16 (1.22-3.71)     | <0.001  |
| Undifferentiated      | 3.83 (2.46-5.96)     | <0.001  |
| Unknown               | 1.47 (0.91-2.39)     | 0.108   |

| Surgery Type          | Hazard Ratio (95% CI) | p-value |
|-----------------------|-----------------------|---------|
| Nephron-sparing surgery | 1.00 (reference)     | 0.750   |
| Radical nephrectomy   | 0.96 (0.68-1.33)     | 0.838   |
| Nephrectomy NOS       | 1.19 (0.66-2.14)     | 0.568   |

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).