Young age is associated with decreased recurrence for renal cell carcinoma

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Introduction: *We aimed to examine stage-specific oncologic outcomes for young versus conventional-age patients with localized disease in a modern cohort.*

Materials and methods: *The Surveillance, Epidemiology and End Results database was queried for patients with T1-T2N0M0 kidney cancer from 1975-2016, including clear cell, papillary, and chromophobe renal cell carcinoma. Patients were stratified into ≤ 40 years-old or > 40 years-old cohorts and underwent definitive treatment via percutaneous ablation, partial nephrectomy, or radical nephrectomy. Primary outcome was cancer-specific survival. Cox regression and Kaplan-Meier analysis were performed.*

Results: *A total of 44,673 patients were identified with 41,812 patients in the conventional-age and 2,861 patients in the young cohort with mean ages of 62.1 and 34.7 years old, respectively. The young cohort had a higher proportion of T1a disease compared to the conventional-age cohort (65.2% vs. 58.6%) and a lower proportion of the cT1b (24.4% vs. 29.3%), cT2a (6.8% vs. 8.4%), and cT2b (3.6% vs. 3.7%) disease. Chromophobe histology was more prevalent in the younger population (10.5% vs. 6.6%). Nuclear grade 3 or 4 were more prominent in the conventional-age population (24.8% vs. 19.1%). Cancer-specific death was significantly higher in the conventional-age cohort (2.4% vs. 0.7%). Cox regression analysis demonstrated patients > 40 years old, increasing stage, and higher grade were at independently increased risk of cancer-specific death. Kaplan-Meier analysis showed significantly improved 5-year cancer-specific survival for the young versus conventional-age cohorts when sub-stratified by stage.*

Conclusion: *When stratified by stage, young patients with localized kidney cancer experience improved cancer-specific survival.*

Key Words: renal cell carcinoma, clinical practice pattern, survival, age

Introduction

Kidney cancer accounts for approximately 4.1% of all new cancers in the United States with an estimated 79,000 new cases and 13,920 deaths in 2022.[1] Conventional renal cell carcinoma (RCC) occurs primarily in older adults between 60 and 70 years of age with a 1.5:1 predominance in men over women.[2] Several histologic subtypes of RCC have been identified, including clear cell, papillary, and chromophobe variants.[3] It remains unclear what effect younger age can have on RCC diagnosis and prognosis.

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The development and widespread use of abdominal imaging has led to an increased incidental detection of RCC in all age groups.[4] Although sporadic RCC in adults younger than 40 years old accounts for a small percentage of cases, RCC incidence has been increasing over the past several decades, even in younger adults.[5,6] Furthermore, studies have shown that incidentally discovered renal cell tumors are of significantly lower stage and grade than symptomatic tumors and that patients with symptomatic RCC had worse survival than those diagnosed incidentally.[7,8] While age has also been shown to be an independent prognostic factor for cancer-specific survival (CSS) in historical series, the etiology of age-related cancer outcomes is unclear and has not been examined in a modern cohort.[9] The rising incidence of RCC in younger adults and the prognostic significance of age warrants further investigation into the association between age and CSS. We aim to

examine stage-specific oncologic outcomes for young versus conventional-age patients with localized disease from a national cohort.

Materials and methods

The Surveillance, Epidemiology, and End Results (SEER) Program provides information on cancer statistics and is supported by the Surveillance Research Program in the National Cancer Institute's Division of Cancer Control and Population Sciences. The chosen dataset spans 18 regions across the United States and represents 27.8% of the population.[10] We queried this dataset for patients with kidney cancer, including clear cell, papillary, and chromophobe histology. Patients in whom this was not their first malignancy were excluded. Demographic and clinical variables collected from the population of interest included age, race, sex, insurance status, clinical stage, treatment type, nuclear grade, and mortality status.

Descriptive analysis was performed for the entire cohort and categorized by age, labeled as young (≤ 40 years-old) and conventional-age (> 40 years-old), and cancer-specific death. Kaplan-Meier analysis was performed for cancer specific survival, sub-stratified by presenting clinical stage. Cox regression for cancer-specific death was performed and included factors that were statistically significant on univariate analysis (age, insurance status, stage, treatment type, histology, nuclear grade). We utilized SPSS v27 (New York, USA) for all analyses, with p value of < 0.05 denoting statistical significance. Our primary outcome was a cancer-specific survival.

Results

The patient demographics and clinical tumor characteristics for non-metastatic disease with definitive treatment (cT1-2N0M0) can be found in Table 1. A total of 44,673 patients were identified with 41,812 patients in the conventional-age and 2,861

TABLE 1. **Patient demographics and clinical tumor characteristics for localized disease with definitive treatment (cT1-2N0M0)**

Variable	All (n = 44,673)	Age > 40 (n = 41,812)	Age ≤ 40 (n = 2,861)	Sig
Mean age	60.3 ± 12.3	62.1 ± 10.6	34.7 ± 4.7	< 0.001
Race				0.001
White	35,680 (79.9%)	33,411 (79.9%)	2,269 (79.3%)	
Black	5,778 (12.9%)	5,433 (13.0%)	345 (12.1%)	
Other	2,816 (6.3%)	2,611 (6.2%)	205 (7.2%)	
Unknown	399 (0.9%)	357 (0.9%)	42 (1.5%)	
Male	27,741 (62.1%)	26,058 (62.3%)	1,683 (58.8%)	< 0.001
Insurance status				< 0.001
Unknown	676 (1.5%)	623 (1.5%)	53 (1.9%)	
Insured	37,930 (84.9%)	35,790 (85.6%)	2,140 (74.8%)	
Medicaid	4,912 (11.0%)	4,412 (10.6%)	500 (17.5%)	
Uninsured	1,155 (2.6%)	987 (2.4%)	168 (5.9%)	
cT Stage				< 0.001
cT1				
cT1a	26,383 (59.1%)	24,517 (58.6%)	1,866 (65.2%)	
cT1b	12,929 (28.9%)	12,232 (29.3%)	697 (24.4%)	
cT2				
cT2a	3,723 (8.3%)	3,528 (8.4%)	195 (6.8%)	
cT2b	1,638 (3.7%)	1,535 (3.7%)	103 (3.6%)	
Treatment type				< 0.001
Ablation	1,096 (2.5%)	1,074 (2.6%)	22 (0.8%)	
Partial	21,551 (48.2%)	19,818 (47.4%)	1,733 (60.6%)	
Radical	22,026 (49.3%)	20,920 (50.0%)	1,106 (38.7%)	

TABLE 2. **Histology and survival outcomes for localized disease with definitive treatment (cT1-2N0M0)**

Variable	All (n = 44,673)	Age > 40 (n = 41,812)	Age ≤ 40 (n = 2,861)	Sig
Histology				< 0.001
Clear cell	34,463 (77.1%)	32,154 (76.9%)	2,309 (80.7%)	
Chromophobe	3,071 (6.9%)	2,770 (6.6%)	301 (10.5%)	
Papillary	7,139 (16.0%)	6,888 (16.5%)	251 (8.8%)	
Nuclear grade				< 0.001
1 or 2	27,067 (60.6%)	25,165 (60.2%)	1,902 (66.5%)	
3 or 4	10,922 (24.4%)	10,375 (24.8%)	547 (19.1%)	
Unknown	6,684 (15.0%)	6,272 (15.0%)	412 (14.4%)	
All cause death	4,383 (9.8%)	4,326 (10.3%)	57 (2.0%)	< 0.001
Cancer specific death	1,028 (2.3%)	1,009 (2.4%)	19 (0.7%)	< 0.001
T1a	285 (27.7%)	281 (27.8%)	4 (21.1%)	
T1b	409 (39.8%)	401 (39.7%)	8 (42.1%)	
T2a	206 (20.0%)	201 (19.9%)	5 (26.3%)	
T2b	128 (12.5%)	126 (12.5%)	2 (10.5%)	

patients in the young cohort with mean ages of 62.1 ± 10.6 and 34.7 ± 4.7 years old, respectively. The studied population was predominantly male (62.1%) and white (79.9%). The young cohort had a higher proportion of T1a disease compared to the conventional-age cohort (65.2% vs. 58.6%) and a lower proportion of the cT1b (24.4% vs. 29.3%), cT2a (6.8% vs. 8.4%), and cT2b (3.6% vs. 3.7%) disease, $p < 0.001$. The young cohort was predominantly treated with partial nephrectomy (60.6%) and rarely received ablative therapy (0.8%). The conventional-age cohort was more likely to receive radical nephrectomy (50.0% vs. 38.7%) and ablative therapy (2.6% vs. 0.8%).

Table 2 includes the histology and survival outcomes for the study population. Chromophobe histology was more prevalent in the younger population (10.5% vs. 6.6%) while papillary type was less so (8.8% vs. 16.5%). Nuclear grade 3 or 4 were more prominent in the conventional-age population (24.8% vs. 19.1%). The rate of cancer-specific death was significantly higher in the conventional-age cohort (2.4% vs. 0.7%, $p < 0.001$).

Patient demographics and disease characteristics including stage, histology, and nuclear grade for cancer-specific death are displayed in Table 3. Of the studied population, 1,028 patients had cancer-specific death that presented with non-metastatic disease and received definitive treatment, while 43,645 had a non-cancer death. Majority of those with a cancer-specific death had the clear cell histology subtype (82.0%) while papillary was the next most common (15.3%) followed by chromophobe (2.7%). Those with a cancer-specific death were more likely to have a more advanced stage and a higher-grade malignancy (both $p < 0.001$).

Cox regression analysis summarized in Table 4 demonstrated patients > 40 years old (HR = 2.94), increasing stage (HR = 2.16-4.82), and higher grade (HR = 2.35) were at independently increased risk of cancer-specific death (all $p < 0.001$). Kaplan-Meier analysis represented in Figures 1-3 shows a significantly improved 5-year cancer-specific survival for the young versus conventional-age cohorts when sub-stratified by presenting clinical stage, with increasing differences associated with advancing stage (cT1a 99.5% vs. 98.3%, cT1b 97.3% vs. 95.3%, cT2 95.6% vs. 90.8%; all $p < 0.05$).

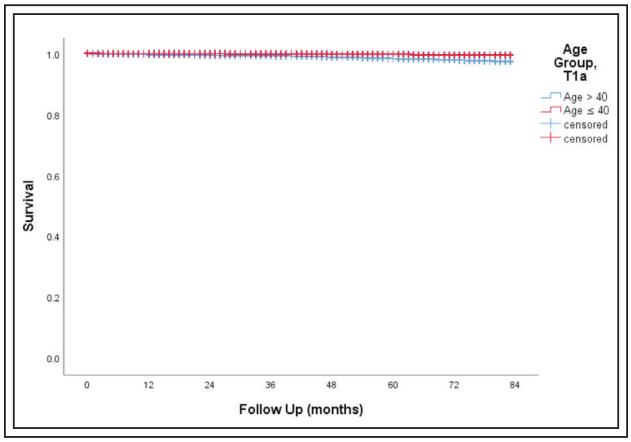

Figure 1. Kaplan-Meier cancer specific survival (includes T1a patients).

TABLE 3. **Patient demographics and disease characteristics for cancer specific death with localized disease and definitive treatment (cT1-2N0M0)**

Variable	All (n = 44,673)	No cancer death (n = 43,645)	Cancer specific death (n = 1,028)	Sig
Mean age	60.3 ± 12.3	60.2 ± 12.3	65.7 ± 11.4	< 0.001
Race				0.981
White	35,680 (79.9%)	34,854 (80.6%)	826 (80.4%)	
Black	5,778 (12.9%)	5,642 (13.0%)	136 (13.2%)	
Other	2,816 (6.3%)	2,750 (6.4%)	66 (6.4%)	
Unknown	399 (0.9%)	399	0	
Male	27,741 (62.1%)	27,079 (62.0%)	662 (64.4%)	0.127
Insurance status				0.005
Unknown	676 (1.5%)	662 (1.5%)	14 (1.4%)	
Insured	37,930 (84.9%)	37,086 (85.0%)	844 (82.1%)	
Medicaid	4,912 (11.0%)	4,764 (10.9%)	148 (14.4%)	
Uninsured	1,155 (2.6%)	1,133 (2.6%)	22 (2.1%)	
cT stage				< 0.001
cT1				
cT1a	26,383 (59.1%)	26,098 (59.8%)	285 (27.7%)	
cT1b	12,929 (28.9%)	12,520 (28.7%)	409 (39.8%)	
cT2				
cT2a	3,723 (8.3%)	3,517 (8.1%)	206 (20.0%)	
cT2b	1,638 (3.7%)	1,510 (3.5%)	128 (12.5%)	
Treatment type				< 0.001
Ablation	1,096 (2.5%)	1,068 (2.4%)	28 (2.7%)	
Partial	21,551 (48.2%)	21,351 (48.9%)	200 (19.5%)	
Radical	22,026 (49.3%)	21,226 (48.6%)	800 (77.8%)	
Histology				< 0.001
Clear cell	34,463 (77.1%)	33,620 (77.0%)	843 (82.0%)	
Chromophobe	3,071 (6.9%)	3,043 (7.0%)	28 (2.7%)	
Papillary	7,139 (16.0%)	6,982 (16.0%)	157 (15.3%)	
Nuclear grade				< 0.001
1 or 2	27,067 (60.6%)	26,649 (61.1%)	418 (40.7%)	
3 or 4	10,922 (24.4%)	10,443 (23.9%)	479 (46.6%)	
Unknown	6,684 (15.0%)	6,553 (15.0%)	131 (12.7%)	

Discussion

Our review of a national dataset comparing cancer-specific survival outcomes for localized RCC patients, stratified by age, has identified a decreased risk of RCC-specific mortality for a younger cohort when controlling for stage and tumor characteristics. Our analysis is novel in our focus on non-metastatic RCC presentation after definitive treatment in a modern cohort. These findings solidify previous literature, providing an updated cohort with a focus on localized disease and definitive treatment, along with highlighting the need to investigate the underlying differences in biology between young and conventional age patients with RCC. Further research analyzing the genetic differences between these tumor types is requisite.

Established prognostic factors of CSS in RCC patients include TNM staging, nuclear grade, and histologic subtype.[11-13] The results of our study are in line with these criteria, as we found increasing stage (HR = 2.16-4.82) and higher grade (HR = 2.35) increased the likelihood of cancer-specific death, Table 4. However in contrast to these prior studies and to the

TABLE 4. **Cox regression for cancer specific death**

Variable	HR	95% CI low	95% CI high	p value
Age > 40	2.943	1.819	4.761	.000
Insurance (uninsured ref)				
Insured	1.305	.827	2.059	.252
Medicaid	1.928	1.191	3.121	.008
Stage (cT1a ref)				
cT1b	2.156	1.811	2.567	.000
cT2a	3.176	2.574	3.920	.000
cT2b	4.821	3.789	6.134	.000
Treatment (ablation ref)				
Partial	.322	.170	.611	.001
Radical	.689	.365	1.302	.252
Histology (clear cell ref)				
Chromophobe	.302	.189	.482	.000
Papillary	.930	.770	1.123	.450
High grade (3 & 4)	2.347	2.051	2.686	.000

best of our knowledge, this is the first study to examine the prognostic significance of age when stratifying for stage for non-metastatic RCC (cT1-2N0M0) after definitive treatment. The results of this retrospective study showed that localized RCC in conventional-aged patients is more likely to be discovered at a higher stage and higher nuclear grade, and yet when stratified by clinical stage and tumor characteristics, is still associated with worse CSS compared to young patients. The underlying genetic and biological differences between young and conventional age patients at diagnosis remain unclear from our analysis; however, our results suggest that age can be a separate prognostic criterion used by clinicians during patient counseling. We hypothesize that time spent "in situ" prior to diagnosis may allow for silent tumor progression and lead to increased aggressiveness, but this hypothesis remains unexplored from our dataset and requires additional research.

The incidence of RCC has been increasing in the US for the past several decades, even in adolescents and young adults.[5,6,14] Studies have also shown that incidental detection of RCC has been associated with better prognosis due to discovery at a lower stage

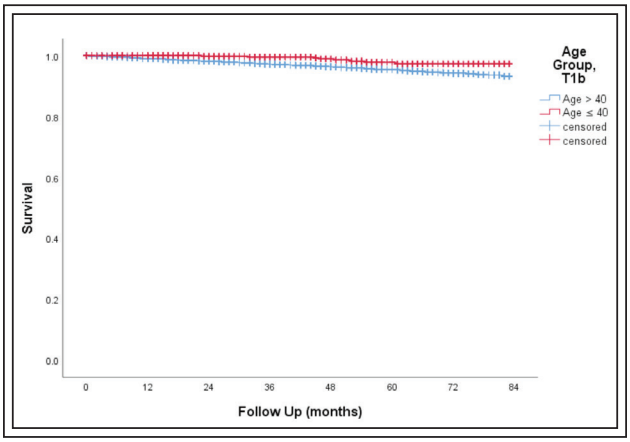

Figure 2. Kaplan-Meier cancer specific survival (includes T1b patients).

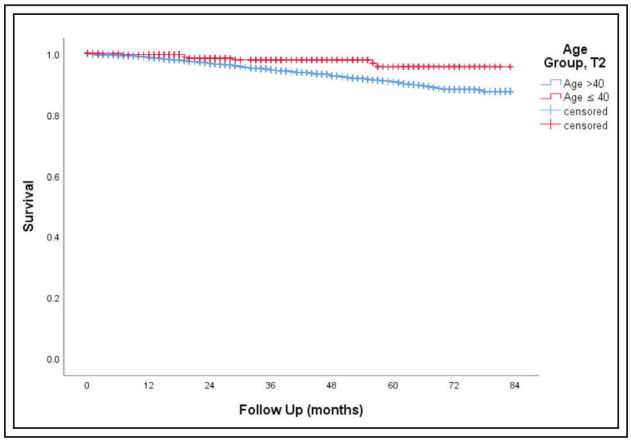

Figure 3. Kaplan-Meier cancer specific survival (includes T2 patients).

and grade compared with patients diagnosed after symptomatic presentation.[7,8,15] While it would be logical to therefore attribute the prognostic significance of age to increased detection at lower stage and grade, the results of our higher level analyses suggest that there may be additional underlying factors that influence CSS among young and conventional-age patients. Our study should serve for hypothesis generation and stimulate additional study, as further research is necessary to determine the tumor-specific factors that relate to age and recurrence.

Despite our findings, the effect of age on the CSS of RCC patients has been previously debated. Some studies showed no significant difference in CSS according to age.[16,17] However, other literature has in fact found age to be an independent prognostic factor in patients with RCC.[9,18-23] In our study, Kaplan-Meier analysis showed a significantly improved 5-year cancer-specific survival for the young versus conventional-age cohorts at all stages, with increasing differences with advancing stage. Some studies have noted that renal tumors in younger patients were associated with lower tumor stages and grades as well as favorable histological subtypes compared with tumors in conventional-age patients.[16,19,24] The results of our study also supported these findings, as our data revealed that higher nuclear grades of 3 or 4 were more prominent in the conventional-age population compared with the young population (24.8% vs. 19.1%). Additionally, our data also showed a significant association between age and histology subtype regarding clear cell, chromophobe, and papillary ($p < 0.001$). The chromophobe histology subtype was more prevalent in the younger population (10.5% vs. 6.6%), which is consistent with findings from other studies.[16,17,25] Interestingly, we found that while patients with chromophobe type accounted for 6.9% of our studied population, this group only accounted for 2.7% of cancer-specific deaths; whereas, clear cell comprised 77.1% of the overall population and accounted for 82.0% of cancer-specific death and papillary comprised 16.0% of the population and accounted for 15.3% of RCC mortality. These results are consistent with previous literature that has demonstrated a chromophobe subtype is associated with a more favorable prognosis relative to clear cell or papillary subtypes.[26-28] The increased prevalence of chromophobe in younger patients compared with conventional-age patients could therefore partially explain why younger age is associated with increased CSS even when stratifying for stage. Yet, our multivariable Cox analysis which controls stage and histology, suggests that other underlying biologic factors are at play but not yet revealed.

In addition to histological differences, age is also thought to be associated with immunological factors that play a role in determining CSS.[29,30] Older patients have been shown to have decline in immune function brought on by natural aging, a phenomenon known as immunosenescence.[31] Immunosenescence is thought to contribute to numerous health issues in an aged population, which may affect the relationship between tumor cells and the immune system known as cancer immunoediting.[32] The age-related decline of the immune system is especially relevant in RCC as it is considered to be a highly immunogenic malignancy with studies demonstrating it is amenable to treatment with immunotherapy, including interferon and programmed death ligand (PD-L) targets.[33,34] To the best of our knowledge, there have been no studies comparing the levels of PD-L expression between younger and older patients with RCC. Future studies should attempt to quantify any differences in PD-L target expression and other immune checkpoint proteins among the different age groups in order to elucidate any potential differences. These findings taken together with our growing knowledge of immunosenescence may shed light into new strategies to optimize immunotherapy protocols for RCC patients of different age groups to increase treatment effectiveness and prolong CSS.

This study has several limitations. Due to the retrospective nature of the SEER database, there is inherent selection bias which impacts our survival analysis. There is also the issue of incomplete data collection, including confounding variables such as tobacco or alcohol use that may affect the rate of cancer-specific death. While all patients in the database received definitive treatment, the database is lacking important information limiting our study. For example, inequality in access to care, whether from a geographical or financial standpoint, does distort our results. As a surrogate to access to care, we note that there is a discrepancy in insurance status between cohorts, with our younger cohort having a higher rate of uninsured patients (5.9% vs. 2.4%). Unfortunately, whether this affected patients' ability to seek care is not something that is tracked in SEER. Similarly, surgical wait time is also not tracked and its potential effects on survival outcomes on localized kidney cancer have been reported on.[35,36] Additionally, information regarding family history or genetic syndromes is lacking. Although rare, these patients are often afflicted with shorter life expectancies and tumors requiring earlier, more aggressive interventions which may alter the results. Notwithstanding these limitations, our analysis encompasses a large study

population with broad representation of the U.S. population, including 2,861 patients 40 years old or younger which is significant given the relative rarity of RCC in younger adults. Overall, this study reveals that conventional-age patients with localized kidney cancer experience worse cancer-specific survival compared to young patients even when stratifying for stage and histology. The increasing incidence of RCC in the U.S., especially in adolescents and young adults, necessitates further prospective research to determine the etiology for this age-specific outcome and note that this study is merely hypothesis generating.

Conclusion

Our study demonstrated that among patients with localized RCC who received definitive treatment, younger patients presented with more favorable clinical stage, nuclear grade, histology and had better 5-year CSS when stratifying for these factors on multivariable analysis. These findings corroborate previous literature that age is an independent prognostic factor in patients with RCC and suggest that there are other underlying biological factors which account for differences in CSS between young and conventional age RCC patients. □

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