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A Gap in Disease-Specific Survival Between Younger and Older Adults With De Novo Metastatic Renal Cell Carcinoma: Results of a SEER Database Analysis

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Abstract

Through an analysis of the Surveillance, Epidemiology, and End Results (SEER) registry, we demonstrate that disease-specific survival (DSS) appears to be inferior in older adults with metastatic renal cell carcinoma (mRCC) compared with younger adults. We further suggest that although DSS has improved for younger patients during the era of targeted therapies, a similar improvement is not seen among older adults.

Background—Consistent with other data sets, our own institutional series suggests that survival in patients aged ≥ 75 years with metastatic renal cell carcinoma (mRCC) is inferior to that in patients < 75 years. We sought to confirm these trends through exploration of the Surveillance, Epidemiology and End Results (SEER) registry.

Patients and Methods—We assessed disease-specific survival (DSS) in 6204 patients with clear cell, papillary, or chromophobe mRCC diagnosed between 1992 and 2009, with the a priori hypothesis that DSS was shorter in patients aged ≥ 75 years. Analyses were further stratified by the period of diagnosis, either between 1992 and 2004 (the “cytokine era”) or 2005 to 2009 (the “targeted therapy” era). Univariate and multivariate analyses were conducted to determine the association between clinicopathologic characteristics and DSS.

Results—DSS was shorter in patients aged ≥ 75 years than in patients aged < 75 years (9 vs. 16 months; $P < .0001$). In patients 18 to 74 years, DSS was superior in the targeted therapy era compared with the cytokine era ($P < .0001$). However, in patients ≥ 75 years, no difference in DSS was noted between these periods ($P = .90$). On multivariate analysis, age ≥ 75 years, female sex, diagnosis during the cytokine era, node-positive disease, and absence of cytoreductive nephrectomy were independently associated with DSS.

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Conclusion—DSS appears to be inferior in older adults with mRCC (specifically, patients aged 75 years). Furthermore, in contrast to their younger counterparts, no improvement in DSS was seen in older adults in the transition from the cytokine era to the targeted therapy era.

Keywords

Cytokine; Metastatic renal cell carcinoma; Older adults; Survival; Targeted therapy; Trends

Introduction

There has been a marked evolution in the treatment paradigm for metastatic renal cell carcinoma (mRCC). A decade ago, immunotherapeutic strategies such as interleukin (IL)-2 and interferon- α (IFN- α) represented the standard of care. Several issues existed with these therapies; the efficacy of IFN- α was modest at best, and IL-2 could be administered only to individuals with reasonable performance status and limited comorbidity.^{1,2} Targeted therapies (directed at vascular endothelial growth factor [VEGF] or the mammalian target of rapamycin) improve on the efficacy of IFN- α and can be used in a wider population of patients compared with IL-2.³ The latter is particularly relevant to older adults with mRCC, and it is widely presumed that targeted therapies have improved outcomes for this subset.

This assumption has been challenged by recent reports, however. The International mRCC Database Consortium reported an analysis of 1385 patients with mRCC who had received first-line VEGF-directed therapies.⁴ In patients aged 75 years, survival was numerically inferior to those patients aged < 75 years (16.8 vs. 19.7 months; $P = .33$). These data were based on a cohort of patients who were candidates to receive targeted therapy. To explore a more heterogeneous pool, we performed an assessment of our institutional database, capturing outcomes associated with 219 patients with mRCC (irrespective of therapeutic assignment).⁵ Survival was significantly shorter in those patients aged 75 years (12.5 vs. 26.4 months; $P = .003$).

These results motivated the current exploration of the Surveillance, Epidemiology, and End SEER) registry. A caveat of both our institutional analysis and the International mRCC Database Consortium report is that the population of interest (patients older than 75 years) composed only about 10% of the overall population in each study. Although SEER has several limitations (ie, only survival data are captured, no treatment-related data are recorded, and so on), the data set includes a sizeable population-based sample. We approached the current report with the a priori hypothesis that patients aged 75 years have shorter disease-specific survival (DSS) than those patients aged < 75 years.

Patients and Methods

Patient Selection

The SEER data set was used to explore the a priori hypotheses of this work. Clinical and outcome data pertaining to approximately 28% of the US population is captured by the 18 SEER regional registries. These data include demographic, pathologic, and stage information, as well as disease-specific and overall survival. Notably, the SEER data set, in contrast to SEER-Medicare, does not contain data pertaining to systemic therapies.

During the period of interest, 1992 to 2009, a total of 60,587 patients with RCC aged 18 years were identified within the SEER data set. We limited our analyses to the 6204 patients with documentation of 1 of 3 histologic types (clear cell, papillary, or chromophobe).

Tumor Classification

The International Classification of Diseases for Oncology (ICD-O), version 3, was used to record tumor histologic type and primary site. As previously stated, we investigated 3 clinically relevant subtypes of RCC: clear cell (ICD-O 8310), papillary (ICD-O 8260), and chromophobe (ICD-O 8317). Although Fuhrman grade was not specifically reported in SEER, an analogous scale characterizing tumors as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated was reported and is included in the current analysis. Criteria from the American Joint Committee on Cancer TNM staging system, seventh edition, was used to identify patients with stage IV disease. Importantly, SEER reports stage at the time of diagnosis, and therefore the patients with stage IV disease identified in our data set all had synchronous metastases.

Statistical Analysis

We explored the a priori hypothesis that patients aged ≥ 75 years had a cumulative DSS that was inferior to that of patients aged < 75 years. Given the marked evolution of the therapeutic strategy for mRCC over the past decade (ie, a shift from immunotherapy to targeted therapies), we also sought to determine if DSS was improved in older adults diagnosed during the targeted therapy era compared with those diagnosed during the era of immunotherapy. The era of immunotherapy was defined as the period from 1992 to 2004, with 1992 representing the year in which IL-2 was approved for mRCC.⁶ In contrast, the era of targeted therapy was defined as the period between 2005 and 2009, with 2005 representing the year in which the first targeted therapy was approved for mRCC (namely, sorafenib).⁷ We additionally compared clinicopathologic characteristics between the 2 groups. Continuous variables were compared using the Student *t* test, whereas categorical variables were compared using the χ^2 test. Finally, univariate and multivariate analyses were conducted to determine the association between clinicopathologic characteristics and DSS. DSS was defined as the time elapsed from the date of diagnosis with metastatic disease until the recorded date of death if attributable to RCC. Patients were censored at the last date of follow-up if a date of death was not recorded and at the date of death if the cause of death was not due to RCC. Patients with an unknown cause of death were excluded from all analyses. SAS (SAS Institute, Cary, NC) was used for all statistical analyses presented here. All *P* values are 2-sided, with a value of $< .05$ deemed statistically significant.

Results

Patient Characteristics by Age Group

Characteristics of the study population, stratified by the age cutoff of 75 years, are presented in Table 1. A higher proportion of patients aged 18 to 74 years were men (69.4% vs. 59.4%, $P < .0001$), whereas more non-Hispanic whites were represented in patients aged ≥ 75 years (77.7% vs. 71.8%; $P < .0001$). Although no significant differences were seen in histologic type across age groups (ie, clear cell vs. non-clear cell), a higher proportion of younger patients had undifferentiated or poorly differentiated tumors. T stage was recorded as “Tx” for the majority of patients in the cohort (66.1%), limiting inferences related to this characteristic; however, a larger proportion of younger patients had node-positive disease (31.6% vs. 23.4%; $P < .0001$).

Analysis of DSS by Age Group and Period

For the overall study period (1992-2009), DSS was shorter in patients aged ≥ 75 years compared with patients aged < 75 years (9 months vs. 16 months; $P < .0001$ (Figure 1). In patients aged 18 to 74 years, it was noted that DSS had improved in the targeted therapy era compared with the immunotherapy era (18 months for patients diagnosed from 2005 to 2009

vs. 14 months for patients diagnosed from 1992 to 2004; $P < .0001$) (Figure 2). However, in patients aged ≥ 75 years, no difference was noted ($P = .90$) (Figure 3).

Univariate and Multivariate Analysis

Several clinical and pathologic characteristics were associated with DSS on univariate analysis. The results of both univariate and multivariate analysis are detailed in Table 2. On univariate analysis, older age (≥ 75 years) and male sex were associated with shorter DSS ($P = .0002$ and $P < .0001$, respectively). Among pathologic characteristics, patients with poorly differentiated or undifferentiated tumors had inferior DSS compared with those with well-differentiated or moderately differentiated tumors, but no difference in DSS was noted among patients with clear cell or non-clear cell histologic type. Patients with node-positive disease had shorter DSS compared with patients with node-negative disease. Patients diagnosed during the targeted therapy era (2005-2009) had improved DSS relative to patients diagnosed during the cytokine era (1992-2004). Furthermore, cytoreductive nephrectomy was also associated with improved clinical outcome ($P < .0001$). On multivariate analysis, older age, female sex, diagnosis during the cytokine era, node-positive disease, and absence of cytoreductive nephrectomy were independent predictors of shortened DSS. Notably, because T stage was recorded as Tx for the majority of patients, this was omitted from the final multivariate analysis. However, in an exploratory multivariate analysis, Tx status served as an independent predictor of DSS.

Discussion

The results presented here provide support for our own institutional experience, suggesting that DSS in patients aged ≥ 75 years with mRCC may be shorter than DSS in patients aged < 75 years. A more provocative finding of our analysis suggests that although targeted therapy extends DSS for patients < 75 years, the same is not true for patients aged ≥ 75 years. Indeed, applying the same age cutoff of 75 years and comparing DSS during the cytokine era with DSS during the targeted era, only patients < 75 years were shown to have improved DSS since the advent of targeted therapies (ie, 2005-2009).

These findings are particularly compelling given that certain immune-based therapies (ie, IL-2) are typically perceived as being applicable to younger patients who have limited comorbidity. In the SELECT trial, a recent prospective evaluation of high-dose IL-2 in 120 patients with mRCC, no patient enrolled was > 70 years.⁸ In contrast, phase III studies evaluating targeted therapies have allowed a more heterogeneous array of patients. Several subset analyses have suggested minimal differences in safety and efficacy with targeted agents in older adults. For instance, in the RECORD-1 study comparing everolimus and placebo in patients with mRCC that had progressed on sunitinib and/or sorafenib (possibly also with previous bevacizumab or immunotherapy exposure), progression-free survival and overall survival were similar in patients aged ≥ 70 years.⁹ Several toxicities were more prevalent in older adults (peripheral edema, cough, rash, and diarrhea) regardless of the treatment arm (ie, everolimus or placebo), but otherwise the toxicity profiles were similar across age groups. In an expanded access program including 2504 patients with mRCC treated with sorafenib, similar overall survival was observed in 736 patients (29%) aged ≥ 70 years (compared with patients aged < 70 years).¹⁰ The most frequent grade ≥ 3 adverse events (hand-foot syndrome, hypertension, and fatigue) occurred at a similar frequency both above and below this age cutoff.

With results showing similar efficacy and safety in older adults treated with targeted therapies, it is challenging to infer why older adults treated in the era of targeted therapies do not have DSS rates comparable to those of their younger counterparts. One potential explanation is that older adults may not be offered or, alternatively, do not accept targeted

therapies. Because the SEER data set does not include systemic therapy status, we were unable to adjust for this in the current study. In our aforementioned institutional experience, we observed that 70% of patients aged ≥ 75 years did not receive systemic therapy.⁵ In contrast, only 33.5% of patients aged < 75 years received no systemic therapy. The reasons for this are unclear; our analyses were limited by a lack of comorbidity data, and it is entirely possible that the older adults in our series were less able to withstand systemic treatment. Nonetheless, our experience represents 1 of the few published reports inclusive of those patients who have not received therapy. The International mRCC Database Consortium experience, for instance, provides valuable insight into outcomes for older adults. The data set, however, comes with the caveat that patients were fit enough to receive first-line therapy with a VEGF-directed agent (a requirement for inclusion).¹¹ Similarly, prospective studies of targeted therapies all have rigorous eligibility criteria. In contrast, evidence suggests that patients with mRCC who do not meet standard eligibility criteria have significantly inferior outcomes.¹² Other studies have assessed the relationship of age and clinical outcome, albeit using a much younger cutoff. Ku et al¹³ assessed clinicopathologic features and survival in a cohort of patients with mRCC ranging in age from 22 to 84 years. It was found that younger patients (specifically, those aged ≤ 40 years) had smaller tumors with lower clinical stage and lower Fuhrman grade. Despite these differences, younger patients were not found to have improved DSS on multivariate analysis.

Several limitations of our study should be noted. First, SEER does not report comorbidity data. The known association between increasing age and extent of comorbidity could possibly confound observations related to survival in older adults.¹⁴ However, the survival analyses conducted by us focused on disease-specific and not overall survival. Second, only the stage at initial diagnosis is noted in the SEER registry. As such, only patients with de novo metastatic disease would be included in the registry. Both Heng and Motzer risk stratification criteria consider a time from diagnosis to initiation of systemic therapy < 1 year to be an adverse prognostic factor.^{11,15} Using the same risk stratification tools, patients with de novo metastatic disease inherently have intermediate- or poor-risk disease. Although the constraints of the SEER data set inherently limited our analyses to de novo disease, it is challenging to envision what would lead to discordance in age-related outcomes by risk group. A third limitation is the aforementioned lack of data related to systemic therapies received. Although the terms *cytokine era* and *targeted therapy era* pertain to periods when these drugs were predominantly used, the actual practice patterns cannot be confirmed. Therefore, as previously noted, statistical adjustment for receipt of systemic treatment was not possible. Notably, Shek et al¹⁶ published an assessment of clinical outcomes for patients with RCC housed in the California Cancer Registry. In their study, survival during the cytokine era (defined as 1998-2003) was compared with survival during the targeted therapy era (defined as 2004-2007). The definition we applied for the targeted therapy era (2005-2009) was much more likely to account for use of these agents, which were approved in late 2005 onward.

There are several limitations and shortcomings of SEER analyses that permeate this study and others using this data set. For instance, coding reliability is variable within SEER. A diagnosis of kidney cancer may encompass both RCC and upper urothelial tract tumors. To account for this, we have limited our analyses to patients in whom a specific histologic type consistent with RCC was noted (ie, clear cell, papillary, and chromophobe). A recent study by Shuch et al¹⁷ suggested that these diagnoses were recorded in SEER with substantial precision. Missing data are another issue in SEER, with several variables relevant to RCC not recorded. For instance, although tumors are classified as well-differentiated, poorly differentiated, and so on, there is no specific designation for Fuhrman grading in the database. Patient migration also complicates assessments of the SEER database. If patients

move in and out of geographic regions encompassed within SEER, their initial capture and follow-up may be compromised. Further issues in SEER analyses are detailed in an eloquent article by Yu et al.¹⁸

Despite these limitations, the data presented here serve as a compelling rationale to further assess our current treatment paradigm for older adults with mRCC. In addition to finding shorter DSS among patients aged ≥ 75 years, we observed that (in contrast to younger adults) clinical outcome did not improve for older adults in the era of targeted therapy. Future research should look toward accurately characterizing patterns of care in older adults in large series. If these data highlight that older adults are consistently receiving less treatment, it would be critical, albeit challenging, to ascertain whether this was the result of competing risks (ie, frailty, comorbidity, and so on) as opposed to practitioner bias. In parallel, prospective studies assessing safety and tolerability of novel targeted therapies for mRCC may be warranted, including investigations of pharmacokinetics and relevant biomarkers. There are several examples of biomarkers that cross over as putative markers of both aging and treatment efficacy. For instance, elevated IL-6 has been associated both with increasing age and clinical outcome with the VEGF tyrosine kinase inhibitor pazopanib.^{19,20} Outside laboratory-based biomarkers, use of novel clinical tools may help identify appropriate candidates for systemic therapy. As 1 prominent example, the Comprehensive Geriatric Assessment includes a battery of brief clinical inventories that allow for a functional assessment of older adults. Indeed, the Comprehensive Geriatric Assessment is being assessed prospectively in a wide array of cooperative group studies coordinated by the Alliance.²¹ These proposed efforts to optimize treatment of older adults with mRCC will certainly require substantial resources. However, unless such efforts are undertaken, alarming trends for clinical outcome in older adults with mRCC may persist.

Acknowledgments

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Clinical Practice Points

- Preliminary data from our institution (consistent with other recent studies) suggest that older adults with mRCC (specifically, patients aged ≥ 75 years) have inferior DSS compared with younger cohorts.
- From the SEER data set, we analyzed 6024 patients with mRCC and documented clear cell, papillary, or chromophobe histologic type.
- DSS was shorter in patients aged ≥ 75 years compared with patients aged < 75 years (9 vs. 16 months; $P < .0001$).
- In patients 18 to 74 years, DSS was superior in the targeted therapy era compared with the cytokine era ($P < .0001$). However, in patients ≥ 75 years, no difference in DSS was noted between these periods ($P = .90$).
- Further research is necessary to determine why older adults do not appear to have the improvement in DSS during the targeted therapy era relative to the cytokine era, as do their younger counterparts.

Figure 1.
Disease-Specific Survival of Patients With De Novo Metastatic Renal Cell Carcinoma
Based on Age. (MS = median survival)

Figure 2. Disease-Specific Survival of Patients Aged 18 to 74 Years With De Novo Metastatic Renal Cell Carcinoma Treated During the Cytokine Era (1992-2004) Compared With That of Patients Treated in the Targeted Therapy Era (2005-2009). (MS = median survival)

Figure 3. Disease-Specific Survival of Patients Aged ≥ 75 Years With De Novo Metastatic Renal Cell Carcinoma Treated During the Cytokine Era (1992-2004) Compared With That of Patients Treated in the Targeted Therapy Era (2005-2009). (MS = median survival)

Table 1**Patient Characteristics by Age Group**

Variable	18-74 Years n (%)	75+ Years n (%)	P Value
Follow-Up Time (Mo)			
Mean (± SD)/median (IQR)	19.8 (± 23.7)/11 (4-25)	14.4 (± 20.1)/7 (2-18)	< .0001
Age			
Mean (± SD)/median (IQR)	59.4 (± 9.4)/60 (53-67)	80.2 (± 4.2)/79 (77-83)	< .0001
Sex			
Men	3400 (69.4)	669 (59.4)	< .0001
Women	1498 (30.6)	457 (40.6)	
Year of Diagnosis			
1992-2004	2246 (45.9)	527 (46.8)	.5652
2005-2009	2652 (54.1)	599 (53.2)	
Race/Ethnicity			
Non-Hispanic white	3506 (71.8)	870 (77.7)	< .0001
Black	424 (8.7)	60 (5.4)	
Hispanic white	673 (13.8)	108 (9.7)	
API	233 (4.8)	74 (6.6)	
AI/AN	45 (0.9)	7 (0.6)	
Histologic Type			
Clear cell	4430 (90.4)	1011 (89.8)	.5005
Non-clear cell	468 (9.6)	115 (10.2)	
Grade			
Well differentiated	161 (5.2)	45 (8.9)	< .0001
Moderately differentiated	877 (28.5)	185 (36.8)	
Poorly differentiated	1382 (44)	197 (39.2)	
Undifferentiated	660 (21.4)	76 (15.1)	
Tumor Size			
5 cm	733 (17)	246 (27.3)	< .0001
> 5 cm	3572 (83)	654 (72.7)	
T Stage			
T1	488 (29.9)	156 (37.8)	.0056
T2	473 (29)	89 (21.5)	
T3	119 (7.3)	24 (5.8)	
T4	541 (33.1)	140 (33.9)	
T0/Tis	11 (0.7)	4 (1)	
N Stage			
N0	2544 (68.4)	549 (76.6)	< .0001
N1	1173 (31.6)	168 (23.4)	
Surgery Type			
No nephrectomy	1773 (36.3)	696 (62.3)	< .0001
Nephrectomy	3105 (63.7)	421 (37.7)	

Abbreviations: AI/AN = American Indian/Alaskan Native; API = Asian Pacific Islander; IQR = interquartile range.

Table 2

Univariate and Multivariate Analysis of Age Group

Variable	n (%)	Univariate		Multivariate	
		Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age Group					
18-74y	4898 (81.3)	1.00 (Reference)	—	—	—
75+ y	1126 (18.7)	1.48 (1.38-1.59)	< .0001	1.18 (1.08-1.30)	.0002
Age					
Mean (± SD)/median (IQR)	63.3 (± 11.9)/63 (55-72)	1.02 (1.01-1.02)	< .0001	—	—
Sex					
Men	4069 (67.5)	1.00 (reference)	—	—	—
Women	1955 (32.5)	1.15 (1.08-1.22)	< .0001	1.22 (1.14-1.31)	< .0001
Year of Diagnosis					
1992-2004	2773 (46)	1.00 (reference)	—	—	—
2005-2009	3251 (54)	0.89 (0.84-0.94)	.0001	0.91 (0.85-0.98)	.0130
Race/Ethnicity					
Non-Hispanic white	4376 (72.6)	1.00 (reference)	—	—	—
Black	484 (8)	1.18 (1.06-1.31)	.0027	1.00 (0.88-1.13)	.9562
Hispanic white	781 (13)	1.02 (0.93-1.12)	.6740	0.95 (0.86-1.05)	.3291
API	307 (5.1)	0.79 (0.69-0.91)	.0009	0.80 (0.68-0.93)	.0050
AI/AN	52 (0.9)	1.04 (0.77-1.40)	.8014	1.17 (0.85-1.61)	.3335
Unknown	24 (0.4)	0.74 (0.43-1.28)	.2828	0.94 (0.54-1.62)	.8203
Histologic Type					
Clear cell	5441 (90.3)	1.00 (reference)	—	—	—
Non-clear cell	583 (9.7)	0.97 (0.88-1.07)	.5657	—	—
Grade					
Well differentiated	206 (3.4)	1.00 (reference)	—	—	—
Moderately differentiated	1062 (17.6)	0.88 (0.74-1.06)	.1819	1.20 (0.98-1.49)	.0820
Poorly differentiated	1579 (26.2)	1.02 (0.85-1.21)	.8358	1.50 (1.22-1.85)	.0001
Undifferentiated	736 (12.2)	1.27 (1.06-1.53)	.0116	1.97 (1.58-2.45)	< .0001
Unknown	2441 (40.5)	1.70 (1.44-2.02)	< .0001	1.37 (1.12-1.67)	.0019
T Stage					
T1	644 (10.7)	1.00 (reference)	—	—	—
T2	562 (9.3)	1.16 (1.00-1.35)	.0494	—	—
T3	143 (2.4)	1.27 (0.99-1.64)	.0582	—	—
T4	681 (11.3)	1.14 (0.99-1.31)	.0690	—	—
T0/Tis	15 (0.2)	1.20 (0.57-2.54)	.6267	—	—
TX	3979 (66.1)	1.48 (1.33-1.66)	< .0001	—	—
N Stage					
N0	3093 (51.3)	1.00 (reference)	—	—	—
N1	1341 (22.3)	1.81 (1.68-1.95)	< .0001	1.72 (1.58-1.87)	< .0001
NX	1590 (26.4)	1.73 (1.62-1.86)	< .0001	1.26 (1.16-1.38)	< .0001

Variable	n (%)	Univariate		Multivariate	
		Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Surgery Type					
No nephrectomy	2469 (41)	1.00 (reference)		—	—
Nephrectomy	3526 (58.5)	0.39 (0.36-0.41)	< .0001	0.37 (0.34-0.41)	< .0001
Unknown	29 (0.5)	0.61 (0.41-0.92)	.0172	0.48 (0.29-0.79)	.0037

Abbreviations: AI/AN = American Indian/Alaskan Native; API = Asian Pacific Islander; IQR = interquartile range.