

# Treatment and Survival Among Medicare Patients With Renal Cell Carcinoma

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## Introduction

Renal cell carcinomas (RCC) account for 80% to 85% of all primary renal neoplasms and impose a substantial burden on patients and the healthcare system.<sup>1</sup> Approximately 58,240 new cases are diagnosed annually in the U.S. and almost 13,000 people will die of the disease each year.<sup>2-3</sup> This represents approximately 2% of all cancers and 2% of all neoplasm-related deaths. The incidence of RCC has increased over time.<sup>4-5</sup> Between 1975 and 1995 in the U.S., for example, the incidence rate (per 100,000 person-years) increased for white men, white women, black men, and black women by 2.3%, 3.1%, 3.9%, and 4.3%, respectively.<sup>4</sup> Since 1950, there has been a 126% increase in the incidence of RCC and a 37% increase in annual mortality,<sup>4-5</sup> although, at least some of that increase is explained by the greater number of incidental tumors detected during abdominal imaging done for other reasons.<sup>5</sup> RCC occurs most often in individuals between the ages of 60 and 80, and is rare in patients younger than 40 years of age.<sup>6</sup>

Survival rates for patients with renal cancers have increased remarkably during the last few decades. The 5-year survival rate approximately doubled from 34% in 1954 to 62% in 1996.<sup>5</sup> These improvements were more likely due to factors such as earlier diagnosis and improvements in surgical treatments rather than to improved systemic medical therapy for advanced disease during this period.<sup>7</sup> Subsequently, newer medical treatments have become available and have shown promise for patients with advanced metastatic RCC.<sup>8-10</sup> Nevertheless, it is not clear that there is, as yet, widespread utilization of these new treatments. Survival rates

remain low for patients with advanced stage disease. Because RCC disproportionately affects older individuals, we sought to both characterize treatment patterns and evaluate survival for patients with RCC who have Medicare as their primary payer.

## Materials and Methods

### Data

Data for this study were from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The SEER-Medicare database was created through a collaboration between the National Cancer Institute (NCI) and the Health Care Financing Administration to assist in the conduct of health services research in oncology.<sup>11</sup> This data set combines tumor registry data from the NCI's SEER program, which covers approximately 14% of the U.S. population, with claims data from Medicare.<sup>12</sup> The Medicare program provides health care coverage for 97% of persons aged 65 years and older and Medicare claims have been used to study the utilization and outcomes of treatment for a variety of medical conditions.<sup>13-17</sup> The SEER-Medicare linked database thus combines demographic features of the patient, clinical characteristics of the tumor, utilization, and Medicare payment information.

### Study Population

The SEER-Medicare data contain tumor registry data for 54,955 patients who were diagnosed with a first RCC between 1973 and 2002.<sup>18</sup> However, because claims data are only available beginning in 1986, we limited our analysis to patients who were diagnosed with a first RCC between 1986 and 2002. We further restricted the set of cases to patients age 65 years and older. Patients were excluded if their tumors were nonepithelial tumors or if the diagnosis of cancer was obtained upon autopsy or from a death certificate only. Patients enrolled in an HMO at the time of diagnosis or thereafter were excluded because billing records would be unavailable. Finally,

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**Table 1. Characteristics of renal cell carcinoma patients and noncancer controls**

Variable	Renal Cell Carcinoma (N = 8,130)	Disease-Free Controls (N = 14,696)	P-value
<b>Age (years)</b>			
Mean	74.2	73.7	< 0.0001
65-69	29.0%	31.3%	
70-79	49.2%	49.8%	
≥ 80	21.7%	18.9%	
<b>Gender</b>			
Male	57.1%	56.2%	0.189
Female	42.9%	43.8%	
<b>Race/Ethnicity</b>			
White	82.2%	81.7%	0.525
Black	7.5%	7.4%	
Hispanic	5.9%	6.4%	
Other	4.4%	4.5%	
<b>Stage</b>			
Localized	45.0%		
Regional	20.7%		
Distal	24.7%		
Unstaged	9.6%		
<b>Laterality</b>			
Right-origin	48.0%		
Left-origin	49.5%		
Paired/Other	2.5%		
<b>Treatment<sup>1</sup></b>			
Surgery	72.2%		
Radiation	4.9%		
Surgery + Radiation	4.1%		
No Surgery or Radiation	18.8%		
Chemotherapy	11.4%		

<sup>1</sup>Note distribution of treatments exceeds 100% since chemotherapy may be adjunct to other treatments.

patients with records missing data on treatment type were excluded.

### Control Groups

The SEER-Medicare data includes 2 cohorts of individuals: persons with cancer and a random sample of Medicare beneficiaries who do not have cancer. The noncancer group is drawn from a random 5% sample of Medicare beneficiaries residing in the SEER areas. Persons in the 5% sample who also appear in the SEER data are removed, leaving a sample of noncancer cases. In this study, we used the noncancer group to select a comparison group. Anticipating that the RCC population would not have a similar distribution of background characteristics as the noncancer Medicare population, we used a propensity score matching technique to select a control group that had a similar distribution of age, gender, and race or ethnicity.<sup>19</sup>

In order to compare survival rates, we required that noncancer patients have a start date analogous to the date of cancer diagnosis for cancer patients. To do this, we randomly assigned noncancer patients a start date

from the set of diagnosis dates of cancer patients. We then matched cancer patients to controls 1:2 on the propensity score using a greedy matching algorithm. After matching, some of the noncancer patients had diagnosis dates that were subsequent to their date of death. These were dropped and rematched. Cases without a suitable match were excluded, and cases with only one match were included. Our final sample included 8,130 patients with RCC and 14,696 matched noncancer controls.

### Covariates

We studied the impact of demographic characteristics, disease characteristics, comorbidities, and treatment choice on overall survival. Demographic variables included patient age at the time of diagnosis, gender, and race/ethnicity (black, white, Hispanic, other). Disease variables included morphologic extent of malignant disease defined using the SEER historic stage (local, regional, distant metastasis, unstaged),<sup>20</sup> and laterality (left, right, paired). A number of comorbidities including diagnosis-based proxies for known prognostic factors in RCC – anemia, hyperlipidemia, and hypercalcemia – were also included as potential covariates. Treatment indicators were mutually exclusive for surgery, radiation, combination surgery and radiation, and absence of any treatment. An indicator was also included for chemotherapy, however, this could have been used in combination with the other treatments. Concomitant use of chemotherapy was identified using ICD-9-CM diagnosis codes, ICD-9-CM procedure codes, and Healthcare Common Procedure Coding Systems codes in billing data.<sup>21</sup> We included codes to identify general chemotherapy administration as well as codes that specifically identified 5-fluorouracil, methotrexate, cyclophosphamide, cisplatin, and carboplatin.

We controlled for comorbidities based on the Charlson comorbidity index (CCI).<sup>22</sup> The CCI is a weighted average of 19 conditions associated with inpatient mortality and has been widely used to study or control for comorbidities among cancer patients and other populations.<sup>23-25</sup> We used Deyo's adaptation of the CCI, which identifies the comorbidities from ICD-9-CM diagnosis codes.<sup>26</sup> Other comorbidities associated with RCC outcomes that were not part of the CCI were identified from ICD-9-CM codes, including anemia (280.9, 281.0, 281.9, and 282.3), hypercalcemia (275.42), and hyperlipidemia (272.4, 272.0, 272.2).<sup>27-28</sup> Rather than insert these additional comorbidities into the index in an *ad hoc* fashion, we created indicator variables for each individual comorbidity and included the indicators as separate potential covariates in multivariate analyses.

### Statistical Analysis

The following statistical analyses were undertaken in order to evaluate treatment patterns and survival among RCC patients. To understand treatment patterns among the cohort of patients with diagnosed RCC, the distribu-

**Table 2. Frequency distribution of treatments among patients diagnosed with renal cell carcinoma by demographic and clinical characteristics**

Variable	Surgery (N = 5,872)	Radiation (N = 401)	Surgery + Radiation (N = 332)	No Surgery or Radiation (N = 1525)	Chemo- therapy <sup>1</sup> (N = 926)	P-value <sup>2</sup>
<b>Age (years)</b>						
Mean	73.6	73.9	71.8	77.5	72.0	< 0.0001
65-69	30.8%	29.9%	41.3%	19.2%	40.5%	
70-79	51.5%	48.1%	50.3%	40.7%	49.4%	
≥ 80	17.7%	21.9%	8.4%	40.1%	10.2%	
<b>Gender</b>						< 0.0001
Male	42.2%	42.9%	35.2%	47.1%	36.3%	
Female	57.8%	57.1%	64.8%	52.9%	63.7%	
<b>Race/Ethnicity</b>						< 0.0001
White	82.4%	82.0%	83.4%	81.3%	85.5%	
Black	7.4%	4.7%	3.9%	9.4%	5.7%	
Hispanic	6.0%	6.5%	4.8%	5.5%	4.5%	
Other	4.2%	6.7%	7.8%	3.7%	4.2%	
<b>Stage</b>						< 0.0001
Localized	58.9%	0.0%	6.0%	11.9%	24.6%	
Regional	25.2%	2.2%	20.2%	8.3%	25.8%	
Distal	8.9%	91.8%	66.9%	59.0%	43.5%	
Unstaged	7.1%	6.0%	6.9%	20.8%	6.0%	
<b>Laterality</b>						< 0.0001
Right-origin	48.0%	51.1%	53.3%	46.1%	48.4%	
Left-origin	51.3%	42.4%	44.0%	45.6%	48.1%	
Paired/Other	0.7%	6.5%	2.7%	8.3%	3.6%	

1 Chemotherapy may be concomitant with other treatments

2 P-value based on chi-square test of distribution of risk categories by treatments, excluding chemotherapy

tion of patients by treatment was compared across key demographic and clinical characteristics, using the chi-square test. Further, 2 multivariate logistic models were estimated, with backward selection, to identify statistically significant demographic and clinical predictors of both absence of surgical/radiation treatment and chemotherapy. To characterize mortality associated with RCC, the Kaplan-Meier product limit approach was used to depict survival in patients with RCC to demographically matched Medicare patients; the log-rank test was used for statistical comparisons. To evaluate the within-RCC cohort determinants of mortality, survival was compared using the log-rank test among RCC patients that differed by treatment, demographics, and medical characteristics. In addition, survival was modeled in a multivariate context using the Cox proportional hazards model to control for other factors simultaneously. Covariates were selected using a backwards stepwise selection algorithm with an inclusion threshold of 0.20. If one element of a set of variables (e.g. race/ethnicity) was included, then all categories were forced into the model. Survival analyses were performed using Stata/MP.

### Results

As seen in **Table 1**, patients with RCC were very similar in terms of gender and race/ethnicity to the matched,

noncancer controls, but despite matching, the former were slightly older. Most of the RCC patients had local disease (45%), followed by distant (24.7%) and regional metastases (20.7%). There were slightly more patients with right-sided disease than left-sided disease (49.5% vs 48%). Most patients were treated with surgery alone (72.2%), while another 9% received radiation therapy alone or postsurgery. Approximately 19% of patients had no evidence of any surgery or radiation.

There was significant variation in treatments used by baseline age, gender, race/ethnicity, staging (all  $P < .0001$ ) and laterality ( $P < .0001$ ) as shown in **Table 2**. Among patients who had surgery, most patients had localized (58.9%) or regional (25.2%) disease. Among patients who had radiation therapy alone or chemotherapy alone, most had distal disease (91.8% and 43.5%,

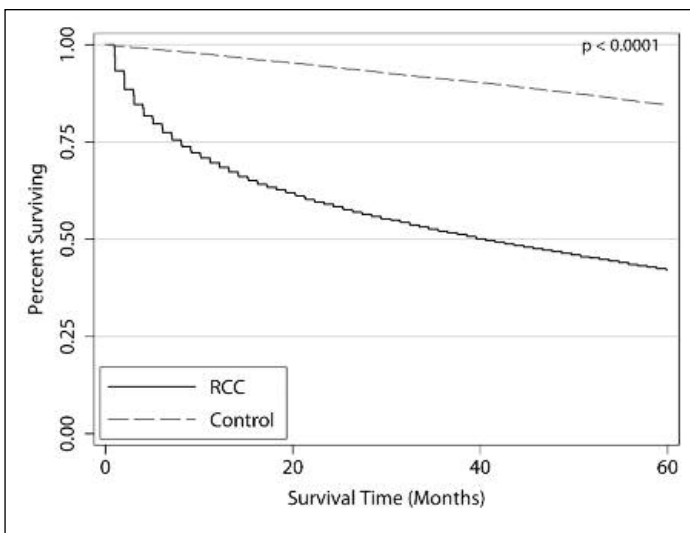
respectively). Among patients who had neither surgery nor radiation, 59% and 20.8% had distal or unstaged disease, respectively, and 40.1% were ≥ 80 years of age.

In multivariate logistic regression analyses to identify which baseline risk factors were associated with the absence of treatment with surgery or radiation therapy, and the absence of chemotherapy, additional characteristics including comorbidities were considered. The findings for the absence of surgery or radiation therapy are presented in **Table 3**. Distal metastasis (odds ratio [OR] = 18.9), unstaged disease (OR = 11.6) and age ≥ 80 years (OR = 3.6) were all confirmed as leading predictors of absence of any surgical or radiation treatment ( $P < .0001$ ), after adjusting for other baseline characteristics. The same was true of paired laterality (OR = 2.4;  $P < .0001$ ) and black race (OR = 1.6;  $P < .0001$ ). Among comorbid conditions, dementia (OR = 2.2;  $P < .0001$ ), congestive heart failure (OR = 1.4;  $P = .001$ ), diabetes (OR = 1.4;  $P = .001$ ), anemia (OR = 1.35;  $P = .025$ ) and renal disease (OR = 1.35;  $P = .048$ ) were identified as being predictive of absence of any surgical or radiation treatment. In the logistic model for chemotherapy distal metastasis emerged as strongly predictive (OR = 3.5;  $P < .0001$ ) for use of chemotherapy as a treatment option, as did metastatic disease (OR = 2.5;  $P < .0001$ ). Older age, especially ≥ 80 (OR = 0.3;  $P < .0001$ ), dementia (OR = 0.3;

**Table 3. A logistic regression model to predict determinants of absence of treatment with surgery and radiation among patients with renal cell carcinoma**

Variable	Odds Ratio	95% Confidence		P-value
		Lower	Upper	
<b>Age (years)</b>				
65-69	Reference			
70-79	1.41	1.19	1.67	< 0.0001
≥ 80	3.55	2.95	4.27	< 0.0001
<b>Race/Ethnicity</b>				
White/Other	Reference			
Black	1.63	1.29	2.07	< 0.0001
<b>Stage</b>				
Localized	Reference			
Regional	1.72	1.35	2.18	< 0.0001
Distal	18.85	15.63	22.73	< 0.0001
Unstaged	11.61	9.32	14.47	< 0.0001
<b>Laterality</b>				
Right/Left	Reference			
Paired/Other	2.44	1.77	3.36	< 0.0001
<b>Comorbidities</b>				
Diabetes (no complications)	1.36	1.13	1.63	0.0010
Metastatic Disease	0.48	0.38	0.60	< 0.0001
COPD	1.18	0.98	1.41	0.0750
HIV	12.25	0.74	201.58	0.0800
Anemia	1.35	1.04	1.75	0.0250
Dementia	2.21	1.42	3.43	< 0.0001
Hyperlipidemia	0.81	0.67	0.97	0.0220
Renal Disease	1.35	1.00	1.82	0.0480
CHF	1.41	1.16	1.73	0.0010
PVD	1.22	0.97	1.53	0.0900

COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; CHF=congestive heart failure; PVD=peripheral vascular disease.



**Figure 1. Five-year Survival of Renal Cell Carcinoma Patients and Non-Cancer Controls.**

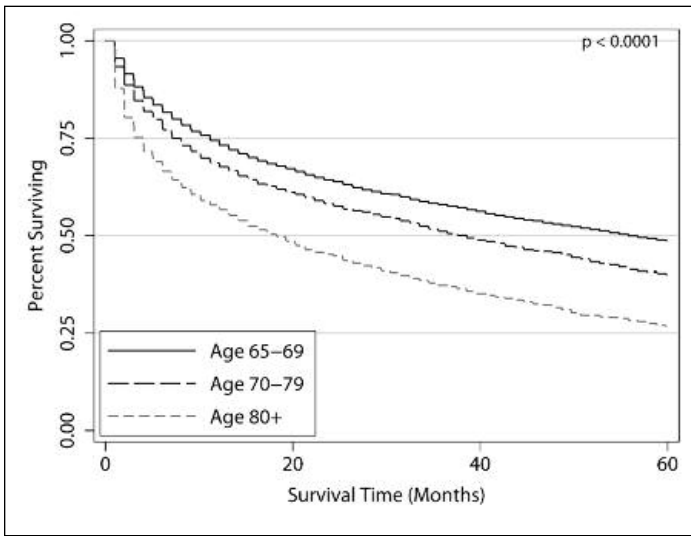
$P = .027$ ) and black race ( $OR = 0.7$ ;  $P = .017$ ) were, on the other hand, associated with significantly reduced odds of chemotherapy. Patients with RCC had a 5-year survival rate of 42% compared with 85% for comparable

Medicare patients without RCC ( $P < .0001$ ), as shown in **Figure 1**. There were also significant differences in survival among RCC patients. Older patients had poorer survival than younger patients ( $P < .0001$ ), as indicated in **Figure 2**. Women had significantly better 5-year survival than men (43.7% vs 40.8%,  $P = .016$ ). Stage was also an important determinant of 5-year survival and is shown in **Figure 3**. RCC patients with localized disease had the best survival, and survival dropped progressively for regional, unstaged, and distant disease ( $P < .0001$ ). As seen in **Figure 4**, patients with RCC treated with single modality surgery had much better 5-year survival (55.2%) than patients treated with combination surgery and radiation therapy (9.2%), radiation alone (1.5%) and no treatment (5.8%). Patients with single modality radiation had the worst 5-year survival rate, as seen in **Figure 5**. Patients who received chemotherapy

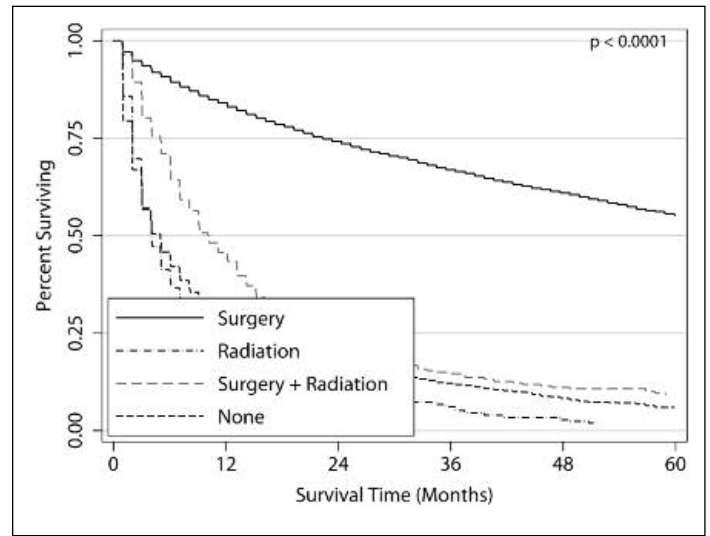
alone or in combination with other treatments had better survival during the first year, but significantly poorer survival by the fifth year (27.7% vs. 44%, respectively,  $P < .0001$ ). Finally, increasing numbers of comorbidities was associated with poorer 5-year survival, as shown in **Figure 6** ( $P < .0001$ ).

These results for 5-year survival were largely replicated in multivariate survival analysis, adjusting for other characteristics. **Table 4** presents the results comparing patients with RCC patients with noncancer controls. Increasing age was associated with significantly poorer adjusted survival while female gender was associated with significantly better adjusted survival. Relative to white patients, black patients had poorer 5-year adjusted survival (hazard ratio (HR): 1.14,  $P = .001$ ), and Hispanic and other race/ethnicities had better 5-year adjusted survival (HR: 0.78 and 0.9, respectively). After controlling for age, gender, and race/ethnicity, RCC was associated with 4 times the hazard of mortality ( $P < .0001$ ).

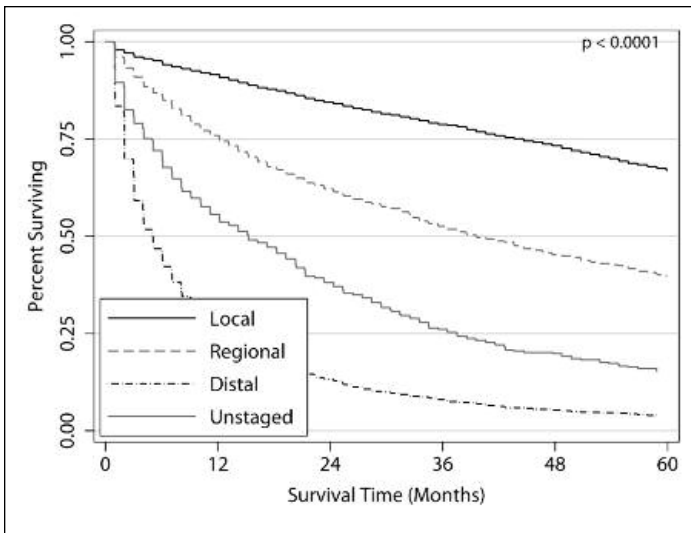
Among patients with RCC, increasing age ( $P < .0001$ ) and male gender ( $P = .0002$ ) were associated with greater hazard of mortality after, as shown in **Table 5**. Race/ethnicity was not significantly associated with survival after controlling for other patient and disease characteristics



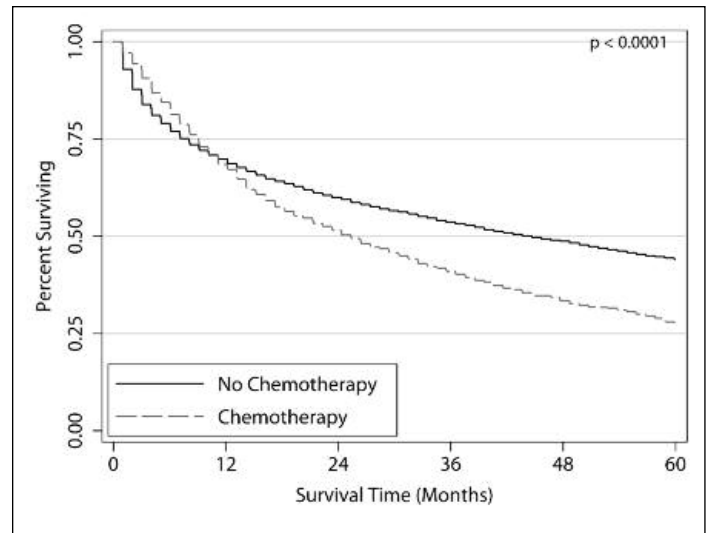
**Figure 2. Five-year Survival of Renal Cell Carcinoma Patients Stratified by Age.**



**Figure 4. Five-year Survival of Renal Cell Carcinoma Patients Stratified by Treatment.**



**Figure 3. Five-year Survival of Renal Cell Carcinoma Patients Stratified by Stage of Disease.**



**Figure 5. Five-year Survival of Renal Cell Carcinoma Patients Stratified by Chemotherapy (Single or Combination) Versus no Chemotherapy. Note: All treatment groups could have included chemotherapy; survival curves by presence or absence of chemotherapy are presented in Figure 5 below.**

and the treatments received. Patients with regional, unstaged, and distal metastatic disease had increasingly poorer adjusted 5-year survival than patients with localized disease ( $P < .0001$ ). Patients treated with combined surgery and radiation, radiation therapy alone, or absence of both, had poorer adjusted survival than patients treated with surgery alone ( $P < .0001$ ). In contrast to the univariate association, radiation therapy was associated with similar adjusted odds of mortality as absence of surgery/radiation, after adjusting for baseline demographic and medical characteristics. Patients treated with chemotherapy had marginally better adjusted survival, but this effect was not statistically significant (HR: 0.94,  $P = .118$ ). Several comorbidities were associated with significantly poorer 5-year adjusted survival including congestive heart failure, renal disease, and anemia ( $P < .0001$ ); dementia ( $P = .027$ ), and cerebrovascular disease ( $P = .042$ ).

## Discussion

Our results suggest that several patient, disease, and treatment factors influence outcomes for elderly patients with RCC. Older age and male gender were consistently associated with poorer outcomes. Patients with regional and distal disease, based on SEER historic staging, also had consistently poorer 5-year survival. In terms of treatment, patients who received surgery alone had the highest 5-year survival. This is not surprising since surgery is the treatment of choice for early stage disease and can be curative. In addition, there may also be a favorable selection bias for patients with metastatic disease who have a debulking nephrectomy as part of their treatment. Consistent with historical data, our study also found that patients who underwent surgery were more likely to

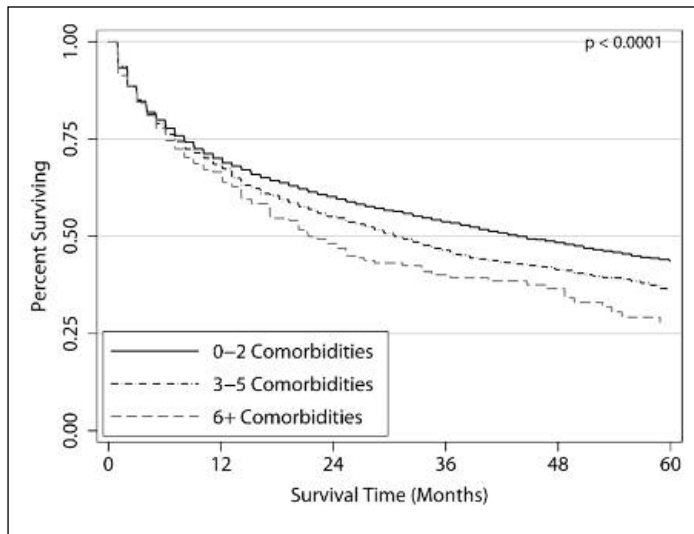


Figure 6. Five-year Survival of Renal Cell Carcinoma Patients Stratified by Number of Comorbidities.

Table 4. A multivariate Cox proportional hazard model to compare survival in renal cell carcinoma patients with noncancer controls

Variable	Hazard Ratio	95% Confidence		P-value
		Lower	Upper	
<b>Renal cell carcinoma</b>	4.02	0.08	66.93	< 0.0001
<b>Age (years)</b>				
65-69	Reference			
70-79	1.58	0.04	17.52	< 0.0001
≥ 80	3.36	0.10	41.21	< 0.0001
<b>Gender</b>				
Male	Reference			
Female	0.81	0.78	0.84	< 0.0001
<b>Race/Ethnicity</b>				
White	Reference			
Black	1.14	1.06	1.23	0.001
Hispanic	0.78	0.71	0.86	< 0.0001
Other	0.90	0.81	11.00	0.056

have localized or regionally localized disease. Conversely, patients with locally advanced or unresectable metastatic disease were not likely to have been considered surgical candidates. In fact, our analysis of treatment predictors found that patients with distal and unstaged RCC were significantly less likely to receive either surgery or radiation, adjusting for other factors. In 2001, 2 separate papers were published supporting the role of cytoreductive nephrectomy in the treatment of metastatic RCC.<sup>29-30</sup> Since that time, cytoreductive nephrectomy followed by treatment with immune modulators or other newly available regimens is increasingly becoming the standard of care for selected patients.<sup>31</sup> Although our study included patients diagnosed with RCC up until 2002, any recent changes in practice pat-

TABLE 5. A multivariate Cox proportional hazard model to identify predictors of mortality among renal cell carcinoma patients

Variable	Hazard Ratio	95% Confidence		P-value
		Lower	Upper	
<b>Age (years)</b>				
65-69	Reference			
70-79	1.24	1.16	1.32	< 0.0001
≥ 80	1.66	1.53	1.80	< 0.0001
<b>Gender</b>				
Male	Reference			
Female	0.92	0.87	0.97	0.002
<b>Race/Ethnicity</b>				
White	Reference			
Black	0.99	0.89	1.10	0.857
Hispanic	1.00	0.88	1.13	0.969
Other	0.90	0.78	1.03	0.118
<b>Stage</b>				
Local	Reference			
Regional	1.97	1.83	2.13	< 0.0001
Distal	5.22	4.76	5.72	< 0.0001
Unstaged	2.14	1.94	2.37	< 0.0001
<b>Treatment</b>				
Surgery	Reference			
Radiation	2.45	2.16	2.78	< 0.0001
Surgery + radiation	1.86	1.64	2.12	< 0.0001
Absence of surgery or radiation	2.51	2.30	2.73	< 0.0001
Chemotherapy	0.94	0.86	1.02	0.118
<b>Comorbidities</b>				
CHF	1.30	1.19	1.42	< 0.0001
Renal disease	1.27	1.11	1.45	< 0.0001
Cerebrovascular disease	1.11	1.00	1.22	0.042
Dementia	1.26	1.03	1.54	0.027
COPD	1.07	0.99	1.16	0.098
Anemia	1.24	1.11	1.40	< 0.0001
Hypercalcemia	1.58	0.85	2.95	0.149
Hyperlipidemia	0.78	0.72	0.85	< 0.0001

COPD=chronic obstructive pulmonary disease.

terns are likely to have been diluted by the overall longer time frame of the data for this paper.

Other findings on demographic factors and comorbid conditions influencing treatment choices and ultimately mortality are also notable. Older age, especially ≥ 80 years, was associated with absence of both surgery/radiation and chemotherapy. Consistent with previous findings, black race and comorbid dementia were also independently associated with absence of any treatment.<sup>32</sup> Given that all 3 of these factors were associated with higher mortality, and with the exception of black race, also with higher adjusted mortality, the finding of absence of treatments for these groups is of concern. Other comorbid conditions, such as congestive heart failure, renal disease, and diabetes were associated with higher probability of not receiving any surgery/radiation

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tion, but not with a higher probability of not receiving chemotherapy. Further, these comorbidities were all associated with higher mortality even after adjusting for treatment choice. Anemia was independently predictive of higher mortality. However, other comorbidities were not significant predictors, reflecting perhaps that these diagnoses were more likely to have been coded by the Medicare billing system in patients who had less severe comorbid conditions.<sup>27-28</sup> Additional studies using clinical data should investigate the comorbidities identified in this paper for development of extended prognostic criteria in RCC.

As already mentioned, the incidence of RCC has increased over time and may be partially due to the increasing availability and widespread use of abdominal imaging. Since the 1969 publication of Robson's landmark surgery article,<sup>33</sup> the complete excision of the tumor and any metastatic deposits has been the mainstay of treatment. Historically, other treatment modalities such as radiation and conventional chemotherapy have added little to the treatment and survival of these patients.<sup>34</sup> In our analysis we attempted to study the effect of chemotherapy before and after 1990 as a proxy for older versus newer agents, but the very small number of observations precluded meaningful analysis.

New treatments for RCC are emerging and show great promise.<sup>35</sup> Currently, the tyrosine kinase inhibitors sorafenib and sunitinib, which target vascular endothelial growth factor (VEGF) and platelet derived growth factor, have been approved for treatment of metastatic RCC.<sup>9-10</sup> In addition, antibodies that sequester VEGF, such as bevacizumab,<sup>36-37</sup> are also being investigated. Notably, two mammalian target of rapamycin inhibitors, a mammalian target of rapamycin inhibitor, and everolimus, have recently been approved for first-line treatment of advanced RCC.<sup>8</sup> In patients with advanced RCC and poor prognostic features, temsirolimus demonstrated improved survival compared with interferon- $\alpha$ .<sup>8</sup> This finding may be consistent with poor outcomes observed with conventional therapies. Accordingly, it is hoped that these newly available regimens will facilitate treatment choices for patients.<sup>34</sup>

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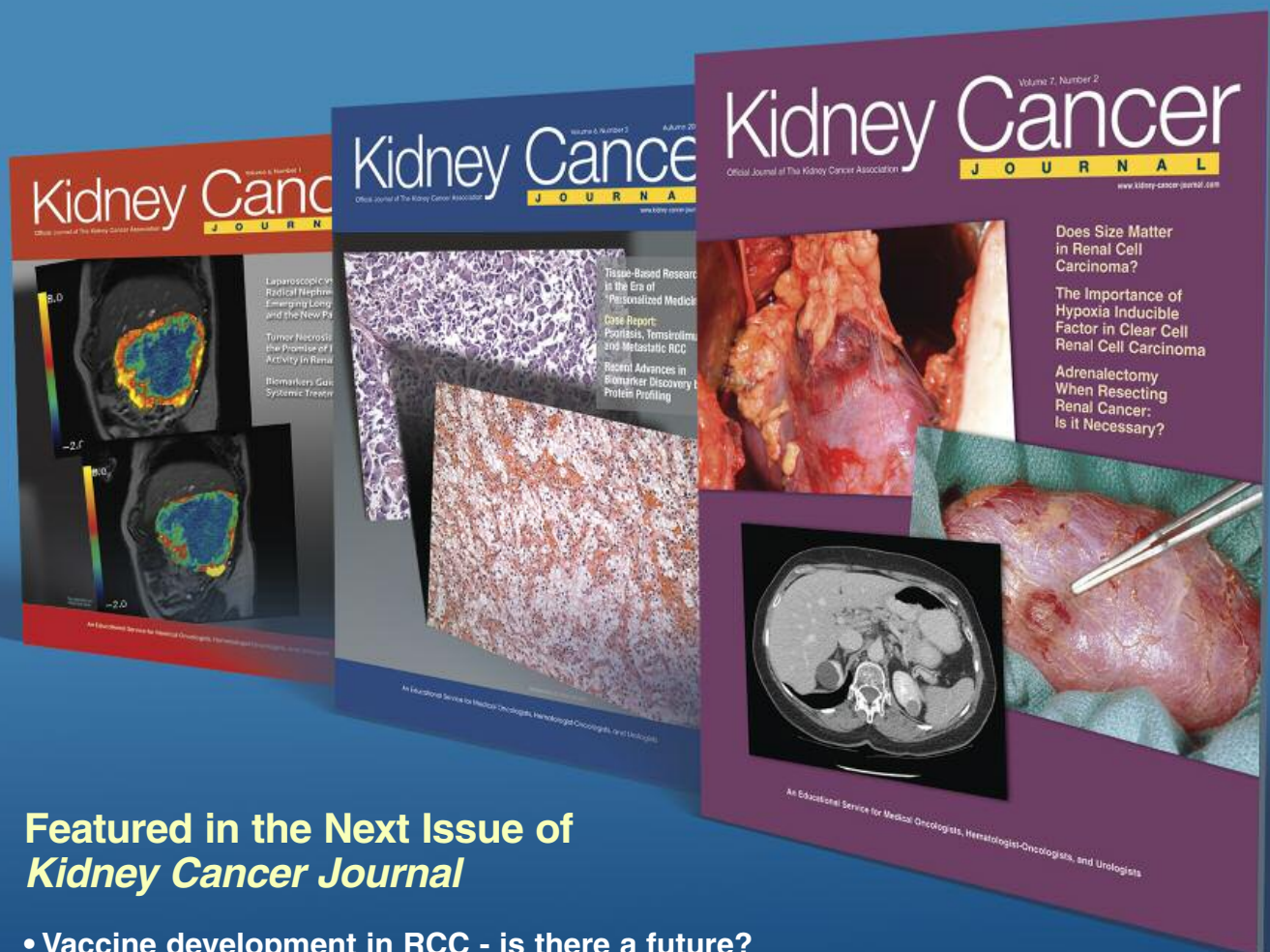
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