

# Disease-free survival as a predictor of overall survival in localized renal cell carcinoma (RCC) following initial nephrectomy

Naomi B. Haas<sup>1</sup>; Yan Song<sup>2</sup>; Jaqueline Willemann Rogerio<sup>3</sup>; Su Zhang<sup>2</sup>; Oluwakayode Adejoro<sup>3</sup>; Christopher Carley<sup>2</sup>; JingJing Zhu<sup>2</sup>; Rituparna Bhattacharya<sup>3</sup>; James Signorovitch<sup>2</sup>; Murali Sundaram<sup>3</sup>

<sup>1</sup>University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA;

<sup>2</sup>Analysis Group, Inc., Boston, MA, USA; <sup>3</sup>Merck & Co., Inc., Kenilworth, NJ, USA

## Background

- Renal cell carcinoma (RCC) is among the 10 most common cancers worldwide. In 2018, over 400,000 new cases of RCC were diagnosed globally<sup>1</sup>
- The prognosis for patients with RCC depends on a range of risk factors, including disease stage, sarcomatoid features, necrosis, and nuclear grade
  - For patients with newly diagnosed localized, regional, and metastatic disease, the 5-year survival rates are 93%, 70%, and 13%, respectively<sup>2</sup>
  - The risk of recurrence also increases with disease stage and nuclear grade at diagnosis<sup>3</sup>
- Recently introduced targeted therapies and immune checkpoint inhibitors have shown promising results and provided new treatment options for patients with advanced RCC.<sup>4</sup> The efficacy of these targeted therapies in advanced disease has led to the development of several phase III clinical trials to investigate their roles in the adjuvant setting
- While overall survival (OS) is the preferred endpoint of efficacy for new therapies in oncology studies, given the long survival post-nephrectomy associated with patients with localized RCC,<sup>5</sup> mature OS data may not be available at the time of regulatory evaluation or health technology assessment. Intermediate endpoints such as DFS may be evaluated and considered as predictors for long-term survival outcomes in these circumstances
- Current evidence on the correlation between DFS and OS endpoints in RCC is inconclusive. Additional evaluations of the association will help inform the interpretation of findings on DFS in the RCC adjuvant setting in the absence of mature OS data

## Objective

- To assess the correlation between DFS and OS among patients with intermediate-/high-risk and high-risk RCC post-nephrectomy

## Study design

- This retrospective observational study used Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data (2007-2016)
- Included patients, those aged >65 years with newly diagnosed, non-metastatic, intermediate/high or high-risk RCC who received a nephrectomy, were identified from the SEER-Medicare database
  - International Classification of Disease for Oncology, 3rd Ed. (ICD-O-3) code: C649 for kidney cancer and 8310 for clear cell adenocarcinoma histology were used to identify the diagnosis of RCC
  - Intermediate-/high-risk or high-risk, non-metastatic RCC was classified based on the collaborative tumor-node-metastasis (TNM) stage and nuclear grading status at diagnosis reported in SEER. Pathology information was used to derive the collaborative TNM stage when available; otherwise, clinical information was used to derive the collaborative TNM stage
- Included patients were grouped in two cohorts based on whether they experienced recurrence after initial nephrectomy. Recurrence was defined as the first additional nephrectomy, the first diagnosis for metastatic disease, or initiation of systemic treatments for advanced RCC
- The index date for patients with recurrence was defined as the date 30 days before indication of recurrence. For patients without recurrence, the index date was assigned randomly based on the distribution of time between the first nephrectomy and recurrence among patients in the recurrence cohort. The baseline period was defined as 12 months before the index date

## Outcome measures

- Disease-free survival (DFS)** was defined as time from initial nephrectomy date to first recurrence or death, whichever occurred first. Patients were censored at the earliest of loss of follow-up and end of data availability
- Overall survival (OS)** was defined as the time from initial nephrectomy, index date, or specified landmark to death. Patients were censored at the earliest of loss of follow-up and end of data availability
- Post-index date** means monthly all-cause costs per patient. Medical and pharmacy costs were inflated to 2019 US dollars using the consumer price index medical care component

## Statistical methods

- OS from the index date was described using Kaplan-Meier (KM) curves and compared between the recurrence cohort and non-recurrence cohort using the log-rank test. Cox proportional hazards models were used to adjust for key baseline characteristics including disease stage at diagnosis, age at index date, gender, race, Charlson Comorbidity Index (CCI), all-cause inpatient admissions during baseline, and all-cause outpatient visit during baseline
- In addition, OS from landmark points (1, 3, and 5 years post initial nephrectomy, respectively) by recurrence status by these landmark points was evaluated and compared. Hazard ratios (HR) of subsequent OS comparing patients with vs without recurrence at landmark points were estimated using multivariable Cox models adjusting for disease stage at diagnosis, age at nephrectomy, gender, race, and CCI
- Correlation between DFS and OS from initial nephrectomy was assessed using the Kendall  $\tau$  rank correlation. A bootstrapping approach with 1,000 replications was used to obtain a 95% confidence interval and *P*-value
- Mean monthly all-cause medical and pharmacy costs post index date per patient were compared between the recurrence and non-recurrence cohorts using generalized linear models with a Tweedie distribution and a log-link function

## Results

- 643 patients met the inclusion criteria (Figure 1), with 269 in the recurrence cohort and 374 patients in the non-recurrence cohort
- Follow-up duration from index date was (mean  $\pm$  SD) 25.0  $\pm$  23.0 months for the recurrence cohort and 35.2  $\pm$  26.0 months for the non-recurrence cohort
- Mean age at index date was approximately 75 years. The majority of patients were male (patients with recurrence: 64.7%; patients without recurrence: 57.8%), and >85% of patients in both cohorts were White. Among patients in the recurrence cohort, 10.8% had locoregional recurrence and 89.2% had distant metastatic recurrence (Table 1)

Figure 1. Sample selection and creation of patient cohorts

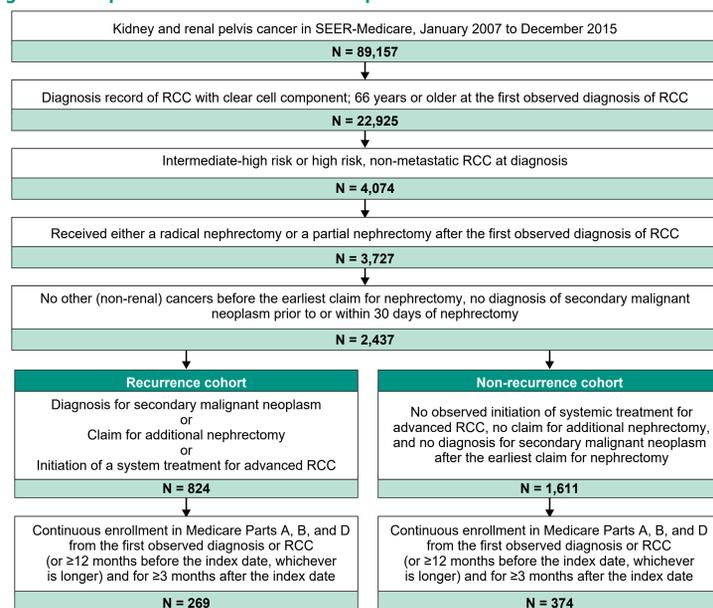


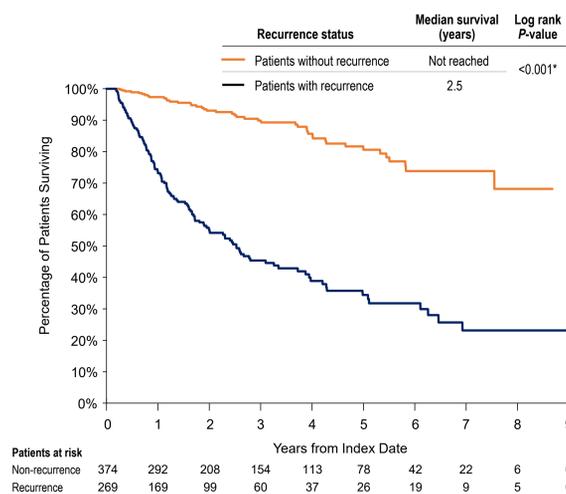
Table 1. Baseline characteristics of patients with RCC recurrence and without recurrence post-nephrectomy

Baseline characteristics	Patients with recurrence (N = 269)	Patients without recurrence (N = 374)	P-value
<b>Demographic characteristics</b>			
Age (years) at index date, mean $\pm$ SD	75.2 $\pm$ 6.1	75.7 $\pm$ 6.0	0.383
Male, N (%)	174 (64.7%)	216 (57.8%)	0.076
White, N (%)	231 (85.9%)	323 (86.4%)	0.991
<b>Disease characteristics, N (%)</b>			
Risk classification			0.126
Intermediate-to-high risk			
T2, N0, M0	6 (2.2%)	12 (3.2%)	
T3, N0, M0	253 (94.1%)	358 (95.7%)	
High risk			
T4, N0, M0	4 (1.5%)	2 (0.5%)	
T any, N+, M0	6 (2.2%)	2 (0.5%)	
Recurrence type			
Locoregional	29 (10.8%)	–	
Metastatic	240 (89.2%)	–	
CCI, mean $\pm$ SD	3.9 $\pm$ 1.7	3.7 $\pm$ 1.7	0.242
<b>All-cause HRU (events PPPM)</b>			
Inpatient admissions	0.097 $\pm$ 0.098	0.082 $\pm$ 0.108	0.068
Emergency department visits	0.064 $\pm$ 0.117	0.055 $\pm$ 0.115	0.356
Outpatient visits	2.303 $\pm$ 1.499	2.052 $\pm$ 1.212	0.024
Skilled nursing facility stays	0.014 $\pm$ 0.046	0.019 $\pm$ 0.118	0.450

## OS of patients with vs without recurrence post-nephrectomy

- Patients with recurrence post-nephrectomy had shorter OS from the index date than patients without recurrence (*P*<0.001) (Figure 2)
  - For patients in the recurrence cohort, the median OS from the index date was 2.5 years; median OS from the index date was not reached for patients in the non-recurrence cohort. The adjusted hazard ratio indicated a 6x increased risk of death for patients with vs without recurrence (95% CI: 4.2-8.5; *P*<0.001)

Figure 2. Overall survival stratified by recurrence status post-nephrectomy



\*Statistical Significance.

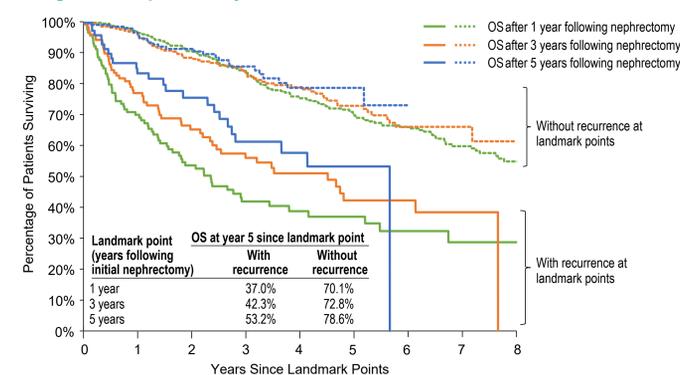
## Landmark analyses

- Patients with recurrence by each landmark point had shorter subsequent OS than those without recurrence
  - The median OS after the landmark of 1, 3, and 5 years following initial nephrectomy was 2.4 vs 9.7 years, 4.5 vs not reached, and 5.7 vs not reached (all *P*<0.001), respectively, for patients with vs without recurrence by each landmark point (Table 2)
  - The 5-year survival rates after the corresponding landmark points were 37.0% vs 70.1%, 42.3% vs 72.8%, and 53.2% vs 78.6%, respectively (Figure 3)
  - Adjusted HRs indicated that patients with recurrence by the landmark of 1, 3, and 5 years following initial nephrectomy had 3.5x, 3.0x, and 2.7x increased risk of death compared with patients without recurrence (all *P*<0.001) (Table 2)

Table 2. Cox proportional hazard model results of overall survival between patients with and without recurrence after 1, 3, and 5 years following initial nephrectomy

Landmark point (years following initial nephrectomy)	Median OS after landmark point, years		Adjusted HR (95% CI)	P-value
	With recurrence	Without recurrence		
1 year	2.4	9.7	3.5 (2.6, 4.6)	<0.001
3 years	4.5	Not reached	3.0 (2.1, 4.3)	<0.001
5 years	5.7	Not reached	2.7 (1.5, 4.7)	<0.001

Figure 3. Overall survival stratified by recurrence status after 1, 3, or 5 years following initial nephrectomy



## Correlation analysis between DFS and OS

- The Kendall  $\tau$  correlation between DFS and OS from initial nephrectomy was 0.7 (95% CI: 0.65-0.74; *P*<0.001), indicating a significantly positive association between DFS and OS

## Health care costs associated with RCC recurrence post-nephrectomy

- RCC recurrence post-nephrectomy was associated with significantly higher mean monthly all-cause health care costs. Adjusted post-index date all-cause medical and pharmacy costs per-patient-per-month (PPPM) were \$4,924 and \$1,387 higher on average, respectively, among patients with recurrence than patients without recurrence (both *P*<0.001)

## Limitations

- Recurrence was inferred from database codes rather than directly determined based on clinical data
- The studied SEER-Medicare data represent patients aged >65 years. Hence, the results from this study may not reflect outcomes among a younger patient population
- Impacts of recurrence may be confounded by unobserved factors such as sarcomatoid features and necrosis

## Conclusions

- To the best of our knowledge, the present study is the first to assess the association between DFS and OS among patients with intermediate-high risk and high risk RCC post-nephrectomy using real-world patient-level data
- This study demonstrated that patients with intermediate-/high-risk and high-risk RCC with recurrence post-nephrectomy had an approximately 3 times increased adjusted risk of death compared with those without recurrence post-nephrectomy following each landmark point
  - This finding is consistent with the observation that patients with recurrence post-nephrectomy had higher risk of death than patients without recurrence after the index date
- Additionally, DFS and OS post-nephrectomy were found to be significantly and positively correlated among patients with intermediate-/high-risk and high-risk RCC
- These findings demonstrate that in SEER longer DFS is prognostic of longer OS among patients with RCC following initial nephrectomy and suggest that DFS can be useful as a predictor of OS in the RCC adjuvant setting when OS data are immature

## References

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