Prognostic Impact of Cytoreductive Nephrectomy in Patients with Metastatic Renal Cell Carcinoma: Data from a Large Population-Based Database

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Purpose: Cytoreductive nephrectomy (CN) was considered a well-established treatment modality for patients with metastatic renal cell carcinoma (RCC) in the interferon era. However, its role after the introduction of multiple targeted therapies is less well established. Herein, We evaluated the effect of CN on overall survival (OS) on patients with RCC who were identified through the Surveillance, Epidemiology, and End Results database (SEER).

Materials and Methods: A total of 5,483 patients with metastatic RCC were identified from 2010 to 2016 using the SEER database. Factors pertaining to the following variables were collected: presence or absence of CN; age; gender; grade; status of metastasis to bone, liver, lung and brain; tumor stage; nodal status; histological subtypes; and chemotherapy status. Subjects who had CN were matched with those who did not in all previously mentioned covariates using inverse probability weighting. These weights were then used in adjusted Cox regression models to report doubly robust estimates.

Results: CN was associated with 67% reduction in the hazards of death. Advanced T-stage, N1 disease, advanced tumor grade, non-clear histology and metastasis to bone, liver, lung or brain are independent risk factors for death. Patients with T4 disease benefited less of CN compared to those with T1 disease, while higher number of metastatic sites didn't predict worse outcome among those who had CN.

Conclusion: CN could provide a survival advantage in favorable risk patients with RCC in the era of targeted therapy.

Keywords: cytoreductive nephrectomy; immunotherapy; interferon; metastatic renal cell carcinoma; overall survival

INTRODUCTION

Renal cell carcinoma (RCC) is an uncommon malignancy that arises from the renal cortex. Pathologically, RCC can be divided into several subtypes based on its morphology, molecular alterations, growth pattern, immunohistochemistry and cell of origin. Clear cell histology (CC) comprises the majority of RCC subtypes (75-85%) while papillary, chromophobe, oncocytic and collecting duct tumors (of Bellini) account for the rest.[1]

Cytoreductive nephrectomy (CN) was considered one of the main modalities of treatment in metastatic renal cell carcinoma (mRCC) in the era of interferon therapy. That was established after the publication of two randomized controlled trials; SWOG-8949 and EORTC; both have shown a survival advantage in patients who were treated with CN along with interferon compared to those who received interferon therapy alone. The median survival of the combined treatment modalities was 11.1 months compared to 8.1 months for the interferon therapy alone in the SWOG 8949 trial and 17 vs. 7 months in the EROTC trial.[2,3] Patients with good performance status (0-1) were included in these trials regardless of their tumor burden.

However, the role of CN after the introduction of targeted therapies, which significantly improved survival in patients with mRCC, is still under debate. Several non-experimental studies demonstrated a survival benefit for CN. However, these studies were subjected to several biases.[4] In regards to experimental studies, the CARMENA trial demonstrated non-inferiority of sunitinib compared to the CN followed by targeted therapy arm in patients with mRCC. However, around 15% of the trial participants deviated from their treatment assignment, which could have contributed to the non-inferiority result of this trial. Also, the trial stratified patients based on their MSKCC prognostic indicators which has lower prognostic value in the targeted therapy era compared to international metastatic renal cell carcinoma database consortium (IMDC) prognostic indicators. Moreover, there was slight imbalance in the T stage between both groups and exclusion of patients with low tumor burden which limits extrapolation of the trial results to this subgroup.[5] The SURTIME trial, a parallel randomized control trial that compared deferred CN after sunitinib to immediate CN. The trial did not show any difference in the progression free rate (PFR) between the groups who received an upfront CN

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Table 1. Baseline characteristics for patients according to their cytoreductive nephrectomy (CN) status

	CN (Partial or total nephrectomy) (median, IQR, Proportions)	No surgery) (median, IQR, Proportions)
N	2991 (55%) 2492 (45%)	
Median age (95% CI)	60 (20-85) years	64 (18-85) years
Gender		
Male	2115 (71%)	1753 (70%)
Female	876 (29%) 739 (30%)	
Number of metastatic sites		
0	199 (8%)	549 (18%)
1	1172 (47%)	1872 (62%)
2	785 (32%)	505 (17%)
3	282 (11%)	88 (3%)
4	38 (2%)	7 (0.2%)
Given chemotherapy		
Yes	1596 (53%)	1477 (59%)
No	1395 (47%)	1015(41%)
Histology		
Clear cell	2436 (81%)	1909 (77%)
Non-clear cell	555 (19%)	583 (23%)
Grade		
Grade I / II	528 (18%)	312 (13%)
Grade III / IV	2099 (70%)	378 (15%)
Unknown	364 (13%)	1802 (72%)
T stage		
T0	0 (0%)	33 (1%)
T1/2	658 (22%)	869 (33%)
T3	1518 (50%)	432 (17%)
T4	282 (10%)	300(12%)
TX	20 (1%)	483 (12%)
Unknown	513 (17%)	408 (16%)
Nodal positivity		
Yes	631 (21%)	692 (28%)
No	1758 (59%)	1075 (43%)
Unknown	602 (20%)	725 (29%)

followed by sunitinib compared to the one who deferred CN after sunitinib, but there was a statistically OS advantage in the deferred CN arm.[6] The trial concluded that deferral of CN would help in identifying subjects with resistance to targeted therapy who are unlikely to benefit from CN. Nonetheless, the trial was limited by poor accrual rate; imbalance between the two arms in the proportion of subjects with three or more poor surgical risk factors and locally advanced disease; and early trial termination which could have biased the result estimate away from the null. In another study using the IMDC, data from 1658 subjects with mRCC were retrospectively analyzed. The trial demonstrated 40% reduction in the hazard of death in mRCC patients who

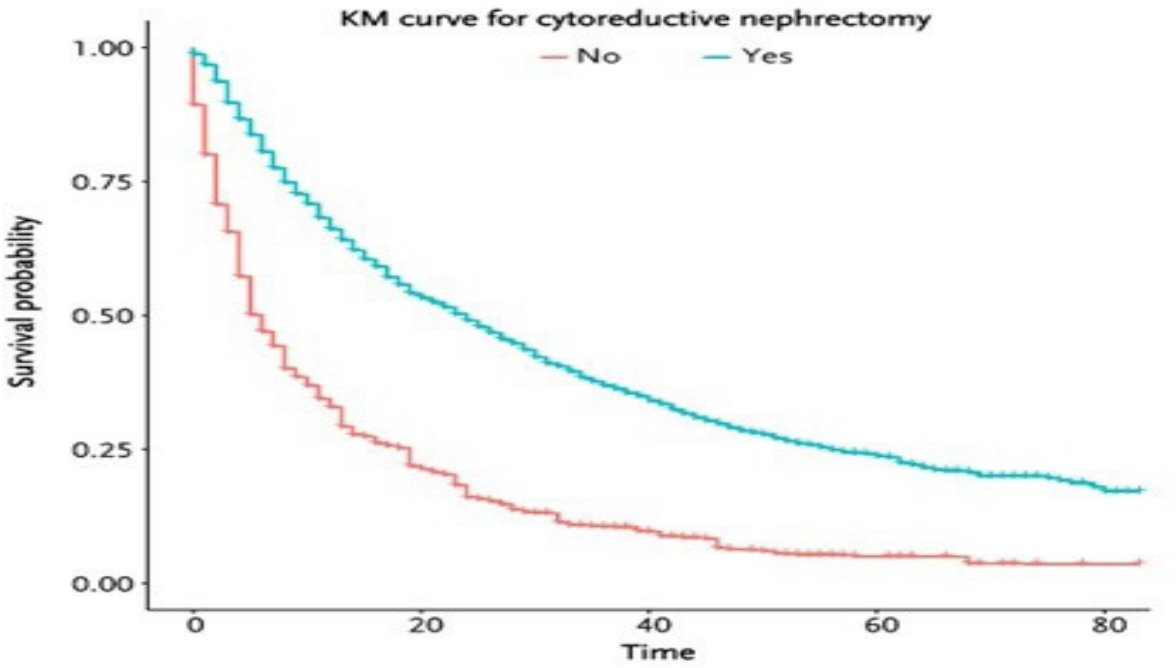

Figure 1. Weighted Kaplan Meier curves for the group who had CN and for those who didn't.

Table 2. Results of the logistic regression comparing the variables that are associated with having CN. The following variables were included in the model to identify the variables that are strong confounders and are strongly associated with the exposure (probability of having CN): age; sex; race; T stage; nodal status; grade; histology; number of metastatic sites; and chemotherapy administration.

Covariates that were strong predictors of treatment assignment.	Reference category	Estimate (OR)	95% CI	*P*_value
Age (years)				
40-60	<40	1.28	0.55-2.78	0.55
> 60		0.69	0.30-1.49	0.37
Sex = male	Female	1.09	0.84-1.41	0.50
Race				
White	Black	1.14	0.74-1.72	0.54
Other		1.40	0.79-2.55	0.27
T stage				
T2		0.75	0.53-1.08	0.12
T3	T1	3.03	2.13-4.31	< 0.001
T4		0.69	0.46-1.04	0.07
Nodal status positive	N0	0.36	0.28-0.48	< 0.001
Grade				
Grade II		4.00	2.21-7.44	< 0.001
Grade III	Grade I	8.50	4.70-15.80	< 0.001
Grade IV		25.4	13.39-49.55	< 0.001
Histology = non-clear cell	Clear Cell	0.80	0.58-1.11	0.17
Number of metastatic sites	No liver, bone, lung or brain metastasis	0.43	0.37-0.50	< 0.001
Received chemotherapy	No chemotherapy	0.62	0.48-0.80	< 0.001

underwent CN after adjustment for prognostic covariates including IMDC predictors. In this study, patients with estimated overall survival (OS) of less than 12 months and those with four or more IMDC prognostic indicators didn't not benefit from CN.[7] On the other hand, CN was associated with improvement in OS across all ranges of follow up in another retrospective study.[8] The latter study included subjects before the era of targeted therapy which limits drawing a firm causal conclusion of the effect of CN on survival after the era of targeted therapy.

Due to the controversy in the literature regarding the role of CN, we identified patients with de novo mRCC using the SEER database after the approval of the targeted therapy. We studied the association between CN and OS in these patients. Also, we identified certain subgroups of patients who could benefit most from the CN. Since CN was demonstrated to have survival benefit in MRCC patients in 2009[9], we have included the SEER data between 2010-2016 to avoid any bias due to secular trend.

MATERIALS AND METHODS

Study population

We used the SEER database to identify subjects who were diagnosed with mRCC (TNM Stage = M1) as their first malignancy from 2010 to 2016. The SEER Case Listing Session was used for analysis. Information was extracted from the database named ""Incidence - SEER 18 Regs Custom Data (with additional treatment

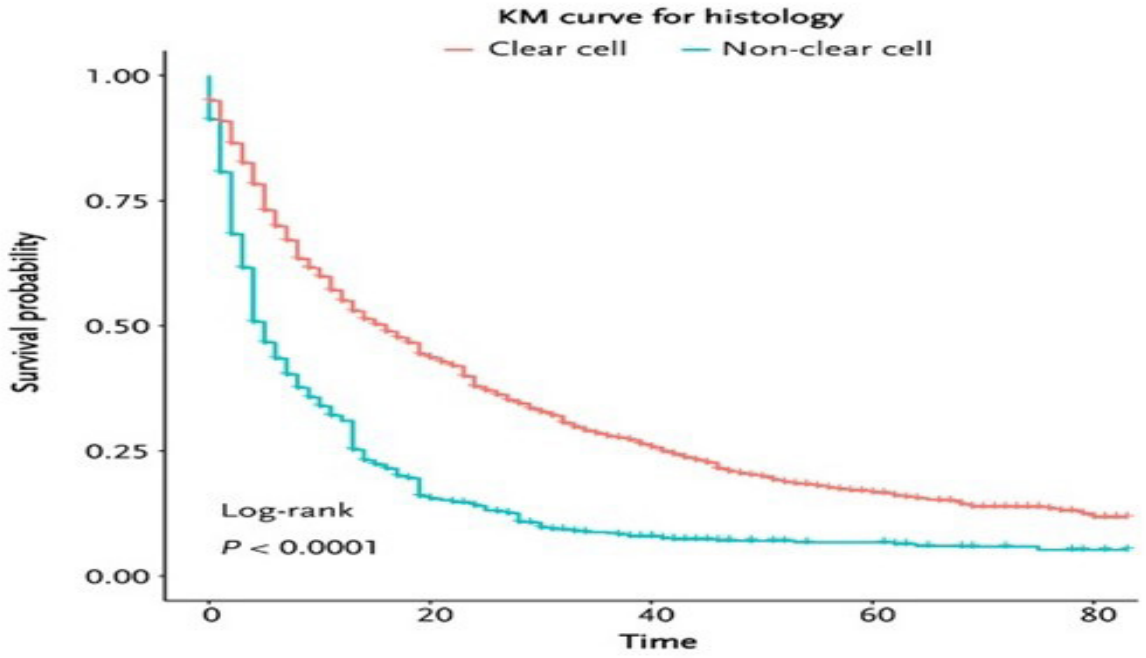

Figure 2. Weighted Kaplan Meier curves for histological subtypes.

Table 3. Results of the weighted Cox regression evaluating the effects of the following covariates on overall survival (OS): Age, sex, race, T stage, nodal status, grade, histological types, number of metastatic sites to bone, liver, lung and brain and cytoreductive nephrectomy. We adjusted for the chemotherapy variable in all models through stratification since the relationship between this variable and survival violates the proportional hazard assumption. A) Regular model. B) Second model with interaction with T stage. C) Third model with interaction with number of metastatic sites.

Variables	A) Regular Model (AIC 36192)				B) T Stage Interaction (AIC 36198)			C) Number of metastatic sites interaction (AIC 36194)		
Covariates that were strong predictors of treatment assignment.	Reference category	Estimate (HR)	95% CI	P value	Estimate (HR)	95% CI	P value	Estimate (HR)	95% CI	*P* value
Age (years)										
40-60	<40	1.24	0.84-1.84	0.29	1.24	0.83-1.85	0.28	1.26	0.85-1.89	0.25
>60		1.33	0.90-1.98	0.16	1.33	0.90-1.98	0.15	1.36	0.92-2.01	0.13
Sex = male	Female	0.87	0.73-1.03	0.11	0.88	0.74-1.04	0.14	0.87	0.74-1.03	0.10
Race										
White	Black	1.16	0.86-1.57	0.32	1.16	0.86-1.57	0.33	1.19	0.88-1.60	0.26
Other		0.91	0.61-1.36	0.66	0.93	0.64-1.36	0.71	0.94	0.64-1.39	0.76
T stage										
T2	T1	0.97	0.76-1.25	0.82	0.82	0.55-1.22	0.34	0.96	0.74-1.23	0.72
T3		1.26	1.00-1.57	0.04	1.08	0.73-1.60	0.69	1.23	0.99-1.54	0.06
T4		1.51	1.14-2.00	0.004	1.17	0.73-1.87	0.51	1.49	1.12-1.98	0.005
Nodal status positive	N0	1.47	1.23-1.76	< 0.001	1.47	1.24-1.75	< 0.001	1.51	1.26-1.81	< 0.001
Grade										
Grade II	Grade I	1.61	1.02 -2.54	0.042	1.63	1.03-2.56	0.04	1.56	0.99-2.44	0.05
Grade III		2.06	1.30-3.27	0.002	2.06	1.30-3.28	0.002	2.02	1.29-3.17	0.002
Grade IV		2.58	1.62-4.11	< 0.001	2.57	1.61-4.11	< 0.001	2.54	1.61-4.00	< 0.001
Histology = non-clear cell	Clear Cell	1.92	1.54-2.39	< 0.001	1.94	1.57-2.42	< 0.001	1.94	1.57-2.39	< 0.001
Number of metastatic sites to bone, liver, lung or brain.	No liver, bone, lung or brain metastasis	1.62	1.45-1.80	< 0.001	1.62	1.46-1.80	< 0.001	1.79	1.48-2.16	< 0.001
Underwent cytoreductive nephrectomy (CN)	No CN	0.33	0.28-0.40	< 0.001	0.24	0.17-0.33	< 0.001	0.42	0.30-0.59	< 0.001
Interaction term CN: T Stage										
CN: T2	CN: T1				1.49	0.93-2.38	0.09			
CN: T3					1.41	0.91-2.19	0.12			
CN: T4					1.78	1.06-2.99	0.03			
Interaction term CN: Number of metastatic sites								0.82	0.67-1.00	0.048

fields), Nov 2018 Sub (1975-2016 varying)-Database ID: 30305". A total of 5,488 patients were identified as having microscopic confirmation of their metastatic disease.

Inclusion and exclusion criteria

Four patients with age of 18 years or less and one patient with missing patient identification number were excluded from the study population. Therefore, a total

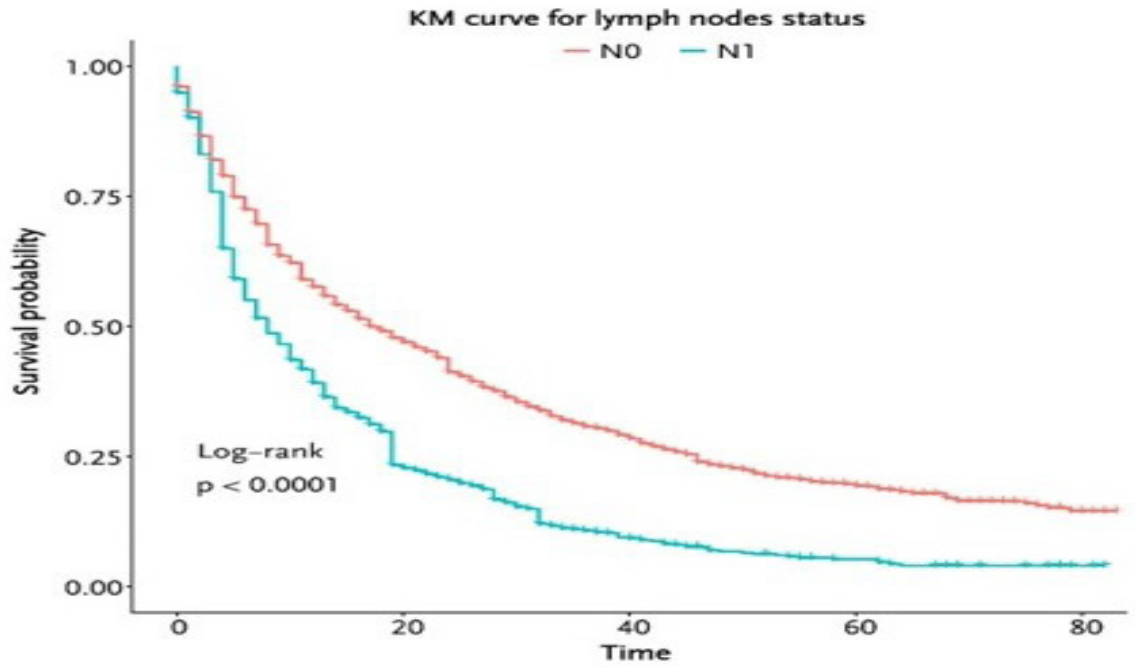

Figure 3. Weighted Kaplan Meier curves for the groups who had N0 disease and those who had N1 disease.

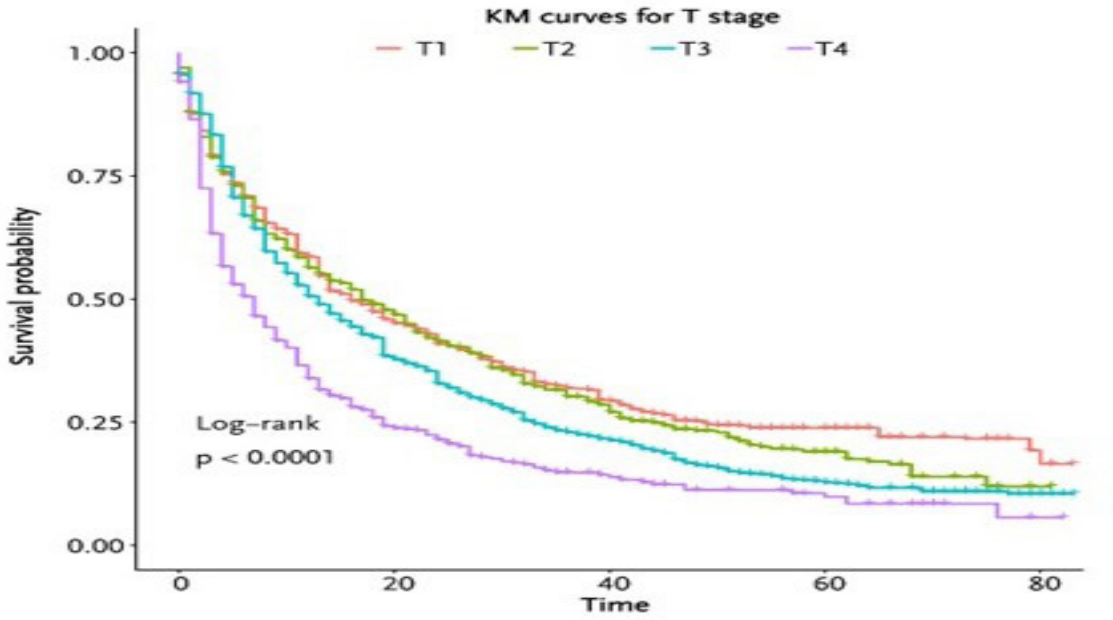

Figure 4. Weighted Kaplan Meier curves for the T-stage categories.

of 5483 patients comprised the study population and were included in our analysis.

Methods

The main purpose of our study is to identify the effect of CN on OS on patients with mRCC. The following covariates of interest that should consider strong confounders for the effect of CN on OS were extracted from the database: age at diagnosis, gender, TNM stage according the 7th American Joint Committee of Cancer (AJCC) edition, nodal status, sites of metastasis (bone, liver, brain, and lung), tumor size, grade, histology, duration of follow-up, date of death or loss to follow up, status of chemotherapy, and type of surgical resection. In order to study the causal effect of CN on OS, we matched subjects who had partial or total nephrectomy with those who didn't using the weights that were created using the generalized boosted model (gbm). This method can achieve a good balance on the covariates of interest even in the absence of significant overlap in the propensity scores between the groups. We used the average treatment effect on the treated (ATT) estimates to study the potential outcome of patients who had CN

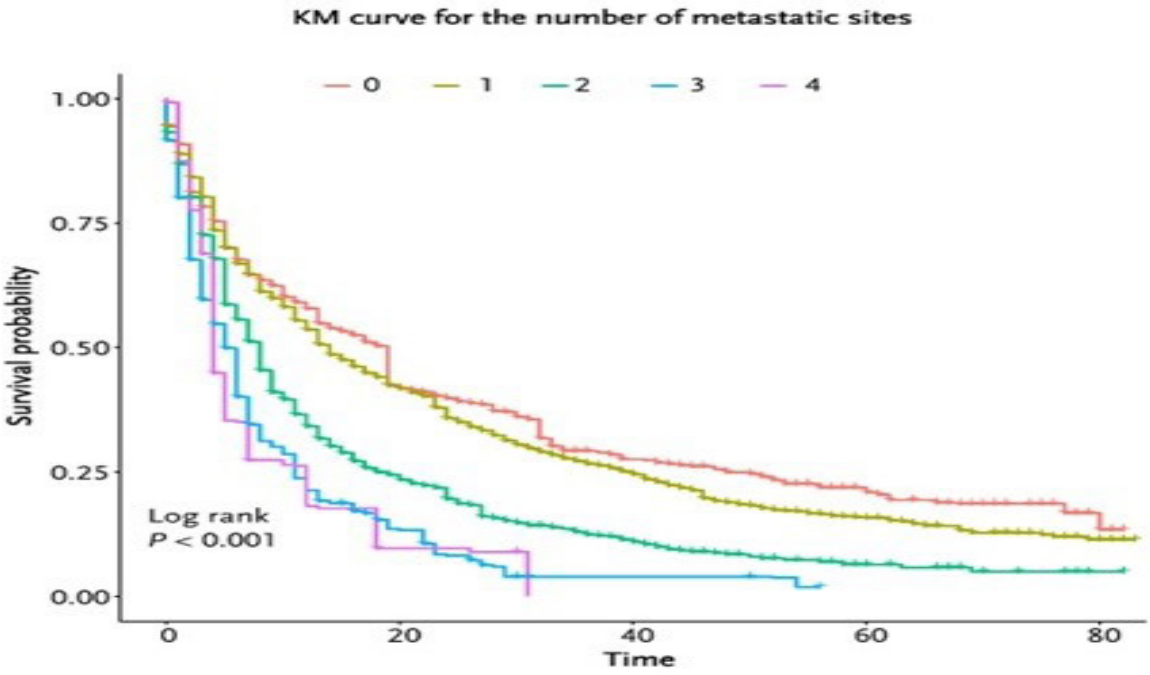

Figure 5. Weighted Kaplan Meier curve for the groups with different number of metastatic sites.

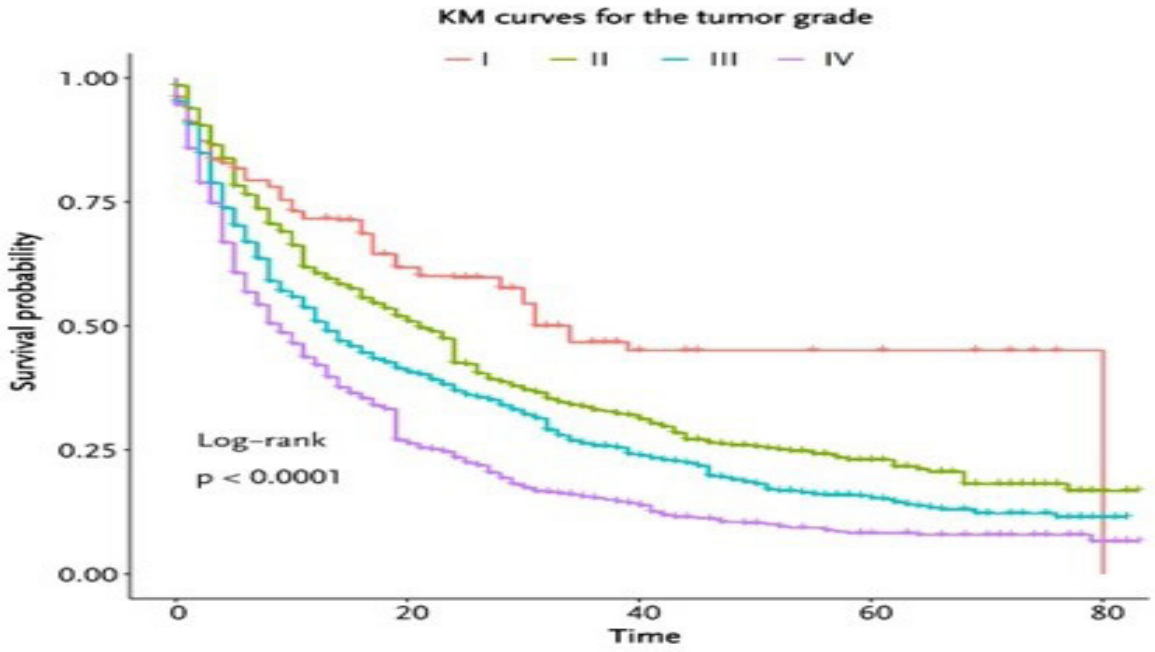

Figure 6. Weighted Kaplan Meier curves for the four levels of the tumor grade.

if they did not have surgery. We matched patients who had CN with those who didn't on the following covariates that we considered as a strong and intermediate confounder: age, gender, nodal status (N0, N1), chemotherapy status, T-stage (T1, T2, T3, T4), grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), number of organs involved by metastasis[1,2,3,4], race (white, Black, others) and histology (clear cell, non-clear cell). We categorized the age into three groups (less than 40, 40-60, more than 60), and chemotherapy was dichotomized as defined in the SEER database into (yes, no or unknown). We created a variable that we named "number of metastatic sites". This indicates the number of organs (brain, bone, liver, and lung) involved by metastasis. We used the twang package in R to balance these covariates by creating weights using the gbm. We didn't use the tumor size as a covariate in our matching process since we considered the T-stage. Stage and grade with values of X in the SEER database were considered NA in our dataset. Nine patients with extreme weights were excluded from the final data analysis. **Supp. Figure 1** (supplementary material) shows the propensity score distribution between patients who had CN and those who did not. Supp. **Figure 2** (supplementary material) shows a significant decrease in the standardized mean difference (SMD) in the pretreatment covariates between the group who had CN and those who did no't. Kaplan Meier (KM) curves for CN pretreatment covariates were created while considering the weights generated by the gbm. Results of weighted KM curves with log-rank test statistic are shown in **Figures**. 1 to 6 (Figures are reported only for the covariates that were significant predictor for survival in the Cox-regression models).

Finally, we ran different models using the "svycoxph" command in R to account for the weights that were generated. All models included CN as an outcome and the following covariates: age, number of metastatic sites, T stage, nodal status, grade, gender, race, histology, and chemotherapy status. Furthermore, different models were considered with an interaction term between CN and grade, CN and nodal status, CN and the number of metastatic sites, CN and the histological types and CN and T stage in addition to a model without any interaction term. Because the KM curves for the chemotherapy variable crossed each other, chemotherapy variable was stratified in Cox regression analysis using strata analysis and therefore we did not generate a hazard estimate for this variable. Models were compared using Akaika information criteria (AIC). Running cox-regression with weights under survey command precluded performing likelihood ratio test on nested models.

Finally, we performed sensitivity analysis to assess our result sensitivity to an unobserved confounder. We relied on Rosenbaum approach to evaluate the strength of the association of an unobserved confounder (U) to our exposure of interest (CN nephrectomy) and to our outcome (OS) to change our results to non-significance. Because this approach relies on 1:1 matching, we created a matched dataset between subjects who had CN and those who didn't using the MATCHIT package in R on the same covariates used in our primary analysis. We used a nearest matching method on propensity score with a caliper of 0.2 to achieve a good balance on the pretreatment covariates. In this analysis, 977 patients who had CN were matched to 977 patients who didn't have CN (36% of the total cohort). Sensitivity analysis was ran using Rosenbaum spread sheet on survival outcome via Wilcoxon rank test.

RESULTS

Between 2010 and 2016, 5483 patients with mRCC were identified using the SEER registry. The patients' median age was 62 years old (range 18-85). The ma-

jority were males (70%) and 4345 (79%) had CC histology while the rest had nonnuclear cell (NCC). NCC included patients with chromophobe, papillary, collecting duct, medullary, oxyphilic, squamous, transitional and sarcomatoid RCC. There was a total of 2996 (54%) patients who underwent partial or radical nephrectomy. Baseline characteristics of the patients are summarized in **Table 1**.

After a median follow-up time of 9 months (3-83 months), the median overall survival (OS) was 13 months. The median survival time for the cohort who had CN was 24 months (CI, 22-25) and 6 months (CI, 6-7) for patients who did not have surgery ($P < 0.01$, Figure 2). Grades III and IV, N1 disease, higher number of metastatic sites, female gender, and non-clear cell histological types were associated with higher risk of death, while CN was associated with improvement in survival in weighted adjusted KM curves using log-rank test statistics. Also, there was a statistically significant increase in the trend of using chemotherapy from 2000 to 2016 with a P value of 0.038 for the trend. On the other hand, there is a trend toward lower numbers of CN from 2010 to 2016 with a P value for a trend of 0.047 (Supplementary Material, **Supp. Table 1**).

All potential confounder variables were included in a logistic regression model to identify variables that strongly predict treatment assignment (CN). Patients with T3 stage, Grade II-IV, lower number of organ involvement with metastasis and those who didn't receive chemotherapy were more likely to have CN. Results of the logistic regression model are shown in **Table 2**.

All pretreatment covariates that were used in weighted matching between subjects who had CN and those who didn't were included in the Cox models to obtain a doubly robust estimate. All models with an interaction term have AIC values slightly above the model without an interaction term, therefore, the latter model with an Akika information criteria (AIC) value of 36192 was considered the primary model for our results. In this model, CN was associated with 67% reduction in the risk of death in patients with mRCC (HR 0.33, 95% CI 0.28-0.40). Non-clear cell histological subtype was independently associated with higher risk of death (HR 1.9, 95% CI 1.54-2.40). Also, patients with nodal involvement and those with T4 disease had a statistically significant higher risk of death compared to those with N-0 and T0 disease (HR 1.50, 95% CI 1.23-1.75, and HR 1.5, 95% CI 1.14-2.0, respectively). Moreover, for each one-point increase in the number of metastatic sites, there was a statistically significant increase in risk of death with a HR 1.60, 95%CI 1.45-1.80. Finally, Grades II, III and IV were independently associated with higher risk of death compared to Grade I (HR 1.60, 95% CI 1.02-2.54; HR 2.1, 95% CI 1.3-3.3; and HR 2.58, 95% CI 1.62-4.11, respectively). Results of doubly robust Cox regression model are shown in **Table 3**.

Only two models with an interaction term had a statistically significant P-value for the interaction. The test that included an interaction between tumor T stage and CN nephrectomy had a statistically significant interaction between CN and T-4 disease with a HR 1.78, 95% CI 1.10-2.99 (The AIC for the model is 36198). This result indicates that patients with T4 stage who had CN had 78% higher risk of death compared to those with T1 disease who had CN. If there is no interaction under the multiplicative interaction model, we would expect the HR to be 0.28 (1.17; the HR for the T4 stage; multiplied by 0.24; the HR of CN). However, the current hazard of death for those who had CN and T4 disease is 0.5 (1.17; the HR for the T4 stage; multiplied by 0.24; the HR of CN, multiplied by 1.78; the HR for the interaction term). In other words, patients with T4 disease would benefit less from CN compared to those with T1 disease. Similarly, the model that included an interaction term between surgery and number of metastatic sites showed a statistically significant estimate with a HR=0.82 (95% CI 0.67-0.997) indicating that patients with increased number of metastatic sites to bone, liver, lung or brain had 18% lower risk of death compared to those with no metastasis to bone, liver, lung or brain (The AIC for this model is 36194)). Under the assumption of no interaction and using the multiplicative interaction model between CN and number of metastatic sites, the HR of death for patients with higher metastatic sites who had CN should equal 0.75 (The HR for CN [0.42] multiplied by the HR for the increasing metastatic sites [1.79] under this model). However, when we multiply the estimates for patients who had CN (0.42) with the HR for the increased metastatic sites (1.79) and with the interaction term (0.82); the HR is 0.62. These results indicate that patients with increased metastatic sites would benefit more from CN compared to those with lower number of organ involvement. Results of doubly robust Cox regression model with interaction terms are shown in **Table 3**.

Our sensitivity analysis showed an unobserved confounder (U) that increase the odds of having CN by 42% and being a near perfect predictor of OS, would change our results toward the null. This U is plausible, since KPS which is not included in our model, could have such an association and it implies that our results could be sensitive to bias. However, this sensitivity analysis should be interpreted with caution since only 36% of the total cohort (1954 patients) were included in this analysis. The results of our sensitivity analysis are demonstrated in the supplementary material (**Supp. Table 2**).

DISCUSSION

The two large prospective randomized trials that evaluated the role of CN in mRCC after the era of targeted have some limitations, mainly poor accrual, early trial termination and unbalanced randomization in regards to surgical risk factors and locally advanced disease in the SURTIME trial and deviation from the treatment assignment and inclusion of high risk patients for the CARMENA trial(Méjean et al., 2018).[5] This highlights the importance of non-experimental study designs in evaluating the role of CN in mRCC patients.

Our data suggests a strong association between CN on OS. The median OS for the subjects who had CN was 24 months (CI, 22-25) compared to 6 months (CI, 6-7) for those who did not have CN with a HR of 0.33 (95%CI 0.28-0.40) in the doubly robust model in favor of CN. This is highly similar to an unadjusted weighted estimate (HR 0.38, 95%CI 0.33-0.44), indicating a great balance in all pretreatment covariates using an inverse probability weights on the treatment assigned (IPTW). Our results go in hand with the results from international metastatic RCC consortium (IMRCC). In this study, subjects who had CN had an OS of 20.6 months compared to 9.5 months for those without CN.[7] Similarly,

Vaishampayan et al and Pulmbo et al found that CN is associated with survival advantage in patients with locally advanced or mRCC using the SEER database.[10,11] However, our study has a larger sample size with 2991 patients who underwent CN compared to 2483 patients who didn't. Also, we applied a doubly robust method with inverse probability weighting and adjustment in regression analysis. This enabled us to effectively adjust for the study confounders without excluding subjects from the CN group. This is important, because our inference measures the effect of CN on the whole subjects who had CN if they did not have surgery. Furthermore, we conducted a sensitivity analysis to evaluate the strength of our association and the efficacy of CN on certain subgroups.

In the SURTIME trial, patients with deferred CN had an OS advantage compared to those with immediate CN. However, the trial result should be interpreted with caution due to early termination which could have biased the study estimate away from the null. Also, higher number of subjects with surgical risk factors and T4 disease were assigned to immediate CN arm. The latter would support our result with a negative quantitative interaction between patients with T4 disease and CN and suggests that deferred CN could be the appropriate approach for patients with advanced T stage.

We measured the average treatment effect on the treated (ATT) in our analysis. Therefore, our results reflect the efficacy of CN on those who had CN if they did not have it. In our logistic regression model, subjects who didn't receive chemotherapy by the time of CN, those with lower number of metastatic sites, and don't have T4 disease were more likely to have CN and thus will have significant survival benefit from it. This supports the current practice, in which many centers perform CN for patients only with intermediate- or low-risk groups. These can be defined as the presence of four of less of the following risk factors: sarcomatoid features, low serum albumin, T3 or T4 disease, retroperitoneal or supradiaphragmatic lymphadenopathy and symptoms from metastatic sites such as bone and brain.[12] Other criteria could be used such as Karnofsky index (KPS) more than 80%, adequate organ function, ability to perform at least 75% tumor debulking and absence of extensive bone, liver and central nervous system metastasis.[13] Furthermore, data from IMRCC database revealed that patients who have four or more MSKCC risk factors (less than 1 year of diagnosis, KPS < 80%, serum lactate dehydrogenase >1.5, elevated serum calcium and low hemoglobin level) are unlikely to benefit from CN.[7] Our analysis shows that higher number of metastatic sites, advanced tumor grade and T stage and non-clear histology are independent risk factors for higher mortality. Although higher number of metastatic sites are associated with 60% higher hazard of death in our analysis, CN offers survival benefit among those subjects more than what would be expected taking into consideration their multiple organ metastases. This support providing CN to patients with more than one metastatic site if they are in good performance status and considered good surgical candidates.

It is important to note here that there is a notable discrepancy between non-experimental studies that showed a significant survival benefit of CN in MRCC patients[7,10] and the randomized clinical trials (CARMENA and SURTIME clinical trials).[5,6] As noted earlier, In the SURTIME trial, quarter of the subjects who had immediate CN had three or more surgical risk factors. OS in those subjects could be negatively affected by immediate CN. About half the subjects in the CARMENA trial had fallen into a poor risk category in the MSKCC model. This could explain the discrepancy between these randomized trials and other non-experimental studies. This highlights the potential benefit of CN in low risk mRCC patients, and the need for a randomized control trial that is enriched with mRCC patients who have low risk features. Moreover, there is lack of enough data on the appropriate timing of CN relative to targeted therapy. Further research on this area could identify the appropriate timing for CN that improves OS.

Since we were unable to capture all the confounding covariates using the SEER database, we used the Rosenbaum approach to test the strength of the association between CN and survival. Because this method and many other sensitivity analysis approaches rely on 1:1 matching, we performed a 1:1 matching analysis. In our sensitivity analysis, our gamma value was 1.421, which indicates an unobserved confounder that has at least 42% odds of association with CN and near prefect predictor of survival would change our estimate on CN toward the null. Usually, a gamma value of 4 or 5 will reflect a strong unbiased association. This indicates that our result is susceptible to bias and highlights the importance of conducting a randomized control trial with strict eligibility criteria to evaluate the effectiveness of CN after the introduction of targeted therapy.

Our study has some limitations. Our analysis relies on an un-confounded assumption. However, given the limitations of the SEER database, some important covariates were not included in our model such as KPS, comorbidities and covariates pertaining to the MSKCC risk model. This made our study susceptible to selection bias, namely confounding by indication. However, we used weights-based method to create a balanced dataset on all pretreatment variables that are strongly related to mRCC and to OS. Our new pseudo-dataset was well balanced on all pretreatment variables. Also, we matched subjects on the distribution of chemotherapy variable. Because patients with good performance status are more likely to receive chemotherapy, our analysis likely accounted for some confounding due to KPS. Metastatic disease was included as categorical variable for each site of metastasis (present or not) in the SEER database with no detailed information pertaining to the tumor burden. This could have resulted in residual confounding that could have affected our study estimates. Also, no information regarding the extent of nodal involvement in the SEER database which precludes evaluating the effect of CN in patients with extensive lymphadenopathy.

Dalong Cao et al. have used the SEER database to evaluate the role of lymphadenectomy along with CN on survival using the SEER database from 2006-2015.[14] In addition, Vaishampayan et al. used the SEER database from 2000-2013 to evaluate the effect of CN on survival.[10] We included data only from 2010-2017 only to avoid the secular trend that have been observed since the introduction of targeted therapies in 2009. Many patients, particularly those without CN have missing values on tumor grade. This could possibly bias our results if these missing values were not missing at random (non-missingness). Nonetheless, we matched

both treatment groups on missing values which will decrease the bias.

CONCLUSIONS

CN could provide a survival advantage to selected patients with mRCC, regardless of histology. The risks and benefits of surgery should be discussed thoroughly and offered to patients on a case-by-case basis. Randomized trials with restricted inclusion criteria to low-risk patients is needed to fully disentangle the causal effect of CN on survival, especially with the new era of widespread use of immune checkpoint inhibitors in patients with mRCC.

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest regarding the publication of this paper.

APPENDIX

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