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The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: A Real-World Multi-Institutional Analysis

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Study Need and Importance: The role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC) was challenged by the results of the CARMENA trial and there is a need to evaluate its role in the era of modern immunotherapy (IO)-based therapies. Using real-world data from an electronic health record-based database Flatiron, we explored the following questions in patients with synchronous mRCC: 1) the role of up-front cytoreductive nephrectomy (uCN) vs systemic therapy alone, including immunotherapy and tyrosine kinase inhibitor-treated patients, and 2) the role of uCN vs deferred CN.

What We Found: In this cohort study of 1,910 patients, after adjusted analyses were conducted via Inverse Probability of Treatment Weighing, median overall survival (OS) was higher in the patients receiving uCN vs systemic therapy (26.6 vs 14.6 months, p <0.001; see Figure). Among patients receiving CN and systemic therapy, the timing of systemic therapy relative to CN was not significantly related to OS (HR=1.0, 95% CI 0.76–1.32, p=0.99). Among the patients receiving IO-based therapy (433), the median OS was 40.2 months in the uCN group and 15.2 months in those receiving IO-based therapy alone.

Limitations: The study is limited by its retrospective nature and nonrandomized analyses. While we determined type of therapy for most patients, 128 patients received an unspecified trial drug. Additionally, in 41% patients Eastern Cooperative Oncology Group performance status could not be determined, and International mRCC Database Consortium intermediate vs poor risk score could not be distinguished in 44% of patients.

Interpretation for Patient Care: Our analysis supports an oncologic role for CN in carefully selected patients, even in the modern IO era, and provides evidence regarding the timing of CN relative to systemic therapy administration.

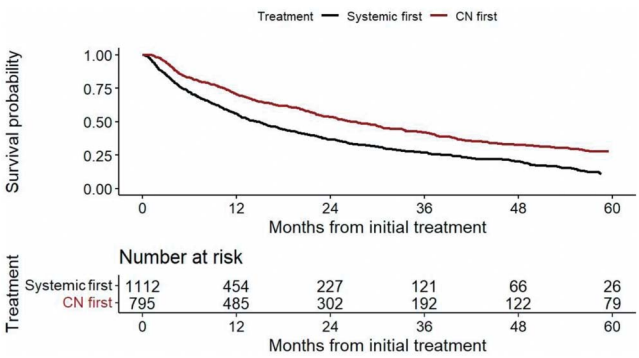

Figure. Adjusted Kaplan-Meier OS in all patients using sensitivity analysis.

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The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: A Real-World Multi-Institutional Analysis

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Abbreviations and Acronyms

BMI = body mass index
CN = cytoreductive nephrectomy
dCN = deferred CN
ECOG = Eastern Cooperative Oncology Group
EHR = electronic health record
IMDC = International mRCC Database Consortium
IO = immunotherapy
IPTW = Inverse Probability of Treatment Weighing
mOS = median overall survival
mRCC = metastatic clear cell renal cell carcinoma
mTOR = mammalian target of rapamycin
OS = overall survival
TKI = tyrosine kinase inhibitor
uCN = up-front CN

Purpose: The role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC) was challenged by the results of the CARMENA trial. Here we evaluate the role of CN in mRCC patients, including those receiving modern therapies.

Materials and Methods: We included patients with synchronous mRCC between 2011–2020 from the de-identified nationwide Flatiron Health database. We evaluated 3 groups: systemic therapy alone, CN followed by systemic therapy (up-front CN [uCN]) and systemic therapy followed by CN (deferred CN [dCN]). The primary outcome was median overall survival (mOS) in patients receiving systemic therapy alone vs uCN. Secondary outcome was overall survival in patients receiving uCN vs dCN. First-treatment, landmark and time-varying covariate analyses were conducted to overcome immortal time bias. Weighted Kaplan-Meier curves, log-rank tests and Cox proportional hazards regressions were used to assess the effect of therapy on survival.

Results: Of 1,910 patients with mRCC, 972 (57%) received systemic therapy, 605 (32%) received uCN, 142 (8%) dCN and 191 (10%) CN alone; 433 (23%) patients received immunotherapy-based therapy. The adjusted mOS was significantly improved in first-treatment, landmark and time-varying covariate analysis (mOS 26.6 vs 14.6 months, 36.3 vs 21.1 months and 26.1 vs 12.2 months, respectively) in patients undergoing CN. Among patients receiving CN and systemic therapy, the timing of systemic therapy relative to CN was not significantly related to overall survival (HR=1.0, 95% CI 0.76–1.32, p=0.99).

Conclusions: Our findings support an oncologic role for CN in select mRCC patients. In patients receiving both CN and systemic therapy, the survival benefit compared to systemic alone was similar for up-front and deferred CN.

Key Words: carcinoma, renal cell; surgery; nephrectomy

The treatment for metastatic clear cell renal cell carcinoma (mRCC) has been revolutionized with vascular endothelial receptor growth factor receptors tyrosine kinase inhibitors (TKIs), immunotherapy (IO) as well

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as IO/IO and IO/TKI combinations. Patients with mRCC are stratified based on prognostic models—the MSKCC (Memorial Sloan Kettering Cancer Center) model and the International mRCC Database Consortium (IMDC) model.[1,2]

In addition to systemic therapy, cytoreductive nephrectomy (CN) has historically been integrated in the management of mRCC patients. Initial evidence supporting its use emerged during the cytokine era when CN improved the median overall survival (mOS) in 2 randomized phase III trials comparing CN prior to interferon alpha compared to interferon alpha alone.[3,4]

Recently, the results of CARMENA and SURTIME reinvigorated debate about the utility of CN and the optimal treatment sequence in mRCC.[5,6] CARMENA was a phase III noninferiority trial comparing CN followed by sunitinib vs sunitinib therapy alone in mRCC.[5] This study concluded that sunitinib alone is noninferior to surgery followed by sunitinib and questioned the standard practice of up-front CN (uCN) for mRCC.[5] SURTIME was a prospective randomized trial evaluating the role of immediate versus deferred CN in the era of sunitinib and suggested that although the rate of progression between the 2 approaches is similar overall survival (OS) may favor the deferred approach, potentially due to the ability to receive systemic therapy.[6]

How to interpret the data surrounding CN in clinical practice is a matter of considerable debate. Factors such as comorbidities, performance status, surgical candidacy and recovery, as well as patient and physician perspectives, likely play a role in determining who receives CN.

Previously published retrospective analyses utilizing the IMDC, National Cancer Database and SEER (Surveillance, Epidemiology, and End Results) data sets have reported a higher mOS with CN compared to systemic therapy alone[7,8] and a benefit of deferred (dCN) over uCN.[9] However, prior analyses had limitations such as lack of modern IO-based therapy, IMDC scores, Eastern Cooperative Oncology Group (ECOG) performance status and names of specific systemic treatments. Using real-world data from an electronic health record (EHR)-based database Flatiron, we explore the following questions in patients with synchronous mRCC: 1) the role of uCN vs systemic therapy alone, including IO and TKI-treated patients, and 2) the role of uCN vs dCN. We describe the problem of immortal time bias, commonly affecting the interpretation of such retrospective studies, and analyze our data using various statistical methods in an attempt to overcome this bias.

PATIENTS AND METHODS

Data Source

This analysis uses data from the nationwide U.S. Flatiron Health EHR-derived de-identified database comprising structured and unstructured data curated via technology-enabled abstraction and supplemented with third-party death information.[10] Mortality information was generated via a composite variable that incorporates structured and unstructured EHR data, commercial source data (obituary data) and data from the U.S. Social Security Death Index.[10] During the study period, this database included de-identified data from approximately 280 U.S. cancer clinics (800 sites of care). Most cases were ascertained from community medical oncology clinics, with the remainder from academic medical centers. Although Flatiron Health data has generally similar patient characteristics to those of other national data sets, there are differences compared to representative samples, such as fewer elderly patients and more late stage diagnoses.[11] Institutional Review Board waiver of informed consent was obtained prior to study conduct.

Study Population

We identified 9,170 cases of mRCC between 2011 and 2020. A conservative selection process was applied and only included patients with clear cell histology and synchronous metastases (Fig. 1 and supplementary Appendix, https://www.jurology.com).

Variables

Covariates of interest included age and date at metastatic diagnosis, gender, race, stage, laboratory variables (calcium, hemoglobin, neutrophils, platelet count), drug names, start and end date of drug administration, date of CN, ECOG performance status (at the time of metastatic diagnosis), insurance type and body mass index (BMI). Survival outcomes of interest were defined based on date of radiographic or clinical progression, date of death and respective censoring dates (last clinic assessment/last date of structured contact).

Since all patients had synchronous mRCC, all patients were either intermediate or poor risk per IMDC definition. We further classified IMDC based on prior recommendations for EHR-based research with partial missingness.[12] Patients with at least 3 known IMDC risk criteria were classified as poor risk. To be classified as intermediate risk, patients were required to have no missing variables and a score of 1−2 per IMDC definition. Remaining patients were classified as intermediate/poor, as further determination of their risk status could not be made. Treatment was classified into IO, IO/IO, IO/TKI, TKI and mammalian target of rapamycin (mTOR) inhibitor groups by 1 author (PG) prior to statistical analysis.

Outcomes and Statistical Analyses

The primary outcome was to compare OS in the uCN vs systemic alone groups in all patients. OS was calculated from the time of initiation of first therapy—either systemic or CN. Patients who were alive at the end of followup were considered censored at their last structured activity date. The key secondary outcome was to assess the association between OS and the timing of CN (uCN vs dCN).

Baseline clinical characteristics were compared using chi-squared tests, Fisher's exact tests, ANOVA tests or t-tests. Kaplan-Meier curves, log-rank tests and Cox proportional hazards regressions were used to assess the

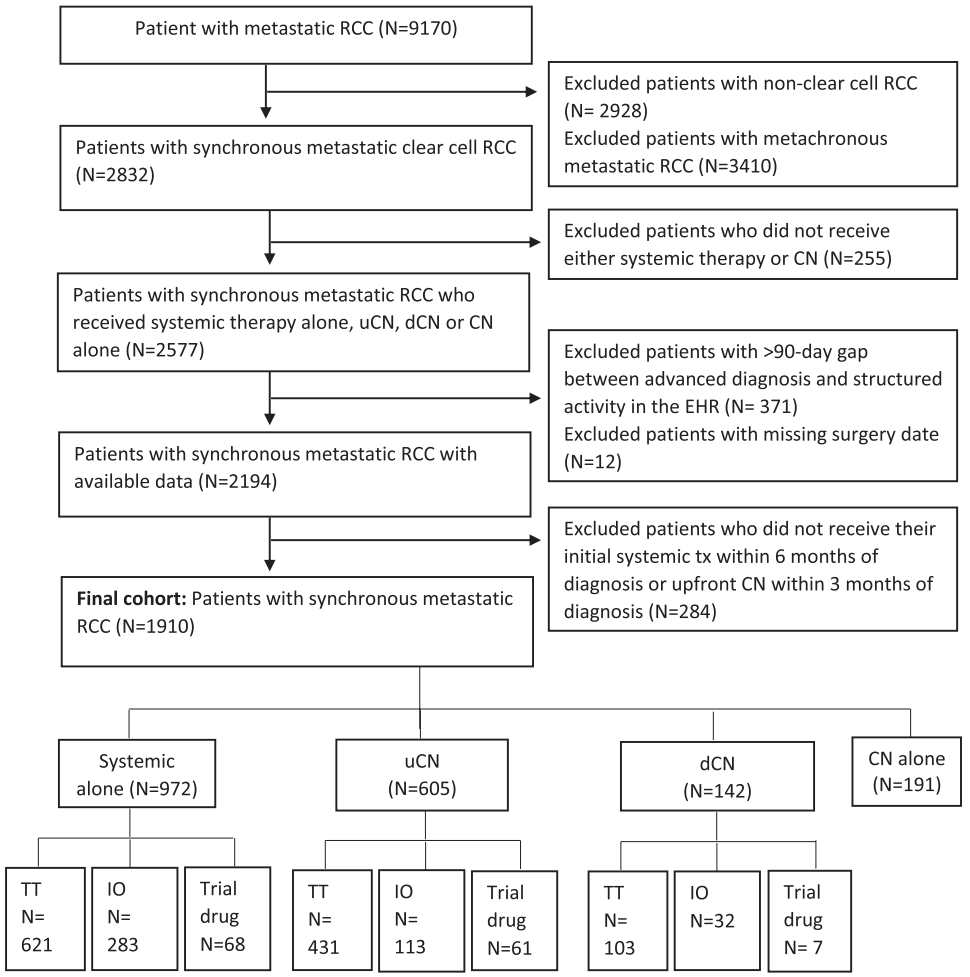

Figure 1. Consort diagram. *RCC*, renal cell carcinoma. *TT*, targeted therapy (includes TKI and mTOR inhibitors). *tx*, treatment.

effect of therapy on survival. Adjusted analyses were conducted via Inverse Probability of Treatment Weighing (IPTW) based on the generalized propensity score,[13] with propensity scores estimated via Bayesian Additive Regression Trees.[14] Covariates in the propensity score model were age, gender, race, insurance at diagnosis and IMDC risk group. Where covariates were missing, we used a missing category in the propensity score model. Propensity scores were assessed for overlap and weighted observations were assessed for covariate balance, with a standardized difference of <0.1 taken to indicate sufficient balance. Weighted Kaplan-Meier curves and Cox models were then used. All statistical analyses were conducted using R Software version 3.6 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided statistical significance was defined as $p < 0.05$.

In all retrospective analyses, the intention to treat is not clear, as we only know the actual treatment received. Immortal time bias occurs when the classification of "exposed" patients requires that the person survive until the date he/she received the treatment.[15] To overcome these biases, we considered several methods such as first-treatment analysis (which included CN only patients), 6-month landmark analysis and time-varying covariate analysis, each with their benefits and limitations as discussed in the supplementary Appendix (https://www.jurology.com).

We also examined the effect of CN in the subgroup of patients receiving IO, and formally assessed whether CN effects differed by systemic treatment (IO vs non-IO), age and IMDC (intermediate vs poor) by testing the interactions between each variable and surgical treatment (Cox model with 6-month landmark).

RESULTS

Patient Characteristics

Our main cohort consisted of 1,910 patients; the average age at diagnosis was 64.9 years (range 29–85), 70% were White and 70% were men. The ECOG performance was missing in 41% of patients. In 880 (46%) patients the IMDC risk category could not be determined and they were thus classified as intermediate/poor. Among 1,030 patients with available variables, 28% were intermediate risk and 72% were poor risk (Table 1).

Of 1,910 patients, 972 (51%) received systemic therapy alone, 605 (32%) received uCN, 142 (7%)

Table 1. *Patient characteristics of all included patients*

	Systemic Alone		uCN		dCN		CN Alone		p Value
No. pts	972		605		142		191		
Median yrs age (Q1, Q3)	67	(60, 75)	62.3	(56, 69)	63.2	(58, 70)	65	(58, 70)	<0.001*
No. male sex (%)	675	(69)	418	(69)	101	(71)	136	(71)	0.925†
No. race (%):									0.614‡
White	670	(70)	438	(72)	101	(71)	135	(79)	
Black	55	(6)	23	(4)	8	(6)	9	(5)	
Hispanic	2	(0.2)	6	(1)	0		1	(1)	
Asian	13	(2)	10	(2)	2	(2)	4	(2)	
Other	130	(13)	84	(14)	21	(15)	21	(12)	
Missing	102	(11)	44	(7)	10	(7)	21	(11)	
No. insurance type (%):									0.003‡
Commercial	336	(35)	51	(36)	51	(36)	85	(45)	
Medicaid	69	(7)	39	(6)	10	(7)	4	(2)	
Medicare	180	(19)	75	(12)	11	(8)	26	(14)	
Medicare/commercial	204	(21)	143	(24)	38	(27)	37	(19)	
Other	110	(11)	74	(12)	21	(15)	25	(13)	
Unknown	73	(8)	38	(6)	11	(8)	14	(7)	
Median kg/m^2 BMI (Q1, Q3)	28	(24, 32)	28	(24, 32)	29	(25, 33)	28	(25, 33)	0.307*
No. ECOG performance status (%):									<0.001‡
0	213	(22)	160	(26)	37	(26)	28	(38)	
1	264	(27)	144	(24)	29	(20)	21	(42)	
2	116	(12)	36	(6)	11	(8)	12	(16)	
3	32	(3)	7	(1)	5	(4)	1	(1)	
4	3	(0.3)	0		1	(1)	2	(3)	
Missing	344	(35)	258	(43)	59	(42)	117	(61)	
No. IMDC risk category (%):									<0.001†
Intermediate	149	(15)	90	(15)	29	(20)	16	(8)	
Poor	443	(46)	211	(35)	47	(33)	45	(24)	
Poor/intermediate	380	(39)	304	(50)	66	(47)	130	(68)	
No. IO/IO									<0.0012
(ipilimumab/nivolumab) (%)	153	(16)	59	(10)	17	(12)			
No. IO/TKI (%):									
Pembrolizumab/axitinib	79	(8)	18	(3)	11	(8)			
Avelumab/axitinib	3	(0.3)	2	(0.2)	0				
Nivolumab/axitinib	1	(0.1)	0		0				
Ipilimumab/nivolumab/cabozantinib	3	(0.3)	0		0				
Nivolumab/pazopanib	2	(0.2)	1	(0.1)	0				
Bevacizumab/INFa2b			3	(0.4)	0				
No. IO alone (%):	1	(0.1)							
Andesleukin	3	(0.3)	16	(3)	2	(1)			
Pembrolizumab	15	(2)	5	(1)	0				
Nivolumab	23	(2)	12	(2)	2	(1)			
Durvalumab			0		0				
VEGFR inhibitor:	2	(0.2)							
Pazopanib	233	(24)	164	(27)	44	(31)			
Sunitinib	206	(21)	180	(30)	45	(32)			
Axitinib	12	(1)	9	(1)	0				
Bevacizumab	10	(1)	4	(1)	0				
Bevacizumab/everolimus	1	(0.1)		0	0				
Bevacizumab/pazopanib	1	(0.1)	3	(0.4)	0				
Cabozantinib	43	(4)	20	(3)	1				
Gemcitabine/sunitinib	2	(0.2)	0		0				
Sorafenib	14	(1)	8	(1)	0				
No. mTOR inhibitor (%):									
Temsirolimus	95	(10)	42	(7)	13	(9)			
Everolimus	6	(0.6)	2	(0.3)	0				
No. clinical study drug (%)	64	(7)	57	(9)	7	(5)			

* ANOVA tests.
† Chi-square tests.
‡ Fisher's exact tests with simulated p value (based on 2,000 replicates).

dCN and 191 (10%) received CN alone. Patients in the systemic alone group were older, more likely to have performance status 2+ and IMDC poor risk compared to the CN group. The race and BMI of patients in the 2 groups were similar (Table 1).

Among the 433 (23%) patients who received IO-based therapy, 285 (66%) received IO therapy alone and 148 (34%) received CN (either before [116] or after [32]) IO therapy. Patients receiving CN were younger, more likely to have ECOG performance status 0 and less likely to have IMDC poor

Table 2. *Patient characteristics of immunotherapy treated patients*

	IO		uCN		dCN		p Value
No. pts	285		116		32		
Median yrs age (Q1, Q3)	66 (60, 75)		63 (56, 70)		64 (59, 70)		<0.001*
No. male sex (%)	211	(74)	79	(68)	20	(63)	0.243†
No. race (%):							0.381†
White	179	(63)	85	(79)	24	(83)	
Black	16	(6)	5	(5)	0		
Hispanic	0		0		0		
Asian/other	52	(21)	17	(16)	5	(17)	
Missing	38	(13)	9	(8)	3	(9)	
No. insurance type (%):							0.252†
Commercial	116	(41)	54	(47)	13	(41)	
Medicaid	16	(6)	5	(4)	1	(3)	
Medicare	49	(17)	10	(9)	3	(9)	
Medicare/commercial	55	(19)	29	(25)	8	(25)	
Other	41	(14)	18	(16)	7	(22)	
Unknown	8	(3)	0	(0.0)	0		
Mean kg/m^2 BMI (SD)	29	(7)	30	(6)	30	(6)	0.172*
No. ECOG performance status (%):							0.036†
0	82	(29)	45	(56)	6	(27)	
1	89	(31)	30	(37)	11	(50)	
2	36	(13)	5	(6)	3	(14)	
3	9	(3)	1	(1)	2	(9)	
4	2	(1)		0	0		
Missing	67	(24)	35	(30)	10	(31)	
No. IMDC (%):							0.348†
Intermediate	45	(16)	21	(18)	5	(16)	
Poor	150	(53)	48	(41)	15	(47)	
Poor/intermediate	90	(32)	47	(41)	12	(38)	

* ANOVA tests.
† Fisher's exact tests with simulated p value (based on 2,000 replicates).

risk disease. Baseline demographics including race, sex and BMI were similar in the 2 groups (Table 2).

Types of Therapy

Of 1,719 patients receiving systemic therapy, 309 patients received IO or IO/IO, 124 patients received IO+targeted therapy and 1,155 patients received targeted therapy. An unknown clinical trial drug was given to 128 patients. The most common IO/IO combination was ipilimumab/nivolumab (229) and IO+targeted combination was pembrolizumab/axitinib (108; Table 1).

Impact of CN on Survival

All survival analyses reported below use IPTW balancing age, race, gender, insurance status and IMDC score. Median OS was 26.1 months in the uCN group and 12.2 months in the systemic alone group. As the observed survival of the uCN group is subject to immortal time bias, we assessed the impact of uCN on outcomes using 3 different methods:

First-treatment analysis. After IPTW mOS was better in the patients receiving uCN vs systemic therapy (26.6 vs 14.6 months, p <0.001; Fig. 2). Progression-free survival, measured from the time of initiating CN or systemic therapy, was also higher in the uCN arm than systemic therapy group (median progression-free survival 7.5 vs 5.1 months, p <0.001).

Landmark analysis. Using a 6-month landmark, 1,157 patients were included in the analysis. Similar to the first-treatment analysis, mOS was improved in the uCN vs systemic alone group (36.3 vs 21.1 months; Fig. 3).

Time-varying covariate analysis. Using a Cox model with time-varying treatments, we found a hazard ratio [HR] of 0.83 for uCN (95% CI 0.7–0.96, p=0.015) versus systemic alone.

Subgroup Effects

Among the patients receiving IO-based therapy (433), the IPTW mOS was 40.2 months in the uCN group and 15.2 months in those receiving IO-based therapy alone; however, this difference was not statistically significant when using regression with time-varying covariates (HR 0.90, 95% CI 0.59–1.36). When formally testing interaction, there were no statistically significant interactions between uCN/dCN and treatment with IO, age or IMDC score.

Impact of Timing of CN on mOS

Next, among patients undergoing CN we sought to evaluate whether the treatment sequence (uCN vs dCN) affected outcomes. Of 747 patients receiving CN, 605 (81%) received uCN and 142 (19%) received dCN.

On IPTW analysis, mOS was 26.1 and 36.5 months in the up-front and deferred CN groups, respectively. However, the long survival in the dCN group is likely due to immortal time bias. After patients received both systemic therapy and a CN (time-varying covariate method), mOS was not statistically different between uCN vs dCN (HR=1.00, 95% CI 0.76–1.32, p=0.99).

DISCUSSION

Using a national, EHR-based cohort, we explored the role of CN in synchronous mRCC patients. The availability of ECOG performance status in approximately 60% of patients, IMDC risk scores, names of drugs received by individual patients, and inclusion of patients who received modern IO/IO and IO/TKI treatments allowed for a rigorous assessment. Our study is unique as it also addressed the problem of immortal time bias by analyzing the data using 3 statistical methods, each with their own benefits and limitations.

We found that after adjusting for key variables, the OS of patients receiving uCN was significantly higher than those receiving systemic therapy alone. This was true using the first-treatment analysis (which included patients receiving CN alone), the

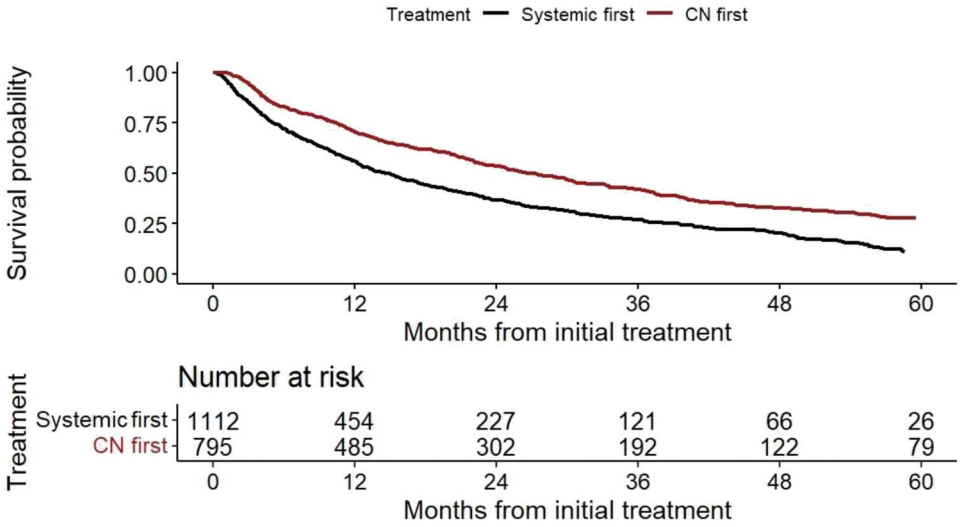

Figure 2. Adjusted Kaplan-Meier OS in all patients using sensitivity analysis. The sensitivity analysis incorporates all patients—those who receive CN alone, CN followed by systemic therapy, systemic therapy followed by CN and systemic therapy alone. Patients were categorized based on the treatment they received first: CN or systemic therapy.

6-month landmark analysis and the time-varying covariate analysis. The purpose of the first-treatment analysis was to mimic the intention to treat analysis conducted in CARMENA in which all patients were included despite 40 (18%) and 16 (7%) in the uCN arm not receiving planned systemic therapy and CN, respectively. Similarly, 11 (5%) patients in the systemic alone arm who did not receive systemic therapy were included.[5] An intention to treat analysis that includes all patients attempts to replicate a real-world scenario wherein a clinician decides whether an uCN vs immediate systemic therapy is appropriate for a given patient with synchronous mRCC. Of note, the magnitude of the OS benefit in the uCN vs systemic group was lower in our study compared to previously reported studies (HR 0.82 in our study vs 0.23[7] and 0.39[16] in other studies). This may be due to stricter inclusion criteria in our study and efforts to overcome selection and immortal time biases.

A key clinical question is how to select appropriate candidates for CN. In attempt to answer these questions, we conducted interaction analyses with systemic therapy type, age and IMDC category. We did not identify any statistically significant subgroup effects, potentially due to sample size constraints in subgroups or the modest overall

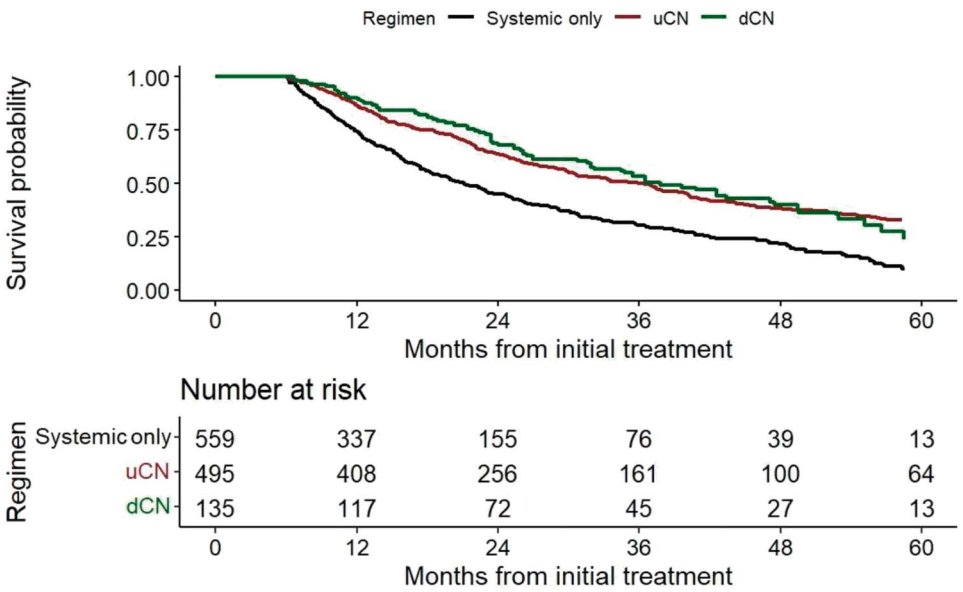

Figure 3. Adjusted Kaplan-Meier OS in all patients using 6-month landmark. We conducted a landmark analysis with the landmark set at 6 months (ie analyzing only patients who survived to 6 months), with the landmark time chosen based on our inclusion criteria.

effect. Therefore, individualized decisions between the surgeon, oncologist and patient in regard to the appropriateness of CN in each case remain critical. More robust models that may help predict the utility of a CN are also necessary.[17]

A common confounding factor which leads to misclassification of patients into systemic vs uCN group is not knowing if patients received nephrectomy at another center and hence represent metachronous metastatic disease. To overcome this bias, we excluded patients with a missing surgery date or who did not initiate therapy in a timely manner after diagnosis. While we included patients who received CN alone in the first-treatment analysis, in the time-varying covariate analysis we excluded 191 patients who received CN alone. With this, we excluded patients who may have had indolent metastatic disease.

The mOS in the systemic alone group was 12−13 months in our study, lower than that expected in the modern era. This may be due to inclusion of patients from 2011, 20% with an ECOG 2+, only IMDC intermediate/poor risk and those from community practice who may have had access to fewer treatment options. Additionally, patients receiving systemic therapy alone tend to have more aggressive disease. Of note, in the 6-month landmark analysis, the mOS was higher at 21.1 months, which is likely due to the exclusion of more frail patients who died before 6 months.

We did not find a significant OS difference between patients receiving uCN vs dCN once a patient had received both treatment components. These results are similar to the results of a retrospective study in which dCN did not improve OS compared to uCN, although a subset with MSKCC intermediate risk benefited.[18] On the contrary, in an IMDC analysis a significant OS benefit (HR = 0.52, 95% CI 0.39−0.70, p <0.001) was noted in the dCN compared to uCN group.[9] Careful patient selection and efforts to overcome immortal time bias in our study may account for these differences. Importantly, in SURTIME,[6] dCN showed an OS benefit, potentially attributed to some uCN patients never receiving necessary systemic therapy, and supporting the notion of a period of up-front systemic therapy as a litmus test in mRCC patients.

A strength of this analysis is that the drug regimen and date of administration were known for all patients with documented receipt of systemic therapy, allowing accurate classification into IO, IO/IO, IO/TKI, TKI and mTOR inhibitor groups. Only 25 patients received cytokine-based IO therapy, indicating that most patients received modern anti-PD1/PDL1-based IO agents which have become standard frontline therapies for mRCC patients.

Despite measures to overcome selection biases, we acknowledge the limitations of retrospective, nonrandomized analyses. While we determined type of therapy for most patients, 128 patients received an unspecified trial drug. Additionally, in 41% patients ECOG performance status could not be determined and IMDC intermediate vs poor risk score could not be distinguished in 44% of patients. Other prognostic factors such as sites of metastases and presence of a sarcomatoid component were not available to us.[19]

CONCLUSIONS

We evaluated the role of CN in mRCC patients by carefully addressing common confounding variables to reduce selection and immortal time biases which affect data interpretation. Our analysis supports an oncologic role for CN in carefully selected patients, even in the modern IO era, and provides evidence regarding the timing of CN relative to systemic therapy administration. Results from ongoing and future prospective trials will further elucidate the role and timing of CN in the setting of IO.

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