Original Article

Optimizing Patient Selection for Cytoreductive Nephrectomy Based on Outcomes in the Contemporary Era of Systemic Therapy

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BACKGROUND: The management of metastatic renal cell carcinoma (mRCC) has evolved rapidly, and results from the Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques (CARMENA) trial bring into question the utility of cytoreductive nephrectomy (CN). The objective of this study was to examine overall survival (OS) and identify risk factors associated with patients less likely to benefit from CN in the targeted therapy era. **METHODS:** Patients with mRCC undergoing CN from 2005 to 2017 were identified. Kaplan-Meier methods and Cox proportional hazards regression analyses were used to assess OS and risk-stratify patients, respectively, on the basis of preoperative clinical and laboratory data. **RESULTS:** Six hundred eight patients were eligible with a median follow-up of 29.4 months. Ninety-five percent of the patients had an Eastern Cooperative Oncology Group performance status less than or equal to 1, and 70% had a single site of metastatic disease. In a multivariable analysis, risk factors significantly associated with decreased OS included systemic symptoms at diagnosis, retroperitoneal and supradiaphragmatic lymphadenopathy, bone metastasis, clinical T4 disease, a hemoglobin level less than the lower limit of normal (LLN), a serum albumin level less than the LLN, a serum lactate dehydrogenase level greater than the upper limit of normal, and a neutrophil/lymphocyte ratio greater than or equal to 4. Patients were stratified into 3 risk groups: low (fewer than 2 risk factors), intermediate (2-3 risk factors), and high (more than 3 risk factors). These groups had median OS of 58.9 months (95% confidence interval [CI], 44.3-66.6 months), 30.6 months (95% CI, 27.0-35.0 months), and 19.2 months (95% CI, 13.9-22.6 months), respectively ($P < .0001$). The median time to postoperative systemic therapy was 45 days (interquartile range, 30-90 days). **CONCLUSIONS:** Patients with more than 3 risk factors did not seem to benefit from CN. Importantly, OS in this group was equivalent to, if not higher than, OS for patients in the CN plus sunitinib arm of CARMENA, and this raises the possibility that a well-selected population might benefit from CN. ***Cancer* 2020;126:3950-3960**. © *2020 American Cancer Society*.

KEYWORDS: cytoreductive surgery, nephrectomy, renal cell carcinoma, urologic neoplasms.

INTRODUCTION

On the basis of randomized controlled trials (RCTs) demonstrating superior overall survival (OS) for patients undergoing upfront nephrectomy followed by interferon-α (IFN-α) in comparison with immunotherapy alone,[1,2] cytoreductive nephrectomy (CN) became the standard of care for the management of metastatic renal cell carcinoma (mRCC) nearly 2 decades ago.[3] These data, however, rely on the use of interferon-based immunotherapy, an outdated and inferior treatment modality.[4-6] Beginning with the introduction in 2005 of therapies designed to target the molecular mechanisms underlying renal cell carcinoma progression (eg, tyrosine kinase inhibitors [TKIs], mammalian target of rapamycin inhibitors, and bevacizumab), the armamentarium of therapeutic options available to patients with mRCC has rapidly expanded.[7]

Ever since the beginning of the targeted therapy era in 2006,[8,9] the rationale for CN use has been based on retrospective series demonstrating a survival advantage.[10-12] Most recently, Mejean et al[13] published the results of CARMENA, a phase 3 RCT, and concluded that TKI therapy (ie, sunitinib) alone was noninferior to initial nephrectomy followed by a TKI in patients with mRCC. Moreover, checkpoint inhibitor immunotherapy clinical trials have demonstrated improved oncologic outcomes in comparison with TKI monotherapy.[14-16] The resultant debate now questions the role of CN in patients with mRCC, with some arguing that CN should no longer be performed for oncologic purposes and with others critiquing the study population and design of the Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques (CARMENA) trial and arguing for a continued role for CN.[17]

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Long recognizing the importance of patient selection for CN, we previously published a retrospective study identifying risk factors that predict inferior OS and, therefore, a subset of patients not likely to benefit from CN.[18] Because of the now over a decade long experience with targeted therapy utilization and toxicity management along with the advent of checkpoint inhibition, present-day risk factors may differ. Therefore, we sought to identify risk factors that affect OS in a contemporary CN cohort at our institution and to evaluate oncologic outcomes in the context of a changing therapeutic landscape following the publication of CARMENA.

MATERIALS AND METHODS

Upon approval by the institutional review board for the protection of human subjects, our institutional renal cell carcinoma database was interrogated to identify patients with mRCC undergoing CN from January 2005 to December 2017. Patients with incomplete clinicopathologic data or those who underwent nephrectomy outside MD Anderson Cancer Center (MDACC) were excluded. OS and median follow-up were calculated from disease diagnosis to either death or last known follow-up. Clinicopathologic data, including clinical, perioperative, preoperative laboratory, and final pathologic data, were indexed for all patients in a comprehensive fashion. All data were reviewed after collection to ensure accuracy and completeness. Clinical and pathologic staging was based on the American Joint Committee on Cancer 2009 TNM classification[19] and was determined at the time of diagnosis and after CN, respectively. Tumor grade was based on the Fuhrman grading system. The number and site (or sites) of metastasis were determined on the basis of preoperative radiographic imaging. Patients with brain metastases underwent CN only if they were treated with either surgical resection or stereotactic radiation before CN; this was in accordance with our standard clinical practice.

The most recent laboratory values before CN were used and classified as normal, below normal, or above normal on the basis of reference ranges at MDACC, with normal serving as the referent group in all analyses. To adjust for timing variations in laboratory draws, the time between the acquisition of laboratory specimens and CN was included in all analyses. Symptoms and/or signs at diagnosis were classified as none, local (palpable mass, flank pain, and/or gross hematuria), systemic (fevers, weight loss, and/or night sweats), and/or metastatic (localized symptoms at the site of metastatic disease; eg, bone pain). Retroperitoneal and supradiaphragmatic lymphadenopathy was identified on the basis of computed tomography findings of clinically suspicious lymph nodes at the time of diagnosis, with the latter including mediastinal and/or supraclavicular but not pulmonary hilar lymph nodes.

Kaplan-Meier analysis was used to determine OS for patients. Independent predictors of OS were identified with a stepwise, multivariable Cox proportional hazards regression analysis. Analyses were controlled for the year of surgery and the time from diagnosis to surgery. Variables that were significant in the multivariable analysis were labeled as risk factors. Subjects were categorized into 3 groups (good, intermediate, and poor) on the basis of the number of risk factors. Chi-square analysis was used to identify clinical, perioperative, and final pathologic variables that differed between the 3 groups. Finally, subsequent Kaplan-Meier and Cox proportional hazards regression analyses were performed to group subjects on the basis of the number of preoperative risk factors in terms of OS and relative risk, respectively. For all analyses, Stata software (version 10.1; Stata Corp., College Station, Texas) was used. All P values $\leq .05$ (2-sided) were considered significant.

RESULTS

We identified a total of 608 patients who underwent CN between 2005 and 2017 and were eligible for analysis. The median follow-up time from diagnosis was 29.4 months (interquartile range, 15.0-54.9 months). Characteristics of the study population are listed in Table 1. The majority of the patients had an Eastern Cooperative Oncology Group performance status less than or equal to 1 (n = 579 or 95.2%) and a single metastatic site of disease (n = 424 or 69.7%). The patients in our database were primarily at intermediate (n = 260 or 42.8%) or poor risk (n = 270 or 44.4%) according to the International Metastatic RCC Database Consortium (IMDC), with a single patient qualifying as having a favorable risk. Seventy-seven patients (12.7%) had at least 1 missing component that rendered us unable to risk-stratify them according to the IMDC criteria. Some form of systemic therapy (ST) was administered to 81.1% of the patients (n = 493), and 79.1% of the cohort (n = 481) received post-CN ST. The median time to ST was 45 days (interquartile range, 30-90 days). Nearly one-third of the patients (n = 187 or 30.8%) were placed on upfront ST (before CN), with 84.5% of those patients (n = 158) receiving targeted therapy. The remaining patients received traditional chemotherapy (n = 7 or 3.7%), immunotherapy (n = 11 or 5.9%), or some combination of these (n = 11 or 5.9%). Of the 481 patients receiving post-CN ST, 350 (72.8%) were placed on targeted therapy.

In the multivariable analysis, clinical factors significantly associated with decreased OS included systemic

TABLE 1. Characteristics of the Study Population (The University of Texas MD Anderson Cancer Center, 2005-2017)

Variable	Value
Male sex, No. (%)	432 (71.1)
Race, No. (%)	
White	435 (71.6)
African American	69 (11.4)
Asian	18 (3.0)
Hispanic	79 (13.0)
Other	7 (1.2)
Age at diagnosis, median (IQR), y	60.6 (52.4-67.1)
BMI, median (IQR), kg/m^2	27.7 (24.6-31.7)
Right-sided tumor, No. (%)	325 (53.5)
ECOG performance status, No. (%)	
0	346 (56.9)
1	233 (38.3)
2	22 (3.6)
3	7 (1.2)
Local signs and symptoms at diagnosis, No. (%)[a]	318 (52.3)
Systemic symptoms at diagnosis, No. (%)[b]	214 (35.2)
Metastatic symptoms at diagnosis, No. (%)	173 (28.5)
Clinical T stage, No. (%)	
T1a	19 (3.1)
T1b	98 (16.1)
T2a	88 (14.5)
T2b	120 (19.7)
T3a	109 (17.9)
T3b	136 (22.4)
T3c	15 (2.5)
T4	23 (3.8)
Retroperitoneal adenopathy, No. (%)	166 (27.3)
Supradiaphragmatic adenopathy, No. (%)[c]	86 (14.1)
Site of metastasis, No. (%)	
Brain	17 (2.8)
Lung	401 (66.0)
Liver	44 (7.2)
Bone	161 (26.5)
Pancreas	24 (4.0)
Adrenal	130 (21.4)
Soft tissue	28 (4.6)
Number of metastatic sites, No. (%)	
0 or 1[d]	424 (69.7)
≥2	184 (30.3)
Systemic therapy, No. (%)	
None	115 (18.9)
Neoadjuvant only	12 (2.0)
Post-CN only	284 (46.7)
Both neoadjuvant and post-CN	197 (32.4)
Time from diagnosis to neoadjuvant therapy, median (IQR), d	36 (21-64)
Time on neoadjuvant therapy, median (IQR), d	62 (52-169)
Postoperative systemic therapy, No. (%)	481 (90.2)
Time to postoperative systemic therapy, median (IQR), d	45 (30-90)
Serum LDH, No. (%)	
Normal (313-618 IU/L)	436 (71.7)
<LLN	31 (5.1)
>ULN	115 (18.9)
Unknown/missing	26 (4.3)
Serum albumin, No. (%)	
Normal (3.5-4.7 g/dL)	480 (79.0)
<LLN	78 (12.8)
>ULN	25 (4.1)
Unknown/missing	25 (4.1)
Serum calcium, No. (%)	
Normal (8.4-10.2 mg/dL)	517 (86.7)
<LLN	18 (3.0)
>ULN	45 (7.4)
Unknown/missing	18 (3.0)
Hemoglobin, No. (%)	
Normal (14-18 [male] or 12-16 g/dL [female])	200 (32.9)
<LLN	399 (65.6)
>ULN	5 (0.8)
Unknown/missing	4 (0.7)
Platelets, No. (%)	
Normal (140-441 K/UL)	503 (82.7)
<LLN	28 (4.6)
>ULN	72 (11.8)
Unknown/missing	5 (0.8)
Alkaline phosphatase, No. (%)	
Normal (38-126 IU/L)	446 (73.4)
<LLN	7 (1.2)
>ULN	136 (22.4)
Unknown/missing	19 (3.1)
Neutrophil count, absolute, No. (%)	320 (52.9)
Normal (1.7-7.3)	485 (79.8)
<LLN	23 (3.8)
>ULN	88 (14.5)
Unknown/missing	12 (2.0)
Lymphocyte count, absolute, No. (%)	
Normal (1-4.8)	381 (62.7)
<LLN	76 (12.5)
>ULN	133 (21.9)
Unknown/missing	18 (3.0)
Neutrophil/lymphocyte ratio, No. (%)	
0-2	241 (39.6)
2-3	120 (19.7)
3-4	98 (16.1)
≥4	131 (21.6)
Unknown/missing	18 (3.0)
Monocyte count, absolute, No. (%)	
Normal (0.08-0.7)	299 (49.2)
<LLN	0 (0)
>ULN	294 (48.4)
Unknown/missing	15 (2.5)

Abbreviations: BMI, body mass index; CN, cytoreductive nephrectomy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; LLN, lower limit of normal; ULN, upper limit of normal.
[a]Includes flank pain, palpable mass, and/or gross hematuria.
[b]Includes fevers, weight loss, and/or night sweats.
[c]Includes mediastinal and/or supraclavicular adenopathy but not hilar adenopathy.
[d]Zero sites of metastasis correspond to patients with nodal metastases only (no visceral metastasis).

symptoms at diagnosis (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.01-1.52), retroperitoneal lymphadenopathy (HR, 1.39; 95% CI, 1.12-1.71), supradiaphragmatic lymphadenopathy (HR, 1.41; 95% CI, 1.07-1.86), bone metastasis (HR, 1.42; 95% CI, 1.14-1.77), and clinical T4 disease (HR, 1.87; 95% CI, 1.18-2.95). In addition, preoperative laboratory values predictive of decreased OS included a hemoglobin level less than the lower limit of normal (LLN; HR, 1.33; 95% CI, 1.08-1.66), a serum albumin level less than the LLN (HR, 1.41; 95% CI, 1.07-1.85), a serum lactate dehydrogenase (LDH) level greater than the upper limit of normal (HR, 1.55; 95% CI, 1.23-1.96), and a neutrophil/lymphocyte ratio greater than or equal to 4 (HR, 1.46; 95% CI, 1.14-1.86; Table 2).

TABLE 2. Independent Predictors of Overall Survival Based on Clinical/Preoperative Variables for Patients Undergoing Cytoreductive Nephrectomy (The University of Texas MD Anderson Cancer Center, 2005-2017)

Variable	HR (95% CI)	*P*
Systemic symptoms at diagnosis[a]	1.24 (1.01-1.52)	.042
Retroperitoneal adenopathy	1.39 (1.12-1.71)	.002
Supradiaphragmatic adenopathy[b]	1.41 (1.07-1.86)	.016
Bone metastasis	1.42 (1.14-1.77)	.002
Hemoglobin < LLN	1.33 (1.08-1.66)	.009
Albumin < LLN	1.41 (1.07-1.85)	.014
LDH > ULN	1.55 (1.23-1.96)	<.001
cT4 disease	1.87 (1.18-2.95)	.007
Neutrophil/lymphocyte ratio ≥ 4	1.46 (1.14-1.86)	.002

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase;LLN, lower limit of normal; ULN, upper limit of normal.
[a]Includes fevers, weight loss, and/or night sweats.
[b]Includes mediastinal and/or supraclavicular adenopathy but not hilar adenopathy.

The risk of death was directly proportional and OS was inversely proportional to the number of preoperative risk factors present (Fig. 1 and Table 3). When patients were stratified into groups according to the most meaningful survival cutoffs, 3 risk groups emerged: low (fewer than 2 risk factors), intermediate (2-3 risk factors), and high (more than 3 risk factors; Fig. 2). Within these groups, the median OS was 58.9 months (95% CI, 44.3-66.6 months), 30.6 months (95% CI, 27.0-35.0 months), and 19.2 (95% CI, 13.9-22.6 months), respectively ($P < .0001$; Table 3).

Perioperative and postoperative characteristics of patients based on risk (low, intermediate, or high) are listed in Table 4. Adverse features on final pathology were significantly associated with a higher risk group. These included sarcomatoid ($P = .001$) and rhabdoid ($P = .012$) dedifferentiation, lymphovascular invasion ($P = .002$), and necrosis ($P = .008$). In addition, tumor size, pathologic T and N stages, positive margin rates, and non–clear cell histology were directly correlated with a higher risk group (all $P < .01$).

In terms of perioperative variables, surgical blood loss ($P = .006$), length of hospitalization ($P = .008$), postoperative complications ($P = .009$), and readmission rate ($P < .001$) were all increased in the higher risk groups. Notably, however, there was no difference between the delivery and timing of postoperative ST between groups ($P = .165$).

DISCUSSION

In the current study, we sought to identify risk factors for inferior OS after CN in our institutional experience; to determine how these factors have evolved since the MDACC risk factors, based on a mostly pre-targeted therapy cohort, were first published in 2010[18]; and to interpret our results in the context of recent literature. We identified 9 independent predictors of OS based on clinical and preoperative variables. Systemic symptoms at diagnosis, bone metastasis, a serum hemoglobin level less than the LLN, and a neutrophil/lymphocyte ratio greater than or equal to 4 all represent additions to the prior work by Culp et al,[18] whereas liver metastasis, metastatic symptoms, and cT3 disease were no longer found to be significant predictors of OS. The remaining 5 risk factors—retroperitoneal lymphadenopathy, supradiaphragmatic lymphadenopathy, a serum albumin

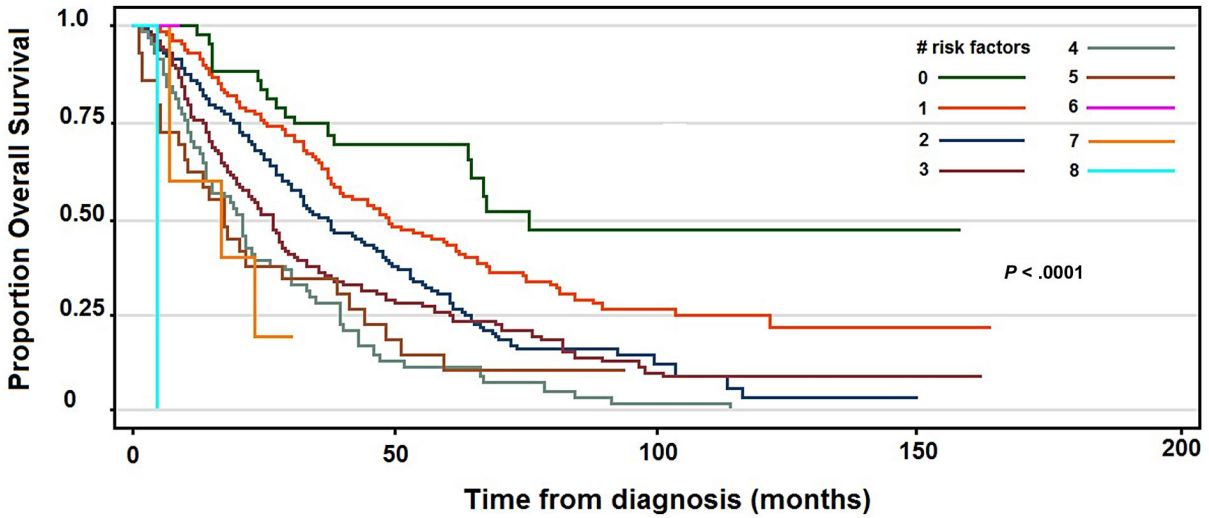

Figure 1. Overall survival was inversely proportional to the number of preoperative risk factors present.

TABLE 3. Overall Survival (From Diagnosis to Follow-Up or Death) for Patients Undergoing Cytoreductive Nephrectomy Based on the Number of Preoperative Clinical and Laboratory Risk Factors and Risk Grouping (The University of Texas MD Anderson Cancer Center, 2005-2017)

	No. (%)	Survival, Median (95% CI), mo
No. of risk factors		
0	43 (7.1)	75.4 (63.4-NE)
1	153 (25.2)	48.7 (39.5-62.0)
2	168 (27.6)	37.1 (29.9-45.9)
3	138 (22.7)	26.6 (20.2-29.4)
4	70 (11.5)	20.6 (13.6-26.1)
5	29 (4.8)	17.1 (8.7-38.4)
6	5 (0.8)	16.4 (6.5-NE)
7	1 (0.2)	—
8	1 (0.2)	—
Groups (No. of risk factors)		
Low (<2)	196 (32.2)	58.9 (44.3-66.6)
Intermediate (2-3)	306 (50.3)	30.6 (27.0-35.0)
High (>3)	106 (17.4)	19.2 (13.9-22.6)

Abbreviation: CI, confidence interval; NE, not evaluable.

level less than the LLN, a serum LDH level greater than the upper limit of normal, and cT4 disease—were consistent with our prior analysis. Elevated serum LDH levels and low serum hemoglobin levels are consistent with the early risk-stratification work by Motzer et al[20] in the IFN-α era, whereas anemia was also a prognostic factor in the IMDC criteria published by Heng et al.[21] Like the IMDC model, our criteria are derived from consecutive patients undergoing CN for mRCC and thus can be considered more generalizable to the mRCC patient population rather than excluded according to clinical trial criteria.

Before 2006, therapy for mRCC included single-agent or combination cytokine-based regimens (eg, IFN-α and IL-2) with or without CN. Level 1 evidence supported the use of CN to extirpate the primary tumor in combination with IFN-α[1,2] because it conferred a significant survival advantage over medical therapy alone in a combined analysis of 2 RCTs.[22] Perioperative mortality was 1.4%, and more than 90% of patients undergoing CN received subsequent ST; this, therefore, expanded the rationale for CN.[22]

The introduction of novel therapeutic agents targeting the molecular mechanisms of renal cell carcinoma angiogenesis in 2006, namely TKIs (eg, sunitinib, pazopanib, and sorafenib),[23-25] mammalian target of rapamycin inhibitors (eg, temsirolimus),[5] and bevacizumab (an anti-VEGF monoclonal antibody),[4,26]

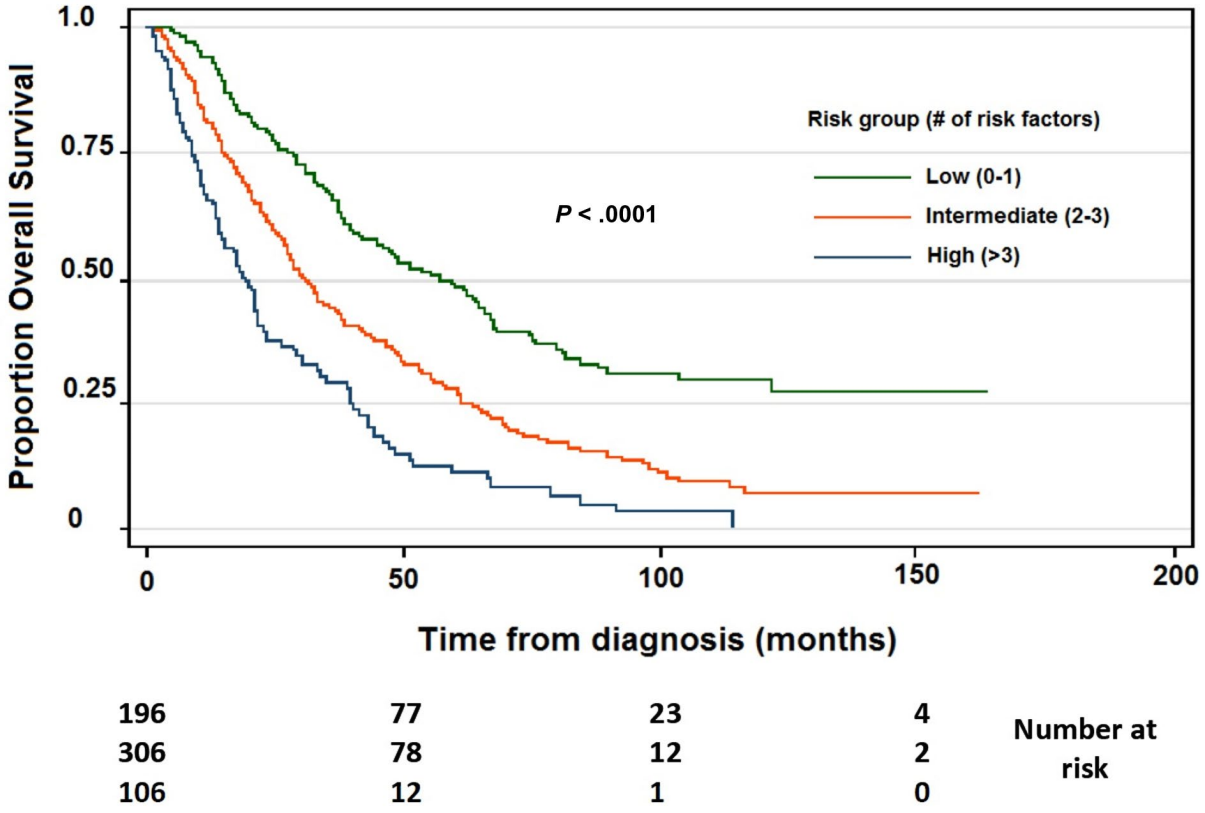

Figure 2. Patients stratified into 3 risk groups according to the most meaningful survival cutoffs.

TABLE 4. Characteristics of Patients Based on Risk: Low, Intermediate, or High (The University of Texas MD Anderson Cancer Center, 2005-2017)

Variable	Low	Intermediate	High	*P*
Clinical and preoperative				
Male sex, No. (%)	136 (69.4)	223 (72.9)	73 (68.9)	.605
Race, No. (%)				.320
White	143 (73.0)	216 (70.6)	76 (71.1)	
African American	18 (9.2)	33 (10.8)	18 (17.0)	
Asian	4 (2.0)	12 (3.9)	2 (1.9)	
Hispanic	29 (14.8)	40 (13.1)	10 (9.4)	
Other	2 (1.0)	5 (1.6)	0 (0)	
Age at diagnosis, median (IQR), y	61.3 (53.2-66.1)	60.8 (52.4-68.2)	59.9 (51.4-65.8)	.555
BMI, median (IQR), kg/m^2	28.4 (25-32.2)	27.7 (24.8-31.8)	26.9 (23.8-30)	.065
Right-sided tumor, No. (%)	110 (56.1)	170 (55.6)	45 (42.5)	.044
ECOG performance status, No. (%)				.001
0	134 (68.4)	164 (53.6)	48 (45.3)	
1	55 (28.1)	129 (42.2)	49 (46.2)	
2	5 (2.6)	9 (2.9)	8 (7.6)	
3	2 (1.0)	4 (1.3)	1 (0.9)	
Symptoms and/or signs at diagnosis, No. (%)				
Local[a]	91 (46.4)	162 (52.9)	65 (61.3)	.045
Systemic[b]	14 (7.1)	131 (42.8)	69 (65.1)	<.001
Metastatic	41 (20.9)	88 (28.8)	44 (41.5)	.001
Clinical T stage, No. (%)				<.001
T1a	4 (2.0)	13 (4.3)	2 (1.9)	
T1b	43 (21.9)	49 (16.0)	6 (5.7)	
T2a	36 (18.4)	46 (15.0)	6 (5.7)	
T2b	39 (19.9)	63 (20.6)	18 (17.0)	
T3a	38 (19.4)	45 (14.7)	26 (24.5)	
T3b	34 (17.4)	70 (22.9)	32 (30.2)	
T3c	2 (1.0)	8 (2.6)	5 (4.7)	
T4	0 (0)	12 (3.9)	11 (10.4)	
Retroperitoneal adenopathy, No. (%)	11 (5.6)	85 (27.8)	70 (66.0)	<.001
Supradiaphragmatic adenopathy, No. (%)[c]	14 (7.1)	37 (12.1)	35 (33.0)	<.001
Site of metastasis, No. (%)				
Brain	7 (3.6)	5 (1.6)	5 (4.7)	.183
Lung	139 (70.9)	194 (63.4)	68 (64.2)	.202
Liver	9 (4.6)	23 (7.5)	12 (11.3)	.095
Bone	31 (15.8)	90 (29.4)	40 (37.7)	<.001
Pancreas	8 (4.1)	12 (3.9)	4 (3.8)	.991
Adrenal	39 (19.9)	69 (22.6)	22 (20.8)	.767
Soft tissue	9 (4.6)	15 (4.9)	4 (3.8)	.892
No. of metastatic sites, No. (%)				.003
0 or 1[d]	153 (78.1)	207 (67.7)	64 (60.4)	
≥2	43 (21.9)	99 (32.4)	42 (39.6)	
Neoadjuvant therapy, No. (%)	64 (32.7)	112 (36.6)	39 (36.8)	.628
Time from diagnosis to neoadjuvant therapy, median (IQR), d	42 (21-65)	31.5 (19.5-63.5)	33 (21-50)	.237
Time on neoadjuvant therapy, median (IQR), d	61 (54-185)	58.5 (49-149.5)	84 (57-196)	.099
Postoperative systemic therapy, No. (%)	151 (77.0)	250 (81.7)	80 (75.5)	.522
Time from surgery to postoperative systemic therapy, median (IQR), d	42 (30-90)	45 (30-60)	40 (30-90)	.948
Serum LDH, No. (%)				<.001
Normal (313-618 IU/L)	168 (85.7)	218 (71.2)	50 (47.2)	
<LLN	8 (4.1)	19 (6.2)	4 (3.8)	
>ULN	9 (4.6)	56 (18.3)	50 (47.2)	
Unknown/missing	11 (5.6)	13 (4.3)	2 (1.9)	
Serum albumin, No. (%)				<.001
Normal (3.5-4.7 g/dL)	173 (88.3)	247 (80.7)	60 (56.6)	
<LLN	5 (2.6)	31 (10.1)	42 (39.6)	
>ULN	10 (5.1)	13 (4.3)	2 (1.9)	
Unknown/missing	8 (4.1)	15 (4.9)	2 (1.9)	
Serum calcium, No. (%)				.004
Normal (8.4-10.2 mg/dL)	169 (86.2)	266 (86.9)	92 (86.8)	
<LLN	3 (1.5)	6 (2.0)	9 (8.5)	
>ULN	15 (7.7)	26 (8.5)	4 (3.8)	
Unknown/missing	9 (4.6)	8 (2.6)	1 (0.9)	

TABLE 4. *Continued*

Variable	Low	Intermediate	High	*P*
Hemoglobin, No. (%)				<.001
Normal (14-18 [male] or 12-16 g/dL [female])	131 (66.8)	64 (20.9)	5 (4.7)	
<LLN	59 (30.1)	239 (78.1)	101 (95.3)	
>ULN	2 (1.0)	3 (1.0)	0 (0)	
Unknown/missing	4 (2.0)	0 (0)	0 (0)	
Platelets, No. (%)				<.001
Normal (140-441 K/UL)	179 (91.3)	250 (81.7)	74 (69.8)	
<LLN	4 (2.0)	17 (5.6)	7 (6.6)	
>ULN	8 (4.1)	39 (12.8)	25 (23.6)	
Unknown/missing	5 (2.6)	0 (0)	0 (0)	
Serum alkaline phosphatase, No. (%)				.001
Normal (38-126 IU/L)	160 (81.6)	216 (70.6)	70 (66.0)	
<LLN	4 (2.0)	1 (0.3)	2 (1.9)	
>ULN	24 (12.2)	79 (25.8)	33 (31.3)	
Unknown/missing	8 (4.1)	10 (3.3)	1 (0.9)	
Neutrophil/lymphocyte ratio, No. (%)				<.001
<2	95 (48.5)	112 (36.6)	34 (32.1)	
2-3	43 (21.9)	71 (23.2)	6 (5.7)	
3-4	39 (19.9)	48 (16.6)	11 (10.4)	
>4	10 (5.1)	69 (22.6)	52 (49.1)	
Unknown/missing	9 (4.6)	6 (2.0)	3 (2.8)	
Monocyte count, No. (%)				.034
Normal	108 (55.1)	148 (48.4)	43 (40.6)	
<LLN	0 (0)	0 (0)	0 (0)	
>ULN	80 (40.8)	153 (50.0)	61 (57.6)	
Unknown/missing	8 (4.1)	5 (1.6)	2 (1.9)	
Final pathology				
Sarcomatoid, No. (%)	26 (13.3)	63 (20.7)	33 (31.4)	.001
% sarcomatoid, median (IQR)	10 (5-32.5)	30 (10-60)	40 (5-70)	.023
Rhabdoid, No. (%)	9 (4.6)	24 (7.9)	15 (14.3)	.012
% rhabdoid, median (IQR)	5 (5-10)	25 (20-60)	35 (5-75)	.105
Lymphovascular invasion, No. (%)	51 (26.0)	110 (36.1)	48 (45.7)	.002
Necrosis, No. (%)	121 (61.7)	224 (73.7)	79 (75.2)	.008
Size, median (IQR), cm	9.8 (8.4-11.2)	12 (8.9-15)	13.8 (11-14.8)	.002
pT, No. (%)				.006
T1a	4 (2.0)	6 (2.0)	1 (1.0)	
T1b	21 (10.7)	16 (5.2)	4 (3.8)	
T2a	9 (4.6)	6 (2.0)	0 (0)	
T2b	4 (2.0)	8 (2.6)	2 (1.9)	
T3a	119 (60.7)	179 (58.5)	53 (50.5)	
T3b	26 (13.3)	53 (17.3)	26 (24.8)	
T3c	4 (2.0)	11 (3.6)	3 (2.9)	
T4	9 (4.6)	27 (8.8)	16 (15.2)	
pN, No. (%)				<.001
N0	95 (48.5)	125 (40.9)	37 (34.9)	
N1	31 (15.8)	101 (33.0)	44 (41.5)	
Nx	70 (35.7)	80 (26.1)	25 (23.6)	
Extranodal extension, No. (%)	11 (5.6)	30 (9.9)	14 (13.5)	.064
Positive margin, No. (%)	6 (3.1)	29 (9.5)	17 (16.0)	<.001
Non–clear cell histology, No. (%)	20 (10.2)	44 (14.4)	25 (23.6)	.007
Fat invasion, No. (%)				.029
None	57 (29.1)	70 (23.0)	13 (12.4)	
Perirenal	17 (8.7)	34 (11.2)	13 (12.4)	
Sinus	39 (19.9)	52 (17.1)	17 (16.2)	
Both	83 (42.4)	149 (48.9)	62 (59.1)	
High grade (Fuhrman grade 3 or 4), No. (%)	166 (84.7)	285 (93.4)	98 (92.5)	.001
Perioperative				
Surgery duration, median (IQR), min	164 (103-229)	178 (109-245)	188 (127-269)	.114
EBL, median (IQR), mL	335 (100-950)	500 (200-1225)	750 (300-2050)	.006
Postoperative complication, No. (%)	59 (30.3)	131 (43.1)	46 (43.8)	.009
pRBCs, median (IQR), U	0 (0-1)	0 (0-3)	2 (0-6)	<.001
Length of hospital stay, median (IQR), d	5 (3-6)	5 (4-8)	6 (4-9)	.008
Readmission within 30 d, No. (%)	11 (5.7)	20 (6.6)	19 (18.1)	<.001

TABLE 4. *Continued*

Variable	Low	Intermediate	High	*P*
Systemic therapy timing, No. (%)				.165
None	44 (22.5)	50 (16.3)	21 (19.8)	
Neoadjuvant only	1 (0.5)	6 (2.0)	5 (4.7)	
Post-RN only	90 (45.9)	147 (48.0)	47 (44.3)	
Both	61 (31.1)	103 (33.7)	33 (31.1)	

Abbreviations: BMI, body mass index; EBL, estimated blood loss; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase;LLN, lower limit of normal; pRBC, packed red blood cell; RN, radical nephrectomy; ULN, upper limit of normal.
[a]Includes flank pain, palpable mass, and/or gross hematuria.
[b]Includes fevers, weight loss, and/or night sweats.
[c]Includes mediastinal and/or supraclavicular adenopathy but not hilar adenopathy.
[d]Zero sites of metastasis correspond to patients with nodal metastases only (no visceral metastasis).

revolutionized the management of mRCC by demonstrating superior survival in comparison with IFN-α alone either as monotherapy or in combination with IFN-α. Subsequently, the rationale for performing CN was derived from level 1 evidence for inferior, outdated therapy. However, significant proportions of the targeted therapy cohorts evaluating these novel agents had undergone nephrectomy before initiating targeted therapy on trial.[4-6,23,25,26] In addition, a number of retrospective analyses demonstrated a significant survival advantage for patients undergoing CN versus targeted therapy alone,[10,18,21] and a recent systematic review noted improved OS associated with CN in patients with mRCC in 10 nonrandomized studies.[11] In the absence of randomized trial data, concerns have been raised regarding the validity of treating patients with mRCC with CN. An analysis by Kutikov et al[27] demonstrated that 30% of CN patients were unable to receive ST after surgery; for approximately half, this was due to disease progression or perioperative mortality. This underscores the potential risks of surgery in this patient population.

In 2018, the results of the first and only RCT evaluating targeted therapy (sunitinib) alone versus sunitinib plus CN in treating mRCC were published.[13] The CARMENA trial concluded that therapy with sunitinib alone demonstrated noninferior OS in comparison with sunitinib plus CN in an intention-to-treat analysis (18.4 vs 13.9 months; stratified HR for death, 0.89; 95% CI, 0.71-1.10; upper boundary of 95% CI for noninferiority, ≤1.20). There were also no significant differences in the response rate or progression-free survival.[13] Although CARMENA is an important and commendable effort to evaluate the impact of CN in patients with mRCC, it should be evaluated within the context of its limitations. The trial did not reach its accrual goal (450 of 576 patients were enrolled), and the number of procedures per center was limited to an average of 0.7. There were contamination issues, with 16 patients in the surgery arm and 38 patients in the sunitinib-alone arm having no surgery and undergoing CN, respectively. The trial included patients with treated bone metastases in addition to patients with liver and bone metastases, to whom CN may not be offered. In addition, the trial was stratified by the Memorial Sloan Kettering Cancer Center criteria,[20] which were initially described as a method of risk-stratifying patients receiving IFN-α alone for mRCC. IMDC criteria would have provided a much more granular assessment of patient risk in the targeted therapy era.[21] It is significant that none of these criteria were ever intended or evaluated for selecting patients for surgery. Finally and most significantly in our view, the OS of the sunitinib plus CN arm was 13.9 months, which is significantly shorter than what has been demonstrated in other cohorts of CN patients; in addition, this arm had a higher metastatic burden than the other cohorts.[10,11,18] This indicates, as described by Arora et al,[28] that the CARMENA cohort likely does not represent the risk-adapted approach to CN demonstrated in the population data, and this suggests that patients with more favorable disease were excluded from the trial. We similarly advocate a risk-adapted approach to CN at our institution. It is possible that the introduction of immuno-oncologic ST, which has demonstrated improved OS in comparison with targeted therapy for intermediate- and poor-risk patients,[14] partially contributed to the differences in OS between our cohort and CARMENA.

We stratified our cohort into 3 risk groups based on the number of risk factors derived from statistically significant differences in OS: low (0-1), intermediate (2-3), and high risk (≥4). The median OS for the entire cohort was 29.4 months with median OS of 59, 31, and 19 months for the low-, intermediate-, and high-risk groups, respectively. Importantly, our high-risk cohort had a median OS similar to that of the sunitinib-only arm of CARMENA.[13] The impressive survival of our cohort likely reflects a significant selection bias toward patients with favorable factors

(95% had an Eastern Cooperative Oncology Group performance status of 0-1; 70% had a single metastatic site; and the median age and body mass index were 61 years and 28 kg/m^2, respectively). However, it also demonstrates that when patients are appropriately risk-stratified according to surgical benefit, CN appears to portend a survival benefit. Opponents of this viewpoint are likely to correctly cite the concern that patients undergoing CN may never recover adequately from surgery to undergo ST[27] and that CN cohorts will, therefore, be put at risk for disease progression. However, approximately 80% of our cohort successfully went on to receive postoperative ST. Of those who did not, 44% (n = 54 or 8.9% of the total population) showed no evidence of disease or went onto surveillance after CN, 29% (n = 35 or 5.8% of the total population) had rapidly progressive disease or failed to thrive, and 0.7% (n = 4) died of intraoperative or postoperative complications. In our cohort of 608 patients, only 14 had rapidly progressive disease or failure to thrive that precluded ST. Furthermore, the median time to ST in our cohort was only 45 days, which suggested relatively rapid recovery for the majority of the patients. The Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) phase 3 RCT compared immediate CN followed by sunitinib with deferred CN after 3 cycles of sunitinib.[29] Although the end result of SURTIME must be interpreted in light of very poor accrual (99 of 458 patients), the results do demonstrate similar progression-free survival between arms and improved median OS (32 vs 15 months; HR, 0.57; $P = .03$) in the intention-to-treat population. Furthermore, an exploratory landmark analysis of OS performed at week 16 suggested that patients who progressed within 16 weeks of surgery in the immediate CN arm or in the arm deferring CN before surgery had similarly poor prognoses. Eighty-eight percent of the SURTIME cohort presented with intermediate-risk disease (according to Memorial Sloan Kettering Cancer Center), and this likely represents a population more generalizable to CN eligibility in comparison with the CARMENA cohort. Taken together, CARMENA and SURTIME are practice confirming: careful patient selection using objective criteria for those eligible for CN and an initial period of ST can determine patients for whom CN is likely to be beneficial. It is clear that immediate CN should not be considered the standard of care for any patient with poor-risk disease, and this is reflected in revised practice guidelines[30]; although initial ST is likely most optimal for most intermediate-risk patients, objective criteria as defined in this study can be used to identify those who may beneficially undergo initial CN, with the potential for deferring ST in select cases.

Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) receptor and its associated cell-surface binding ligand (PD-L1) have further complicated the interpretation of the current literature by ushering in a new generation of immunotherapy for mRCC. Combination therapy with the PD-1 inhibitor pembrolizumab and the TKI axitinib demonstrated a 47% decreased risk of death from all causes ($P < .0001$), a 31% decreased risk of disease progression ($P < .001$), and a 24% higher objective response rate ($P < .001$) across IMDC risk categories in comparison with sunitinib monotherapy in a recent interim analysis of a phase 3 RCT of treatment-naive patients with mRCC.[15] Other level 1 evidence has demonstrated the promise of checkpoint inhibition (PD-L1 inhibitor avelumab[16] and nivolumab/ipilimumab[14]) in comparison with sunitinib monotherapy in this patient population. Although there are no trials evaluating survival outcomes for patients undergoing CN in the context of these novel therapies, it is notable that the majority of patients (>80%) in all 3 trials underwent nephrectomy before randomization.

When evaluating characteristics of patients stratified by risk group in the current study, we observed that adverse features on final pathology (eg, sarcomatoid and rhabdoid dedifferentiation, lymphovascular invasion, and pT and pN stages) were directly correlated with an increasing number of risk factors. Because the presence of these adverse features undoubtedly influences patient survival and the benefit of CN, our risk-stratification model reflects the biology of poor-risk disease, and it may be generalizable to other patients with mRCC as well. Interestingly, perioperative characteristics also differed among risk groups, with increased surgical blood loss, postoperative complications, and readmission rates associated with higher risk. This would indicate that beyond having fidelity in predicting poor pathology, our model may well predict those patients for whom concrete measures of surgical risk are significantly increased.

The limitation of the current study is its retrospective and single-institution nature. We are a largely referral-based practice, and as a result of logistical constraints, some patients received ST at an outside institution. As with any risk-stratification model, our results need external prospective validation. However, we do validate the continued value of several of our risk factors in comparison with the prior work by Culp et al.[18] In addition, our results may be biased by the heterogeneity of tumor pathology because 15% of our cohort had a non–clear cell histology. However, tumor histology is often not known at the time of CN, and this likely reflects true clinical practice. We limited the inclusion of subjective signs and symptoms to very specific parameters

to limit bias introduced by poor reporting, but this remains a limitation. Recognizing the most vague preoperative factor to be "symptoms related to metastatic disease," we performed a sensitivity analysis excluding this component, and our results were unchanged. As with any retrospective cohort, a selection bias exists, and those patients who did not undergo CN would be expected to have a particularly poor prognosis. In addition, the fact that some patients received upfront ST would suggests that only those with a favorable response to therapy would go on to receive CN. Although this reflects current clinical practice, it clearly introduces a further selection bias to our cohort. Despite this selection bias, the OS of our high-risk group was similar to the OS of the sunitinib-alone group in the CARMENA trial,[13] which we hypothesize is representative of the implicit exclusion bias in that trial. Despite these limitations, these results are representative of a large CN cohort at a high-volume quaternary cancer center.

In conclusion, we have identified 9 preoperative risk factors for an increased risk of death in a contemporary CN cohort and stratified patients into 3 progressive risk categories that can help clinicians to identify those patients less likely to benefit from initial CN in the present-day therapy paradigms of mRCC. Deferred CN remains a critical component of the management of mRCC. Further RCTs comparing survival outcomes of patients treated with TKI and/or checkpoint inhibitor therapy with and without deferred CN are needed to further define the role of CN for patients with mRCC.

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AUTHOR CONTRIBUTIONS

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