



Impact of Systemic Therapy for Renal Cell Carcinoma With a Tumor Thrombus: Results From the Intercontinental Collaboration on Renal Cell Carcinoma Database

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Abstract

The role of systemic therapy in the management of these renal cell carcinoma with a tumor thrombus (RCCC-TT) patients is poorly understood. In this multi-institutional analysis, we study preoperative systemic therapy for non-metastatic and metastatic patients as well as postoperative systemic therapy. We find preoperative systemic therapy for metastatic RCC-TT patients was associated with a prolonged overall and cancer-specific survival.

Purpose: The primary objective of this study was to assess the utility of using systemic therapy for patients with renal cell carcinoma with tumor thrombus (RCC-TT) in the setting of both metastatic (mRCC-TT) and non-mRCC-TT disease. **Methods:** This was a multi-institutional retrospective analysis from 1999-present, and every patient underwent radical nephrectomy with tumor thrombectomy (RN-TT) plus/minus systemic therapy. Systemic therapy was defined as chemotherapy, immunotherapy, targeted therapy, or any combination administered ≤ 12 months from RN-TT. Overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS) were studied. We examined the effect of preoperative systemic therapy before RN-TT for non-mRCC-TT, preoperative systemic therapy before RN-TT for mRCC-TT, and postoperative systemic therapy after RN-TT. **Results:** A total of 206 patients were nonmetastatic before RN-TT, and 146 (70.9%) did not receive systemic therapy and 60 (29.1%) did. There was no difference in OS and CSS ($p > .05$), but MFS was significantly better in the no systemic therapy group (Median not reached; 80 months 50.6% of the cohort did not experience metastatic event vs. 13 months; $p < .0001$). 117 patients had mRCC-TT before RN-TT, and of these, 84 (71.2%) received preoperative systemic therapy and 33 (28.2%) did not receive systemic therapy before surgery. Median OS was 24 months in the systemic therapy group and 5.7 months in the non-systemic therapy group

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($p = .0007$). Median CSS was 27.6 months in the systemic therapy grouping and 6 months in the non-systemic therapy grouping ($p = .0007$). 315 patients were in the last analysis, and of these, 119 (37.8%) received systemic therapy after RN-TT and 196 (62.2%) did not. OS, CSS, and MFS did not differ ($p > .05$). **Conclusion:** There appears to be an OS and CSS benefit to preoperative systemic therapy for mRCC-TT. Further analysis is required to elucidate the best therapy regimens and ideal timing.

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Introduction

Renal cell carcinoma (RCC) is the most common kidney cancer worldwide, causing over 170,000 deaths per year.¹ An estimated 10% of people with RCC are diagnosed with a concurrent tumor thrombus (RCC-TT).² Tumor thrombus presents a potential challenge to RCC treatment by necessitating a radical nephrectomy and tumor thrombectomy (RN-TT), a more complex and morbid procedure than radical nephrectomy.^{3,4}

Patients with non-metastatic RCC (non-mRCC) and a tumor thrombus (non-mRCC-TT) have traditionally been treated with surgical resection alone.⁵ Surgical resection remains the mainstay of treatment, but recent advances in systemic therapy may be beneficial such as decreasing tumor thrombus size prior to RN-TT. Albeit small cohorts, important clinical trials on neoadjuvant systemic therapy like the neoadjuvant axitinib for reducing the extent of venous tumour thrombus in clear cell renal cell cancer with venous invasion (NAXIVA) and Neoadjuvant toripalimab plus axitinib for clear cell renal cell carcinoma with inferior vena cava tumor thrombus (NEOTAX) trial have demonstrated reductions of TT levels with neoadjuvant systemic therapy.^{6,7}

Conventional cytotoxic chemotherapy is not standard of care for clear cell RCC, but platinum-based treatments have shown a role in collecting duct carcinoma, renal medullary carcinomas, and SMARCB1-deficient RCC.⁸ Whether chemotherapy is beneficial for patients with RCC-TT is unknown as the current literature is sparse. More evidence is available for targeted and immune therapies, which have recently gained popularity as components of multimodal therapy for RCC. Several case reports and case series of multimodal neoadjuvant/preoperative therapy have demonstrated utility for patients with RCC-TT (ie, reduced thrombus size, downstaging of tumor). Nevertheless, combined-data analyses have yielded mixed results and remain inconclusive, especially with respect to oncologic outcomes.^{9–11} High-powered studies are required to fill this gap in the existing literature and provide more information on whether systemic therapy interventions are beneficial for patients with RCC-TT.

This study aimed to answer 3 separate questions on systemic therapy for RCC-TT patients. The first was for non-mRCC-TT patients, examining if preoperative systemic therapy affected overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS). The second analysis focused on patients diagnosed with metastatic RCC-TT (mRCC-TT) preoperatively, aiming to assess if systemic therapy prior to cytoreductive RN-TT impacted

OS or CSS. The last analysis assessed the effect of postoperative systemic therapy after RN-TT on OS, CSS, and MFS.

Methods

Background

This was a multi-institutional analysis conducted across North America, Central/South America, Europe, and South Korea using data from the Intercontinental Collaboration on Renal Cell Carcinoma (ICORCC) database. All patient information was retrospectively reviewed via the electronic medical record at each participating institution and stored on a master database for statistical analysis. To be included, all patients required a diagnosis of RCC-TT and to have undergone RN-TT for their disease. The range for the analysis window was 1999-present.

Systemic Therapy

Systemic therapy was defined as chemotherapy, immunotherapy, targeted therapy (drugs used to specifically identify cancer cells and attack/alter them), or any combination of these. Systemic therapy regimens were not standardized in the analysis and were at the discretion of providers. In the chemotherapy cohort regimens were platinum based. Immunotherapy was nivolumab, pembrolizumab, or ipilimumab. Targeted therapy was mammalian target of rapamycin inhibitors, sunitinib, axitinib, cabozantinib, or pazopanib. All administration of systemic therapy was done secondary to oncologic control. Any patients who received systemic therapy >12 months from RN-TT were excluded from analysis to limit inclusion of patients receiving systemic therapy after RN-TT due to disease progression.

Patient Data

Pre-, peri-, and postoperative variables collected included age, gender, race, body mass index (BMI), diabetes mellitus (DM), preoperative hemoglobin, chronic kidney disease (CKD), Karnofsky performance score, Charlson Comorbidity Index (CCI), creatinine, tumor size (both preoperatively and postoperatively), tumor stage and grade, OS, CSS, and MFS. Preoperative tumor size was defined as the greatest tumor dimension seen on computerized tomography (CT) scan and/or magnetic resonance imaging (MRI) scan measured in centimeters (cm). Metastases were diagnosed with radiographic imaging, most often CT or MRI scan. MFS was the time to radiographic evidence of metastasis after RN-TT.

Aims and Goals

Analysis one examined non-mRCC-TT patients, to see the effect of preoperative systemic therapy on OS, CSS, and MFS. Patients with mRCC-TT prior to RN-TT were excluded from analysis one entirely.

Analysis 2 examined mRCC-TT patients, to see the effect of preoperative systemic therapy on OS and CSS. For analysis 2, only patients with mRCC-TT who underwent cytoreductive RN-TT were included, and thus, no MFS was calculated.

Analysis 3 examined all patients who underwent RN-TT for RCC-TT, to see the effect of postoperative systemic therapy on OS, CSS, and MFS. Patients with mRCC-TT preoperatively were excluded from calculations on MFS only, in this analysis.

Statistical Testing

Independent samples t-test and chi-squared test were run to compare variables between systemic therapy and no systemic therapy patients for each analysis. Kaplan-Meier survival analysis with log-rank test was also conducted for OS, CSS, and MFS. OS was calculated from the date of surgery until date of death (an event) or last known date alive (censored data). For CSS, only those deaths known to be caused by cancer were considered to be events, with all other survival times treated as censored data at the time of death/last date known alive. For MFS, patients were considered to be event-free if no metastases were observed at any follow-up visit and were censored at the time of death or last known date alive. Some patients had incomplete survival data and so they were excluded from survival analysis where applicable. Analysis of variance (ANOVA) was conducted to compare OS, CSS, and MFS by specific systemic therapy regimen for each of the 3 analyses. There were a minority of patients who were confirmed to have received systemic therapy, but whose regimen was not properly documented (unknown regimen). These patients were included for all analyses aside from ANOVA comparisons between specific systemic therapy types on OS, CSS, and MFS, where they were excluded.

Cox proportional regression modeling was also conducted to assess the effects of clinically relevant and/or significant variables from univariable analysis ($p < .05$) on OS, CSS, and MFS where applicable for each analysis in the study. Included in the model was the era (time) of when systemic therapy was administered to attempt to account for the significantly evolved landscape of systemic therapy during the wide study window we included. We defined the eras as pre-tyrosine kinase inhibitors [TKIs ($<$ the year 2005)], TKI era ($\geq$ the year 2005 and $\leq$ the year 2018), and the immunotherapy combination era (>2019).

Statistical significance was set to $P < .05$ and was carried out using SPSS Statistics Version 28 (Armonk, NY) and SAS Statistics Version 9.4 (Cary, NC).

Results

Preoperative Systemic Therapy for Non-mRCC-TT

This analysis included all patients who were non-metastatic at the time of RN-TT, and compared patients based on whether they received preoperative systemic therapy. The aim was to assess the effect of preoperative systemic therapy on OS, CSS, and MFS. Of all RN-TT, 75% of patients had their RN-TT performed in the year

2011 or beyond and 50% of all patients had their RN-TT in the year 2016 and beyond. A total of 206 patients were nonmetastatic before RN-TT and as shown in [Table 1](#). Of these, 146 (70.9%) did not receive systemic therapy, and 60 (29.1%) did. The age at operation was significantly greater in the group without systemic therapy (64.7 years) than with systemic therapy (59.7 years; $p = 0.007$). BMI was significantly smaller in the systemic therapy cohort (26.7 vs. 29.7; $P = .009$). No other demographic differences were appreciated between the 2 groupings, including gender, race, Karnofsky performance status, CCI, preoperative hemoglobin, DM, CKD, and preoperative tumor size ($P > .05$). Operative time (OT), length of stay (LOS), operative approach, thrombus level, tumor stage, tumor grade, LN dissection, LN yield, positive and negative LNs, tumor subtype, and number of patients who developed metastasis were alike in both cohorts ($P > .05$). Postoperative tumor size was significantly greater in the systemic therapy group (9.8 cm vs. 8.6 cm; $P = .039$). The median number of cycles used for systemic therapy was 5 (4-7.25). On Kaplan-Meier survival analysis, median OS was 73.6 (32.5-124.1) months in the systemic therapy group and 59.5 (17.2-172.2) months in the non-systemic therapy group which was not significantly different ([Figure 1](#); $P > .05$). Median CSS was not different based on systemic therapy (94.1 [36.3-124.1] months) vs. no systemic therapy administration [median not yet reached; last event at 48 months, 64% (25.2-49.9) of the cohort still alive; $P > .05$]. Median MFS was significantly greater in the nonsystemic therapy grouping [Median not reached; at 80 months, 50.6% (27.0-49.9) of the cohort had not experienced a metastatic event] vs. systemic therapy (13.0 [4.0-48.2] months; $P < .0001$). The specific systemic therapeutic regimen administered was not associated with OS, CSS, nor MFS ([Supplementary Table 1A-C](#); $P > .05$). Median follow-up was 27 (8.2-71.9) months in the systemic therapy group and 42.6 (13.0-104.5) months in the non-systemic therapy group. When comparing median follow-up times, this was not statistically different ($P > .05$).

On cox regression analysis, patients who had RN-TT performed $<$ the year 2005 had a 3.1 greater hazard of death compared to those with RN-TT between 2005-2018 ([Supplementary Table 4A](#); $p = .0005$), and 6.1 greater hazard of death compared to those with RN-TT $>$ the year 2019 ($p < .0001$). Patients whose self-identified race was black had a 1.9 greater hazard of death compared to Caucasian patients ($p = .03$) and self-identified "other races" had a 2.6 greater hazard of death compared to Caucasian patients ($p = .008$). Patients undergoing RN-TT $<$ the year 2005 had a 4.4 greater hazard of cancer-specific death relative to those with RN-TT between 2005 and 2018 ([Supplementary Table 4B](#); $p = .0002$) and 16.8 greater hazard of cancer-specific death compared to patients who underwent RN-TT $>$ the year 2019 ($p < .0001$). Further, black patients had a 4.7 greater hazard of cancer-specific death compared to Caucasian patients ($p = .021$), Hispanic patients had a 2.3 times greater hazard of cancer-specific death relative to Caucasian patients ($p = .031$), and patients self-identified as "other races" had a 3.5 greater hazard of cancer-specific death relative to Caucasian patients ($p = .0066$). Systemic therapy had no association with OS nor CSS ($p > .05$). No significant associations on cox regression were identified with MFS aside from systemic therapy ([Supplementary Table 4C](#); $p > .05$). Lack of systemic therapy

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Table 1 Systemic Therapy Versus no Systemic Therapy for Non-Metastatic Patients

Variable	Systemic Therapy	No systemic Therapy	Lower	Upper	P-value
N	60	146			
Age (years)	59.7 (12.6)	64.7 (10.9)	1.4	8.5	.007
Female	16 (26.7)	49 (34)			.304
Race					.424
White	29/56 (51.8)	84/136 (61.8)			
Black	5/56 (9)	8/136 (5.9)			
Hispanic/Latino	15/56 (26.8)	35/136 (25.7)			
Asian	7/56 (12.5)	8/136 (5.9)			
Other	0/56 (0)	1/136 (0.7)			
BMI	26.7 (4.5)	29.3 (7)	0.7	4.7	.009
Karnofsky	87.1 (9.3)	86.7 (10.3)	-4.1	3.3	.839
Charlson comorbidity index	3.4 (2.7)	4.5 (2.9)			
Preoperative hemoglobin (g/dL)	12.2 (2.1)	12.1 (2.1)	-0.8	0.5	.646
Diabetes mellitus	17 (28.3)	34/130 (26.2)			.753
Chronic kidney disease	6 (10)	25/130 (19.2)			.109
Preoperative tumor size (cm)	9.4 (3.1)	9 (4.1)	-1.5	0.8	.558
Operative time (minutes)	296.4 (117.6)	291.7 (142.2)	-50.5	41.1	.841
Length of stay (days)	9.1 (8.8)	15.1 (84.1)	-15.8	27.6	.591
Years to last Follow up	3.4 (3.4)	2.3 (3)	-2	-0.1	.025
Approach					.193
Open	43 (71.7)	103 (70.5)			
Laparoscopic	10 (16.7)	35 (24.0)			
Robotic	7 (11.7)	8 (5.5)			
Renal vein level					
I	25/56 (38.5)	63/138 (45.7)			.767
II	11/56 (19.6)	35/138 (25.4)			
III	14/56 (25)	28/138 (20.3)			
IV	5/56 (9)	12/138 (8.7)			
Postoperative tumor size (cm)	9.8 (3.7)	8.6 (3.4)	-2.3	-0.1	.039
Stage					.63
T3a	14/53 (26.4)	47/137 (34.3)			
T3b	29/53 (54.7)	70/137 (51.1)			
T3c	7/53 (13.2)	17/137 (12.4)			
T4	3/53 (5.7)	3/137 (2.2)			
Grade					.068
1	0/57 (0)	3/136 (2.2)			
2	6/57 (10.5)	26/136 (19.1)			
3	35/57 (61.4)	57/136 (42)			
4	16/57 (28.1)	50/136 (36.8)			
Lymph node dissection	26/52 (50)	57/128 (44.5)			.505
Lymph node yield	3.6 (5.2)	4.5 (5.4)	-2	3.6	.536
Lymph nodes positive	0.4 (0.9)	0.2 (0.8)	-0.5	0.2	.448
Lymph nodes negative	4 (5)	3.8 (5.2)	-2.6	2.2	.873
Clear cell	48/58 (82.8)	119/142 (83.8)			.901
Papillary	6/58 (10.3)	12/142 (84.5)			
Other	4/58 (6.9)	11/142 (77.4)			
Developed metastasis after surgery	40 (66.7)	29 (20.1)			.397
Dead	21 (35)	51 (34.9)			.955
Cancer-specific death	17 (28.3)	27 (18.5)			.009
Systemic therapy					
Chemotherapy	4 (6.7)	-			
Immunotherapy	10 (16.7)	-			

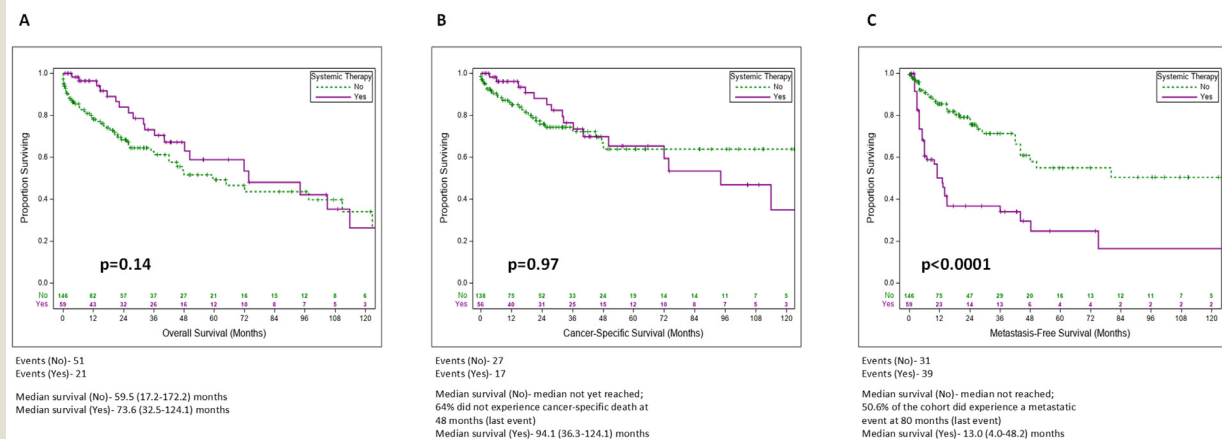
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Table 1 (continued)

Variable	Systemic Therapy	No systemic Therapy	Lower	Upper	P-value
Chemotherapy and immunotherapy	2 (3.3)	-			
Targeted therapy	23 (38.3)	-			
Targeted therapy and chemotherapy	1 (1.7)	-			
Targeted therapy and immunotherapy	12 (20)	-			
Unknown	8 (13.3)	-			
Cycles used	5 (4-7.25)	-			
Follow-up (months)	42.6 (13.0-104.5)	27.0 (8.2-71.9)	-	-	.11

The following table shows results from the primary analysis comparing patients who did versus did not receive systemic therapy preoperatively that were non-metastatic. Patient variables are shown in the leftmost column, followed by the systemic therapy grouping and no systemic therapy grouping. For categorical variables, total numbers are represented with percentage of the cohort in parentheses. For continuous variables, mean values are shown with standard deviation in parentheses aside from cycles used and follow-up which is a median with interquartile range. Associated *P*-values from each variable comparison are also displayed.

Figure 1 Preoperative systemic therapy for non-metastatic patients. The following figure represents Kaplan-Meier survival analysis for (A)-overall survival, (B)-cancer-specific survival, (C)-metastasis-free survival between patients who did versus did not receive preoperative systemic therapy in the study that were not metastatic prior to radical nephrectomy with tumor thrombectomy. Log-rank test *P*-values are provided on each graph along with number at risk tables. Median survival times with interquartile range and number of events are also reported below each graph.



remained significantly associated with a 68% lower hazard of metastasis ($p < .0001$).

Preoperative systemic therapy for mRCC-TT

This analysis included all patients who were metastatic at the time of RN-TT, and compared patients based on whether they received preoperative systemic therapy. The aim was to assess the effect of preoperative systemic therapy on OS and CSS. The second analysis included 117 patients and is shown in Table 2. Of these, 84 (71.8%) were patients with mRCC-TT who received preoperative systemic therapy before cytoreductive nephrectomy, and 33 (28.2%) patients had mRCC-TT and did not receive systemic therapy before cytoreductive nephrectomy. The systemic therapy group was significantly younger (60.8 years) than the non-systemic therapy group (66.6 years; $p = .007$). Preoperative tumor size was significantly smaller in the systemic therapy cohort (8.8 cm vs. 10.8 cm; $p = .002$). No other demographic differences were appreciated between the 2 groupings including gender, race, BMI, Karnofsky performance status, CCI, preoperative hemoglobin, DM,

and CKD ($p > .05$). OT was significantly shorter in the systemic therapy group (264.2 minutes vs 336.2 minutes; $p = .049$). LOS, operative approach, thrombus level, tumor stage, tumor grade, LN dissection, LN yield, positive and negative LNs, tumor subtype, and number of patients who developed metastasis were alike in both cohorts ($p > .05$). The median number of systemic therapy cycles used was 6.5 (4.8-8.3). On Kaplan-Meier survival analysis, median OS was 24 (13.5-63.3) months in the systemic therapy group and 5.7 (1.1-29.4) months in the non-systemic therapy group which was significantly different (Figure 2; $p = .0007$). Median CSS was 27.6 (14.4-69.2) months in the systemic therapy grouping and 6 (1.1-29.4) months in the non-systemic therapy grouping ($p = .0007$). Chemotherapy plus immunotherapy was the systemic therapeutic regimen associated with the greatest OS and CSS (Supplementary Table 2A-B; $p = .003$, $p = .028$). Median follow-up was 67.6 (20.5-86.8) months in the systemic therapy group and 34.5 (4.6-43.7) months in the non-systemic therapy group. When comparing median follow-up times this was statistically different ($p = .0063$).

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Table 2 Preoperative Metastatic Patients With Systemic Therapy vs. no Systemic Therapy Comparisons

Variable	Systemic Therapy	No Systemic Therapy	Lower	Upper	P-value
N	84	33			
Age (years)	60.8 (10.1)	66.6 (10.4)	1.6	9.9	.007
Female	20 (24.7)	5 (15.2)			.264
Race					.245
White	44/79 (55.7)	16/32 (50)			
Black	4/79 (5.1)	2/32 (6.3)			
Hispanic/Latino	13/79 (16.5)	9/32 (28.1)			
Asian	18/79 (22.8)	4/32 (12.5)			
Other	0/79 (0)	1/32 (3.1)			
BMI	27.2 (5.2)	27.1 (6.8)	-2.5	2.2	.918
Karnofsky	85.8 (8.1)	83.1 (18.9)	-12.9	7.5	.586
Charlson comorbidity index	6.4 (3.2)	7.9 (3.1)	-0.4	3	.125
Preoperative hemoglobin (g/dL)	12.2 (2.2)	14.1 (12.7)	-3.0	6.8	.439
Diabetes mellitus	22 (27.2)	10/29 (34.5)			.456
Chronic kidney disease	8 (9.9)	4/29 (13.8)			.562
Preoperative tumor size (cm)	8.8 (2.9)	10.8 (3.5)	0.8	3.3	.002
Operative time (minutes)	264.2 (103.5)	336.2 (174.7)	0.4	143.7	.049
Length of stay (days)	8 (9.5)	8.4 (5.3)	-3.3	4	.839
Years to Last Follow up	2.2 (2.2)	0.9 (1.1)	-2	-0.8	<.001
Approach					.832
Open	62 (76.5)	25 (75.8)			
Laparoscopic	12 (14.8)	6 (18.2)			
Robotic	7 (8.6)	2 (6.1)			
Renal vein level					.073
I	41/77 (53.2)	11 (33.3)			
II	21/77 (27.3)	8 (24.2)			
III	6/77 (7.8)	7 (21.2)			
IV	9/77 (11.7)	7 (21.2)			
Postoperative tumor size (cm)	9.7 (3.4)	11.3 (3.8)	0.1	3.1	.039
Stage					.373
T3a	22/77 (28.6)	4/30 (13.3)			
T3b	39/77 (50.6)	18/30 (60)			
T3c	8/77 (10.4)	5/30 (16.7)			
T4	8/77 (10.4)	3/30 (10)			
Grade					.872
1	2/77 (2.6)	0/29 (0)			
2	9/77 (11.7)	3/29 (10.3)			
3	32/77 (41.6)	13/29 (44.8)			
4	33/77 (42.9)	13/29 (44.8)			
Lymph node dissection	36/75 (48)	17/30 (56.7)			.422
Lymph node yield	4 (5.6)	4.5 (5.2)	-3.1	4.1	.775
Lymph nodes positive	1.2 (1.9)	1.2 (2.2)	-1.2	1.1	.982
Lymph nodes negative	3.4 (5.1)	3.2 (3.9)	-3	2.5	.844
Clear cell	64/79 (81)	25/32 (78.1)			.505
Papillary	8/79 (10.1)	2/32 (6.3)			
Other	7/79 (8.9)	5/32 (15.6)			
Dead	55 (65.5)	21 (63.4)			.661
Cancer-specific death	43 (51.2)	17 (51.5)			.702
Systemic therapy					
Chemotherapy	5 (6.0)	-			
Immunotherapy	14 (16.9)	-			

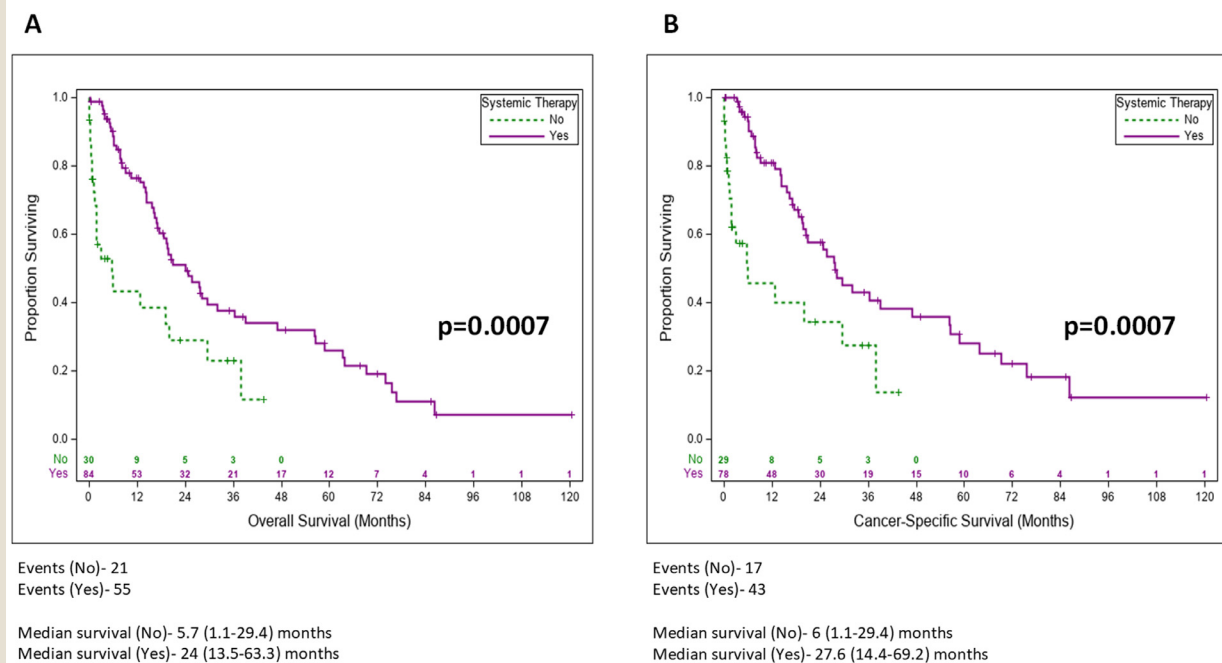
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Table 2 (continued)

Variable	Systemic Therapy	No Systemic Therapy	Lower	Upper	P-value
Chemotherapy and immunotherapy	6 (7.2)	-			
Targeted therapy	27 (32.5)	-			
Targeted therapy and chemotherapy	2 (2.4)	-			
Targeted therapy and immunotherapy	12 (14.5)	-			
Targeted therapy and chemotherapy and immunotherapy	2 (2.4)	-			
Unknown	17 (20.5)	-			
Cycles used	6.5 (4.75-8.25)	-			
Follow-up (months)	67.6 (20.5-86.8)	34.5 (4.6-43.7)	-	-	.0063

The following table shows results from the primary analysis comparing patients who did vs. did not receive systemic therapy preoperatively that were metastatic. Patient variables are shown in the leftmost column, followed by the systemic therapy grouping and no systemic therapy grouping. For categorical variables, total numbers are represented with percentage of the cohort in parentheses. For continuous variables, mean values are shown with standard deviation in parentheses aside from cycles used and follow-up which is a median with interquartile range. Associated *p*-values from each variable comparison are also displayed.

Figure 2 Preoperative systemic therapy for metastatic patients. The following figure represents Kaplan-Meier survival analysis for (A)-overall survival and (B)-cancer-specific survival between patients who did versus did not receive preoperative systemic therapy in the study that were metastatic prior to radical nephrectomy with tumor thrombectomy. Log-rank test *P*-values are provided on each graph along with number at risk tables. Median survival times with interquartile range and number of events are also reported below each graph.



On Cox regression analysis, no significant associations aside from systemic therapy were identified with OS nor CSS (Supplementary Table 5A-B; $p > .05$). Lack of systemic therapy remained significantly associated with a 2.72 greater hazard of death ($p < .0001$). Systemic therapy also had a 68% lower hazard of cancer-specific death ($p < .0001$).

Postoperative Systemic Therapy

This analysis included all patients and compared them based on whether they received postoperative systemic therapy. The aim was

to assess the effect of postoperative systemic therapy on OS, CSS, and MFS. The third analysis included 315 patients and is shown in Table 3. Of these, 119 (37.8%) were patients that received postoperative systemic therapy after RN-TT, and 196 (62.2%) were patients that underwent RN-TT and did not receive postoperative systemic therapy. The median time to systemic therapy administration after RN-TT was 2.7 months. The systemic therapy group was significantly younger (60 years) than the non-systemic therapy grouping (64.9 years; $p < 0.001$). Race was different between the 2 cohorts as well, with the systemic therapy grouping having a greater

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Table 3 Postoperative Systemic Therapy vs. no Systemic Therapy Anytime During the Study Window Comparisons

Variable	Systemic therapy	No systemic therapy	Lower	Upper	P-value
N	119	181			
Age (years)	60 (11.3)	64.9 (11)	3.3	8.5	<.001
Female	34 (28.6)	59 (30.1)			.773
Race					.006
White	48/114 (42.1)	104 (57.5)			
Black	10/114 (8.8)	14 (7.7)			
Hispanic/Latino	33/114 (28.9)	48 (26.5)			
Asian	23/114 (20.2)	13 (7.2)			
Other	0/114 (0)	2 (1.1)			
BMI	26.8 (5.1)	28.7 (6.9)	0.5	3.2	.008
Karnofsky	85.8 (10)	86.2 (12.3)	-2.9	3.8	.808
Charlson comorbidity index	5.3 (3.4)	5.2 (3.2)	-1.3	0.9	.749
Diabetes mellitus	34 (28.6)	45/178 (25.3)			.529
Chronic kidney disease	14 (11.8)	32/178 (18)			.147
Preoperative hemoglobin (g/dL)	11.8 (2.0)	12.4 (5.5)	-0.5	1.6	.287
Preoperative tumor size (cm)	9.3 (3.1)	9.4 (4)	-0.8	1	.821
Operative time (minutes)	291.8 (119.1)	296.5 (144.4)	-29	37.1	.783
Length of stay (days)	8.2 (7)	13.8 (73.9)	-7.8	19	.41
Years to Last Follow Up	2.5 (2.7)	2.2 (2.9)	-0.9	0.4	.407
Approach					.24
Open	82 (68.9)	141 (71.9)			
Laparoscopic	25 (21)	45 (23)			
Robotic	12 (10.1)	10 (5.1)			
Renal vein level					.935
I	48/109 (44)	77/178 (43.3)			
II	24/109 (22)	44/178 (24.7)			
III	22/109 (20.2)	36/178 (20.2)			
IV	15/109 (13.8)	21/178 (11.8)			
Postoperative tumor size (cm)	9.9 (3.6)	9.2 (3.6)	-1.6	0.2	.128
Stage					.176
T1b	0/108 (0)	1/180 (0.6)			
T3a	21/108 (19.4)	55/180 (30.6)			
T3b	64/108 (59.3)	91/180 (50.6)			
T3c	15/108 (13.9)	26/180 (14.4)			
T4	8/108 (7.4)	7/180 (3.9)			
Grade					.013
0	2/113 (1.8)	0/181 (0)			
1	1/113 (0.9)	4 (2.2)			
2	6/113 (5.3)	31 (17.1)			
3	53/113 (46.9)	76 (42)			
4	51/113 (45.1)	70 (38.7)			
Lymph node dissection	52/107 (48.6)	79/167 (47.3)			.834
Lymph node yield	4.5 (6.1)	4.5 (5.3)	-2.1	2.3	.939
Lymph nodes positive	0.9 (1.7)	0.5 (1.3)	-1	0.04	.072
Lymph nodes negative	3.6 (4.9)	3.6 (4.9)	-1.7	1.6	.964
Clear cell	91/115 (79.1)	148 (81.8)			.503
Papillary	13/115 (11.3)	14 (7.7)			
Other	11/115 (9.6)	19 (10.5)			
Developed metastasis after surgery	36 (30.3)	35 (17.9)			.026
Dead	60 (50.4)	76 (42.0)			.025
Cancer-specific death	47 (39.4)	45 (24.9)			.016

(continued on next page)

Table 3 (continued)

Variable	Systemic therapy	No systemic therapy	Lower	Upper	P-value
Systemic therapy					
Chemotherapy	12 (10.1)	-			
Immunotherapy	19 (16)	-			
Chemotherapy and immunotherapy	7 (5.9)	-			
Targeted therapy	43 (36.1)	-			
Targeted therapy and chemotherapy	1 (0.8)	-			
Targeted therapy and immunotherapy	13 (10.9)	-			
Targeted therapy and chemotherapy and immunotherapy	2 (1.7)	-			
Unknown	22 (18.5)	-			
Cycles used	6 (4-7)	-			
Follow-up (months)	42.6 (13.0-120.5)	28.3 (8.2-71.8)	-	-	.031

The following table shows results from the primary analysis comparing patients who did vs. did not receive systemic therapy postoperatively. Patient variables are shown in the leftmost column, followed by the systemic therapy grouping and no systemic therapy grouping. For categorical variables, total numbers are represented with percentage of the cohort in parentheses. For continuous variables, mean values are shown with standard deviation in parentheses aside from cycles used and follow-up which is a median with interquartile range. Associated *P*-values from each variable comparison are also displayed.

proportion of Asian patients (20.2% vs 7.2%; $p = .006$). BMI was significantly smaller in the systemic therapy cohort (26.8 vs 28.7; $p = .008$). No other demographic differences were appreciated between the 2 groupings including gender, Karnofsky performance status, CCI, preoperative hemoglobin, DM, and CKD ($p > .05$). OT, LOS, operative approach, thrombus level, tumor stage, LN dissection, LN yield, positive and negative LNs, tumor subtype, and number of patients who developed metastasis were alike in both cohorts ($p > .05$). Tumor grade was different, and the non-systemic therapy cohort had a greater proportion of grade 2 disease (17.1% vs. 5.3%; $p = .013$). The median number of systemic therapy cycles used was 6 (4-7). On Kaplan-Meier survival analysis, OS was 29.5 (16.3-75.5) months in the systemic therapy group and 45.2 (10.6-172.2) months in the non-systemic therapy group which was not significantly different (Figure 3; $p > .05$). CSS was 36.3 (18.6-86.2) months in the systemic therapy grouping and the median CSS was not reached in the nontherapy grouping with 55.9% of the cohort not experiencing cancer-specific death at 48 months [17.2-50; ($p > .05$)]. MFS was 5 (3.0-13.0) months in the systemic therapy group and 15 (4.0-42.0) months in the nonsystemic therapy group which was similar ($p > .05$). The specific systemic therapeutic regimen administered was not associated with OS, CSS, or MFS (Supplementary Table 3A-C; $p > .05$). Median follow-up was 42.6 (13.0-120.5) months in the systemic therapy group and 28.3 (8.2-71.8) months in the nonsystemic therapy group. When comparing median follow-up times this was statistically different ($p = .031$).

On Cox regression analysis, patients that underwent RN-TT < the year 2005 had a 2.6 greater hazard of death (Supplementary Table 6A; $p = .0025$). Further, patients that underwent RN-TT < the year 2005 had a 2.3 greater hazard of death relative to patients that underwent RN-TT > the year 2019 ($p = .024$). Greater preoperative hemoglobin was associated with an 11% lower hazard of death per one unit increase ($p = .012$). Patients who underwent RN-TT < the year 2005 had a 2.8 greater hazard of cancer-specific death compared to patients who underwent RN-TT between 2005-2018 (Supplementary Table 6B; $p = .0003$) and

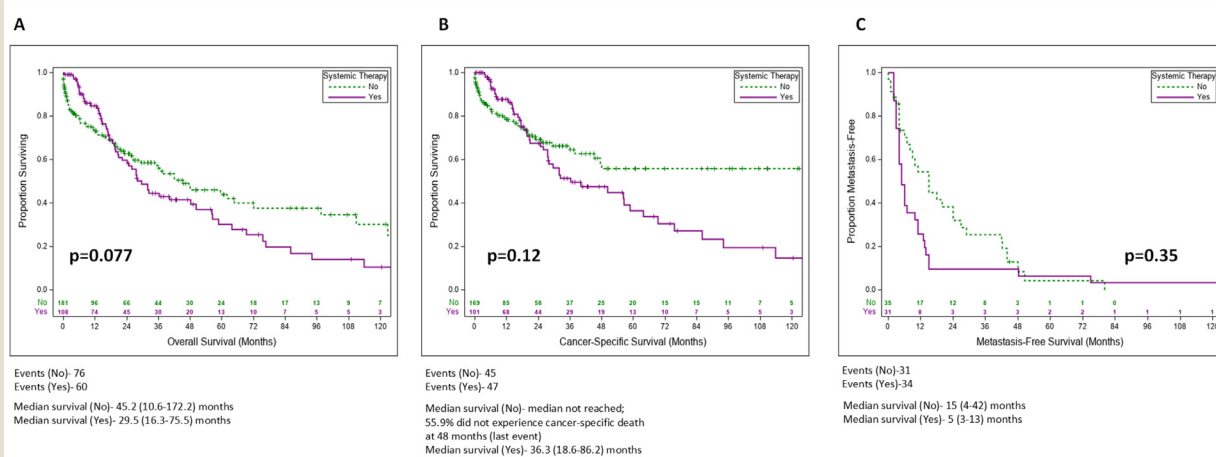
they had a 10.6 greater hazard of cancer-specific death compared to patients who underwent RN-TT > the year 2019 ($p < .0001$). Further, patients who underwent surgery between 2005 and 2018 had a 3.8 greater hazard of cancer-specific death compared to patients whose RN-TT was > the year 2019 ($p = .0009$). On pathology, tumor grade 4 was associated with a 2.9 greater hazard of cancer-specific death relative to grade 2 disease ($p = .019$) and a 1.8 greater hazard of cancer-specific death relative to grade 3 disease ($p = .011$). Patients whose RN-TT was < the year 2005 had a 4.9 greater hazard of metastasis compared to those undergoing RN-TT between 2005 and 2018 (Supplementary Table 6C; $p = .043$). Tumor grade 4 had a 2.7 greater hazard of metastasis compared to grade 2 ($p = .039$) and 1.9 greater hazard of metastasis compared to grade 3 ($p = .048$). Systemic therapy was not associated with OS, CSS, nor MFS in the model ($p > .05$).

Discussion

We present a large series of patients with RCC-TT focusing on the effect of systemic therapy on OS, CSS, and MFS. The multi-institutional nature and diversity of patients from across the globe makes the results particularly compelling. We elected to focus on 3 different analyses for this study: preoperative systemic therapy for non-mRCC-TT patients, preoperative systemic therapy for mRCC-TT patients before cytoreductive nephrectomy, and postoperative systemic therapy after RN-TT. Our results indicate that MFS may be worse in non-mRCC-TT patients who receive preoperative systemic therapy. For mRCC-TT patients, systemic therapy seemed to provide both an OS and CSS benefit, a compelling finding. Lastly, postoperative systemic therapy showed no effect on OS, CSS, nor MFS. In the past, various studies have shown improvement in survival for RCC and systemic therapy, but results are either not specific to RCC-TT or limited by population size.¹²⁻¹⁴ Given the high mortality associated with RCC, and more specifically RCC-TT, studies like this are timely.

Analysis one focused on the utility of preoperative systemic therapy in non-mRCC-TT patients. Comparison focused on OS,

Figure 3 Postoperative systemic therapy for non-metastatic patients. The following figure represents Kaplan-Meier survival analysis for (A)-overall survival, (B)-cancer-specific survival, (C)-metastasis-free survival between patients who did versus did not receive postoperative systemic therapy in the study after radical nephrectomy with tumor thrombectomy. Metastatic patients prior to surgery were excluded from graph C. Log-rank test p-values are provided on each graph along with number at risk tables. Median survival times with interquartile range and number of events are also reported below each graph.



CSS, and MFS between patients that received or did not receive preoperative systemic therapy. No advantage was identified with systemic therapy on OS and CSS. Systemic therapy for RCC has been proven to be of benefit to OS and CSS survival in the past, but as noted, few studies focus specifically on RCC-TT.^{15,16} Master et al. showed neoadjuvant nivolumab and ipilimumab for non-mRCC-TT improved tumor histology and allowed for an easier RN-TT with improved morbidity.¹³ Stewart et al used neoadjuvant axitinib to treat clear cell RCC-TT patients in a prospective phase II trial, finding that 75% of participants had a decrease in TT size with systemic therapy.⁶ Gu et al.¹⁰ performed a metanalysis on neoadjuvant systemic therapy for RCC-TT, including 29 single-arm studies and 5 cohort studies. The authors concluded that neoadjuvant therapy resulted in significantly shorter OT for RN-TT and less blood loss but no difference in oncologic outcomes.¹⁰ In their review article on systemic therapy for localized RCC, Khaleel et al.¹⁷ explain that one of the main goals of systemic therapy in the localized setting for RCC is elimination of potential micro-metastatic disease and easing surgical complexity. We did not capture the specific reasons behind systemic therapy administration in this cohort, but did find a significantly shorter OT in the systemic therapy grouping and greater final tumor sizes on pathology. Perhaps the most interesting finding from this analysis was a worse MFS in the patients who received preoperative systemic therapy. Cumulative evidence is inconclusive regarding the benefit of neoadjuvant/preoperative systemic therapy for nonmetastatic RCC overall.¹⁷ Hara et al.¹⁸ recently published that neoadjuvant systemic therapy improves disease-free survival for RCC-TT patients before RN-TT. We feel in our cohort that it is unlikely preoperative therapy worsened MFS. Rather, there could be confounding variables we did not fully capture that predis-

posed these patients to developing metastases and thus made them more likely to receive preoperative systemic therapy. Regardless, further investigation is required. On Cox regression, patients whose RN-TT was < the year 2005 had worse OS and CSS. This is highly relevant as patients in the early study window likely had less robust and efficacious options available for systemic therapy. Further this finding demonstrates the significant progress and success in researching the various systemic therapies discussed in this manuscript. Caucasian race also afforded patients a lower hazard of death and cancer-specific death. Prior research has identified minority races as having worse outcomes when receiving systemic therapy for mRCC and less access to systemic therapy for RCC.¹⁹ Additional investigation to rectify these disparities is warranted.

Analysis 2 looked at the role of preoperative systemic therapy before cytoreductive nephrectomy for mRCC-TT patients. Both OS and CSS were superior in mRCC-TT patients that did receive preoperative systemic therapy. The literature examining preoperative systemic therapy for mRCC-TT is sparse. Mittal et al.²⁰ compared RCC-TT patients treated with systemic therapy who then subsequently did or did not undergo cytoreductive nephrectomy, finding improved OS in the cytoreductive nephrectomy grouping. Field et al.²¹ compared RCC-TT patients receiving neoadjuvant sunitinib against those who did not before cytoreductive nephrectomy, concluding that CSS was improved in the neoadjuvant grouping. One critique we recognize is that systemic therapy alone could have caused the survival benefits observed, rather than preoperative systemic therapy plus cytoreductive RN-TT. Prior study, however, seems to imply that it is not just systemic therapy that causes the survival benefits we saw in this analysis, but we recognize this as an ongoing area of research requiring more prospective confirmation as we did not have a comparative arm that underwent systemic therapy

alone without RN-TT. Regardless, it has been shown that preoperative metastases before RN-TT predicts worse survival in patients, making our findings in this analysis a key takeaway point from this study.²² Additionally, when comparing specific regimens, patients who received a combination of chemotherapy plus immunotherapy had the best OS and CSS. Due to the paucity of comparative literature on this unique patient population, it is difficult to assess the optimal systemic therapeutic regimen. Nevertheless, our results do represent a promising avenue for future research, especially given that prior study has not typically focused on the role of chemotherapeutics in RCC-TT. Moreover, on Cox regression, the findings of better OS and CSS with systemic therapy remained, even when accounting for possible confounding variables like year of RN-TT, adding strength to our results.

Our last analysis compared postoperative systemic therapy for RCC-TT patients after RN-TT vs. no systemic therapy after RN-TT. No difference in OS, CSS, and MFS were observed. Prior study is mixed as to whether postoperative systemic therapy may provide disease and survival benefits for RCC after tumor resection. Gu et al.²³ performed a prospective study on non-mRCC-TT patients where treatment arms received either adjuvant sorafenib, adjuvant sunitinib, or no systemic therapy. They failed to demonstrate a difference in OS or disease-free survival. In a landmark study on RCC, but not focusing on RCC-TT patients specifically, Choueiri et al.¹² found that pembrolizumab improved disease-free survival after radical nephrectomy with a trend noted towards improved OS. Despite this, a multitude of immunotherapy directed studies have failed to demonstrate any OS benefit to adjuvant systemic therapy.^{24–27} We attempted to limit this analysis to patients who received systemic therapy in an adjuvant setting rather than due to disease progression by excluding patients receiving systemic therapy >12 months from RN-TT and with extensive chart review. This is evidenced as the median time to systemic therapy administration after RN-TT was only 2.7 months. Despite this, the retrospective nature of this study makes it so that we cannot be certain as to the reasons behind systemic therapy administration on each patient after RN-TT. Ultimately, we did not demonstrate any survival benefit to systemic therapy after RN-TT. Like in analysis one, an earlier year of surgery in the study window was associated with greater hazards of death, cancer-specific death, and metastasis. Lower preoperative hemoglobin also had an association with hazard of death, which is not unexpected as studies have found an association between lower preoperative hemoglobin and worse outcomes in RCC-TT patients.²⁸ Lastly, grade 4 disease on final pathologic specimen was linked to greater cancer-specific death and likelihood of metastasis. We feel there is clinical relevance in this, and while univariable analysis did not demonstrate survival benefits to postoperative systemic therapy, patients with grade 4 disease may be a target subpopulation when considering postoperative systemic therapy administration.

Strengths of our study include a robust sample size from a multitude of institutions across the globe from the ICORCC database. Additionally, inclusion of multiple categories and combinations of systemic therapies makes our results broadly applicable, especially in countries where newer and more expensive systemic therapies are not necessarily readily available to practitioners for use. Never-

theless, there are several limitations to acknowledge, notably the analysis's retrospective nature. Any retrospective study opens itself to significant selection bias which restricts the ability to make definitive conclusions on clinical impact. We also elected to include patients without a specific documented systemic therapy regimen in our survival analysis. The primary aim of our study was to analyze systemic therapy's effect overall for patients' with RCC-TT, not specific therapeutic regimens, which guided this decision. We also attempted to account for this by running ANOVA sub analysis on OS, CSS, and MFS based on therapeutic regimen, where some significant differences were appreciated. However, we recognize this is not optimal and some may disagree with this decision. Moreover, the specific agents used were not standardized and there is significant heterogeneity in the way RCC has been treated over time given that we include patient data spanning over 25 years. We accounted for this by running a Cox regression analysis for OS, CSS, and MFS where applicable for each analysis, and relevant findings remained statistically significant. Additionally, follow-up times were not equivalent in each analysis between those that received systemic therapy vs. those who did not, which could play a role in some of the survival outcomes we identified. Despite these shortcomings, we feel the data presented is strong and can impact practice patterns and additionally can guide prospective study to confirm its results. Future perspectives should focus on the role of biomarkers in identifying patients most likely to benefit from systemic therapy, and early studies have found favorable results thus far.^{29,30}

Conclusions

In this multi-center retrospective study of systemic therapy for RCC-TT patients from the ICORCC database, we sought to answer 3 different questions about systemic therapy for RCC-TT. These were regarding the role of preoperative systemic therapy for non-mRCC-TT patients, preoperative systemic therapy for mRCC-TT patients before cytoreductive nephrectomy, and postoperative systemic therapy after RN-TT. A key takeaway was our ability to demonstrate that there does appear to be an OS and CSS benefit to preoperative systemic therapy for mRCC-TT patients prior to cytoreductive nephrectomy. Additionally, we observed that MFS was worse in non-mRCC-TT patients receiving preoperative systemic therapy, with no benefit to postoperative systemic therapy after RN-TT. The literature is sparse in examining systemic therapy for RCC-TT patients, with mixed results, making our series one of the largest to ever be reported on. The multi-institutional and multi-continental nature also increases the external validity of our findings. The results noted in this study require prospective trials for validation, with a focus on specific therapeutic regimens, cycles, dosages, and biomarkers of response. We present an exciting avenue for further research on an important understudied patient population.

Clinical Practice Points

- There is a paucity of information for practitioners to follow on systemic therapy for renal cell carcinoma with tumor thrombus patients.
- This manuscript reports on systemic therapy for renal cell carcinoma tumor thrombus patients from a large multi-institutional

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cohort (Intercontinental Collaboration on Renal Cell Carcinoma).

- Preoperative systemic therapy was studied for non-metastatic and metastatic patients as well as postoperative systemic therapy.
- Preoperative systemic therapy for metastatic patients prior to cytoreductive nephrectomy with tumor thrombectomy provided a significantly prolonged overall and cancer-specific survival benefit.
- These findings have the potential to guide prospective clinical trials and change the landscape of how metastatic renal cell carcinoma patients with a tumor thrombus are managed.

CRedit authorship contribution statement

Maxwell Sandberg: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gregory Russell:** Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Dana Feldman:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Mitchell Hayes:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Reuben Ben David:** Writing – review & editing, Validation, Supervision, Investigation, Data curation, Conceptualization. **Justin Miller:** Writing – review & editing, Investigation, Data curation. **Kartik Patel:** Writing – review & editing, Methodology, Investigation, Data curation. **Brejjette Aljabi:** Writing – review & editing, Methodology, Investigation, Data curation. **Seok-Soon Byun:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Oscar Rodriguez Fabá:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Donato Cannolella:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Tatiana Letowski:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Gustavo Villoldo:** Writing – review & editing, Methodology, Investigation, Data curation. **Patricio Garcia Marchinena:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. **Thiago Mourao:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Gaetano Ciancio:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Charles C. Peyton:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Rafael Zanotti:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Steven Chang:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Philippe E. Spiess:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Reza Mehrazin:** Writing – review & editing, Validation, Supervision, Software, Methodology, Investigation, Data curation,

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Consent: Informed consent was waived for this study as it was retrospective.

Disclosure

The authors of this manuscript have no declarations to declare as it pertains to this manuscript.

Data Statement

The data used in this manuscript is not publicly available but is available in de-identified format upon reasonable request from the corresponding author.

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Supplementary Material

Supplementary Table 1A, 1B, 1C		Survival Comparisons by systemic therapy regimen for preoperative therapy in non-metastatic patients. The Following Table Compares A-Overall Survival, B-Cancer-Specific Survival, and C-Metastasis-Free Survival by Systemic Therapy Regimen Using an Analysis of Variance. Patients With an Unknown Regimen Were not Included in This Analysis	
A			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	4	2.0 (1.7)	.343
Immunotherapy	10	2.2 (1.9)	
Chemotherapy and immunotherapy	23	1.8 (1.9)	
Targeted therapy	1	3.9 (3.6)	
Targeted therapy and chemotherapy	12	8.7	
Targeted therapy plus immunotherapy	8	4.0 (4.3)	
Targeted therapy, chemotherapy, and immunotherapy	0	-	
B			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	7	2.0 (1.2)	.770
Immunotherapy	17	2.4 (1.9)	
Chemotherapy and immunotherapy	3	3.6 (3.4)	
Targeted therapy	38	2.9 (3.2)	
Targeted therapy and chemotherapy	3	4.0 (4.1)	
Targeted therapy plus immunotherapy	15	3.6 (3.9)	
Targeted therapy, chemotherapy, and immunotherapy	2	1.1 (0.6)	
C			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	2	0.8 (0.5)	.803
Immunotherapy	4	1.1 (1.3)	
Chemotherapy and immunotherapy	1	0.3	
Targeted therapy	12	0.9 (1.6)	
Targeted therapy and chemotherapy	1	0.2	
Targeted therapy and immunotherapy	8	2.7 (4.9)	
Targeted therapy, chemotherapy, and immunotherapy	0	-	

Supplementary Table 2A and 2B

Survival Comparisons by Systemic Therapy Regimen for Preoperative Therapy in Metastatic Patients. The Following Table Compares A-Overall Survival and B-Cancer-Specific Survival, by Systemic Therapy Regimen Using an Analysis of Variance. Patients With an Unknown Regimen Were not Included in This Analysis

A			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	5	2.6 (1.6)	.003
Immunotherapy	14	1.7 (1.6)	
Chemotherapy and immunotherapy	6	5.6 (2.2)	
Targeted therapy	27	1.7 (2.0)	
Targeted therapy and chemotherapy	2	1.7 (0.7)	
Targeted therapy plus immunotherapy	12	2.4 (2.5)	
Targeted therapy, chemotherapy, and immunotherapy	2	1.1 (0.6)	
B			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	7	2.8 (1.5)	.028
Immunotherapy	19	1.6 (1.5)	
Chemotherapy and immunotherapy	7	4.9 (2.8)	
Targeted therapy	34	1.9 (2.3)	
Targeted therapy and chemotherapy	2	1.7 (0.7)	
Targeted therapy plus immunotherapy	15	2.6 (2.4)	
Targeted therapy, chemotherapy, and immunotherapy	2	1.1 (0.6)	

Supplementary Table 3A, 3B, 3C

Survival Comparisons by Systemic Therapy Regimen for Postoperative Therapy After Radical Nephrectomy With Tumor Thrombectomy. The Following Table Compares A-Overall Survival, B-Cancer-Specific Survival, and C-Metastasis-Free Survival by Systemic Therapy Regimen Using an Analysis of Variance. Patients With an Unknown Regimen Were not Included in This Analysis

A			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	12	1.6 (1.2)	.275
Immunotherapy	19	1.4 (1.5)	
Chemotherapy and immunotherapy	7	3.8 (2.6)	
Targeted therapy	43	3.0 (3.6)	
Targeted therapy and chemotherapy	1	1.2	
Targeted therapy plus immunotherapy	13	2.5 (1.1)	
Targeted therapy, chemotherapy, and immunotherapy	2	1.1 (0.6)	
B			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	12	1.6 (1.2)	.271
Immunotherapy	22	1.5 (1.5)	
Chemotherapy and immunotherapy	7	3.8 (2.6)	
Targeted therapy	51	2.9 (3.5)	
Targeted therapy and chemotherapy	2	1.7 (0.7)	
Targeted therapy plus immunotherapy	15	2.7 (1.4)	
Targeted therapy, chemotherapy, and immunotherapy	2	1.1 (0.6)	
C			
Systemic Therapy Regimen	N	Time (years)	P-value
Chemotherapy	3	0.7 (0.4)	.822
Immunotherapy	3	0.3 (0.1)	
Chemotherapy and immunotherapy	3	0.1 (0.1)	
Targeted therapy	14	0.9 (1.6)	
Targeted therapy and chemotherapy	0	-	
Targeted therapy plus immunotherapy	7	0.5 (0.4)	
Targeted therapy, chemotherapy, and immunotherapy	0	-	

Impact of Systemic Therapy for Renal Cell Carcinoma

Supplementary Table 4A, B, C

The Following Tables are Cox Regression Models Performed for Analysis 1 (Non-metastatic Patients Receiving Preoperative Systemic Therapy vs. No Systemic Therapy). Table A is for OS, Table B is CSS, and Table C is MFS. Covariates, Directionality, *P*-value, and Confidence Intervals Are Provided. If Certain Covariates are not Displayed in the Model, There Was no Statistical Significance

A			
Variables	P-values	Hazard ratio (Confidence Intervals)	Directionality
Systemic therapy	.36	1.3 (0.8-2.2)	No vs. yes
Year of surgery	<.0001 (overall)	-	-
	.0005	3.1 (1.6-5.9)	<2005 vs. 2005-2018
	<.0001	6.1 (2.5-15.0)	<2005 vs. >2019
	.1	2.0 (0.9-4.4)	2005-2018 vs. >2019
Race	.031 (overall)	-	-
	.03	1.9 (1.1-3.4)	Black vs. Caucasian
	.008	2.6 (1.3-5.2)	Other vs. Caucasian
B			
Variables	P-values	Hazard ratio (Confidence Intervals)	Directionality
Systemic therapy	.42	0.8 (0.4-1.5)	No vs. yes
Year	<.0001 (overall)	-	-
	.0002	4.4 (2.0-9.4)	<2005 vs. 2005-2018
	<.0001	16.8 (4.4-64.2)	<2005 vs. >2019
	.037	3.9 (1.1-13.7)	2005-2018 vs. >2019
Race	.014 (overall)	-	-
	.021	4.7 (1.3-17.3)	Black vs. Caucasian
	.031	2.3 (1.1-4.8)	Hispanic vs. Caucasian
	.0066	3.5 (1.4-8.5)	Other vs. Caucasian
C			
Variables	P-values	Hazard ratio (Confidence Intervals)	Directionality
Systemic therapy	<.0001	0.32 (0.2-0.5)	No vs. yes
Year	.64 (overall)	-	-
	.8	0.8 (0.3-2.9)	<2005 vs. 2005-2018
	.5	0.7 (0.2-2.3)	<2005 vs. >2019
	.4	0.8 (0.5-1.4)	2005-2018 vs. >2019

Supplementary Table 5A-B

The Following Tables are Cox Regression Models Performed for Analysis 2 (Metastatic Patients Receiving Preoperative Systemic Therapy vs. No Systemic Therapy). Table A is for OS and Table B is CSS. Covariates, Directionality, *p*-value, and Confidence Intervals are Provided. If Certain Covariates are not Displayed in the Model, There Was no Statistical Significance

A			
Variables	P-values	Hazard Ratio (Confidence Intervals)	Directionality
Systemic therapy	.0009	2.7 (1.5-4.9)	No vs. yes
Year	.56 (overall)	-	-
	.55	0.8 (0.4-1.7)	<2005 vs. 2005-2018
	.76	1.2 (0.5-2.8)	<2005 vs. >2019
	.31	1.4 (0.7-2.9)	2005-2018 vs. >2019
B			
Variables	P-values	Hazard Ratio (Confidence Intervals)	Directionality
Systemic therapy	<.0001	0.32 (0.2-0.5)	Yes vs. no
Year	.64	-	-
	.78	0.8 (0.3-2.9)	<2005 vs. 2005-2018
	.53	0.7 (0.2-2.3)	<2005 vs. >2019
	.41	0.8 (0.5-1.4)	2005-2018 vs. >2019

Supplementary Table 6A, B, C

The Following Tables are Cox Regression Models Performed for Analysis 3 (Patients Receiving Postoperative Systemic Therapy vs. No Systemic Therapy). Table A is for OS, Table B is CSS, and Table C is MFS. Covariates, Directionality, *P*-value, and Confidence Intervals are Provided. If Certain Covariates are not Displayed in the Model, There Was no Statistical Significance

A			
Variables	<i>P</i>-values	Hazard Ratio (Confidence Intervals)	Directionality
Systemic therapy	.14	0.8 (0.5-1.1)	No vs. yes
Year	.0091 (overall)	-	-
	.0025	2.6 (1.1-6.1)	<2005 vs. 2005-2018
	.69	1.2 (0.6-2.3)	<2005 vs >2019
	.024	2.3 (1.3-3.9)	2005-2018 vs. >2019
Preoperative hemoglobin	.012	0.9 (0.8-0.9)	Per 1 unit increase
B			
Variables	<i>P</i>-values	Hazard ratio (Confidence Intervals)	Directionality
Systemic therapy	.1	0.7 (0.4-1.1)	No vs. yes
Year	<.0001 (overall)	-	-
	.0003	2.8 (1.6-4.8)	<2005 vs. 2005-2018
	<.0001	10.6 (4.4-25.5)	<2005 vs >2019
	.0009	3.8 (1.7-8.5)	2005-2018 vs. >2019
Grade	.016 (overall)	-	-
	.019	2.9 (1.2-7.0)	4 vs. 2
	.011	1.8 (1.2-2.9)	4 vs. 3
C			
Variables	<i>P</i>-values	Hazard Ratio (Confidence Intervals)	Directionality
Systemic therapy	.081	0.32 (0.2-0.5)	No vs. yes
Year	.13 (overall)	-	-
	.043	4.9 (1.1-22.8)	<2005 vs. 2005-2018
	.067	4.3 (0.9-20.0)	<2005 vs. >2019
	.62	0.9 (0.5-1.5)	2005-2018 vs. >2019
Grade	.047 (overall)	-	-
	.039	2.7 (1.1-7.0)	4 vs. 2
	.048	1.8 (1.0-3.1)	4 vs. 3