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Association of an organ transplant-based approach with a dramatic reduction in postoperative complications following radical nephrectomy and tumor thrombectomy in renal cell carcinoma

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ABSTRACT

Objectives: Our aim was to determine whether using an organ transplant-based(TB) approach reduces postoperative complications(PCs) following radical nephrectomy(RN) and tumor thrombectomy(TT) in renal cell carcinoma(RCC) patients with level II-IV thrombi.
Methods: A total of 390(292 non-TB/98 TB) IRCC-VT Consortium patients who received no preoperative embolization/IVC filter were included. Stepwise linear/logistic regression analyses were performed to determine significant multivariable predictors of intraoperative estimated blood loss(IEBL), number blood transfusions received, and overall/major PC development within 30days following surgery. Propensity to receive the TB approach was controlled.
Results: The TB approach was clearly superior in limiting IEBL, blood transfusions, and PC development, even after controlling for other significant prognosticators/propensity score($P < .000001$ in each case). Median IEBL for non-TB/TB approaches was 1000 cc/300 cc and 1500 cc/500 cc for tumor thrombus Level II-III patients, respectively, with no notable differences for Level IV patients(2000 cc each). In comparing PC outcomes between non-TB/TB patients with a non-Right-Atrium Cranial Limit, the observed percentage developing a: i) PC was 65.8%(133/202) vs. 4.3%(3/69) for ECOG Performance Status(ECOG-PS) 0–1, and 84.8%(28/33) vs. 25.0%(4/16) for ECOG-PS 2–4, and ii) major PC was 16.8%(34/202) vs. 1.4%(1/69) for ECOG-PS 0–1, and 27.3%(9/33) vs. 12.5%(2/16) for ECOG-PS 2–4. Major study limitation was the fact that all TB patients were treated by a single, experienced, high volume surgeon from one center (non-TB patients were treated by various surgeons at 13 other centers).
Conclusions: Despite this major study limitation, the observed dramatic differences in PC outcomes suggest that the TB approach offers a major breakthrough in limiting operative morbidity in RCC patients receiving RN and TT.

Abbreviations

AL	Above Liver
CPB	Cardiopulmonary Bypass
CCI	Charlson Comorbidity Index
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
IEBL	Intraoperative Estimated Blood Loss
IRCC-VTC	International Renal Cell Carcinoma-Venous Thrombus Consortium
IVC	Inferior Vena Cava
N-Z	Neves-Zincke
PC	Postoperative Complication
RA	Right Atrium
RCC	Renal Cell Carcinoma
RN	Radical Nephrectomy
SE	Standard Error
TB	Transplant-Based
TT	Tumor Thrombectomy
UM	University of Miami

Introduction

Renal cell carcinoma(RCC) [1] carries a special tropism for vascular involvement, extending into the inferior vena cava(IVC) and right atrium(RA) in 4–10% and 1% of cases, respectively [2–4]. Radical nephrectomy(RN) and tumor thrombectomy(TT) remain the only current strategy able to provide long-term freedom-from-disease in acceptable candidates [3–6]. However, due to technical complexity, intraoperative estimated blood loss(IEBL) and the incidence of postoperative complications(PCs) following RN and TT remain high [7–10].

IEBL and PCs following RN and TT depend mainly on the level of vascular involvement, venous redistribution in response to IVC occlusion, and possibly on the types/sequences of surgical steps performed [3–5,8,10]. Moreover, as the tumor thrombus progresses upward, the number and complexity of maneuvers required for its removal also increase. While the use of cardiopulmonary bypass(CPB) brings relative technical ease, it can trigger systemic inflammatory responses leading in some cases to life-threatening multi-organ dysfunction and even death [11,12].

An organ transplant-based(TB) approach has been developed with the aim of reducing IEBL/PC development [13–18]. This approach is defined by a number of differential operative characteristics, including the use of i) a triradiate Chevron incision and liver self-retaining retractor to enhance exposure in the supra-hepatic/infradiaphragmatic space; ii) posterior access to renal artery ligation(via Cattell-Braasch and Mattox maneuvers) which facilitates the avoidance of venous collaterals dissection until the renal artery is deprived of flow(thus, promoting tumor decompression and minimizing the risk of bleeding); iii) “piggy-back" liver detachment to fully expose the IVC, thereby, improving visibility/access in the right area; iv) left upper quadrant mobilization(when required) in order to gain an expeditious path to this location; and v) greater use of the Pringle maneuver and other thrombus handling techniques which favor circumferential control of the IVC, thus, avoiding thoracic access/extracorporeal circulation in most instances, further decreasing the potential risk of intraoperative bleeding and major PC development.

Given the low prevalence of RCC involving the IVC, no direct comparisons of outcomes following RN and TT between the TB and other (non-TB) surgical approaches have previously been reported. In fact, PC reporting has been limited to mostly small, single-center experiences [19]. In an attempt to provide a more comprehensive assessment, the International Renal Cell Carcinoma-Venous Thrombus Consortium(IRCC-VTC) was established [20]. One of its specific aims was to identify in a multivariable fashion the most important baseline(non-surgical and surgical) predictors of PCs following RN and TT in a large cohort of patients, with a particular focus on comparing the non-TB vs. TB approaches. Results of an observational study using IRCC-VTC data to address this specific aim are presented here.

Methods

Patients

Data were retrospectively obtained from the IRCC-VTC central database [20], which contains information on 2549 patients (23 centers) diagnosed with RCC involving the IVC who underwent RN and TT between 1971 and 2012(last follow-up: 12/31/2014). Study approval was obtained from each center's Institutional Review Board prior to data collection and participation in the IRCC-VTC.

Patients with Neves-Zincke(N-Z) level II-IV thrombi [21] who received no preoperative embolization/IVC filter and had complete information on PCs(Clavien-Dindo [22] grade) were included, yielding 390 study patients(from 14 centers). Of the 2159 excluded patients, 1368 patients had either a level 0-I or missing information on tumor thrombus, 398 patients had no available Clavien grade, 304 patients were missing multiple baseline variables including comorbidity status, and 89 patients received pre-surgical embolization. The TB group comprised 98 patients, all from one center; the non-TB group comprised 292 patients(from 13 other centers).

Baseline non-surgical characteristics included patient demographics, performance status, biochemical determinations, RCC features, and annual center volume(Table 1A). Baseline surgical characteristics included incision type/surgical access and mobilization/vascular maneuvers(Table 1B).

Outcomes analyzed

In order to comprehensively compare the non-TB and TB approaches, 7 outcome variables were analyzed. Two blood loss variables, IEBL(cc) and total number of intraoperative and postoperative blood transfusions(units) received(within 30 days following surgery), were analyzed. Two primary PC outcomes(occurring within 30 days following surgery) according to Clavien-Dindo [22] were analyzed: the development of any PC(grade 1–5), and Clavien grade scored as an ordinal variable: 0 representing no PC(grade 0), 1 representing development of a minor PC(grade 1–2), and 2 representing development of a major PC(grade 3–5). Three time-to-death outcomes were analyzed: death due to a PC(within 30 days following surgery), death due to tumor progression, and death due to other causes. Since the TB approach was implemented with the goal of reducing blood loss and PCs following surgery, it was expected that surgical approach would have no influence on the longer-term death rates. However, any impact of surgical approach on these rates would clearly be important to know, even if unanticipated.

Statistical analysis

Frequency distributions were determined for baseline categorical variables; mean and standard error(SE) were calculated for continuous variables(natural logarithm transformed values/geometric means for skewed distributions except for those containing zero as a possible value, in which case, comparisons were based on ranks and reported using median values). Univariable tests of association were performed using Pearson(uncorrected) Chi-squared and ordinary t-tests. In all analyses, the type I error was set at 0.01, in the attempt to avoid reporting spurious associations.

For each outcome, stepwise regression was performed with the goal of selecting the most important multivariable predictors of that outcome. Specifically, for IEBL and total number of blood transfusions, stepwise linear regression based on ranks(nonparametric) were performed. For the two PC outcomes, stepwise logistic regression was performed. For each of the time-to-death outcomes, stepwise Cox regression was performed.

Stepwise linear regression to determine the significant multivariable predictors of receiving the TB approach(yes/no) was also determined(note: parameter estimation for the effect of high volume center was not possible using logistic regression). For each outcome, the stepwise regression was re-run after first controlling for the propensity to receive the TB approach [23], as a statistical attempt to control for any potential selection bias existing between non-TB and TB patients.

Lastly, observed percentages(and median values) were calculated in comparing the non-TB vs. TB approaches, particularly after stratifying patients by levels of the other significant multivariable predictors. Unless stated otherwise, mean values were imputed for any missing covariate values in the multivariable analyses [24].

Results

Baseline characteristics

Distributions of baseline non-surgical and surgical characteristics, stratified by surgical approach, appear in Tables 1A and 1B, respectively. Numerous non-surgical characteristics, Hispanic ethnicity, lower Charlson Comorbidity Index(CCI), higher(poorer) Eastern Cooperative Oncology Group Performance Status(ECOG-PS), non-metastatic debut, tumor thrombus level $\geq$ III, and being a high volume center, were each highly associated with a greater likelihood of receiving the TB approach($P \leq .002$).

As expected, most of the operative characteristics were highly associated with the surgical approach. For instance, median sternotomy and CPB were required in only 4.1%(4/98) of TB recipients, while thoracic access(via median sternotomy or thoracoabdominal incision) and CPB were performed in 48.8%(142/291) and 28.1%(82/292) of non-TB patients, respectively($P < .000001$ each). In fact, in patients having a cranial limit $\geq$ Above Liver(AL), the percentage receiving CPB was 88.5%(69/78) vs. 9.7%(3/31) among non-TB vs. TB patients($P < .000001$).

Piggyback liver detachment and posterior dissection for renal artery ligation were used in 98.0%(96/98) and 99.0%(97/98) of TB patients vs. in none of the non-TB patients(0/292)($P < .000001$ each). Left upper quadrant mobilization was used in all TB cases 100%(21/21) having left kidney RCC and in one additional right vs. in none of the non-TB patients(0/292)($P < .000001$).

Milking maneuver, atrial descent, and two-step cavotomy were only used among TB cases($P < .000001$ each). Milking maneuver was performed for all 22 TB cases having University of Miami(UM) thrombus level IIIb(level of major hepatic veins) [17]. With the exception of 3 TB cases with a RA Cranial Limit who received CPB, an atrial descent was used in the other 28 TB recipients having UM thrombus level $\geq$ IIIc(i.e., $\geq$AL). In 23/28 of these TB cases, a two-step cavotomy was used. The Pringle maneuver was also significantly more likely to be performed among TB cases, 50.0%(49/98) vs. only 11.6%(29/249) among non-TB cases($P < .000001$); all 49 TB recipients receiving the Pringle maneuver had a UM thrombus level $\geq$ IIIb.

Univariable comparisons

Univariable comparisons of the 7 outcome variables between the non-TB and TB approaches appear in Table 1C. Median IEBL(cc) and median number of blood transfusions(units) received were significantly higher(nearly double) among those receiving the non-TB(1300 cc and 4units) vs. TB(650 cc and 2.5units) approaches($P = .00003$ and .005, respectively). The percentage who developed any PC and PC categorized by minor and major grades were both significantly higher among those receiving the non-TB(vs. TB) approach, with 70.5%(206/292) vs. 15.3%(15/98) developing any PC,

Table 1A
Distributions of selected baseline non-surgical characteristics, stratified by non-transplant based (Non-TB) and transplant based (TB) Approaches.

	Mean ±SE if continuous; Geometric Mean */SE if continuous distribution is skewed; % if categorical		
	Non-TB: (N = 292)	TB: (N = 98)	P-value
Baseline Characteristic[1]			
Age at Surgery (yr)	62.28 ± 0.65 (N = 291)	60.67 ± 1.15	.22
Race/Ethnicity			
White	88.4% (258/292)	54.1% (53/98)	<.000001
Hispanic	2.7% (8/292)	38.8% (38/98)	<.000001
Black	5.8% (17/292)	7.1% (7/98)	.64
Other	3.1% (9/292)	0.0% (0/98)	
Sex			
Male	71.9% (210/292)	63.3% (62/98)	.11
Female	28.1% (82/292)	36.7% (36/98)	
Charlson Comorbidity Index	7.53 ± 0.25	4.38 ± 0.29	<.000001
ECOG Performance Status	0.89 ± 0.04	1.28 ± 0.12	.002
Preoperative Serum Creatinine Level[2]	1.24 */1.02 (N = 291)	1.21 */1.04 (N = 96)	.70
Lateralilty			
Left Kidney Involved	29.1% (85/292)	21.4% (21/98)	.14
Right Kidney Involved	71.9% (210/292)	78.6% (77/98)	.20
2009-cTNM stage:			
Tumor Size (cm)	9.69 ± 0.21	10.71 ± 0.47	.05
Nodal Spread at Presentation[3]	32.5% (95/292)	19.4% (19/98)	.01
Metastasis at Presentation[4]	31.8% (93/292)	12.2% (12/98)	.0002
Clinical T-stage			.95[5]
T3b	70.9% (207/292)	72.4% (71/98)	.77
T3c	24.0% (70/292)	22.4% (22/98)	
T4	5.1% (15/292)	5.1% (5/98)	
Thrombus Anatomic Level/Cranial Limit			<.000001[6]
Below Liver (BL)	46.6% (136/292)	18.4% (18/98)	<.000001
IntraHepatic (IH)	26.7% (78/292)	50.0% (49/98)[7]	
Above Liver (AL)	4.5% (13/292)	9.2% (9/98)	
IntraPericardial (IP)	2.7% (8/292)	9.2% (9/98)	
Right Atrium (RA)	19.5% (57/292)	13.3% (13/98)	.16
Neves-Zincke Classification			<.000001[5]
Level II (i.e., BL)	46.6% (136/292)	18.4% (18/98)	<.000001
Level III (i.e., IH or AL)	31.2% (91/292)	59.2% (58/98)	
Level IV (i.e., IP or RA)	22.3% (65/292)	22.4% (22/98)	
Fuhrman Histologic Grade	2.97 + 0.04 (N = 276)	3.11 + 0.08 (N = 96)	.11
Pathologic Variant			
Clear Cell	80.6% (232/288)	89.8% (88/98)	.04
Mixed	3.8% (11/288)	1.0% (1/98)	
Papillary (I or II)	11.5% (33/288)	7.1% (7/98)	
Other	4.2% (12/288)	2.0% (2/98)	
Date of Surgery			.02
<2000	18.5% (54/292)	16.3% (16/98)	.63
≥2000 but <2006	26.7% (78/292)	41.8% (41/98)	
≥2006	54.8% (160/292)	41.8% (41/98)	
Annual Center Volume[8]			<.000001
Low	15.8% (46/292)	0.0% (0/98)	
Medium	57.5% (168/292)	0.0% (0/98)	
High	26.7% (78/292)	100.0% (98/98)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

[1] Other non-surgical baseline variables that were considered in the statistical analysis but not shown in the above table include: Body Mass Index, Modified Charlson Comorbidity Index (excluding the contribution of tumor score, 2 points if non-metastatic, and 6 points if metastatic), American Society of Anesthesiologists (ASA) Physical Status, and Preoperative Serum Albumin Level.

[2] Skewed distribution; thus, geometric mean is shown.

[3] Among the 114 patients having nodal spread at presentation, an extended lymph node dissection was performed in 70.5% (67/95) of non-TB patients vs. 78.9% (15/19) of TB patients (P = .46).

[4] Among the 105 patients having metastasis at presentation, a simultaneous metastasectomy was performed in 28.0% (26/93) of non-TB patients (24 complete, 2 partial) and 66.7% (8/12) of TB patients (4 complete, 4 partial).

[5] Chi-square test with 2 degrees of freedom.

[6] Chi-square test with 4 degrees of freedom.

[7] The University of Miami Classification was only available for the N = 98 patients who received the TB approach (all at the University of Miami). Of note, 27 and 22 of the 49 patients with an IH Cranial Level were below and at the major hepatic veins (IIIa and IIIb according to this classification).

[8] Annual Center Volume was defined as follows: Low (<3 cases/year), Medium (3–7 cases/year), and High ≥8 cases/year). The distribution of Annual Center Volume among the 13 centers using the non-TB approach was: Low (N = 4), Medium (N = 6), and High (N = 3), respectively. Center Volume was High for the single center that used the TB approach. Of note, center-specific numbers of patients from the 4 non-TB, low volume centers were 5, 9, 11, and 21, respectively. Center-specific numbers of patients from the 6 non-TB, medium volume centers were 33, 9, 23, 38, 42, and 23, respectively. Center-specific numbers of patients from the 3 non-TB, high volume centers were 35, 3, and 40, respectively.

Table 1B
Distributions of selected baseline surgical characteristics, stratified by non-transplant based (Non-TB) and transplant based (TB) Approaches.

Surgical Characteristic:	Non-TB: (N = 292)	TB: (N = 98)	P-value
Incision Type/Surgical Access			
Surgical Incision			<.000001
Vertical Abd	50.5% (147/291)	0.0% (0/98)	
Vertical Abd + Med Sternotomy	22.3% (65/291)	0.0% (0/98)	
Chevron Abd	0.7% (2/291)	0.0% (0/98)	
Chevron Abd + Med Sternotomy	0.7% (2/291)	0.0% (0/98)	
ThoracoAbd	25.8% (75/291)	0.0% (0/98)	
Triradiate Chevron Abd	0.0% (0/291)	95.9% (94/98)	
Triradiate Chevron Abd + Med Sternotomy	0.0% (0/291)	4.1% (4/98)	
Surgical Approach			<.000001
Abdominal	51.2% (149/291)	95.9% (94/98)	
ThoracoAbdominal	48.8% (142/291)	4.1% (4/98)	
Mobilization and Vascular Maneuvers			
Langenbuch Liver Mobilization			<.000001
No	53.9% (145/269)	100.0% (98/98)	
Yes	46.1% (124/269)	0.0% (0/98)	
Piggyback Liver Mobilization			<.000001
No	100.0% (269/269)	2.0% (2/98)	
Yes	0.0% (0/269)	98.0% (96/98)	
Posterior Approach to the Renal Artery			<.000001
No	100.0% (292/292)	1.0% (1/98)	
Yes	0.0% (0/292)	99.0% (97/98)	
Left Upper Quadrant Mobilization			<.000001
No	100.0% (292/292)	77.6% (76/98)	
Yes	0.0% (0/292)	22.4% (22/98)	
Pringle Maneuver			<.000001
No	88.4% (220/249)	50.0% (49/98)	
Yes	11.6% (29/249)	50.0% (49/98)	
Cardiopulmonary Bypass			<.000001
No	71.9% (210/292)	95.9% (94/98)	
Yes	28.1% (82/292)	4.1% (4/98)	
IVC and Thrombus Handling			
Cavotomy (IVC Opening)			.00002
No	16.1% (46/286)	0.0% (0/98)	
Yes	83.9% (240/286)	100.0% (98/98)	
Cavectomy (IVC Resection)[1]:			<.000001
No (or Limited)	75.0% (219/292)	0.0% (0/98)	
Yes	25.0% (73/292)	100.0% (98/98)	
IVC Reconstruction[1]			<.000001
CF Resection + Graft Patch Reconstruct	2.2% (6/268)	4.1% (4/98)	
CF + IVC Interruption	1.1% (3/268)	0.0% (0/98)	
CF + IVC Interruption/Stapled	0.0% (0/268)	13.3% (13/98)	
TG + Autologous Vein Patch Reconstruct	14.9% (40/268)	0.0% (0/98)	
TG + Simple Repair	0.0% (0/268)	82.7% (81/98)	
None	81.7% (219/268)	0.0% (0/98)	
Milking Maneuver			<.000001
No	100.0% (292/292)	77.6% (76/98)	
Yes	0.0% (0/292)	22.4% (22/98)	
Atrial Descent			<.000001
No	100.0% (292/292)	71.4% (70/98)	
Yes	0.0% (0/292)	28.6% (28/98)	
Two-Step Cavotomy			<.000001
No	100.0% (292/292)	76.5% (75/98)	
Yes	0.0% (0/292)	23.5% (23/98)	

Abbreviations: Abd, Abdominal; Med, Median; CF, Circumferential; TG, Tangential.
[1] Cavectomy = Yes refers to an IVC resection ≥0.5 cm in length. In addition, all of the non-TB patients who receveived no (or limited) cavectomy had no IVC reconstruction performed (thus, the category "None").

49.3%(144/292) vs. 7.1%(7/98) developing a minor PC, and 21.2%(62/292) vs. 8.2%(8/98) developing a major PC, respectively(P < .000001 each). As expected, none of the death rates were significantly different between the non-TB and TB approaches(P = .29, .79, and .47, respectively).

Propensity score determination

Stepwise linear regression of receiving the TB approach yielded 3 significant multivariable predictors(listed by order of selection)(Table 2): High Volume Center(P < .000001), Hispanic Ethnicity(P < .000001), and No Metastasis at Presentation(P = .000004). Propensity scores generated by this model were highly discriminatory between the non-TB vs. TB approaches(C-statistic: 0.944).

IEBL/number of blood transfusions

Stepwise linear regression of Rank{IEBL,cc} yielded 2 significant multivariable predictors(listed by order of selection)(Table 3A): higher N-Z Thrombus Level(P < .000001), and a non-TB approach(P < .000001). Stepwise linear regression of Rank{Total Number of Blood Transfusions Received, units} yielded 4 significant multivariable predictors(Table 3B): higher N-Z Thrombus Level(P < .000001), a non-TB approach(P < .000001), Receiving a

Table 1C
Univariable comparisons of the 7 outcome variables between the Non-TB and TB approaches.

	Observed Median or Percentage Experiencing the Event		
Outcome Variable:	Non-TB: (N = 292)	TB: (N = 98)	P-value
1) Median IEBL (cc) {Interquartile Range}	1300 {750–2800} (N = 215)	650 {375–1825} (N = 96)	.00003[1]
2) Median Number of Intraoperative and Postoperative Blood Transfusions Received (Units) {Interquartile Range}	4 {2–8} (N = 193)	2.5 {0–6} (N = 96)	.005[1]
3) Percentage Developing Any Postoperative Complication (Clavien Grade 1–5)	70.5% (206/292)	15.3% (15/98)	<.000001[2]
4) Percentage Developing			<.000001[3]
None (Clavien Grade 0)	29.5% (86/292)	84.7% (83/98)	
Minor (Clavien Grade 1–2)	49.3% (144/292)	7.1% (7/98)	
Major (Clavien Grade 3–5)	21.2% (62/292)	8.2% (8/98)	
Postoperative Complication			
5) Hazard Rate of Death Due to a Postoperative Complication (Clavien Grade 5)	5.8% (17/292)	3.1% (3/98)	.29[4]
6) Hazard Rate of Death Due to Tumor Progression from RCC	42.8% (125/292)	36.7% (36/98)	.79[4]
7) Hazard Rate of Death Due to Other Causes	8.9% (26/292)	10.2% (10/98)	.47[4]

Abbreviations: TB, Transplant Based.
[1] T-test based on ranks.
[2] Pearson (uncorrected) chi-square test with 1 degree of freedom.
[3] Pearson (uncorrected) chi-square test with 2 degrees of freedom.
[4] Log-rank test.

Table 2
Stepwise linear regression results for the likelihood of receiving the TB approach.

	Note: (✓) Represents Selection into the Linear Model.		
	Univariable	Multivariable	Model[b]
Baseline Variable[a]:	P-value	P-value	Coeff ±SE
High Volume Center	<.000001	(✓) <.000001	0.474 ± 0.032
Hispanic Ethnicity	<.000001	(✓) <.000001	0.425 ± 0.049
Metastasis at Presentation	.0001	(✓) .000004	−0.160 ± 0.034

Abbreviations: TB, Transplant Based; Coeff, Coefficient.
[a] The 3 variables selected into the linear model were defined as follows: High Volume Center = {1 if the Center is High Volume, 0 otherwise}; Hispanic Ethnicity = {1 if Hispanic Ethnicity, 0 otherwise}; Metastasis at Presentation = {1 if Patient has Metastasis at Presentation, 0 otherwise}. The order of selection for the 3 selected variables is shown as listed in the table.
[b] Propensity Score for TB Approach = 0.03025 + 0.47423*High Volume Center+0.42511*Hispanic Ethnicity-0.16016*Metastasis at Presentation. C-statistic for the model's fit, i.e., area under the curve (AUC) comparing sensitivity vs. one minus specificity, was 0.944.

Table 3A
Stepwise Linear Regression Results for Rank {Intraoperative Estimated Blood Loss, cc} (N = 311).

	Note: (✓) Represents Selection into the Linear Regression Model.		
	Univariable	Multivariable	Model[2]
Baseline Variable[1]:	P-value	P-value	Coeff ±SE
N-Z Thrombus Level	.000001	(✓) <.000001	40.812 ± 6.595
TB Approach	.00003	(✓) <.000001	−57.751 ± 7.390

Abbreviations: Coeff, Coefficient; N-Z, Neves-Zincke; TB, Transplant Based.
[1] The 2 variables selected into the stepwise linear regression model were defined as follows: N-Z Thrombus Level = {ordinal variable, scored 0–2 for N-Z Thrombus Level II, III, and IV, respectively}; and TB Approach = {1 if TB Approach, 0 otherwise}. The order of selection for the 2 selected variables is shown as listed in the table.
[2] Note that if Propensity Score for the TB approach was retained first in the linear regression model, then the same 2 variable model would still be selected.

Table 3B
Stepwise linear regression results for rank {total number of intraoperative and postoperative blood transfusions received, in units} (N = 289).

	Note: (✓) Represents Selection into the Linear Regression Model.		
	Univariable	Multivariable	Model[2]
Baseline Variable[1]:	P-value	P-value	Coeff ±SE
N-Z Thrombus Level	<.000001	(✓) <.000001	38.061 ± 5.904
TB Approach	.005	(✓) <.000001	−81.095 ± 12.692
Cavectomy	.24	(✓) .0001	46.293 ± 12.003
ECOG Performance Status	.008	(✓) .002	16.354 ± 5.232

Abbreviations: Coeff, Coefficient; N-Z, Neves-Zincke; TB, Transplant Based; ECOG, Eastern Cooperative Oncology Group.
[1] The 4 variables selected into the stepwise linear regression model were defined as follows: N-Z Thrombus Level = {ordinal variable, scored 0–2 for N-Z Thrombus Level II, III, and IV, respectively}; TB Approach = {1 if TB Approach, 0 otherwise}; Cavectomy = {1 if Cavectomy was performed, 0 if no (or limited) Cavectomy}; and ECOG Performance Status (ordinal variable, scored 0–4). The order of selection for the 4 selected variables is shown as listed in the table.
[2] Note that if Propensity Score for the TB approach was retained first in the linear regression model, then the same 4 variable model would still be selected.

Table 3C
Median intraoperative estimated blood loss (cc), stratified by N-Z thrombus level and TB approach.

Thrombus Level	TB Approach	N	Median IEBL (cc){Interquartile Range}
II	Non-TB	97	1000 {600–1500}
II	TB	18	300 {200–500}
III	Non-TB	80	1500 {800–3000}
III	TB	58	500 {500–1500}
IV	Non-TB	38	2000 {1100–3600}
IV	TB	20	2000 {1100–5500}

Abbreviations: IEBL, Intraoperative Estimated Blood Loss.

Cavectomy(P = .0001), and higher(poorer) ECOG-PS(P = .002). For both linear regressions, if TB propensity score was retained first in the model, then the same 2 and 4 variable models would still be selected, respectively.

Table 3D
Median total number of intraoperative and postoperative blood transfusions received (Units), stratified by N-Z thrombus level, cavectomy, and TB approach.

Thrombus Level	Cavectomy	TB Approach	N	Median # Transfusions (Units) {Interquartile Range}
II	N	Non-TB	73	3 {1–5}
II	Y	Non-TB	20	5 {0–7}
II	Y	TB	18	0 {0–3}
III	N	Non-TB	41	3 {2–7}
III	Y	Non-TB	20	9.5 {5.5–12.5}
III	Y	TB	58	2 {0–4}
IV	N	Non-TB	27	7 {2–9}
IV	Y	Non-TB	12	14 {10.5–19}
IV	Y	TB	20	9 {4.5–14.5}

Table 4A
Stepwise logistic regression results for clavien grade as an ordinal outcome: 0, 1, and 2 for No (Grade = 0), minor (Grade 1–2), and major (Grade 3–5) complication, respectively.

	Note: (✓) Represents Selection into the Logistic Regression Model.		
	Univariable	Multivariable	Model[2]
Baseline Variable[1]:	P-value	P-value	Coeff ±SE
TB Approach	<.000001	(✓)<.000001	−2.802 ± 0.340
ECOG Performance Status	.03	(✓) .00009	0.529 ± 0.134
Cranial Limit RA	.00002	(✓) .0003	0.973 ± 0.262
T4 Clinical T-stage	.005	(✓) .006	1.228 ± 0.459

Abbreviations: Coeff, Coefficient; TB, Transplant Based; ECOG, Eastern Cooperative Oncology Group; RA, Right Atrium.
[1] The 4 variables selected into the stepwise logistic model were defined as follows: TB Approach = {1 if Transplant Based Approach, 0 otherwise}; ECOG Performance Status (ordinal variable, scored 0–4); Cranial Limit RA = {1 if Cranial Limit is Right Atrium, 0 otherwise}; and T4 Clinical T-stage = {1 if Clinical T-stage is T4, 0 otherwise}. The order of selection for the 4 selected variables is shown as listed in the table.
[2] Note that if Propensity Score for the TB approach was retained first in the logistic model, then the same 4 variable model would still be selected.

Using the results of these models, Table 3C shows a clear multivariable association of higher Thrombus Level(II, III, and IV) and Surgical Approach(non-TB vs. TB) with median IEBL(cc). For instance, median IEBL for non-TB vs. TB approaches was 1000 cc vs. 300 cc among Thrombus Level II patients, 1500 cc vs. 500 cc among Level III patients. No notable differences in median IEBL between non-TB and TB approaches were observed for Level IV patients(2000 cc in both groups). Table 3D shows that among Level II patients, median number of blood transfusions received was 3 and 5units for No Cavectomy and Cavectomy in non-TB patients vs. 0units in TB patients(all received Cavectomy). Among Level III patients, median number of blood transfusions received was 3 and 9.5units for No Cavectomy and Cavectomy in non-TB patients vs. 2units in TB patients(all received Cavectomy). Among Level IV patients, median number of blood transfusions received was 7 and 14units for No Cavectomy and Cavectomy in non-TB patients vs. 9units in TB patients(all received Cavectomy).

PCs (primary outcomes)

Stepwise logistic regressions of the likelihood of developing any PC(Clavien Grade 0 vs. 1–5) and minor/major PC as an ordinal variable(Clavien Grade 0 vs. 1–2 vs. 3–5) yielded the same 4 significant multivariable predictors – results for the ordinal PC outcome are shown in Table 4A(listed by order of selection): Non-TB approach(P < .000001), poorer ECOG-PS(P = .00009), RA Cranial Limit(P = .0003), and T4 Clinical Stage(P = .006). For both logistic regressions, if TB propensity score was retained first in the model, then the same 4 variable model would still be selected. Of note, no significant differential effects of the 4 baseline predictors for minor PC vs. none and major PC vs. none were found; thus, the additive logistic model as shown in Table 4A appeared to be appropriate.

Observed percentages of patients developing any PC(grade 1–5) and major PC(grade 3–5), stratified by ECOG-PS(0–1 vs. 2–4), Cranial Limit(non-RA vs. RA), and Surgical Approach(non-TB vs. TB), show dramatic differences between the non-TB and TB approaches(Table 4B). For instance, among patients having a non-RA Cranial Limit, the percentage developing: i) any PC between non-TB vs. TB recipients was 65.8%(133/202) vs. 4.3%(3/69) for ECOG Status 0–1, and 84.8%(28/33) vs. 25.0%(4/16) for ECOG Status 2–4, and ii) a major PC between non-TB vs. TB recipients was 16.8%(34/202) vs. 1.4%(1/69) for ECOG Status 0–1, and 27.3%(9/33) vs. 12.5%(2/16) for ECOG Status 2–4. Among patients with a RA Cranial Limit and ECOG-PS 2–4, the percentage developing i) any PC between non-TB vs. TB recipients was 85.7%(6/7) vs. 61.5%(8/13), and ii) a major PC between non-TB vs. TB recipients was 57.1%(4/7) vs. 38.5%(5/13).

Observed percentages of patients developing any PC(grade 1–5) and major PC(grade 3–5), stratified by Metastasis at Presentation(No vs. Yes), ECOG-PS(0–1 vs. 2–4), and Surgical Approach(non-TB vs. TB), also show dramatic differences between the non-TB and TB approaches(Table 4C). For instance, among patients having a Cranial Limit <RA and no metastasis at presentation, the percentage developing: i) any PC between non-TB vs. TB recipients was 64.9%(87/134) vs. 4.5%(3/67) for ECOG Status 0–1, and 87.5%(21/24) vs. 33.3%(3/9) for ECOG Status 2–4, and ii) a major PC between non-TB vs. TB recipients was 15.7%(21/134) vs. 1.5%(1/67)

Table 4B
Percentages of Patients Developing any PC (Clavien Grade 1–5) and a Major PC (Clavien Grade 3–5), Stratified by ECOG-PS, Cranial Limit, and TB Approach.

ECOG Status	Cranial Limit	TB Approach	% Developing AnyPC (Clavien Grade 1–5)	% Developing a Major PC (Clavien Grade 3–5)
0–1	Non-RA	Non-TB	65.8% (133/202)	16.8% (34/202)
0–1	Non-RA	TB	4.3% (3/69)	1.4% (1/69)
0–1	RA	Non-TB	78.0% (39/50)	30.0% (15/50)
0–1	RA	TB	0.0% (0/0)	0.0% (0/0)
2–4	Non-RA	Non-TB	84.8% (28/33)	27.3% (9/33)
2–4	Non-RA	TB	25.0% (4/16)	12.5% (2/16)
2–4	RA	Non-TB	85.7% (6/7)	57.1% (4/7)
2–4	RA	TB	61.5% (8/13)	38.5% (5/13)

Table 4C
Percentages of Patients Developing any PC (Clavien Grade 1–5) and a Major PC (Clavien Grade 3–5), Stratified by Metastasis at Presentation, ECOG-PS, and TB Approach (Non-TB vs. TB), Among Those with a Cranial Limit < RA.

Metastasis at Presentation	ECOG Status	Surgical Approach	% Developing a PC (Clavien Grade 1–5)	% Developing a Major PC (Clavien Grade 3–5)
No	0–1	Non-TB	64.9% (87/134)	15.7% (21/134)
No	0–1	TB	4.5% (3/67)	1.5% (1/67)
No	2–4	Non-TB	87.5% (21/24)	37.5% (9/24)
No	2–4	TB	33.3% (3/9)	11.1% (1/9)
Yes	0–1	Non-TB	67.6% (46/68)	19.1% (13/68)
Yes	0–1	TB	0.0% (0/2)	0.0% (0/2)
Yes	2–4	Non-TB	77.8% (7/9)	0.0% (0/9)
Yes	2–4	TB	14.3% (1/7)	14.3% (1/7)

Table 5A
Stepwise Cox regression results for the hazard rate of death due to a post-operative complication (clavien Grade = 5).

	Note: (✓) Represents Selection into the Cox Model.		
	Univariable	Multivariable	Model[2]
Baseline Variable[1]:	P-value	P-value	Coeff ±SE
Cardiopulmonary Bypass	.0002	(✓) .0003	1.487 ± 0.450
Log {Serum Creatinine Level}	.0003	(✓) .0006	1.264 ± 0.371

Abbreviations: Coeff, Coefficient.
[1] The 2 variables selected into the stepwise Cox model were defined as follows: Cardiopulmonary Bypass = {1 if Cardiopulmonary Bypass was performed, 0 otherwise}; and Log {Serum Creatinine Level} (continuous variable). The order of selection for the 2 selected variables is shown as listed in the table.
[2] Note that if Propensity Score for the TB approach was retained first in the Cox model, then the same 2 variable model would still be selected.

Table 5B
Percentage of patients dying of a post-operative complication (clavien Grade = 5), stratified by cardiopulmonary bypass and preoperative serum creatinine level (mg/dL).[1]

Cardiopulmonary Bypass	Preoperative Serum Cr	% Dying of a Post-Operative Complication
N	<2.0	2.1% (6/280)
N	2.0–2.49	5.9% (1/17)
N	≥2.5	28.6% (2/7)
Y	<2.0	11.8% (9/76)
Y	2.0–2.49	16.7% (1/6)
Y	≥2.5	25.0% (1/4)

Abbreviations: Cr, Creatinine.
[1] Note: Among patients having a preoperative Serum Creatinine <2.5 mg/dL, the percentage of patients dying of a post-operative complication was 2.4% (7/297) vs. 12.2% (10/82) for Cardiopulmonary Bypass = N vs. Y, respectively (P = .0001).

for ECOG Status 0–1, and 37.5%(9/24) vs. 11.1%(1/9) for ECOG Status 2–4.

Death outcomes

Stepwise Cox regression analysis of the hazard rate of death due to a PC (Clavien grade 5, 20 events) yielded 2 significant predictors(Table 5A): Use of CPB(P = .0003) and a higher Log{Preoperative Serum Cr}(P = .0006). Surgical approach(non-TB vs. TB) had no apparent association with the hazard rate of death due to a PC in either univariable or multivariable analysis(P = .29 and .95, respectively). Observed percentages of patients dying of a PC stratified by CPB and Preoperative Serum Cr(Table 5B) show strong prognostic effects of each variable. For instance, among patients with a Preoperative Serum Cr < 2.5 mg/dL, the observed percentage dying of a PC was 2.4%(7/297) vs. 12.2%(10/82) among those not receiving vs. receiving CPB(P = .0001), implying an excess mortality due to CPB of approximately 10%.

Stepwise Cox regression of the hazard rate of death due to tumor progression(161 events) yielded 4 significant predictors: Metastasis at presentation(P < .000001), Non-clear cell pathology(P = .00004), Nodal spread at presentation(P = .0002), and N-Z Thrombus Level ≥ III(P = .001). Stepwise Cox regression analysis of the hazard rate of death due to other causes(36 events) yielded 1 significant predictor: CCI, Excluding Tumor Score(P = .0004). Surgical approach(non-TB vs. TB) was not associated with either hazard rate in either univariable or multivariable analysis.

Discussion

We believe that this is the first study to compare clinical outcomes following RN and TT between the non-TB and TB approaches in a rather large series of patients with RCC and level II-IV thrombi. This study was also rather comprehensive both in terms of number of baseline variables considered for their prognostic value and in number of outcomes variables analyzed. Our results show that, even after controlling for other significant prognosticators, the TB approach was clearly superior in limiting IEBL, the need for intra-operative and/or postoperative blood transfusions, and development of PCs. Furthermore, these results remained unchanged even after controlling for TB propensity score, indicating that the favorable TB effect was not due to selection bias.

While the study cohort(390 patients) analyzed was relatively large, with 25.1%(98/390) receiving the TB approach, a major study limitation was the fact that all of the TB patients were treated by a single, experienced, high volume surgeon from one referral center. None of the patients treated at this particular referral center had received the non-TB approach. Thus, while there were numerous surgeons from the non-TB centers that also had high volume/experience(making selection bias due to surgeon experience being an unlikely solitary explanation of these results), it is still possible that this particular TB surgeon's/center's vast experience with tumor thrombus cases could account for at least part of the dramatic PC differences observed rather than being solely due to utilization of the TB approach.

In an attempt to address this study limitation, comparisons of the multivariable results shown in Tables 3C, 3D, and 4B were re-run using only the 176 patients who were treated at the 4 high volume centers(see Supplementary Tables 1A–1C). Median IEBL and number of blood transfusions were consistently higher for non-TB (vs. TB) patients across Thrombus Level(Supplementary Tables 1A–1B). Observed percentages of patients developing any PC and major PC were also consistently higher for non-TB (vs. TB) patients across ECOG-PS and Cranial Limit levels(Supplementary Table 1C).

Numerous surgical maneuvers were used in mostly or exclusively non-TB or TB patients; thus, exact reasons/explanations for the TB approach yielding a lower PC incidence could not be determined. However, in considering the multivariable results for

Table 6
Comparison of our results with those reported by 8 other studies for IEBL (cc), number of blood transfusions (Units), and percentages developing a PC.

Study	Thrombus Level	N	Median IEBL (cc)	Median # of Blood Transfusions[a]	% Developing any PC	% Developing a Major PC
TB Group	II-IV	98	650 (N = 96)	2.5 (N = 96)	15.3% (15/98)	8.2% (8/98)
Non-TB Group	II-IV	292	1300 (N = 215)	4 (N = 193)	70.5% (206/292)	21.2% (62/292)
Sweeney et al. [37]	I-IV	96	2880	–	38.5% (37/96)	19.8% (19/96)
Kaag et al. [5]	I-IV	78	–	2.5	42.9% (33/77)	18.2% (14/77)
Toren et al. [7]	I-IV	816	–	–	77.6% (633/816)	–
Blute et al. [29]	II-IV	125	1806	6.3	17.6% (22/125)	–
Patil et al. [38]	III-IV	87	–	14	54.0% (47/87)	23.0% (20/87)
Nguyen et al. [30]	III-IV	116	–	–	52.6% (61/116)	26.7% (31/116)
Lue et al. [32]	I-IV	144	–	–	50.0% (72/144)	22.9% (33/144)
Vergho et al. [39]	I-IV	50	–	4.5[b]	14.0% (7/50)	6.0% (3/50)

[a] These calculations were based on all patients (i.e., includes those who received no blood transfusion).
[b] Mean value.

number of blood transfusions received in Table 3B, it was not unexpected to observe that performing a cavectomy had significantly increased the need for blood transfusions. A major goal of the TB approach is to isolate the IVC in such a way that blood loss is minimized when performing the cavectomy. The magnitude of effect(i.e., parameter estimate in the linear regression model) for the TB approach was nearly double in the opposite direction compared with that for cavectomy(-81.1 vs. 46.3), suggesting that the increase in blood loss occurring when performing a cavectomy with the non-TB approach is more than overcome when using the TB approach.

Other significant, multivariable predictors of early outcomes found in our study included: higher tumor thrombus level implying greater IEBL and requirement for blood transfusions; poorer ECOG-PS, RA cranial limit, and T4 clinical T-stage implying a greater incidence of PC development; and CPB use and a higher preoperative serum Cr implying a higher death rate due to a PC.

These multivariable findings were mostly consistent with other studies. For instance, increased rates of blood loss, transfusion requirements, and PCs have been reported for more proximal tumor thrombus locations [5,8,25–29], use of sternotomy [25], and CPB use [7,18,25,27], although one study reported no elevated risks associated with CPB use [30]. RCC patients with a poorer ECOG-PS are known to have a more difficult recovery after surgery [10], and the observed associations of CPB and higher preoperative serum Cr with a greater death rate due to PC were consistent with other reports [7,31,32], advising the judicious use of CPB [33,34].

Our multivariable predictors of higher mortality due to tumor progression(distant and nodal metastases at presentation, non-clear cell histology, and N-Z thrombus level $\geq$ III) were in full agreement with other studies, including previous reports by the IRCC-VTC [20,35,36]. As expected, surgical approach had no impact on long-term mortality rates.

Lastly, a comparison of our results with those reported by 8 other studies [5,7,29,30,32,37–39] for IEBL, number of blood transfusions, and percentages developing a PC is presented in Table 6. Results for the non-TB group fall within the range reported by others. The results for the TB group is dramatically superior to those reported by 6 of the 8 other studies. While the PC results for 2 of the other studies [29,39] was comparable to the TB group, the TB group showed clearly superior results for IEBL and number of blood transfusions.

The present study is not without other limitations. Although the threshold for statistical significance was set at $P < .01$, and potential sources of bias were statistically controlled, the study remains retrospective in nature; therefore, the quality of evidence provided has to be evaluated accordingly. In addition, while the determination of Clavien grade(primary study endpoint) was made in an a priori manner and was available with reasonable accuracy for these patients, identification of the exact type(s) of each PC was not part of the original study plan; thus, multivariable analyses of predictors of PC types were not possible.

Conclusion

Despite the study limitations as outlined, the observed dramatic differences in PC outcomes suggest that the TB approach offers a major breakthrough in limiting operative morbidity in RCC patients receiving RN and TT.

Authors' contribution statement

Javier González: Protocol/Project Development, Data Collection or management, Data Analysis, Manuscirpt writing/editing. Jeffrey J. Gaynor: Protocol/Project Development, Data Collection or management, Data Analysis, Manuscirpt writing/editing. Juan I. Martínez-Salamanca: Protocol/Project Development. Umberto Capitanio: Protocol/Project Development. Derya Tilki: Protocol/Project Development. Joaquín A. Carballido: Protocol/Project Development. Venancio Chantada: Protocol/Project Development. Siamak Daneshmand: Protocol/Project Development. Christopher P. Evans: Protocol/Project Development. Claudia Gasch: Protocol/Project Development. Paolo Gontero: Protocol/Project Development. Axel Haferkamp: Protocol/Project Development. William C. Huang: Protocol/Project Development. Estefania Linares Espinós: Protocol/Project Development. Viraj A. Master: Protocol/Project Development. James M. McKiernan: Protocol/Project Development. Francesco Montorsi: Protocol/Project Development. Sascha Pahernik: Protocol/Project Development. Juan Palou: Protocol/Project Development. Raj S. Pruthi: Protocol/Project Development. Oscar Rodriguez-Faba: Protocol/Project Development. Paul Russo: Protocol/Project Development. Douglas S. Scherr: Protocol/Project Development. Shahrokh F. Shariat: Protocol/Project Development. Martin Spahn: Protocol/Project Development. Carlo Terrone: Protocol/Project Development. Cesar Vera-Donoso: Protocol/Project Development. Richard Zigeuner: Protocol/Project Development. Markus Hohenfellner: Protocol/Project Development. John A. Libertino: Protocol/Project Development. Gaetano Ciancio: Protocol/Project Development, Data Collection or management, Data Analysis, Manuscirpt writing/editing.

Disclosure of potential conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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