Survival Benefits After Surgery of Renal Cell Carcinoma Patients with Inferior Vena Cava Thrombus

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Abstract

OBJECTIVE: To evaluate surgical and oncological outcomes after surgery in renal cell carcinoma (RCC) patients with inferior vena cava (IVC) tumor thrombus

METHODS: A total of 58 patients from 2002 to 2019 underwent radical nephrectomy and IVC thrombectomy at Siriraj Hospital, Bangkok, Thailand, were retrospectively reviewed. Kaplan-Meier analysis was utilized to compare survival benefits between cohorts and Cox regression to evaluate predictors of patient survival.

RESULTS: There were 5 (8.6%), 21 (36.2%), 23 (39.7%) and 9 (15.5%) patients with tumor thrombus level I, II, III and IV respectively. The major complications (Clavien 3-5) were observed in 15 patients (25.8%) and 80% were patients with high thrombus level (III-IV). There was 9% mortality (5 patients): 2 intraoperatively and 3 postoperatively. Median follow-up was 15 months (IQR:5-41). Two-year overall survival (OS) was 80% and 75% in all patients and pN0M0 cohort, respectively. There was significant difference in OS among each IVC thrombus level cohort ($p<0.02$). Two-year OS of metastatic RCC patients was 67% and not significantly different when compared to non-metastatic cohort ($p=0.12$). On multivariate analysis, only sarcomatoid dedifferentiation was associated with OS ($p=0.04$). Disease-free survival was not significantly different among thrombus-level cohorts ($p=0.65$).

CONCLUSION: Our study suggested that surgical treatment for RCC with IVC thrombus provided acceptable OS outcomes, even in a small volume experience. Although the survival was significantly reduced with higher IVC thrombus level cohort, the level of thrombus itself was not an independent factor. Only sarcomatoid dedifferentiation was a predictor for OS after radical nephrectomy and tumor thrombectomy.

Introduction

Renal cell carcinoma (RCC) has a unique propensity to develop tumor thrombus into the inferior vena cava (IVC) about 4-10%^{1,2}. Patients can be asymptomatic or present with symptoms based upon extension of tumor thrombus such as leg edema, varicocele, or dyspnea due to pulmonary embolism³. Data from Reese and colleagues demonstrated that untreated patients had median survival of 5 months⁴. Radical nephrectomy and IVC thrombectomy remain the only potential treatment for these patients. Patients with and without metastatic disease who have undergone surgical removal of kidney and IVC thrombi have survival of 60% and 90% at 1 year, respectively². However, the perioperative morbidity and mortality are high^{1,2}. Regarding to the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC), 30-day mortality rate was 1.8%¹. The level of tumor thrombus was also a predictor of perioperative complications, especially high-grade complications ($p=0.03$)^{1,2}.

Nonetheless, the impact of thrombus level on survival is still controversial¹. Among untreated patients, supradiaphragmatic thrombi and distant metastases were associated with reduced disease-specific

survival (DSS)⁴. The 5-year DSS was 40-60% after surgery^{2,3}. Several prognostic factors were found associated with survival including tumor size and grade, tumor necrosis, positive lymph nodes, sarcomatoid differentiation, IVC thrombus, perinephric fat and adrenal gland invasion and distant metastases⁵. Data from IRCC-VTC, also demonstrated that tumor-thrombus level was an independent factor of survival⁶. However, another study from a Chinese institution found that thrombus level was not associated with DSS while IVC wall and nodal invasion and metastatic disease were⁷.

Our center has initiated this operation since 2002 using liver mobilization technique and reported our initial experience in 2008⁸. We evaluate surgical and survival outcomes and also assess predictive factors of survival among patients with RCC and IVC thrombi. To our knowledge, this is the largest study of RCC patients with IVC thrombi in Southeast Asian population.

Methods

After Siriraj Institutional Review Board, Human Research Protection Unit approved, medical records were reviewed to identify all RCC patients with IVC tumor thrombi. Informed consent was waived by the ethics committee regarding to retrospective study. All methods were performed in accordance with the relevant guidelines and regulations. From February 2002 to August 2019, 58 patients underwent radical nephrectomy and IVC thrombectomy at Siriraj hospital. The existence of tumor thrombus has been evaluated preoperatively using computerized tomography, magnetic resonance imaging or color doppler ultrasound imaging. The level of tumor thrombus was determined according to Neves and Zinke classification⁹. Tumor thrombus extending to only renal vein (level 0) was excluded. The surgical techniques of IVC thrombectomy was described previously^{2,8,10}. Briefly, surgery was performed transabdominally. For thrombus level I (<2cm), thrombectomy was performed with simple vascular control. Liver mobilization technique without any forms of venous bypass procedure was performed in patients with thrombus level II-III. In patients with supradiaphragmatic IVC thrombus, additional diaphragm cutting for cephalic IVC control to avoid cardiopulmonary bypass (CPB) were applied. CPB was only used in intra-atrial thrombus removal procedure.

Patients were evaluated for tumor recurrence at 3-6 months interval postoperatively. The data included patient demographic, perioperative parameters, tumor characteristic, tumor recurrence and follow-up time. Disease free survival (DFS) was calculated from the date of surgery to radiologic evidence of tumor recurrence, the last follow-up or death. Overall survival (OS) was defined from date of surgery to the date of last follow-up or death.

Statistical analysis

Continuous variables were showed as median [interquartile range(IQR)] while categorical variables were in numbers (percentages). Comparing between cohorts were performed using Kruskal-Wallis and Chi-square tests. The survival graphs were created by Kaplan-Meier curve and compared using log-rank test.

Univariate and multivariate analyses to define the predictors of survival were performed using Cox-proportional-hazards model. All statistical significance were defined at $p < 0.05$. SPSS version 18.0 was utilized for all analyses.

Results

A total of 58 patients underwent radical nephrectomy and IVC thrombectomy in our center (2002-2019). No preoperative renal arterial embolization (RAE) was performed. Patients with tumor thrombus level I, II, III, and IV were 5(8.6%), 21(36.2%), 23(39.7%) and 9(15.5%), respectively. Of 9 patients in level IV tumor thrombus, 6 patients had thrombus extending to right atrium. Patient demographic, tumor characteristic and surgical outcomes are shown in **Table 1**. Median age was 58 years with male predominance. There was no significant difference in patients' demographic except right-sided tumor ($p = 0.003$), compared between thrombus-level patients. Median operative time was 300 minutes (IQR:239-363) and significant longer in higher thrombus level ($p = 0.002$). Median estimated blood loss was 3 liters (IQR:1.3-5.25) and blood transfusion was 5 units. Both were also significantly greater in higher thrombus-level cohort ($p \leq 0.001$). Median intensive-care-unit (ICU) stay was also significantly longer in higher thrombus level ($p = 0.007$), but length of hospital stay was not different ($p = 0.18$). The major complications (Clavien 3-5) were observed in 15 patients (25.8%) including intra-abdominal-organ injury (6.8%), acute kidney injury (3.4%), cardiac arrhythmia (3.4%), postoperative ileus (1.7%), spinal headache (1.7%), coagulopathy (1.7%), pulmonary embolism (1.7%), and sepsis (1.7%). Eighty percentage of the complications (12 patients) were observed in patients with high thrombus level (III-IV). The perioperative mortality rate was 8.6%; 2(3.4%) intraoperatively and 3(5.2%) postoperatively. Two intraoperative deaths were floating massive pulmonary emboli during intra-atrial thrombus surgery using CPB and unexplained cardiac arrest post-uneventful IVC thrombus level II removal. All of 3 postoperative mortality occurred in thrombus level IV patients, due to coagulopathy, pulmonary embolism and sepsis.

Table 1

Patient demographics, tumor characteristics and surgical outcomes

IVC thrombus level	Total	Level 1	Level 2	Level 3	Level 4	p-value
Number	58	5	21	23	9	
Age	58 (51-65)	62 (44-72)	60 (54-66)	55 (49-62)	63 (53-72)	0.33
Male gender	45 (78)	4 (80)	17 (81)	18 (78)	6 (67)	0.86
Right side	37 (64)	5 (100)	8 (38)	15 (65)	9 (100)	0.003
BMI	23 (21-27)	23 (20-24)	24 (22-28)	24 (21-28)	23 (13-33)	0.74
ASA						0.17
1	8 (14)	2 (40)	3 (14)	3 (13)	0 (0)	
2	23 (40)	1(20)	9 (43)	11 (48)	2 (22)	
3	3 (23)	2(40)	8 (38)	6 (26)	7 (78)	
4	1 (2)	0 (0)	0 (0)	1 (4)	0 (0)	
Preoperative eGFR	61 (47-79)	68 (48-98)	57 (46-80)	68 (41-86)	55 (47-76)	0.80
Postoperative eGFR	50 (40-70)	49 (40-80)	54 (36-67)	57 (41-77)	41 (36-53)	0.45
Operative time (min)	300 (239-363)	150 (130-210)	255 (225-345)	320 (270-390)	360 (285-575)	0.002
EBL (L)	3.00 (1.30-5.25)	0.35 (0.30-2.00)	2.00 (0.80-3.00)	4.50 (1.80-7.40)	6.40 (3.50-8.00)	<0.001
Blood transfusion (unit)	5 (2-10)	1 (0.25-1.75)	3.5 (2-5.75)	7 (3-10)	10 (5-15)	0.001
ICU (days)	2 (1-3)	0 (0-0.5)	2 (1-2)	2 (1-3)	3 (1-16)	0.007
LOS (days)	10 (8-14)	8 (7.5-10)	9 (8-11)	11 (8-14)	15 (5-20)	0.18
Size (cm)	10 (7-14)	8 (5-12)	10 (7-14)	11 (9-14)	11 (7-14)	0.73
Histology						0.48
Clear cell	39 (67)	5 (100)	13 (62)	15 (65)	6 (67)	
Papillary	9 (16)	0	5 (24)	2 (9)	2 (22)	
Sarcomatoid	2 (3)	0	0	2 (9)	0	
Fumarate Hydratase	2 (3)	0	1 (5)	1 (4)	0	
	1 (2)	0	1 (5)	0	0	

Translocation						
Grade						0.24
1	1(2)	0	0	1 (4)	0	
2	13 (22)	2 (40)	4 (19)	3 (13)	4 (44)	
3	29 (50)	3 (60)	10 (48)	13 (57)	3 (33)	
4	5 (9)	0	3 (14)	2 (9)	0	
Venous wall invasion	42 (72)	5 (100)	15 (71)	17 (74)	5 (56)	0.36
Positive surgical margin	15 (26)	0	6 (29)	7 (30)	2 (22)	0.54
Node metastases						0.42
N0	27 (47)	3 (60)	13 (62)	8 (35)	3 (33)	
N1	16 (28)	0	4 (19)	9 (39)	3 (33)	
Nx	15 (26)	2 (40)	4 (19)	6(26)	3 (33)	
Distant metastasis	12 (21)	0	4 (19)	6 (26)	2 (22)	0.64
2-year OS	80%	100%	85%	81%	56%	0.025
6-month DFS	78%	100%	71%	85%	50%	0.47
12-month DFS	64%	75%	47%	85%	0%	0.15
Follow up time (months)	15 (5-41)	61 (16-92)	22 (10-47)	13 (3-41)	3 (0-6)	0.002
Abbreviations: BMI: body mass index; DFS: disease-free survival; EBL: estimated blood loss; eGFR: estimated glomerular filtration rate; ICU: intensive care unit; LOS: length of stay; OS: overall survival						

Tumor characteristic, including tumor size/histology/grade, venous-wall invasion, positive-surgical margin and node status were not significantly different among thrombus-level patients. Twelve patients (21%) presented with distant metastases preoperatively; 9 patients (75%) with single metastasis and 3 patients (25%) with multiple metastases. The metastatic sites included lungs, bones, liver and adrenal gland. Five of 12 patients (42%) received adjuvant treatments. One patient underwent metastatectomy of lung lesions is still alive with stable disease at 110 months follow-up time.

Median follow-up was 15 months (5-41). Overall survival (OS) was significantly different between tumor-thrombus-level cohorts($p<0.02$; **Fig.1A**). Two-year OS was 80% in all patients and significantly lower in thrombus level IV patients (56%; $p=0.03$). Patients with supradiaphragmatic thrombus (level IV) had worse OS compared with infradiaphragmatic thrombus (level II-III)($p\leq 0.03$). In addition, 2-year OS of pN0M0 and metastatic patients were 75% and 67%, respectively. There was no significant difference of

OS between metastatic and non-metastatic cohorts ($p=0.12$; **Fig.1B**). Furthermore, there was no significant difference in disease-free survival (DFS) among thrombus-level patients($p=0.65$).

On univariate analysis, tumor size, papillary and sarcomatoid histology, supradiaphragmatic tumor thrombus and positive-tumor margin were associated with OS (**Table 2**). However, only sarcomatoid dedifferentiation was associated with reduced OS (HR 31.3;1.27-767.8). There was no factor associated with DFS on univariate and multivariate analyses.

Table 2

Univariate and multivariate analyses for overall and disease-free survival

<i>Overall survival</i>			
	Univariate	Multivariate	
	p-value	p-value	HR (95%CI)
Age	0.64		
Male	0.19		
BMI	0.97		
Size	0.03	0.07	1.25 (0.98-1.60)
Histology			
Clear cell	Ref	Ref	
Papillary	0.037	0.29	2.91 (0.40-21.2)
Sarcomatoid	0.028	0.04	31.3 (1.27-767.8)
FHD	0.99	0.99	0
Translocation	0.99	0.99	0
Perinephric fat invasion	0.81		
Thrombus level			
Infradiaphragmatic	Ref	Ref	Ref
Supradiaphragmatic	0.009	0.08	7.20 (0.82-63.4)
Venous invasion	0.53		
Positive surgical margin	0.04	0.34	2.42 (0.40-14.7)
Node			
N1	0.34		
Nx	0.69		
Distant metastasis	0.13	0.08	5.24 (0.82-33.6)
<i>Disease-free survival</i>			
	Univariate	Multivariate	
	p-value	p-value	HR (95%CI)
Age	0.84		

Male	0.31		
BMI	0.27		
Size	0.20	0.21	1.09 (0.95-1.25)
Histology			
Clear cell	Ref		
Papillary	1.00		
FHD	1.00		
Translocation	1.00		
Perinephric fat invasion	0.12	0.26	1.88 (0.62-5.70)
Thrombus level			
Infradiaphragmatic	Ref	Ref	Ref
Supradiaphragmatic	0.19	0.38	2.29 (0.37-14.2)
Venous invasion	0.07	0.29	0.46 (0.11-1.92)
Positive surgical margin	0.12	0.17	2.03 (0.73-5.64)
Abbreviations: BMI: body mass index; CI: confidence interval; FHD: fumarate hydratase deficiency; HR: hazard ratio			
Note: One patient with sarcomatoid histology had metastasis at diagnosis and one lost to follow up.			

Discussion

The prognosis of untreated patients who present with RCC and IVC tumor thrombi is dismal⁴. Although surgical extirpation was performed, long-term survival of patients remains reduced compared to localized disease. Five-year OS rate of 35% to 70% has been reported^{2,7,11}. In our study, 2-year OS of 80% for the entire cohort was observed; however, OS was significantly reduced in patients with IVC thrombus level IV ($p=0.025$). Radical nephrectomy with IVC thrombectomy is surgically challenging especially in large renal mass and high tumor thrombus level. The surgical technique depends on the cranial extent of IVC thrombus^{2,3,8,10}. An infrahepatic IVC thrombus (level I-II) can be safely removed via abdominal isolation of the IVC. On the other hand, thrombus extending to right atrium requires mandatory of large thoracoabdominal access with CPB. Controversy exists in the management of a thrombus extending to retrohepatic and/or supradiaphragmatic IVC (level III-IV) because of complex anatomical region. Liver mobilization technique has been developed for the IVC control and prevention of emboli from tumor thrombi. We retrospectively reviewed our 18-year experience in surgical management of RCC patients with IVC thrombi focusing on surgical outcomes and survival benefits in Thai (Southeast Asian) population.

Mortality and morbidity of radical nephrectomy and IVC thrombectomy were considered high; 1.5-10% and 15-80% for mortality and morbidity, respectively^{2,3,12}. Previous study from IRCC-VTC, a total of 2147 patients from 22 institutions in the US and Europe, demonstrated 34% postoperative complications; 13% were classified as Clavien grade 3-5. Mortality rate was 2% within 30 days and high level of tumor thrombus was associated with increased complication rate particularly high-grade complications ($p=0.03$)¹. In our study, perioperative morbidity and mortality were unsurprisingly high especially in supradiaphragmatic thrombus patients. As a result, operative time, blood loss and transfusion, and ICU stay were significantly greater in these patients ($p<0.01$). Furthermore, 80% of major complications were observed in patients with thrombus level III-IV. Recent study of 62 patients with tumor-thrombus level III-IV from four tertiary centers in the US reported that preoperative limited performance status and reduced serum albumin were associated with increased postoperative ninety-day mortality¹².

The role of preoperative renal arterial embolization (RAE) to reduce intraoperative blood loss and perioperative complications has been debating¹⁻³. RAE, generally performed on the operation day, could cut off blood supply to renal mass and thus reduce blood loss and complications. Previous study from Cleveland Clinic demonstrated significant risk of perioperative mortality in patients with preoperative embolization (OR 5.5, $p=0.03$) as well as postoperative complications¹³. Recent study from Tang and colleagues, however, supported reduced blood loss and transfusion in patients receiving perioperative embolization($p<0.03$)¹⁴. Notably, patients from Cleveland Clinic cohort had higher thrombus level when compared to Tang's study. No preoperative RAE was performed in our series.

Level of IVC thrombus on patients' survival has been controversial^{5,6,11,15}. Our study showed that tumor size and histology, supradiaphragmatic tumor thrombus and positive surgical margin were associated with OS on univariate analysis. However, tumor thrombus level was not an independent factor for OS on multivariate analysis. A study of 1192 pT3b and pT3c patients from 13 European institutions also demonstrated similar results¹⁵. IVC thrombus level was not a predictor for OS after radical surgery. Nevertheless, subsequent study based on a pooled analysis of 11 international centers (IRCC-VTC), the level of IVC thrombus was shown to be an independent factor of survival; HR 2.1(1.53-3.0)⁶. Our study also demonstrated that sarcomatoid dedifferentiation was associated with reduced overall survival. Similar results were reported from the recent study, including 125 RCC with IVC tumor thrombus patients (14% sarcomatoid histology). Sarcomatoid dedifferentiation was a significant factor associated with progression-free and cancer-specific survival (CSS)¹⁶.

The greater risk of cancer recurrence after tumor thrombectomy is observed. Residual tumor may be entrapped in the vessel intima and 40-50% of patients will develop disease-recurrence within 3 years¹⁷. Sanli and colleagues showed that microscopic venous invasion was associated with tumor recurrence and reduced CSS¹⁸. In non-metastatic RCC patients with IVC tumor thrombi, seven risk factors were found associated with tumor recurrence – BMI, preoperative hemoglobin, tumor size, non-clear cell histology, IVC thrombus height, nuclear grade and perinephric fat invasion¹⁹. In our study, median follow-up time

was 15(5-41) months, none of patients with IVC thrombus level IV experienced disease free beyond 12 months postoperatively. In pN0M0 cohort, DFS was reported 42.8%.

Neoadjuvant systemic treatment to reduce tumor thrombus and then facilitate surgery has been discussed²⁰⁻²³. A previous retrospective study of 14 patients received neoadjuvant sunitinib or sorafenib for 2 cycles demonstrated limited results. Eighty-five percentage of patients had stable disease while one patient had an upstage. Only one tumor decreased in this report²¹. Contrarily, a recent multicenter comparison study of 53 RCC patients with IVC tumor thrombi demonstrated survival advantages of neoadjuvant sunitinib²⁰. High risk patients due to either surgical or medical cause received preoperative sunitinib. IVC thrombus significantly decreased by 1.3 cm and 40% percent of patients had reduced tumor-thrombus level in neoadjuvant cohort. Also, neoadjuvant sunitinib was an independent factor of improved CSS ($p=0.02$). Currently, immune checkpoint inhibitors play an important role in RCC field. Labbate and colleagues reported a complete response of level IV tumor thrombus after neoadjuvant nivolumab and ipilimumab²³. The patient had disease-free after surgery up to last follow-up of a year.

Metastatic renal cell carcinoma with IVC tumor thrombus has been reported 30-50% and the role of cytoreductive nephrectomy has been disputed^{15,17,24-27}. Radical nephrectomy and complete removal of tumor thrombus is the key to prolong survival and provide better quality of life¹⁷. However, only RCC patients with tumor thrombus below diaphragm had advantages from such surgery^{26,27}. Abel and colleagues proposed preoperative factors associated with reduced overall survival after cytoreductive nephrectomy of metastatic RCC with IVC thrombus patients – high serum lactate dehydrogenase, systemic symptoms, supradiaphragmatic tumor thrombi and sarcomatoid features. These could be considered for preoperative counselling and neoadjuvant therapy. In our study, 21% of patients had distant metastases before surgery which was comparable to the prevalence in Asian studies⁷. The advantages of surgery in metastatic patients were found in our study with 2-year OS rate of 67% and no significant difference when compared to non-metastatic group($p=0.12$). Additionally, one patient after thrombectomy and lung metastatectomy has been alive with stable disease at 110 months follow-up time.

Retrospective design with single center is the limitation of this study. Regarding to tertiary center, some patients were loss to follow-up and OS was utilized as our primary outcome instead of CSS. Nevertheless, our study provides medium to long term experience with the number of patients with RCC and IVC thrombi in Thailand and represents Southeast Asian population. Limited number of the patients in this study is another limitation regarding to low incidence of disease in our area and some were not fit for surgery. No prior study has ever been addressed this clinical information of such patients in the Southeast Asian region. Even though, multicenter study from this area would be required.

Conclusion

Our experience over 18 years suggested that surgical treatment for RCC with IVC thrombus was feasible and provided acceptable surgical and oncological outcomes. However, major complications and

perioperative mortality in high-thrombus level(III-IV) were greater when compared to low-thrombus level(I-II). Although our experience demonstrated that tumor-thrombus level was associated with patient survival, the level of tumor thrombus itself was not an independent factor. Cytoreductive surgery in mRCC patients provided acceptable outcomes in selected patients. Only sarcomatoid variant was a significant adverse factor associated with reduced OS in this study.

Abbreviations

BMI = body mass index

CPB = cardiopulmonary bypass

CI = confidence interval

CSS = cancer-specific survival

DFS = disease-free survival

DSS = disease-specific survival

EBL = estimated blood loss

eGFR = estimated glomerular filtration rate

FHD = fumarate hydratase deficiency

HR = hazard ratio

ICU = intensive care unit

IQR = interquartile range

IRCC-VTC = International Renal Cell Carcinoma – Venous Thrombus Consortium

IVC = inferior vena cava

LOS = length of stay

OS = overall survival

RAE = renal arterial embolization

RCC = renal cell carcinoma

Declarations

Disclosures:

None of the authors have any disclosures or conflicts of interest to report

Research involving Human Participants:

retrospective review of patients' chart

Informed consent:

non-applicable

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Authors' contributions

Taweemonkongsap: Protocol development, Data collection, Manuscript writing

Chotikawanich: Protocol development, Data collection

Jitraphai: Protocol development, Data collection

Woranisarakul: Data collection, Manuscript writing

Hansomwong: Data collection, Manuscript writing

Suk-Ouichai: Protocol development, Data collection, Data analysis, Manuscript editing

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Figures

Figure 1

Overall survival after radical nephrectomy and tumor thrombectomy in patients (A) level I-IV IVC tumor thrombus and (B) with and without distant metastases at presentation