

Analysis of surgical outcomes in 102 patients with renal cell carcinoma with venous tumor thrombus A retrospective observational single-center study

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Abstract The aim of the study was to assess short- and long-term results following radical nephrectomy with renal vein and inferior vena cava thrombectomy in patients with renal cell cancer with venous thrombus and to investigate impact of various demographical, clinical and histological factors on overall survival (OS). The medical records of 102 adult patients with renal cell cancer with venous thrombus admitted for surgery in Department of General, Vascular and Transplant Surgery from 2012 to 2019 were retrospectively analyzed. The tumor was more frequently located on the right side compared to the left one (55 vs. 47). According to Neves Zincke classification, the levels of venous thrombus were as follows: 1 to 48 (47%), 2 to 47 (46%), 3 to 6 (6%), and 4 to 1 (1%). Postoperative complications were noted in 16 (15.7%) patients. One (3%) patient (Neves Zincke 2) died of intraoperative pulmonary embolism during hospitalization. Clear cell carcinoma was the most common pathological type reported in 92 (90.2%) patients. Thirty nine (38.2%) patients were alive at the time of last follow-up. The median OS was 21.50 (0–101.17) months. The 1-year OS was 75.5%. Significantly better OS (median 38.03 months) was noted in patients with RCC Neves Zincke 1 compared to OS (median 14.79 months) in patients with Neves Zincke 2-4 VT (P = .008). Higher tumor staging (T3 vs. T4) (P = .038), nodal staging (N0 vs. N1) (P = .0008), Fuhrman histological grading (G1-2 vs. G3-4) (P = .033) were associated with a shorter OS. Patients with renal cell cancer with venous thrombus, with an acceptable perioperative risk, should be treated surgically, because radical nephrectomy with thrombectomy performed in a high volume surgical center is a safe procedure. Neves Zincke 2-4 venous thrombus, higher tumor and nodal staging, as well higher Fuhrman histological grading are associated with a shorter OS.

Abbreviations: CT = computed tomography, DFS = disease-free survival, IVC = inferior vena cava, OS = overall survival, RCC = renal cell carcinoma, RCC-IVCTT = renal cell carcinoma with inferior vena cava tumor thrombus, RCC-VT = renal cell carcinoma with venous thrombus, RV = renal veno, VTT = venous tumor thrombus.

Keywords: inferior vena cava, nephrectomy, renal cell carcinoma, renal vein, surgery, survival, venous thrombus

1. Introduction

Renal cell carcinoma (RCC) is a common malignant neoplasm of the urinary system accounting for 2% to 3% malignant neoplasms in adults.^[1,2] RCC accounts for about 90% of all kidney cancers. Inferior vena cava (IVC) tumor thrombus is noted in 4% to 10% of locally advanced RCC.^[1] IVC tumor thrombus may be located within the infra-, intra-, and supra-hepatic IVC portion and right atrium.^[3] According to literature, 5-year cancer-specific survival is nearly 60% for patients with the most favorable tumors.^[4] In patients with untreated RCC with IVC tumor thrombus (RCC-IVCTT), a median survival is about 5 months and 1-year disease-free survival (DFS) is about 29%.^[5]

Data included in tables and figures. The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

*Correspondence: Beata Jablońska, Department of Digestive Tract Surgery, Medical University of Silesia, 40-752 Katowice, Poland (email: bjablonska@poczta.onet.pl). Radical nephrectomy with IVC thrombectomy is the most effective treatment of RCC-IVCTT. It can significantly improve the prognosis and increase 5-year DFS to 40% to 65%.^[1,3] However, it is one of the most challenging and complex surgical procedures associated with significant morbidity and mortality. According to literature, mortality rate in patients following this procedure is up to 10%.^[3,4,6,7] Therefore, surgical treatment of patients with RCC-IVCTT needs very careful selection in order to improve prognosis without significant increase of risk of post-operative mortality and morbidity. In our opinion, the benefits of treatment, including improvement of patients' survival, should be greater than the risk of potential complications and mortality rate associated with surgery.

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This is a retrospective study of medical records and it did not require ethical approval. All data were fully anonymized. Our study is exempted from institutional review board approval according to local and national legislation. The study was conducted in accordance with the Declaration of Helsinki.

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The aim of our study was to assess short- and long-term results of radical nephrectomy with renal vein (RV) and IVC thrombectomy in RCC patients with venous thrombus (RCC-VT) and to investigate impact of various demographical, clinical and histological factors on overall survival (OS).

2. Materials and Methods

2.1. Patients

One hundred two adult patients with RCC-VT were admitted for surgery in Department of General, Vascular and Transplant Surgery from 2012 to 2019. There were 71 (69.6%) men and 31 (30.4%) women aged 66.1 ± 10 years in the studied group. The inclusion criteria were as follows: locally advanced primary RCC with RV or IVC tumor thrombus (T3-T4, N0-N1, M0-M1), age > 18 years. Exclusion criteria included: RCC without venous tumor thrombus (T1-T2), cancer recurrence, incomplete demographic and or clinical data.

2.2. Study design

This was a retrospective study of medical records and all data were fully anonymized. Written informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. According to national and local legislation, only a medical experiment needs to obtain ethical approval. The retrospective study including analysis of patients' medical records does not need this approval.

Medical records were retrospectively reviewed. Clinical and pathological features, including age, gender, laterality, body mass index, blood less and transfusion, duration of hospitalization, duration of surgery, laboratory results before (0) and after surgery (1), tumor size, the level of venous tumor thrombus, clinical and histopathological staging and grading, post-operative complications, OS, were collected and analyzed.

The venous tumor thrombus level was defined according to Neves-Zincke classification.^[8] Level 1: renal vein, Level 2: infrahepatic IVC, 3: retrohepatic IVC, 4: right atrium.^[8] We decided to use Neves-Zincke classification, because it is the most frequently used and simple classification system to determine the level of RCC-VT.

RCC staging was determined according to the 8th edition of the American Joint Committee on Cancer tumor nodes metastases classification system^[9] and assessed based on before-surgery abdominal; computed tomography (CT) and post-surgery pathological results. In Figure 1, CT scan showing a large RCC with IVC thrombus is presented.

Histological type was defined according to according to the World Health Organization classification of tumors of the urinary system and male genital organs (2004 edition).^[10,11] Tumor grading was defined according to Fuhrman classification.^[10,12]

We had written letters to all surgically treated patients in order to obtain the follow-up information. Information on OS was collected using statistical database.

2.3. Surgical technique

The surgical procedure was as follows: The laparotomy via transverse subcostal incision was performed. The right/left renal artery and right/left ureter were dissected and transected. Ipsilateral adrenalectomy was performed. For Neves Zincke level 1, the IVC was exposed and partially occluded using Satinsky forceps if it was needed. For the higher Neves Zincke levels, the proximal and IVC ends and the contra-lateral RV were dissected and occluded. After venous clamping, the IVC wall opened, and the tumor thrombus was removed. After thrombus removing IVC was primarily sutured in two layers of continuous vascular suture 4-0.

2.4. Statistical analysis

The categorical variables were presented as numbers and percentages and compared using the Pearson χ^2 test. Continuous variables with normal distribution were expressed as the means and standard deviations and analyzed using Student t test for data. Continuous variables with non-normal distribution were shown as the median and interguartile range and analyzed using Mann-Whitney test. The Shapiro-Wilk test was used to determine statistical distribution in the analyzed patients. The Wilcoxon test was used to compare pre- and post-treatment parameters. Prevalence and frequency were expressed as number and percentage. For analysis of long-term results and OS the F Cox test with construction of Kaplan-Meyer survival curves was performed. The Cox proportional hazard survival regression analyses was used to determine prognostic factors for survival. The results were summarized with hazard ratios and 95% confidence interval. A P < .05 was considered to be statistically significant. The statistical analyses were performed using the Stat Soft version 13.0 (StatSoft Poland, Kraków, Poland).

3. Results

3.1. Short-term results

3.1.1. General patients' characteristics. The general clinical characteristic of 102 patients is presented in Table 1. The basic laboratory results in all patients before and after surgery are presented in Table 2. The tumor was more frequently located on the right side (n = 55) compared to the left one (n = 47). The most frequently, the tumor venous thrombus was located within the RV (n = 48) and infrahepatic IVC (n = 47). Only one thrombus was located on the level of the right atrium. In 3 (2.9%) patients, distant metastases to the lungs and liver were noted. Nephrectomy with adrenalectomy was the most common procedure (99%). Grading 2 (n = 35) and 3 (n = 37) according to Fuhrman classification were the most frequent in our patients.

3.1.2. Correlations between clinicopathological parameters and laboratory results before and after surgery. Correlations between various parameters were analyzed. There was no correlation between body mass index and following factors:



Figure 1. An abdominal computed tomography scan showing a left renal cell cancer with inferior vena cava tumor thrombus.

Table 1

The general patients clinicopathological characteristics and basic laboratory results.

Feature	Value
Age (yr)	66.1 ± 10 (45-87)
Gender	
Male	71 (69.61%)
Female	31 (30.39%)
BMI (kg/m ²)	25.77 (IQR 5.00) (18.03–40.90)
Tumor side	
Right	55 (53.92%)
Left	47 (46.08%)
Tumor diameter (mm)	85.00 (IQR 34.00) (4.00–190.00)
Hospital stay (d)	8.00 (IQR 4.00) (2.00–32.00)
Operative time (min)	125.00 (IQR 60.00) (45.00–285.00)
Blood loss volume (mL)	50.00 (IQR 1000.00) (0.00-4000.00)
Blood transfusion volume (units)	0.00 (IQR 1.92) (0.00–10.00)
Neves-Zincke classification	
1	48 (47.06%)
2	47 (46.08%)
3	6 (5.88%)
4	1 (0.98%)
Surgery type	
Nephrectomy + adrenalectomy	101 (99.02%)
Laparotomy	1 (0.98%)
TNM classification	
T T2o	40 (47 060()
T3a T3b	48 (47.06%) 40 (39.21%)
T4	()
14 N	14 (13.73%)
NO	15 (14.70%)
N1	87 (85.30%)
M	07 (03.30 %)
MO	99 (97.06%)
M1	3 (2.94%)
Histopathological type	0 (210 170)
Clear cell	92 (90.20%)
Papillary + clear cell	2 (1.96%)
Papillary	1 (0.98%)
Chromophobe + papillary	1 (0.98%)
Fuscocellular	1 (0.98%)
Urothelial	4 (3.92%)
Planoepithelial	1 (0.98%)
Fuhrman classification	
1	1 (0.98%)
2	41 (40.20%)
3	42 (41.18%)
4	18 (17.64%)
Postoperative complications	
No	86 (84.31%)
Yes	16 (15.69%)
Mortality	
No	101 (99.02%)
Yes	1 (0.98%)

Values are presented as: mean \pm standard deviation (ranges) or median \pm interquartile range (ranges).

BMI = body mass index, IQR = interquartile range, TNM = tumor nodes metastases.

operative time (P = .49), hospital stay (P = .57), blood loss (P = .44), blood transfusion (P = .53). We noted no correlations between the level of thrombus and following factors: operative time, hospital stay, morbidity and mortality rates (P > .05). There was a significant statistical correlation between blood transfusion and operative time (R Spearman = 0.28, P = .003) and duration of hospitalization (R Spearman = 0.33, P < .001). There was a significant statistical correlation between blood transfusion and operative time (R Spearman = 0.28, P = .003) and hospital stay (R Spearman = 0.33, P < .001). However, there was no correlation between blood transfusion and complications rate (P = .68). Also, there was no correlations between

thrombus laterality and duration of hospitalization (P = .17) and operation time (P = .21) as well as between histological grading according to Fuhrman classification and operative time (P = .26). However, a significant interesting correlation between Fuhrman classification and hospital stay (P = .02) was noted. Kruskal Wallis test revealed a significantly longer hospital stay in patients with G2 and G3 tumors compared to patients with G4 tumors. We observed significant differences between preand postoperative Hb, WBC, PLT, creatinine, and potassium values. Serum natrium concentrations before and after surgery were comparable (Table 2).

3.1.3. Postoperative complications. Postoperative morbidity was 15.7%, and mortality 1%. A hemorrhagic shock was the most frequently noted complication (7.84%). All postoperative complications are presented in Table 3.

3.2. Long-term results

The median follow-up time was 21.50 months (0-101.17 months). The OS information from all participants was available. Thirty nine (38.2%) patients were alive at the time of last follow-up. The median OS was 21.50 months. The 1-year OS was 75.5%. OS in all patients is presented in Figure 2. There was no statistically significant difference between men and women (P = .26). The tumor side did not influence on OS in our analysis (P = .20). Due to the small number of patients with tumor thrombus of level 4, we did not compare the subgroups according to the original Neves Zincke classification. Therefore, we divided all patients into two groups according to thrombus level: I: within RV (Neves-Zincke 1), II: within IVC (Neves Zincke 2-4). Significantly better OS (median 38.03 months) was noted in patients with RCC Neves Zincke 1 compared to OS (median 14.79 months) patients with higher level (Neves Zincke 2-4) venous thrombus (P = .008) (Fig. 3). In our study, histopathological grading and tumor nodes metastases classification were significant prognostic factors for OS (P < .05). The cohort was divided into two subgroups depending on tumor staging: T3 versus T4 and N0 versus N1, in order to compare OS between above mentioned distinguished groups. A significantly better OS for patients with T3 staging (median OS 25.38 months) RCC compared to T4 staging (median OS 9.15 months) was noted (P = .038) (Fig. 4). Also, a significantly better OS for patients with N0 staging (median OS 56.05 months) RCC compared to N1 staging (median OS 11.32 months) was noted ($\hat{P} < .001$) (Fig. 5). Similarly, our cohort was divided into two subgroups depending on Fuhrman histopathological grading: G1-2 versus G3-4, in order to compare OS between above mentioned distinguished groups. A significantly better OS for patients with G1-2 grading (median OS 47.75 months) RCC compared to G3-4 grading (median OS 21.50 months) was noted (P = .033) (Fig. 6).

The other prognostic factors for OS in Cox regression analysis are presented in Table 4. In this analysis, higher preoperative hemoglobin concentration (hazard ratio = 0.6446; 95% confidence interval: 0.4203-0.9888; P = .0442) was a significant good prognostic factor for OS. The other laboratory results did not impact significantly on OS in Cox regression analysis.

4. Discussion

The first nephrectomy with cavotomy for RCC-IVCTT was reported by Berg in 1913.^[13] Currently, it is a safe and effective RCC-IVCTT treatment. According to literature, the 30-day mortality for this procedure is 1.5% to 10%. The morbidity rate is 18%, 20%, 26%, and 47% for I, II, III, and IV VT level, respectively.^[14,15] In our study, very low morbidity rate (8.82%) and 30-day mortality rate (0.98%) were reported. These results are similar to literature data. Our results confirm that nephrectomy

Laboratory	results	before an	d after	surgery.*

Parameter	Before surgery	After surgery	Р
Hemoglobin [g/dL]	11.65 ± 2.17 (6.90–17.40)	9.79 ± 1.68 (6.20–14.00)	<.001
WBC [/mm ³]	7.88 (IQR 2.80) (2.50–19.80)	10.81 (IQR 5.30) (2.26–23.10)	<.001
PLT [/mm ³]	271.00 (IQR 141.00) (76.00–697.80)	224.50 (IQR 90.50) (50.00–681.00)	<.001
Creatinine [µmo/L]	91.52 (IQR 32.10) (43.99–448.90)	105.46 (ÌQR 41.50) (59.00–1065.90)	<.001
Sodium [mmol/L]	137.00 (IQR 4.50) (128.00–144.00)	138.00 (IQR 4.00) (101.00–169.00)	.213
Potassium [mmol/L]	4.51 ± 0.54 (3.20–6.00)	4.30 (IQR 0.80) (2.70–5.70)	.007

Values are presented as: mean \pm standard deviation (ranges) or median \pm interquartile range (ranges). IQR = interquartile range, PLT = platelet cells, WBC = white blood cells.

*Wilcoxon test.

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Table 3	
Postoperative complications.	

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Hemorrhagic shock	8 (7.84%)
Preoperative pulmonary embolism	1 (0.98%)
Intraoperative pulmonary embolism	1 (0.98%)
Postoperative pulmonary embolism	2 (1.96%)
Ischemic stroke	1 (0.98%)
Renal insufficiency requiring dialysis	1 (0.98%)
Septic shock, multiorgan insufficiency due to intraabdominal abscess	1 (0.98%)
Atonia of the digestive tract	1 (0.98%)
Acute respiratory insufficiency	1 (0.98%)
Acute respiratory and circulatory insufficiency	1 (0.98%)

with cavotomy can be a safe surgical procedure for patients with RCC-VT. We observed no correlation between the VT level and complications rate in our patients.

According to literature, a median survival of 5 months and 1-year DFS rate of 29% is reported in patients with untreated RCC-VT.^[5,15] It has been proven that the surgically treated RCC-VT has significantly better prognosis and survival. A 5-year survival rate of 45 to 69% in patients with RCC-VT,

without distal metastases following radical nephrectomy with thrombectomy has been reported.^[16]

In Cao et al^[17] conducted on 128 patients, the median OS was 127 months and 5-year and 10-year DFS rate was 67.9% and 57.0%, respectively. In Hirono et al,^[18] including 292 RCC patients with 152 RV tumor thrombus patients, the 5-year DFS of 50.9% was noted. In Sidana et al^[19] including 132 RCC patients involving 64 RCC with RV tumor thrombus, the 5-year DFS was 65.0%. In Lambert et al,^[20] the 5-year OS was 40.7%. The 5-year DFS was 60.3% in those without metastasis and 10% in those with metastasis. This study involved 118 patients with stage pT3b or pT3c RCC. The authors reported statistically significant difference in DFS depending on metastatis presence (P < .001). In Berczi et al^[21] including 46 patients with RCC-IVCTT, the median duration to progression was 37 ± 27 months, and the 5-year OS was 43.7%.

The literature and our results confirm that radical nephrectomy with cavotomy is effective surgical procedure. The significantly better survival in patients with RCC-VT surgically treated compared to untreated ones is noted. Our study confirms that median OS (21.50 months) and 1-year OS (75.5%) are significantly better compared to median OS (5 months) and 1-year OS (29%) reported in the world literature.

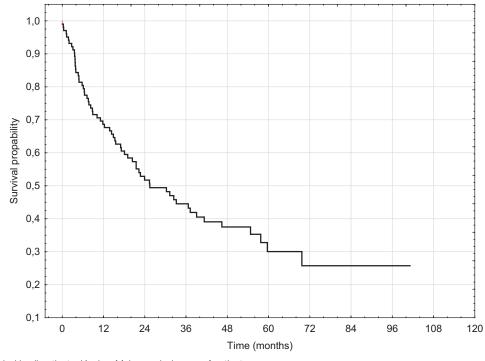


Figure 2. Overall survival in all patients. Kaplan–Meier survival curve of patients.

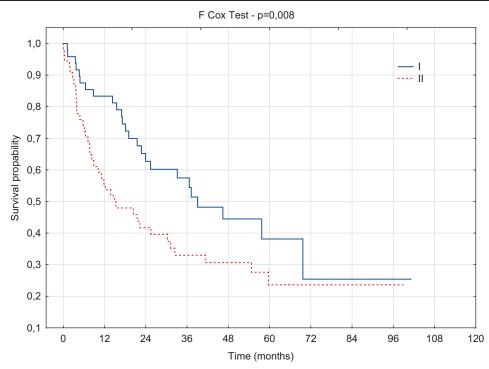
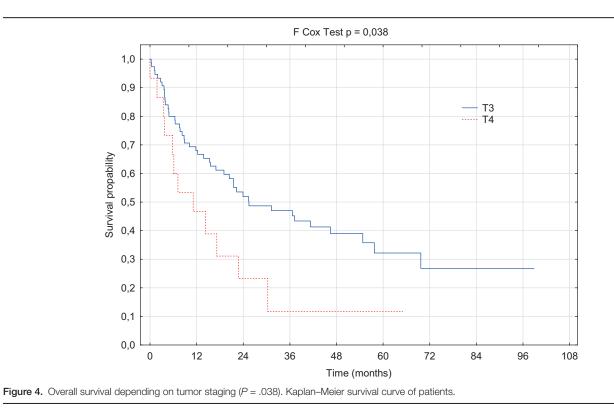


Figure 3. Overall survival depending to modified Neves Zincke classification: I: 1, II-2-4. (P = .008). Kaplan-Meier survival curve of patients.



The association between the VT level and survival is controversial.^[18] According to some authors, there is no association between the thrombus level and prognosis.^[22-24] In contrast, others reported differences in prognosis between patients with a infra-diaphragmatic and supra-diaphragmatic IVCTT.^[25-27] According to another authors, CT location in RV or IVC is the cut-line for predicting prognosis for RCC patients^[4,28,29] which is in accordance with our observations. In a multi-center study by Wagner et al^[28] including 1192 patients undergoing a radical nephrectomy for pT3b and pT3c RCC, the VT level within the IVC did not significantly impact OS in patients with RCC, but there was a statistical difference in OS between patients with a tumor thrombus in the RV compared to IVC location.

Blute et al^[4] analyzed 540 treated surgically for RCC-VT. There were 349 (64.6%) patients with RV thrombus (level 0)

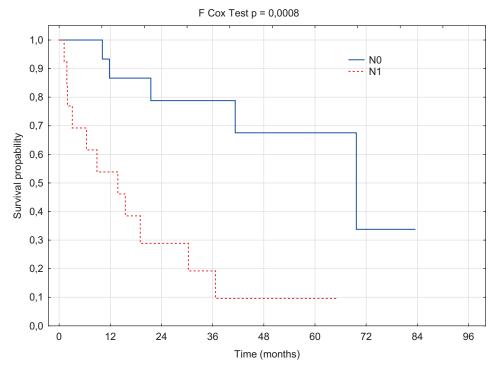


Figure 5. Overall survival depending on lymph nodes staging (P = .0008). Kaplan-Meier survival curve of patients.

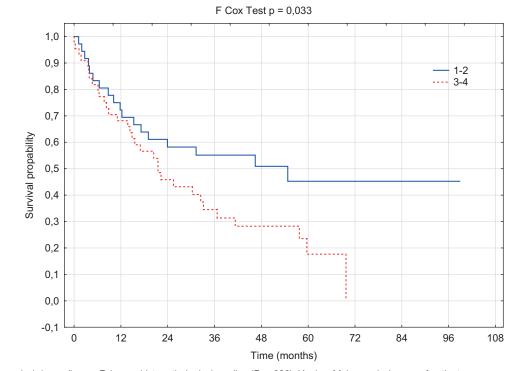


Figure 6. Overall survival depending on Fuhrman histopathological grading (P = .033). Kaplan-Meier survival curve of patients.

and 191 (35.4%) with IVC thrombus, including 66 (12.2%) with level I, 77 (14.3%) with level II, 28 (5.2%) with level III, and 20 (3.7%) with level IV thrombus. In this study, a higher number of surgical early complications (respectively for level 0 to IV, 8.6%, 15.2%, 14.1%, 17.9% and 30.0%) (P < .001) was reported in patients with the higher thrombus level. The outcome was statistically different in patients with level 0 (RV) versus those with level > 0 (IVC) thrombus (P = .002), and

comparable in patients with IVC tumor thrombus regardless the thrombus level (P = .868).

In a study by Moinzadeh et al^[29] including 153 patients with RCC-VT, the following VT level were reported: RV (n = 46), IVC: level I (n = 68), level II (n = 17) and level III (n = 22). In this study, the 10-year DFS in analyzed patients was 30%, 19% and 29% for level I, II and III, respectively. Five- and-10 years survival was not significantly different between the three IVC

Table 4		
Prognostic fa	actors for overall survival: Cox regree	ssion analysis.

Variable	HR	95% CI	Р
Age	0.9796	0.9237-1.0389	.4921
Tumor diameter [mm]	1.0005	0.9826-1.0187	.9570
Operative time [min]	1.0097	0.9903-1.0295	.3273
Hospital stay [d]	0.7084	0.05470-0.9173	.0089
Intensive care hospitalization [d]	1.7396	0.3124-9.6852	.5274
Blood loss [mL]	1.0000	0.9993-1.0007	.9254
Blood transfusion [units]	0.8553	0.6029-1.2220	.3967
Preoperative Hb [g/dL]	0.6446	0.4203-0.9888	.0442
Preoperative WBC [/mm ³]	1.3338	0.9880-1.3846	.0599
Preoperative PLT [/mm ³]	1.0009	0.9921-1.0098	.8406
Preoperative creatinine [µmo/L]	0.9853	0.9676-1.0033	.1088
Preoperative sodium [mmol/L]	1.1430	0.9088-1.1728	.359
Preoperative potassium [mmol/L]	1.3191	0.3559-4.8888	.6786

 $\label{eq:cl} CI = \text{confidence intervals}, Hb = \text{hemoglobin level}, HR = \text{hazard ratio}, PLT = \text{platelet cells count}, \\ WBC = \text{white blood cells count}.$

levels (P = .48). There was a statistical difference in 10-years survival between patients with RV thrombus (66%) versus level I (29%) (P = .0001).

Our study confirmed the third above mentioned observation. We have noted significantly better survival in patients with tumor thrombus located within the RV compared to patients with tumor thrombus located within IVC.

In addition to the tumor thrombus level, we noted the significantly better OS in patients with the lower RCC staging and lower grading. The T4, N2 and G3-4 were adverse prognostic factors in our patients. This observation is consistent with the some literature reports.

In above-mentioned Wagner et al,^[28] median survival was 52, 25.8 and 18 months for grading 1, 2, and 3, respectively. The univariate analysis showed significantly better OS in grading 1 grading compared to grading 2 (P < .001) and grading 3 ($P \le .001$). OS in gradings 2 and 3 (P = .613) was comparable. Fuhrman grading (P < .001) and lymph node invasion (P < .001) and tumor size (P < .001) were dependent prognostic factors for OS, whereas tumor size (P = .013) and lymph node invasion were independent prognostic factors (P < .001).^[28]

In Lambert et al,^[20] the tumor grading (P = .006) was a dependent prognostic factor of outcome in the univariate analysis. Nodal staging was also a significant prognostic factor of outcome (P = .05) in division into node-negative disease (N0 or Nx) and node-positive disease (N1-N2).^[20] In our study, we similarly characterized the lymph nodes staging and our conclusions were similar to this report.

Chen et al^[30] in their retrospective study, analyzed 86 patients following nephrectomy with thrombectomy for RCC-VT from 2003 to 2013. The multivariate Cox regression analysis showed that nodal staging, and invasion of the IVC wall were the independent prognostic factors for DFS in all patients.^[30]

The limitations of this study are as follows: This is a single-center, retrospective study based on a small-sample size. The different surgeons were involved in surgical procedures. Besides surgery, systemic, molecular-targeted therapy may significantly affect the survival of patients with RCC-VT. A multi-center prospective randomized study should be performed in order to validate the results.

5. Conclusions

Thrombus location within IVC, T4 and N1 staging, as well as Fuhrman histological grading G3 are independent poor prognostic factors for OS in our patients with RCC-VT. Our study showed that nephrectomy with venous thrombectomy was a challenging but feasible procedure for experienced surgeons in patients with RCC-VT. This procedure is associated with a low risk of postoperative morbidity and mortality. OS in patients with RCC thrombus located within RV is significantly better compared to patients with higher thrombus levels located within IVC. Therefore, patients with RCC-VT, with an acceptable perioperative risk, should be treated surgically.

Author contributions

All authors have read and agreed to the published version of the manuscript.

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