

Prognostic Factors in Renal Cell Carcinoma With Vena Cava Extension

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ABSTRACT

INTRODUCTION: The objectives were to: (1) analyze clinical and pathological features of renal cell carcinoma (RCC) with caval thrombosis in order to identify independent prognostic factors, and (2) analyze perioperative morbidity and mortality.

METHODS: The authors retrospectively analyzed clinical and pathological data of 56 patients treated for RCC with caval thrombosis during a 20-year period. The surgical procedure was essentially unchanged. Independent variables were: TNM, creatinine value, age, histological extent, histological type, adjuvant treatment, and surgical technique; the dependent variable was overall survival. Contingency and logistic regression tables were used. Kaplan-Meier method, log-rank, and Cox models were used to analyze survival rates.

RESULTS: There were complications in 15 patients and 2 perioperative deaths. Overall mean (SD) survival rates were 32% (7%) and 24% (6%) at 3 and 5 years, respectively. Multivariate results showed that the significant prognostic indicators of survival were: the size of the tumor > 8 cm ($P < .01$), the presence of metastasis ($P < .04$), and lymph node invasion ($P < .009$). These were also regarded as the relevant variables, independent of patient survival.

CONCLUSIONS: The surgical approach for this disorder is challenging and not exempt of complications. Nodal involvement, tumor size, and distant metastases are the most important prognostic factors; thrombus extension has a clear impact on surgical planning and performance.

INTRODUCTION

A distinctive feature of renal cell carcinoma (RCC) is extension into the venous system. This may lead to the development of a tumor thrombus that may extend through the inferior vena cava (IVC), as far as the right atrium, and even into the right ventricle [1]. Extension into the renal vein, including microvascular (microscopic) invasion, is noted in 20% to 35% of the cases at the time of diagnosis, with 4% to 10% of the cases presenting with extension into the IVC. Caval thrombus

extends above the suprahepatic veins in 10% to 15% of the cases [2,3]. These patients often present with severe symptoms and seek immediate treatment [4].

Advances in surgical techniques and perioperative care over the last 30 years currently ensure safe care [5,6]. The treatment strategy is radical nephrectomy with thrombectomy and extended lymphadenectomy [7]. Removal of the thrombus in totality often requires the intervention of a cardiovascular surgical team. Such interventions must be performed in

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Abbreviations and Acronyms

ECC = extracorporeal circulation

IVC = inferior vena cava

RCC = renal cell carcinoma.

experienced medical centers, because the perioperative mortality rate ranges from 10% to 50% [8-10]. The presence of tumor thrombus does not necessarily worsen the prognosis and, in the absence of distant metastases, the patient has a relatively long postoperative life expectancy [5,11].

There is some degree of discrepancy regarding prognostic factors and surgical approaches for patients with RCC. Therefore, the objectives of the present study were: (1) to analyze clinical and pathological features of RCC with caval thrombosis in order to identify independent prognostic factors, and (2) to analyze perioperative morbidity and mortality.

METHODS

Study Design

Data were obtained retrospectively from a surgical database. From 1985 to 2005, 453 patients with RCC had radical nephrectomies at the authors' institution. Thrombus in the vena cava was diagnosed in 56 cases; these were the targeted sample. The surgical procedure was essentially unchanged over this 20-year period.

Surgical Selection Criteria and Surgical Procedures

The surgical procedure chosen and the necessity for using extracorporeal circulation (ECC) was based on a variation of the classification described by Neves and Zinke [12] and the TNM [13] classification system (Figure 1). In patients with B1-type, extended nephrectomy followed by thrombectomy was performed with selective clamping of the vena cava. In patients with B2-type and C-type, extended nephrectomy was carried

out with ECC, hypothermia, and cardiac arrest.

To plan the surgical strategy, 3 thrombus levels were determined. For the purpose of analysis, tumors were classified according to TNM into T3b and T3c. Patients seen early in the series were evaluated by cavography; later patients were evaluated by magnetic resonance imaging and color Doppler ultrasound. ECC was done whenever the thrombus level was at the level of the suprahepatic veins or above (level III-IV, or T3B2 [Figure 1]).

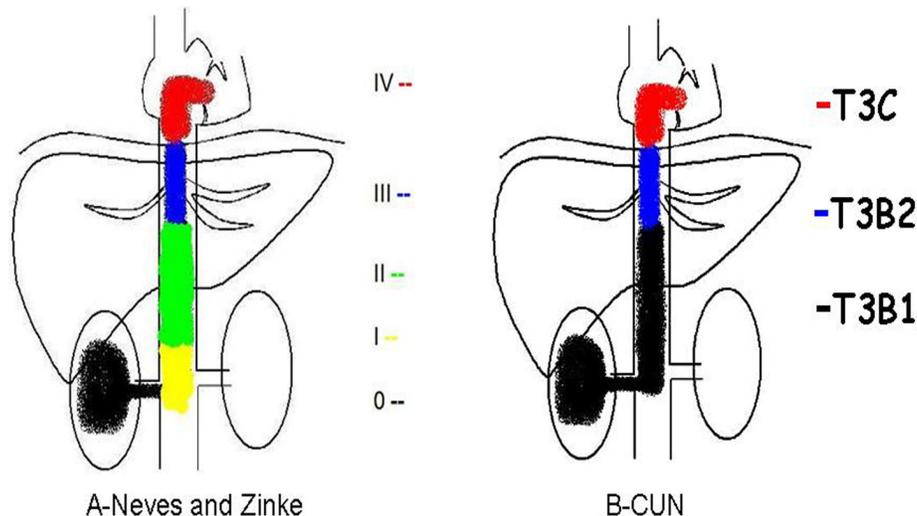
Patients were excluded from the study if visceral metastases were observed, expected residual disease was very high (> 30% of total disease), complete tumor resection seemed impossible to achieve, or performance status was very low.

Cava resection was performed systematically in the first 15 cases; subsequently, cava resection was performed only in those cases with cava infiltration, due to the surgeon's experience in performing sharp thrombectomy. Nineteen patients with metastasis at diagnosis followed a treatment with either adoptive immunotherapy, tumor-infiltrating lymphocytes (TIL), or lymphokine-activated killer cell (LAK cells).

Data Analysis

Receiver operating characteristic (ROC) analysis was used to detect the most appropriate tumor size for predicting survival. Kaplan-Meier was used to study patient survival. A univariate analysis was performed for subgroup survival comparison using the log-rank test. An *ad hoc* analysis was conducted to develop a predictive model for survival. The independent variables were: TNM classification, creatinine value, age, histological

Figure 1. Classification of Tumor Thrombus According to the Neves and Zinke (1987) Variation. doi: 10.3834/uij.1944-5784.2010.08.18f1



extent, histological type, adjuvant treatment, and surgical technique. Cox models were used to develop a predictive model; the dependent variable was overall survival. The significance threshold was $P < .05$. The statistical analysis was carried out using SPSS (Version 14.0: Chicago, IL, USA).

RESULTS

Descriptive Statistics and Complications

Descriptive statistics are shown in Table 1. The median patient age was 57.2 years (range, 47-68 years). Thrombus type and

Table 1. Descriptive Data for the Patient Sample (N = 56).
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Characteristic	n	% n
Sex		
Male	46	82
Female	10	18
Bone scan		
No	9	16.1
Negative	40	71.4
Positive	7	12.4
Symptoms		
Asymptomatic	12	21.4
Pain in side	5	8.9
Mass	6	10.7
Hematuria	5	8.9
Constitutional	5	8.9
Varicocele	1	1.8
> 1 symptom	22	39.3
Extracorporeal circulation		
Yes	25	44.6
No	31	55.4
pT status (surgery)		
pT3b	43	76.7
pT3c	13	23.2
N status (surgery)		
N0	35	62.5
N1	20	35.7
N2	1	1.8
M status		
M0	37	66.1
M1	19	33.9
Histological type		
Clear cell	50	89.2
Papillary	4	7.2
Sarcomatoid	2	3.6
Fuhrman grade		
2	9	16.1
3	36	64.3
4	11	19.6

pathological states of the nodes (TNM) are specified in the table. A GORE-TEX soft tissue patch (WL Gore & Associates, Inc; Newark, DE, USA) was used to repair the vena cava in 17 out of 56 (30%) patients, in order to correct the vena cava wall defects. This procedure was used after the resection of the renal ostium and the surrounding areas. Complete surgical resection was achieved in most of the patients, with surgical margins in 4 patients. There were 3 cases with caval invasion and 4 cases with positive surgical margins. Complete resection of the thrombus was achieved in all cases. ECC was used in 25 patients, 13 pT3c and 12 pT3b (at the level of the suprahepatic veins).

Perioperative complications that occurred within a period of 30 days postoperatively are summarized in Table 2. Complications occurred in 15 patients (27%); 8 were considered major complications and 7 were considered minor. There 2 perioperative deaths (3.5%) related to massive pulmonary embolism: 1 death occurred during surgery and the other occurred 2 days after surgery.

Table 2. Major and Minor Complications for the Patient Sample (N = 56). doi: 10.3834/uij.1944-5784.2010.08.18t2

Complication	n
Perioperative death	2
Major complications	8
Acute renal insufficiency	2
Dialysis	1
Temporal psychotic episode	1
Pericarditis	1
Transitory hemianopsia	1
Intestinal perforation	1
Hemorrhage (surgical)	1
Minor complications	7
Urinary tract infection	3
Pneumonia	2
Wound infection	2

Survival Rate and Prediction of Survival

Patients were followed after treatment for a median period of 37 months (range, 18-75 months). At the end of this period, 40 out of 56 (72%) patients had died due to their disease, 12 (21%) patients are still living, (2 of them are in progression), and 4 (7%) patients were lost to follow-up. The median time to death was 28.3 months (range, 13-56 months), and the median time to relapse was 19.3 months (range 4.5-35 months). The overall mean (SD) survival rate was 32% (7%) at 3 years and

Table 3a. Global Survival Rates After 3 Years: Mean, Standard Deviation, Odds Ratio, and Probability of Significance (Univariate Analysis).

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Variable	3-Year Rate (%)		OR	P
	Mean	SD		
Lymph nodes				
N+	13.1	8.0	2.02	< .029
N-	46.7	9.1		
Metastasis				
M+	21.15	10.0	2.53	< .007
M-	38.02	9.0		
Size				
> 8 cm	27.1	9.6	2.34	< .012
< 8 cm	46.5	11.6		
Number nodes				
N1	15.5	13.9	0.34	.345
N2	0	0		
Fuhrman Grade				
2	29.6	16.4	0.54	.673
3	28.2	8.7		
4	0	0		
Level of thrombus				
pT3b	19.4	7.1	0.26	.259
pT3c	18.2	11.6		
Extracorporeal circulation				
Yes	27.8	14.2	0.35	.321
No	29.4	12.3		

24% (6%) at 5 years. Excluding perioperative deaths, 67.8% of the patients died because of the disease.

The median tumor size was 11.3 cm (range, 6.1-25 cm). An 8 cm tumor size was calculated as the best cut-off (95% specificity and 95% sensibility) for predicting survival ($P < .0001$).

Table 3a contains the results of the univariate analysis (log-rank test). Three variables were significant prognostic indicators of 3-year survival: the presence of lymph node invasion ($P < .029$), the presence of metastasis at the time of the diagnosis ($P < .007$), and tumor size > 8 cm ($P < .012$). The number of nodes, Fuhrman grade, level of the thrombus, and the type of surgery were not significant prognostic factors.

Table 3b contains the results of the multivariate analysis. The results were similar to the univariate analysis. The 3 significant prognostic indicators of 3-year survival were: the size of the tumor > 8 cm ($P < .01$), the presence of metastasis ($P < .04$), and lymph node invasion ($P < .009$). Other prognostic variables

were not significant.

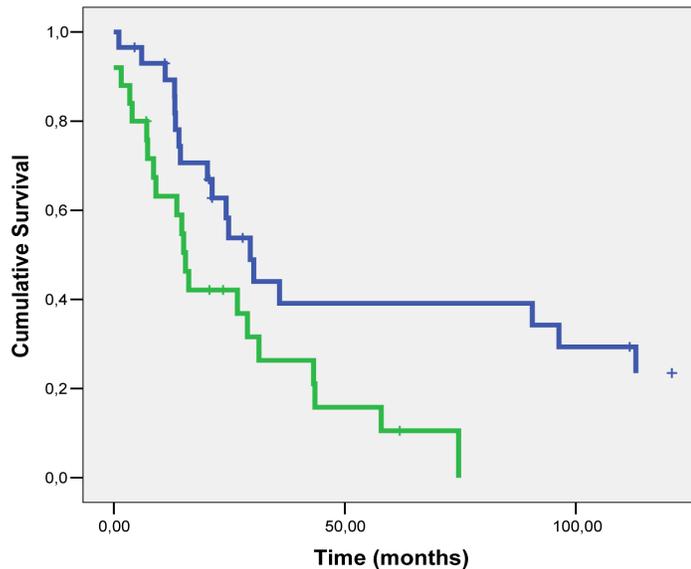
The best model for predicting survival was obtained by dividing the patients into 2 groups: 1) patients classified as N0M0, and 2) the remaining patients (N+M0, N0M+, N+M+). Patients without metastatic disease (N0M0) had a mean (SD) survival rate of 44% (10%) and 39% (10%) at 3 and 5 years, respectively. Patients who presented with some lesion had survival rates of 24% (9%) and 9% (6%) at 3 and 5 years, respectively (Figure 2).

Table 3b. Global Survival Rates After 3 Years: Odds Ratio (OR) and Probability of Significance (Multivariate Analysis). doi: 10.3834/uij.1944-5784.2010.08.18t3b

Variable	OR	P
Size > 8 cm	2.42	<.01
Metastasis +	2.02	<.04
Nodes +	2.47	<.009

Figure 2. Kaplan-Meier Curves Showing Overall Survival for Patients Without Metastatic Disease (N0M0) (green line) Versus Patients With Some Lesion (blue line).

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When analyzing the level of the thrombus, there was no significant difference in survival among patients classified as pT3b N0M0 and pT3c N0M0 ($P = .345$), or in patients classified as pT3b (N+M0, N0M+, N+M+) or pT3c (N+M0, N0M+, N+M+) ($P = .136$).

Tumor size was added into the predictive model and patients were stratified into 4 groups (N0M0 < 8 cm; N0M0 > 8 cm; others < 8 cm; others > 8 cm). The survival rate for those with N0M0 < 8 cm was significantly superior.

DISCUSSION

The standard treatment of RCC with tumor thrombus in the vena cava is nephrectomy with thrombectomy [3,14,15]. However, due to the very low incidence of this entity, it is very difficult to gather a long and homogeneous series of such patients. Multicenter studies are needed to confirm a standard surgical technique. Current treatment objectives include: survival increase, improved quality of life, prevention of pulmonary embolism caused by tumor mass, amelioration of symptoms, and reduction of tumor size [16-18].

An argument against radical surgical intervention is its high morbidity (up to 6% and 16% of the patients present with major and minor complications, respectively) and mortality rates (up to 8% perioperatively), which increase with higher

thrombus level [11,19]. The results of the present study showed an acceptable 3-year and 5-year mean survival rate for patients classified as N0M0 ($44\% \pm 10\%$ and $39\% \pm 10\%$, respectively), with a higher complication rate (27% for both minor and major complications) and low perioperative mortality rate (3.5%).

Tumor size was identified in this study as an independent factor relative to prognosis, with a statistically significant impact on survival rate. The survival rate for patients with tumors > 8 cm is lower when compared with that of patients with smaller tumors, confirming the prognostic value of tumor size that was found in a previous study [11]. The size of the tumor matched the median in the study by Wagner et al [20]. In this series, patients without distant lesions and with a tumor size < 8 cm had the best prognosis.

The results of the present study are consistent with previous reports [16] showing that the extension is not a significant predictor of survival. However, thrombus level is a significant factor that should be considered for surgical procedure planning [12,21]. Knowledge of whether or not the thrombus extends to the suprahepatic veins facilitates the development of a standard surgical strategy [15]. Tumor thrombus extension into the suprahepatic veins poses a particular challenge, because the access and control of the vena cava is more difficult in such cases [19].

When tumor thrombus does not extend into the suprahepatic veins (T3b1), tumor resection is carry out by clamping the vena cava. It has been recommended that the vena cava be exposed for the full length of the thrombus, because reducing the extent of cavotomy may increase the risk of pulmonary embolism during thrombus removal. A number of studies have shown, however, that a reduced cavotomy procedure may be successfully accomplished [22]. This approach has been criticized because of the neurologic and hematologic risks, and because of the risk that ECC may contribute to the tumor spread. The risk of neurological damage, as a consequence of hypothermia and cardio circulatory arrest, is time-dependent. It was thought that the safety period could be as long as 59 minutes, but recent studies have shown that it is, in fact, much shorter: 29 minutes at 15°C. When this time limit is exceeded, the probability of neurological damage rises almost exponentially. The use of ECC in any surgical procedure involves a 3% risk of coagulopathy [23]. The results of the present study indicate that the surgical approach, either with ECC or without ECC, is not a prognostic factor in the survival.

The mortality rate in the present study was low (3.5%), whereas the incidence of major surgical complications was higher

compared with other series (27%). In order to decrease the morbidity of this aggressive approach, different techniques have been proposed for thrombus below the atrium that avoid the use of ECC [24]. For the thrombus extending up to the atrium, modifications of the classical ECC with ministernotomy have been proposed and popularized with good results [25]. Jibiki et al [26] reported their experience with normothermic bypass. They had 1 intraoperative death due to pulmonary embolism and major complications in 11 out of 30 patients who survived the surgery. Tsuji et al [27] had a similar perioperative mortality and morbidity, with 2 intraoperative deaths out of 33 patients: 1 due to pulmonary embolism and another because of caval injury. They also reported a perioperative death due to pulmonary embolism. Katkooi et al [28] recently published their results with 3 perioperative deaths out of 54 patients with high thrombus level: 1 each due to cardiac arrhythmia, hepatic failure, and pulmonary failure. The surgical approach used by the present authors might be more aggressive than others, resulting in a higher complication rate. However, the approach has a lower mortality rate, which gives the authors more confidence in using it. All ECC approaches include some degree of hypothermia in order to decrease the neurological complications. Cardiovascular arrest is avoided in some of them, but there is no proven benefit aside from surgeon expertise and confidence.

The first studies concerning the surgical treatment of RCC with cava thrombus suggested that thrombus extension was a significant prognostic factor [29]. However, later studies on larger cohorts and with longer follow-up concluded that thrombus level is not a significant factor in the evaluation of prognosis [30]. Recent published studies [16,31] support this conclusion, but others still maintain that the tumor level is a prognostic factor [4]. Authors of a recent large series of 1192 patients suggested that TNM has to be changed for T3b above the renal vein [20]. In the present study, it had no significance on the survival.

Tumor ingrowths into the wall of the vena cava were present in 2 cases, which facilitated the removal of thrombus from vein walls in all other cases. This has been shown to be a negative prognostic factor because of the low probability of positive results from surgical intervention [29]. Unlike other studies, [11] no link to prognosis was detected in the present study.

One of the most significant factors for survival is the presence of lymph node invasion. The survival rate of patients with N+ is much lower than for patients with N-. In accordance with other investigators, the presence of metastasis in the present patients had an impact on the survival rate that was similar to

the impact of nodal involvement [11,30].

Another controversial issue in relation to radical surgical intervention is the presence of metastasis at the time of the initial diagnosis. The debate affects the type of surgical procedure eventually chosen and also impacts the results obtained in studies published on this subject. Some of these studies present results that are very pessimistic [32], whereas others seem considerably more encouraging [16].

The mean (SD) survival rates of patients without remote metastasis or lymph node involvement were 44% (10%) and 39% (10%) at 3 and 5 years, respectively. These figures confirm that thrombus extension into the vena cava has little influence on survival rate and is not a negative factor in terms of prognosis, as the multivariate analysis confirmed. These conclusions are in accordance with previous studies [11,33].

The present study was limited by the fact that the authors were from a single institution and the targeted disorder is uncommon. Although the total N is larger than that presented in other single-institution studies on this topic, it took 20 years to gather sufficient data and some minor changes in evaluation procedures and surgical techniques occurred during that time span. There is also some heterogeneity in secondary treatment procedures, and the patient population was not entirely homogeneous (eg, some patients had known metastasis with positive bone scans). Despite these limitations, the findings are consistent with clinical observations that aggressive surgical approaches to RCC are needed, even in the presence of venous involvement.

CONCLUSIONS

RCC with vena cava tumor thrombus has a poor prognosis. Surgical approaches are challenging and not exempt of complications. Nodal and distant metastases and tumor size are the most important prognostic factors for survival. Thrombus extension also has a clear impact in surgical planning and performance.

Conflict of Interest: none declared

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