ORIGINAL ARTICLE

Prognostic value of venous tumor thrombus in renal cell carcinoma


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Received 2 May 2011; accepted 5 June 2011
Available online 17 March 2012

Abstract
Objective: To evaluate the prognostic value of venous tumor thrombus in renal cell carcinoma.
Material and methods: A retrospective study of 167 patients with renal cell carcinoma and stage pT3 who underwent radical nephrectomy and extended lymphadenectomy from July 1969 to May 2008 was conducted. Patients with any kind of venous involvement were selected for the analysis (73 patients; 43.7%). The Kaplan–Meier survival curves and log-rank test for comparisons were used for the survival analysis. Multivariate analysis was done by Cox regression.
Results: Lymph node involvement was present in 30 patients (41.1%) and metastatic disease in 9 patients (12.3%). The most frequent histologic renal cell carcinoma subtype was 50 (68.5%) conventional carcinoma, followed by nondifferentiated in 11 (15.5%), and chromophobe in 9 (12.3%). High-grade tumors (Furhman 3–4) were present in 57% of the cases. Venous thrombus level extended to renal vein in 61 patients (83.6%), to inferior vena cava in 9 patients (12.3%) and to the cardiac right atrium in 3 cases (4.1%). The survival analysis showed worse survival in those patients with venous tumor thrombosis (p = 0.001) and with vein wall invasion (p = 0.0042), but not in function on the level of the thrombus (p = 0.12). The multivariate analysis identified the Furhman grade and venous tumor thrombosis as independent survival prognostic factors.
Conclusions: In our series, venous tumor thrombosis, together with the Furhman nuclear grade, is an independent survival prognostic factor. However, neither cephalic extension of the thrombus nor the invasion of the vein wall showed independent prognostic value.

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KEYWORDS
Renal cell carcinoma; Prognostic factors; Venous thrombosis

PALABRAS CLAVE
Cáncer de células renales; Factores pronósticos; Trombosis venosa

Análisis del valor pronóstico de la trombosis tumoral venosa en el adenocarcinoma renal

Resumen
Objetivo: Analizar el valor pronóstico de la trombosis tumoral venosa en el carcinoma de células renales (CCR).

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Material y métodos: Estudio retrospectivo de 167 pacientes con carcinoma de células renales (estadio pT3) intervenidos mediante nefrectomía radical y linfadenectomía (julio de 1969 a mayo de 2008). Para el análisis se seleccionaron los pacientes con afectación venosa (73 pacientes; 43,7%). Para el análisis de supervivencia, se utilizaron las curvas de Kaplan-Meyer y el test de log-rank. El análisis multivariante se realizó mediante regresión de Cox.

Resultados: En 30 pacientes (41,1%) existía afectación ganglionar, y en 9 pacientes (12,3%) enfermedad metastásica. El subtipo histológico más frecuente fue el carcinoma convencional en 50 pacientes (68,5%), seguido del indiferenciado en 11 pacientes (15,5%) y el cromófobo en 9 pacientes (12,3%). El 57% de los tumores fueron de alto grado (Furhman 3-4). El nivel de trombo tumoral se extendía hasta la vena renal en 61 pacientes (83,6%), hasta la vena cava infradiaphragmática en 9 pacientes (12,3%), y en 3 casos (4,1%) al atrió. El análisis de supervivencia mostró peor supervivencia en aquellos pacientes con trombosis tumoral venosa (p=0,001) y con invasión de la pared venosa (p=0,0042) pero no en función del nivel del trombo (p= 0,12). El análisis multivariante identificó el grado de Furhman y la trombosis tumoral venosa como factores pronósticos independientes de supervivencia.

Conclusiones: En nuestra serie la trombosis tumoral venosa es un factor pronóstico independiente de supervivencia, junto al grado nuclear de Furhman. Ni el nivel de extensión cefálica del trombo ni la invasión de la pared venosa mostraron valor pronóstico independiente.

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Introduction and aim
Renal cell carcinoma (RCC) represents 2—3% of all solid neoplasias in general, and 90% of malignant renal tumors, with an overall incidence in Spain of 4.1—4.5 cases per 100,000 inhabitants/year. In recent years, its incidence has increased at a rate of 2.5% per year. Despite being the third most prevalent urological tumor in men and the second in women, it remains the most lethal, with a cancer-specific mortality of about 40%.

The main prognostic factors for these tumors are anatomical, histological, clinical and molecular. One of their features is that venous invasion is often associated, spreading in 23% of the cases to the renal vein, in 7% of the inferior vena cava, and reaching the cardiac atrium in 1%. In previous TNM classifications for RCC, patients with impaired renal vein and inferior vena cava were grouped in the same stage (pT3b). However, after showing the independent prognostic value of the invasion of the vena cava compared with involvement of the renal vein only, in the last version of the TNM these two groups are separated.

In initial studies, a reduced survival associated with the extension of the thrombus was postulated, taking the level in the hepatic veins as a critical point. More recent studies argue that both the involvement of the vena cava and the venous wall invasion (pT3c stage of the 2002 TNM classification) modify the survival.

The influence that venous thrombus associated with this type of tumors can have on patient survival is something that has not yet been elucidated. The aim of this study is to evaluate whether the existence of venous tumor thrombus or its greater or lesser cephalic extension in patients with RCC implies a worse prognosis of cancer-specific survival.

Material and methods
An analytical retrospective study of 167 patients diagnosed with pathological pT3 stage RCC (regardless of lymph node or metastatic involvement) and undergoing surgery at the Hospital Universitario La Fe in Valencia was conducted between July 1969 and May 2008. Of these patients, 73 (43.7%) had venous involvement. All the patients in the series were treated by radical nephrectomy (associating thrombectomy in pT3b and pT3c) and locoregional lymphadenectomy. 15 patients (8.9%) were given immunotherapy or chemotherapy as adjuvant therapy (8 patients [4.7%] received immunotherapy with interferon alfa, 4 [2.39%] chemotherapy with 5-fluorouracil, and 3 [1.8%] both). There were 3 cases (1.8%) of venous thrombus in the supradiaphragmatic inferior vena cava, carrying out surgery by a multidisciplinary team of members from the Departments of Urology, Liver Surgery and Transplantation, and Cardiovascular Surgery.

In all the patients, computed tomography (CT), transesophageal ultrasound, or magnetic resonance imaging (MRI) was performed prior to the operation to identify the tumor and, in cases with venous involvement, to accurately delimit the cephalic extension of the thrombus. In 28 patients (16.7%), corresponding to the first years of the series, a cavography was also performed.

Staging was performed according to the 2002 TNM consensus classification criteria of the International Union Against Cancer. The nuclear grade was evaluated according to the system described by Furhman.

After the operation, we carried out the follow-up of the patients according to the oncological protocols of the Urology Department of the Hospital Universitario La Fe in Valencia, with four-monthly check-ups during the first year, half-yearly from the second year, and yearly from the fifth year. In each of these controls, general analysis with determination of ferritin, hepatorenal ultrasound, and thoracic-abdominal-pelvic CT were included. Biological progression was defined as local, regional recurrence, and/or presence of distant metastasis.

Since the aim of this study was to analyze the prognostic value of venous thrombus in RCC, we performed an analysis of cancer-specific survival according to pathological stage including the 167 patients. However, for the analysis
of the clinical features only the 73 patients (43.7%) who had some degree of venous involvement were selected. Within the group of 73 patients with venous invasion, 2 patients with pT4 stage were also included, because as well as presenting invasion beyond Gerota’s fascia, they had venous involvement. The variables studied were sex distribution, the existence of lymph node or metastatic disease at diagnosis (stages N and M), the size of the tumor, histology, Fuhrman’s differentiation grade, invasion of the vein wall by the tumor thrombus and its cephalic extension. All the surgical pieces were analyzed by the same pathologist (J.S.F.).

**Statistical analysis**

The cancer-specific survival was analyzed with the Kaplan–Meier method using the log-rank test for the comparison of 2 or more groups. The date of the surgical intervention was considered the starting date of the follow-up; and the date of the last check-up or the moment when the event (death) occurred was considered the final date. For the analysis of prognostic factors influencing cancer-specific survival, we selected multiple Cox proportional-hazards regression as the most appropriate statistical method to determine the association between a set of continuous or categorical predictor variables and a continuous response variable (survival). We identified the likelihood ratio and global Chi-square as statistical. For the variables in the model, we calculated parameter estimates, standard and statistical Wald errors. The effect measure of each variable was calculated by means of the hazard ratio (HR) or relative risk (RR). We considered a 0.05 statistical significance and estimates with a confidence interval of 95%.

**Results**

The group of patients with venous involvement consisted of 41 men (56.2%) and 32 women (43.8%), with a median age of 61 years (range 48–77). In 37 patients (50.7%), the tumor affectioned the right kidney, while in 36 patients (49.3%), it was located on the left one. The median tumor size was 10 cm (range 4–15). In 30 patients (41.1%), there was lymph node involvement at the time of surgery, and 9 patients (12.3%) had metastatic disease.

The most common histological subtype was clear cell carcinoma, identified in 50 patients (68.5%), followed by undifferentiated one in 11 patients (15.5%), and chromophobe one in 9 patients (12.3%). Only 3 tumors (4.1%) were papillar carcinoma. 57% of the tumors (42 patients) were high-grade (grade 3–4).

The tumor thrombus stretched to the renal vein in 61 patients (83.6%), to the infradiaphragmatic vena cava in 9 (12.3%), and in 3 cases (4.1%), to the heart atrium. Within the group of patients with involvement of the infradiaphragmatic vena cava, in 5 cases, the location was infrahepatic, in 2, it was hepatic, and in 2, suprahepatic.

Microscopic analysis showed invasion of the renal vein wall by the tumor in 4 patients (5.4%). In no case was there invasion of the wall of the vena cava. Sarcomatoid component was evident in 7 patients (9.6%), and perinephric fat invasion in 30 (41.1%).

The median follow-up of the patients with venous involvement was 13 months (range 1–222.6). Tumor recurrence was detected in 19 patients (26%), the median disease-free interval in patients with relapse being 8.5 months (1–180). In 10 patients (52.6%), recurrence was locoregional, while in 9 patients (47.4%), it was distant.

Intraoperative mortality was 2.69% (2 cases) due to massive pulmonary embolism at the time to mobilize the kidney. Other 2 patients (2.69%) died in the immediate postoperative because of surgical complications related to cavotomy and extracorporeal circulation.

The actuarial survival analysis according to the T classification of the 2002 TNM (Fig. 1), including the 167 patients with RCC and pT3–pT4 stage, showed worse survival in patients with venous tumor thrombus (p = 0.001), as shown in Table 1.

Fuhrman’s high grade tumors (grade 3–4) had a worse chance of survival compared to low grade ones (grade 1–2) with statistically significant differences (p = 0.02) (Fig. 2). Patients with microscopic invasion of the renal vein wall also showed a significantly worse survival compared to those who did not have it (Fig. 3). However, no statistically significant differences were found when assessing the likelihood of survival based on the level of the tumor thrombus (Fig. 4) (p = 0.12).

Multivariate analysis using Cox regression, entering all the variables described above, only identified Fuhrman’s grade, and venous tumor thrombus as variables with

| Table 1 | Probability of survival at 3, 5, and 10 years according to the 2002 TNM classification grouped by stages |
|---------|-------------------|-------------------|-------------------|
|         | 3 years | 5 years | 10 years |
| pT3a stage | 61.03% | 55.65% | 51.37% |
| pT3b stage | 44.74% | 31.55% | 27.70% |
| pT3c stage | 0% | 0% | 0% |
| pT4 stage | 0% | 0% | 0% |

![Figure 1](http://www.elsevier.es) Actuarial survival according to the 2002 TNM classification grouped by stages.
in which the degree of Fuhrman’s nuclear differentiation showed prognostic value for survival regardless of tumor stage.\textsuperscript{14,15} Venous invasion is characteristic of RCC, appearing as a tumor thrombus that, ascending from the renal vein, can reach the cardiac chamber. In these cases, the only treatment that seems to improve survival is radical nephrectomy together with thrombectomy.\textsuperscript{16} The latter increases the level of technical difficulty of surgery, and it increases the surgical risk for the patient. Hatcher et al., in their study, concluded that the prognosis of this type of tumors was not dependent on venous tumor thrombus,\textsuperscript{17} the optimal treatment being the one described by Robson in 1963, complete radical nephrectomy with thrombectomy. However, despite the fact that venous invasion is not correlated with the presence of lymph node or metastatic disease (neither Glazer and Novick nor Wagner et al. found differences in the presence of metastases in the group with involvement of the cava versus the one with renal vein involvement,\textsuperscript{9} or in patients with atrial versus those with the cava involvement\textsuperscript{11}), numerous works have been published demonstrating that venous involvement and tumor stage have an impact on survival.\textsuperscript{18–24} In our series, the results have followed this line, since the group of patients with RCC and venous tumor thrombus showed worse survival than those without.

The impact of the cephalic extension of the thrombus on survival has been a controversial issue. Initially, it was postulated that there was a reduction in survival probability associated with the extension of the thrombus, taking as a critical point the level of hepatic veins as a critical point (overall survival at 2 years and median survival of 80% and 61.4 months in the group with infrahepatic thrombus vs. 21%, and 22.9 months in the group with suprarepatic thrombus).\textsuperscript{10} However, recent studies pointed out that while the tumor would not spread to other organs or would not invade the vein wall, the thrombus level did not affect survival.\textsuperscript{5,11}

The group of Haferkamp et al., however, published opposite results. He concluded, after analyzing a series of 134 patients, that thrombus level I and II versus III and IV was an independent predictor.\textsuperscript{10} Other series, like that by Al Otaibi
et al., reported that the thrombus level influences the rate of recurrence but not overall survival.  

Recently, the results of the largest series of patients with RCC and venous involvement have been published (1192 patients from 13 European centers). As in the work by Molinazadeh and Libertino, we found no differences in survival according to the level of involvement of the cava, although we did between the involvement of renal vein or cava. In our series, coinciding with the literature, the cephalic extension of the thrombus has not shown a worse likelihood of cancer-specific survival. Thus, tumor stage and the presence of tumor thrombus have more influence on the probability of cancer-specific survival than the cephalic extension of the same.

Another aspect to consider is the microscopic involvement of the vein wall that ranges, in the published series, from 4.7 to 40.5%. Our series reflects a rate of 5.4%. Hatcher et al. published a series with patients with thrombus in the cava but without invasion of the wall of the same with a survival rate of 69% at 5 years, compared to 26% (p = 0.04) in those who did have invasion. However, the thrombus resection with cavotomy increased survival at 57%. Another recent study published by Bocardo et al. also reflected a higher rate of local recurrence (22.7% vs. 4.1%; p = 0.01) and distant (45% vs. 15%; p = 0.003) in patients with venous wall invasion. Nevertheless, other studies, such as the one by Ljungberg et al., have not shown the independent prognostic value of the venous wall invasion. In our study, the venous wall invasion did not show an independent prognostic value for cancer-specific survival either. It is probably due to the few patients with venous wall invasion there are in our series (only 4 patients) that limits the value of the prognostic analysis of the variable.

Regardless of the prognostic value of the venous involvement, perioperative mortality of these tumors is high, ranging from 3 to 10%. Our data are consistent with the literature, with a perioperative mortality of 5.38% (2 patients died intraoperatively due to massive pulmonary thromboembolism at the time to mobilize the kidney, and other 2 patients in the immediate postoperative). Bleeding, thromboembolism, and septicemia are factors to be controlled and prevented at all times. The comorbidity of the patients plays a crucial role, especially by increasing the risk of surgery. In many cases, in the case of T3c-T4 stages, collaboration in the operating room of a multidisciplinary team of experienced liver surgeons and cardiovascular surgeons is essential.

The main limitations of our study were the small number of patients with invasion of the vein wall, which does not make it possible to properly analyze the prognostic value of such variable. However, the analysis of the series of patients with tumor thrombus, regardless of their vein wall involvement, has shown that tumor thrombosis is an independent prognostic variable for cancer-specific survival, along with Furman’s nuclear grade. However, neither the level of cephalic thrombus extension nor vein wall invasion behaved as an independent prognostic value in our study.

### Conflict of interest

The authors declare that they have no conflict of interest.

### Acknowledgements

To Dr. J.V. Salom Fuster for his professionalism and dedication.

### References