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Evaluation of microvascular invasion as a prognostic factor in the progression of non-metastatic renal cancer

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Introduction The aim of this study was to describe the prognostic impact of microvascular invasion (MVI) in patients with non-metastatic renal cell cancer.

Material and methods We carried out a retrospective, descriptive and analytical study of patients with non-metastatic renal cell carcinoma who had undergone a radical or partial nephrectomy. Patients were divided according to the presence of MVI. In each group, clinical and pathological characteristics were evaluated. Metastasis-free and cancer-specific survival was evaluated by the Kaplan Meier method. The multivariate analysis was performed with Cox proportional method in order to predict risk factors of metastasis and cancer-specific mortality.

Results A total of 221 patients with a median of 40-month long follow-up were evaluated. Patients with MVI+ were 40 (18%) while those with MVI – were 181 (82%). In the univariate analysis, the presence of MVI had a strong correlation with symptomatic tumors (OR 3.56; p 0.0003), tumor size (OR 12.08; p <0.0001), nuclear grade (OR 6.99; p <0.0001), pathological stage (OR 35.8; p <0.0001), distance metastasis (OR 4.16; p 0.0001), and death by cancer (OR 4.7; p 0.0004). However, in the multivariate analysis it is not presented as an independent predictor of metastasis (HR 0.45; p 0.11) or cancer-specific mortality (HR 0.93; p 0.91).

Conclusions In our series, MVI is associated with unfavorable tumors characteristics. In spite of this, it does not seem to be an independent predictor for metastasis and death by non-metastatic renal cancer.

Key Words: cancer specific survival ‹› microvascular invasion ‹› prognostic ‹› renal cancer

INTRODUCTION

Renal cancer is a pathological entity with various presentation forms and clinical progression profiles. Although the tumor grade, TNM staging and histological type are recognized risk factors, patients with similar neoplasms may have different clinical presentation [1, 2, 3].

This data has motivated the search for new tumor characteristics that can influence the outcomes for patients. While microvascular invasion (MVI), defined as the presence of cancer cells at the microvasculature level or the presence of neoplastic emboli in those vessels, has demonstrated to be an important risk factor in other urological tumors (urothelial and testicular) [4, 5], the meaning of this in renal cancer has not yet been clearly defined. The results of previous initial experiences vary between absence of influence [6, 7, 8] to a strong prognostic impact on the progression of the above mentioned neoplasms [9, 10].

The objective of our study was to evaluate the prognostic value of microvascular invasion in patients with non-metastatic renal cell carcinoma.

MATERIAL AND METHODS

We carried out a retrospective, descriptive and analytical study of patients with renal cell carcinoma

who had undergone a radical or partial nephrectomy between January 1998 and July 2014. Localized or locally advanced renal cancer patients were included. Patients with compromised nodes, distant metastases or incomplete follow-up were excluded. From a total of 287 patients, 66 were excluded because of lymph node involvement and/or distant metastases at the time of diagnosis, and had incomplete or shorter than 12 months of follow-up. Preoperative imaging included ultrasound, computerized axial tomography, nuclear magnetic resonance and a thorax x-ray. The extracted surgical specimen was evaluated by a single anatomy pathologist (VB). The presence of MVI was defined as the microscopic detection of neoplastic cells that invaded the wall of the microvasculature or the presence of neoplastic emboli in those vessels. The patients were divided according to the presence or lack of MVI. In each group, clinical characteristics (age, gender, presence of clinical manifestations such as lumbar pain, hematuria and a palpable mass) and pathological characteristics (tumor diameter, histological type, pathological staging according to TNM) were evaluated. Histological grade, presence of coagulative necrosis, peripheral fat involvement, and vascular macroscopic involvement in the renal vein or inferior vena cava (IVC) were also noted. The follow-up included both thorax and abdomen computerized axial tomography and complete blood testing every 6 months for the first 3 years and annually thereafter.

Metastases-free survival (MFS) was defined as time (in months) from the date of diagnosis to the date of distance metastases and cancer-specific survival (CSS) was defined as time to the date the patient died of disease.

The statistical analysis was performed with the SPSS Statistics 17.0. A $p < 0.05$ value was considered significant in all tests carried out. The univariate analysis of variable categories was executed either by Chi-square method or Fischer test when most suitable; continuous variables were calculated according to Student test. The principal objectives of this research, metastases-free survival and cancer-specific survival were evaluated by the Kaplan Meier method and the differences between groups were evaluated with the Log-rank test. Multivariate analysis was performed using the Cox proportional method in order to predict risk factors of metastases and cancer-specific mortality.

RESULTS

The study population analysis included 221 patients of which 78 were female (35%) and 143 were male (65%). The median follow-up period was 40 months (range 6–144). The mean age was 61 years old (range 28–88); the predominant histological subtype was clear-cell carcinoma with 205 patients (93%), while 16 patients (7%) presented with non-clear cell carcinoma (papillary and chromophobe). A total of 41 (19%) patients presented with lymph node invasion or distant metastases, while 180 (81%) patients were metastases-free.

There were 40 (18%) patients with MVI+, while 181 (82%) patients did not present with MVI (82%).

We observed that patients with microvascular invasion presented a higher possibility for being symptomatic (p 0.0003), higher tumor diameter ($p < 0.0001$), high histological grade III–IV ($p < 0.0001$) and higher stage tumor ($p < 0.0001$).

The presence of distance metastases was shown in 25 (13.8%) patients without MVI and in 16 (40%) patients with MVI (OR 4.16; p 0.0001). When evaluating death from renal cancer, it was evidenced in 12 patients (6.6%) without MVI and in 10 patients (25%) with MVI (OR 4.7; p 0,0004) (Table 1).

Table 1. *Association of different variables and microvascular invasion (MVI)*

Variable	MVI(-) (n:181)	MVI(+) (n:40)	OR	p
Age (mean)	60.5	61		0.79
Gender			1.12	0.74
Male	118 (65.2%)	25 (62.5%)		
Female	63 (34.8%)	15 (37.5%)		
Clinical manifestations			3.56	0.0003
Incidental	119 (65.7%)	14 (35%)		
Symptomatic	62 (34.3%)	26 (65%)		
Surgery type			3	0.02
Open radical	120 (66.3%)	38 (95%)		
Open partial	40 (22.1%)	2 (5%)		
Laparoscopic radical	16 (8.8%)	0		
Laparoscopic partial	5 (2.8%)	0		
Tumor diameter (cm)	5.36	8.50	12.08	<0.0001
>7 cm	36 (19.9%)	30 (75%)		
Histological type			1.05	0.94
Clear-cell	168 (92.8%)	37 (92.5%)		
Non clear-cell	13 (7.2%)	3 (7.5%)		
Pathological stage			35.8	<0.0001
T1	138 (76.2%)	1 (2.5%)		
T2	29 (16%)	9 (22.5%)		
T3	14 (7.8%)	30 (75%)		
Histological grade			6.99	<0.0001
I–II	143 (79%)	14 (35%)		
III–IV	38 (21%)	26 (65%)		
Presence of necrosis	36 (20%)	36 (90%)	36	<0.0001
Presence of sarcomatous features	0	3 (7.5%)		0.002
Peripheral fat invasion	14 (7.7%)	30 (75%)	35.8	<0.0001
Renal vein invasion	0	7 (17.5%)		<0.0001

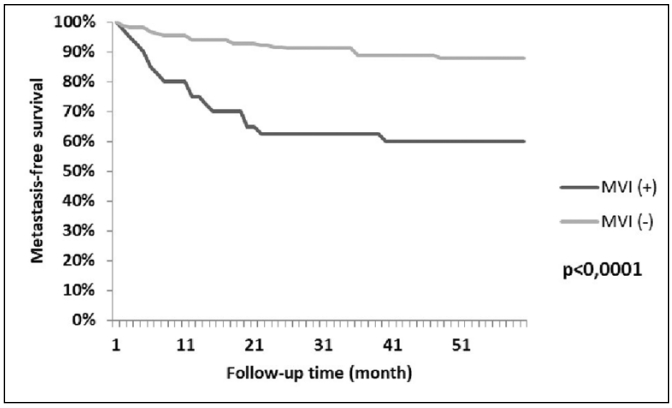

Figure 1. *Metastases-free survival in patients with M0 renal cell carcinoma with vs without microvascular invasion.*

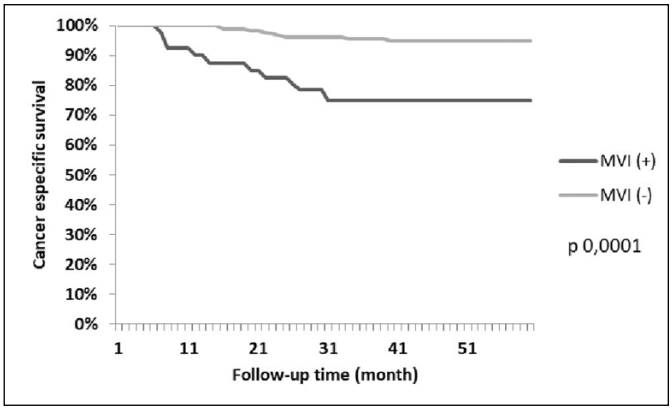

Figure 2. *Cancer-specific survival in patients with renal cell carcinoma with vs without microvascular invasion.*

Distant metastases-free survival at 5 years was 60% for the MVI+ group and 87.8% for the MVI- group (log-Rank test <0.0001) (Figure 1). Cancer-specific survival at 5 years was 75% and 95% for the MVI+ group and MVI-group, respectively. These differences were also statistically significant (log-Rank test 0.0001) (Figure 2).

When performing the multivariate analysis, we demonstrated that independent predictors for distant metastases include symptomatic tumors (p 0.02), tumor staging ≥pT3 (p 0.04) and tumor size (p 0.01).

The multivariate analysis using the Cox proportional method in order to determine risk factors for cancer-specific mortality demonstrated that a tumor size 7 cm or higher (p 0.02) and presence of symptomatic tumors (p 0.05) are independent predictors for death related to renal cancer in this group of patients (Table 2). Microvascular invasion was not present as an independent predictor for metastases or cancer-specific mortality.

DISCUSSION

Renal cell carcinoma (RCC) has an unpredictable natural history and presents with a wide spectrum of possibilities in its evolution [8, 11, 12, 13]. For this reason, the need to establish predictive prognostic elements is essential in order to identify patients with high risk of recurrence or progression. The tumor staging (TNM), size of the primary tumor, nuclear grade and the presence of sarcomatoid elements have been correlated with the prognosis of renal cancer after nephrectomy [14–17].

In the last few years, the importance of MVI as a prognostic factor in renal cell carcinoma has been reason for debate; this has emerged due to the importance of this has proven when defining aggressive tumors in various urological or non-urological malignancies. However, the evidence is currently conflicting when correlating MVI as a predictive factor for metastases and death in renal cancer (Table 3).

Sorbellini et al., examined patients with clear cell carcinomas and found that only the nuclear grade of Fuhram and MVI remained as independent predictors for recurrence.

Lang et al., demonstrated that MVI is associated with a lower cancer-specific survival in the multivariate analysis. This research represents the greatest follow-up (183 months) and it was carried out only on patients with non-metastatic renal cell carcinoma; nevertheless, MVI did not demonstrate to have influence in MFS.

Kroeger et al., correlated MVI with bad prognostic factors in renal cancer and was demonstrated as an independent predictor of metastasis. However, it was not a strong predictor for cancer-specific mortality in the multivariate analysis (p 0.79).

In a recent study, Katz et al., evaluated patients with non-metastatic renal cell carcinoma and demonstrated a strong relation between MVI and adverse tumor characteristics in renal carcinoma in the univariate analysis; nonetheless, there was no statistical significance in the multivariate analysis for the three primary objectives outlined: MFS, CSS and total survival (TS). Only the pathological staging and tumor size remained as independent factors. In addition, they did not objectify correlations when analyzing subgroups of patients according to their stage (T1–T2), nor did they evaluate histological subtypes (clear cells).

In the last 5 years, new research has emerged in relation to this topic. Bedke et al., studied 201/747 (26.9%) patients with MVI and showed that it presented as a prognostic factor for poor results in RCC. The authors recommended a stricter follow-up due to the disease progression and referred this group of patients to adjuvant treatment trials [26].

Table 2. *Independent predictors for distance metastasis and renal cancer mortality in non-metastatic patients*

Variable	Distance metastases		Cancer-specific mortality	
	p	OR	p	HR
Age (60 years old)	0.96	1.02	0.52	1.33 (0.55–3.23)
Clinical presentation? (symptomatic)	0.04	3.67	0.08	3.07 (0.85–11.15)
Size (7 cm)	0.02	4.50	0.01	4.68 (1.32–16.56)
Nuclear grade (F 3–4)	0.84	0.88	0.86	1.08 (0.42–2.80)
Microvascular invasion	0.94	1.04	0.62	1.29 (0.46–3.64)
Stage (≥pT3)	0.03	4.29	0.04	3.70 (1.05–12.87)

Table 3. *Previous studies evaluating the impact of microvascular invasion in survival rate*

Study (year)	n	Primary objective	p
Van Poppel (1997) [1]	180	MFS	<0.0001
Sevinec (2000) [18]	41	MFS	NS
Ishimura (2004) [19]	171	MFS – CSS	NS both
Yildiz (2004) [20]	48	CSS	0.003
Lang (2004) [21]	255	MFS – CSS – TS	NS; 0.001; 0.0015
Sorbellini (2005) [22]	833	MFS	0.012
Dall`Oglio (2007) [23]	230	MFS – CSS	0.015; 0.002
Kroeger (2011) [24]	2596	MFS – CSS	0.05; NS
Katz (2011) [25]	841	MFS – CSS – TS	All NS
Our series	221	MFS – CSS	NS

MFS – metastes-free survival; CSS – cancer-specific survival; TS – total survival

However, previously in 2013, a Mayo Clinic study assessed 119/1433 patients with MVI and observed an association with unfavorable prognostic characteristics, risk of metastasis and death from cancer in the univariate analysis, but in the multivariate analysis does not remain significant after being controlled with other prognostic variables established [27].

These findings have clear similarity with our series, where we found that MVI was strongly associated with symptomatic tumors, tumor size, pathological staging and histological grade. Nevertheless, it was not revealed as an independent predictor for metastasis or death by cancer.

Finally, the only metaanalysis and systematic review with respect to the topic arises in 2015 and is aimed at an association of MVI with unfavorable pathological characteristics and statistical significance in CSS but it was not when evaluating OS [28].

This present research had some limitations. First of all, the microscopic visual inspection was the method with which MVI was determined, while other studies have used immunohistochemistry in their diagnosis (antibodies such as anti-factor VII or anti-CD34) [21]. It should be pointed out that the routine use of these methods would be justified only if clear evidence in favor of MVI as a prognostic factor existed. Second of all, our series only analyzed non-metastatic renal tumors. The question lies in relation to the effect that MVI could have in patients with metastasis from renal carcinoma. In conclusion, our follow-up was limited to 43 months and it may be possible that for a longer time period, MVI could demonstrate higher statistical significance in multivariate analysis.

Based on our data and the conflicting evidence in the literature, MVI seems to have a limited clinical advantage for identifying patients with high-risk of recurrence and death by cancer.

CONCLUSIONS

In our series, MVI was associated with unfavorable tumor characteristics. However, MVI does not seem to be an independent predictor for metastases and death in patients with non-metastatic renal cancer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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