

SIGNIFICANCE OF INTRATUMORAL MICROSCOPIC VASCULAR INVASION IN PATIENTS WITH RENAL CELL CARCINOMA

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ABSTRACT

Objective: To study the presence of intratumoral microvascular invasion and the follow-up of patients submitted to nephrectomy due to kidney cancer.

Materials and Methods: From January/88 to July/99, 115 patients underwent surgical treatment for renal cell carcinoma. A single pathologist revised all the pathological specimens, looking for neoplastic cells in the tumor microvasculature.

Results: Tumor size ranged from 0.5 - 19.5 cm (5.9 ± 2.9). Three tumors measured up to 4 cm (7%), 9 (21%) between 4.1 - 7 cm, 8 (42%) between 7.1 -10 cm and 6 (50%) were larger than 10 cm ($p < 0.001$). Microvascular invasion was observed in 23% of the cases, being 7% in incidentally diagnosed tumors and 39% in symptomatic tumors ($p < 0.001$). By the end of the study, there were 5 cases of disease progression and 8 deaths, when the microvascular invasion was present. In the absence of invasion, only one progression and two deaths were observed.

Conclusion: In this series, the presence of microvascular invasion was associated with an important increase in morbidity and mortality. This finding represents another prognostic factor in the survival rates of renal cell carcinoma patients.

Key words: kidney; kidney neoplasms; carcinoma; renal cell; microvascular invasion; prognosis

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INTRODUCTION

Renal cell carcinoma (RCC) is the third most frequent genitourinary neoplasm, and represents 85% of all renal parenchymal cancers (1). Due to its variable biological behavior, it provokes constant research interest, and researchers try to identify prognostic factors and to define groups of patients most probable to develop disease recurrence.

There are well-known pathologic prognostic factors for the progression of RCC, such as nuclear grade (2,3), tumor size (4-6), stage (7-9) and presence of sarcomatous degeneration (10,11). Some studies have shown that the presence of neoplastic cells in the intratumoral microcirculation is an important independent factor in the recurrence of localized RCC (12-14). Angiogenic factors confer hypervascular

characteristics to RCC (15,16); however, the significance of macrovascular invasion is, up to the present time, still controversial, thus raising important discussion (17-19).

Our objective is to study the significance of intratumoral microscopic vascular invasion in patients who underwent surgical treatment for RCC.

MATERIAL AND METHODS

From January 1988 to July 1999, 115 patients with RCC, 86 men (75%) and 29 women (25%) with mean age of 59.1 years (9-87), underwent nephrectomies, being 96 radical (83.5%) and 19 nephron sparing (16.5%). The surgeries were performed by the same group of surgeons. Data were evaluated retrospectively. The preoperative evaluation included ul-

Table 1 - Correlation between tumor size and intratumoral microvascular invasion.

Tumor Size (cm)	Microvascular Invasion		Total
	Present (%)	Absent (%)	
0.5 a 4	3* (7)	38 (93)	41
4.1 a 7	9 (21)	34 (79)	43
7.1 a 10	8 (42)	11 (58)	19
> 10	6 (50)	6 (50)	12
Total	26	89	115

χ^2 for linear tendency = 11.45 $p < 0.001$; * tumors with 4 cm of diameter

trasonography (US), computed tomography (CT), magnetic resonance, intravenous urography and chest film. The post-operative follow-up varied from 2 to 138 months (median: 33 months), and it was performed every three months during the first year, every six months from the second to the fifth year, and once a year after that. It included chest film, blood tests, US and/or abdominal CT.

All pathologic samples (slides and fragments included in paraffin) were revised by a single pathologist under light microscope. Presence of intratumoral microvascular invasion was evaluated and defined as positive when there were neoplastic cells in the endothelium and/or in the intratumoral microcirculation tunica media. Presence of microvascular invasion was correlated to the disease stage, tumor size, and diagnosis type (incidental or symptomatic). Recurrence and mortality were also analysed.

The statistical analysis was performed by using the Kaplan-Meier and Log Rank Tests, as well as the Chi-square, with a p value < 0.05 considered statistically significant.

RESULTS

The distribution of the 115 patients according to the tumor stage was as follows: 75 patients with PT1 tumors, 16 PT2, 16 PT3, 8 PT4. Tumor size varied from 0.5 to 19.5 cm (mean: 5.9 ± 2.9 cm).

Intratumoral microvascular invasion occurred in 26 patients (23%), and it was only observed in tumors larger than 4 cm, as presented in Table-1. According to the disease stage, there was microvascular invasion in 5 PT1 tumors, 3 PT2, 11 PT3 e 7 PT4.

Dividing the RCC by incidental and symptomatic diagnosis, we verified that 7% of the incidental tumors had positive microvascular invasion, while 39% of the symptomatic tumors had microvascular invasion.

By the end of the study (Table-2) and with a median follow-up of 33 months, 4 patients out of 89 without microvascular invasion were lost during follow-up. In addition, only one presented recurrence, and 2 died of the disease. From 26 patients with microvascular invasion, 5 presented disease progression and 8 died of cancer.

Table 2 - Status by the end of the study, according to intratumoral microvascular invasion.

Status by the End of the Study	Microvascular Invasion		Total
	Absent	Present	
Alive, without evidence of the disease	77	13	90
Alive, with disease progression	1	5	6
Death of kidney cancer	2	8	10
Death of other cause (not related to the disease)	5	-	5
Lost in the follow-up	4	-	4
Total	89	26	115

MICROSCOPIC VASCULAR INVASION IN RCC

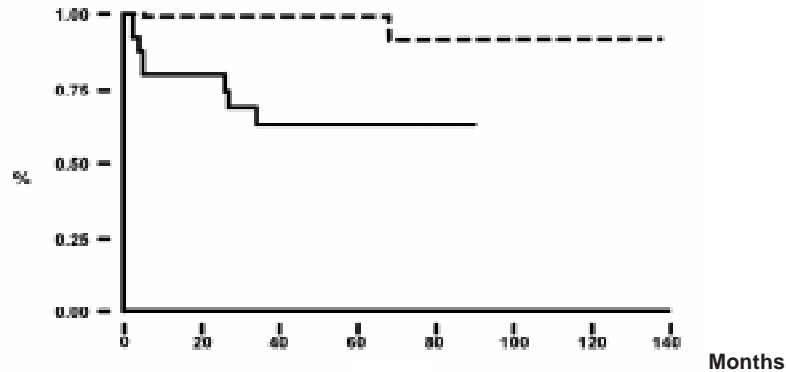


Figure 1 - Cancer-specific survival curves. Log-rank test: $\chi^2 = 21.65$, $p < 0.001$; Intratumoral microvascular invasion: absent(---), present (—).

The cancer survival curves are shown on Figures-1 e 2, respectively.

DISCUSSION

The RCC is known for having an unpredictable development (1,20). Presently, with the advent of radiologic techniques such as the US and the CT, there has been an increase in the detection of small incidental tumors, which have better prognosis for being confined to the kidney (21-25).

However, it is not rare to observe that individuals treated for tumors in similar pathologic stages have quite distinct clinical behaviours. Certainly, the known pathologic factors known provide prognostic information after the surgery, being the hematogenic dissemination an important mechanism of RCC extention and metastasis (12).

It is believed that the intratumoral microvascular invasion is a differentiating data in tumor biological behavior (14), and it is correlated to a worse prognosis (12-14). PT1 tumors do not present intratumoral microvascular invasion; however, in PT3-4 tumors the microvascular invasion varies from 50 to 64% (12,13). Nuclear grade I tumors did not present microvascular invasion, but it occurs in 26% of grade II, 35% of grade III, 60% of grade IV (14). According to tumor size, it has been observed that neoplasms from 1 to 3 cm present 7% of microvascular invasion. The incidence of microvascular invasion increases with size: from 4 to 6 cm, 26%; from 7 to 9 cm, 36%; from 10 to 17 cm, 55%, respectively (14).

In our casuistics, 3 (7%) out of the 41 cases of tumors ≤ 4 cm, presented microvascular invasion and all of them had 4 cm of diameter. On the other

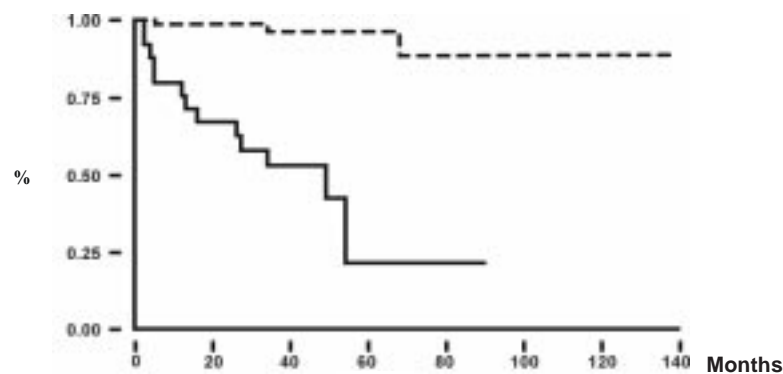


Figure 2 - Disease-free survival curves. Log-rank test: $\chi^2 = 37.74$, $p < 0.001$; Intratumoral microvascular invasion: absent(---), present (—).

hand, Van Poppel et al. (12) observed 7% of microvascular invasion in tumors ranging from 1 to 3 cm. In our study, only 4 patients (7%) with incidental tumors presented microvascular invasion, while 22 (39%) symptomatic patients had microvascular invasion (Figure-1) ($p < 0.001$). This finding was not observed in the reviewed literature.

Intratumoral microvascular invasion is a predictive factor for poor prognosis (13). Van Poppel et al. (12) described disease progression in 39% of the tumors with intratumoral microvascular invasion. This was observed in 6% of the tumors without invasion. Mrstik et al. (14) described a 5-year survival of 35% in patients with microvascular invasion, and 90% in patients with invasion.

Paradoxically, renal vein invasion does not confer worse prognosis (7,19); however, intratumoral microvascular invasion is an important indicator of the malignant potential of the renal tumor (12).

During the period of the study, despite the relatively short follow-up (median of 33 months), we observed that in the groups of patients without microvascular invasion, one presented disease progression and 2 died, while in the group of patients with microvascular invasion, 5 had the progression and 8 died (Table-2). There was statistical significance in the survival curve specific for cancer and in survival free of the disease, with a clear association with recurrence and mortality.

This study only compared the intratumoral microvascular invasion as a unique independent prognosis factor, which was associated with a worse development. However, this tumor characteristic was considered the most important prognostic factor when submitted to multivariate analysis (12). Our study has shown that the presence of intratumoral microvascular invasion is a relevant prognostic factor; therefore, this information should routinely be included in the pathological report.

In conclusion, we observed that the presence of intratumoral microvascular invasion was more frequent in symptomatic tumors and in the larger ones, and is associated to a higher risk of RCC progression and death from the disease.

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