Prognostic value of microvascular invasion in renal cell carcinoma

Nguyen Huy Hoang[1, 2], Do Ngoc Son[2]

1. Hanoi Medical University, 2. Viet Duc University Hospital

Corresponding author:
Nguyen Huy Hoang
Viet Duc University Hospital
40 Trang Thi, Hoan Kiem, Ha Noi
Mobile: +(84) 977135086
Email: hoangnt35@gmail.com

Received date: 14/8/2024
Accepted date: 26/9/2024
Published date: 30/9/2024

Abstract

Introduction: Renal cell carcinoma (RCC) is the most common type of renal cancer. Nowadays, most tumors are discovered incidentally at an early stage, thus changing the overall prognosis of the disease. Histological prognostic factors have been accepted as major prognostic factors for decades however, the predictive value of microvascular invasion (MVI) remains debatable. We performed this study to evaluate the prognostic role of MVI in RCC.

Patients and Methods: A cohort study, including 191 RCC patients undergoing laparoscopic retroperitoneal radical nephrectomy from January 2013 to April 2021 at Viet Duc University Hospita.

Results: the rate of microvascular invasion was 18/191 patients (9.4%), no microvascular invasion was 90.6%. The 3-5 year RFS of the MVI – and MVI + groups were 98.76 % and 81.45 %, respectively. The 3-5-year OS of the MVI – and MVI + groups were 99.28 % and 86.27 %, respectively; difference of $p < 0.05$. The MVI + group had an average tumor size of 60.8 mm, which was significantly larger than the MVI – group (52.8 mm) with p=0.038. In addition, MVI + is also associated with more unfavorable pathological features such as higher sRCC (sarcomatoid RCC) rate and higher Fuhrman grade ($p<0.05$).

Conclusion: The microvascular invasion group showed worse overall survival, and recurrence-metastasis results than the non-microvascular invasion group and was associated with more adverse factors. We suggest that MVI should be considered as an independent prognostic factor in renal cell carcinoma.

Keywords: renal cell carcinoma, microvascular invasion, recurrence-free survival

Introduction

While macroscopic tumor invasion into major vessels has been recognized as a prognostic factor in the TNM system, microvascular invasion (MVI) has not been recognized. MVI is defined by the presence of tumor cells in small blood vessels that cannot be detected macroscopically. Although there is still controversy regarding the role and

prognostic value of MVI in RCC, several recent studies have shown that MVI is strongly associated with adverse outcomes.[1] Other studies have also shown 2-3 times increased risk of recurrence, metastasis, and death from RCC in RCC patients with MVI.[2] However, there are still some issues that need to be clarified, especially the definition of "microvascular" and the overlap in determining the boundary between microvascular invasion and main vascular invasion. Routine assessment of MVI in kidney specimens is a widely used clinical practice in most pathology centers in Europe and the US, however in Vietnam assessment of MVI in patient specimens is only performed in major pathology centers. We performed this study to evaluate the prognostic role of MVI factors for RCC patients.

Patients and methods

Included 191 patients who met the following criteria.

Selection criteria:

Patients undergo retroperitoneal laparoscopic radical nephrectomy (RN) based on the following criteria: Preoperative diagnosis of the tumor at the local stage (T1-2-3a). The opposite kidney function is still good.

Pathology results confirmed renal cell carcinoma.

Exclusion criteria:

Patients with other cancers before surgery.

Incomplete medical records

Patients were not followed up

Methods

Research design: descriptive study with longitudinal follow-up, retrospective data collection.

Research location: at Viet Duc University Hospital

Research time: from February 2013 to April 2022, in which the patient's surgery was from January 2013 to April 2021, and the patient was scheduled for a follow-up in April 2022.

Sampling method: convenient sampling.

Research variables: general characteristics of patients: age, gender, TNM stage, tumor size, Pathological characteristics: MVI, Fuhrman grade, histological type. At the end of the study, determine whether the patients are alive or have died, determine the time of death, cause of death (due to cancer or not due to cancer); whether there is recurrence-metastasis or not (time of recurrence-metastasis calculated from after surgery, location, number of recurrence-metastasis, treatment method), results of overall survival (OS), and recurrence-free survival (RFS). Determine the association between OS, RFS, and other pathological features with MVI.

Data collection method: make a list of study patients and fill in study variables in a pre-built medical record form. Patients were scheduled for follow-up at the end of the study by telephone or letter. For deceased patients, information was collected from the patient's family.

Data analysis: using SPSS software. Descriptive statistical analysis was used to describe patient characteristics (frequency and percentage for qualitative variables; mean and standard deviation for quantitative variables). Kaplan-Meier survival analysis was used to evaluate the survival rate of patients after surgery, and the log-rank test to compare survival rates between subgroups of interest. The difference is considered significant when $p < 0.05$.

Research ethics: Written informed consent was obtained from all patients and their family members before participation. The study was approved by our research committee, Viet Duc University Hospital, Hanoi, Vietnam, and this was approved by Hanoi Medical University Institutional Ethical Review Board (No NCS07/ BB-HĐĐĐ) date February 14, 2019

Result

There were 18 patients (9.4%) whose tumors showed microvascular invasion on pathology. The majority of patients do not have microvascular invasion, accounting for 90.6%.

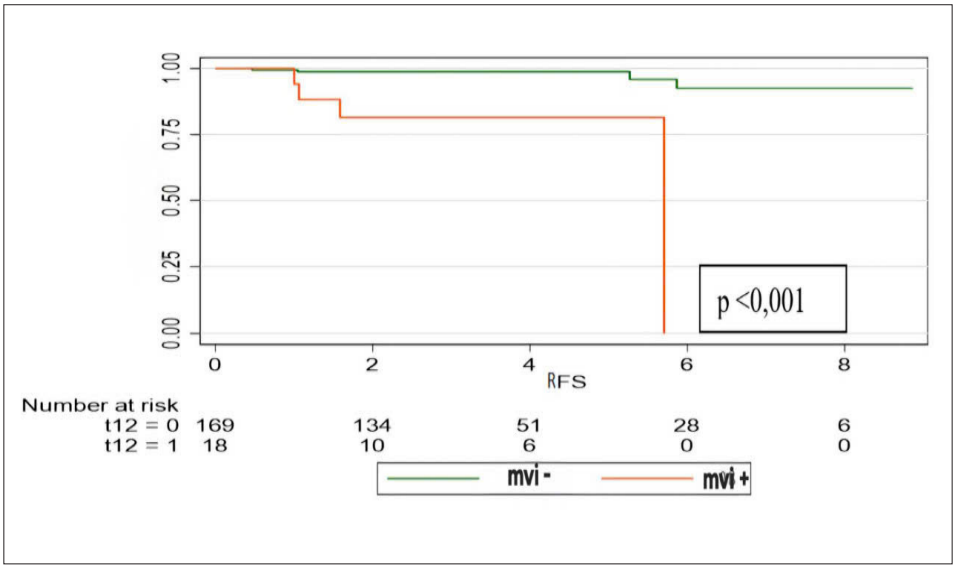

Figure 1. Recurrence-free survival time according to microvascular invasion

The 1-year RFS of the MVI – and MVI + groups were: 99.4% and 100% with no difference. The 3-year RFS and 5-year RFS of the MVI – and MVI + groups were 98.76 % and 81.45 %, respectively. The MVI + group RFS was significantly lower than the MVI – group at 3 and 5 years with $p < 0.001$.

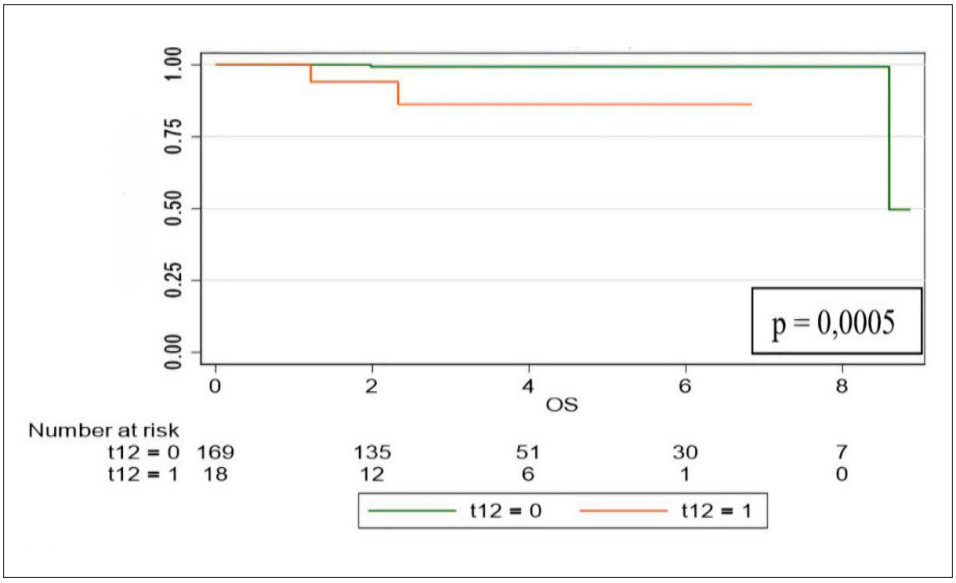

Figure 2. Overall survival according to microvascular invasion

The 1-year OS of the MVI – and MVI + groups were both: 100%, with no difference. The 3-year OS and 5-year OS of the MVI – and MVI + groups were both 99.28 % and 86.27%, respectively; difference with $p = 0.0005$.

Table 1. Association between Microvascular Invasion and patient characteristics and surgical outcomes

		MVI			
		MVI -	MVI +	p	N (%)
Number of patients (%)		173 (90,6)	18 (9,4)		191
Tumor size (mm)		52,8±16,7	60,8±19	0,038	53,5±17
Pathology type (%)	ccRCC	116/124 (93,5)	8/124 (6,5)		124 (100)
	chRCC	44/49 (89,9)	5/49 (10,2)		49 (100)
	pRCC	9/11 (81,8)	2/11 (18,2)	0,017	11 (100)
	sRCC	2/4 (50)	2/4 (50)		4 (100)
	Rarely type	2/3 (66,7)	1/3 (33,3)		3 (100)
Fuhrman %	1	13/13 (100)	0/13 (0)		13 (100)
	2	83/86 (96,5)	3/86 (3,5)		86 (100)
	3	26/33 (78,8)	7/33 (21,2)	0,002	33 (100)
	4	4/6 (66,7)	2/6 (33,3)		6 (100)
	Total	126 (100)	12 (100)		138 (100)
Stage	1	127/134 (94,8)	7/134 (5,2)		134 (100)
	2	25/30 (83,3)	5/30 (16,7)	0,006	30 (100)
	3	21/27 (77,8)	6/27 (22,2)		27 (100)
Average follow-up time (month)		43±25	34,9±20,8		42,3±24,7
PSM (port site metastasis)		0 (0)	2 (11,1)		2
Local recurrence		2 (1,1)	1 (5,5)		3
Distant metastases		2 (1,1)	1(5,5)		3
Mortality n (%)					4 (2,1)
	Cancer-specific	2(1,1)	2(11,1)		4 (2,1)
	Unrelated	0	0		0
OS/CSS 5 year %		99,28%	86,27%	0,0005	94,04%
RFS 5-year %		98,76%	81,45%	<0,001	92,7%

MVI + was highest in stage 3 (p=0.006). Tumor size was significantly larger in the MVI + group with p= 0.038. The Fuhrman 3- 4 group had a higher rate of MVI + than the Fuhrman 1-2 group (p=0.002). Among histological types, sRCC has a higher rate of MVI + than other types (p = 0.017). RFS 5-years and OS 5-years were significantly lower in the MVI+ group, with p < 0.001 and p= 0.0005.

Discussion

The relationship between microscopic pathological features of the tumor and survival outcomes receives special attention because today the majority of RCC is diagnosed in the non-metastatic stage.[3] Gross tumor invasion into the renal vein and vena cava has long been recognized as a prognostic factor,[4] in contrast, MVI is not recognized as a prognostic factor in the 2018 revised TNM system. However, some reports have shown an adverse prognosis of MVI.[2,3]

JR Rey showed that localized tumors undergoing radical nephrectomy, besides T-stage and Fuhrman, MVI is a variable with good predictive value for RFS and CSS.[5] This emphasizes the importance of MVI in clinical practice and confirms the independent association of MVI with metastasis (N+ and/or M+).[1] Huang H's study showed a 2-3-time increased risk of recurrence, metastasis, and death from RCC with MVI+.[2]

In Jens Bedke's study, MVI was evaluated systematically and routinely at pathology centers in Europe. Results showed: that MVI was more common in ccRCC than in non-ccRCC (p=0.001) and correlated with higher T stage, higher Fuhrman grade, presence of sarcomatoid features, lymph nodes, and metastasis (p < 0.001). There was no gender difference in MVI (p = 0.280). The authors found that MVI was a variable that could independently predict invasion and metastasis (p = 0.007). Kaplan -Meier analysis showed that CSS was significantly worse for MVI+ in the overall cohort and the localized tumor group, but for metastatic RCC, MVI was not significantly associated with CSS (p = 0.314).[1]

Kroeger N reported that MVI is strongly correlated with adverse pathological features. MVI+ is associated with higher age at disease (p = 0.001), larger tumor diameter (p < 0.0001), higher Fuhrman grade (p < 0.0001), more advanced pT (p < 0 .0001), presence of lymph nodes and distant metastases (p < 0.0001). In particular, in the absence of metastasis, survival was worse in the MVI + group than in the MVI - group (p < 0.0001; HR 2.38). Univariate analysis demonstrated a strong correlation between MVI and CSS (p < 0.0001). According to the author, MVI is an independent predictor of recurrence and metastasis, even in the early stages.[3] Research by Santiago-Agredano B, SY Kwon, H Huang, and RG Bengió also showed similar results.[6,7,2,8] This result helps doctors predict more accurately, and MVI + patients need to be monitored more closely.[7]

Takeshi Ishimura studied among MVI + patients, 24.7% of patients recurrence, and 17.1% of patients died from cancer, while in MVI - patients only 6.9% of patients recurrence and 3.5% of patients died of cancer.[9] MF Dall'Oglio (2007): Recurs in 46% of MVI+, while MVI - only 6%.[10] MVI + was significantly associated with age, tumor size, stage, tumor grade, and sarcomatoid characteristics. RFS in MVI + was significantly lower than in MVI -. From there, the author believes that MVI is an independent predictor of recurrence and death in pT1 or pT2 patients.[9,10]

In our study, there were 18 patients (9.4%) MVI +, MVI - accounting for the majority with 90.6%. Our MVI + rate is lower than that of most foreign authors (table 2), which was explained by the fact that MVI assessment may not have been routinely performed in pathology and most of the patients in the early stages, therefore, the MVI + ratio is lower

Table 2. Percentage of microvascular invasion according to studies

Study	MVI (%)	
	MVI +	MVI -
H Huang (2015)[2]	14,4	85,6
Nils Kroeger (2012)[3]	20,0	80,0
B Santiago-Agredano (2013)[6]	33,2	66,8
RG Bengió (2018)[8]	18,0	82,0
Jens Bedke[1]	27,0	73,0
Nguyen Huy Hoang (2023)	9,4	90,6

Research shows that stage 3 has a higher rate of patients with microvascular invasive tumors (22.2%) than stage 2 (16.7%) and stage 1 (5.2%). %) (table1), the difference with p=0.006. At the same time, MVI is closely associated with unfavorable characteristics such as larger tumor size (p=0.038), and higher Fuhrman grade (p=0.002). Among histological types, sRCC accounts for a higher proportion than other types in the microvascular invasion group (p=0.017), 1/1 collecting duct RCC microvascular invasion, which was also completely understandable because sRCC and collecting duct RCC are highly malignant. Our results were also consistent with the comments of Jens Bedke[1], Kroeger N[3] and other authors pointed out that tumor cells infiltrating microvasculature are one of the highly malignant cells in RCC.[1]

In our study (Figure 1 and 2), the 5-year RFS and 5-year OS of the MVI + group were significantly lower than the MVI – group (p=<0.001 and p=0.0005). The results in Table 2 also show that the rate of PSM occurrence, local recurrence, metastasis, and death in the MVI + group is much higher than that in the MVI - group. Our results are similar to those of Huang H[2], JR Rey[5], Kroeger N[3], and Takeshi Ishimura[9]. Therefore, we also agree with the viewpoint of RG Bengió[8] suggested that MVI should be considered among the independent prognostic factors for recurrence and mortality in RCC.

Conclusion

Our research shows that MVI + is closely associated with unfavorable features as well as negative effects on recurrence, metastasis, and survival outcomes of the patient. We believe that systematically determining MVI in RCC specimens in clinical practice is necessary and consider MVI as one of the important prognostic variables, it can be used in devising surveillance protocols, and indications for adjuvant treatments in RCC.

References

1. Bedke J, Heide J, Ribback S, et al. Microvascular and lymphovascular tumour invasion are associated with poor prognosis and metastatic spread in renal cell carcinoma: a validation study in clinical practice. Bju International. 2018;121(1):84-92.
2. Huang H, Pan X-W, Huang Y, et al. Microvascular invasion as a prognostic indicator in renal cell carcinoma: a systematic review and meta-analysis. International journal of clinical and experimental medicine. 2015;8(7):10779.
3. Kroeger N, Rampersaud EN, Patard J-J, et al. Prognostic value of microvascular invasion in predicting the cancer specific survival and risk of metastatic disease in renal cell carcinoma: a multicenter investigation. The Journal of urology. 2012;187(2):418-423.
4. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. European urology. 2016;70(1):93-105.
5. Rey JR, Ramírez DL, García SL, Vázquez PF, Delgado JB, Calvo AO. Pathological prognostic indicators in renal cell carcinoma. Actas Urológicas Espa#olas (English Edition). 2010;34(1):71-77.
6. Santiago-Agredano B, Álvarez-Kindelán J, Font-Ugalde P, Blanca-Pedregosa A, López-Beltrán A, Requena-Tapia MJ. Prognostic value of microvascular invasion in predicting survival in renal cell carcinoma. Actas Urológicas Espa#olas (English Edition). 2013;37(8):504-512.
7. Kwon SY, Lee JN, Kim BS, et al. Impact of microvascular invasion and tumor necrosis on the prognosis of Korean

patients with pT1b renal cell carcinoma. Urologia internationalis. 2015;95(1):65-71.
8. Bengió RG, Arribillaga LC, Epelde J, et al. Evaluation of microvascular invasion as a prognostic factor in the progression of non-metastatic renal cancer. Central European journal of urology. 2018;71(4):386.
9. Ishimura T, Sakai I, Hara I, Eto H, Miyake H. Microscopic venous invasion in renal cell carcinoma as a predictor of recurrence after radical surgery. International journal of urology. 2004;11(5):264-268.
10. DallOglio MF, Antunes AA, Sarkis ÁS, et al. Microvascular tumour invasion in renal cell carcinoma: the most important prognostic factor. BJU international. 2007;100(3):552-555.