

# Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy?

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**Objective:** Microvascular invasion (MVI) has been proved to be an independent risk factor for the recurrence of HCC. If promptly treated, the recurrence rate can be reduced and the total survival time can be prolonged. The aim of this study is to analyze the effect of sorafenib on the clinical outcomes in HCC patients with MVI after curative hepatectomy.

**Methods:** HCC patients who underwent hepatectomy and were pathologically diagnosed with MVI were retrospectively analyzed. Patients were divided into sorafenib group and control group. Sorafenib 400 mg, twice daily, was administered orally after surgery in the sorafenib group. The recurrence-free survival (RFS) and overall survival (OS) were observed during follow-up, and associated factors were analyzed using univariate and multivariate COX regression.

**Results:** There was no significant difference in demographics, clinical staging, and tumor index between sorafenib group (16 patients) and control group (33 matched patients). The RFS and OS were both longer in the sorafenib group, and the 3-years RFS rates of the sorafenib group and control group were 56.3% (9 of 16) and 24.2% (8 of 33), respectively ( $P=0.027$ ). The 3-year OS rate of the sorafenib group was 81.3% (13 of 16), which was significantly higher than that of the control group (39.4%,  $P=0.006$ ). The results of multivariate COX regression indicated that treatment with sorafenib was an independent associated factor for RFS and OS.

**Conclusion:** We believe that using sorafenib therapy after curative hepatectomy in HCC patients with MVI is effective and beneficial as it can reduce recurrence and prolong the survival time.

**Keywords:** sorafenib, hepatocellular carcinoma, microvascular invasion, hepatectomy, survival rate

## Introduction

Liver cancer is the second leading cause of cancer deaths worldwide. Most of the cases are reported with hepatocellular carcinoma (HCC),<sup>1</sup> which is the third cause of cancer-related deaths, and the fifth most common cancer in males and the seventh most common in females.<sup>2</sup> Hepatitis B virus (HBV) infection, hepatitis C virus infection, and liver cirrhosis are the most significant risk factors for HCC,<sup>3,4</sup> and the prognosis is highly dependent on tumor extension and liver functions.<sup>5</sup> In patients with early-stage HCC, hepatectomy, tumor ablation, and liver transplantation are potentially curative treatments. However, the recurrence of HCC reaching a probability of more than 50% at 2 years<sup>6,7</sup> and 70% at 5 years<sup>8</sup> remains a serious problem affecting long-term survival after curative treatment. Various postoperative treatments such as antiviral therapy are used to decrease the probability of recurrence after curative treatment,<sup>9</sup> but none of them are widely accepted.

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Metastasis of HCC begins with vascular invasion, which are characterized into two types: macrovascular invasion and microvascular invasion (MVI). Even though both represent metastatic invasion by aggressive tumor cells and are regarded as critical factors predicting HCC recurrence,<sup>10–12</sup> they have their own unique biological and clinical characteristics. Since many years, macrovascular invasion has been recognized and reported in up to 44% of patients with end-stage HCC.<sup>13</sup> Moreover, patients with macrovascular invasion and non-resectable HCC have a significantly reduced median survival (2–4 months) compared to those without macrovascular invasion (10–24 months).<sup>14,15</sup> Macrovascular invasion is well recognized clinically as it involves tumor invasion into major blood vessels and is defined clearly by established staging systems, such as Barcelona Clinic Liver Cancer (BCLC) classification, as it can be easily identified in radiological images. In contrast, MVI is entirely a histological feature associated with adverse prognosis, and due to limitations on morphology-based criteria, it is poorly defined.<sup>11,16</sup> Even though some characteristics of MVIs are partially defined, such as the presence of tumor emboli in a portal radicle vein, a large capsule vessel, or a vascular space lined by endothelial cells, few controversies exist in other aspects, like intravascular floating tumor clusters (usually covered by endothelium), distance from the invaded vessel to tumor edge, the number of vessels affected, and small vascular intratumoral spaces. Due to the uncertainty in completely defining its characteristics, it has been extremely difficult to predict which features have the strongest prognostic association.<sup>17</sup> Although controversies exist, MVI is widely considered as an important marker of aggressive biological tumor behavior that dramatically worsens the prognosis in HCC.<sup>18–20</sup>

Prognosis is very poor in advanced cases of HCC, mainly due to limited treatment options and partially due to high chances of recurrences appearing in the remaining liver tissue after surgical resection and liver transplantation. Moreover, management of advanced HCC is particularly challenging because of poor liver function from underlying cirrhosis, even though advanced modalities of local directive therapies are widely available, such as radiofrequency ablation, radio-embolization, trans-arterial chemoembolization, and stereotactic body radiation therapy.<sup>21</sup> As early recurrence of HCC represents the major risk factor affecting the survival after curative hepatectomy, identifying the risk levels of recurrence may help to implement additional therapeutic strategies in clinical practice. This has been facilitated by much clinicopathological data of HCC-based prognostic staging systems formulated in the last two

decades. Among them, the BCLC staging system is widely used to guide HCC treatment options. The BCLC system highly recommends that sorafenib should be prescribed as the first-line drug for treating patients with advanced-stage HCC (stage C) with portal invasion, extrahepatic spread, and preserved liver function.<sup>22</sup>

Sorafenib, a novel targeted agent, has been widely used after gaining US Food and Drug Administration approval for HCC in 2007. It is regarded as a promising treatment option for advanced HCC and remained as the only treatment option for more than a decade.<sup>23</sup> Moreover, it is the only approved agent recommended by the American Association for the Study of Liver Diseases (AASLD) for patients with advanced and non-resectable HCC. Sorafenib is an oral multi-kinase inhibitor that blocks several molecular pathways through its antiangiogenic and antiproliferative effects. It blocks the serine/threonine kinases (c-RAF and b-RAF) and receptor tyrosine kinases (vascular endothelial growth factor receptors 2 and 3, platelet-derived growth factor receptor  $\beta$ , and FMS-like tyrosine kinase 3);<sup>24</sup> among them, VEGF is the main molecule that drives tumor angiogenesis. An independent randomized clinical trial showed that sorafenib was effective in improving survival time in patients with advanced HCC.<sup>23</sup> Furthermore, previous studies have reported that sorafenib suppressed postoperative intrahepatic recurrence and abdominal metastasis, which consequently led to prolonged postoperative survival.<sup>25–27</sup>

To our knowledge, no study has been performed to evaluate the combined efficiency of sorafenib and hepatectomy in HCC patients with MVI and without any signs of macrovascular invasion compared to patients undergoing hepatectomy alone. In this retrospective study, we tried to analyze and evaluate the effect of sorafenib as an adjuvant therapy on tumor recurrence and prolonging survival time after potentially curative resection in HCC patients with apparent MVI without any macrovascular invasion.

## Materials and methods

### Patients

Patients with HCC who underwent curative hepatectomy and were pathologically diagnosed with MVI at the Department of Hepatobiliary Surgery, Xiangya Hospital of Central South University, between January 2009 and December 2016 were retrospectively enrolled in this study.

Inclusion criteria were: 1) aged 18–75 years old; 2) newly diagnosed with HCC without any previous treatment such as chemotherapy, molecular-targeted agent therapy, and surgical or radiological therapy; 3) tumor classified as BCLC

stage 0-B; 4) absence of tumor thrombus; 5) Eastern Cooperative Oncology Group performance status  $\leq 2$ ; 6) liver function classified as Child–Pugh grade A or B; 7) underwent curative hepatectomy with negative surgery margin (R0 resection); and 8) presence of MVI confirmed by pathology.

Exclusion criteria were: 1) presence of metastases or suspected metastatic lesions outside the liver; 2) presence of primary tumor in other organs outside the liver; 3) presence of macrovascular invasion; and 4) receiving any treatment other than sorafenib after hepatectomy and before tumor recurrence or metastasis.

Patients were divided into two groups according to whether they received sorafenib treatment (sorafenib group) or not (control group) after surgery. The two groups were matched according to age, gender, liver function, and tumor characteristics, which were noted from their medical records. The study was approved by the ethics committee of Xiangya Hospital of Central South University (no 2018071021), and was conducted in accordance with the Declaration of Helsinki. Patient consent to review their medical records was waived due to the retrospective nature of the study. Patient data were reviewed confidentially.

## Curative hepatectomy

The patients underwent general anesthesia in supine position. The operation was performed through an L-type incision in the right upper abdomen. Under the circumstance that complete removal of tumor could be ensured, anatomic resection was the prior choice. The extent of anatomic resection was defined according to Couinaud's classification.<sup>28</sup> We tried to obtain R0 resection if anatomic resection was not technically possible. Pringle's maneuver was performed to control bleeding if necessary.

## Postoperative treatment

The patients in the sorafenib group were treated with oral sorafenib (Nexavar<sup>®</sup>; Bayer Healthcare Co., Ltd., Beijing, China) 400 mg, twice a day, after surgery. The dose was reduced to 400 mg per day when any drug-related adverse events occurred.

## Outcomes

Recurrence-free survival (RFS) and overall survival (OS) were evaluated. RFS was defined as the time from the day after curative hepatectomy to the recurrence of HCC or death, and OS was defined as the time from the day after curative hepatectomy to death.

## Follow-up

The patients underwent, at least once, B-type ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) examination every 3 months after surgery. If B-type ultrasound found a new lesion, a confirmatory CT/MRI scan was performed. Outpatient follow-up was completed on March 15, 2018.

## Statistical analyses

All statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). The continuous variables obeying normal distribution were expressed as mean  $\pm$  SD and analyzed using independent-sample *t*-test, while the continuous variables violating normal distribution were expressed as median (range) and analyzed using Mann–Whitney *U* test. Categorical variables were expressed as frequency (percentage) and analyzed using chi-squared or Fisher's exact test. RFS and OS are represented using Kaplan–Meier curves, and differences between groups were analyzed using the log-rank test. The associated factors of RFS and OS were identified using univariate and multivariate Cox proportional hazard regression. All statistical assessments were two-tailed, and  $P < 0.05$  was considered statistically significant.

## Results

### Patient and tumor characteristics

A total of 49 patients were enrolled in the study, 16 in the sorafenib group and 33 in the control group. A comparison of baseline characteristics between patients in the sorafenib group and patients in the control group is shown in Table 1. Most of the patients in the study were male (75.0% in the sorafenib group and 90.9% in the control group,  $P=0.195$ ), and the average age of patients in the sorafenib group and the control group was  $52.25 \pm 11.94$  and  $51.52 \pm 11.87$  years, respectively ( $P=0.840$ ). Positive hepatitis B surface antigen which indicates HBV as the predominant cause of underlying liver disease was found in 14 of 16 patients in the sorafenib group and 26 of 33 patients in the control group ( $P=0.698$ ). While only one patient in the control group was classified as BCLC stage 0, most of the patients were classified as BCLC-stage A in the sorafenib group and control group (14 of 16 vs 28 of 33,  $P=1.000$ ). Except two patients in the control group whose liver function was classified as Child–Pugh B, the liver function of rest of the patients was classified as Child–Pugh A ( $P=1.000$ ). Five of 16 patients in the sorafenib group and 5 of 33 patients in the control group received post-recurrence antitumor therapy ( $P=0.261$ ). There

**Table 1** Baseline characteristics

Characteristics	Sorafenib group (n=16)	Control group (n=33)	P-value
Age (years)	52.25±11.94	51.52±11.87	0.840
Male	12 (75.0)	30 (90.9)	0.195
HBsAg			0.698
Positive	14 (87.5)	26 (78.8)	
Negative	2 (12.5)	7 (21.2)	
BCLC stage			1.000
0	0	1 (3.0)	
A	14 (87.5)	28 (84.9)	
B	2 (12.5)	4 (12.1)	
AFP (ng/mL)			0.617
≤400	8 (50.0)	19 (57.58)	
>400	8 (50.0)	14 (42.42)	
Tumor size (cm)			0.468
≤5	6 (37.5)	16 (48.5)	
>5	10 (62.5)	17 (51.5)	
Number of tumors			1.000
1	14 (87.5)	30 (90.9)	
2	2 (12.5)	3 (9.1)	
Child–Pugh classification			1.000
A	16 (100)	31 (93.9)	
B	0	2 (6.1)	
Post-recurrence antitumor therapy			0.261
Yes	5 (31.3)	5 (15.2)	
No	11 (68.7)	28 (84.8)	
Edmondson classification			0.762
I and II	7 (43.8)	17 (51.5)	
III and IV	9 (56.3)	16 (48.5)	

**Note:** Data are expressed as mean ± SD or n (%).

**Abbreviations:** AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen.

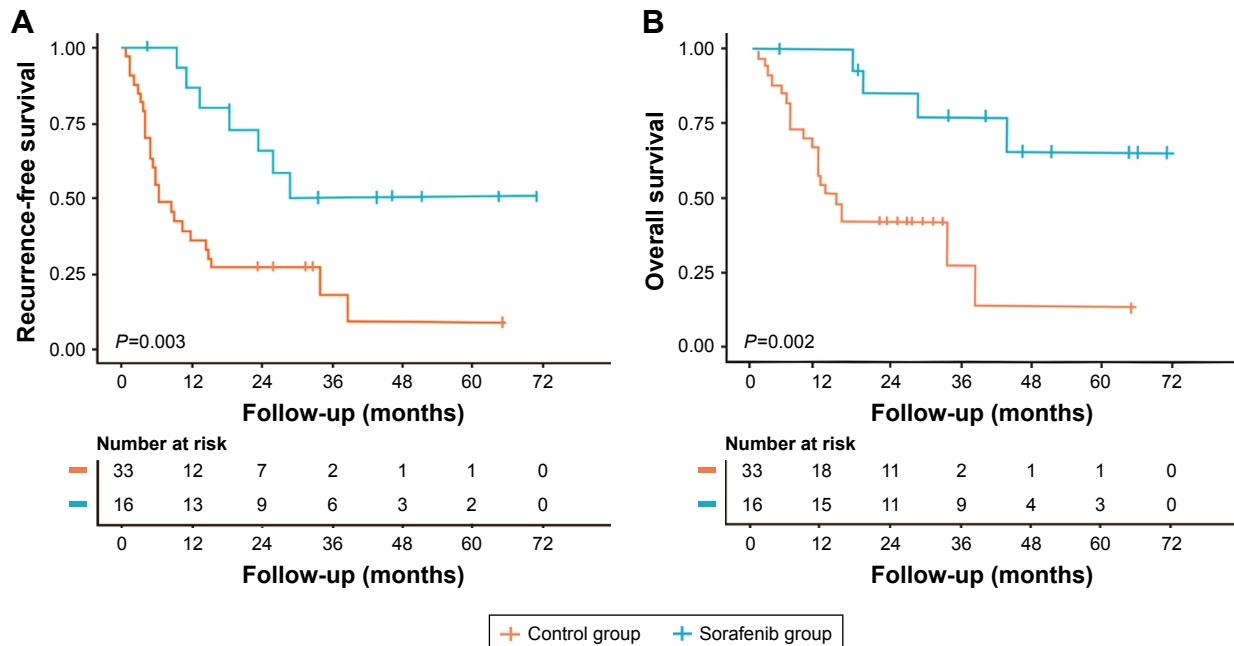
were no significant differences in Edmondson classification and alpha fetoprotein levels (all  $P>0.05$ ).

On analysis of tumor characteristics, patients in the sorafenib group showed a similar tumor size compared to the control group ( $P=0.468$ ). Multiple tumors were present in 2 of 16 patients in the sorafenib group and in 3 of 33 patients in the control group ( $P=1.000$ ).

Overall, there was no statistically significant difference in baseline clinical and pathological features between the two groups.

### Survival analyses

A comparison of survival analysis between the sorafenib and control groups is shown in Figure 1. The median follow-up time was 22.2 months. The median duration of sorafenib treatment was 45.52 months (range, 1.10–70.97 months). The median RFS and OS were 6.20 (95% CI: 2.82–9.58) and 14.30 months (95% CI: 10.14–18.46) in the control group, respectively, while these did not reach the data cutoff date in the sorafenib group. The log-rank test showed that the difference between the two groups in both RFS ( $P=0.003$ ) and OS ( $P=0.002$ ) was significant, suggesting that the patients who received sorafenib therapy after surgery exhibited longer RFS and OS compared to patients who underwent only surgery. Especially, 1- and 3-year RFS rates were 36.4% (12 of 33 patients) and 24.2% (8 of 33 patients) in the control group, while they were up to 87.5% (14 of 16 patients,  $P=0.001$ ) and 56.3% (9 of 16 patients,  $P=0.027$ ) in the sorafenib group,



**Figure 1** Kaplan–Meier analysis and the log-rank test for recurrence-free survival (A) and overall survival (B).

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**Table 2** 1- and 3-year RFS and OS

Variables	Sorafenib group (n=16)	Control group (n=33)	P-value
RFS			
1 year	14 (87.5)	12 (36.4)	0.001
3 years	9 (56.3)	8 (24.2)	0.027
OS			
1 year	16 (100)	18 (54.5)	0.001
3 years	13 (81.3)	13 (39.4)	0.006

**Note:** Data are expressed as n (%).

**Abbreviations:** OS, overall survival; RFS, recurrence-free survival.

respectively. The 1- and 3-year OS rates were 54.5% (18 of 33 patients) and 39.4% (13 of 33 patients) in the control group, and 100% (16 of 16 patients,  $P=0.001$ ) and 81.3% (13 of 16 patients,  $P=0.001$ ) in the sorafenib group (Table 2), respectively. Five patients had recurrence of HCC and four patients died in the sorafenib group. Among them, three patients had intrahepatic recurrence; one patient had intrahepatic and lung recurrence, and died of HCC; one patient had intrahepatic, lung, and bone recurrence, and died of HCC; one patient died of decompensated cirrhosis; and one patient died of unknown reason. Fourteen patients had recurrence of HCC and 21 patients died in the control group. Among them, six patients had intrahepatic recurrence, and half of them died of HCC; three patients had intrahepatic and lung recurrence, and one of them died of HCC; three patients had intrahepatic, lung, and bone recurrence, and all died of HCC; one patient had intrahepatic, lung, and brain recurrence, and died of HCC; one patient had lung recurrence and died of HCC; six patients died of decompensated cirrhosis; five patients died of non-liver-related diseases; and one patient died of infection.

Univariate and multivariate analyses of the factors related to RFS and OS in the whole cohort are shown in Tables 3 and 4. Sorafenib therapy and Child–Pugh classification were

significantly correlated to RFS, while absence of sorafenib therapy was the only independent significant risk factor of OS.

## Discussion

This study was performed among HCC patients with MVI after curative hepatectomy, but without any apparent macrovascular invasion. The results of the present study revealed that sorafenib could significantly prolong both RFS and OS in these patients. Although the guidelines recommend hepatectomy only for patients with BCLC stage A, current clinical practice prefers to use hepatectomy in stage B and C patients as well.<sup>29</sup> The safety and effectiveness of hepatectomy are promising. Nevertheless, the presence of MVI indicates a high risk of recurrence after curative hepatectomy. Therefore, the antiangiogenic, proapoptotic, and antiproliferative effects of sorafenib make it an ideal drug of choice after hepatectomy in a theoretical point of view.

The effectiveness of sorafenib in HCC has been universally acknowledged, and it is the only approved agent recommended to HCC patients after hepatectomy by the AASLD. Animal studies have indicated that sorafenib inhibited tumor growth and prevented tumor recurrence after resection of HCC.<sup>30</sup> Recently, more than three researches demonstrated that sorafenib could reduce recurrence and prolong survival rate in patients after surgery.<sup>31–34</sup> Zhuang et al<sup>31</sup> revealed that sorafenib may be effective after liver resection in intermediate stage and in advanced HCC. Li et al<sup>32</sup> and Xia et al<sup>33</sup> found that HCC patients with BCLC stage C, who received oral sorafenib treatment after curative resection, had significantly longer disease-free survival and OS than patients subjected to only surgery. Wang et al<sup>34</sup> demonstrated that sorafenib prescribed as an adjuvant therapy for HCC could prevent early recurrence after hepatic resection. However, there are a few papers with inconsistent results as well.

**Table 3** Univariate and multivariate analyses for recurrence-free survival

Variables	Reference	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	<60	0.784 (0.353, 1.744)	0.551		
Gender	Male	0.399 (0.122, 1.313)	0.131		
HBsAg	Negative	1.374 (0.53, 3.562)	0.513		
BCLC stage	0-A	0.964 (0.291, 3.189)	0.952		
AFP	≤400	1.097 (0.548, 2.196)	0.794		
Tumor size	≤5	0.665 (0.334, 1.323)	0.245		
Number of tumors	I	0.685 (0.163, 2.883)	0.606		
Sorafenib treatment	No	0.295 (0.126, 0.688)	0.005	0.308 (0.131, 0.724)	0.007
Child–Pugh classification	A	7.190 (1.538, 33.611)	0.012	5.336 (1.136, 25.056)	0.034
Post-recurrence antitumor therapy	No	1.438 (0.646, 3.200)	0.373		
Edmondson classification	I and II	1.296 (0.652, 2.576)	0.460		

**Abbreviations:** AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen.

**Table 4** Univariate and multivariate analyses for overall survival

Variable	Reference	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	<60	0.866 (0.357, 2.099)	0.750		
Gender	Male	0.41 (0.096, 1.742)	0.227		
HBsAg	Negative	1.21 (0.415, 3.527)	0.728		
BCLC stage	0-A	0.612 (0.144, 2.6)	0.506		
AFP	≤400	1.802 (0.817, 3.972)	0.145		
Tumor size	≤5	1.08 (0.484, 2.408)	0.851		
Number of tumors	I	0.909 (0.214, 3.862)	0.897		
Sorafenib treatment	No	0.186 (0.06, 0.578)	0.004	0.219 (0.071, 0.672)	0.008
Child–Pugh classification	A	1.038 (0.139, 7.747)	0.971		
Post-recurrence antitumor therapy	No	0.120 (0.016, 0.887)	0.038	0.147 (0.020, 1.091)	0.061
Edmondson classification	I and II	1.634 (0.733, 3.642)	0.230		

**Abbreviations:** AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen.

Zhang et al's research<sup>35</sup> indicated that adjuvant sorafenib significantly reduced mortality and prolonged OS of HCC patients after curative resection, but did not decrease tumor recurrence.

According to the AASLD guidelines of HCC,<sup>36</sup> sorafenib therapy is only recommended when HCC is associated with macrovascular invasion. However, in the present study, we found that HCC patients with MVI but without macrovascular invasion also exhibited a significant benefit in terms of recurrence and OS. To our knowledge, this study is the first to compare the combined efficacy of sorafenib and hepatectomy over hepatectomy alone in the management of HCC with MVI in patients without macrovascular invasion. Though more elaborate studies are needed to confirm the effectiveness of the therapy in these particular patients before wide recommendation, it is reasonable to hypothesize that offering sorafenib therapy to postoperative HCC patients with MVI, even without macrovascular invasion, is still effective and beneficial according to our results.

The univariate and multivariate analyses in the present study showed that sorafenib therapy was a significant risk factor for RFS and OS, which was consistent with our hypothesis. However, the analysis also showed that worse Child–Pugh classification, with high HR, was a significant independent risk factor of RFS. Generally speaking, worse Child–Pugh classification represents more serious liver cirrhosis. Currently, it has been proved that high levels of TGF- $\beta$ , as a consequence of liver cirrhosis, result in activation of stellate cells to myofibroblasts and massive hepatocyte cell death.<sup>36</sup> Moreover, activation of TGF- $\beta$  signaling might contribute to tumor progression and recurrence.<sup>37,38</sup> However, no similar result was found during this study. On the one hand, we consider that the few patients with Child–Pugh classification B

in our study may be responsible for creating such a situation. On the other hand, we highly recommend that further studies need to be conducted to confirm the influence of Child–Pugh classification on recurrence of HCC.

A recently published Phase III, international, randomized, double-blind, placebo-controlled trial study (Systemic Treatment of Resistant Metastatic disease) has also included Chinese patients.<sup>39</sup> But the study recruited unselected patients, who underwent surgical resection or local ablation, and the subgroup analysis showed that sorafenib was not much effective than placebo for improving RFS in patients with surgical resection. However, this study did not analyze the subgroup of patients with MVI. On the other hand, in our study, we also enrolled patients who underwent curative hepatectomy, but we focused only on patients with MVI. Although this was a retrospective study, it might provide some evidence for patients with HCC and MVI. These patients should be further studied.

## Limitations

The major limitation of our study is its retrospective design. Although we tried to lower selection bias through case matching, the possibility of other biases certainly exists. The small size of the study cohort may have hampered our ability to demonstrate a significant difference in survival. Considering the influence of reduced-dose sorafenib therapy in patients with severe adverse effect, the differential effect of reduced dose and standard dose should be analyzed. However, a Japanese team<sup>40</sup> in their study had reported that the difference between patients who received 800 mg sorafenib per day and those who received 400 mg per day was not significant in either duration of treatment (117 vs 81 days,  $P=0.05$ ) or number of dosing days (107 vs 78 days,  $P=0.10$ ). In the

present study, the efficacy at reduced doses has not been investigated, but in order to gain a more precise conclusion, we may explore this part in the future research studies. Also, the median follow-up time in our study was not long enough to calculate 5-year RFS and OS. We may prolong the follow-up duration of our study subjects in order to investigate the long-term effect of sorafenib therapy after hepatectomy.

## Conclusion

Our study showed that sorafenib therapy after curative hepatectomy in HCC patients with MVI is effective and beneficial as it can significantly reduce recurrence and prolong the survival time. An elaborate study with a large sample size and a longer period of follow-up, and an investigation on differential dosage of drugs may derive more promising outcomes which may help to recommend the drug for clinical use in such patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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