Int J Clin Exp Med 2017;10(1):1615-1623
www.ijcem.com /ISSN:1940-5901/IJCEM0025348

*Original Article*

# Postoperative sorafenib prolongs survival of hepatocellular carcinoma patients with Portal vein tumor thrombus following hepatic resection

Wei-Xing Guo*, Lei Guo*, Kang Wang*, Bin Huang, Jie Shi, Nan Li, Fei-Guo Zhou, Meng-Chao Wu, Shu-Qun Cheng

*Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China. *Equal contributors.*

Received January 31, 2016; Accepted April 27, 2016; Epub January 15, 2017; Published January 30, 2017

**Abstract:** Portal vein tumor thrombus (PVTT) is a complication of hepatocellular carcinoma (HCC). Our aim was to determine if sorafenib given postoperatively prolongs the survival of HCC patients with PVTT who undergo hepatic resection. Between 2009 and 2013 advanced HCC with PVTT who underwent surgical resection were given the option to take sorafenib postoperatively. Overall survival (OS) and disease-free survival (DFS) of patients that had resection alone and those that took sorafenib were compared. Seventy patients were included; 45 (64.3%) received resection alone, and of the 25 (35.7%) patients who received resection plus sorafenib, 10 began sorafenib after surgery, 15 began after recurrence. The median survival times of the resection and resection + sorafenib groups were 10 months (IQR: 1, 30 months) and 15 months (IQR: 3, 62 months), respectively. The median DFS of surgical resection and resection + sorafenib groups were 3 months (IQR: 1, 7 months) and 4 months (IQR: 1, 36 months), respectively. Patients who began sorafenib within 2 weeks after surgery had longer OS and DFS than patients who received resection alone or who began sorafenib after recurrence. Sorafenib improves OS and DFS of HCC patients with PVTT who undergo surgical resection.

**Keywords:** Hepatocellular carcinoma, portal vein thrombosis, sorafenib, resection, prognosis

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer, and the third leading cause of cancer mortality globally [1]. Approximately half of yearly deaths due to HCC occur in China [2]. Portal vein tumor thrombosis (PVTT) in patients with HCC is a major complication associated with poor survival [3, 4], and if left untreated the median survival is less than 6 months [5]. Portal or hepatic vein invasion as demonstrated by magnetic resonance imaging (MRI) and ultrasonography occurs in 50% to 80% of HCC cases [6]. However, the optimal treatment for HCC with vascular invasion remains unclear [7, 8].

Sorafenib is a small molecular inhibitor of a number of tyrosine protein kinases including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), tyrosine kinase inhibitor (TKI), and Raf kinases [9]. The drug is indicated for the treatment of advanced renal cell carcinoma and thyroid cancer, and in 2007 was approved for the treatment of unresectable HCC [9]. Two large randomized trials have shown that sorafenib improved survival in patients with advanced HCC [10, 11] with subsequent studies showing similar results [12, 13].

According the American Association for the Study of the Liver Diseases/Barcelona Clinic for Liver Cancer (AASLD/BCLC) Staging System and Treatment Guidelines, the only treatment option for PVTT in patients with BCLC stage C disease is sorafenib [10, 14]. However, recent reports from Asia and the United States indicate that surgical resection with complete extirpation of the tumor provides a chance of cure for patients with HCC, and can provide significantly better long-term survival for certain

select groups with PVTT [4, 15, 16]. We have established a PVTT type system to guide the treatment of PVTT, and found liver resection is the only therapeutic option that offers a chance of cure in HCC patients with PVTT, especially for patients with PVTT type I or II [3, 17].

The outcome of surgical resection of HCC with PVTT, however, is still unsatisfactory with a 3-year median survival of only 17% [4]. The results of our previous study using an animal model and PVTT-1 cell lines strongly suggest that sorafenib has a potential application in HCC patients who have undergone hepatectomy by effectively reducing postoperative recurrence and metastasis [18]. The present study was performed to translate the findings of the animal study into clinical practice.

The purpose of this study was to determine if sorafenib given postoperatively prolongs the survival of HCC patients with PVTT who have undergone surgical resection.

## Methodology

### *Patients*

From January 2009 to December 2013, 1345 hepatic resections for HCC were performed at our study team, and of these there were 121 patients with macroscopic PVTT. All patients were encouraged to take oral sorafenib postoperatively, and provided detailed information about sorafenib, including its efficacy and potential adverse effects. The decision to take sorafenib was based on a patient's personal preference and economic status as the cost of sorafenib is not covered by health insurance in China.

Criteria for inclusion in this study were: 1) BCLC stage C disease, which is generally considered an indication for surgical resection, diagnosed by 2 experienced hepatic surgeons; 2) Macroscopic PVTT identified before surgery; 3) No hepatic vein invasion and/or extrahepatic spread; 4) Child-Pugh classification A or B, with no history of encephalopathy, ascites refractory to diuretics, or variceal bleeding; 5) No previous treatment of HCC. Patients were divided into 2 groups for analysis; those that underwent surgical resection alone and those that underwent surgical resection and received sorafenib postoperatively. Patients who received sorafenib were divided into 2 subgroups; preventive sorafenib therapy subgroup, i.e., patients that began sorafenib immediately postoperatively, and post-relapse sorafenib therapy, i.e., patients that began sorafenib after a recurrence was diagnosed. The Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital (the Second Military Medical University, Shanghai, China) approved this study, and informed consent was obtained from all patients.

### *Surgery*

Surgery was performed through a right subcostal incision with a midline extension. Intraoperative ultrasonography (IOUS) was routinely performed to accurately determine the number and location of the lesions, and their relationship to major vessels. The aim of surgery was R0 resection with clear resection margin of at least 1 cm. The Pringle maneuver was used to occlude hepatic blood inflow, and liver resection was carried out by a clamp crushing method. Thrombectomy was performed according to the location and extent of PVTT. For patients with PVTT located within the resected area, the PVTT was resected en bloc with the tumor. For patients with PVTT protruding into the main portal vein beyond the resection line, the PVTT was extracted from the opened stump of the portal vein. For patients with PVTT extending into the main portal trunk and its primary branches on both sides, the main portal trunk was exposed and was clamped distal to the PVTT. The portal vein was incised at the bifurcation of the right and left portal veins, and the PVTT was extracted. After flushing with normal saline and confirming that no PVTT remained, the stump was closed by a continuous suture. In all cases, PVTT was confirmed by pathological examination.

### *Sorafenib treatment*

Patients who chose to receive sorafenib received oral sorafenib (400 mg) twice daily after surgery. In cases where toxicity limited administration, the dose was reduced to 200 mg twice daily. Treatment was stopped temporarily when intolerable side effects occurred. Toxicity and side effects were evaluated in accordance with the official drug information [19]. Some patients chose to begin sorafenib within 2 weeks after surgery (preventive group),

**Table 1.** Patient characteristics

| | Surgical resection (n=45) | Surgical resection + sorafenib (n=25) | *P* value |
|---|---|---|---|
| Sex | | | 0.410 |
| Male | 40 (88.9) | 24 (96) | |
| Female | 5 (11.1) | 1 (4) | |
| Age, years | 50.1 ± 9.2 | 48.2 ± 10.1 | 0.475 |
| Total bilirubin, μmol/L | 14.6 (11.9, 19.6) | 13.2 (9.9, 16.7) | 0.155 |
| Albumin, mg/dL | 40.8 (39.3, 42.8) | 42 (38.9, 47.6) | 0.177 |
| ALT, U/L | 47.2 (30.4, 69.9) | 49.2 (33.9, 57.9) | 0.936 |
| Tumor size, cm | 9.4 ± 2.3 | 8.9 ± 3.7 | 0.507 |
| AFP | | | 0.305 |
| < 400 ng/mL | 19 (42.2) | 7 (28) | |
| ≥ 400 ng/mL | 26 (57.8) | 18 (72) | |
| Liver cirrhosis | | | 0.236 |
| Yes | 37 (82.2) | 17 (68) | |
| No | 8 (17.8) | 8 (32) | |
| Encapsulation | | | 0.474 |
| Complete | 7 (15.6) | 2 (8) | |
| Incomplete | 38 (84.4) | 23 (92) | |
| PVTT type | | | 1.000 |
| Type I, II | 31 (68.9) | 17 (68) | |
| Type III, IV | 14 (31.1) | 8 (32) | |

AFP, alpha fetoprotein; ALT, alanine aminotransferase; PVTT, portal vein tumor thrombosis. Data are presented as mean ± standard deviation, number (%), or median (interquartile range).

and other chose to begin sorafenib only after recurrence occurred (sorafenib after recurrence group). Unless limited by toxicity, all patients continued sorafenib until death. Liver function tests and evaluation of toxicity was performed monthly in all patients receiving sorafenib.

*Follow-up*

All patients received postoperative follow-up by the same team. For the first year after surgery, patients were seen every 1-3 months, and thereafter every 3 months. Patients received serum alpha fetoprotein (AFP), liver function tests, and abdominal ultrasound monthly, and abdominal computed tomography (CT) with contrast and chest X-ray every 3 months. If tumor recurrence or metastases were suspected because of an elevated AFP level or ultrasound findings, contrast-enhanced CT or MRI was performed. Fine needle aspiration biopsies were done when necessary. The diagnosis of tumor recurrence was based on cytological or histological evidence, or on the noninvasive diagnostic criteria for HCC used by the European Association for the Study of the Liver (EASL) [20]. Patients with intrahepatic or extrahepatic recurrences were treated according to the location and number of recurrent tumors, liver function status, presence/absence of extrahepatic metastases, and presence/absence of tumor thrombus in the portal vein, hepatic vein, and/or inferior vena cava. Treatments included surgery, local ablative therapy, regional therapy, or systemic therapy.

*Statistical analysis*

Patient demographic and clinical data were summarized as mean ± standard deviation (SD) for continuous data with a normal distribution, median (interquartile range [IQR]: 1st and 3rd quartiles) for data non-normally distributed, and number (%) for categorical data by group. Difference between groups were compared using 2-sample t-test or Mann-Whitney U test for continuous data with and without a normal distribution, respectively, and Pearson chi-square or Fisher's exact test for categorical data. Overall survival (OS), defined as the time from surgery to last follow-up, and disease-free survival (DFS), defined as the time from surgery to recurrence, were analyzed and represented using Kaplan-Meier curves compared with the log-rank test. A 2-tailed value of $P<0.05$ was considered to indicate statistical significance. All analyses were performed using SPSS Medical Pack for Windows (version 11.0; SPSS, Chicago, IL, USA).

## Results

*Patient characteristics*

A total of 70 HCC patients with PVTT were included in the analysis; 45 (64.3%) were treated with surgical resection alone and 25 (35.7%) with resection and sorafenib and the mean age of patients in the 2 groups was 50.1 ± 9.2 years and 48.2 ± 10.1 years, respective-

**Table 2.** Operative and postoperative outcomes

| Variables | Surgical resection (n=45) | Surgical resection + sorafenib (n=25) | *P* value |
|---|---|---|---|
| Median blood loss, mL | 400 (200, 800) | 500 (375, 850) | 0.151 |
| Blood transfusion, yes (%) | 10 (22.2) | 4 (16) | 0.756 |
| Blood transfusion amount, mL | 1400 (1200, 1500) | 1600 (1450, 3400) | 0.106 |
| Pleural effusion, yes (%) | 10 (22.2) | 7 (28) | 0.772 |
| Subphrenic collection/abscess, yes (%) | 3 (12.0) | 6 (13.3) | 1.000 |
| Bile Leak, yes (%) | 3 (6.7) | 2 (8.3) | 1.000 |
| Postoperative hemorrhage, yes (%) | 3 (6.7) | 1 (4) | 1.000 |
| Liver failure | 2 (4.4) | 1 (4) | 1.000 |
| Infected ascites | 2 (4.4) | 0 (0) | 0.534 |

Data are presented as number (%), or median (interquartile range).

ly. Demographic and clinical data of the 2 groups are summarized in **Table 1**. The 2 groups were comparable in all demographic and clinical characteristics. There were also no significant differences in treatments after tumor recurrence between the 2 groups (Supplementary Table 1).

*Surgical resection and postoperative outcomes*

Open surgical resection was performed in all cases. The Pringle maneuver was used in 65 patients with a median clamp time of 16 min (IQR: 8, 58 min). Surgical and postoperative outcomes, including blood loss and transfusions and postoperative bleeding, were similar between the 2 groups and are summarized in **Table 2**. There were no cases of surgery-related mortality in either group. The postoperative complications included 17 patients with pleural effusions, 9 with subphrenic fluid collections/abscesses, 5 with bile leakage, 4 with hemorrhage, 3 with liver failure, and 2 with infected ascites, and there was no difference in the rate of complications between the 2 groups (all, P>0.05).

*Survival analysis*

The median OS of both groups was 13.2 months (IQR: 1, 62 months). A total of 60 patients died during the follow-up period; 41 (91.1%) in the surgical resection group and 19 (76%) in surgical resection + sorafenib group. The median survival times of the surgical resection and surgical resection + sorafenib groups were 10 months (IQR: 1, 30 months) and 15 months (IQR: 3, 62 months), respectively. The 6, 12, and 18 months survival rates of the 2 groups were 73.3%, 42.2%, and 15.2%, and 84%, 68%, and 38.8%, respectively. Kaplan-Meier curves and log-rank test indicated that OS was significantly greater in the surgical resection + sorafenib group (**Figure 1A**; log-rank P=0.011).

The median DFS of both groups was 3 months (IQR: 1, 36 months). There were 69 patients with recurrence after surgery, 45 (100%) in the surgical resection group and 24 (96%) in the surgical resection + sorafenib group. The median DFS of the surgical resection, and surgical resection + sorafenib groups were 3 months (IQR: 1, 7 months) and 4 months (IQR: 1, 36 months), respectively. The 3 and 6 month DFS rates of the 2 groups were 28.9% and 4.4%, and 56% and 16%, respectively. Kaplan-Meier curves and log-rank test indicated that DFS was significantly greater in the surgical resection + sorafenib group (**Figure 1B**; log-rank P=0.0151).

*Sorafenib subgroups*

The 25 patients who receive sorafenib were divided into 2 subgroups; 10 patients began sorafenib within 2 weeks after surgery and 15 began therapy after recurrence. The 2 subgroups had similar demographic and clinical characteristics (all, P>0.05; **Table 3**). Furthermore, the number and size of the hepatic lesions and the extent of PVTT were similar between the preventive sorafenib and surgical resection groups, and between the preventive sorafenib and sorafenib after recurrence groups (Supplementary Tables 2 and 3, respectively).

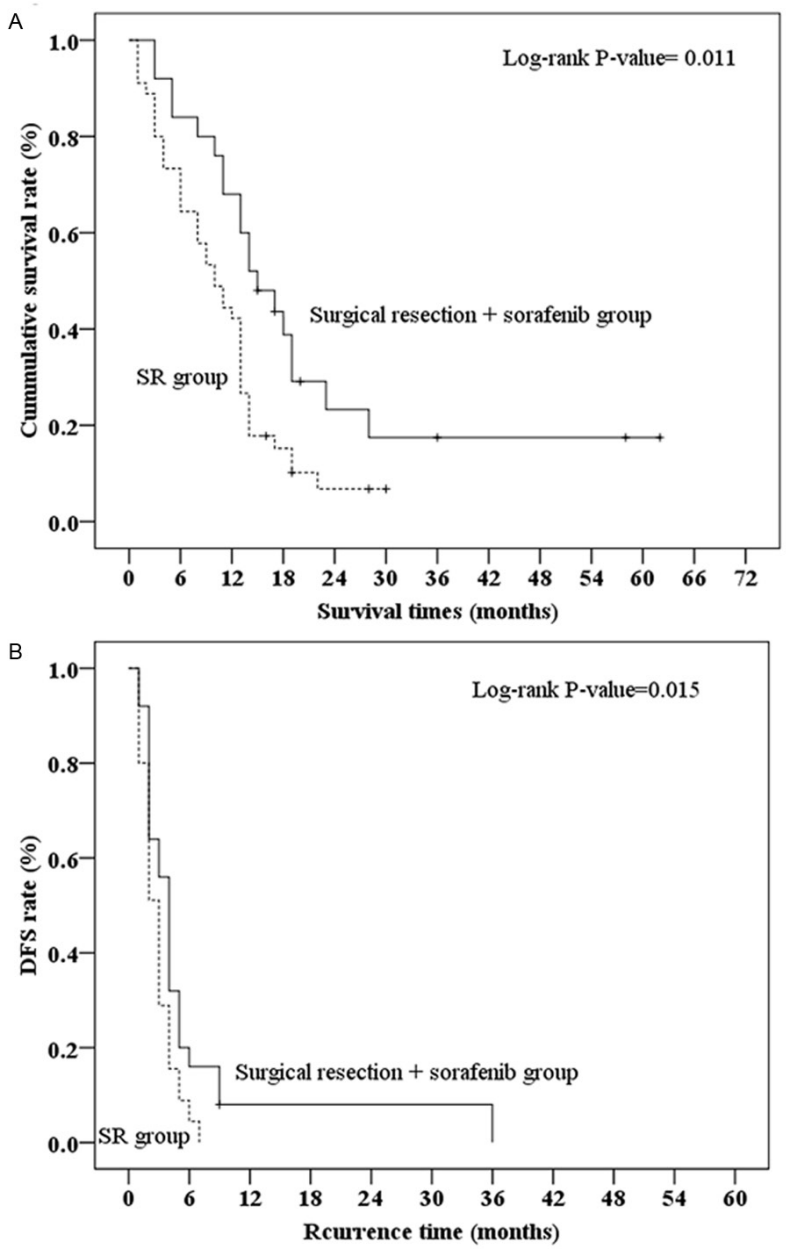


**Figure 1.** Kaplan-Meier curve for (A) overall survival (OS), and (B) disease-free survival (DFS) between the surgical resection (SR) and surgical resection + sorafenib groups. Difference between groups was compared using the log-rank test (P=0.011, 0.015, for OS and DFS, respectively).

Among these 25 patients who receive sorafenib, the major complications that occurred were rash, diarrhea, alopecia, and arthralgia, and there were no differences in the rate of complications between the 2 subgroups (Supplementary Table 4).

The median OS of the surgical resection, preventive sorafenib, and sorafenib after recurrence groups was 10 months (IQR: 1, 30 months), 18.5 months (IQR: 3, 62 months), and 13 months (IQR: 3, 28 months), respectively. Kaplan-Meier analysis indicated that OS was significantly different among 3 groups (log-rank P=0.012; **Figure 2A**). The OS of the preventive sorafenib group was significantly greater than that of the other 2 groups, and there was no difference in OS between the surgical resection and sorafenib after recurrence groups.

The median DFS of the surgical resection, preventive sorafenib, and sorafenib after recurrence groups was 3 months (IQR: 1, 7 months), 5 months (IQR: 1, 36 months), and 3 months (IQR: 1, 9 months), respectively. Kaplan-Meier analysis indicated that DFS was significantly different among 3 groups (log-rank P=0.009; **Figure 2B**). The DFS of the preventive sorafenib group was significantly greater than that of the other 2 groups, and there was no difference in DFS between the surgical resection and sorafenib after recurrence groups.

## Discussion

The results of this study indicate that sorafenib administered postoperatively can improve the OS and DFS of patients with BCLC stage C disease and PVTT who have undergone hepatic resection. Importantly, the improvement in survival was only seen when patients began sorafenib within 2 weeks after surgery and not if treatment was begun once recurrence had occurred. Furthermore, the drug was well tolerated with minimal serious adverse events.

According to the EASL HCC management for guidelines, sorafenib is the standard first-line treatment for patients with PVTT [20]. However,

**Table 3.** Comparison of patients who received preventative sorafenib or after recurrence

| | Preventive sorafenib (n=10) | Sorafenib after recurrence (n=15) | *P* value |
|---|---|---|---|
| Sex | | | 1.000 |
| Male | 10 (100) | 14 (93.3) | |
| Female | 0 (0) | 1 (6.7) | |
| Age, years | 52.1 ± 6.6 | 45.5 ± 11.4 | 0.114 |
| Total bilirubin, μmol/L | 13.9 (9.6, 17.8) | 12.9 (11.7, 16.5) | 0.807 |
| Albumin, mg/dL | 43.9 (38.4, 51.1) | 41.3 (39, 45.2) | 0.461 |
| ALT, U/L | 45.8 (38.2, 70.2) | 50.9 (31.1, 58.4) | 0.765 |
| Tumor size, cm | 9.6 ± 4.3 | 7.8 ± 3.7 | 0.269 |
| AFP | | | 0.659 |
| < 400 ng/mL | 2 (20) | 5 (33.3) | |
| ≥ 400 ng/mL | 8 (80) | 10 (66.7) | |
| Liver Cirrhosis | | | 1.000 |
| Yes | 7 (70) | 10 (66.7) | |
| No | 3 (30) | 5 (33.3) | |
| Encapsulation | | | 1.000 |
| Complete | 1 (10) | 1 (6.7) | |
| Incomplete | 9 (90) | 14 (93.3) | |
| PVTT type | | | 0.667 |
| Type I, II | 6 (60) | 11 (73.3) | |
| Type III, IV | 4 (40) | 4 (26.7) | |

AFP, alpha fetoprotein; ALT, alanine aminotransferase; PVTT, portal vein tumor thrombosis. Data are presented as mean ± standard deviation, number (%), or median (interquartile range).

other therapies are available for these patients such as surgical resection, transarterial chemoembolization (TACE), and radiotherapy [15, 21, 22]. Recent studies have suggested that hepatic resection is a more optimal treatment option which may yield better long-term survival for these patients [15, 17, 23], although the prognosis is still poor with early tumor recurrence [24]. Taken together, the aforementioned studies indicate that treatment of PVTT is complicated and the outcomes of monotherapy are unacceptable. Thus, combination therapy might be indicated to prevent the recurrence of HCC with PVTT after surgery. However, it is currently not recommended in Western guidelines (AASLD, EASL) [14, 20].

A significant amount of research is currently being devoted to determining the value of sorafenib given postoperatively after liver resection [25]. In a recent study, Wang et al. [26] administered sorafenib postoperatively for 4 months to patients with HCC and risk factors for recurrence who had undergone surgical resection and found that the time to recurrence in the sorafenib arm was 21.45 ± 1.98 months as compared to 13.44 ± 2.66 months in the control arm (P=0.006) and the recurrence rate of the 2 groups was significantly different (29.4% vs 70.7%, respectively, P=0.032). Interestingly, Cox regression analysis showed that taking sorafenib was the only prognostic variable associated with HCC recurrence (hazard ratio [HR] =0.24, P=0.014).

The recently published STORM study was a phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of HCC [27]. The primary endpoint was recurrence-free survival (RFS), and secondary endpoints included time to recurrence (TTR) and OS, and a total of 1114 patients were randomized to receive soranefib (n=556) or placebo (n=558) after treatment. Baseline characteristics were balanced between groups, and no differences RFS, TTR, and OS were observed. While these results are different than ours, it must be noted there are differences between the 2 studies. The STORM trial examined the adjuvant use of sorafenib post surgery in BCLC A patients, but did not examine the use of sorafenib after surgery for advanced staged HCC patients, particularly patients with PVTT (i.e., BCLC C stage), as was done in our study and thus the cancer burden of the patients in the 2 studies was different. The STORM study included patients with microvascular invasion, whereas our study focused on patients with macroscopic PVTT. Thus, the results of the STORM study do not contradict the results of the current study because the study populations were different, and do not preclude the use of sorafenib in BCLC C patients.

Published cases of a major or complete response of advanced HCC treated with sorafenib have led several centers to consider surgery after downstaging with sorafenib [28,

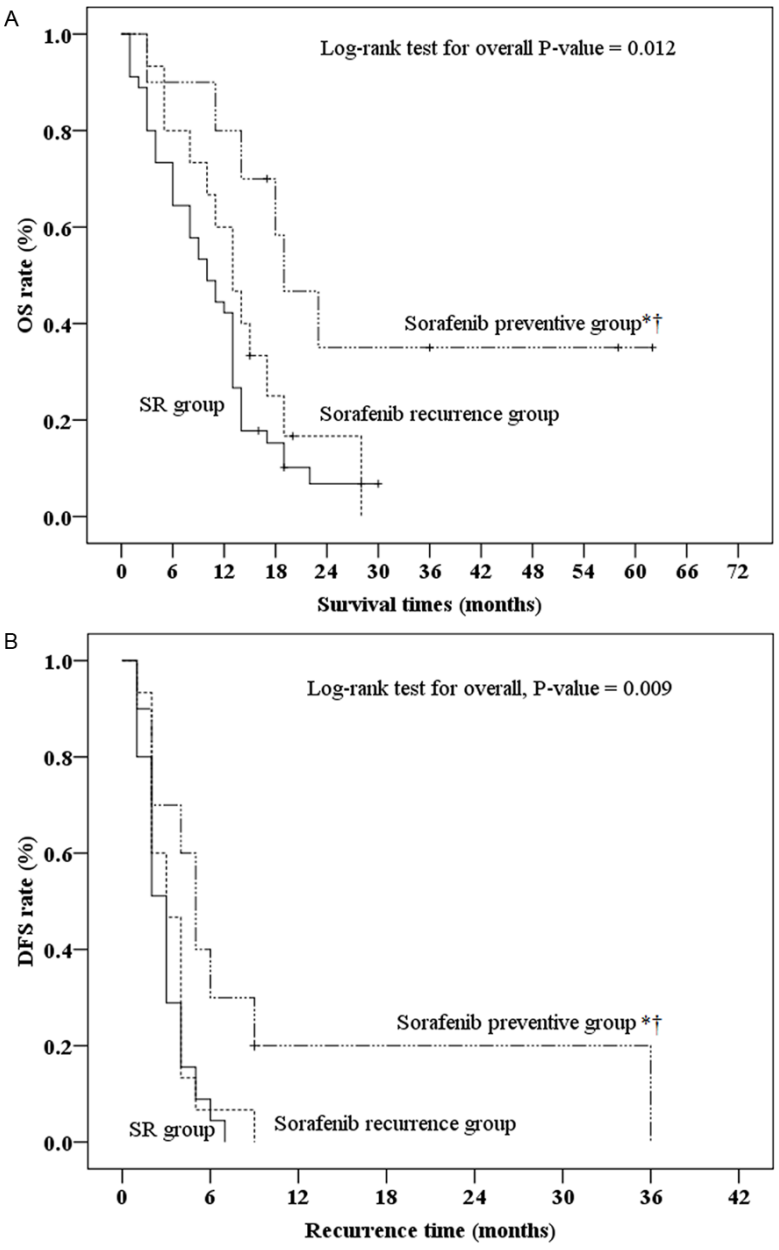


**Figure 2.** A. Kaplan-Meier curves for overall survival (OS) of the surgical resection (SR), preventive sorafenib, and sorafenib after recurrence groups. Differences between groups were compared with the log-rank test. The log-rank test indicated OS was significantly different among the 3 groups (P=0.012). OS was significantly greater in the preventive group than the other 2 groups, and there was no difference between the SR and recurrence group (SR vs. recurrence: P=0.260; *SR vs. preventive group: P=0.005; †Recurrence vs. preventive group: P=0.049). B. Kaplan-Meier curves for disease-free survival (DFS) of the surgical resection (SR), preventive sorafenib, and sorafenib after recurrence groups. Differences between groups were compared with the log-rank test. The log-rank test indicated DFS was significantly different among the 3 groups (P=0.009). The DFS was significantly greater in the preventive group than the other 2 groups, and there was no difference between the SR and recurrence group (SR vs. recurrence: P=0.324; *SR vs. preventive group: P=0.004; †Recurrence vs. preventive group: P=0.044).

29], and no adverse effect of preoperative administration of sorafenib has bene observed during and immediately after liver resection for HCC [30]. It has also been shown that sorafenib may be a feasible treatment option for recurrent HCC after liver transplantation [31]. While most studies have focused on patients with good liver function (Child-Pugh class A), recent reports have suggested that sorafenib may be tolerable and of value in Child-Pugh class B patients with HCC [32-34].

The primary limitations of this study are the small number of patients, especially in the sorafenib subgroups, and that it was performed at a single center. In addition, patients were not randomized to receive sorafenib; instead their decision to take the drug was based on their personal preference and concern over adverse effects after discussion of the risks and benefits, and their own economic situation. Thus, one potential bias is that patients who received sorafenib were better off financially than the general population, and that both the patients and the treating physicians were more aggressive with respect to anti-cancer therapy. The prolongation of DFS with sorafenib was small, and may be due to the small sample size of the study. However, despite these limitations the results clearly indicate that sorafenib improved survival in the patients studied.

## Conclusions

Sorafenib administered postoperatively can improve the OS and DFS of patients with BCLC stage C disease and PVTT who have undergone surgical resection, in particular for patients who began sorafenib within 2 weeks after surgery. Further studies of the postoperative use of sorafenib in patients with HCC are warranted.

## Acknowledgements

This work was supported by the grants of the Science Fund for Creative Research Groups (No: 81221061); The State Key Project on Diseases of China (2012zx10002016016003); The China National Funds for Distinguished Young Scientists (No: 81125018); Chang Jiang Scholars Program (2013) of China Ministry of Education; The National Key Basic Research Program "973 project" (No: 2015CB554000); New Excellent Young Talents of Shanghai Municipal Health Bureau (No: XQY 2013112); Shanghai Science and Technology Committee (No: 134119a0200); Natural Science Foundation (No: 81301876).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Shu-Qun Cheng, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225 Changhai Road, Shanghai 200000, China. Tel: (86)21-81875251; Fax: +86-21-65562400; E-mail: shuqun_chengsq@sina.com

## References

[1] Yamane B and Weber S. Liver-directed treatment modalities for primary and secondary hepatic tumors. Surg Clin North Am 2009; 89: 97-113.

[2] Nordenstedt H, White DL and El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liver Dis 2010; 42 Suppl 3: S206-S214.

[3] Shuqun C, Mengchao W, Han C, Feng S, Jiahe Y, Guanghui D, Wenming C, Peijun W and Yuxiang Z. Tumor thrombus types influence the prognosis of hepatocellular carcinoma with the tumor thrombi in the portal vein. Hepatogastroenterology 2007; 54: 499-502.

[4] Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC and Cheng SQ. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol 2010; 17: 2073-2080.

[5] Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J and Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999; 29: 62-67.

[6] Llovet JM and Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 2008; 48 Suppl 1: S20-S37.

[7] Konishi M, Ryu M, Kinoshita T and Inoue K. Surgical treatment of hepatocellular carcinoma with direct removal of the tumor thrombus in the main portal vein. Hepatogastroenterology 2001; 48: 1421-1424.

[8] Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, Kianmanesh R, Ng IO, Curley SA, Yamaoka Y, Lauwers GY and Vauthey JN. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 2005; 137: 403-410.

[9] Hasskarl J. Sorafenib: targeting multiple tyrosine kinases in cancer. Recent Results Cancer Res 2014; 201: 145-164.

[10] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.

[11] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D and Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.

[12] Berk V, Kaplan MA, Tonyali O, Buyukberber S, Balakan O, Ozkan M, Demirci U, Ozturk T, Bilici A, Tastekin D, Ozdemir N, Unal OU, Oflazoglu U, Turkmen E, Erdogan B, Uyeturk U, Oksuzoglu B, Cinkir HY, Yasar N and Gumus M. Efficiency and side effects of sorafenib therapy for advanced hepatocellular carcinoma: a retrospective study by the anatolian society of medical oncology. Asian Pac J Cancer Prev 2013; 14: 7367-7369.

[13] Gauthier A. Role of sorafenib in the treatment of advanced hepatocellular carcinoma: An update. Hepatol Res 2013; 43: 147-154.

[14] Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management

of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.
[15] Liu PH, Lee YH, Hsia CY, Hsu CY, Huang YH, Chiou YY, Lin HC and Huo TI. Surgical resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. Ann Surg Oncol 2014; 21: 1825-1833.
[16] Roayaie S, Jibara G, Taouli B and Schwartz M. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol 2013; 20: 3754-3760.
[17] Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC and Cheng SQ. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011; 18: 74-80.
[18] Feng YX, Wang T, Deng YZ, Yang P, Li JJ, Guan DX, Yao F, Zhu YQ, Qin Y, Wang H, Li N, Wu MC, Wang HY, Wang XF, Cheng SQ and Xie D. Sorafenib suppresses postsurgical recurrence and metastasis of hepatocellular carcinoma in an orthotopic mouse model. Hepatology 2011; 53: 483-492.
[19] Nexavar product information. Bayer Australia LTD. 2014. Available at: www.bayerresources.com.au/resources/uploads/PI/file9402.pdf Accessed March 3, 2014.
[20] European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer: EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943.
[21] Nakazawa T, Hidaka H, Shibuya A, Okuwaki Y, Tanaka Y, Takada J, Minamino T, Watanabe M, Kokubu S and Koizumi W. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterol 2014; 14: 84.
[22] Tawada A, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Saito T, Ogasawara S, Suzuki E, Maruyama H, Kanai F, Yoshikawa M and Yokosuka O. Efficacy of transarterial chemoembolization targeting portal vein tumor thrombus in patients with hepatocellular carcinoma. Anticancer Res 2014; 34: 4231-4237.
[23] Peng ZW, Guo RP, Zhang YJ, Lin XJ, Chen MS and Lau WY. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. Cancer 2012; 118: 4725-4736.
[24] Chok KS, Cheung TT, Chan SC, Poon RT, Fan ST and Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg 2014; 38: 490-496.
[25] Zhong Y, Liu B, Deng M and Xu R. Adjuvant systemic drug therapy and recurrence of hepatocellular carcinoma following curative resection. Drug Discov Ther 2013; 7: 164-166.
[26] Wang SN, Chuang SC and Lee KT. Efficacy of sorafenib as adjuvant therapy to prevent early recurrence of hepatocellular carcinoma after curative surgery: A pilot study. Hepatol Res 2014; 44: 523-531.
[27] Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G, Llovet JM; STORM investigators. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015; 16: 1344-1354.
[28] Vagefi PA and Hirose R. Downstaging of hepatocellular carcinoma prior to liver transplant: is there a role for adjuvant sorafenib in locoregional therapy? J Gastrointest Cancer 2010; 41: 217-220.
[29] Barbier L, Muscari F, Le Guellec S, Pariente A, Otal P and Suc B. Liver resection after downstaging hepatocellular carcinoma with sorafenib. Int J Hepatol 2011; 2011: 791013.
[30] Barbier L, Fuks D, Pessaux P, Muscari F, Le Treut YP, Faivre S and Belghiti J. Safety of liver resection for hepatocellular carcinoma after sorafenib therapy: a multicenter case-matched study. Ann Surg Oncol 2013; 20: 3603-3609.
[31] Sotiropoulos GC, Nowak KW, Fouzas I, Vernadakis S, Kykalos S, Klein CG and Paul A. Sorafenib treatment for recurrent hepatocellular carcinoma after liver transplantation. Transplant Proc 2012; 44: 2754-2756.
[32] Inghilesi AL, Gallori D, Antonuzzo L, Forte P, Tomcikova D, Arena U, Colagrande S, Pradella S, Fani B, Gianni E, Boni L, Laffi G, Di Costanzo F and Marra F. Predictors of survival in patients with established cirrhosis and hepatocellular carcinoma treated with sorafenib. World J Gastroenterol 2014; 20: 786-794.
[33] Zugazagoitia J, Manzano A, Sastre J, Ladero JM, Puente J and Díaz-Rubio E. Sorafenib for non-selected patient population with advanced hepatocellular carcinoma: efficacy and safety data according to liver function. Clin Transl Oncol 2013; 15: 146-153.
[34] Pressiani T, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, Ferrari D, Cortesi E, Porta C, Mucciarini C, Latini L, Carnaghi C, Banzi M, Fanello S, De Giorgio M, Lutman FR, Torzilli G, Tommasini MA, Ceriani R, Covini G, Tronconi MC, Giordano L, Locopo N, Naimo S and Santoro A. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol 2013; 24: 406-411.

**Supplementary Table 1.** Summary of treatments after tumor recurrence

| Treatment after tumor recurrence | Surgical resection (n=45) | Surgical resection + sorafenib (n=25) | *P* value |
|---|---|---|---|
| Repeat resection | 2 (4.4) | 2 (8) | 0.613 |
| TACE | 30 (66.7) | 18 (72) | 0.645 |
| Radiotherapy | 18 (40) | 12 (48) | 0.517 |
| Systemic chemotherapy | 9 (20) | 8 (32) | 0.262 |
| Best supportive care | 10 (22.2) | 3 (12) | 0.353 |

TACE, transcatheter arterial chemoembolization. Data are presented as number (%).

**Supplementary Table 2.** Comparison of lesion number and size and extent of PVTT between the preventive sorafenib and surgical resection groups

| | Preventive sorafenib (n=10) | Surgical resection (n=45) | *P* value |
|---|---|---|---|
| PVTT type | | | 0.713 |
| Type I, II | 6 (60) | 31 (68.9) | |
| Type III, IV | 4 (40) | 14 (31.1) | |
| Lesion number | | | 0.287 |
| Single | 8 (80) | 26 (57.8) | |
| Multiple | 2 (20) | 19 (42.2) | |
| Tumor size, cm | 9.61 ± 4.26 | 11.98 ± 4.76 | 0.154 |

PVTT, portal vein tumor thrombosis. Data are presented as number (%).

**Supplementary Table 3.** Comparison of lesion number and size and extent of PVTT between the preventive sorafenib and sorafenib after recurrence groups

| | Preventive sorafenib (n=10) | Sorafenib after recurrence (n=15) | *P* value |
|---|---|---|---|
| PVTT type | | | 0.667 |
| Type I, II | 6 (60) | 11 (73.3) | |
| Type III, IV | 4 (40) | 4 (26.7) | |
| Lesion number | | | 1.000 |
| Single | 8 (80) | 12 (80) | |
| Multiple | 2 (20) | 3 (20) | |
| Tumor size, cm | 9.61 ± 4.26 | 7.78 ± 3.74 | 0.269 |

PVTT, portal vein tumor thrombosis. Data are presented as number (%).

**Supplementary Table 4.** Summary of major complications in sorafenib groups

| Complication | Preventive sorafenib (n=10) | Sorafenib after recurrence (n=15) | *P* value |
|---|---|---|---|
| Rash | 5 (50) | 8 (53.3) | 1.000 |
| Diarrhea | 5 (50) | 6 (40) | 0.697 |
| Alopecia | 3 (30) | 6 (40) | 0.691 |
| Arthralgia | 4 (40) | 4 (26.7) | 0.667 |

Data are presented as number (%).