JBUON 2019; 24(4): 1382-1389
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Hepatectomy combined with sorafenib in patients with intermediate-advanced hepatocellullar carcinoma

Hongfei Zhu[1]*, Bogen Ye[1]*, Zhenguo Qiao[2], Li Zeng[1], Qigen Li[1]

[1]Department of Organ Transplantation, Changhai hospital, Navy Military Medical University, Shanghai 200433, China; [2]Department of Gastroenterology, Affiliated Wujiang Hospital of Nantong University, Suzhou, Jiangsu 215200, China.

* These authors contributed equally to this work.

Summary

Purpose: *To evaluate the efficacy and tolerability of hepatectomy in combination with sorafenib in the treatment of intermediate-advanced hepatocellular carcinoma (HCC).*

Methods: *One hundred and eighty-sixty consecutive patients with intermediate-advanced HCC who were treated with sorafenib were enrolled in this study. They were divided into two groups: sorafenib group (39) and hepatectomy combined with sorafenib group (147). Survival rates of the patients were analyzed by the Kaplan-Meier method. Cox's proportional hazards model was used to analyze variables associated with survival. Adverse events induced by sorafenib were observed and recorded.*

Results: *The median follow-up duration was 13.0 months (range 1-41). There were 77 patients with intermediate HCC (BCLC stage B) (41.4%) and 109 patients with advanced HCC (BCLC stage C) (58.6%). The overall survival was greater in patients with intermediate HCC than in patients with advanced HCC (p=0.011). Surgery before administration of sorafenib did not contribute to overall survival of patients with intermediate HCC (p=0.312). For patients with advanced HCC, the survival of those who underwent surgery before sorafenib was significantly longer than that of patients who received sorafenib alone (15.0 months, 95% CI 12.3-17.7 vs. 8.0 months, 95% CI 5.5-10.5; p=0.024) and surgery before sorafenib was identified as the only predictor of survival for patients with advanced HCC (HR, 0.582; 95%CI, 0.353-0.932; p=0.035).*

Conclusions: *The combination of surgery and sorafenib is safe and significantly prolongs overall survival of patients with advanced HCC.*

Key words: *advanced hepatocellular carcinoma, hepatectomy, sorafenib, survival*

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the third most frequent cause of cancer-related death [1]. For optimal management, the treatment choice is guided by staging systems and treatment guidelines. Until now numerous staging systems have been proposed and treatment guidelines vary by region. The Barcelona Clinic Liver Cancer (BCLC) classification, which is approved by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases, is widely used in western countries [2]. It incorporates variables related to tumor burden, liver functional reserve, and general performance status. According to the BCLC classification, liver resection should be performed only in patients with very early and early-stage HCC (BCLC stages 0 and A), whereas patients with intermediate and advanced stages (BCLC stages B and C) should receive palliative treatment [3]. However, some other factors modulate the

Corresponding author: Qigen Li, MD. Department of Organ Transplantation, Changhai Hospital, Navy Military Medical University, 168 Changhai Rd, Shanghai 200433, China.
Tel and Fax: +86 21 31162867, Email: liqigen@126.com
Received: 26/11/2018; Accepted: 05/01/2018

therapeutic decisions in daily clinical practice, such as presence of comorbidities, anatomical location of tumors and expertise of the involved teams. Recently, many papers reported experience with surgical management of intermediate and advanced HCC, showing that in selected patients a radical approach could be offered with encouraging survival and morbidity [4-7].

Sorafenib, a multikinase inhibitor with antiangiogenic and antiproliferative properties [8,9], has been shown to prolong the median overall survival and the median time to radiological progression compared to placebo in randomized controlled trials [10,11] and has become the current standard of care for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors or those tumors progressing on loco-regional therapies (concept of treatment migration) [12]. We believe that combining surgery and sorafenib may have the potential to increase the efficacy of treatment. Herein, we conducted this study to evaluate the safety and efficacy of liver resection in combination with continuous sorafenib treatment in patients with intermediate-advanced HCC.

Methods

Patients and study design

This was a retrospective study. From June 2014 to June 2016, 202 consecutive patients with HCC received sorafenib at our department. Of the 202 patients, 186 who were regarded as having intermediate-advanced HCC according to the BCLC classification were enrolled in this study. A hundred and forty-seven patients underwent hepatectomy before administration of sorafenib, which was defined as surgery+sorafenib group. The remaining 38 patients were the sorafenib-alone group. The diagnosis of HCC was made by imaging methods following the European Association for the Study of the Liver (EASL) criteria [13]. The research protocol of this study was carried out after approval of the Clinical Research Ethics Committee of the Eastern Hepatobiliary Surgery Hospital. Informed consent was obtained from all participants.

Preoperative evaluation

All patients had chest X-ray, ultrasonography (USG) of abdomen, and contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. Laboratory blood tests including complete blood counts, serum albumin, total bilirubin, aspartate amino transferase (AST), alanine aminotransferase (ALT), prothrombin time , hepatitis B surface antigen, antibodies to hepatitis C, serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were obtained. Resectability of each primary tumor mass and metastatic focus was assessed cautiously by USG, CT and MRI. Liver function was evaluated carefully by the Child-Pugh classification.

Surgical algorithms and procedures

Resection criteria were constant over the study period, including resectable tumor, tumor thrombus, gross metastatic focus and adequate liver function reserve. Besides, maximum resection of the intrahepatic HCC, angiotomy and thrombus removal were considered in cases accompanied with portal venous, hepatic venous or inferior caval vein thrombus. Hepatic resection was carried out under general anesthesia using a right subcostal incision with a midline extension. Pringle's maneuver was routinely used with a clamp/unclamp time of 30 min/5 min. Liver resection was carried out by a clamp crushing method. Major hepatectomy was defined as resection of three or more hepatic segments according to Couinaud's classification, and minor hepatectomy was defined as resection of fewer than three hepatic segments.

Sorafenib

Sorafenib was administered as 400 mg b.i.d. Discontinuation and dose reduction was based on tolerance. The selection criteria for sorafenib included well-preserved

Table 1. Characteristics of the study population

BCLC stage (n)	*B (77)*	*C (109)*
Age (years) [a]	54 (16-74)	49 (16-80)
Male gender	89.6% (69)	93.6% (102)
HbsAg positive	81.8% (63)	83.5% (91)
Total bilirubin (μmol/L) [a]	14.9 (5.0-63.9)	16.4 (5.8-142.6)
ALT (IU/L) [a]	44 (10.0-177.1)	35.6 (6.6-208.1)
AST (IU/L) [a]	46.7 (16.1-188.9)	45.7 (17.3-264.0)
Albumin (g/L) [b]	39.4±4.8	39.8±4.5
AFP (ng/ml) [a]	302.2 (0.6-2041000.0)	1210.0 (9634000.0)
Child-Pugh A class	94.9% (75)	97.2% (106)
Cirrhosis	80.5% (62)	75.2% (82)
Tumor number		
Solitary	0	62.4% (68)
Multiple	100% (77)	37.6% (41)
Maximum tumor size (mm) [a]	98.5 (11-180)	100 (32-189)
Macrovascular invasion	0	97.2% (106)
Extrahepatic spread	0	25.7% (28)
Operation	24.7% (19)	18.3% (20)
Other treatment(s)		
TACE	59.7% (46)	52.3% (57)
Radiotherapy	5.2% (4)	3.7% (4)
PEI	2.6% (2)	0
RFA	3.9% (3)	0

Results are expressed as % (n) unless otherwise specified; [a] Median (range); [b] Mean (standard deviation); HbsAg: hepatitis B surface antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: alpha-fetoprotein; TACE: transarterial hemoembolization; PEI: percuraneous ethanol injection; RFA: radiofrequency ablation

liver function (Child-Pugh A class or B class); tumors in BCLC C stage; tumors in BCLC B stage with poor arterial supply or those tumors progressing on loco-regional therapies (concept of treatment migration). Sorafenib was administered 4-6 weeks after surgery for patients who also had undergone hepatectomy.

Follow-up

The follow-up program included serum AFP assay, abdominal USG, chest X-ray and liver function tests every month. Contrast CT scan was performed every 3 months for surveillance of recurrence. Safety and tolerance evaluation involved documented history and physical examinations, laboratory tests, whereas grading of adverse events was assessed using the National Cancer Institute Common Terminology Criteria version 3.0. Patients who underwent surgical treatment were observed prospectively for postoperative residual tumors with assessment by serum AFP assay, abdominal USG, CT/MRI, and chest X-ray one month later after operation.

Statistics

Quantitative values were compared using the Student's t-test or the Mann-Whitney nonparametric U test, and the x^2 test or Fisher's exact test were used to compare categorical data between groups. Continuous variables were summarized as medians (ranges) or mean±SD, and categorical variables as percentages. Clinically applicable cut-offs were chosen for easy interpretation. The Kaplan-Meier method was utilized to estimate survival and log-rank test to estimate differences between groups. The clinicopathologic variables identified by univariate analysis with $p<0.05$ were included in multivariate analysis by the Cox's proportional hazards model for potential associations with the survival outcomes of HCC patients. All statistical analyses were conducted using SPSS version 16.0 (SPSS, Chicago, IL, USA). P values <0.05 were considered statistically significant.

Results

Patient characteristics

Characteristics of the 186 newly diagnosed, previously untreated patients with intermediate-advanced HCC who were retrospectively studied are shown in Table 1. Of the 186 patients, 77 (41.4%) were in BCLC stage B and the remaining were in BCLC stage C. Time zero was the day patients underwent operation or the day they had sorafenib for the first time. The median follow-up duration was 13.0 months (range 1-41). Patients who were subjected to liver resection were administered sorafenib with a median of 30 days after operation (range 26-53). The overall survival was greater in patients with intermediate HCC than in patients with advanced HCC (p=0.011).

Table 2. Surgical procedures and outcomes of patients stratified according to the Barcelona Clinic Liver Cancer (BCLC) classification

Procedures/Outcomes	*n*	*n*
BCLC stage (n)	B (77)	C (109)
Surgery, No. (%)	19 (24.7)	20 (18.3)
Major/minor	13/6	8/12
Thrombus removal from portal vein	0	19
Type of PVTT removal		
Removal via PV stump	0	6
Removal via main trunk	0	13
Thrombus removal from bile duct	0	1
Combined organ resection		
Partial diaphragmatic resection	0	3
Partial gastric wall resection	0	1
Intraoperative blood loss, median (range), mL	400 (50-3000)	500 (200-2000)
Intraoperative transfusion, n (%)	5 (26.3)	9 (45)
Duration of Pringle maneuver, median (range), mL	19 (9-45)	24 (10-50)
Hospital mortality	0	0
Length of hospital stay, median (range), days	14 (9-28)	16 (9-27)
Complications		
Pleural effusion	4	5
Ascites	4	4
Respiratory infection	1	0
Hyperbilirubinemia	1	1
Enteroplegia	1	0

Table 3. Univariate analysis of factors related with survival of patients included into the study according to BCLC staging

	BCLC stage B			*BCLC stage C*		
	N	*Median survival* (range, months)	*Log rank test* (p value)	*N*	*Median survival* (range, months)	*Log rank test* (p value)
Age (yr)			0.811			0.371
≤60	52	17.0 (10.5-23.5)		89	8.0 (6.2-9.8)	
>60	25	18.0 (7.6-28.4)		20	12.0 (7.0-17.0)	
Gender			0.951			0.452
Male	69	17.0 (12.0-22.0)		102	13.3 (6.9-11.1)	
Female	8	13.6 (7.3-19.9)		7	34.0	
HbsAg			0.348			0.240
Positive	63	17.0 (10.9-23.1)		91	9.0 (6.3-11.7)	
Negative	14			18	12.0 (7.7-16.3)	
AFP (ng/ml)			0.288			0.290
≤400	40	17.0 (6.4-27.6)		41	10.0 (6.5-13.5)	
>400	37	15.7 (11.1-22.9)		68	8.0 (5.4-10.6)	
Total bilirubin (μmol/L)			0.323			0.238
≤17.1	50	21.0 (16.3-25.7)		61	10.0 (7.6-12.4)	
>17.1	27	12.0 (9.4-14.6)		48	6.0 (1.8-10.2)	
ALT (IU/L)			0.837			0.455
≤40	38	17.0 (9.4-24.6)		61	10.0 (5.1-14.9)	
>40	39	18.0 (10.3-25.7)		48	8.0 (5.2-10.8)	
AST (IU/L)			0.815			0.038
≤40	28	17.0 (5.5-28.5)		45	11.0 (3.5-18.5)	
>40	49	18.0 (10.5-25.4)		64	6.0 (3.1-8.9)	
Albumin (g/L)			0.116			0.144
≤40	35	12.0 (9.8-14.2)		55	9.0 (5.0-13.0)	
>40	42	17.6 (15.7-22.3)		54	9.0 (6.7-11.3)	
Cirrhosis			0.924			0.319
Yes	62	17.0 (11.2-22.9)		82	10.0 (6.9-13.1)	
No	15	18.0 (4.7-31.3)		27	8.0 (5.1-10.9)	
Tumor number						0.650
Solitary	0	-		68	9.0 (7.0-11.0)	
Multiple	77	17.0 (11.7-22.3)		41	8.0 (2.7-13.3)	
Macrovascular invasion						0.604
Present	0	-		106	9.0 (7.0-11.0)	
Absent	77	17.0 (11.7-22.3)		3	3.0 (0-15.4)	
Extrahepatic spread						0.112
Present	0	-		28	6.0 (2.4-9.6)	
Absent	77	17.0 (11.7-22.3)		81	11.0 (6.9-15.1)	
Operation			0.312			0.024
Yes	19	19.0 (13.8-24.2)		20	15.0 (12.3-17.7)	
No	58	13.0 (8.2-17.9)		89	8.0 (5.5-10.5)	
Other treatment(s)[a]			0.431			0.247
Yes	47	18.0 (13.8-22.2)		57	12.0 (9.1-14.9)	
No	30	13.7 (8.0-16.0)		52	8.0 (5.4-10.6)	

[a] includes TACE, PEI, Radiotherapy, RFA; HbsAg: hepatitis B surface antigen; AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Analysis by BCLC stage

BCLC-B

Patients in BCLC stage B consisted of 69 men and 8 women with a median age of 54 years (range 16-74). Most of the patients (94.5%) are in Child-Pugh A liver function. The patient characteristics are summarized in Table 1. Among the 77 patients, 19 underwent hepatectomy before been treated with sorafenib. Surgical procedures and outcomes for the patients are shown in Table 2. Forty-seven (61.0%) patients received other adjuvant therapies (TACE 59.7%, radiotherapy 5.2%, RFA 3.9%, PEI 2.6%). No adjuvant therapy contributed to overall survival of patients in BCLC stage B with the treatment of sorafenib (Table 3).

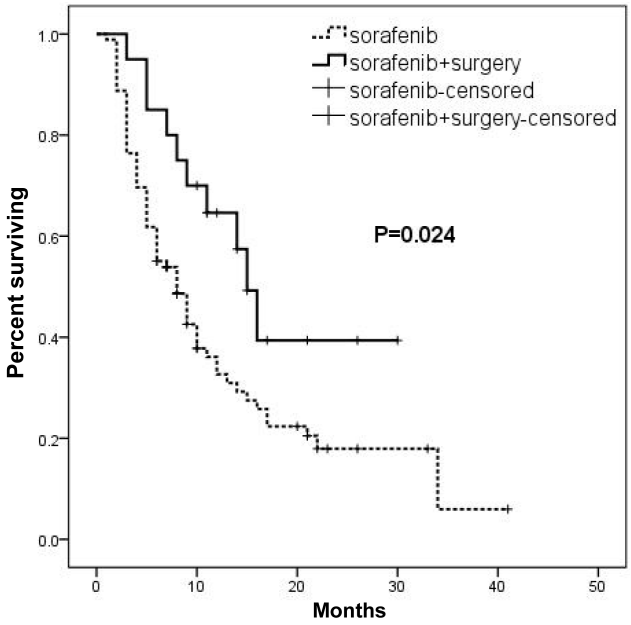

Figure 1. Kaplan-Meier overall survival for patients with advanced HCC who were treated with surgery combined with sorafenib or sorafenib alone.

BCLC-C

Among the BCLC stage C patients, there were 102 men and 7 women. The median age was 49 years (range 16-80). A hundred and six (97.2%) patients presented with macrovascular invasion and 28 (25.7%) presented with extrahepatic spread. Twenty-four (22.0%) patients were inflicted with both macrovascular invasion and extrahepatic spread. The characteristics of patients were shown in Table 1. Although 82 (75.2%) patients had cirrhosis, most of the patients (97.2%) presented with Child-Pugh A liver function. The HbsAg-positive rate was 83.5%. Fifty-seven patients (52.3%) received TACE and 4 (3.7%) underwent radiotherapy during the treatment of sorafenib. Twenty of the 109 patients underwent surgery before administration of sorafenib. The complication rate was 50.0% and the most common complications were ascites and pleural effusion, which usually resolved with diuretics or paracentesis. No patient died during the hospitalization period. Table 2 summarizes the surgical procedures and outcomes.

Survival

The survival of patients with advanced HCC who underwent surgery before sorafenib was significantly longer than that of patients who received sorafenib alone (15.0 months, 95% CI 12.3-17.7 vs. 8.0 months, 95% CI 5.5-10.5; p=0.024; Figure 1). Baseline demographic data were well-

Table 4. Comparison of baseline characteristics between patients with advanced HCC treated with sorafenib and treated with sorafenib combined with surgery

Characteristics	*Sorafenib*	*Sorafenib combined with surgery*	*p value*
Age, years[a]	49.7±11.8	48.4±8.7	0.643
Gender, M/F	83/6	19/1	0.774
Total bilirubin, μmol/L[a]	20.2±15.3	14.4±7.4	0.102
ALT, IU/L[a]	44.1±30.6	48.8±41.5	0.565
AST, IU/L[a]	63.2±42.6	43.2±24.5	0.007
Albumin, g/L[a]	39.0±4.2	39.4±4.9	0.671
AFP, ng/ml[a]	140402.1±1020553.2	12520.1±43099.8	0.578
Prothrombin time, s[a]	12.6±1.2	12.0±1.3	0.051
HBS/eAg, positive/negative	75/14	16/4	0.642
Child-Pugh class, A/B	86/3	20/0	0.405
No. of tumor, Solitary/multiple	54/35	14/6	0.437
Macrovascular invasion, present/absent	87/2	19/1	0.334
Extrahepatic spread, present/absent	24/65	4/16	0.519

[a]mean±SD. ALT:alanine aminotransferase; AST:aspartate aminotransferase; AFP:alpha-fetoprotein

Table 5. Multivariate Cox's model for factors related with survival of patients with advanced HCC

Variables	*HR*	*95%CI for HR*	*p value*
Surgery before administration of sorafenib	0.582	0.353-0.932	0.035
AST (≤40 UI/L vs >40 IU/L)	1.267	0.856-1.874	0.237

HR:hazard ratio; CI:confidence interval; AST:aspartate aminotransferase

Table 6. The adverse events after intaking of sorafenib

Adverse events	*N=186 (%)*	
	All grades n (%)	*Grade ¾ n (%)*
Hand-foot skin reaction	132 (70.9)	15 (8.2)
Diarrhea	102 (55.1)	15 (8.2)
Fatigue	84 (44.9)	0 (0)
Alopecia	54 (29.2)	0 (0)
Erythra	44 (23.8)	0 (0)
Liver function lesion	39 (21.1)	0 (0)
Arthralgia	24 (12.9)	0 (0)
Hypertension	5 (2.7)	0 (0)

matched between the two groups of patients except for AST (Table 4). Univariate analysis revealed that surgical treatment before sorafenib (p=0.024) and AST (p=0.038) were associated with the prognosis of patients with advanced HCC (Table 3). Factors showing statistical significance were analyzed using a multivariate Cox proportional hazard regression. Here, only operative treatment before sorafenib was identified as a predictor of survival (HR, 0.582; 95%CI, 0.353-0.932; p=0.035; Table 5).

Safety and adverse events

All patients experienced at least one adverse event during sorafenib administration. The most common drug-related adverse events (DRAEs) were hand-foot-skin reaction (70.7%), diarrhea (55.1%) and fatigue (44.9%). Infrequent adverse events included arthralgia (12.9%) and hypertension (2.7%). Most DRAEs were mild to moderate. Seventeen patients received reduced doses of sorafenib (400 or 600 mg/day) and 5 patients discontinued drug administration, 3 for hyperbilirubinemia and 2 for diarrhea. No statistically significant differences were observed in the incidence rates of toxicities according to whether patients were operated or not. All the adverse events and their severity are detailed in Table 6.

Discussion

In the current study we evaluated the efficacy and safety of sorafenib in combination with surgery in patients with intermediate-advanced HCC. We established that the combination of sorafenib and surgery was well-tolerated and significantly prolonged the overall survival of patients with advanced HCC.

It is known that the BCLC staging system which takes into account tumor stage, liver function and physical status is endorsed by renowned scientific societies [2,13]. This staging system not only identifies subgroups of HCC patients with different prognosis but also offers treatment guidance. According to BCLC staging system, surgical treatment should be reserved for patients with single lesions not exceeding 5cm and without portal hypertension or hyperbilirubinemia. For patients with stage B or C HCC, the BCLC classification recommends palliation using TACE or sorafenib [3]. However, there is no consensus on the definition of unresectable HCC. During the past years, many surgeons have published their experience with surgical management of intermediate and advanced HCC and they found that in selected patients surgery could be offered with encouraging survival and morbidity [4,14-17]. However, the high incidence of postoperative recurrence remained a big challenge for sustained remission. Meanwhile, Feng and colleagues found that sorafenib significantly suppressed postsurgical intrahepatic recurrences as well as abdominal metastasis in orthotopic HCC xenograft model [18] and similar results were found in the Wang's et al. research [19]. So, comprehensive therapy based on combination with systemic therapy may play an important role in improving the efficacy of therapy for advanced HCC. In our study, we used both treatments sequentially for synergy to complement each other and the median survival of patients who received surgery before sorafenib was 15.0 months, which was significantly longer than that of patients who received sorafenib alone (Figure 1).

The time of using sorafenib can be different. We think the anti-angiogenic effects of sorafenib may delay the time of wound healing and adverse events induced by sorafenib may have adverse effect on recovery. To avoid such disadvantages from sorafenib, we administered sorafenib 4-6 weeks after the operation when patients recovered. This approach is similar to that of an ongoing phase

III randomized clinical trial (RCT) (STORM) [20]. The incidence of adverse events observed in the combination group was similar to the group with sorafenib as monotherapy and there were no unexpected side effects in the combination group. This demonstrated it was safe for patients to receive sorafenib treatment when they recovered from surgery.

Now, another combination treatment – TACE plus sorafenib – is widely studied. The results of these studies show that the combination of sorafenib and TACE is well tolerated in patients with HCC [21-27]. Wolfgang and associates recently reported a median overall survival of 10.6 months for patients with TACE and sorafenib treatment [28]. In another study, Duan et al. showed that patients with advanced HCC benefited from the combination of TACE and sorafenib with a median overall survival of 12 months [23]. Compared with our study, overall survival of patients with advanced HCC in our study was longer than in patients who received TACE and sorafenib. It is interesting to conduct further research to compare the two modalities of combination therapy.

The small number of patients, especially in the combination group and its retrospective design are the main limitations of this study. Although efforts were applied to avoid selection bias and the characteristics of patients matched well in the two groups, 20 patients in the combination group were still too small. Additionally, most patients had chronic hepatitis B virus (HBV) infection, which is common in eastern Asia and sub-Saharan Africa, and the results may not be applicable to patients in the North America, Europe, and Japan, where the dominant risk factor of HCC is chronic infection with hepatitis C virus (HCV).

In conclusion, sorafenib combined with surgery is well tolerated and significantly prolongs overall survival of patients with advanced HCC.

Conflict of interests

The authors declare no conflict of interests.

References

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245-55.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
4. Vitale A, Saracino E, Boccagni P et al. Validation of the BCLC prognostic system in surgical hepatocellular cancer patients. Transplant Proceed 2009;41:1260-3.
5. Ho MC, Huang GT, Tsang YM et al. Liver resection improves the survival of patients with multiple hepatocellular carcinomas. Ann Surg Oncol 2009;16:848-55.
6. Chen CH, Hu FC, Huang GT et al. Applicability of staging systems for patients with hepatocellular carcinoma is dependent on treatment method--analysis of 2010 Taiwanese patients. Eur J cancer 2009;45:1630-9.
7. Torzilli G, Donadon M, Marconi M et al. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: results of a prospective analysis. Archiv Surg 2008;143:1082-90.
8. Chang YS, Adnane J, Trail PA et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. Cancer Chemother Pharmacol 2007;59:561-74.
9. Wilhelm SM, Carter C, Tang L et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099-109.
10. Cheng AL, Kang YK, Chen Z et al. 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.
11. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359:378-90.
12. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
13. Bruix J, Sherman M, Llovet JM et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol 2001;35:421-30.
14. Yang T, Lin C, Zhai J et al. Surgical resection for advanced hepatocellular carcinoma according to Barcelona Clinic Liver Cancer (BCLC) staging. J Cancer Res Clin Oncol 2012;138:1121-9.
15. Kim BK, Kim SU, Park JY et al. Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-I patients with hepatocellular carcinoma. Liver Int 2012;32:1120-7.
16. Chang WT, Kao WY, Chau GY et al. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? Surgery 2012;152:809-20.

17. Lin DX, Zhang QY, Li X, Ye QW, Lin F, Li LL. An aggressive approach leads to improved survival in hepatocellular carcinoma patients with portal vein tumor thrombus. J Cancer Res Clin Oncol 2011;137:139-49.
18. Feng YX, Wang T, Deng YZ et al. Sorafenib suppresses postsurgical recurrence and metastasis of hepatocellular carcinoma in an orthotopic mouse model. Hepatology 2011;53:483-92.
19. Wang Z, Hu J, Qiu SJ et al. An investigation of the effect of sorafenib on tumour growth and recurrence after liver cancer resection in nude mice independent of phosphorylated extracellular signal-regulated kinase levels. Exp Opin Investig Drugs 2011;20:1039-45.
20. Printz C. Clinical trials of note. Sorafenib as adjuvant treatment in the prevention of disease recurrence in patients with hepatocellular carcinoma (HCC) (STORM). Cancer 2009;115:4646.
21. Sansonno D, Lauletta G, Russi S, Conteduca V, Sansonno L, Dammacco F. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. Oncologist 2012;17:359-66.
22. Qu XD, Chen CS, Wang JH et al. The efficacy of TACE combined sorafenib in advanced stages hepatocellullar carcinoma. BMC Cancer 2012;12:263.
23. Duan F, Wang MQ, Liu FY, Wang ZJ, Song P, Wang Y. Sorafenib in combination with transarterial chemoembolization and bronchial arterial chemoinfusion in the treatment of hepatocellular carcinoma with pulmonary metastasis. Asian Pac J Clin Oncol 2012;8:156-63.
24. Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29:3960-7.
25. Kudo M, Imanaka K, Chida N et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47:2117-27.
26. Cabrera R, Pannu DS, Caridi J et al. The combination of sorafenib with transarterial chemoembolisation for hepatocellular carcinoma. Aliment Pharmacol Therapeutics 2011;34:205-13.
27. Dufour JF, Hoppe H, Heim MH et al. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phase I study. Oncologist 2010;15:1198-204.
28. Sieghart W, Pinter M, Reisegger M et al. Conventional transarterial chemoembolisation in combination with sorafenib for patients with hepatocellular carcinoma: a pilot study. Eur Radiol 2012;22:1214-23.