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Original Article

Treatment results and prognostic factors in resectable hepatocellular carcinoma—Results from a local general hospital

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ABSTRACT

Objective: Hepatocellular carcinoma (HCC) is a common cause of cancer mortality. Resection is the best choice for HCC. Our objective was to evaluate the impact of various factors that affected survival in patients with resectable HCC.
Materials and methods: Between January 1, 2007 and December 31, 2013, 107 patients with a diagnosis of HCC who underwent surgery were enrolled retrospectively. The analysis was carried using *t* tests, the Kaplan–Meier method, and Cox proportional hazard regression model to identify potential confounding and predicting variables.
Results: The 3-year overall survival rates in patients with surgical margins >1 mm and ≤1 mm were 79% and 59% ($p = 0.02$), respectively, and those in patients with and without vascular invasion were 57% and 93% ($p < 0.001$), respectively. Based on multivariate analysis, postoperative pathological vascular invasion (hazard ratio, 6.25; 95% confidence interval, 2.01–19.37) and surgical margin (hazard ratio, 0.37; 95% confidence interval, 0.14–0.96) remained independent predictors of an adverse long-term outcome.
Conclusion: Patients with vascular invasion combined with surgical margins ≤1 mm are at risk of poor survival and have a worse locoregional control rate. Further studies are warranted to identify the optimal strategy for the prevention and management of intrahepatic recurrence in order to further improve the prognosis of HCC after resection.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer mortality in Taiwan. The 5-year survival rate of individuals is low, and there is an increasing mortality rate [1]. Several modalities, including surgical resection, transcatheter arterial chemoembolization, arterial infusion chemotherapy, percutaneous ethanol injection therapy, microwave coagulation therapy, radiotherapy, and liver transplantation, have been used to treat HCC [2–4]. The traditional approach to the treatment of HCC has been hepatic resection, because resection can be performed without delay and it is associated with low mortality [4]. However, the rate of intrahepatic recurrence has been high [5].

The main causes of late death after hepatectomy are related to intrahepatic cancer recurrence or progressive liver insufficiency due to cirrhosis. Various factors, such as patient age, size and number of tumors, presence of a tumor capsule, vascular invasion, histological grading, pathological stage, and surgical margins, have all been demonstrated to influence recurrence postoperatively [6,7]. Importantly, improved survival after hepatectomy for HCC has been attributed mainly to the prevention of recurrence. The aim of this study was to evaluate the results after surgical treatment of 107 patients with HCC in the same institution; a range of prognostic factors were also analyzed.

Conflicts of interest: none.

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2. Materials and methods

2.1. Patients

Between January 1, 2007 and December 31, 2013, 107 patients with the diagnosis of HCC, who underwent partial hepatectomy with complete gross resection of the disease, were enrolled retrospectively. The study was approved by the Institutional Review Boards of the respective institutions [DTCRD101(2)-I-18]. All patients were evaluated based on a baseline history and physical examination, serum laboratory tests, and a computed tomography or magnetic resonance imaging scan of the abdomen and pelvis.

2.2. Follow-up

Postoperatively, patients were followed up by physical examinations, serial computed tomography scans or ultrasonography, and alpha-fetoprotein levels at 3–6-month intervals for the 1st year and every 6 months thereafter. All patients in this analysis had a minimum of a 6-month follow-up examination. Recurrence of HCC was identified by new lesions on imaging, with an appearance typical of HCC, or by a rising alpha-fetoprotein level. Lesions that were not typical of HCC were confirmed by biopsy. Pathological specimens were reviewed for the following tumor characteristics: number and size of tumors, tumor grade, vascular invasion, and microscopic margins. A margin of >1 mm was considered a negative margin, whereas a margin between 0 mm and ≤1 mm was considered a close margin. A positive margin indicated histological involvement. Pathological vascular invasion was defined as encroachment into blood vessels by a pathological process. Macrovascular involvement was defined as histological involvement of the lobar or segmental branches of portal or hepatic veins, or gross invasion of the right or left main branches of the portal or hepatic veins.

2.3. Analysis

Patient demographics, tumor, operative treatment, and treatment characteristics were evaluated. The following variables were analyzed: age, sex, Child–Pugh classification of cirrhosis, alpha-fetoprotein level, hepatitis serological condition, and extent of resection. Stage was determined by the seventh American Joint Commission on Cancer (AJCC) system.

Comparisons between groups were performed using the Chi-square test for categorical variables and *t* test for continuous variables. Time to recurrence (disease-free survival) and time to death were determined by Kaplan–Meier analysis, and the results for subgroups of patients were compared with a log-rank test (SPSS software version 17.0; SPSS Inc., Chicago, IL, USA). All variables that appeared to be associated significantly with survival ($p < 0.05$) were entered into a Cox proportional hazards model to test for significant effects and adjustment for multiple factors simultaneously. A probability value of <0.05 was considered to be statistically significant.

3. Results

Demographics of this cohort are shown in Table 1. Of the patients, 49.5% were <60 years of age and 76.7% were male. Most patients had Barcelona-clinic liver cancer (BCLC) stages 0 and A (67%), based on clinical and laboratory evaluation. Nine patients were classified as BCLC stage C. Most of the tumors were AJCC T-stage 1/2 (85%) and Stage I/II (84%). Twenty-three patients (21.5%) had close (≤0.1 cm) margins, 10 of whom had positive margins (9.3%). Pathological vascular invasion was common and found in 55 patients (51%). In 39 patients (63%), the tumors were larger than 4.5 cm in size. Fifty-seven patients (53.3%) had liver cirrhosis. Forty-eight patients (44.8%) and 38 patients (35.5%) were hepatitis B virus (HBV) and hepatitis C virus (HCV) carriers, respectively. The number of non-HBV and non-HCV HCC patients was 14 (13.1%). Seven patients (6.5%) had concurrent HBV and HCV infections.

Table 1
Characteristics of 107 patients with hepatocellular carcinoma.

Variable	Number of patients	%
Age (y)		
<60	53	49.5
≥60	54	50.5
Sex		
Male	82	76.6
Female	25	23.4
pT		
pT 1–2	91	85.0
pT 3–4	16	15.0
Vascular permeation		
No	52	48.6
Yes	55	51.4
Tumor size		
<45	68	63.6
≥45	39	36.4
Surgical margin		
(+)	10	9.3
(−)	97	90.7
≤1(mm)	23	21.5
>1	84	78.5
Stage		
I	39	36.4
II	51	47.7
III	17	15.9
BCLC stage		
0	25	23.4
A	47	43.9
B	26	24.3
C	9	8.4
HBV carrier	48	44.8
HCV carrier	38	35.5
Non-HBV and non-HCV carriers	14	13.1
Concurrent with HBV and HCV carriers	7	6.5%

BCLC = Barcelona-clinic liver cancer; HBV = hepatitis B virus; HCV = hepatitis C virus; pT = pathological T.

The median follow-up time was 22.3 months. The 3-year overall survival (OS), disease-free survival, disease-specific survival, locoregional recurrence-free, and distant metastasis-free rates were 68%, 35%, 73%, 36%, and 93%, respectively. The 3-year OS rates for Stages I, II, and III were 91%, 71%, and 49%, respectively ($p = 0.001$). The 3-year OS rates for surgical margins of >1 mm and ≤1 mm were 79% and 59%, respectively ($p = 0.02$; Fig. 1A); however, no differences were observed in these rates for surgical margins of >2 mm and ≤2 mm ($p = 0.1$; Fig. 1B). The 3-year OS rates in patients with or without vascular invasion were 57% and 93%, respectively ($p < 0.001$). Moreover, pathological T (pT) stage and cirrhosis status also influenced the OS rates (Table 2).

The median time to recurrence was 8.8 months (range, 2–43 months); 44 patients (41%) had recurrent cancer. Among these patients, initial tumor recurrence was confined to the original segment of the liver in 12 patients (11%) or to different segments of the liver in 36 patients (34%). Two patients had both distant lung and brain failure.

Based on univariate analysis, the factors with the greatest influence on the OS rate were tumor diameter, vascular permeation, stage, margin, sex, and BCLC status. Stage, pT stage, BCLC status, and vascular invasion also affected locoregional recurrence significantly, whereas a positive surgical margin did not affect the time to recurrence ($p = 0.28$).

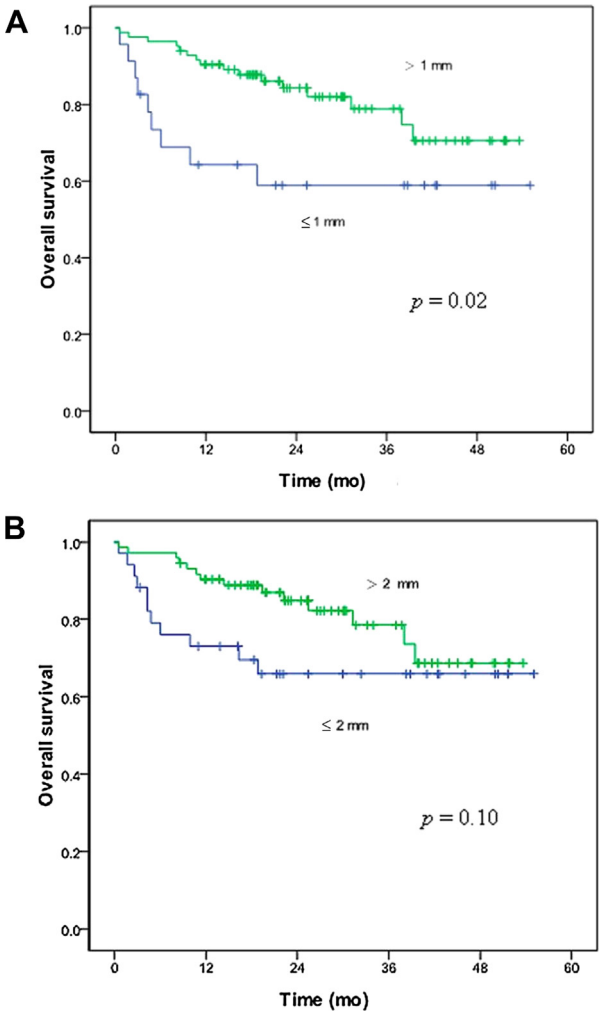

Fig. 1. Three-year overall survival curve for all hepatocellular carcinoma patients according to surgical margins of (A) ≤1 mm or >1 mm and (B) ≤2 mm or >2 mm ($N = 107$).

All factors with $p < 0.05$ after univariate analysis were then included in the multivariate Cox model (Table 3). Based on multivariate analysis, postoperative pathological vascular invasion (hazard ratio, 6.25; 95% confidence interval, 2.01–19.37) and surgical margins (hazard ratio, 0.37; 95% confidence interval, 0.14–0.96) remained independent predictors of adverse long-term outcomes. Age, sex, and BCLC stage were found not to affect OS.

4. Discussion

The outcome of hepatic resection for HCC has improved significantly because of superior surgical techniques and improved perioperative care. Partial hepatectomy for select patients with HCC can now be performed with low operative morbidity and mortality [8]. However, long-term survival is still unsatisfactory due to the high incidence of recurrence, especially in the liver remnant [9]. Intrahepatic recurrence after resection of HCC can be the result of intrahepatic metastasis or multicentric occurrence of a new tumor in the liver remnant, or both. A recurrence rate as high as 74% was reported at 5 years after hepatic resection [10]. In addition, intrahepatic recurrence occurred in 43% at a median follow-up of 24 months [9]. Another study also revealed that recurrent disease accounted for 60% of late deaths after partial hepatectomy [11]. In the current study, 41% of patients had recurrent cancer in the original segment (11%) or in multiple segments of the liver (34%), which also suggested that the majority of the recurrent tumors after hepatectomy arose from intrahepatic metastasis.

Chronic active hepatitis and cirrhosis have been reported to be significant risk factors for intrahepatic recurrence of HCC [12]. Kosuge et al [13] reported an unfavorable effect of liver disease, particularly cirrhosis, which became more pronounced over time. Moreover, the presence of moderate-to-severe fibrosis/cirrhosis has been found to be the most important predictor of death [12]. In our study, there was a trend that liver cirrhosis may influence the control rate ($p = 0.07$). The possible reasons for the lack of a statistically significant difference could be the limited case number and shorter follow-up time.

Vascular invasion is a known prognostic factor after resection of HCC [6]. In a study of 164 patients who underwent liver resection for HCC, multivariate analysis showed that only tumor size >5 cm and vascular invasion were significant predictors of recurrence [14].

Table 2
Three-year clinical outcomes according to prognostic factors.

Factor	Overall survival (%)	p	Disease free survival (%)	p	Disease specific survival (%)	p	Locoregional recurrence survival (%)	p	Distant recurrence survival (%)	p
Age (y)										
<60/≥60	75.2/75.2	0.35	56.7/36.2	0.50	78.4/75.2	0.76	66.2/61.7	0.72	93.6/91.5	0.73
Sex										
Male/female	70.1/90.2	0.04*	44.4/57.4	0.34	72.1/90.2	0.07	61.1/68.6	0.94	94.4/87.2	0.29
pT										
pT 1–2/pT 3–4	79.6/46.4	<0.001*	51.9/11.2	<0.001*	81.5/46.4	<0.001*	65.8/43.5	0.001*	94.3/75.0	0.13
Vascular permeation										
No/yes	93.1/56.6	<0.001*	60.0/31.4	<0.001*	95.0/57.6	<0.001*	77.6/46.7	0.01*	100.0/84.1	0.004*
Tumor size										
<45/≥45	80.4/64.9	0.04*	52.6/32.0	0.04*	82.9/64.9	0.01*	65.9/57.9	0.07	95.3/87.0	0.20
Surgical margin										
(+)/(−)	50.0/77.2	0.01*	30.0/46.6	0.16	50.0/78.9	0.005*	53.3/62.0	0.62	100.0/92.0	0.49
≤1/>1 (mm)	58.9/78.8	0.02*	37.1/46.6	0.14	61.6/79.9	0.02*	75.0/60.4	0.46	88.7/93.4	0.41
≤2/>2 (mm)	65.9/78.5	0.10	33.7/50.7	0.17	67.9/79.7	0.08	73.3/59.0	0.50	92.9/92.5	0.96
Stage										
I/II/III	90.6/71.3/48.9	0.001*	63.0/43.4/12.4	<0.001*	93.0/72.7/48.9	<0.001*	72.1/61.0/44.6	0.004*	100.0/89.6/75.8	0.07
BCLC stage										
0/A/B/C	78.4/85.9/66.0/51.9	0.01*	53.5/47.5/44.7/0.0	<0.001*	78.4/87.9/68.7/51.9	0.005*	85.2/56.6/57.2/0.0	<0.001*	91.7/97.8/91.7/40.0	0.03*

*$p < 0.05$.
BCLC = Barcelona-clinic liver cancer; pT = pathological T.

Table 3
Prognostic factors affecting clinical outcomes in multivariate analysis.

Factor	*B*	HR	95% CI	*p*
Age (y)	−0.02	0.97	(0.93–1.01)	0.25
Sex				
Male (reference)		1		0.12
Female	−1.19	0.30	(0.06–1.37)	
Vascular permeation				
No (reference)		1		0.002*
Yes	1.83	6.25	(2.01–19.37)	
Surgical margin				
≤1 (mm) (reference)		1		0.04*
>1	−0.98	0.37	(0.14–0.96)	
BCLC stage				
0 (reference)		1		0.59
A	0.04	1.04	(0.32–3.33)	
B	0.62	1.87	(0.63–5.47)	
C	0.56	1.75	(0.43–7.07)	

*$p < 0.05$.
CI = confidence interval; HR = hazard ratio.

Pawlik et al [15] also reported that patients with vascular invasion had a significantly shorter median survival compared with those without evidence of vascular invasion. In the current study, we had similar results. When patients with and without vascular invasion proved by pathology were compared, the 3-year OS was 57% and 93% ($p < 0.001$), respectively.

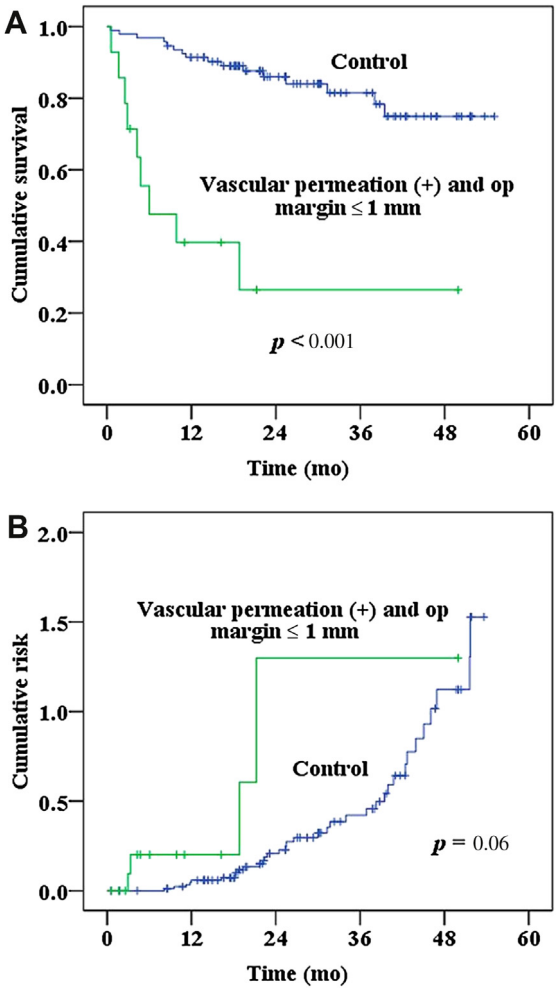

Fig. 2. All hepatocellular carcinoma patients, according to surgical margin concurrent with pathological vascular invasion. (A) The 3-year actuarial overall survival curve and (B) the 3-year actuarial locoregional control curve ($N = 107$).

In previous reports, patients, tumor characteristics, and surgical variables have been found to influence recurrence after surgical resection for HCC. Controversy persists regarding what is an adequate surgical margin for recurrence. In our study, close surgical margins (≤1 mm) were associated with poor survival compared to margins of >1 mm ($p = 0.02$; Fig. 1A and B). Shah and colleagues [16] noted that vascular invasion and microscopic margins had positive predictive values of 77% and 73%, respectively. However, limited studies have mentioned an association between concurrent surgical margins and microscopic vascular invasion. We analyzed these patients and showed that patients with both factors have a poor OS ($p < 0.001$) and a trend toward locoregional recurrence ($p = 0.06$; Fig. 2A and B). Although we had limitations in terms of case numbers and short follow-up times, the results are significant. Given the robustness of the evidence and statistical analysis in this study, these limitations are unlikely to have compromised our results.

The improved survival that has begun to be seen recently after hepatectomy for HCC is attributable mainly to the prevention of recurrence. In one study, out of 164 patients who underwent liver resections for HCC with a median follow-up of 26 months, 74% had isolated recurrence in the liver; based on this, the authors suggest a role for adjuvant therapy after hepatectomy [14]. Aggressive treatment with a multimodality strategy has been suggested for patients with intrahepatic recurrence after curative resection because patients' survival was found to be improved by additional therapy. Shah et al [6] revealed that among 98 recurrence patients, 53 (54%) who underwent additional therapy (ablation, 31 patients; re-resection, 11 patients; transarterial chemoembolization, 8 patients; liver transplantation, 3 patients) showed improvement in survival. A number of adjuvant therapies are available [17–20]. Further randomized trials are needed to compare these therapies and assess fully their benefits to patients at high risk of intrahepatic metastasis.

5. Conclusion

In conclusion, this study demonstrated that TNM stage, BCLC stage, tumor size, cirrhosis, vascular invasion, and surgical margin are associated with survival after resection of HCC. Patients with both pathological vascular invasion and a surgical margin of <1 mm are at a risk for poorer survival and worse locoregional control. These findings emphasize the need for effective adjuvant therapy in HCC that has specific risk factors. Further studies are warranted to identify the optimal strategy, or strategies needed to prevent and manage intrahepatic recurrences; such management ought to further improve the prognosis of HCC and have a significant impact on the quality of life after curative resection.

Acknowledgments

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References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[2] Ohto M, Yoshikawa M, Saisho H, Ebara M, Sugiura N. Nonsurgical treatment of hepatocellular carcinoma in cirrhotic patients. World J Surg 1995;19:42–6.
[3] Pacella CM, Francica G, Di Lascio FM, Arienti V, Antico E, Caspani B, et al. Long-term outcome of cirrhotic patients with early hepatocellular carcinoma treated with ultrasound-guided percutaneous laser ablation: a retrospective analysis. J Clin Oncol 2009;27:2615–21.
[4] Tabrizian P, Schwartz ME. Surgical management of hepatocellular carcinoma. Mt Sinai J Med 2012;79:223–31.

[5] Fuster J, Garcia-Valdecasas JC, Grande L, Tabet J, Bruix J, Anglada T, et al. Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series. Ann Surg 1996;223:297–302.
[6] Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery 2007;141:330–9.
[7] Esnaola NF, Mirza N, Lauwers GY, Ikai I, Regimbeau JM, Belghiti J, et al. Comparison of clinicopathologic characteristics and outcomes after resection in patients with hepatocellular carcinoma treated in the United States, France, and Japan. Ann Surg 2003;238:711–9.
[8] Chok KS, Ng KK, Poon RT, Lo CM, Fan ST. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. Br J Surg 2009;96:81–7.
[9] Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg 1999;229:216–22.
[10] Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Ozaki H, et al. Recurrence of hepatocellular carcinoma after surgery. Br J Surg 1996;83:1219–22.
[11] Nagasue N, Uchida M, Makino Y, Takemoto Y, Yamanoi A, Hayashi T, et al. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. Gastroenterology 1993;105:488–94.
[12] Bilimoria MM, Lauwers GY, Doherty DA, Nagorney DM, Belghiti J, Do KA, et al. Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. Arch Surg 2001;136:528–35.
[13] Kosuge T, Makuuchi M, Takayama T, Yamamoto J, Shimada K, Yamasaki S. Long-term results after resection of hepatocellular carcinoma: experience of 480 cases. Hepatogastroenterology 1993;40:328–32.
[14] Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003;197:753–8.
[15] Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 2005;140:450–7. discussion 7–8.
[16] Shah SA, Greig PD, Gallinger S, Cattral MS, Dixon E, Kim RD, et al. Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. J Am Coll Surg 2006;202:275–83.
[17] Wu L, Hu A, Tam N, Zhang J, Lin M, Guo Z, et al. Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. PLoS One 2012;7:e41820.
[18] Lee DH, Lee JM, Lee JY, Kim SH, Han JK, Choi BI. Radiofrequency ablation for intrahepatic recurrent hepatocellular carcinoma: long-term results and prognostic factors in 168 patients with cirrhosis. Cardiovasc Intervent Radiol 2014;37:705–15.
[19] Huang WY, Jen YM, Lee MS, Chang LP, Chen CM, Ko KH, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2012;84:355–61.
[20] 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.