



Predictors of Micrometastases in Patients with Barcelona Clinic Liver Cancer Classification B Hepatocellular Carcinoma

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Purpose: Transarterial chemoembolization (TACE) is indicated for Barcelona Clinic Liver Cancer (BCLC) B hepatocellular carcinoma (HCC). Whether TACE provides any long-term survival benefits remains unclear. We aimed to investigate micrometastases predictors with which to identify patients who would benefit from surgical resection (SR).

Materials and Methods: First, we analyzed risk factors of micrometastases, microvascular invasion, and poor histologic grade in 38 patients with newly diagnosed resectable BCLC stage B HCC limited to one or two segments with well-preserved liver function and who underwent SR between January 2006 and December 2013. Second, we validated identified risk factors in 54 newly diagnosed resectable BCLC B HCC patients with well-preserved liver function who underwent TACE during the same period to determine their influence on survival.

Results: Risk factors of micrometastases in SR patients were α -fetoprotein (AFP) ≥ 110 [hazard ratio (HR)=5.166; 95% confidence interval (CI), 1.031–25.897; $p=0.046$] and prothrombin induced by vitamin K absence-II (PIVKA-II) ≥ 800 (HR=5.166; 95% CI, 1.031–25.897; $p=0.046$). The cumulative probability of tumor recurrence ($p=0.009$) after SR differed according to levels of AFP and PIVKA-II. After validation of these risk factors in the TACE group, patients with SR and AFP < 110 and PIVKA-II < 800 had superior survival outcomes than other patients (HR=0.116; 95% CI, 0.027–0.497; $p=0.004$).

Conclusion: AFP and PIVKA-II levels predict micrometastases and survival. Therefore, they should be considered when selecting SR for BCLC B HCC.

Key Words: Predictors, micrometastases, Barcelona Clinic Liver Cancer classification B hepatocellular carcinoma, surgical resection, transarterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is a devastating disease with poor prognosis and is one of the most common causes of cancer-related deaths worldwide.^{1,2} The prognosis for HCC patients is determined by tumor status, liver function reserve,

general performance, and treatment efficacy.³ To improve patient survival, several staging systems have been described for HCC including the Barcelona Clinic Liver Cancer (BCLC) classification, Okuda et al., Cancer of the Liver Italian Program, and French scores.⁴⁻⁷ Among them, only the BCLC classification has been approved by the European Association for Study of the Liver and the American Association for the Study of Liver Disease for the prognostic classification and treatment selection of HCC.^{4,8,9} This staging system, which has been validated in regards to its clinical usefulness in several studies, is associated with treatment indications and aspects of estimated life expectancy.^{10,11}

BCLC stage B HCC includes Child-Pugh scores A and B, as well as preserved performance status, with asymptomatic multifocal tumors without vascular invasion or extrahepatic spread. For this group of patients, the BCLC staging system indicates

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transarterial chemoembolization (TACE) as the main treatment option.⁴ A previous study showed that TACE provided a better 2-year survival rate than supportive treatment;¹² however, it is unclear whether TACE provides any long-term survival benefit. BCLC stage B is a heterogeneous category that includes patients who vary widely in tumor stage, liver function, and disease etiology. Owing to this heterogeneity, TACE may not be the optimal therapy for all patients with BCLC stage B HCC. Recent studies have verified that surgical resection (SR) can be safely performed on a subset of patients with BCLC stage B HCC who exhibit good liver function, resulting in a long-term survival rate comparable to that of patients treated with TACE.^{1,3,13,14} However, the indication of SR for BCLC stage B HCC remains controversial and needs further assessment.

If HCC progresses, venous outflow might be obstructed and portal backflow could develop. This can be a route of micrometastases, one of the major causes of multinodular HCC.¹⁵ Micrometastases, which cannot often be detected by various imaging modalities, can remain in remnant liver, holding a strong possibility of causing local recurrence after SR. Therefore, we hypothesized that if a patient has few risk factors for the presence of micrometastases, such as microvascular invasion or poor histologic differentiation,¹⁶ the intrahepatic spread of the tumor might be limited. In the event of limited intrahepatic tumor spread, SR may confer a greater chance of curative treatment and may represent a better treatment option. Additionally, determining preoperative risk factors for intrahepatic tumor spread in patients with multinodular HCC would allow for a more accurate prediction of the possibility of curative SR. SR could, therefore, be recommended in patients with no risk factors who are predicted to have a good prognosis.

The aims of this study were to identify preoperative risk factors for the micrometastases of tumors in patients who underwent SR for BCLC stage B HCC and to validate these identified risk factors in terms of overall survival in a group of patients who underwent TACE.

MATERIALS AND METHODS

Patients

This retrospective cohort study was approved by the Institutional Review Board of Chung-Ang University Hospital (Seoul, Korea) and was exempted from the requirement to obtain informed consent. The first step of this study was to identify preoperative risk factors in 38 patients with well-preserved liver function, indicated as Child-Turcotte-Pugh (CTP) A liver cirrhosis, and newly diagnosed resectable BCLC stage B HCC limited to one or two segments, and who underwent SR between January 2001 and December 2013 at Chung-Ang University Hospital. Patients with a previous treatment history of HCC or insufficient clinical data were excluded from analysis. The risk for micrometastases, which represents the possibility

of intrahepatic spread of the tumor, was defined as the presence of Edmonson and Steiner histologic grade 3 or 4, and/or microvascular invasion. The following data were collected for all patients to determine risk factors for tumor aggressiveness: age, sex, body mass index, presence of hepatitis B virus and hepatitis C virus, preoperative laboratory results (levels of total bilirubin, albumin, and the international normalized ratio), tumor marker levels [α -fetoprotein (AFP) and prothrombin induced by vitamin K absence-II (PIVKA-II)], and tumor characteristics (tumor size, histologic grade, and presence of microvascular invasion).

The second step of the study was to validate identified risk factors in 52 patients who met the same criteria as the SR group, including well-preserved liver function and resectable BCLC stage B HCC limited to one or two segments initially treated with TACE during the same period as the first step of the study. We validated the identified risk factors after adjusting for several parameters that might have influenced the overall survival of patients in the TACE group, such as demographics, laboratory results, and radiologic findings. Clinical variables were the same as those outlined for the first step of the study, with the following exceptions: pathologic results were collected from patients who underwent TACE, and risk factors for overall survival after TACE were identified. The probability of overall survival was analyzed according to the type of treatment and the presence of identified risk factors.

All patients were followed-up at 1, 3, and 6 months post-treatment and every 3 to 6 months thereafter, as necessary. At each visit, imaging studies, such as computed tomography, magnetic resonance imaging, and ultrasonography, were performed. Serologic tests, such as tumor marker analyses and biochemical liver function tests, were performed at each visit. If tumor recurrence was found after SR, multiple modalities, such as re-SR, radiofrequency ablation, or TACE, in consideration of tumor characteristics were performed as early as possible before progression of the recurrent tumor. Also, TACE was repeatedly performed until the disappearance of viable tumor was noted, and if the tumor progressed, TACE was continued.

Procedure

The SR was performed under low central venous pressure at less than 5 mm Hg. Anatomic partial hepatectomy was performed in a standardized manner; however, if the patients had poor liver function, non-anatomic partial hepatectomy was also performed. All SRs were performed based on a curative aim by ligating the feeding vessels, and securing at least 2 cm of resection margin using ultrasonographic guidance and after resection, the frozen section was performed to confirm the minimal length of resection margin.

The TACE was performed under local anesthesia: a 2.4F highly flexible microcatheter (Progreat, Terumo Corporation, Tokyo, Japan) was introduced into the abdominal aorta via the superficial femoral artery using the Seldinger technique.

Hepatic arterial angiography was performed using fluoroscopy to guide the catheter into the celiac artery. Then, the feeding arteries, tumor stain, and vascular anatomy surrounding the tumor were identified. A microcatheter was introduced through the catheter and directed to the feeding arteries. A mixture of doxorubicin hydrochloride (Adriamycin; Ildong Pharm., Seoul, Korea) and iodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-Sous-Bois, France) was injected under fluoroscopic control, followed by embolization of the feeding arteries using 1-mm diameter absorbable gelatin sponge particles (Gelform; Upjohn, Kalamazoo, MI, USA). The volume of iodized oil ranged from 2 to 10 mL, and the amount of Adriamycin ranged from 10 to 70 mg.

Statistical analysis

For intergroup comparisons, the distribution of the data was first evaluated for normality using the Shapiro-Wilk test. Normally distributed data are presented herein as mean±standard deviation. Groups were compared using Student's t-test. Descriptive variables were subjected to χ^2 analysis or Fisher's exact test, as appropriate. The optimal cut-off values for the levels of AFP and PIVKA-II were determined by the area under the receiver operating characteristic analysis. Multivariate analysis using an ordinary logistic regression model was performed to investigate risk factors for intrahepatic spread of the tumor in SR patients, as well as the influence of these factors on overall survival in TACE patients. Survival and recurrence after each type of procedure, as well as the presence of identified risk factors, were plotted using the Kaplan-Meier method and compared using the log-rank test. A multivariate analysis using the Cox proportional hazard regression method was performed to investigate the risk factors for recurrence-free survival and

overall survival. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS ver. 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A comparison of patient demographics in each group (low risk/SR, high risk/SR, low risk/TACE, high risk/TACE) is shown in Table 1. Mean age was significant highest in the TACE/low risk group (*p*=0.003). Laboratory results indicative of liver function showed slight differences in each group, although all laboratory results were within normal limits, representing well-preserved liver function as CTP A liver cirrhosis. Expression of the tumor markers, such as AFP and PIVKA-II, showed significant differences in each group, and high risk groups had elevated serum levels, compared with low risk groups (Table 1).

In the first step of the study, 60.5% (23/38) of patients who underwent SR were designated as being at high risk for micro-metastases, indicating the possibility of intrahepatic spread. These patients displayed the presence of either poor histologic grade (34.2%) or microvascular invasion (50.0%). AFP ≥ 110 [hazard ratio (HR)=5.166; 95% confidence interval (CI), 1.031–25.897; *p*=0.046] and PIVKA-II ≥ 800 (HR=5.166; 95% CI, 1.031–25.897; *p*=0.046) were the only significant risk factors identified using multivariate analysis (Table 2).

Patients with AFP <110 and PIVKA-II <800 had lower tumor recurrence (57.1%) and long disease-free survival (36.7±28.5 months), compared with the patients who had AFP ≥ 110 or PIVKA-II ≥ 800 (87.5% and 14.5±21.8 months). Multiple (33.3%) or extrahepatic tumor recurrence (19.0%) were observed more

Table 1. Demographics of Patients in the SR and TACE Groups

Variable	SR group		TACE group		<i>p</i> value
	Low risk (n=14)	High risk (n=24)	Low risk (n=34)	High risk (n=18)	
Age	54.4 (±6.4)	56.1 (±11.0)	64.2 (±10.1)	62.7 (±11.2)	0.003
Sex (male)	14 (100)	20 (83.3)	25 (73.5)	12 (66.7)	0.101
Presence of HBV	14 (100)	21 (87.5)	29 (85.3)	17 (94.4)	0.399
Presence of HCV	0 (0)	1 (4.2)	1 (2.9)	1 (5.6)	0.843
BMI	24.1 (±3.7)	22.8 (±2.6)	22.5 (±3.2)	22.8 (±2.6)	0.414
Total bilirubin	0.9 (±0.3)	0.9 (±0.5)	1.3 (±0.6)	0.9 (±0.6)	0.040
Albumin	4.2 (±0.3)	3.9 (±0.4)	3.5 (±0.4)	3.5 (±0.3)	0.000
PT-INR	1.1 (±0.1)	1.0 (±0.2)	1.2 (±0.1)	1.1 (±0.1)	0.007
Tumor size (sum)	7.3 (±3.0)	11.7 (±5.9)	7.1 (±4.7)	10.1 (±4.7)	0.002
Tumor number	2.9 (±1.5)	2.7 (±1.3)	3.4 (±1.6)	3.0 (±1.1)	0.271
AFP (ng/mL)	16.3 (±28.0)	8390 (±20422.8)	24.0 (±27.1)	6477.0 (±15005.8)	0.044
AFP ≥ 110 (ng/mL)	0 (0)	15 (62.5)	0 (0)	14 (77.8)	0.000
PIVKA-II (nAU/mL)	164.2 (±188.3)	6658.8 (±10994.5)	120.5 (±158.2)	612.8 (±608.4)	0.000
PIVKA-II ≥ 800 (nAU/mL)	0 (0)	15 (62.5)	0 (0)	8 (44.4)	0.000

HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; PT-INR, prothrombin time-international normalized ratio; AFP, α -fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II; SR, surgical resection; TACE, transarterial chemoembolization.

Data are presented as the mean±standard deviations or numbers with percentages in parentheses unless otherwise indicated.

Table 2. Risk Factor Analysis for Tumor Aggressiveness in the SR Group

Variable	Univariate analysis			Multivariate analysis	
	Low risk group (n=15)	High risk group (n=23)	p value	Relative risk (95% CI)	p value
Age	54.1 (±10.1)	56.4 (±9.2)	0.491		
Sex (male)	14 (93.3)	20 (87.0)	0.531		
Presence of HBV	14 (93.3)	21 (91.3)	0.821		
Presence of HCV	0 (0)	1 (4.3)	0.413		
BMI	24.4 (±3.7)	22.5 (±2.5)	0.068		
Total bilirubin	1.0 (±0.3)	0.9 (±0.4)	0.245		
Albumin	4.1 (±0.3)	3.9 (±0.4)	0.192		
PT-INR	1.1 (±0.1)	1.0 (±0.2)	0.497		
Tumor size (sum)	8.1 (±3.5)	11.4 (±6.1)	0.064		
Tumor number	2.9 (±1.4)	2.7 (±1.3)	0.703		
AFP ≥110 (ng/mL)	3 (20.0)	12 (52.2)	0.047	5.166 (1.031–25.897)	0.046
PIVKA-II ≥800 (nAU/mL)	3 (20.0)	12 (52.2)	0.047	5.166 (1.031–25.897)	0.046

SR, surgical resection; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; PT-INR, prothrombin time-international normalized ratio; AFP, α-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II. Data are presented as the mean±standard deviations or numbers with percentages in parentheses unless otherwise indicated.

Table 3. Recurrence Patterns of Hepatocellular Carcinoma in the SR Group According to AFP and PIVKA-II Levels

	AFP <110 and PIVKA-II <800 (n=14)	AFP ≥110 or PIVKA-II ≥800 (n=24)	p value
Recurrence	8 (57.1)	21 (87.5)	0.034
Disease free survival (month)	36.7±28.5	14.5±21.8	0.011
Pattern of tumor recurrence			
Intrahepatic			
Single tumor			
<1 cm	1 (12.5)	2 (9.5)	
≥1 and <2 cm	4 (50.0)	5 (23.8)	
≥2 and <3 cm	0 (0)	3 (14.3)	
Multiple tumor			
	2 (25.0)	7 (33.3)	
Extrahepatic			
	1 (12.5)	4 (19.0)	

SR, surgical resection; AFP, α-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II. Data are presented as the mean±standard deviations or numbers with percentages in parentheses unless otherwise indicated.

often in patients with AFP ≥110 or PIVKA-II ≥800; however, most patients who had AFP <110 and PIVKA-II <800 showed only single tumor recurrence of less than 2 cm (Table 3). The cumulative probability of tumor recurrence ($p=0.009$) after SR differed significantly according to AFP and PIVKA-II levels (Fig. 1).

In the second step of the study, we validated the identified risk factors stated above in the TACE group. Overall survival rates at 1, 3, and 5 years, respectively, were as follows: 78.6, 42.9, and 42.9% for Group 1 (SR, AFP <110 and PIVKA-II <800); 20.8, 12.5, and 12.5% for Group 2 (SR, AFP ≥110 or PIVKA-II ≥800); 73.5, 41.2, and 8.8% for Group 3 (TACE, AFP <110 and PIVKA-II <800); and 83.3, 50.0, and 16.7% for Group 4 (TACE, AFP ≥110 or PIVKA-II ≥800). The survival curve of Group 1 differed significantly from those of the other groups ($p=0.001$) (Fig. 2). Multivariate analysis of overall survival showed a significant difference between Group 1 and the other groups (HR=0.116; 95% CI, 0.027–0.497; $p=0.004$).

DISCUSSION

The BCLC staging system is considered the standard of care for patients with HCC.^{16,17} TACE is the first line treatment option of BCLC stage B HCC, because it confers a median survival of 20 months, which represents an improvement when compared with supportive treatment.^{12,18} It remains unknown, however, whether TACE confers a survival advantage over other treatment options, such as SR. The indications for SR have expanded with advances in surgical techniques and pre-operative preparation in recent decades. Several studies have reported improved overall survival after SR for BCLC B HCC as compared with TACE.^{19–21} Our results were consistent with the results of these reports, demonstrating that patients treated with SR had superior overall survival than those treated with TACE (57.4±6.4 months vs. 27.2±2.8 months; $p=0.000$). Many studies have examined prognostic factors for survival of BCLC stage B HCC patients after SR, and patients with select risk factors are predicted to have lower overall survival. There-

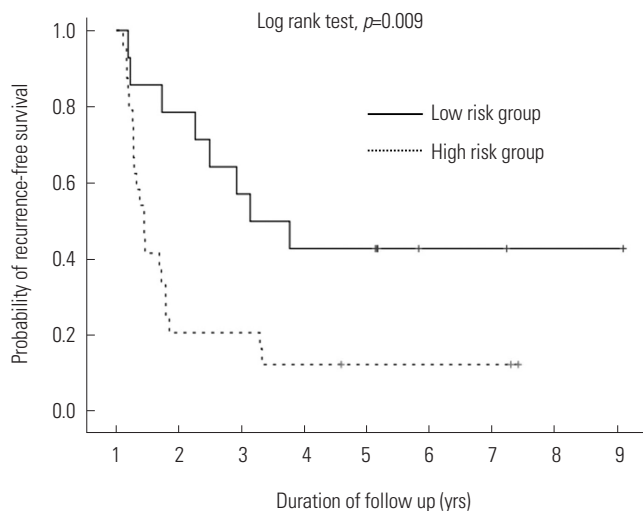


Fig. 1. Recurrence-free survival and overall survival in surgical resection patients. The cumulative probability of tumor recurrence. The frequency of recurrence was significantly different according to the levels of AFP and PIVKA-II, especially during the first year (1-year recurrence-free survival: AFP <110 and PIVKA-II <800, 78.6%; AFP \geq 110 or PIVKA-II \geq 800, 20.8%). The curves continued to diverge during 2 years of follow-up, but then continued parallel ($p=0.009$). AFP, α -fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II.

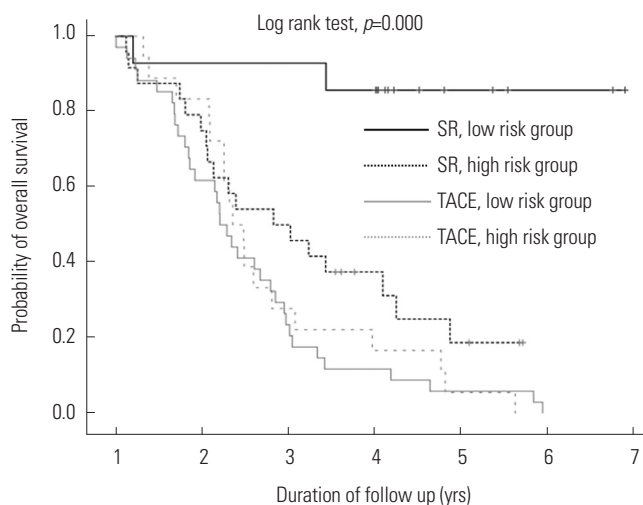


Fig. 2. The cumulative probability of overall survival in all patients. A significant difference was found in overall survival according to the type of procedure and combined levels of AFP and PIVKA-II ($p=0.001$). The curve of Group 1 significantly diverged from that of the other groups (HR=0.116; 95% CI, 0.027–0.497; $p=0.004$). SR, surgical resection; TACE, transarterial chemoembolization; AFP, α -fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II; HR, hazard ratio; CI, confidence interval.

fore, the identification of patients suitable for SR is of critical importance.^{7,22,23} Based on the clinical observation of a marked heterogeneity in the clinical benefit of TACE, one study has proposed a subclassification of the BCLC stage B score into four stages (B1–B4) to facilitate therapeutic decisions, and patients who classified as the B1 subgroup showed acceptable survival rates after SR.²⁴

Among the patients who underwent SR, patients who had

an identified risk factor had significant earlier tumor recurrence, compared with other patients (14.5 \pm 21.8 months vs. 36.7 \pm 28.5 months; $p=0.011$). Early recurrence of HCC is the likely result of local tumor recurrence, which may have arisen either from micrometastases that were left untreated by SR or from the intrahepatic spread of the primary tumor via the portal venous system. Micrometastases are common in patients with HCC and are noted more often in HCC patients with either microvascular invasion or poor histologic differentiation.^{16,25} The possibility remains that some micrometastases will persist, increasing the possibility of intrahepatic tumor spread and thereby presenting difficulty in achieving curative SR. Our study showed that patients in the SR group with an identifiable risk factor of AFP \geq 110 or PIVKA-II \geq 800 had higher rates of multiple tumor recurrence (33.3%) and extrahepatic metastasis (19.0%). These features represent increased tumor aggressiveness, as defined by the possibility of micrometastases or intrahepatic tumor spread, when compared with SR patients who had AFP <110 and PIVKA-II <800.

Several studies have demonstrated the clinical significance of serum AFP or PIVKA-II in patients with HCC. However, these two markers involve different synthetic pathways, such that the levels of these two markers show independent patterns.^{26–29} Therefore, it appears that AFP and PIVKA-II are complementary markers for clinical usefulness. Accordingly, we defined the high-risk group as AFP \geq 110 or PIVKA-II \geq 800 to reflect levels of both markers. Despite high recurrence rates of HCC, Group 1 had significantly superior survival outcomes than the other groups. Patients with AFP <110 and PIVKA-II <800 usually had long disease-free survival (36.7 \pm 28.5 months) and single tumor recurrence (62.5%), the latter of which we suspect arose as a result of *de novo* tumorigenesis due to underlying cirrhosis.

There are some limitations to this study. It is a retrospective study, forcing us to rely on the integrity of completed medical records for our analysis. In addition, the background characteristics of the SR and TACE groups were significantly different; selection bias, therefore, cannot be eliminated. The study population was relatively small, and further studies with prospectively randomized large populations are warranted to confirm these promising results.

In conclusion, serum levels of AFP and PIVKA-II are useful predictors of tumor aggressiveness and micrometastasis in BCLC B HCC. AFP and PIVKA-II levels can also predict early tumor recurrence after SR. The type of treatment and the combined levels of AFP and PIVKA-II carry significant prognostic value in relation to overall survival rates. The findings in the current study may be helpful to determining optimal treatment strategies in BCLC B HCC. We propose that if a patient has no risk of micrometastasis as defined by AFP and PIVKA-II levels, SR should be considered for first-line therapy.

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