Clinical relevance of alpha-fetoprotein in determining resection margin for hepatocellular carcinoma

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Abstract

Liver resection for hepatocellular carcinoma (HCC) is associated with high recurrence rates. Adequate resection margin which is carried out by surgeons may reduce tumor recurrence. Nevertheless, the margin width remains controversial particularly in cirrhotic patients where optimal parenchymal preservation is necessary. This study aims to find a reference for proposing the resection margin when liver resection is planning.

Totally, 534 patients who received liver resection for HCC were included. The clinical profiles of the patients, tumor characteristics and patients' survival were all collected. The patients were classified according to resection margin (<0.5 cm, 0.5–0.99 cm, and ≥1 cm) and preoperative α-fetoprotein (AFP) levels (<15 ng/ml, 15–200 ng/ml, and >200 ng/ml), then survival was calculated.

Most of the patients had hepatitis B (52.4%) and hepatitis C (24.0%) infection. Multivariate analysis showed that narrow resection margin (<0.5 cm) (hazard ratio [HR]: 1.323, $P = .024$), high AFP level (≥15 ng/ml) (HR: 1.305, $P = .039$), major extent of resection (≥3 segments) (HR: 1.507, $P = .034$), and underlying cirrhosis (HR: 1.404, $P = .009$) were independent risk factors for disease-free survival. In further survival analysis, resection margin was not significant for disease-free survival if serum AFP levels were <15 ng/ml. However, for the patients with AFP level between 15 and 200 ng/ml, resection margin ≥0.5 cm was significant to improve 5-year disease-free survival from 24.6 months to 38.7 months ($P = .040$). For the patients with AFP >200 ng/ml, resection margin had to be extended to ≥1 cm to improve 5-year disease-free survival from 33.9 months to 48.8 months ($P = .012$). When the patients meeting AFP <15 ng/ml with tumor-free margin, AFP between 15 and 200 ng/ml with margin ≥0.5 cm, and AFP level >200 ng/ml with margin ≥1 cm were compared, their survival rates were not different.

Adequate resection margin can be guided by pre-operative AFP levels. Tumor-free margin is enough for patients with normal AFP level. A resection margin ≥0.5 cm is advised for the patients with AFP between 15 and 200 ng/ml, and ≥1 cm for the patients with AFP over 200 ng/ml.

Abbreviations: AFP = alpha-fetoprotein, CT = computed tomography, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, ICG = indocyanine green, RFA = radiofrequency ablation.

Keywords: a-fetoprotein, hepatocellular carcinoma, liver resection, resection margin

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy in the liver. Because the prevalence of chronic hepatitis B (HBV) and hepatitis C (HCV) viral infection is high in Taiwan,[1] HCC is one of the leading cancers for both males and females. HCC in its early stage can be treated by liver resection, radiofrequency ablation (RFA) and liver transplantation. Liver resection and RFA are still the major treatments for HCC in Taiwan because liver allografts are always short.

According to the recommendations of Asian Pacific Association for the study of the liver or Barcelona clinic liver cancer treatment strategy, liver resection is the first-line curative treatment for solitary or multifocal HCC if HCC is confined to the liver and liver functional reserve after the operation is enough.[2,3] However, liver resection for HCC has a high recurrence rate of 65% to 100% in 5 years.[4–8] To our knowledge, most of the recurrence is resulted from residual intrahepatic metastasis or from multicentric carcinogenesis.[6] The predisposing factors of postoperative HCC recurrence include tumor size, satellite nodule, vascular invasion, absence of encapsulation, poor differentiation, alpha-fetoprotein (AFP) levels, and resection margin.[9–11] Among these prognostic factors, most of them are the characteristics of the tumors. What a surgeon can improve disease-free survival is to make an adequate resection margin. However, majority of HCC develop in cirrhotic liver, liver parenchyma has to be preserved as much as possible to keep adequate postoperative liver function. It becomes a dilemma to obtain adequate resection margin and preserve liver parenchyma simultaneously during liver resection.

How to decide the range of liver parenchymal resection and achieve an adequate resection margin is an important issue for liver resection. Based on tumor hemodynamics studied by Sakon et al, tumor blood was drained into peritumor area for most of the tumors.[12] When liver resection was carried out, the main tumor should be excised with an adequate resection margin. Nevertheless, what is an adequate resection margin remains controversial. Resection margins of 0.5 cm, 1 cm, or 2 cm all were mentioned to improve prognosis in the literature.[13–15] Contrarily, these resection margins were described without prognostic contributions in meta-analysis studies.[5,16–18] Obviously, adequate resection margin of liver resection for HCC is still in deep debate.

The aim of this study is to determine or propose the adequate resection margin which can be decided preoperatively by surgeons. We included 534 patients with long-term following-up in this retrospective study to determine what factors could be used by surgeons to decide the optimal resection margin of liver resection for HCC and improve the survival for HCC patients.

2. Patients and methods

2.1. Patients

Six hundred seventy-one consecutive patients underwent liver resections for HCC at the Department of General Surgery, Chang-Gung Memorial Hospital from April 2003 to January 2007. Diagnosis of HCC was confirmed by pathological reports. The patients were excluded from this study if

(1) RFA, transcatheter arterial chemoembolization or radiotherapy was applied to treat HCC before liver resection,
(2) hospital mortality occurred,
(3) the following-up period was less than 3 months,
(4) the HCC TNM stage was 4A or 4B, and
(5) resection margin was positive for tumor.

Therefore, totally 534 patients were included for analysis. This study was approved by the local ethic committee of Chang-Gung Memorial Hospital.

2.2. Preoperative liver function assessment and liver resection

Preoperative liver function was accessed by indocyanine green (ICG) test if the liver was cirrhotic. Briefly, this test was performed by injecting 0.5 mg/kg of ICG into a peripheral vein and drawing a blood sample from another site 15 minutes later to calculate the retained ratio of ICG. After the liver function was assessed, liver resection was carried on. During operation, intraoperative sonography was performed to demarcate the tumor and determine the parenchymal resection route. Intermittent Pringle's maneuver, 15-minute clamping followed by 5-minute release, was applied for most of the patients to control bleeding during liver resection. Parenchymal transection was performed by ultrasonic dissector or kellyclasy.

2.3. Definition of resection margin and tumor recurrence

The extent of surgical resection is defined according to Couinaud classification system. Tumors were graded according to the World Health Organization classification of tumors of the digestive system and were staged according to the American Joint Committee on Cancer (TNM) classification system (7th ed. 2010). The resection margin is defined as the shortest distance from the edge of the lesion to the cutting line of parenchymal resection by histological examination. After liver resection, the patients were followed up regularly at the outpatient clinic. Liver function tests, measurement of α-fetoprotein, and liver sonography were performed every 3 months. Dynamic computed tomography (CT) of the liver was performed if deemed necessary. Recurrence of HCC was defined when dynamic CT detected a tumor with typical HCC imaging pattern in the liver or extrahepatic tumors, and the date of recurrence was the day that CT was done. The recurrence of HCC counted all local recurrence and distant metastasis.

2.4. Clinical profiles

Patients' clinical information was obtained from the medical charts and the Taiwan Cancer Registry. The information comprised of the patients' demographics, preoperative laboratory examination, hepatitis serology, histological grades, tumor staging, surgical features, pathologic features, resection margin, postoperative complications, tumor recurrence, treatment of tumor recurrence, and the last following-update or date of death.

2.5. Grouping of patients

The patients were classified according to the width of the resection margin (<0.5 cm, 0.5–0.99 cm, and ≥1 cm) and the preoperative AFP level (<15 ng/ml [normal range], 15–200 ng/ml and >200 ng/ml) for further analysis.

2.6. Biostatistics

Preoperative clinical condition and tumor characteristics were analyzed to identify the factors which could determine the needs of the width of resection margin. Univariate and multivariate analysis of disease-free survival was performed on the patient's clinical condition, tumor characteristics and surgical factors. All statistical analyses were performed using IBM SPSS 22 (SPSS, Inc, Chicago, IL) software. Baseline characteristics were compared using the Chi-square test for categorical variables and by analysis of variance for continuous variables. The disease-free survival period was defined as the period between the date of surgery to the date of recurrence proven by CT or the date of the last follow-up, and the disease-free survival rate was calculated using the Kaplan–Meier method and compared using log-rank tests. Statistical significance was determined at $P < .05$.

3. Results

3.1. Characteristics of patients

Liver resections were carried out for 617 HCC patients in this study period. Among them, 534 patients meeting the criteria were included in this study. The mean age of the patients was 56.4 ± 13.0 years old, and 80.1% of them were male. Most of the patients had HBV infection (52.4%) or HCV infection (24.0%). The liver function was Child's classification A in 98.7% of patients. The mean size of tumors was 4.8 ± 3.6 cm. Most of the tumors had encapsulated (83.6%) and did not have vascular invasion (74.7%) or satellite nodule (74.0%). The distribution of TNM staging was 59.9% of patients in stage I, 23% in stage II, 7.7% in stage IIIA, 5.4% in stage IIIB and 3.9% in stage IIIC, respectively (Table 1). The mean following-up period was 66.3 ± 35.5 months. The 5-year recurrence rate was 58.4%. Among the patients with tumor recurrence, 96.4% of tumor recurrence was

Table 1

Prognostic factors for disease-free survival rate according to univariate and multivariate analyses.

Factors	Median, mo	95% CI	5-yr (%)	P-value	Hazard ratio	95% CI	P-value
Age, yr				.554			
≤60 (n=320)	36.9	24.9–48.8	41.9				
>60 (n=214)	40.9	32.8–48.9	36.0				
Sex				.611			
Male (n=428)	39.9	31.7–48.1	40.4				
Female (n=106)	33.0	17.9–48.1	36.7				
Hepatitis				.452			
HBV (n=280)	31.9	18.7–45.1	40.6				
HCV (n=128)	44.5	36.9–52.1	34.3				
HBV+HCV (n=24)	61.9	18.3–105.6	51.1				
NBNC (n=79)	43.2	32.2–54.3	42.3				
Albumin, g/dl				.002			
≤4 (n=196)	24.1	15.9–32.3	31.6		1.199	0.932–1.544	.158
>4 (n=331)	46.5	38.1–54.9	43.6				
ICG (R15)				.019			
>10 (n=166)	25.8	19.8–31.8	31.9		1.091	0.849–1.400	.496
≤10 (n=314)	46.2	37.5–55.0	43.7				
AFP, ng/ml				.001			
>200 (n=140)	20.9	10.3–31.5	38.0		1.305	1.014–1.680	.039
15–200 (n=145)	26.9	14.2–39.5	31.5				
<15 (n=209)	47.3	36.4–58.2	45.2				
Post-OP AFP, ng/ml at 3 mo*				<.001			
≥15 (n=105)	5.3	3.7–6.9	13.5				
<15 (n=171)	54.0	33.7–74.3	47.2				
Child classification				.456			
A (n=527)	38.0	30.5–45.5	39.6				
B (n=7)	38.9	36.1–41.6	42.9				
Extend of resection				.026			
Major (n=55)	13.8	0.0–29.1	30.1		1.507	1.032–2.203	.034
Minor (n=479)	40.9	33.6–48.1	40.7				
Post-OP complication grade				.050			
0–1 (n=500)	39.4	31.8–47.0	40.4				
2–3 (n=34)	10.4	0.0–41.5	28.7				
Tumor size, cm				.012			
>3 (n=223)	29.7	19.6–39.8	36.4		1.295	0.966–1.683	.054
≤3 (n=311)	45.3	34.8–55.9	44.1				
Capsule				.435			
Yes (n=443)	38.1	30.0–46.3	40.2				
No (n=87)	37.1	12.6–61.5	35.2				
Satellite nodule				<.001			
Yes (n=139)	21.4	14.5–28.3	28.7		1.281	0.840–1.954	.250
No (n=395)	45.3	36.3–54.4	43.4				
Vessel invasion				<.001			.176
Portal vein (n=36)	7.2	3.0–11.4	29.1		0.335	0.079–1.427	.139
Microvascular (n=99)	16.2	10.4–22.1	27.2		1.204	0.822–1.763	.340
No (n=399)	45.6	37.6–53.6	43.7				
Resection margin, cm				.027			
<0.5 (n=274)	32.6	24.5–40.8	35.1		1.323	1.038–1.685	.024
≥0.5 (n=260)	45.6	33.9–57.3	44.3				
Resection margin, cm				.042			
<1.0 (n=391)	35.6	27.1–44.0	37.0				
≥1.0 (n=143)	46.5	25.7–67.3	46.6				
Histological grade				.007			
III-IV (n=215)	25.3	13.9–36.7	35.4		1.201	0.932–1.547	.158
I-II (n=317)	44.4	36.1–52.7	42.4				
Necrosis				.788			
>33% (n=98)	27.4	10.2–46.7	40.6				
≤33% (n=436)	39.9	32.9–46.9	39.4				
Fatty change				.824			
>33% (n=42)	39.5	17.6–61.4	38.1				
≤33% (n=492)	37.8	30.3–45.3	39.8				
Rupture				.001			

(continued)

Table 1

(continued).

Factors	Median, mo	95% CI	5-yr (%)	*P*-value	Hazard ratio	95% CI	*P*-value
Yes (n=25)	16.0	6.5–25.4	16.0		1.672	0.794–3.521	.176
No (n=509)	40.9	33.8–47.9	40.8				
HAI				.001			
>3 (n=309)	33.0	25.3–40.7	33.8		1.427	1.107–1.841	.006
≤3 (n=217)	54.0	30.7–77.3	48.8				
Cirrhosis				.010			
Yes (n=235)	35.4	26.8–44.0	33.8		1.404	1.087–1.814	.009
No (n=299)	44.4	32.1–56.7	44.2				
TMN stage				<.001			.087
II (n=123)	26.9	14.6–39.1	33.7		1.115	0.702–1.770	.646
IIIa (n=41)	9.9	2.6–17.2	23.0		1.393	0.757–2.563	.287
IIIb (n=29)	5.3	1.1–9.5	22.7		5.671	1.225–26.240	.026
IIIc (n=21)	18.4	8.2–28.7	28.6		0.740	0.293–1.867	.523
I (n=320)	49.2	38.8–59.7	46.3				

AFP = a-fetoprotein, HAI = histological activity index, HBV = hepatitis B virus, HCV = hepatitis C virus, ICG = indocyanine green.
* The factor exclude patients with normal pre-OP AFP (<15ng/ml). The factor is not included in multivariate analyses.

in the liver, 2.8% was in distant organs, and 0.8% was seeding in the peritoneum.

3.2. Univariate and multivariate analysis

To determine the risk factors of disease-free survival, univariate and multivariate analysis were performed. By univariate analysis, low albumin level (≤4 g/dl), high 15 minutes ICG level (>10%), high preoperative AFP level, major extension of resection (≥3 segments), large tumor size (>3 cm), presence of satellite nodule, vascular invasion, high histological grade (III-IV), high histological activity index (HAI) score (>3), underlying cirrhosis, advanced TNM staging and narrow resection margin (both <0.5 cm and <1 cm) were significantly associated with poor disease-free survival outcome. Multivariable cox proportional hazards regression models identified narrow resection margin (<0.5 cm) (hazard ratio [HR]: 1.323, *P* = .024), high AFP level (≥15 ng/ml) (HR: 1.305, *P* = .039), major extent of resection (≥3 segments) (HR: 1.507, *P* = .034), high HAI score (HR: 1.427, *P* = .006) and underlying cirrhosis (HR: 1.404, *P* = .009) as independent risk factors for poor disease-free survival (Table 1).

3.3. Survival rates according to the resection margin

Among the independent factors of disease-free survival, most of the factors were related to tumor and liver characteristics, and only liver resection margin was the factor settled by surgeons. Among 534 patients, 274 patients had resection margin <0.5 cm and 260 patients had their resection margin ≥0.5 cm. By Kaplan–Meier analysis, the 1-, 3- and 5-year survival rates for the patients with resection margin ≥0.5 cm was 76.2%, 55.2%, and 44.3%, respectively, which were better than those for the patients with resection margin <0.5 cm (Fig. 1A, *P* = .027). To determine whether the extension of resection margin could further improve the survival, the patients with resection margin over 0.5 cm (n = 260) were further divided into 2 groups of patients with resection margin between 0.5 and 0.9 cm and resection margin ≥1 cm. Kaplan–Meier analysis of disease-free survival showed no significant difference if resection margin was increased from 0.5 cm to 1 cm (Fig. 1B, *P* = .354).

3.4. Survival rates according to preoperative AFP levels

Among the risk factors of disease-free survival, AFP was the only factor related to tumor biology that was known before the operation. Kaplan–Meier analysis of disease-free survival according to preoperative AFP levels was performed. For patients with normal preoperative AFP level, the 5-year disease-free survival rate was significantly better than the patients with AFP between 15 and 200 ng/ml (45.2 months vs 31.5 months, *P* = .001) and >200 ng/ml (45.2 months vs 38.0 months, *P* = .001) (Fig. 2).

3.5. Survival rates according to preoperative AFP levels and resection margin

To determine the optimal resection margin according to AFP, the patients were classified by preoperative AFP level into 3 groups (except 40 patients with missing AFP data): <15 ng/ml (within normal range, n=209), between 15 and 200 ng/ml (n=145) and >200 ng/ml (n=140). For the patients with AFP level <15 ng/ml, neither 0.5 cm nor 1 cm of resection margin was a significant prognostic factor for disease-free survival (Table 2, *P* = .617 and .455, respectively). For the patients with AFP level between 15 and 200 ng/ml, resection margin greater than 0.5 cm was a favorable prognostic factor, compared to resection margin <0.5 cm (*P* = .040). The 5-year disease-free survival rate was improved from 24.6 months to 38.7 months (Fig. 3A), but there was no further benefit when the resection margin was extended to 1 cm or greater in these patients (Table 2, *P* = .679). For the patients with AFP >200 ng/ml, resection margin greater than 0.5 cm did not increase the disease-free survival rate (*P* = .140) unless the resection margin was widened to 1 cm and greater (Table 2, *P* = .012). By Kaplan–Meier analysis, the patients with resection margin greater than 1 cm had significantly better disease-free survival compared to patients with resection margin less than 0.5 cm (*P* = .017) or between 0.5 and 0.99 cm (*P* = .025). The 5-year disease-free survival was improved from 34.3 and 33.9 months to 48.8 months (Fig. 3B). These results implied that optimal or adequate resection margin was tumor-free for patients with AFP <15 ng/ml, ≥0.5 cm for patients with AFP level between 15 and 200 ng/ml and ≥1 cm for the patients with AFP level >200 ng/ml.
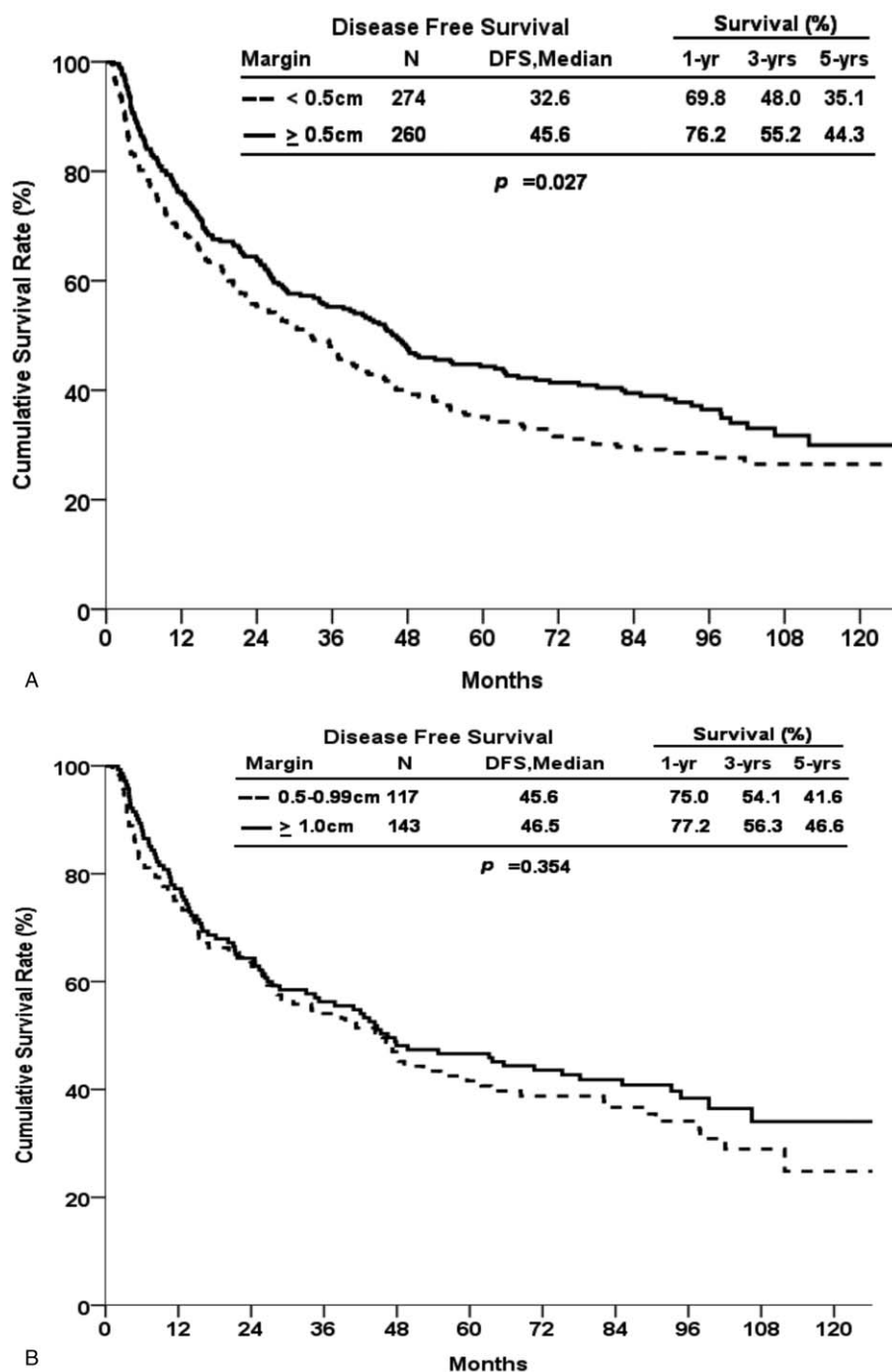
Figure 1. Disease-free survival according to the resection margin. (A) Among 534 patients, the 1-, 3- and 5-year disease-free survival rates for the patients with resection margin ≥0.5 cm was 76.2%, 55.2%, and 44.3%, respectively, which were better than those for the patients with resection margin <0.5 cm (P = .027). (B) Among 260 patients with resection margin ≥0.5 cm, they were further divided into 2 groups with resection margin between 0.5 and 0.9 cm and resection margin ≥1 cm. The disease-free survival rates were not different between the 2 groups (P = .354).

3.6. Survival rates with an adequate resection margin

According to proposed adequate resection margin, all 209 patients in AFP <15 ng/ml group, 71 patients in AFP level between 15 and 200 ng/ml group and 38 patients in AFP level >200 ng/ml group had adequate resection margins. The 5-year disease-free survival rates were 45.2%, 38.7%, and 48.8% for the patients with AFP <15 ng/ml, between 15 and 200 ng/ml and AFP >200 ng/ml, respectively (Fig. 4, P = .408). This result

implied that the resection margin had to be extended along with the elevated levels of AFP to achieve the best results.

4. Discussion

Liver resection is one of the most effective treatments for solitary HCC if reserved liver function is satisfactory.[2] But, postoperative recurrence rate is around 65% in 5-year and 10-year
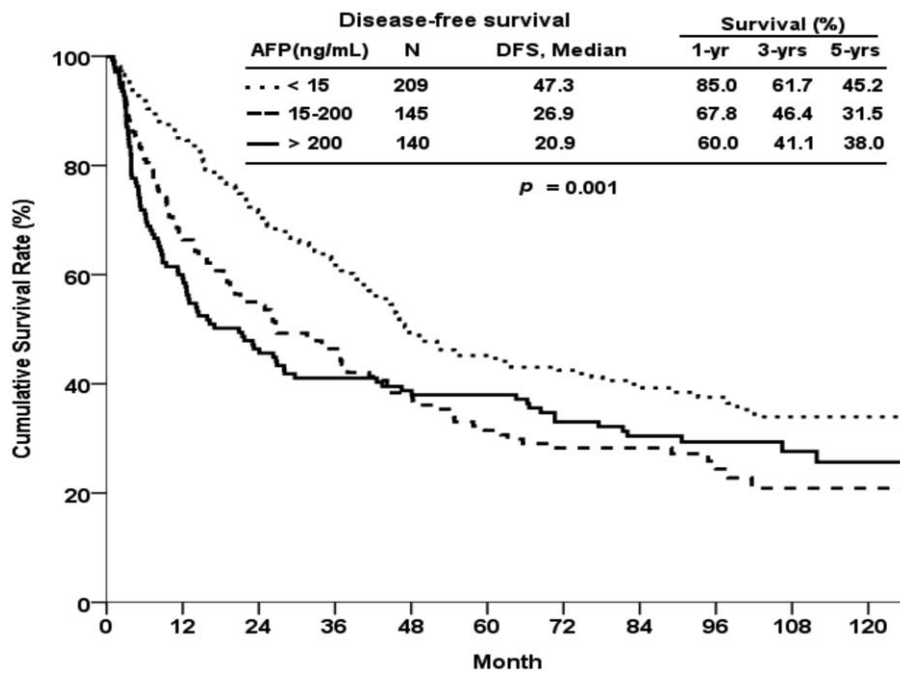
Figure 2. Disease-free survival according to preoperative AFP levels. For patients with normal preoperative AFP level, the 5-year disease-free survival rate was significantly better than the patients with AFP between 15 and 200 ng/ml and >200 ng/ml (*P*=.001). AFP = α-fetoprotein.

disease-free survival might be just only 7.8%.[4–8] Most of the postoperative recurrence may come from residual intrahepatic metastasis or multicentric carcinogenesis.[6] This study showed 96.4% of recurrence located in the liver. Although the intrahepatic recurrence may be due to multicentric carcinogenesis or spread by portal vein flow, surgeons always attempt to create a safe margin during liver resection to prevent tumor recurrence. Obviously, the policy of liver resection for HCC is not only to eradicate the main tumor but also create a safe margin which may contain non-detectable micro-metastasis.[12] As no adjuvant therapy can be applied to prevent tumor recurrence until now, a safe margin is always emphasized by surgeons.

Resection margin in HCC remains controversial. Most of the clinical studies suggested a resection margin of 0.5 cm[7,19] or 1

cm[13,14,20] to achieve good prognosis. To our knowledge, micrometastasis less than 0.2 cm is an important cause of postoperative intrahepatic recurrence. Shi et al demonstrated that the distance of micro-metastasis spread ranged from 0.05 to 6.10 cm based on pathological pictures and recommended a 1.0 proximal resection margin and a 2.0 cm distal margin according to direction of portal flow.[21] Zhou et al also used pathological pictures to demonstrate that the most distance of micrometastasis was 6 mm and the distance would extend to 19 mm if having macroscopic tumor thrombi or macrosatellites.[22] They recommended that 19 mm and 6 mm resection margins were required in patients with and without macroscopic tumor thrombi or macrosatellites, respectively. Shi et al further showed that a resection margin of 2 cm efficaciously decreased postoperative recurrence rate in a prospective randomized trial.[23] However, other studies did not

| Table 2						
Survival rates according to preoperative AFP and resection margin.						
Factors	**Margin**	**n**	**Median**	**95% CI**	**5-yr (%)**	**P-value**
AFP						
<15 ng/ml	<0.5 cm	109	45.5	34.6–56.4	42.1	.617
	≥0.5 cm	100	54.8	28.1–81.5	48.5	
	<1 cm	156	46.2	37.9–54.4	43.6	.455
	≥1 cm	53	62.7	18.1–109.4	50.1	
15–200 ng/ml	<0.5 cm	74	21.4	13.7–29.1	24.6	.040
	≥0.5 cm	71	37.8	17.5–58.1	38.7	
	<1 cm	109	26.7	12.8–40.5	28.5	.407
	≥1 cm	36	34.5	9.3–59.8	40.0	
>200 ng/ml	<0.5 cm	76	14.3	2.6–25.9	34.3	.140
	≥0.5 cm	64	26.7	0.0–55.6	42.3	
	<1 cm	102	12.7	6.8–18.5	33.9	.012
	≥1 cm	38	46.5	0.0–121.6	48.8	

AFP = α-fetoprotein.
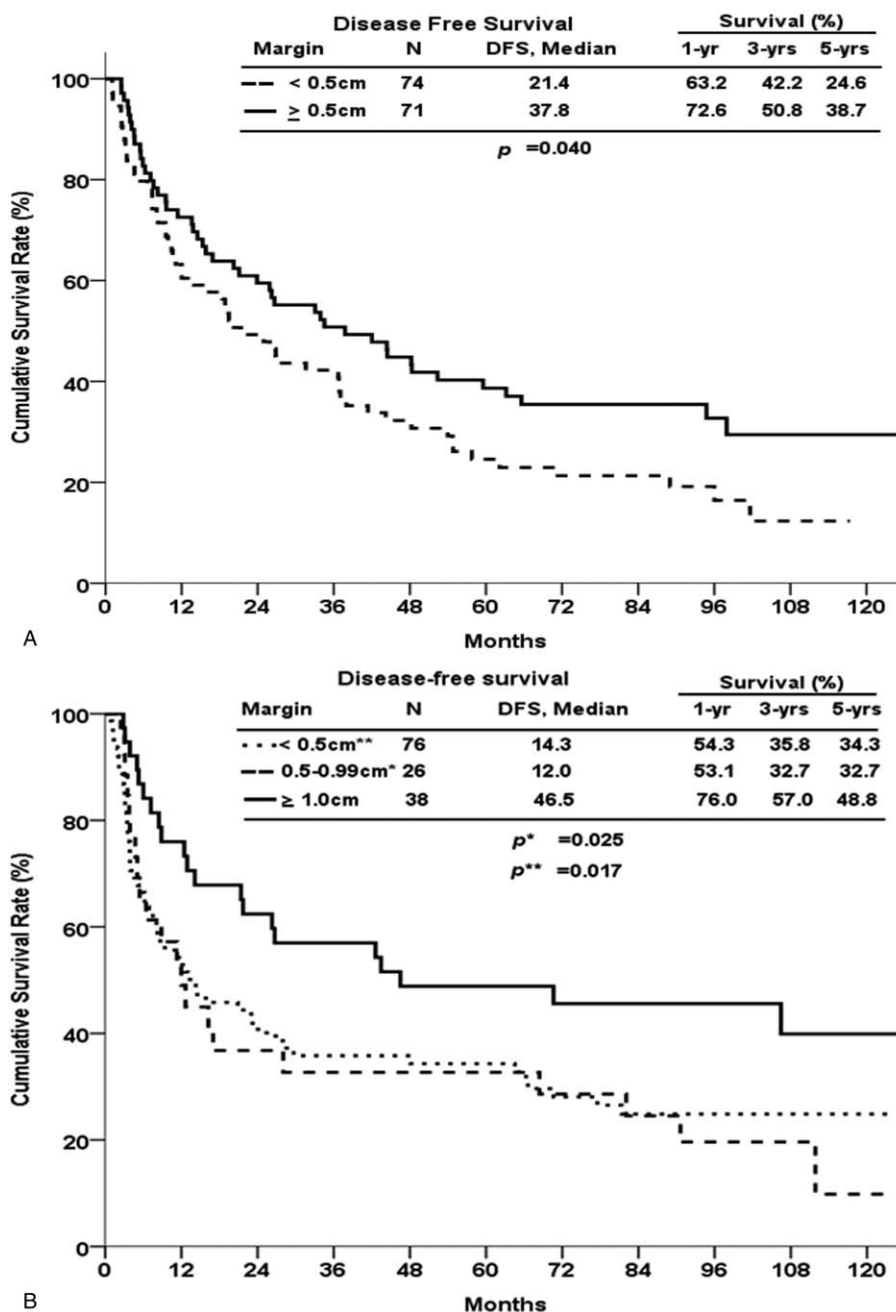
Figure 3. Disease-free survival rate according to preoperative AFP levels and resection margins. (A) For the 145 patients with AFP level between 15 and 200 ng/ml, the disease-free survival rates were better for the patients with resection margin ≥0.5 cm than <0.5 cm (P=.040). (B) For 140 patients with AFP >200ng/ml, the patients with resection margin greater than 1 cm had significantly better disease-free survival rates compared to patients with resection margin less than 0.5 cm (P=.017) or between 0.5 and 0.99 cm (P=.025). AFP = α-fetoprotein.

show any prognostic difference with wider resection margins.[5,16–18] In clinical practice, the tumor may be adjacent to major vessels in a cirrhotic liver and limits wide excision of liver parenchyma. Therefore, a controversy of optimal resection margin remains until now.

According to the results of this study, optimal resection margin could be guided by preoperative AFP levels. This study showed that neither 0.5 cm nor 1 cm resection margin demonstrated superior prognosis to resection margin <0.5 cm for the patients with normal level AFP. However, when AFP was elevated to 15 to 200 ng/ml, a resection margin of ≥0.5 cm was needed to achieve a favorable prognosis. When AFP was further

increased over 200 ng/ml, the resection margin was needed to be extended to ≥1 cm to achieve a better disease-free survival rate. With adequate resection margins proposed by the results of our study, both groups of patients with AFP between 15 and 200 ng/ml and over 200 ng/ml could achieve disease-free survival rates comparable with the patients with normal AFP. Therefore, an adequate resection margin could be tumor-free margin for patients with normal AFP (<15 ng/ml), 0.5 cm for patients with AFP between 15 and 200 ng/ml, and 1 cm for patients with AFP over 200 ng/ml.

AFP is synthesized in the liver and is used as a tumor marker for HCC. Peng et al found that patients with high AFP (>200 ng/ml)
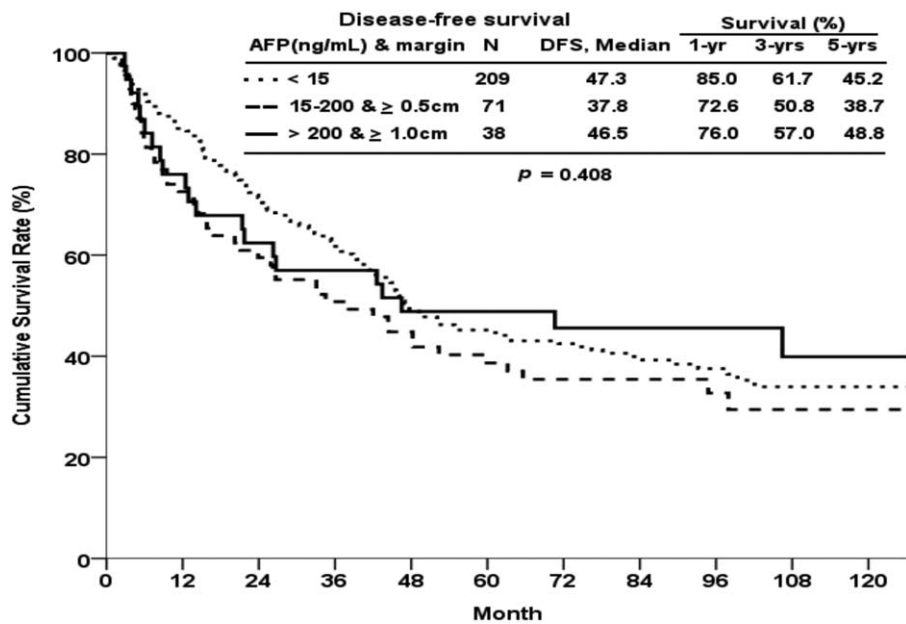
Figure 4. Disease-free survival rate according to the proposed adequate resection margin. The survival rates for 209 patients in AFP <15 ng/ml group with tumor-free margin, 71 patients in AFP level between 15 and 200 ng/ml group with ≥0.5 cm resection margin and 38 patients in AFP level >200 ng/ml group with ≥1 cm resection margin were calculated. The 5-year disease-free survival rates for these patients were not different (*P*=.408). AFP = α-fetoprotein.

had worse 10-year survival than the patients with low AFP level.[24] AFP was a predictor of overall survival and disease-free survival and was association with progression and metastasis of HCC via unknown mechanisms.[25] Ma et al showed the degree of differentiation of AFP-negative HCC was relatively high, and microscopic vascular involvement was less common.[26] High AFP was reported to be correlated with large tumors (>5 cm), high-grade (grades II to IV) tumors, vascular invasion, and early tumor recurrence.[24] Therefore, extended resection margin should be carried out for the HCC with high AFP levels.

Resection margin for HCC is still in debate because wide excision of liver parenchyma in a cirrhotic liver may cause postoperative liver failure. However, parenchymal preservation to prevent immediate postoperative liver failure may expense the disease-free survival if resection margin is not adequate. There is no exact guidance of adequate resection margin in liver resection until now. This study employed AFP biomarker as a guide to request adequate resection margin for HCC treatment. Based on our proposed resection margin, the patients with adequate resection margin had significant better disease-free survival rate than the patients without adequate resection margin. The limitation of this study is that this is a retrospective analysis. A prospective study may undergo to validate this proposed resection margin.

In conclusion, adequate resection margin is a favorable factor in liver resection for HCC. The optimal resection margin can be guided by preoperative AFP levels. For patients with normal AFP (less than 15 ng/ml), tumor-free margin is enough. For patients with increased preoperative AFP level, a resection margin of 0.5 cm is advised for the patients with AFP between 15 and 200 ng/ml, and 1 cm for the patients with AFP over 200 ng/ml.

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