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Clinical Management of Recurrent Hepatocellular Carcinoma

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Objective
The aim of this study was to evaluate the long-term benefits of the aggressive treatments with resection or transarterial chemoembolization (TACE) for recurrent hepatocellular carcinoma (HCC).

Summary Background Data
Primary HCC is one of the most fatal malignancies in Taiwan. The result of resection for HCC remains unsatisfactory, primarily due to the high recurrence rate. To improve surgical results, recurrent HCC must be treated with aggressive resection or TACE.

Methods
The authors evaluated the results of repeated hepatic resection among 25 patients with recurrent HCC and of TACE among 12 patients with resectable recurrent HCC. The outcomes of an additional 64 patients with unresectable recurrent HCC were also evaluated.

Results
During the follow-up period from 2–112 months, 52% (13/25) of patients receiving repeat resection (group 1) were alive, whereas 42% (5/12) of patients receiving TACE (group 2) were alive. No perioperative deaths within 30 days after surgery occurred in the repeated resection group. The cumulative survival rates at 1, 2, 3, and 5 years after the first operation were 92%, 84%, 71.6%, and 65.1% in group 1 and 83.3%, 75%, 75%, and 22.5% in group 2. The survival rates at 6 months and at 1, 2, and 3 years after recurrence were 92%, 72%, 64%, and 44.8% in group 1 and 83.3%, 75%, 66.7%, and 48% in group 2.

The survival of patients with unresectable recurrent HCC was much worse: 1-, 2-, 3-, and 5-year survival after surgery was 57.8%, 29.8%, 15.5%, and 0%; and 6-month and 1-, 2-, and 3-year survival after recurrence was 46.5%, 29.2%, 12.5% and 7.8%.

Conclusions
More aggressive treatment with repeated hepatic resection can prolong survival time after recurrence of HCC in selected patients. However, TACE can also achieve good results although it is not thought of as curative.

Hepatocellular carcinoma (HCC) is the most common cause of death from malignant diseases among the male population in Taiwan.[1] Through periodic examination of high-risk individuals (men older than age 40 years who have liver cirrhosis, who are carriers of hepatitis B virus carriers, and who have a family history of HCC) using serum alpha-fetoprotein and hepatic ultrasound examination, subclinical asymptomatic HCC has been detected. The frequency of resectability has increased dramatically in recent years. The 5-year survival rate for patients with resected HCC has also increased to approximately 30%. However, the results of tumor resection for HCC remain unsatisfactory, primarily because of the high incidence of postoperative recurrence.[2-6] This recurrence might be due to undetected tumor tissue during operation or new primary growth in the remnant liver. Preoperative imaging procedures, intraoperative ultrasound examination, careful manipulation at operation, wider resection margins, and some postoperative adjuvant therapies have used to prevent HCC recurrence.

To improve the survival rate of patients with HCC by prevention of recurrence, we should attempt more aggressive treatment. However, the reduced hepatic parenchyma, associated liver cirrhosis, and technical problems encountered in repeated operation often make such treatment difficult and challenging. Repeated hepatic resection for recurrent HCC is a technically safe procedure among selected patients, and the results of the initial reports are encouraging.[5-12] Moreover, TACE has been shown to result in a better survival rate than systemic or oral chemotherapy and is as an alternative treatment for recurrent HCC.[13,14]

In the current article, we evaluated and reported the effect of repeated hepatic resection and TACE for treatment of patients with recurrent HCC.

PATIENTS AND METHODS

Patients

From January 1986 to December 1992, 207 hepatic resection for primary HCC were performed by one of the authors (P.H.L.) at the Surgical Department of the National Taiwan University Hospital. Two hundred one hepatic resections were curative, but the remaining six were only palliative. Five patients died either within 1 month after the operation or during the first admission for resection of HCC. The remaining 196 patients who received curative hepatic resection and who were regularly followed at outpatient clinics formed the basis of this study.

It is impossible to distinguish recurrence due to residual tumor or new primary tumors. In the current study, we included as recurrence intrahepatic tumor and distant metastasis that developed after a curative resection.

During the follow-up period (range, 2 months to 60 months; mean, 27 months) until the end of August 1994, recurrence occurred in 101 patients. Eighty patients had intrahepatic recurrence, 11 had both intrahepatic recurrence and distant metastasis, and the remaining 8 had distant metastasis. The sites of distant metastasis included the lung (14 cases), bone (4 cases), and peritoneal cavity (1 case). Two patients who had undergone initial hepatic resection elsewhere received regular postoperative follow-up at our institution as well as a second hepatic resection for recurrence. We included these two patients in the current study. After the second operation, all patients were observed for a period of 2 months to 112 months, with a mean of 27.13 months and median of 21 months.

Follow-Up Study

Follow-up evaluation involved a clinical physical examination and blood chemistry tests at each visit. Serum alpha-fetoprotein was measured by radioimmunoassay at least every 2 months. The remnant liver was examined by hepatic ultrasonography every 2 months in the 1st year and every 3 to 4 months thereafter. When a new lesion within the liver was detected by ultrasound examination, computed tomography of the abdomen was performed for confirmation. Chest x-ray examination was performed every 6 months to evaluate pulmonary metastasis. If a patient reported bone pain, a bone scan was performed for the detection of metastasis. If any of the above procedures indicated recurrence, the patient was readmitted for further investigation, including angiographic evaluation.

Treatment

The principle of selection for treatment was that repeated hepatic resection was the first choice whenever the tumor was considered resectable. Thirty-seven patients with tumor recurrence were considered eligible for repeated resection because they met the criteria of fewer than four recurrent intrahepatic tumors and good functional liver reserve. The functional liver reserve was evaluated by blood chemical tests, Child's classification of liver function, and retention rate of Indocyanine green at 15 minutes. The remaining 64 patients were considered ineligible for repeated hepatic resection because of main

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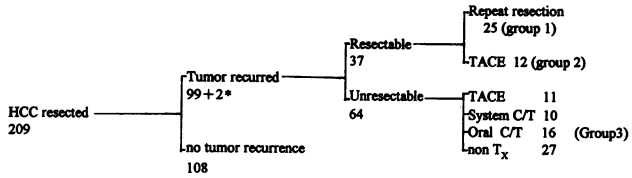

Figure 1. Treatment of 209 patients with HCC.

portal vein thrombosis, combined distant metastasis, tumors numbering more than three, or poor functional liver reserve. Twenty-five patients who received hepatic resection were defined as group 1.

Twelve patients who were eligible for hepatic resection but who instead chose TACE for treatment of recurrence were defined as group 2. The TACE procedure was performed as follows: An emulsion consisting of 5 ml lipiodol, 5 ml contrast medium, and 40 mg doxorubicin was infused immediately before embolization. Then, 10 ml contrast medium and 1-mm cubes of surgical powder were used to embolize the feeding arteries.

The remaining 64 patients who were ineligible for repeated hepatic resection were defined as group 3. These patients received various modes of treatment, including TACE for 11 patients, systemic chemotherapy for 10, oral chemotherapy for 16, and supportive treatment for 27. The overall treatment regimens are listed in Figure 1.

Clinicopathologic Features

The clinical data and pathologic features of initial and recurrent HCC of our patients are shown in Table 1. The sex of patients, age at initial hepatic resection, interval between initial hepatic resection and recurrence, rate of hepatitis B surface antigen and anti-hepatitis C virus positivity, rate of associated liver cirrhosis, pathologic findings of initial and recurrent HCC, and functional liver reserve were similar among the three groups. However, compared with groups 1 and 2, group three patients evidenced shorter disease-free interval, larger initial tumor, more advanced pTNM stage of initial HCC, and more tumors present in recurrent HCC.

Statistical Analysis

Statistical comparisons of clinicopathologic features were made with the chi square test and Fisher's exact test. Cumulative survival rates were obtained by means of the Kaplan–Meier method, and the survival curves were compared by the log-rank test and the generalized Wilcoxon test. The survival rates were compared again after adjusting the disease-free interval by Cox's proportional hazards survival analysis. A probability value of less than 0.05 was considered statistically significant.

RESULTS

Repeated Hepatic Resection

The clinical data of 25 patients in group 1 are listed in Table 2. At the first operation for HCC, hepatic lobectomies were performed on 8 patients, segmentectomies on 7 patients, and wedge resections on 10 patients. At the second operation for recurrent HCC, hepatic lobectomy was performed on 1 patient, segmentectomy on 1 patient, and wedge resections on the remaining 23 patients. One patient received a third operation involving wedge resection of the liver for a second recurrence of HCC. The operation time ranged from 130 to 460 minutes (mean, 267 minutes). Several surgical techniques were used for the 26 hepatic resections, including anatomic hepatic resection with vascular control in 1 operation, Lin's clamp in 2, and microwave tissue coagulation in 23. The amount of blood transfused during the operation ranged from 500 to 3500 ml whole blood (mean, 1060 ml). No patients died within 1 month after the repeated hepatic resection. Six patients had postoperative complications: two patients experienced wound infection; two, pleural effusion; one, hepatic failure; and one, bile leakage. Conservative treatment was successful for all six patients.

At the end of the follow-up period, six patients were alive and disease free from 19 to 40 months after the resection for recurrence. Seven patients were alive but with tumor recurrence. Twelve patients died 7 to 35 months after the second operation: nine died of tumor recurrence, one of variceal bleeding, and two of hepatic failure.

Transarterial Chemoembolization

The clinical data of the 12 patients in group 2 are given in Table 3. They received one to nine sessions of TACE (mean, 3.4 sessions) for treatment of recurrent HCC. Seven patients died of tumor recurrence during the follow-up period and the remaining five survived 24 to 62 months after the diagnosis of recurrence.

Survival

Figure 2 shows the cumulative survival rates after the first hepatic resection of group 1, 2, and 3. The risks of patient deaths decreased with hazard ratios of 0.9022 and 0.9930, respectively, for each 1-month increase in the disease-free interval.

Figure 3 shows the cumulative survival rates of groups 1, 2, and 3 after tumor recurrence. The survival rates after recurrence of HCC for groups 1 and 2 were significantly better than that of group 3.

The hazard ratio after adjusting for the disease-free interval is shown in Table 4. The disease-free interval in each

Table 1. COMPARISON OF CLINICOPATHOLOGIC FINDING IN PATIENTS WITH RECURRENT HEPATOCELLULAR CARCINOMA

	Group 1 (n = 25)	Group 2 (n = 12)	Group 3 (n = 64)	p-Value
Sex (M/F)	17/8	10/2	48/16	NS
Age (yrs)	55.8 ± 10.6	56.3 ± 11.2	57.1 ± 11.3	NS
Follow-up period (mos)	10–112	6–85	2–56	
Mean	49.8 ± 26.2	41.0 ± 21.6	16.9 ± 12.9	
Median	48	43	13	
Disease-free interval (mo)	25.6 ± 23.6	13.8 ± 15.6	9.0 ± 9.6*	<0.05†
HBsAg (+)	68.0%	58.3%	60.9%	NS
AntiHCV (+)	32.0%	33.3%	35.9%	NS
Cirrhosis (+)	76.0%	75.0%	62.5%	NS
Initial HCC				
Tumor size <3 cm	28.0%	16.7%	9.4%	<0.05†
3–5 cm	44.0%	41.7%	26.6%	
>5 cm	28.0%	41.7%	64.1%	
Tumor number 1	80.0%	75.0%	76.6%	NS
2–3	20.0%	25.0%	23.4%	
Fibrous capsule (+)	64.0%	75.0%	60.9%	NS
Vascular invasion (+)	36.0%	50.0%	54.7%	NS
Satellite nodule (+)	28.0%	25.0%	50.0%	NS
pTNM Stage I	4.0%	8.3%	3.1%	<0.05†
II	56.0%	33.3%	28.1%	
III	40.0%	50.0%	45.3%	
IVA	0%	8.3%	23.4%	
Recurrent HCC				
Tumor size‡ <3 cm	32.0%	50.0%	20.3%	NS
3–5 cm	56.0%	41.7%	51.6%	
>5 cm	12.0%	8.3%	15.6%	
Tumor number 1	60.0%	41.7%	28.1%	<0.05†
2–3	40.0%	58.3%	20.3%	
diffuse	0%	0%	39.1%	
ICGR15§ <20%	32.%	33.3%		
20–35%	60.0%	58.3%		NS
>35%	8.0%	8.3%		

NS = not statistically significant.
* $p < 0.05$ compared with group 1, mean ± standard deviation.
† Not statistically significant for group 1 *vs.* group 2.
‡ 8 cases in group 3 with only distant metastasis are excluded.
§ Not checked in group 3.

group was adjusted to be the same, and group 1 was used as a reference. The risk of death per month from the time of first recurrence to the end of follow up was 0.9853 in group 2 and 4.353 in group 3 compared with group 1. The difference between groups 1 and 3 was significant. The risk of death per month from time of first operation to the end of follow-up was 1.100 in group 2 and 4.962 time in group 3 compared with group 1. The difference was significant between groups 1 and 3. The risks of patient deaths decreased with hazard ratios of 0.9022 and 0.9930, respectively, for each 1-month increase in the disease-free interval.

DISCUSSION

Currently, surgical resection appears to be the only way to potentially cure malignant hepatic tumor. The outcome for resection of HCC has been improved in recent years through advances in diagnostic imaging studies, surgical techniques, and postoperative care. Screening methods using alpha-fetoprotein and abdominal ultrasound examination for high-risk populations has increased the resectability of HCC. The 5-year survival rate for resection of HCC reported by most authors is approximately 30%.[3,4,15,16] The major cause of death is tumor recurrence, and the frequency of tumor recurrence is estimated to be nearly 50%.[3–6] In our study, the recurrence rate of 48% is similar to that reported by other authors. Prevention and treatment of recurrence is thought to be the best way to improve surgical results of HCC.

Several patterns of tumor recurrence in the remnant liver after resection of HCC have been reported.[6,8] The

Table 2. CLINICAL DATA OF 25 PATIENTS WHO UNDERWENT REPEATED RESECTION FOR RECURRENT HEPATOCELLULAR CARINOMA

Patient			Repeated Hepatic Resection				
No.	Sex	Age	First Operation	Second Operation	Third Operation	Survival Time (mos)*	
1	M	68	Segmentectomy	Wedge resection	—	7 + 40, alive,	Free of disease
2	F	66	Wedge resection	Wedge resection	—	13 ± 21, alive,	Free of disease
3	M	64	Wedge resection	Wedge resection	—	22 + 26, alive,	With disease
4	F	74	Right lobectomy	Wedge resection	—	28 + 27, alive	With disease
5	M	66	Wedge resection	Wedge resection	—	5 + 21, alive	Free of disease
6	M	67	Right lobectomy	Wedge resection	—	12 + 34, alive,	With disease (brain metastasis)
7	F	72	Segmentectomy	Wedge resection	—	5 + 12, dead,	With disease
8	M	52	Right lobectomy	Wedge resection	—	19 ± 44, alive	With disease
9	M	57	Segmentectomy	Wedge resection	—	24 + 36, alive,	With disease
10	F	49	Left lobectomy	Wedge resection	—	18 + 39, alive,	Free of disease
11	F	37	Right lobectomy	Wedge resection	—	13 + 13, dead,	With disease
12	F	43	Segmentectomy	Segmentectomy	—	3 + 7, dead,	With disease
13	M	57	Wedge resection	Wedge resection	—	33 + 37, alive,	Free of disease
14	M	53	Wedge resection	Wedge resection	—	48 + 27, dead,	Free of disease
15	M	64	Right lobectomy	Wedge resection	—	63 + 35, dead,	With disease
16	M	41	Segmentectomy	Wedge resection	—	55 + 11, dead,	Free of disease
17	M	50	Right lobectomy	Wedge resection	—	104 + 8, dead,	With disease
18	M	58	Segmentectomy	Wedge resection	Wedge resection	7 + 9 + 24, alive,	With disease
19	M	49	Wedge resection	Wedge resection	—	39 + 18, dead,	With disease
20	F	53	Wedge resection	Wedge resection	—	8 + 26, dead,	Free of disease
21	F	35	Wedge resection	Left lobectomy	—	17 + 10, dead,	With disease
22	M	59	Wedge resection	Wedge resection	—	12 + 7, dead,	With disease
23	M	53	Left lobectomy	Wedge resection	—	39 + 43, alive,	With disease
24	M	45	Segmentectomy	Wedge resection	—	3 + 9, dead,	With disease
25	M	63	Wedge resection	Wedge resection	—	44 + 19, alive,	Free of disease

* From first operation to recurrence + from recurrence to death or end of followup.

first pattern is that of residual tumors that went undetected at the operation but that resulted in disease recurrence shortly after the operation. It usually grew near the resectional margin. Careful manipulation of tumor during the operation and anatomic resection, including standard segmentectomy and lobectomy, could decrease this pattern of recurrence. However, a wider resection of cirrhotic liver carries a higher mortality rate because of hepatic failure.[2,17,18] The second pattern is tumor dissemination through the portal vein due to tumor biologic behavior or surgical manipulation. The third pattern is unnoticed multicentric synchronous carcinogenesis. Advanced preoperative imaging procedures, such as selective angiography, magnetic resonance imaging, and contrast enhancement with CO_2 microbubble ultrasonography, have been prepared to provide valuable information regarding these lesions, but they can not detect smaller lesions.[6,8,9,19,20] The fourth pattern is metachronous tumor growth in the remnant liver. Intensive periodic follow-up must include measurement of serum alpha-fetoprotein, ultrasound examination, and computed tomography for early detection of tumor recurrence and opportunity for treatment.

The principles of therapy for recurrent HCC are the same as those for primary HCC. In our opinion, hepatic resection remains the first choice of treatment whenever recurrent tumor is considered resectable because we believe that operation offers the only method for total extirpation or radical ablation of recurrent HCC. Although repeated hepatic resection is made more difficult by decreased volume of liver parenchyma, adhesion, anatomic distortion after previous operations, and portal hypertension, we believe that with some surgical techniques and patient selection, this procedure is safe for treatment of recurrent HCC. Because intraoperative bleeding is the major cause of early death after hepatic resection,[3,4] we used Lin's clamp and a microwave tissue coagulator to prevent severe bleeding during parenchymal transection, especially for patients with cirrhosis. Lin's clamp can temporarily block inflow and outflow of liver parenchyma to achieve reduced blood loss and was applied in two hepatic resections.[21] Insertion of probe of

Table 3. CLINICAL DATA FOR 12 PATIENTS WHO UNDERWENT TACE FOR RECURRENT HEPATOCELLULAR CARCINOMA

Patient					
No.	Sex	Age	Operation	TACE (sessions)	Survival time (mos)*
1	M	65	Segmentectomy	7	5 + 31, dead
2	M	67	Left lobectomy	1	20 + 24, alive
3	M	67	Wedge resection	6	22 + 25, alive
4	M	62	Wedge resection	1	7 + 5, dead
5	M	49	Segmentectomy	1	59 + 26, alive
6	M	31	Right lobectomy	2	11 + 12, dead
7	M	63	Left lobectomy	6	5 + 62, alive
8	M	42	Right lobectomy	3	6 + 36, dead
9	M	57	Wedge resection	1	10 + 36, alive
10	M	61	Wedge resection	9	15 + 23, dead
11	M	49	Left lobectomy	1	2 + 4, dead
12	M	62	Wedge resection	3	4 + 42, dead

TACE = transarterial chemoembolization.
* From first operation to recurrence + from recurrence to death or end of follow-up.

microwave tissue coagulator into the edge of resection before parenchyma resection can also decrease blood loss and was used in 23 hepatic resections.[22] The mean operation time of 267 minutes (range, 130–460 minutes) in repeated hepatic resection is similar to that of 265 minutes (range, 100–580 minutes) in first hepatic resection at our institution. The mean transfusion amount of whole blood (1060 ml; range, 500–3500 ml) used in repeated hepatic resection was similar to that used in first hepatic resection (1000 ml whole blood; range, 0 to 6000 ml). There were no operation deaths in the repeated resection group. Repeated hepatic resection appears to be a safe procedure, thus to completely remove the tumor we favor repeated resection for recurrent HCC if feasible.

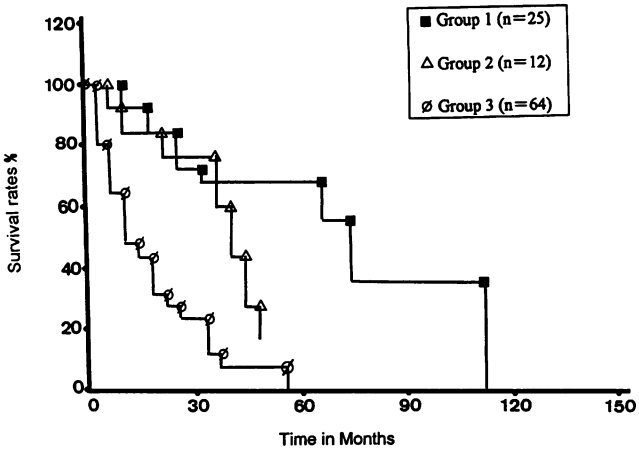

Figure 2. Cumulative survival rates of patients with recurrent HCC after the first hepatic resection by group. The survival rate in group 1 was significantly better than those in groups 2 and 3 ($p < 0.05$).

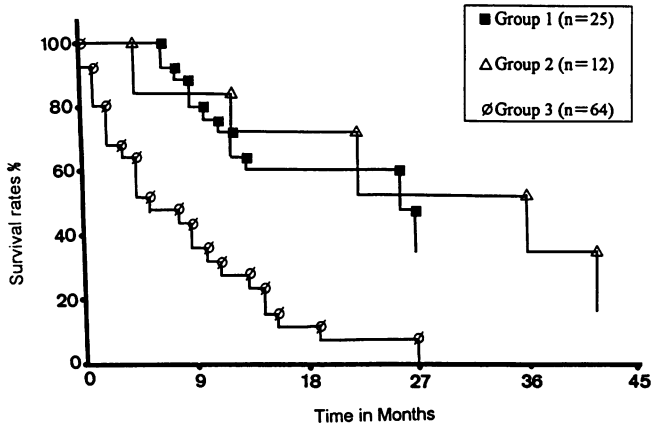

Figure 3. Cumulative survival rates for patients with recurrent HCC after time of recurrence by group. The survival rates in groups 1 and 2 were significantly better than that in group 3 ($p < 0.05$).

In the current study, 12 candidates for repeated resection refused operation and instead received TACE for treatment of recurrent HCC. Because the patients in these two groups had similar backgrounds, we were able to evaluate the efficacy of the different treatments. The remaining 64 patients in group 3, however, tended to have larger tumors and more advanced tumor stage of primary HCC. These factors may cause shorter disease-free interval after the first operation, recurrence of a larger number of tumors, and higher incidence of main portal vein thrombosis and distant metastasis. Presence of these conditions as well as poor functional liver reserve among the patients in group 3 made hepatic resection impossible. Because of the selection criteria, the resectability rate of recurrent HCC is usually less than 30%, as confirmed by our (24.8%) and other reports.[5,6,13]

Table 4. THE RISK OF MONTHLY PATIENT DEATH AFTER ADJUSTING DISEASE-FREE INTERVAL

	Hazard Ratio	
	First Operation to End of Followup or Patient's Death	Second Operation to End of Followup or Patient's Death
Group 1	1	1
Group 2	1.100	0.9853
Group 3	4.962	4.353
DFI	0.9022	0.9930

DFI = disease-free interval.

Transarterial chemoembolization is an alternate treatment for recurrent HCC but presents problems, such as anatomic changes due to previous operation, neovascularization or collaterals to feed the recurrent tumor, damage to the nontumorous liver tissue, and accumulation of drug toxicity from repeated TACE sessions.[12] Moreover, the remaining tumor tissue may continue to grow and spread where feeding collaterals develop. Because of these problems, TACE is used as an alternative, noncurative treatment for recurrent HCC, and repeated sessions are necessary for control of recurrent tumor.

For evaluation of long-term results, all patients who had undergone operation before December 1992 were observed until August 1994, the end point in this study. The 1-, 2-, and 3-year survival rates from first operation to end of follow-up in groups 1 and 2 were similar, but the 5-year survival rate in group 1 was far better than that in group 2. The 1-, 2-, and 3-year survival rates from recurrence to death or to end of follow-up in groups 1 and group 2 were similar. Currently, 52% of patients (13/25) in group 1 are alive with longer follow-up periods, and 42% of patients (5/12) in group 2 are alive. We believe that with a larger sample size and longer follow-up, the result in group 1 would be better than that of group 2. Our results with TACE are better than those reported by others.[12] The good results that were achieved with TACE may be due to the selection of patients and repeated sessions of this procedure, even though TACE is considered a noncurative treatment for recurrent HCC. Although the difference in length of disease-free interval between groups 1 and 2 was not statistically significant, it still seemed longer in group 1. When the disease-free interval was adjusted to be the same among the three groups, the risk of patient death was higher in group 3, and there was no difference between groups 1 and group 2. We believe that the biologic nature of the tumor determines the risk of patient death.[23] Tumors with longer disease-free intervals have slower growth rates and had result in better patient outcomes.

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