Prognosis of Recurrent Hepatocellular Carcinoma: A 10-Year Surgical Experience in Japan

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Background & Aims: **Little has been addressed on the characteristics and prognostic factors of recurrent hepatocellular carcinoma after undergoing a hepatic resection for primary hepatocellular carcinoma. The aim of this study was to clarify the aforementioned matters of recurrent hepatocellular carcinoma.** ***Methods:*** **One hundred fifty-nine patients with recurrent hepatocellular carcinoma were studied retrospectively. Twenty-four clinicopathologic variables, including the period until recurrence (less than or more than 1 year), types of recurrence (intrahepatic nodular type, intrahepatic multiple type, and extrahepatic type), and types of treatment after recurrence (no treatment, lipiodolization, ethanol injection, or hepatectomy) were univariately and multivariately analyzed.** ***Results:*** **The following three variables were finally selected as independent and prognostic indicators after recurrence: (1) period until recurrence, (2) type of recurrence, and (3) types of treatment after recurrence.** ***Conclusions:*** **The prognostic factors in patients with recurrent hepatocellular carcinoma were as follows: (1) period until recurrence, (2) types of recurrence, and (3) types of treatments received after recurrence. The establishment of a follow-up system, including an examination for extrahepatic recurrence, and the development of an effective method of adjuvant chemotherapy are required to obtain better treatment results.**

The surgical results of hepatocellular carcinoma (HCC) have steadily improved because of various advancements including improved perioperative management, diagnostic modalities, and surgical techniques.[1,2] However, the long-term outcome of patients with HCC is still not satisfactory, because the recurrence rate of HCC after a curative hepatic resection still remains high. Until recently, many investigators have reported the prognostic factors related to the recurrence of HCC.[3–8] Furthermore, several investigators, including ourselves, have reported the usefulness of a repeat hepatic resection for recurrent HCC.[9–11] However, there have been few detailed investigations of survival rates after recurrence including the prognostic factors of patients with recurrent HCC after a hepatic resection for primary HCC. It is considered to be of great interest whether the period until recurrence, the types of recurrence, or the types of treatments after recurrence are related to the prognosis or not.

Therefore, the aim of this study was to clarify the characteristics of recurrent HCC and identify the prognostic factors in patients with recurrent HCC after a hepatic resection for primary HCC.

Materials and Methods

Three hundred twelve patients underwent a curative hepatic resection at Kyushu University Hospital, Fukuoka, during a 10-year period (April 1985 to March 1995). The operative procedures were as follows: 10 trisegmentectomies, 88 lobectomies, 45 segmentectomies, and 169 partial resections. The overall incidence of postoperative complications was 22.1%, including nine hospital deaths (2.9%). One hundred fifty-nine (51.0%) of 312 patients, in whom the tumor recurrence was clinically confirmed, were included in this study. A curative operation was defined as an operation in which all the tumors were macroscopically resected during the operation.

The survival rate after recurrence was compared using various clinicopathologic variables (Table 1). The following is a list of host factors: sex; age at recurrence; Child's classification at recurrence; viral status such as hepatitis B and C virus; the liver function test results at recurrence such as the levels of bilirubin, albumin, glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, and platelet; and the histological grade of fibrosis and hepatitis in the first hepatectomy. The following is a list of tumor factors: the period until recurrence (0, >1 year; 1, $\leqq 1$ year), the recurrent types (nodular, multiple, extrahepatic), the types of treatment after recurrence (no treatment, lipiodolization, percutaneous ethanol injection therapy [PEIT], hepatectomy), the α-fetoprotein (AFP) level at recurrence, the histological findings at first hepatectomy including the maximum tumor diameter, tumor differentiation,

Abbreviations used in this paper: AFP, α-fetoprotein; PEIT, percutaneous ethanol injection therapy; TAE, transcatheter arterial embolization.

0016-5085/96/$3.00

Table 1. Demographic Variables of Patients With Recurrent HCC

Variables	3-yr survival (%)	*P* value
Host factors		
Sex		
1: male (n = 127)	42.1	0.9740
2: female (n = 32)	37.6	
Age at REC (*yr*)		
0: ≦65 (n = 105)	43.0	0.7889
1: >65 (n = 54)	35.2	
Child's classificatio at REC		
1: A (n = 90)	49.5	0.0037
2: B (n = 48)	30.1	
3: C (n = 12)	29.2	
Hepatitis B surface antigen		
0: negative (n = 130)	41.2	0.4387
1: positive (n = 27)	33.1	
HCV		
0: negative (n = 20)	40.3	0.6687
1: positive (n = 77)	41.7	
Bilirubin at REC (*mg/dL*)		
0: ≦1.0 (n = 98)	42.2	0.1066
1: >1.0 (n = 45)	35.2	
Albumin at REC (*g/dL*)		
0: ≧3.5 (n = 94)	48.2	0.0033
1: <3.5 (n = 54)	27.1	
GOT at REC (*IU/dL*)		
0: ≦100 (n = 100)	39.9	0.6571
1: >100 (n = 46)	39.3	
GPT at REC (*IU/dL*)		
0: ≦100 (n = 114)	37.9	0.1452
1: >100 (n = 33)	47.6	
Platelet at REC (mm^3)		
0: ≧100,000 (n = 80)	48.0	0.0826
1: <100,000 (n = 65)	31.9	
Histological finding of noncancerous parts of the liver		
Fibrosis		
0: none (n = 21)	54.4	0.1170
1: precirrhosis (n = 52)	32.5	
2: cirrhosis (n = 86)	41.7	
Active hepatitis		
0: (−) (n = 86)	40.7	0.7553
1: (+) (n = 73)	40.6	
Tumor factors		
Period until REC		
0: >1 year (n = 104)	49.1	<0.0001
1: ≦1 year (n = 55)	24.8	
REC types		
1: nodular (n = 85)	58.5	<0.0001
2: multiple (n = 54)	27.9	
3: extrahepatic (n = 20)	6.2	
Treatment types after REC		
0: none (n = 21)	0	<0.0001
1: LPD (n = 106)	38.3	
2: PEIT (n = 10)	76.2	
3: Hx (n = 22)	70.5	
AFP at REC (*ng/mL*)		
0: ≦50 (n = 80)	50.8	0.0039
1: >50 (n = 65)	29.0	
Tumor size at 1st Hx (*cm*)		
0: ≦5 (n = 128)	45.1	0.1593
1: >5 (n = 31)	24.2	
TW at 1st Hx		
0: negative (n = 70)	42.4	0.8119
1: positive (n = 86)	41.0	
Histology at 1st Hx		
1: well (n = 23)	42.9	0.0274
2: moderately (n = 91)	46.0	
3: poorly (n = 41)	24.2	
FC at 1st Hx		
0: absent (n = 35)	40.3	0.4639
1: present (n = 124)	41.0	
VP at 1st Hx		
0: absent (n = 113)	48.8	0.0008
1: present (n = 46)	23.0	
IM at 1st Hx		
0: absent (n = 102)	48.9	0.0022
1: present (n = 57)	26.0	
Tumor stage[a]		
1: stage I (n = 29)	52.6	0.0420
2: stage II (n = 68)	45.8	
3: stage III (n = 54)	26.8	
4: stage IV-A (n = 8)	50.0	
Other factors		
Transfusion at 1st Hx		
0: absent (n = 84)	46.2	0.2622
1: present (n = 75)	36.3	

REC, recurrence; HCV, anti-hepatitis C virus antibody; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; TW, surgical margin <5 mm; LPD, lipiodolization[13,14]; 1st Hx, firs hepatectomy; Hx, hepatectomy; FC, microscopic capsular formation; VP, microscopic invasion to the portal vein; IM, microscopic intrahepatic metastases.
[a]The staging was determined according to the TNM classification [12]

surgical margin, capsular formation, invasion to the portal vein, intrahepatic metastases, tumor staging by TNM classification,[12] and perioperative blood transfusion. All the significant variables, which were obtained by a univariate analysis, were then put into Cox's proportional hazards model to identify any independent variables closely related to the survival rate after recurrence.

The three types of recurrence were defined as the nodular type, which meant there were three or less intrahepatic recurrent nodules; the multiple type, which meant there were more than four multiple recurrent nodules; or the extrahepatic type, which indicated there was extrahepatic recurrence such as to the lung and bone.

Treatment Strategy for Recurrent HCCs

Every effort was made to perform a repeat hepatectomy whenever possible. Lipiodolization[13,14] was primarily indicated for patients for whom a repeat hepatectomy was not indicated

because of patient refusal, as well as a large number of tumors, a difficult location, or a poor liver function. Some patients who had been referred by their physician received PEIT[15]; however, most of the patients undergoing PEIT also simultaneously underwent either transcatheter arterial embolization (TAE) or lipiodolization. No treatment was indicated for patients who had either extrahepatic recurrence or refused any kind of treatment.

Follow-up

The patient follow-up after hepatic resection has been described previously.[11] Briefly, both a monthly measurement of AFP and protein induced by vitamin K absence-II[16] and a monthly bedside ultrasonography were performed. Every 3 months, ultrasonography and dynamic computed tomography were performed by radiologists, and an angiographic examination was performed after admission when recurrence was strongly suspected.

Only 1 of 312 patients was lost to the follow-up without any recurrence 17 months after the operation. The follow-up for 159 patients with HCC was completed to assess the clinical outcome, which included the period until recurrence, the recurrent types, and the types of treatment after recurrence.

Statistics

The survival rate was calculated by the product limit method of Kaplan–Meier,[17] and the differences in the survival rates between the groups were compared using the log rank test.[18] Cox's proportional hazards model[19] was used for the multivariate analysis. The BMDP P2L program (Los Angeles, CA) was used for the multivariate adjustment of all covariates by using a stepwise regression analysis on an IBM system 4381 computer (New York, NY). A P value of <0.05 was considered significant.

Results

During the period from first hepatectomy to recurrence, 0.5-, 1-, 2-, and 3-year cumulative recurrence rates of patients studied were 15%, 35%, 64%, and 84%, respectively. Nodular, multiple, and extrahepatic types of recurrence were 46%, 34%, and 18%, respectively. Types of treatment after recurrence, such as hepatectomy, PEIT, lipiodolization, and no treatment, were performed in 12%, 9%, 67%, and 12%, respectively.

Table 1 shows the results of a univariate analysis used to identify the significant factors closely related to the survival rate in patients with recurrent HCC. The poor prognostic host factors were a Child's classification at recurrence (Child's B or C) and an albumin value at recurrence of <3.5 g/dL. The poor prognostic tumor factors were recurrence appearing <1 year after operation, multiple or extrahepatic recurrent types, no significant therapy in the treatment types after recurrence, an AFP level at recurrence of >50 ng/mL, positive portal vein invasion, positive intrahepatic metastasis, a poorly differentiated histology, and stage III at the time of the first hepatectomy.

Table 2 shows the results of a multivariate analysis using Cox's proportional hazards model. The period until recurrence, the types of recurrence, and the types of treatment after recurrence were selected as independent prognostic indicators in patients with recurrent HCC.

Figure 1 shows the comparison of survival rates after recurrence of HCC between recurrence that occurred before 1 year and after more than 1 year. The 3- and 5-year survival rates in patients with recurrence before 1 year were 24.8% and 14.2%, respectively, whereas those with recurrence rates after more than 1 year were 49.1% and 28.4%, respectively. The survival rate in patients with recurrence before 1 year was significantly lower than that of patients with recurrence after more than 1 year.

Figure 2 depicts the comparison of survival rates after recurrence of HCC according to the types of recurrence. The 3- and 5-year survival rates of patients with nodular-type recurrence were 58.5% and 30.1%, respectively, whereas those with multiple-type recurrence were 27.9% and 18.6%, respectively. Moreover, those with extrahepatic recurrence were 6.2% and 0%, respectively. The survival rate of patients with nodular-type recurrence was significantly higher than those with the multiple-type or extrahepatic-type recurrence.

Figure 3 shows the comparison of survival rates after recurrence of HCC according to types of treatment. The survival rate of patients with hepatectomy was significantly higher than those with either lipiodolization or no treatment. The 3- and 5-year survival rates of patients with hepatectomy were 70.5% and 70.5%, respectively, whereas those with PEIT were 76.2% and 0%, respectively. Those with lipiodolization alone were 38.3% and 20.0%, respectively, whereas the 3-year survival of patients without any treatment after recurrence was 0%. Moreover, the difference in survival rates was not statistically significant between patients with PEIT and those undergoing a hepatectomy.

Table 2. Results of a Multivariate Analysis Using Cox's Proportional Hazards Model

Variables	Coefficien	SE	Relative risk	P value
Types of treatments after recurrence	−0.9185	0.2239	0.3991	<0.001
Type of recurrence	0.5591	0.1659	1.7490	0.001
Period until recurrence	0.6669	0.2137	1.9482	0.002

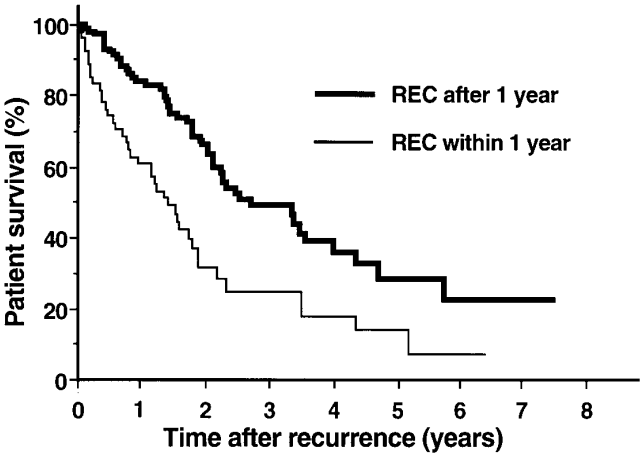

Figure 1. Comparison of survival rates after recurrence of HCC between recurrence before 1 year and that 1 year after a curative firs hepatectomy. The survival rate of patients with recurrence before 1 year after hepatectomy was significantl lower than that for recurrence developing more than 1 year thereafter. REC, recurrence.

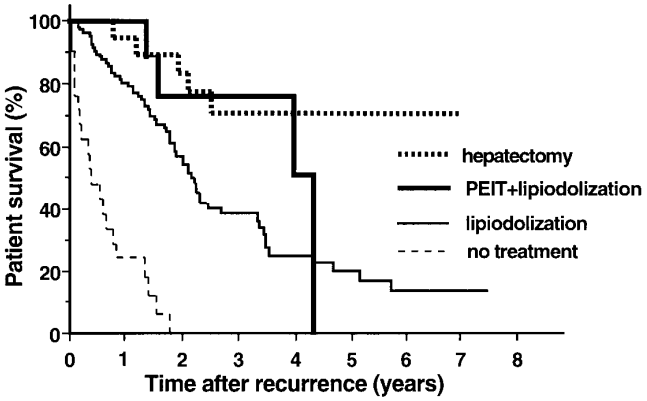

Figure 3. Comparison of survival rates after the recurrence of HCC according to the types of treatment after recurrence. The survival rate of patients who underwent a hepatectomy was significantl higher than those who either underwent lipiodolization or no treatment. Moreover, the survival rate of patients with PEIT after recurrence was not significantl different from the survival rate of patients undergoing a hepatectomy after recurrence.

Table 3 shows the comparison of poor prognostic variables among the aforementioned four treatment groups. There was no significant difference observed in the Child's classification at recurrence; however, the incidence of an albumin value of <3.5 g/dL in both the no treatment and the lipiodolization groups were greater than those in both the PEIT and operation groups. The incidence of an AFP level of >50 ng/mL in the no treatment group was greater than those in other treatment groups. In the variables of the first hepatectomy, the incidence of positive portal vein invasion and stage III in the no treatment group were greater than those in other treatment groups; however, no significant difference was observed in the positive intrahepatic metastasis. Types of recurrence were the major factors of postrecurrence treatments, and the incidence of the extrahepatic type in the no treatment group was greater than those in other treatment groups. On the contrary, no significant tendency in the period until recurrence was observed among the four groups.

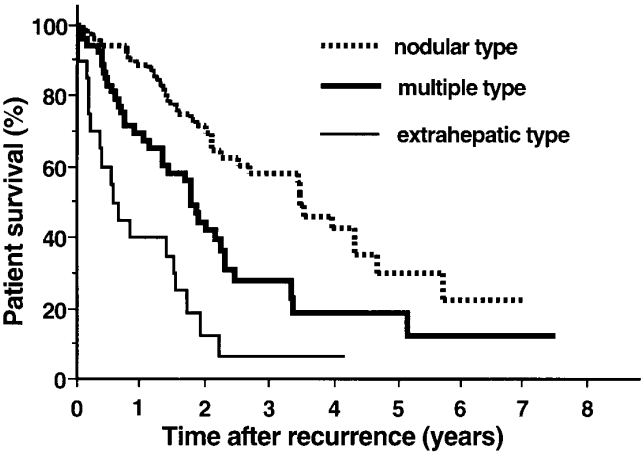

Figure 2. Comparison of survival rates after a recurrence of HCC according to the types of recurrence. The survival rate of patients with nodular-type (three or less intrahepatic nodules) recurrence was significantl greater than those with either multiple-type (four or more intrahepatic nodules) or extrahepatic-type recurrence.

Discussion

Nine of 24 clinicopathologic variables, which are related to the prognosis of patients after recurrence, were selected. The host factors related to liver function at recurrence were the albumin value of <3.5 g/dL and Child's classification (class C). These factors, indicating a poor liver function, were considered to be naturally related to the prognosis after recurrence. As for the tumor factors in the first hepatectomy, a poorly differentiated histology, positive portal vein invasion, positive intrahepatic metastasis, and stage III were found to be related to patient survival rates after recurrence. Portal vein invasion and intrahepatic metastasis are widely known to be prognostic factors related to both recurrence and survival rates. Therefore, the selection of such factors as prognostic indicators after recurrence is considered to be natural. According to TNM classification,[12] the survival rate of patients with stage IV-A HCC was no worse than that in patients with stage III HCC. This phenomenon is not considered to be unusual because Izumi et al.[7] also reported that the TNM classification did not always reflect the clinical long-term outcome of HCC. We have recently reported that the survival rate of patients with

Table 3. Comparison of Poor Prognostic Factors Among the Four Postrecurrence Treatment Groups

Factors	No treatment (n = 21)	LPD (n = 106)	PEIT (n = 10)	Operation (n = 22)	*P* value
Child's class at REC					
A	8	58	7	17	0.2711
B	8	35	1	4	
C	2	9	0	1	
Albumin at REC (*g/dL*)					
<3.5	10	40	1	3	0.0214
≧3.5	8	31	3	19	
AFP at REC (*ng/mL*)					
≦50	4	55	6	12	0.0084
>50	13	43	0	9	
VP at 1st Hx					
Absent	9	77	10	17	0.0052
Present	12	29	0	5	
IM at 1st Hx					
Absent	11	65	8	18	0.1265
Present	10	41	2	4	
Tumor stage[a] at 1st Hx					
I	1	17	5	6	0.0042
II	5	50	2	11	
III	14	35	2	2	
IV-A	1	4	1	2	
Period until REC					
>1 year	10	38	1	6	0.1837
≦1 year	11	68	9	16	
REC types					
Nodular	3	52	10	22	<0.0001
Multiple	8	46	0	0	
Extrahepatic	10	8	0	0	

REC, recurrence; LPD, lipiodolization[13,14]; VP, microscopic invasion to the portal vein; IM, microscopic intrahepatic metastases; 1st Hx, firs hepatectomy.

[a] The staging was determined according to TNM classification [12]

stage IV-A HCC was similar to that of those with stage I–III when the curative hepatectomy was performed.[20] Stage IV-A HCC, which is curatively resected, is considered to include multicentric and relatively small tumors. The period until recurrence, the types of recurrence, and the types of treatments after recurrence were all closely related to the survival rate after recurrence. It is of great interest that only three of the above mentioned factors out of nine significant variables were chosen as independent prognostic indicators by a multivariate analysis. Thus, this fact suggests that such factors involve most of the important values of other significant variables selected by a univariate analysis because they are considered to have a close relationship among them, i.e., between the type of recurrence and the types of treatment after recurrence.

It was confirmed in a preliminary analysis that 1 year was the most discriminant choice for the time point of recurrence when compared with other such time periods as 0.5, 2, and 3 years; therefore, the borderline of 1 year was selected for this analysis. Matsumata et al.[21] reported that most diffuse types of recurrence occur within 1 year after the first hepatectomy; such diffuse types were probably because of intrahepatic metastases through the portal vein, which was caused by the manipulation of the liver during the hepatectomy. Hayashi et al.[22] reported that both a poorly differentiated histology and portal invasion were related to recurrence within 1 year after hepatic resection. On the contrary, Nagasue et al.[4] reported no significant correlation between the types of intrahepatic recurrence and the period until recurrence.

Matsumata et al.[21] classified intrahepatic recurrence into the following three types: (1) stump type, recurrence near the resected hepatic stump; (2) nodular type, either a solitary nodule or a few nodules in the other segments away from the resected margin; and (3) multiple type, a widespread multinodular recurrence in the remnant liver. We previously reported that the surgical margin was not related to postoperative recurrence[23]; therefore, the intrahepatic recurrence patterns were classified into two groups: nodular type and multiple type. In a preliminary study, there was no significant difference in patient survival rates between the occurrence of solitary recurrent nodules and the occurrence of three or less recurrent nodules.

A repeat hepatectomy is now widely accepted as one of the most effective treatments for recurrent HCC.[9–11] However, a surgical resection for recurrent HCC also has several problems to overcome such as an impaired liver function caused by the progression of hepatitis, an altered anatomy caused by the previous operation, and the presence of tight perihepatic adhesions. A repeat hepatectomy is indicated mostly for nodular-type recurrence; therefore, repeat hepatectomies are actually quite limited in number. With respect to other options for the treatment of recurrent HCC, lipiodolization has been advocated as an important modality,[24] although Ouchi et al.[5] has reported the usefulness of TAE. Recently, PEIT has also been reported to be effective for recurrent HCC.[15] In this study, the results of PEIT in combination with lipiodolization or TAE tended to be better than those for lipiodolization alone. Therefore, a repeat hepatectomy is ideal; however, when a hepatectomy is not indicated, the combined treatment of PEIT and lipiodolization is recommended.

At present, our treatment strategy for recurrent HCCs is shown in Figure 4. Once recurrence is confirmed, the types of recurrence must be evaluated. In either intrahepatic nodular type or the intrahepatic multiple type, which is when there is a small number of tumors, a repeat hepatectomy remains the primary choice of treatment when the liver function is preserved for surgery, whereas either PEIT or lipiodolization is indicated when the liver function is not considered to be sufficient for a hepatectomy. In the intrahepatic multiple type, which is in case of a large number of tumors, lipiodolization is indicated. In such cases reduction surgery is considered to be indicated for a few rapid growing nodules that cannot be completely controlled by lipiodolization alone. In extrahepatic recurrence, a surgical resection is indicated only in the case of isolated recurrence without any intrahepatic recurrence or with a well-controlled intrahepatic recurrence. The incidence of extrahepatic recurrence was 18.5% in this study, either with or without simultaneous intrahepatic recurrence. This incidence appears to be somewhat high, yet Lo et al.[25] reported 25.8% of extrahepatic recurrence in their incidence. They also reported that a surgical resection was effective in selected patients with an isolated extrahepatic recurrence of HCC and offered the only chance of a long-term survival. In fact, only a small number of patients can undergo such surgical management; therefore, further investigation is required to elucidate this matter.

The following important problems in the treatment strategy for HCC were revealed: (1) the need to establish a more sophisticated follow-up system including extrahepatic recurrence, i.e., periodical bone scintigraphy for bone metastases; (2) the need to develop an effective method of adjuvant chemotherapy for high-risk groups of patients or patients with extrahepatic recurrence; and (3) the need to further investigate the risk factors closely linked to early recurrence, multiple recurrence, or extrahepatic recurrence. To obtain better treatment results for HCC, further efforts should focus on finding the solutions to such important problems.

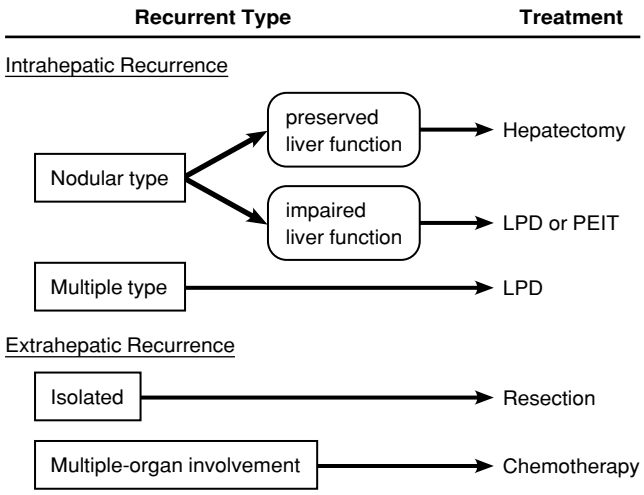

Figure 4. Treatment strategy schema for recurrent HCC. The appropriate treatment is selected according to the types of recurrence and the liver function at recurrence. LPD, lipiodolization.

In conclusion, the prognostic factors in patients with recurrent HCCs were as follows: the period until recurrence, the types of recurrence, and the types of treatments received after recurrence. The following strategy is required to obtain better treatment results: (1) the establishment of a follow-up system including an examination for extrahepatic recurrence; (2) the development of an effective method of adjuvant chemotherapy; and (3) a further investigation of the risk factors related to early recurrence, multiple recurrence, or extrahepatic recurrence.

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Received February 12, 1996. Accepted May 9, 1996.

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