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Intrahepatic Recurrence After Curative Resection of Hepatocellular Carcinoma

Long-Term Results of Treatment and Prognostic Factors

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Objective
This study aimed to evaluate the long-term results of treatment and prognostic factors in patients with intrahepatic recurrence after curative resection of hepatocellular carcinoma (HCC).

Summary Background Data
Recent studies have demonstrated the usefulness of re-resection, transarterial oily chemoembolization (TOCE), or percutaneous ethanol injection therapy (PEIT) in selected patients with intrahepatic recurrent HCC. The overall results of a treatment strategy combining these modalities have not been fully evaluated, and the prognostic factors determining survival in these patients remain to be clarified.

Methods
Two hundred and forty-four patients who underwent curative resection for HCC were followed for intrahepatic recurrence, which was treated aggressively with a strategy including different modalities. Survival results after recurrence and from initial hepatectomy were analyzed, and prognostic factors were determined by univariate and multivariate analysis using 27 clinicopathologic variables.

Results
One hundred and five patients (43%) with intrahepatic recurrence were treated with re-resection (11), TOCE (71), PEIT (6), systemic chemotherapy (8) or conservatively (9). The overall 1-year, 3-year, and 5-year survival rates from the time of recurrence were 65.5%, 34.9%, and 19.7%, respectively, and from the time of initial hepatectomy were 78.4%, 47.2%, and 30.9%, respectively. The re-resection group had the best survival, followed by the TOCE group. Multivariate analysis revealed Child's B or C grading, serum albumin $\leq$ 40 g/l, multiple recurrent tumors, recurrence $\leq$ 1 year after hepatectomy, and concurrent extrahepatic recurrence to be independent adverse prognostic factors.

Conclusions
Aggressive treatment with a multimodality strategy could result in prolonged survival in patients with intrahepatic recurrence after curative resection for HCC. Prognosis was determined by the liver function status, interval to recurrence, number of recurrent tumors, any concurrent extrahepatic recurrence, and type of treatment.

The perioperative outcome of hepatic resection for hepatocellular carcinoma (HCC) has improved significantly in recent years because of better surgical techniques and perioperative care. However, the long-term survival is still unsatisfactory due to the high incidence of recurrence, especially in the liver remnant.

Repeat hepatectomy has been considered by many authors to be the most effective treatment for intrahepatic recurrent HCC.[1–6] Unfortunately, repeat hepatectomy could only benefit a small group of patients, because most of the recurrent tumors are unresectable. Other authors have reported the use of transarterial oily chemoembolization (TOCE) or percutaneous ethanol injection therapy (PEIT) in the management of intrahepatic recurrent HCC.[7–9] Although these studies have shown the value of the particular treatment modality in selected patients, the overall impact of a treatment strategy combining these modalities on the survival of patients with intrahepatic recurrent HCC has not

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been fully evaluated. Furthermore, little attention has been given to the prognostic factors affecting survival in these patients, although the risk factors for the development of intrahepatic recurrence after hepatectomy for HCC have been widely studied.[10–13]

In this study, we evaluated the long-term results of an aggressive treatment strategy employing various modalities in patients with intrahepatic recurrence after curative resection of HCC, and analyzed the prognostic factors affecting survival in these patients.

PATIENTS AND METHODS

From January 1989 to June 1997, 308 hepatectomies for HCC were performed by the Department of Surgery at Queen Mary Hospital in Hong Kong. Twenty-one patients who died within the same hospital admission were excluded from this study. Another 43 patients who had palliative resection or positive resection margin were also excluded. The remaining 244 patients who had curative resection with histologically clear margin were followed for any intrahepatic recurrence. The clinicopathologic data of all patients were prospectively collected in a computerized database.

Patient Follow-up

All patients had regular follow-up with serum alpha-fetoprotein (AFP) level and ultrasonography at 1 month after hepatectomy and then every 2 to 4 months thereafter. Suspected intrahepatic recurrence was confirmed using computerized tomography (CT) scan, hepatic angiography, and in some cases postlipiodol CT scan or percutaneous biopsy. Chest radiograph, CT scan, and, if indicated, bone scan were used to detect any concurrent extrahepatic recurrence.

Treatment Strategy

Repeat hepatectomy was considered the treatment of choice for resectable recurrent tumors. Determination of resectability was based on the number and site of the tumors, any concurrent extrahepatic recurrence, liver function, and the general status of the patient. However, the majority of patients had unresectable tumors and were treated with repeated courses of TOCE using cisplatinum as the chemotherapeutic agent. Some patients initially treated with TOCE received PEIT when further TOCE was not possible for technical reasons, such as the development of arteriovenous shunting. PEIT alone was given to patients not suitable for TOCE due to technical reasons or unsatisfactory liver function. For patients with concurrent extrahepatic recurrence but good general status, systemic chemotherapy using epirubicin was given. Patients with extensive systemic recurrence or very poor liver function or general condition were treated conservatively.

Analysis of Survival

Long-term survival after recurrence was analyzed for the entire group of patients with intrahepatic recurrence and then separately according to the primary treatment modality. The survival rates from initial hepatectomy of these patients were also compared with patients who did not develop an intrahepatic recurrence.

Analysis of Prognostic Factors

The survival after recurrence was correlated with 27 clinicopathologic variables to determine the prognostic factors. Host factors included sex, age at recurrence, hepatitis B surface antigen (HBsAg) status, alcohol abuse, Child's grading at recurrence, histologic status of the liver, liver function tests at recurrence (bilirubin, albumin, SGOT, SGPT, platelet count and prothrombin time), and any perioperative blood transfusion during initial hepatectomy. Tumor factors at initial hepatectomy included maximum tumor size, number of tumors, tumor differentiation, resection margin, encapsulation, venous infiltration, type of resection, and TNM staging.[14] Tumor factors at recurrence included AFP level, maximum tumor size, number of tumors, interval from initial hepatectomy, any concurrent extrahepatic recurrence, and type of treatment.

Statistical Analysis

Comparison between groups was performed using chi-square test with Yates correction for nominal variables and unpaired t test for continuous variables. The survival rates were calculated by the Kaplan-Meier method and compared between groups using the log-rank test. The Cox proportional hazards model was used for multivariate analysis of prognostic factors. All statistical analyses were performed using the SPSS statistical package (Los Angeles, CA). A p value of < 0.05 was considered to be statistically significant.

RESULTS

During a median follow-up period of 24 months (range 2–98 months), 105 of the 244 patients (43%) developed recurrence in the liver remnant. The median interval from initial hepatectomy to recurrence was 6 months (range 1–44 months). There were 90 men and 15 women, and the mean age at recurrence was 53.6 years (SD 11.6, range 30–82 years). Twenty-nine of these patients (28%) had concurrent (15) or subsequent (14) extrahepatic recurrence, and 28 of the other 139 patients (20%) without intrahepatic recurrence developed extrahepatic recurrence ($p = 0.172$). Table 1 shows the clinicopathologic variables at initial hepatectomy of patients with and without intrahepatic recurrence. Intrahepatic recurrence was significantly associated with multi-

Table 1. CLINICOPATHOLOGIC VARIABLES AT INITIAL HEPATECTOMY OF PATIENTS WITH AND WITHOUT INTRAHEPATIC RECURRENCE

	Intrahepatic Recurrence		
	With (n = 105)	Without (n = 139)	p Value
Sex (male/female)	90/15	113/26	0.361
Age in years (SD)	52.5 (11.4)	53.5 (14.5)	0.578
HBsAg status			
Positive	84 (80%)	114 (82%)	0.690
Negative	21 (20%)	25 (18%)	
AFP level			
≤20 ng/ml	25 (24%)	43 (31%)	0.272
>20 ng/ml	80 (76%)	96 (69%)	
Liver status			
Normal	18 (17%)	28 (21%)	0.813
Chronic active hepatitis	40 (38%)	53 (38%)	
Cirrhotic	47 (45%)	58 (41%)	
Initial tumor size (cm)			
≤5	36 (34%)	59 (42%)	0.196
>5	69 (66%)	80 (58%)	
Tumor number			
Solitary	66 (63%)	105 (76%)	0.032
Multiple	39 (37%)	34 (24%)	
Type of resection*			
Major	68 (65%)	92 (66%)	0.817
Minor	37 (35%)	47 (34%)	
Resection margin			
≤1 cm	62 (59%)	72 (52%)	0.260
>1 cm	43 (41%)	67 (48%)	
Tumor encapsulation			
Present	52 (50%)	72 (52%)	0.750
Absent	53 (50%)	67 (48%)	
Venous infiltration			
Present	58 (55%)	43 (31%)	<0.001
Absent	47 (45%)	96 (69%)	
Perioperative transfusion			
Yes	71 (68%)	70 (50%)	0.006
No	34 (32%)	69 (50%)	
Tumor staging (TNM)			
I	6 (6%)	10 (7%)	<0.001
II	33 (31%)	76 (55%)	
III	54 (51%)	48 (34%)	
IVA	12 (12%)	5 (4%)	

Figures indicate number of patients unless otherwise specified.
* Major resection = resection of 3 or more segments; minor resection = resection of 2 or fewer segments

ple tumors, venous infiltration, advanced TNM staging, and perioperative blood transfusion.

Long-Term Results of Treatment

The overall 1-year, 3-year, and 5-year survival rates of the 105 patients after intrahepatic recurrence were 65.5%, 34.9%, and 19.7%, respectively. At the end of the follow-up period, 62 patients had died of malignant cachexia (50), liver failure (8), gastrointestinal bleeding (2), or sepsis (2).

Figure 1 shows the survival curves after recurrence of patients treated by different modalities. Eleven patients (10%) underwent re-resection of the recurrent tumors without operative mortality. The 1-year, 3-year, and 5-year survival rates of these patients after recurrence were 80.8%, 69.3%, and 69.3%, respectively. Five patients were alive and disease-free for 9 to 56 months after re-resection, three were alive with recurrence, and four had died of recurrent disease. Seventy-one patients (68%) received TOCE as the primary treatment (1 to 19 sessions, mean = 5.2 sessions), including six patients who received PEIT subsequently when further TOCE became technically impossible. The 1-year, 3-year, and 5-year survival rates were 72.1%, 38.2%, and 20.9%, respectively, lower than the re-resection group ($p = 0.085$). Two patients were alive and radiologically disease-free after four and eight courses of TOCE respectively, 29 patients were alive with disease and 40 patients had died by the end of the follow-up period. Six patients (6%) received PEIT alone (1–20 sessions, mean = 7.4 sessions). The 1-year, 3-year, and 5-year survival rates were 66.7%, 22.0%, and 0%, respectively, lower than those treated with TOCE, but the difference was not statistically significant ($p = 0.292$). Only one of these patients remained alive with recurrent disease. Eight patients (8%) were treated with systemic chemotherapy, with a 1-year survival rate of 37.5%, but no 3-year survival. The median survival was 9.2 months and all had died. Nine patients (9%) were treated conservatively, with a median survival of 2.7 months and no 1-year survival, and the results were significantly worse than patients treated with systemic chemotherapy ($p = 0.012$).

The overall 1-year, 3-year, and 5-year survival rates after initial hepatectomy in the whole group of 244 patients were 83.2%, 61.6%, and 44.5%, respectively. The 1-year, 3-year, and 5-year survival rates of the 105 patients with intrahepatic recurrence from initial hepatectomy were 78.4%, 47.2%, and 30.9%, respectively, significantly lower than the

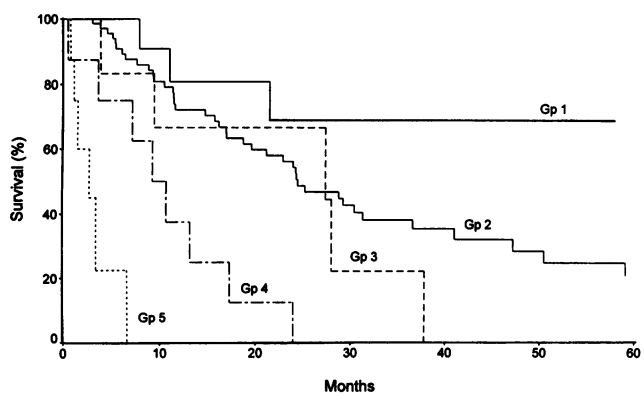

Figure 1. Survival from recurrence of patients treated with re-resection (Gp 1), TOCE (Gp 2), PEIT (Gp 3), systemic chemotherapy (Gp 4), and conservative management (Gp 5).

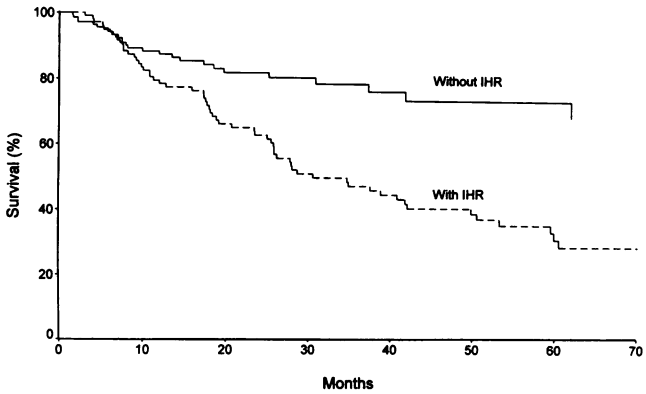

Figure 2. Survival from initial hepatectomy of patients with and without intrahepatic recurrence (IHR).

corresponding 87.4%, 78.5%, and 73.6% survival rates of patients without intrahepatic recurrence ($p < 0.001$; Figure 2). However, the 1-year, 3-year, and 5-year survival rates of patients from initial hepatectomy who underwent re-resection (100%, 70%, and 70%, respectively) were similar to patients without intrahepatic recurrence ($p = 0.975$). The survival rates of the 77 patients treated with TOCE or PEIT (83.9%, 52.1%, and 31.2%, respectively) were significantly lower than patients without intrahepatic recurrence ($p < 0.001$). For patients with intrahepatic recurrence treated with systemic chemotherapy or conservatively, the 1-year, 3-year, and 5-year survival rates from initial hepatectomy were 50% and 0%, 0% and 20%, and 0% and 0% respectively.

Prognostic Factors

Univariate analysis showed that 10 variables were significant adverse prognostic factors of survival after intrahepatic recurrence: Child's B or C grading at recurrence, serum albumin level ≤ 40 g/l at recurrence, serum bilirubin level > 20 umol/l at recurrence, serum SGOT level > 50 u/l at recurrence, initial tumor size > 5 cm, advanced initial tumor stage, interval to recurrence ≤ 1 year, multiple intrahepatic recurrent tumors, concurrent extrahepatic recurrence, treatment with chemotherapy, or conservative treatment (Table 2).

The following host factors were found to have no significant prognostic value: age at recurrence (≤ 60 *vs.* > 60 years, $p = 0.982$), sex (male *vs.* female, $p = 0.511$), HBsAg status (positive *vs.* negative, $p = 0.399$), liver histology (normal *vs.* chronic active hepatitis *vs.* cirrhosis, $p = 0.234$), serum SGPT level at recurrence (≤ 50 *vs.* > 50 u/l, $p = 0.131$), prothrombin time at recurrence (≤ 13 *vs.* > 13 sec, $p = 0.091$), platelet count at recurrence (≤ 100 *vs.* > 100 × 10^9 /l, $p = 0.968$), and perioperative transfusion during initial hepatectomy (present *vs.* absent, $p = 0.441$).

The following initial or recurrent tumor factors did not have significant influence on the survival after recurrence: initial tumor number (solitary *vs.* multiple, $p = 0.813$), tumor differentiation (well *vs.* moderately *vs.* poorly differentiated, $p = 0.281$), resection margin (≤ 1 *vs.* > 1 cm, $p = 0.324$), tumor encapsulation (present *vs.* absent, $p = 0.332$), venous infiltration (present *vs.* absent, $p = 0.153$), type of resection (major *vs.* minor, $p = 0.666$), recurrent tumor size (≤ 2 *vs.* > 2 cm, $p = 0.436$) and AFP level at recurrence (≤ 20 *vs.* > 20 ng/ml).

Using multivariate analysis, the following were shown to be independent prognostic factors: Child's grading at recurrence, serum albumin level at recurrence, interval between initial hepatectomy and recurrence, number of recurrent tumors, any concurrent extrahepatic recurrence, and type of treatment (Table 3).

DISCUSSION

Intrahepatic recurrence is the most common cause of treatment failure after curative resection of HCC. A previ-

Table 2. SIGNIFICANT PROGNOSTIC FACTORS OF SURVIVAL BY UNIVARIATE ANALYSIS

Factor	3-yr Survival	p Value
Child's grading*		
A (n = 80)	44.0%	<0.001
B or C (n = 25)	5.3%	
Serum bilirubin*		
≤20 ng/ml (n = 84)	40.2%	<0.001
>20 ng/ml (n = 21)	13.0%	
Serum albumin*		
≤40 g/l (n = 45)	11.2%	<0.001
>40 g/l (n = 60)	50.3%	
Serum SGOT*		
≤50 u/l (n = 61)	47.5%	<0.001
>50 u/l (n = 44)	20.5%	
Initial tumor size		
≤5 cm (n = 36)	44.8%	0.026
>5 cm (n = 69)	29.3%	
Initial tumor staging		
I (n = 6)	55.6%	0.014
II (n = 33)	39.6%	
III (n = 54)	36.8%	
IVA (n = 12)	0%	
Interval to recurrence		
≤1 year (n = 77)	29.7%	0.011
>1 year (n = 28)	48.3%	
No. of recurrent tumors		
Solitary (n = 53)	42.3%	0.025
Multiple (n = 52)	28.7%	
Extrahepatic recurrence		
Absent (n = 90)	37.8%	0.029
Present (n = 15)	17.5%	
Type of treatment		
Re-resection (n = 11)	69.3%	<0.001
TOCE (n = 71)	38.2%	
PEIT (n = 6)	22.0%	
Chemotherapy (n = 8)	0%	
Conservative (n = 9)	0%	

* At time of recurrence

Table 3. SIGNIFICANT PROGNOSTIC FACTORS OF SURVIVAL BY MULTIVARIATE ANALYSIS

Factor	Coefficient	Standard Error	Hazard Ratio	p Value
Child's grading at recurrence (A *vs.* B or C)	−7.6531	0.2318	0.4652	0.0010
Albumin level at recurrence (≤40 g/l *vs.* > 40 g/l)	0.3385	0.1463	1.4028	0.0207
Interval to recurrence (≤1 year *vs.* > 1 year)	0.3600	0.1844	1.4333	0.0409
No. of recurrent tumors (solitary *vs.* multiple)	−0.4239	0.1550	0.6545	0.0062
Concurrent extrahepatic recurrence (present *vs.* absent)	0.8582	0.4171	2.3589	0.0396
Type of treatment (nonsurgical *vs.* re-resection)	0.4851	0.1882	1.6243	0.0099

ous study from our department has shown that the improved survival after hepatectomy for HCC in recent years was attributable mainly to the effective treatment of recurrence.[15] In this study, we have elucidated in detail the factors associated with intrahepatic recurrence, the overall long-term results of aggressive treatment with various modalities, and the prognostic factors affecting survival.

Intrahepatic recurrence after resection of HCC can be the result of intrahepatic metastasis or multicentric occurrence of a new tumor in the liver remnant, and controversy exists about the significance of each. The incidence of intrahepatic recurrence in our series was similar to other series.[11–13] In our patients, intrahepatic recurrence was significantly associated with multiple tumor nodules, mostly daughter nodules, and venous infiltration, both suggestive of intrahepatic spread via the portal venous system.[13] Intrahepatic recurrence was most significantly associated with advanced TNM staging, which was in turn determined by the number of tumors and the presence of venous infiltration. Perioperative transfusion was also significantly associated with intrahepatic recurrence, and it probably enhanced intrahepatic metastasis by suppressing antitumor immune mechanism.[16] Intrahepatic recurrence occurred within 1 year after hepatectomy in most of our patients (73%), which also suggested that the majority of the recurrent tumors arose from intrahepatic metastasis rather than new multicentric occurrence. Chronic active hepatitis and cirrhosis have been found by Japanese studies to be a significant risk factor for intrahepatic recurrence of HCC, presumably due to multicentric carcinogenesis.[13,17] In our study, no significant association was found between the histologic status of the liver and intrahepatic recurrence. In our Chinese patients, the main cause of HCC was hepatitis B virus (80%), while in Japanese patients, the majority of HCC was related to hepatitis C virus (HCV).[13,17] This difference in etiology could have resulted in a different prevalence of multicentric occurrence, as a recent analysis differentiating intrahepatic metastasis and multicentric occurrence by histologic criteria has shown that patients with anti-HCV had a significantly higher multicentric recurrence rate than patients with HBsAg.[18] In contrast, HBsAg has been found to be a significant risk factor for intrahepatic metastasis.[18]

Our results showed that an aggressive management strategy using multiple modalities could result in prolonged survival in patients with intrahepatic recurrent HCC. The overall 5-year survival from recurrence and initial hepatectomy was about 20% and 30% respectively. Re-resection gave the best long-term results, with a 5-year survival rate from recurrence of 69% and a survival rate from initial hepatectomy similar to patients without intrahepatic recurrence. Our results suggest that re-resection should be the treatment of choice for recurrent HCC if possible. However, the favorable results in the re-resection group could be due in part to selection of patients who probably had good prognosis regardless of treatment. The re-resection rate in our series was only 10%, lower than the re-resection rate of 24% to 44% reported by some authors.[1,2,6] Most of our patients had large tumors requiring major resection at first hepatectomy (65%), the majority had cirrhosis or chronic active hepatitis (83%), and many patients had multiple recurrent tumor nodules (50%). As a result, there was usually inadequate liver parenchyma and functional reserve for a second hepatectomy. In those series with a high re-resection rate, 70% to 90% of patients who underwent re-resection had only minor resection before.[1,2,6] Most of our patients (68%) were treated with TOCE, which was largely considered a palliative measure but could prolong survival in some patients, with a 5-year survival rate of 21%. Complete response with disease-free survival could occasionally be achieved. Other authors have reported a 5-year survival rate of 0% to 27% for intrahepatic recurrence treated with TOCE.[7,8,19] TOCE was repeated every 2 to 3 months in our patients if possible, which was considered important to achieve prolonged survival.[20] The result of repeated PEIT was less satisfactory, but this may be partly related to patient selection, as PEIT was reserved for patients considered not suitable for TOCE. Similarly, the better survival with systemic chemotherapy than conservative treatment may be due to patient factors in addition to the treatment itself. To avoid bias due to patient selection, prospective randomized studies would be required to confirm the benefits of different treatment modalities.

The identification of prognostic factors for survival after intrahepatic recurrence could help to clarify the optimal management strategy, but little in the literature has addressed this issue.[19] By multivariate analysis, the prognosis

after intrahepatic recurrence was found to be independently influenced by the liver function status (Child's grading and serum albumin level) at recurrence, the interval from initial hepatectomy to recurrence, the number of recurrent tumors, concurrent extrahepatic recurrence, and type of treatment. None of the initial tumor factors had independent prognostic significance. The most significant prognostic factor after intrahepatic recurrence was Child's grading, which is also one of the most important factors in determining prognosis after treatment of a primary HCC.[21] Early recurrence (within 1 year) and multinodular recurrence have been found to be significant prognostic factors in a previous report,[19] and our study confirmed the same findings. Early recurrence and multinodular recurrence have been shown to be associated with the presence of tumor thrombi in the portal vein and were considered to be related to intrahepatic metastasis rather than multicentric carcinogenesis.[22] Presumably, concurrent extrahepatic metastasis would also be more likely to be associated with intrahepatic metastasis than a new multicentric tumor. The significant adverse prognostic influence of these three variables in our study is thus considered to indicate that intrahepatic metastasis was associated with a worse prognosis than multicentric occurrence.

Our findings may provide some insight into the optimal management strategy for intrahepatic recurrence. The differentiation between intrahepatic metastasis and multicentric occurrence could be important because of the different prognostic implications. Patients with intrahepatic metastasis, which is usually multifocal, may be less favorable candidates for re-resection. Re-resection would, however, be the best treatment for a solitary recurrence due to multicentric carcinogenesis in patients with Child's A grading. A recent study of prognosis after repeat hepatectomy for recurrent HCC has found a significantly worse survival in patients with portal vein infiltration at first hepatectomy, which was considered to be predictive of intrahepatic multifocal micrometastasis.[23] TOCE may be a better option to treat intrahepatic metastasis. Alternatively, TOCE may be used as an adjunctive treatment after re-resection for intrahepatic metastasis. However, this remains speculative and requires further studies to confirm. It is impossible to differentiate clinically or radiologically between intrahepatic metastasis or multicentric occurrence, but this is now possible by clonal genetic analysis of tumor cells.[24]

Despite an aggressive treatment strategy, the long-term survival of patients with intrahepatic recurrence remained significantly worse than patients without intrahepatic recurrence. This indicates the need to prevent intrahepatic recurrence, which could be another important strategy to improve the prognosis of patients with HCC after curative resection. Possible preventive measures against intrahepatic metastasis include avoiding manipulation of the tumor during resection, avoidance of perioperative blood transfusion by minimizing blood loss, and the use of an effective adjuvant therapy. Adjuvant systemic chemotherapy has not been shown to be effective,[25,26] but there may be a possible benefit of postoperative adjuvant regional chemotherapy or lipiodalization.[27,28] New adjuvant modalities such as immunotherapy and antiangiogenesis therapy may also prove to be useful in the future.[29–31] Liver transplantation could theoretically prevent recurrence due to multicentric occurrence in the cirrhotic liver, but transplantation, especially for large HCC, has been associated with a high incidence of recurrence due to immunosuppression. Nevertheless, promising results have been recently reported after transplantation for small HCC in cirrhotic patients.[32]

In conclusion, an aggressive multimodality treatment strategy could result in prolonged survival in patients with intrahepatic recurrence after curative resection for HCC, and prognosis was determined by liver function status, interval to recurrence, number of recurrent tumors, any concurrent extrahepatic recurrence, and type of treatment. The majority of intrahepatic recurrent tumors are considered to represent intrahepatic metastasis rather than multicentric occurrence. Our results suggest that intrahepatic metastasis is associated with a worse prognosis. Optimal management may be different for recurrence due to intrahepatic metastasis and multicentric occurrence. Further studies are needed to identify the optimal strategy in the prevention and management of intrahepatic recurrence, in order to further improve the prognosis of HCC after curative resection.

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