Aggressive Multimodality Treatment for Intra-Hepatic Recurrence of Hepatocellular Carcinoma following Hepatic Resection

Kun-Ming Chan, MD; Wei-Chen Lee, MD; Chien-Fu Hung[1], MD; Ming-Chin Yu, MD; Yi-Yin Jan, MD, FACS; Miin-Fu Chen, MD, FACS

Background: Intra-hepatic recurrence following hepatic resection is the primary challenge for patients with hepatocellular carcinoma (HCC). The aim of this investigation was to evaluate the long-term results of multimodality treatment of patients with intra-hepatic recurrent HCC following hepatic resection.

Methods: From January 1995 through December 2001, a total of 846 patients who underwent hepatic resection for primary HCC at the Chang Gung Memorial Hospital (Taoyuan, Taiwan) were analyzed through long-term follow-up; intra-hepatic recurrence of HCC was identified in 444 (52.5%) patients. Patients with intra-hepatic recurrence were categorized into two groups based on whether they underwent regional treatment. A comparison analysis of the survival rates of these two groups following treatment for recurrent intra-hepatic HCC was performed.

Results: Patients treated with multiple modalities exhibited significantly better survival results, both after initial hepatectomy and intra-hepatic recurrence compared with patients in the non-regional-treatment group. ($p < 0.001$) The 1-, 3-, and 5-year survival rates of patients in the regional-treatment group after initial hepatic resection were 88.1%, 60.1%, and 35.8%, respectively. The 1-, 3-, 5-year survival rates after treatment of intra-hepatic recurrence in the regional-treatment group were 74.8%, 39.3%, and 25.2%, respectively.

Conclusion: The incidence of intra-hepatic recurrence following hepatic resection for HCC remains high. Aggressive multimodality treatment could extend the survival for patients with recurrent postoperative intra-hepatic HCC.

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Keywords: hepatocellular carcinoma, hepatic resection, intra-hepatic recurrence, recurrent hepatocellular carcinoma.

Hepatocellular carcinoma (HCC), a relatively common malignant tumor that occurs throughout the world, ranks first and second as the causes of death by cancer in men and women in Taiwan, respectively.[1] Numerous treatment modalities, including surgical resection, transarterial chemoembolization (TACE), percutaneous chemical agent injection and radiofrequency ablation (RFA) have

From the Department of General Surgery, [1]Department of Radiology, Chang Gung Memorial Hospital, Taipei.
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Address for reprints: Dr. Miin-Fu Chen, Department of General Surgery, Chang Gung Memorial Hospital, No. 5, Fushing St., Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-3281200 ext. 3219; Fax: 886-3-3285818; E-mail: chenmf@cgmh.org.tw

been employed in treating HCC. Among these treatment methods, hepatic resection is the preferred treatment course producing relatively long-term survival rates. Furthermore, recent progress in imaging studies and increased understanding of HCC have substantially improved early detection of small HCCs and successful resection.[2-4] However, the long-term outcomes of HCC remain unsatisfactory with dismal prognoses. The main cause for the dismal outcomes is the high incidence of postoperative recurrence with most recurrent HCCs presenting as intra-hepatic.[5-7] Therefore, effective treatment in cases of postoperative recurrent HCC, especially for intra-hepatic recurrence, is extremely important in improving the survival rate of patients with HCC.

In this study, we gathered data from the Chang Gung Memorial Hospital (Taoyuan, Taiwan) that documented the treatment of postoperative recurrent HCC and examined the benefits of treating recurrent intra-hepatic HCC following hepatic resection.

METHODS

From January 1995 through December 2001, 911 consecutive patients underwent hepatic resections for hepatocellular carcinomas at the Chang Gung Memorial Hospital in Taoyuan, Taiwan. The medical records of the patients were retrospectively reviewed. Among the 911 patients, the 44 patients who died from surgery-related complications and 21 who were lost to follow-up were excluded from the series. The remaining 846 patients aged 4-88 years (54.9 $\pm$ 13.3 years, mean $\pm$ Standard deviation; 668 males and 178 females) were included in this study. There is a list of the clinical features of patients, hepatic resection types and tumor recurrence locations in Table 1.

Each patient who underwent hepatic resection at the Chang Gung Memorial Hospital received regular follow-up with serum alpha-fetoprotein and abdominal ultrasonography. In cases that raised suggestion of recurrence, computed tomography (CT), hepatic angiography and, in some cases, echo-guide percutaneous biopsies were performed for confirmation. Additionally, according to the clinical symptoms and signs, chest radiography, CT and bone scans were used to detect concurrent extra-hepatic recurrence. At the end of the study, 444 patients (52.5%) had intra-hepatic recurrence, 31 patients (3.7%) had concurrent extra-hepatic and intra-hepatic recurrence, and 47 patients (5.6%) had distant metastasis.

Table 1. Clinical Features of 846 Patients with Primary Hepatocellular Carcinoma Who Underwent Hepatic Resection

Characteristics	No. of patients (%)
Age (years)	54.9 $\pm$ 13.3
Male: Female	668: 178
Hepatitis B surface antigen (+)	563 (66.5)
Hepatitis C antibody (+)	258 (30.5)
α-fetoprotein > 20 (ng/ml)	483 (57.1)
Tumor size (cm)	
< 5	484 (57.2)
5-10	220 (26.0)
> 10	134 (15.8)
Hepatic resection	
Major hepatic resection ($\geq$ 3 segment)	390 (46.1)
Minor hepatic resection (< 3 segment)	456 (53.9)
Recurrent types	
Intra-hepatic	444 (52.5)
Intra-hepatic and extra-hepatic	31 (3.7)
Extra-hepatic	47 (5.6)

The principles utilized for selecting the treatment methods for patients with intra-hepatic recurrent HCC initially detected in the hospital were as follows. Each patient with intra-hepatic recurrence was assessed for repeat hepatic resection. Whenever the tumor was regarded as resectable, repeat hepatic resection was the preferred treatment. Patients with poor liver functions, numerous recurrent tumors, difficult to approach tumor location, unsuitable conditions for hepatic resection, or if the patient refused repeated hepatic resection, alternative treatment included transcatheter arterial chemoembolization (TACE)-injection of chemotherapeutic agent with emulsion of adriamycin and lipiodol followed by gelfoam cubes for embolization as indicated. Some patients received local ablation with percutaneous ethanol injection (PEI), percutaneous acetic acid injection (PAI) or radiofrequency ablation (RFA). However, most patients who underwent local ablation also received simultaneous or sequential TACE treatment. Patients who underwent treatments, including a repeat hepatic resection, TACE, PEI, PAI, RFA or a combination of these treatment methods that directly approached intra-hepatic recurrent tumors were categorized into the regional-treatment group. In contrast, the patients who received systemic treatment with, say traditional herbs,

Tamoxifen or Thalidomide, but whose intra-hepatic lesions were not directly treated, were defined as having no regional treatment, and were categorized into the non-regional-treatment group.

The Fisher's exact test was used to compare clinicopathologic characteristics between the two groups. The survival rates of the patients were evaluated according to whether regional treatment was performed. The disease-free survival rates and cumulative survival rates were calculated using the Kaplan-Meier method. Survival curve comparisons were obtained by applying the log-rank test. All statistical analyses were conducted with the SPSS 11.5 statistical package (Chicago, Illinois, U.S.A.). A value of $p < 0.05$ was considered statistically significant.

RESULTS

The median follow-up period was 51.6 months (range, 1.2 to 107 months). The disease-free 1-, 3- and 5-year survival rates of the 846 patients with HCC in this series were 57.7%, 38.6% and 30.0%, respectively. A total of 522 (61.7%) patients were identified with HCC recurrence.

The demographic characteristics and clinical features of patients at the time of recurrence, recurrence types, and initial hepatic resection types in relation to whether patients received regional treatment are listed in Table 2. The differences in the period of recurrence at less than 1 year and recurrence type were not statistically significant between the two groups. The treatment modalities applied for intra-hepatic recurrent HCC are listed in Table 3. Most patients were treated only with TACE. A small number of patients who underwent repeated hepatic resection, or local ablation, simultaneously or sequentially received TACE treatment. One patient received an orthotopic liver transplantation at another medical center after recurrence and was alive at the end of this study.

The comparisons of survival rates after HCC recurrence are shown in Figure 1. Patients with intra-hepatic recurrent HCC received definitive regional treatment and had significantly improved survival rates with 1- and 3-year survival rates of 74.8% and 39.3%, respectively. The 1- and 3-year survival rates of the non-regional-treatment group were 32.4% and 12.5%, respectively.

The cumulative overall survival rates of patients with intra-hepatic recurrent HCC are illustrated in Figure 2. The 1-, 3-, and 5-year survival rates of the regional-treatment group were 88.1%, 60.1% and 35.8%, respectively. The 1-, 3-, and 5-year survival rates of the non-regional-treatment group were 55.3%, 24.6% and 6.5%, respectively. The survival

Table 2. Clinical Features of 444 Patients with Postoperative Intra-hepatic Recurrent Hepatocellular Carcinoma

Characteristics	Regional- treatment (%)	Non- regional- treatment (%)	*p* values
Age at recurrence (years) (n = 444)	56.08 ± 13.08	56.45 ± 13.86	0.807
Male: Female	277: 69	82: 16	0.422
Hepatitis B surface antigen (n = 424)			0.809
Positive	227 (65.6)	65 (66.3)	
Negative	104 (30.0)	28 (28.6)	
Hepatitis C antibody (n = 383)			0.062
Positive	127 (36.7)	23 (23.5)	
Negative	179 (51.7)	54 (55.1)	
Initial hepatic resection			0.835
Major hepatic resection (≥ 3 segment)	163 (47.1)	45 (45.9)	
Minor hepatic resection (< 3 segment)	183 (52.9)	53 (54.1)	
Period of recurrence			0.098
≤ 1 year	212 (61.3)	69 (70.4)	
> 1 year	134 (38.7)	29 (29.6)	
Intra-hepatic recurrent types			0.124
Nodular type (< 3 recurrent tumor)	227 (65.6)	56 (57.1)	
Multiple type (≥ 3 recurrent tumor)	119 (34.4)	42 (42.9)	

Values are number of patients.

Table 3. Treatment Methods for Patients with Recurrent Intra-hepatic Hepatocellular Carcinoma Following Hepatic Resection

Treatment modalities	No. of patient (%)
Repeat hepatic resection	35 (7.9%)
TACE	293 (66.0%)
Local ablation	
PEI	45 (10.1%)
PAI	4 (0.9%)
RFA	19 (4.3%)
Liver transplantation	1 (0.2%)

Abbreviations: TACE: Transarterial chemoembolization; PEI: percutaneous ethanol injection; PAI: percutaneous acetic acid injection; RFA: radiofrequency ablation.

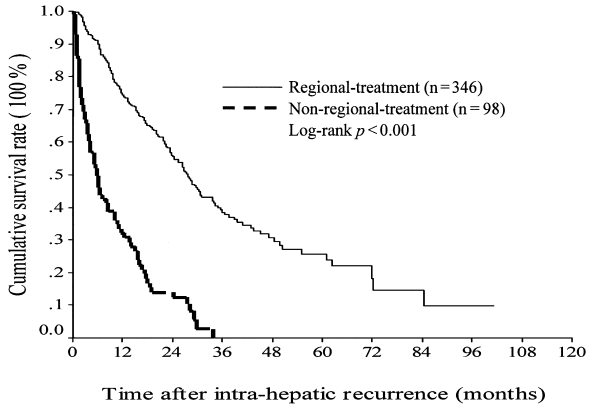

Fig. 1 Comparison of survival rates of patients with intra-hepatic recurrent after HCC recurrence. The survival rate of the regional-treatment group was significantly better that that of non-regional-treatment group. ($p < 0.001$)

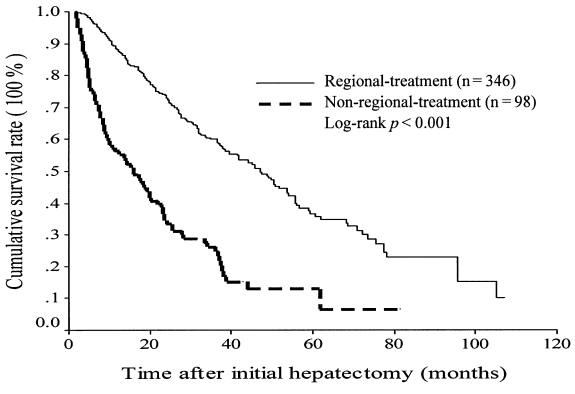

Fig. 2 Comparison of cumulative overall survival rates of patients with intra-hepatic recurrent HCC after initial hepatectomy. The survival rate of the regional-treatment group was significantly better that that of non-regional-treatment group. ($p < 0.001$)

rates for patients who underwent regional treatment were significantly higher than those of patients without regional treatment.

The comparisons of survival rates after recurrence of HCC according to the intra-hepatic recurrent types were depict in Figure 3 and Figure 4. Patients with nodular-type intra-hepatic recurrence, who received regional treatment, had 1- and 3-year survival rates of 74.1% and 43.3%, respectively, whereas those without regional treatment had 1- and 3-year survival rates of 27.2% and 0%, respectively. Moreover, those with multiple-type intra-hepatic

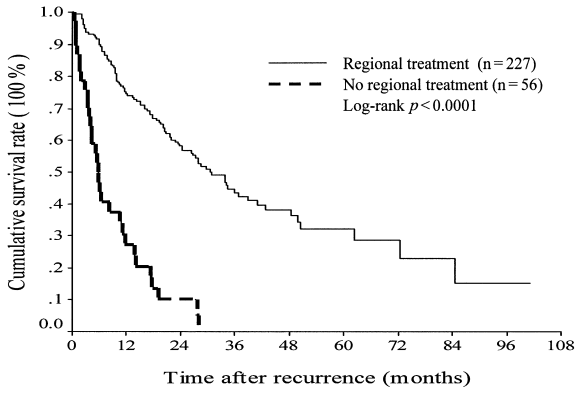

Fig. 3 Comparison of survival rates of patients with nodular-type intra-hepatic recurrent HCC. The survival rate of patients with regional treatment was significantly greater than those without regional treatment. ($p < 0.001$)

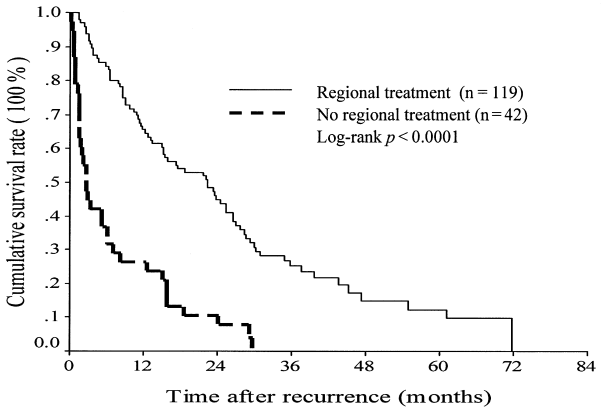

Fig. 4 Comparison of survival rates of patients with multiple-type intra-hepatic recurrent HCC. The survival rate of patients with regional treatment was significantly higher than those without regional treatment. ($p < 0.001$)

recurrence, who received regional treatment, had 1- and 3- year survival rates of 64.5% and 23.4%, respectively, whereas those without regional treatment had 1- and 3-year survival rates of 23.6% and 0%, respectively. The survival rates of patients with regional treatment were significantly higher than those without regional treatment in patients with both nodular-type and multiple-type HCC. ($p < 0.001$)

DISCUSSION

Hepatic resection for hepatocellular carcinoma has an estimated 5-year survival rate of 40% to 50%.[8-10] In response to this unsatisfactory surgical outcome that has resulted from the high incidence of postoperative recurrence, recurrence treatment is the most important strategy for improving the overall survival of HCC. Currently, aggressive multiple modality treatment has been employed for recurrent intra-hepatic HCC. In this study, the long-term results of treatment with multiple modalities for patients with recurrent intra-hepatic HCC following hepatic resection were analyzed.

The numerous risk factors that affect the postoperative tumor recurrence of HCC have been extensively studied. These risk factors can be divided into three core groups, related to host, tumor and surgery.[8] Tumor characteristics and patient factors are identified prior to operation. Although these risk factors have been extensively investigated, their efficacy in reducing the incidence of recurrent postoperative HCC remains controversial. The surgeon can only control surgical factors. Many factors including wider resection margin, careful manipulation during surgery, and the prevention of perioperative blood transfusion, have been considered as factors that decrease the incidence of postoperative recurrence; however, their effectiveness in reducing tumor recurrence cannot be easily determined.[11-13] Therefore, the treatment of recurrent intra-hepatic HCC is currently considerably more important than prevention from a clinical perspective.

In addition to the treatment of the primary HCC, various regional treatments such as TACE, percutaneous chemical agent injection (PAI and PEI), radiofrequency ablation and repeat hepatic resection have been introduced for treatment of recurrent intrahepatic HCC during the last decade. Of these treatment modalities, repeat hepatic resection is the preferred treatment for specific patients and has recently been reported by some authors to yield favorable results.[14-16] The proportion of cases in which repeat hepatic resection is employed to treat recurrent intrahepatic HCC has been reported to range from 10% to 48%[16-18], and exceeds the 7.9% value in this series. Nevertheless, repeat hepatic resection engenders a potentially higher risk of complications than other modalities because it involves surgery and anesthesia. Moreover, several factors such as major resection at the initial hepatectomy, presence of liver cirrhosis, multiple recurrences of tumor nodules, tight peri-hepatic adhesion after hepatic resection, and patient choice, may affect the re-resection rate reported in various series.

Transarterial chemoembolization is currently widely applied at different stages of HCC treatment, which includes the palliative treatment for unresectable HCC, preoperative treatment, postoperative prophylactic treatment, and treatment of intra-hepatic recurrence. The primary advantage of TACE is that it can be performed every 2 to 3 months if indicated. Most patients in this study with intra-hepatic recurrent HCC (66%) were treated with TACE and one patient underwent 20 sessions before the study ended. Considerably fewer patients underwent local ablation (PEI, PAI and RFA) in this series, partly because of the criteria of local ablation; local ablation is usually applied when the recurrent nodules have no more than three lesions each smaller than 3 cm. Additionally, patients with coagulopathy or prolonged prothrombin time are unsuitable for local ablation. Studies have shown that both TACE and local ablation have positive palliative effects and increased survival times for patients with recurrent postoperative HCC.[19,20] Moreover, researchers have demonstrated that liver transplantation is the best curative treatment for hepatocellular carcinoma with a 5-year survival rate of 60-80% and a low recurrence rate of 8-11%. Liver transplantation totally removes the tumors and the underlying cirrhosis responsible for both postoperative hepatic failure and tumor recurrence after partial hepatic resection.[21,22] Undoubtedly, when patients have recurrent postoperative intra-hepatic HCC and concurrent liver cirrhosis, liver transplantation is a good treatment.

The presence of more than three nodules has been found to adversely affect the outcome, and

patients with this type of HCC are not suitable for a repeat hepatic resection.[14,23,24] Consequently, recurrent intra-hepatic types affect not only the choice of treatment methods but also the prognosis of patients. Nonetheless, the ratio of recurrent intra-hepatic types showed no statistically significant differences between the two groups in this study. Moreover, patients who received regional treatment in both the recurrent intra-hepatic types showed significantly better survival curves. Therefore, recurrent intra-hepatic type may be very important, but not the main factor that affected the statistical results of this investigation.

The survival curves in this series demonstrated that patients for whom recurrent HCC was treated with multiple modalities survived longer after recurrence than those in the non-regional-treatment group. Additionally, the group that underwent regional treatment also had significantly better overall long-term survival than those in the non-regional-treatment group. These findings suggest that aggressive multimodality treatment strategies promoted prolonged survival of patients with intra-hepatic recurrent HCC.

In conclusion, the incidence of intra-hepatic recurrence following hepatic resection for HCC remains high. The principles that govern therapy for recurrent intra-hepatic HCC are the same as those for primary HCC with hepatic resection as the preferred treatment when the recurrent tumor is safely resectable. Furthermore, aggressive treatment should be encouraged in managing recurrent HCC, and multiple modality treatment of intra-hepatic recurrence might prolong the survival of patients after curative resection of the primary HCC.

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肝細胞癌術後肝內復發的積極治療

詹昆明 李威震 洪建福[1] 游明晉 詹益銀 陳敏夫

背 景： 肝細胞癌術後肝內復發對於治療肝細胞癌仍然是一個很棘手的問題。因此本篇研究的目的主要在探討肝細胞癌術後肝內復發的治療，以及就這類病患的長期治療效果。

方 法： 本篇研究搜集林口長庚醫院自西元 1996 至 2001 共六年期間總共 846 位病患，因肝細胞癌接受部份肝臟切除手術的長期追蹤分析。於追蹤期間共有 444 位病患 (52.5%) 被發現有術後肝內肝細胞癌的復發。這些有肝內復發的病患，根據有無接受局部治療分成兩個族群，進而分析比較其長期追蹤治療的效果。

結 果： 術後肝內肝細胞癌復發有接受局部治療的病患，在整體存活率及復發後的存活率於統計上皆優於沒有接受局部治療的病患。($p < 0.001$) 有接受局部治療的病患，其整體存活率於第一，三及五年分別爲 88.1%，60.1% 及 35.8%。於肝細胞癌復發後的存活率第一，三及五年分別爲 74.8%，39.3% 及 25.2%。

結 論： 肝細胞癌的病患接受肝臟部份切除手術後肝內復發的比率仍然很高。但以目前各種局部治療方式的配合，對於術後肝內復發的病患作積極的治療，應可以有效延長肝細胞癌術後肝內復發病患的壽命。

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關鍵字： 肝細胞癌，肝臟部份切除，肝內復發，復發性肝細胞癌。

長庚紀念醫院 台北院區 一般外科，[1]放射診斷科
受文日期：民國94年2月2日；接受刊載：民國94年6月14日
索取抽印本處：陳敏夫醫師，長庚紀念醫院 林口院區 一般外科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉3219; Fax: (03)3285818; E-mail: chenmf@cgmh.org.tw