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Prognostic Factors After Repeat Hepatectomy for Recurrent Hepatocellular Carcinoma

Mitsuo Shimada, M.D., Ph.D.,* Kenji Takenaka, M.D., Ph.D.,* Kenichi Taguchi, M.D.,†
Yuh Fujiwara, M.D.,* Tomonobu Gion, M.D.,* Kiyoshi Kajiyama, M.D.,†
Takashi Maeda, M.D., Ph.D.,* Ken Shirabe, M.D., Ph.D.,* Katsuhiko Yanaga, M.D., Ph.D.,*
and Keizo Sugimachi, M.D., Ph.D., F.A.C.S.*

From the Departments of Surgery II and Pathology II,† Faculty of Medicine, Kyushu University, Fukuoka, Japan*

Objective
The aims of this study were to identify prognostic factors in patients who developed recurrent hepatocellular carcinoma (HCC) after repeat hepatectomy and to elucidate the role of multicentric occurrence in the second tumor after a first hepatectomy.

Summary Background Data
A repeat hepatectomy for recurrent HCC has been established as the most effective treatment modality, whenever it is possible. However, the prognostic factors for recurrent HCC after repeat hepatectomy have yet to be clarified.

Methods
Forty-one patients who underwent a curative repeat hepatectomy were retrospectively studied. Patient survival and disease-free survival after recurrence were univariately and multivariately analyzed using 38 clinicopathologic variables. The histologic grade of HCC at repeat hepatectomy was also compared with that at first hepatectomy.

Results
Patient survival after repeat hepatectomy did not differ substantially from that in 312 patients undergoing primary hepatectomy. However, the disease-free survival after repeat hepatectomy was significantly lower than that in patients with only a primary hepatectomy ($p < 0.05$). Multivariate analysis revealed only portal vein invasion in the first hepatectomy to be an independent and significantly poor prognostic factor. Regarding multicentric occurrence at repeat hepatectomy, only 6 of 40 patients (15%) whose specimens could be evaluated histologically were determined to be Edmondson and Steiner's Grade 1.

Conclusions
The only prognostic factor identified in patients with recurrent HCC after repeat hepatectomy was portal vein invasion in the first hepatectomy. Most second tumors after the first hepatectomy are considered to be caused by metastatic recurrence, not by multicentric occurrence.

Hepatocellular carcinoma (HCC) has a high intrahepatic recurrence rate, but long-term survival is possible when the recurrence is appropriately treated on a timely basis.

A repeat hepatectomy for recurrent HCC is the most effective treatment modality,[1-5] whenever it is possible. However, the prognostic factors for recurrent HCC after repeat hepatectomy have yet to be clarified, even though those for primary hepatectomy have been well documented.[6-12] It is important to elucidate the prognostic factors in repeat hepatectomy and to clarify the optimal treatment strategy for recurrent HCC.

The controversy over whether the second tumor is caused by true recurrence or is the result of a multicentric occurrence of HCC remains unresolved.[13] Resected specimens obtained at repeat hepatectomy may provide some insight into this issue.

The aims of this study are to identify the prognostic factors in patients with recurrent HCC after repeat hepatectomy and to elucidate the role of multicentric occurrence in second tumors after a first hepatectomy.

MATERIALS AND METHODS

Forty-one patients who underwent a curative repeat hepatectomy at Kyushu University Hospital between November 1978 and December 1995 were retrospectively studied. The operative procedures consisted of a lobectomy in 2, a segmentectomy in 6, a subsegmentectomy in 2, and other minor resections in 31. No incidence of postoperative hospital death was observed. The operative time ranged from 115 to 500 minutes (mean, 257 minutes). Blood loss ranged from 250 to 9600 mL (mean, 1980 mL). A curative operation was defined as one in which all the tumors were macroscopically resected.

Patient survival and disease-free survival in patients with repeat hepatectomy were compared with those in 312 patients who underwent only a primary hepatectomy at our institution between April 1985 and March 1995. Patient survival and disease-free survival after recurrence was compared using the following clinicopathologic variables (Table 1). Host factors at recurrence were gender, age, presence of diabetes mellitus, hypertension, and esophageal varices, Child and Pugh's classification, viral status (*e.g.*, hepatitis B and C), liver function tests at recurrence (*e.g.*, prothrombin time, hepaplastin test, bilirubin, albumin, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), indocyanine green dye retention rate at 15 minutes), white blood cell count, platelet count, and the histologic findings of the noncancerous part, including cirrhosis and active hepatitis. Operative factors at repeat hepatectomy were operative time, estimated blood loss, and the need for blood transfusion. Tumor factors at repeat hepatectomy were the period until recurrence (0: >1 year, 1: 1 year or less), the α-fetoprotein level, tumor number, maximum tumor diameter, and histologic findings (*e.g.*, histology classified by Edmondson and Steiner,[14] surgical margin, capsular formation, invasion to the portal vein, and intrahepatic metastases). Tumor factors at first hepatectomy were tumor number, maximal tumor diameter, surgical margin, histology, capsular formation, invasion to the portal vein, and intrahepatic metastases.

The histologic grade of HCC, according to Edmondson and Steiner's classification,[14] at repeat hepatectomy was compared with that at first hepatectomy.

Follow-Up

Patient follow-up after hepatic resection has been described elsewhere.[3] Briefly, a monthly measurement of α-fetoprotein and protein induced by vitamin K absence-II[15] and monthly bedside ultrasonography were performed. Ultrasonography and dynamic computed tomography were performed every 3 months by radiologists. An angiographic examination was done after admission when recurrence was strongly suspected.

Statistical Analysis

Regarding the survival analysis of the prognostic factors for both patient survival and disease-free survival, the survival was calculated by the product limit method of Kaplan and Meier,[16] and the differences in the survival between the groups were then compared using the log-rank test.[17] The results of a univariate analysis helped us reduce substantially the number of study variables. Only a few significant variables were used in the multivariate analysis using Cox's proportional hazard model.[18] The BMDP P2L program (Los Angeles, CA) was simultaneously used for the multivariate adjustment of all covariates by using a stepwise regression analysis on an IBM System 4381 (Armonk, NY) computer. A p value < 0.05 was considered to be significant.

RESULTS

Survival after repeat hepatectomy did not substantially differ from that of the patients who underwent only a primary hepatectomy (Fig. 1). However, disease-free survival after repeat hepatectomy was significantly lower than that in the primary hepatectomy patients ($p < 0.05$; Fig. 2).

In the univariate analysis, 3 variables were determined

Address reprint requests to Mitsuo Shimada, M.D., The Department of Surgery II, Faculty of Medicine, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan; phone: 81-92-642-5466; fax: 81-92-642-5482.

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Table 1. DEMOGRAPHIC VARIABLES OF PATIENTS WITH A REPEATED HEPATECTOMY OF RECURRENT HEPATOCELLULAR CARCINOMA

Variable		3-year Survival (%)	p Value
Host factors at recurrence			
Gender			
1: male	(n = 33)	79.4	0.4163
2: female	(n = 8)	67.3	
Age			
0: ≦60	(n = 18)	65.5	0.1695
1: >60	(n = 23)	100	
Diabetes			
0: absent	(n = 33)	74.2	0.4857
1: present	(n = 8)	66.7	
Hypertension			
0: absent	(n = 33)	68.3	0.4742
1: present	(n = 8)	100	
Varices			
0: absent	(n = 35)	71.4	0.5824
1: present	(n = 6)	80.0	
HBs-Ag			
0: negative	(n = 35)	74.8	0.2483
1: positive	(n = 6)	60.0	
HCV			
0: negative	(n = 5)	75.0	0.8360
1: positive	(n = 25)	79.4	
Child's class			
1: A	(n = 32)	73.4	NS
2: B	(n = 6)	66.7	
3: C	(n = 3)	100	
WBC			
0: ≧3500/mm^3	(n = 27)	80.6	0.4912
1: <3500/mm^3	(n = 14)	57.3	
Platelet			
0: ≧100,000/mm^3	(n = 22)	79.7	0.6825
1: <100,000/mm^3	(n = 13)	66.7	
PT			
0: ≦12 sec	(n = 19)	88.2	0.1063
1: >12 sec	(n = 22)	51.9	
HPT			
0: ≧60%	(n = 17)	85.7	0.2457
1: <60%	(n = 21)	54.8	
Bilirubin			
0: ≦1.0 mg/dL	(n = 26)	81.6	0.2752
1: >1.0 mg/dL	(n = 15)	50.8	
Albumin			
0: ≧3.5 g/dL	(n = 30)	71.8	0.4093
1: <3.5 g/dL	(n = 11)	75.0	
GOT			
0: ≦70 IU/dL	(n = 25)	73.0	0.8161
1: >70 IU/dL	(n = 16)	72.7	
GPT			
0: ≦90 IU/dL	(n = 26)	66.7	0.2501
1: >90 IU/dL	(n = 15)	81.5	
ICG R_{15}			
0: ≦18%	(n = 22)	66.7	0.1834
1: >18%	(n = 19)	80.8	
AFP			
0: ≦100 ng/mL	(n = 27)	80.7	0.2448
1: >100 ng/mL	(n = 14)	54.0	
Operative factors at repeat hepatectomy			
Operation			
0: ≦4 hr	(n = 18)	82.4	0.1958
1: >4 hr	(n = 23)	57.0	
Blood loss			
0: ≦2000 mL	(n = 25)	75.0	0.8543
1: >2000 mL	(n = 16)	76.2	
Transfusion			
0: present	(n = 14)	83.8	0.3706
1: absent	(n = 27)	65.1	
Tumor factors at repeat hepatectomy			
Period until recurrence			
0: >1 yr	(n = 32)	82.8	0.0013†
1: ≦1 yr	(n = 9)	25.0	
Tumor number			
0: single nodule	(n = 27)	72.9	0.8370
1: multiple nodules	(n = 14)	70.0	
Tumor size			
0: ≦3 cm	(n = 29)	84.3	0.0750
1: >3 cm	(n = 12)	44.4	
tw			
0: negative	(n = 12)	78.7	0.4936
1: positive	(n = 27)	65.7	
Histology			
0: Grades* 1 and 2	(n = 28)	84.7	0.0083†
1: Grade 3	(n = 12)	37.5	
fc			
0: absent	(n = 16)	90.0	0.3600
1: present	(n = 24)	63.2	
vp			
0: absent	(n = 33)	72.2	NS
1: present	(n = 6)	100	
im			
0: absent	(n = 24)	73.9	0.9730
1: present	(n = 15)	70.0	
Histological findings of noncancerous parts at repeat hepatectomy			
Cirrhosis			
0: absent	(n = 16)	82.5	0.8838
1: present	(n = 23)	69.0	
Active hepatitis			
0: absent	(n = 17)	70.0	0.2300
1: present	(n = 21)	74.8	
Tumor factors at first hepatectomy			
Tumor number			
0: single nodule	(n = 30)	78.7	0.7149
1: multiple nodules	(n = 9)	83.3	
Tumor size			
0: ≦3 cm	(n = 21)	85.7	0.0809
1: >3 cm	(n = 20)	57.8	
tw			
0: negative	(n = 20)	76.9	0.9318
1: positive	(n = 19)	71.2	
Histology			
0: Grades 1 and 2	(n = 23)	87.8	0.0836
1: Grade 3	(n = 91)	45.6	
fc			
0: absent	(n = 14)	87.5	0.1733
1: present	(n = 24)	59.3	
vp			
0: absent	(n = 30)	85.6	0.0002†
1: present	(n = 9)	16.7	
im			
0: absent	(n = 30)	75.8	0.1608
1: present	(n = 10)	57.1	

HBs-Ag = hepatitis B surface antigen; HCV = anti-hepatitis C virus antibody; Child's class = Child and Pugh's classification; WBC = white blood cells; PT = prothrombin time; HPT = hepaplastin time; GOT = glutamine oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; ICG R_{15} = indocyanine green dye retention rate at 15 min; AFP = alpha-fetoprotein; NS = not significant; tw = surgical margin < 5 mm; fc = capsular formation; vp = invasion to the portal vein; im = intrahepatic metastases.

* The Edmondson and Steiner classification.[14]

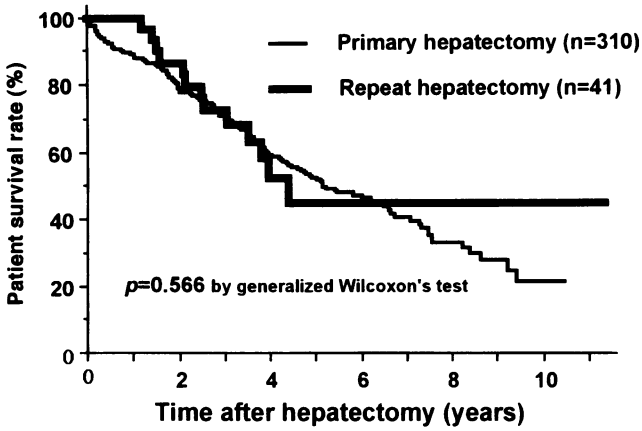

Figure 1. Comparison of survival rates between first and repeat hepatectomies. No significant difference was observed between the two groups, even if the survival of patients with a repeat hepatectomy was calculated from the time of the repeat hepatectomy.

to be significantly the worst of the 38 studied: period until recurrence of <1 year, histology at repeat hepatectomy of Edmondson and Steiner's[14] Grade 3, and microscopic presence of portal vein invasion at first hepatectomy (see Table 1). The multivariate analysis finally revealed only the presence of portal vein invasion at the first hepatectomy to be an independent and significant poor prognostic factor (Table 2).

Regarding multicentric occurrence at repeat hepatectomy, Figure 3 shows that only 6 patients of 40 (15%) whose specimens could be histologically evaluated were Grade 1. The histologic Grade of 4 cases with Grade 1 HCC at repeat hepatectomy was the same as that at the first hepatectomy. In the 2 cases with Grade 2 HCC at first hepatectomy, the histologic grade at repeat hepatectomy changed to Grade 1. Therefore, all 6 cases with Grade 1 HCC at repeat hepatectomy are considered to demonstrate a multicentric origin.

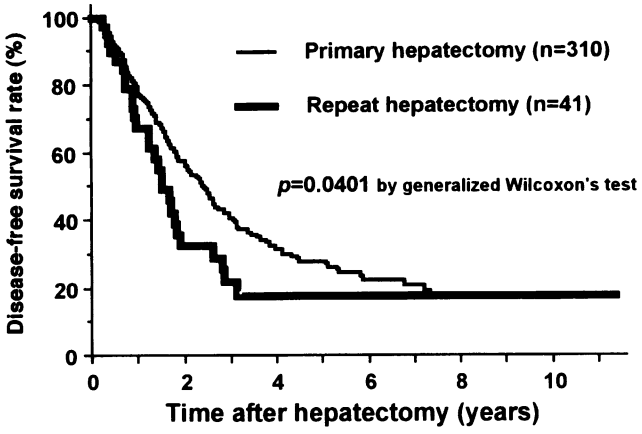

Figure 2. Comparison of disease-free survival rates between first and repeat hepatectomies. The disease-free survival rate for a repeat hepatectomy was significantly worse than that in a first hepatectomy ($p < 0.05$).

Table 2. THE RESULTS OF A MULTIVARIATE ANALYSIS USING COX'S PROPORTIONAL HAZARD MODEL

Variable	Coefficient	SE	Relative Risk	p Value
Portal vein invasion at first hepatectomy	1.180	0.422	3.26	0.0052

SE = standard error.

DISCUSSION

Survival of the patients with recurrent HCC after repeat hepatectomy was similar to that of those with primary HCC after first hepatectomy. Findings recently reported by us and by other authors[1-5] reinforce the importance of repeat hepatectomy for recurrent HCC, whenever the liver function and the patient's general condition allow surgical treatment. Disease-free survival of patients with recurrent HCC after repeat hepatectomy was worse than that of

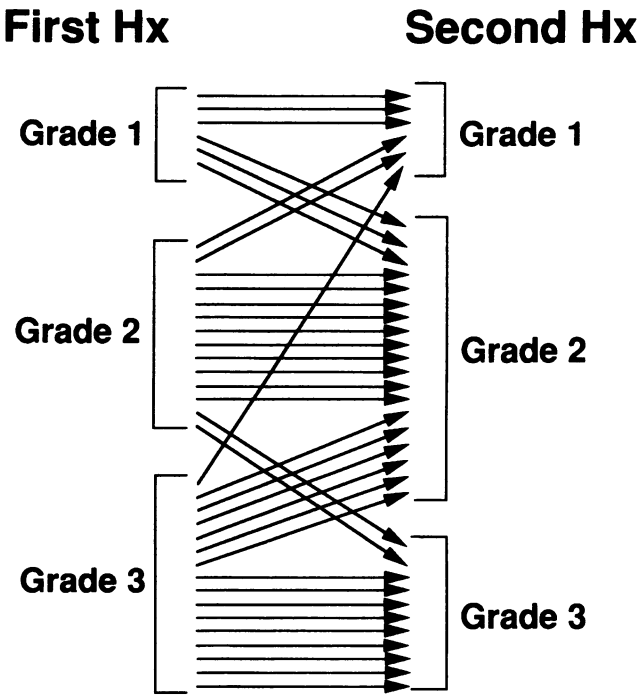

Figure 3. Comparison of the histologic differentiation between first and repeat hepatectomies. Edmondson and Steiner's[14] Grade 1 hepatocellular carcinoma (HCC) was found in 6 of 40 patients in repeat hepatectomies (15%), and these findings could be histologically evaluated. The histologic grade of 4 cases with Grade 1 HCC at repeat hepatectomy was the same as at first hepatectomy. In the 2 cases with Grade 2 HCC at first hepatectomy, the histologic grade at repeat hepatectomy was found to have changed to Grade 1. Therefore, all 6 cases with Grade 1 HCC at repeat hepatectomy are considered to demonstrate a multicentric origin.

patients with primary HCC after first hepatectomy. The reason is thought to be that micrometastasis in the remnant liver may exist even when no macroscopically detectable tumors are found by preoperative or intraoperative examination.

Only 3 variables were found to be significant prognostic factors after repeat hepatectomy: period until recurrence of <1 year, histology at repeat hepatectomy of Edmondson and Steiner's[14] Grade 3, and the presence of portal vein invasion at first hepatectomy. Of these three variables, only the histology was found to be a variable at repeat hepatectomy; the other two variables were closely related to the first hepatectomy.

It is interesting that portal vein invasion and intrahepatic metastases at repeat hepatectomy were not significantly correlated with survival after repeat hepatectomy, because both have been well documented as poor prognostic indicators of HCC. One possibility is that the incidence of portal vein invasion in repeat hepatectomy was not high enough to make a statistical difference. It is also possible that the tumor cells, which were infiltrated into the portal vein as well as a main tumor in repeat hepatectomy, are not so malignant in patients with recurrent HCC who undergo a repeat hepatectomy.

The period until recurrence of <1 year after first hepatectomy was previously confirmed to be one of the most important prognostic indicators in patients with recurrent HCC.[19] Matsumata et al.[20] reported that most diffuse types of recurrence occur within 1 year after the first hepatectomy; such diffuse types were thus probably due to intrahepatic metastases through the portal vein, caused by manipulation of the liver during the hepatectomy. Both a poorly differentiated histology (Grade 3) and portal invasion were reported to be related to recurrence within 1 year after hepatic resection. A histologic grade of 3 at repeat hepatectomy was thus considered to reflect the proliferative activity of recurrent HCC, and the prognosis of patients with HCC of Grade 3 was therefore worse than that of those with other histologic types.

It is also interesting that the presence of portal vein invasion at first hepatectomy was the only significantly poor prognostic indicator of patients with recurrent HCC after repeat hepatectomy. This indicates that the prognosis after HCC recurrence may already be predetermined by the presence of portal vein invasion at first hepatectomy.

The above findings suggest that micrometastases occur through the portal vein in primary HCC, and a few of them grow as large as present diagnostic devices can detect. The detectable tumor masses are surgically resected, but any remaining metastases from the primary HCC may still grow after repeat hepatectomy. Therefore, the indications should be carefully determined for a repeat hepatectomy in patients in whom portal vein invasion was histologically recognized at the first hepatectomy. A new multidisciplinary treatment strategy may be required to obtain a better prognosis.

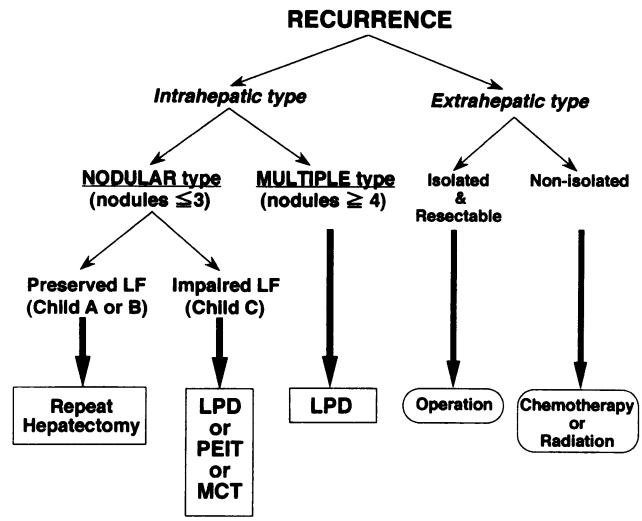

Figure 4. Treatment strategy for recurrent hepatocellular carcinoma. Child = Child and Pugh's classification; LPD = lipiodolization; PEIT = percutaneous ethanol injection therapy; MCT = microwave coagulation therapy.

Controversy remains among hepatologists regarding the multicentric occurrence of HCC in second tumors after a first hepatectomy of primary HCC. In fact, the multicentric occurrence of HCC has been proved[13,21–24]; however, its rates in the recurrence after first treatment of primary HCC may be overestimated. This overestimation is probably due to assessment using needle biopsy specimens, because an accurate evaluation would require obtaining whole specimens of recurrent HCC by a surgical resection. In this study, the multicentric occurrence rate was estimated to be 23%, based on the assumption that the recurrent HCC of Edmondson and Steiner's Grade 1 is due to a multicentric occurrence. This number was also calculated based on the assumption that Grade 1 HCC can hardly metastasize.[25–27] Therefore, the true rate of multicentric occurrence is considered to be <15%. Moreover, we have recently reported that approximately 25% of all recurrences are considered to be caused by possible multicentric occurrence, based on the findings of a study using cirrhotic patients with solitary small HCC (<3 cm in greatest diameter).[28] Such patients show an especially high risk of multicentric occurrence after hepatectomy; therefore, the risk of multicentric occurrence in second tumors after first hepatectomy in all patients with HCC is considered to be much lower than the above rates. Recurrent HCC after hepatectomy for a primary HCC is thus not considered to be a second primary HCC; instead, it is thought to represent recurrent tumors.

Figure 4 shows our treatment strategy for recurrent HCC. For an extrahepatic recurrence, surgical treatment is indicated only when the recurrence is isolated and resectable; otherwise, systemic chemotherapy or radiation

is indicated. For an intrahepatic recurrence, repeat hepatectomy is indicated when liver function is preserved (Child's classification A or B) and there are fewer than three recurrent nodules. Lipiodolization[29,30] or percutaneous ethanol injection therapy is indicated when liver function is impaired or more than four recurrent nodules are found. Patients whose first HCC demonstrated microscopic portal vein invasion should be closely followed and may need a prophylactic postoperative lipiodolization,[31] even if a repeat hepatectomy has already been performed for recurrent HCC.

In conclusion, the only prognostic factor found to be significant in patients with recurrent HCC after repeat hepatectomy was the presence of portal vein invasion in the first hepatectomy. Recurrences of HCC after the first hepatectomy are thus considered to represent metastatic recurrence, not multicentric occurrence. Therefore, for patients with recurrent HCC, a repeat hepatectomy is indicated. Surgical indications should be carefully determined for patients in whom the presence of portal vein invasion was histologically recognized at the first hepatectomy.

References

1. Huguet C, Bona S, Nordlinger B, et al. Repeat hepatic resection for primary and metastatic carcinoma of the liver. Surg Gynecol Obstet 1990;171:398–402.
2. Matsuda Y, Ito T, Oguchi Y, Nakajima K, Izukura T. Rationale of surgical management for recurrent hepatocellular carcinoma. Ann Surg 1993;217:28–34.
3. Shimada M, Matsumata T, Taketomi A, et al. Repeat hepatectomy for recurrent hepatocellular carcinoma. Surgery 1994;115:703–706.
4. Suenaga M, Sugiura H, Kokuba Y, Uehara S, Kurumiya T. Repeated hepatic resection for recurrent hepatocellular carcinoma in eighteen cases. Surgery 1994;115:452–457.
5. Nagasue N, Kohno H, Hayashi T, et al. Repeat hepatectomy for recurrent hepatocellular carcinoma. Br J Surg 1996;83:127–131.
6. The Liver Cancer Study Group of Japan. Predictive factors for long-term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. Cancer 1994;74:2772–2780.
7. Shirabe K, Kanematsu T, Matsumata T, et al. Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analysis. Hepatology 1991;14:802–805.
8. Nagasue N, Uchida M, Makino Y, et al. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. Gastroenterology 1993;105:488–494.
9. Ouchi K, Matsubara S, Fukuhara K, Tominaga T, Matsuno S. Recurrence of hepatocellular carcinoma in the liver remnant after hepatic resection. Am J Surg 1993;166:270–273.
10. Chen MF, Hwang TL, Jeng LB, et al. Postoperative recurrence of hepatocellular carcinoma: two hundred five consecutive patients who underwent hepatic resection in 15 years. Arch Surg 1994;129:738–742.
11. Izumi R, Shimizu K, Ii T, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. Gastroenterology 1994;106:720–727.
12. Okada S, Shimada K, Yamamoto J, et al. Predictive factors for postoperative recurrence of hepatocellular carcinoma. Gastroenterology 1994;106:1618–1624.
13. Takenaka K, Adachi E, Nishizaki T, et al. Possible multicentric occurrence of hepatocellular carcinoma: a clinicopathological study. Hepatology 1994;19:889–894.
14. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462–503.
15. Liebman H, Furie BC, Tong MJ, et al. Des-γ-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med 1984;310:1427–1431.
16. Kaplan GL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
17. Petro R, Pike MC. Conservation of the approximation $(O\text{-}E^2)/E$ in the log-rank test for survival data on tumor incidence data. Biometrics 1973;29:579–584.
18. Cox DR. Regression models and life tables. J R Stat Soc Ser B 1972;34:187–220.
19. Shimada M, Takenaka K, Gion T, et al. Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. Gastroenterology 1996;111:720–726.
20. Matsumata T, Kanematsu T, Takenaka T, et al. Patterns of intrahepatic recurrence after curative resection of hepatocellular carcinoma. Hepatology 1989;9:457–460.
21. Tsuda H, Hirohashi S, Shimosato Y, Terada M, Hasegawa H. Clonal origin of atypical adenomatous hyperplasia of the liver and clonal identity with hepatocellular carcinoma. Gastroenterology 1988;95:1664–1666.
22. Sakamoto M, Hirohashi S, Tsuda H, et al. Multicentric independent development of hepatocellular carcinoma revealed by analysis of hepatitis B virus integration pattern. Am J Surg Pathol 1989;13:1064–1067.
23. Hsu HC, Chiou TJ, Chen JY, Lee PH, Peng SY. Clonality and clonal evolution of hepatocellular carcinoma with multiple nodules. Hepatology 1991;13:923–928.
24. Tsuda H, Oda T, Sakamoto M, Hirohashi S. Different pattern of chromosomal allele loss in multiple hepatocellular carcinomas as evidence of their multifocal origin. Cancer Res 1992;52:1504–1509.
25. Kondo Y, Wada K. Intrahepatic metastasis of hepatocellular carcinoma: a histopathologic study. Hum Pathol 1991;22:125–130.
26. Kanai T, Hirohashi S, Upton MP, et al. Pathology of small hepatocellular carcinoma: a proposal for a new gross classification Cancer 1987;60:810–819.
27. Sakamoto M, Hirohashi S, Shimosato Y. Early stages of hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Pathol 1991;22:172–178.
28. Shirabe K, Takenaka K, Taketomi A, et al. Postoperative hepatitis status as a significant risk factor recurrence in cirrhotic patients with small hepatocellular carcinoma. Cancer 1996;77:1050–1055.
29. Kanematsu T, Furuta T, Takenaka K, et al. A 5-year experience of lipiodolization: selective regional chemotherapy for 200 patients with hepatocellular carcinoma. Hepatology 1989;10:98–102.
30. Urata K, Matsumata T, Kamakura T, Hasuo K, Sugimachi K. Lipiodolization for unresectable hepatocellular carcinoma: an analysis of 205 patients using univariate and multivariate analysis. J Surg Oncol 1994:56:54–58.
31. Takenaka K, Yoshida K, Nishizaki T, et al. Postoperative prophylactic lipiodolization reduces the intrahepatic recurrence of hepatocellular carcinoma. Am J Surg 1995;169:400–405.