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Recurrence Pattern of Hepatocellular Carcinoma after Curative Resection

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Even after curative operation for small hepatocellular carcinoma (HCC) the postoperative intrahepatic recurrence rate is still high. In this study we analyzed the recurrence pattern of 106 patients who underwent curative primary resection between October, 1983 and December, 1994 in our hospital. While the cumulative survival rates 2 and 5 years after the operation were 82 and 64 %, respectively, the corresponding cumulative disease-free survival rates after the operation were 56 and 31 %, respectively. Recurrence was seen in 45 patients. Among 41 patients with intrahepatic recurrence, one to three nodules in the same lobe as the primary tumor were seen in 9, those in a different lobe in 12, multiple nodules in 18 and marginal recurrences in 2. In 29 patients whose recurrent HCC were analyzed for clonality, 14 showed metachronous multicentric (MC) HCC and 10 metastatic HCC. Repeat resection was performed in 10 patients with the form of one to three nodular recurrence and in 8 the recurrences were MC. The survival rate after the re-operation was the same as that after the first resection. It seems important to detect MC in the early stage after the first operation and perform radical treatments in order to prolong the survival.

Key words: Hepatocellular carcinoma, Postoperative recurrence, Treatments, Multicentric occurrence

Introduction

Since our hospital opened in October, 1983, we have treated more than 200 patients with hepatocellular carcinoma (HCC) with hepatic resection. At the beginning of this period HCC nodules were relatively large when first detected, so the extent of hepatic resection was probably greater than that now[1]. Because imaging diagnosis for screening has improved and the particular subgroups at risk have been identified, earlier HCC is now detected and radical treatment such as hepatic resection is considered more often than was once the case[2]. These developments have increased the dimensions of the problem of postoperative recurrence. Even after curative operation for small HCC, the postoperative intrahepatic recurrence rate is still high[3]. One cause of this high incidence might be the occurrence of multicentric HCC, which is a new HCC different from the primary tumor based on impaired liver which has high malignant potential, but it is difficult to differentiate it from metastatic HCC[4-5].

In this report, we present the clinicopathological features of the patients with HCC who underwent curative hepatic resection at our hospital and their survival rate. We then analyze the postoperative recurrence pattern and incidence of metachronous multicentric occurrence as elucidated by histopathological and molecular biological examinations[4,6], and discuss ways of prolonging patient survival.

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Patients and methods

Patients

Between October, 1983 and December, 1994, 175 patients with primary HCC underwent hepatic resection at our hospital. Fifteen patients with intrahepatic recurrent HCC underwent second hepatic resection, and one patient underwent a third hepatic resection. Curative resection, performed in 106 patients, is defined herein according to the criteria of the Liver Cancer Study Group of Japan, as follows[7]: liver resection with the excised tumor tissue in Stage I regardless of surgical free margin, or liver resection in Stage II or III with more than 1 cm of surgical free margin. In either case, no tumor emboli must remain in the portal vein, hepatic vein, or bile duct as depicted on images of the remnant liver. The definitions of T factor and tumor stage are listed in Table 1 and 2, respectively.

The characteristics of the patients are shown in Table 3. Hepatitis B surface antigen was positive in 27 patients (25.5 %). Hepatitis C virus antibody was positive in 55 (60.1 %) of 90 patients examined. The extent of hepatic resection was classified as follows:

Table 1. T factor

T factor	Description
T1	A single tumor of 2 cm or less in its greatest dimention without vascular invasion
T2	A single tumor with a diameter exceeding 2 cm, without vascular invasion; a single tumor of 2 cm or less in its greatest dimention with vascular invasion; multiple tumors with a maximum tumor diameter of 2 cm or less confined to one lobe
T3	A single tumor with a diameter exceeding 2 cm, with vascular invasion; multiple tumors with diameters exceeding 2 cm confined to one lobe
T4	Multiple tumors in more than one lobe; associated vascular invasion in the first branch of the portal or hepatic veins

* Determining T factor depends on the three items: cancer size, whether there are single or multiple tumors, and vascular invasion. Multiple tumors can be either multicentric tumors or intrahepatic metastatic tumors.

Table 2. Tumor Stage

Stage	T factor	N factor	M factor
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1-3	N1	M0
IV-A	T4	N0-1	M0
IV-B	T1-4	N0-1	M1

Hr0, resection of less than one subsegment; HrS, resection of one subsegment; Hr1, resection of one segment; and Hr2, resection of two segments. The Edmondson-Steiner classification expresses the degree of cellular atypia[8]. Grades I, II, III, and IV in the Edmondson-Steiner classification system correspond with well-differentiated, moderately-differentiated, poorly-differentiated, and undifferentiated carcinomas, respectively.

During the operation, to minimize blood loss, a microwave tissue coagulator and/or ultrasonic surgical dissector, known as Cavitron ultrasonic surgical aspirator (CUSA), was applied in parenchymal dissection. The range of dissection was determined by intraoperative ultrasonic guidance.

Postoperatively patients received regular follow-up with measurement of alpha-fetoprotein once a month, ultrasonography once every 3 months, and computed tomography (CT) once every 6 months. When intrahepatic recurrence was suspected, the patient was hospitalized and angiography and arterioportal CT were performed.

Table 3. Evaluation of risk factors for recurrence

Variables	Recurrence Yes n = 45	Recurrence No n = 61	Significance
Mean age (Years)	62.4	59.3	N. S.
Sex (M : F)	36 : 9	40 : 21	N. S.
Tumor Stage			
I	8	16	
II	28	39	N. S.
III	9	6	
Tumor size in greatest diameter (cm)			
0—2.0	11	15	
2.1—5.0	26	42	N. S.
5.1—10.0	7	4	
10.1<	1	0	
Number of tumors			
solitary	34	59	
multiple	11	2	p=0.0008
Extent of hepatic resection			
Hr0	11	20	
HrS	13	4	
Hr1	12	25	N. S.
Hr2	9	12	
Accompanying cirrhosis			
absence	1	0	
fibrosis/chronic hepatitis	12	29	p=0.004
cirrhosis	32	32	
Edmondson-Steiner classification			
I	11	14	
II	17	33	
III	12	6	N. S.
IV	1	0	
necrosis	4	8	

Definition of metachronous multicentric occurrence for intrahepatic recurrent HCC

Multicentricity of intrahepatic recurrent HCC was determined by histopathological and/or molecular biological examination as described below.

Histopathological criteria. The criteria of multicentric occurrence (MC) were: (1) multiple well-differentiated HCC tumors; or (2) remote and smaller nodules showing microscopically well-differentiated HCC, besides the major nodule showing poorer differentiation; or (3) multiple HCC indicating "nodule-in-nodule" form[5]. The criteria of intrahepatic metastasis (IM) were: (1) multiple satellite nodules surrounding a large main tumor; or (2) satellite nodules apparently growing from portal vein thrombi[5].

Molecular biological criteria. The criteria of MC were: (1) integration pattern of hepatitis B virus (HBV) DNA in host nuclear DNA in a recurrent nodule differing from that in the primary nodule as assessed using Southern blot hybridization technique[4]; or (2) *p53* mutation pattern in exon 5-8 in a recurrent nodule differing from that in the primary nodule as assessed using the polymerase chain reaction-single strand conformation polymorphism method[5], and presence of mutation in the primary nodule but absence in a recurrent nodule[5].

Statistical analysis

Statistical comparisons for tests of significance were made with use of unpaired Student's t-test and the chi-square test with a single degree of freedom ; p values of less than 0.05 were considered statistically significant. Cumulative survival rates were obtained by means of the Kaplan-Meier method.

Results

Survival rates

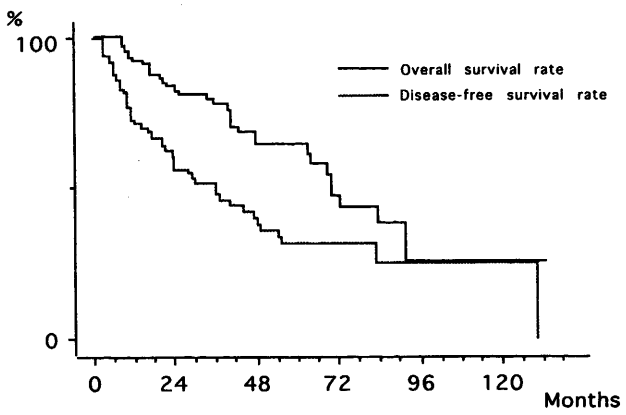

Fig. 1. Overall and disease-free survival rates

The overall survival rate and the disease-free survival rate are shown in Figure 1. While the cumulative survival rates 2, 5, and 10 years after the operation were 82 %, 64 %, and 25 %, respectively, the cumulative disease-free survival rates 2 and 5 years after the operation were only 56 % and 31 %, respectively.

Recurrence pattern

Table 4. Recurrence pattern after curative resection (n=45)

Intrahepatic recurrence	41	
near surgical margin		2
solitary or a few nodule(s)		
in the same lobe		9
in the different lobe		12
multiple nodules		18
Distant metastasis	7	
bone		3
skin		1
peritoneum		3

Recurrence was seen in 45 patients. Recurrence pattern in each is shown in Table 4. Thirty-eight patients had intrahepatic recurrence between 3 and 130 months with a mean of 30±25 months after the primary resection. The intrahepatic recurrences were classified into three patterns. In 2 patients with marginal recurrences, the Edmondson-Steiner classification of the primary HCC was III, poorly differentiated HCC, and the distance between the surgical margin and the cut surface was less than 1 cm.

Four patients developed intrahepatic recurrences and distant metastasis simultaneously. In 2 patients with bone metastasis, the primary HCC tumor became completely necrotic because of preoperative percutaneous ethanol injection (PEI) into the tumors. Skin metastasis was found 2 years after the first operation and was thought to have arisen from the site where the preoperative percutaneous fine needle aspiration biopsy had been inserted, indicating possible implantation by the needle. The metastatic tumor was resected and the patient has lived for 4 years without any sign of recurrence. In 3 patients with peritoneal dissemination consisting of 1, 1 and 3 nodules, respectively, all gross tumors were thought to have been removed and re-resections were carried out.

Clinicopathologic variables in the recurrence group were compared with those in the disease-free group (Table 3). The sex of the patients, hepatitis B surface antigen and hepatitis C virus antibody did not affect the incidence of recurrence, but recurrence occurred less frequently in the patients with noncirrhotic liver (p=0.004) and in the patients with multiple HCC (p=0.0008).

Multicentricity for intrahepatic recurrent nodules

Multicentricity for intrahepatic recurrence was determined in 29 patients from whom tissues of recurrent lesions were obtained by repeat resection or fine needle aspiration biopsy. The results are shown in Table 5.

MC occurred in 14 patients. Histopathologically 6

Table 5. Multicentricity for intrahepatic reccurence (n=29)

metachronous multicentric occurrence	14	
histopathologically determined		8
genetically determined		3
both		3
metastasis from primary HCC	10	
histopathologically determined		6
genetically determined		2
both		2
unclassified	5	

patients had well- differentiated recurrent HCC and 2 patients had well- to moderately-differentiated HCC,

Table 6. Recurrence pattern and time between hapatic resection and intrahepatic recurrence

	time between hapatic resection and recurrence					
	months 0－6	7－12	13－24	25－36	37－	Total
Intrahepatic recurrence						
near surgical margin		1		1		2 (0)*
soletary or a few nodule(s)						
in the same lobe		3		1(1)	5(3)	9 (4)
in the different lobe	2(2)	1(1)	4(3)	2(2)	3(2)	12 (10)
multiple nodules	9	5	2	2		18 (0)
						41 (14)

* The numerals in parenthesis represent the number of patients whose recurrent HCC occurred metachronously multicentrically.

Table 7. Recurrence pattern and treatment methods

	hepatic resection	MTC	PEI	chemotherapy			no treatment	Total
				intra-arterial				
				TAI, TAE	port	per os		
Intrahepatic recurrence								
near surgical margin	1					1		2
solitary or a few nodule(s)								
in the same lobe	1		1(1)	3(1)	4(2)			9(4)
in the different lobe	8(8)		1(1)	2	1(1)			12(10)
multiple nodules		1	2	5	2	4	4	18
								41(14)

*The numerals in parenthesis represent the number of patients whose recurrent HCC occurred metachronously multicentrically.

**MTC : microswave tissue coagulation, PEI : percutaneous ethanol injection, TAI : transcatheter arterial injection, TAE : transcatheter afterial embolization, and port : arterial infusion therapy using subcutaneous implantable pump

while their primary HCC were poorly-differentiated. Because in 3 patients both the primary and recurrent nodules were moderately- or poorly-differentiated HCC, the histological examination did not elucidate the clonality. Among them, in 2 patients the HBV-DNA integration pattern was different and in 1 patient the *p53* mutation pattern was different.

IM occurred in 10 patients. Histopathologically in 6 patients the differentiation of the recurrent HCC was the same as that of the primary HCC. In 2 patients the histopathological examination did not identify the clonality. In 1 patient soon after the start of hemodialysis a solitary recurrent HCC was detected 48 months after the primary tumor resection and immediately thereafter multiple nodules were noted occupying the entire remnant liver. The HBV-DNA integration patterns of the recurrent HCC nodules and metastatic lung tumor were the same as that of the primary HCC[4].

In 5 patients the clonality could not be determined either because the tumors were necrotic, or because neither histopathological nor genetical analysis was informative.

Recurrence pattern and time between hepatic resection and intrahepatic recurrence (Table 6)

Most of the multiple or surgically marginal intrahepatic recurrences occurred within 2 years after the operation, especially within 6 months. One- to three-nodular recurrences occurred at any time from 6 to 130 months after the operation. In 10 of the 12 patients with recurrent nodules located in a lobe other than that of the primary tumor, the recurrence was MC.

Recurrence pattern and treatment methods

The main treatment methods for intrahepatic recurrence are shown in Table 7. When possible, radical treatments such as hepatic resection and PEI

were performed. The basic selection criteria for repeat hepatectomy were presence of fewer than three recurrent nodules with liver function remaining almost the same as that at the first operation. In 8 of 10 patients who underwent repeat hepatectomy, the recurrent nodules were MC. The mean time between primary and repeat hepatectomy was 41±20 months (range, 6-130 months). When the patient's liver function was thought to be so poor as to preclude operation, PEI or microwave coagulation therapy (MTC) was chosen. The two-year survival rate after repeat hepatectomy was 75% and significantly better than that after any of the other treatments.

Discussion

The five-year survival rates reported in the 1980s by several authors were only 20 to 30 % after hepatic resection[1-2]. The incidence of small HCC has recently increased because of great advances in diagnostic imaging modalities such as ultrasonography, CT, MRI, arterioportal CT and digital subtraction angiography, combined with close follow-up systems for population at risk with liver dysfunction caused by hepatitis B or C virus[2]. This has given hepatologists a good opportunity to perform radical treatments such as hepatic resection, PEI and MTC. In 1995, according to the Liver Cancer Study Group of Japan, the 2- and 5-year survival rates after hepatic resection in 9099 patients were 68.0 % and 40.8 %, respectively, and the rates at the same intervals after the curative resection were 76.0 % and 48.4 %, respectively[7].

Most deaths after hepatic resection are a result of intrahepatic recurrence[2]. According to our present data the incidence of the recurrence 2 and 5 years after the resection is about 40% and 65%, respectively. Intrahepatic recurrence may be grossly classified into the two patterns of IM and MC. IM may occur relatively early after the operation in the form of multiple nodular lesions, so chemotherapy such as arterial infusion therapy through hepatic artery may be chosen. In 2 patients with recurrence near the surgical margin the histological characterization of the tumors was poorly-differentiated HCC. In such cases the distance between the tumor and the cut surface should be at least 1 cm.

Because MC may occur any time after the operation and most often as one to three nodular lesions, radical treatments such as operation, MTC and PEI could be selected; after repeat resection the survival rate is almost the same as that after the first resection.

In the patients with recurrence the incidence of accompanying cirrhosis was significantly higher than that in the disease-free patients. This may indicate that in the cirrhotic-liver, because of the high carcinogenic potential[7], metachronous multicentric HCC occurs in spite of complete removal for the primary HCC.

We have made an effort to improve not only the survival rate after the operation but also quality of life in patients with HCC. Because there is no modality at our disposal by which to prevent newly occurring HCC, we must detect recurrence as early as possible and perform radical treatment.

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