

Clinicopathological Study of Hepatocellular Carcinoma in Relation to Tumor Size

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Received for publication, June 28, 1988

ABSTRACT : In order to evaluate the factors affecting the patient's survival, 32 patients of hepatic resection in which the liver had a solitary hepatocellular carcinoma (HCC) smaller than 5 cm in size were studied. 1) Chronic liver diseases were associated in 96.9 % of patients. Minor resection was done in 30 patients, and right hepatectomy in two. 2) 87.5 % of all cases were diagnosed during periodic follow-up examination for the patients with chronic liver disease, mostly cirrhosis. For small HCC, ultrasonography (US) had the highest detection rate (90%) compared with CT (66.7%) and angiography (55.6%). Preoperative serum AFP values were abnormal in 73%. 3) Grossly, all tumors were nodular or expanding and none was diffuse. Encapsulation appeared to be complete as tumor grew. Portal vein tumor thrombus (12.5%) and/or satellite tumor (31.2%) were frequent in those with larger than 2 cm in diameter. 4) The mortality rate was 9.4% and the hospital mortality rate was 6.3%. The survival rate of the group with small HCC was far better than that of the groups with HCC larger than 2 cm in size ($p < 0.05$). Above findings indicate that early detection of the tumor without portal vein thrombus and/or satellite tumor, and an adequate hepatic resection such as subsegmentectomy or segmentectomy are most important for the patient's survival.

INTRODUCTION

Prognosis of hepatocellular carcinoma (HCC) has been extremely poor, because of the frequency of underlying liver diseases, malignant nature of tumor which spreads to the portal vein or entire liver even at the early stage, and difficulty of early detection. According to the study of the Japan Liver Cancer Study Group,¹⁾ overall survival rate after the onset of disease was 21.5% in one year, and 2.4% in five years. Recently, with the progress in diagnostic proce-

dures such as ultrasonography (US), computed tomography (CT) and angiography, small HCC can be detected, and early surgery in suitable patients have increased. However, the resectability rate of HCC has remained rather low, mainly because of coexisting cirrhosis which results in fatal complications after surgery. Therefore, standard major liver resections in cirrhosis have an operative mortality of 20.7% to 60%, much higher than in patients with non-cirrhotic livers.^{2~5)} We have previously reported that the major hepatic resection more than two segments of cirrhotic liver facilitated degeneration

of liver cells, and most of these patients died from hepatic failure rather than recurrent tumor.⁶⁾ The purpose of this study is to investigate the pathological features of HCC which might affect the patient's survival, with reference to surgical procedures, and to assess the utility of imaging modalities in detection of small HCC.

MATERIALS AND METHODS

From January 1975 to December 1987, 32 patients with HCC smaller than 5cm in diameter, who underwent resection at The First Department of Surgery, Nagasaki University Hospital, were studied. Among them, 11 patients had tumors smaller than 2cm (group A), eight had tumor between 2 and 3cm (group B), and 13 had tumor between 3 to 5cm (group C). There were 28 men and four women ranging from 39 to 74 years of age, with an average of 54.8 years. In preoperative clinical status, 25 had Child's class A and seven had class B liver disease. Twenty-four of the HCC were located in the right lobe and 8 in the left lobe. Cell differentiation of the tumors were graded according to the criteria suggested by Edmondson and Steiner.⁷⁾ Underlying liver diseases were separated into categories of cirrhosis, precirrhosis, chronic hepatitis and normal.⁸⁾ HCC smaller than 2cm is defined as small HCC in this paper.

RESULTS

Clinical Features

Diagnostic Clue: In 28 of 32 patients (87.5%), tumor was detected during follow-up examination for underlying liver disease. Two patients

were diagnosed during gastric ulcer operation and one patient underwent emergency operation due to spontaneous rupture of tumor.

Elevation of serum AFP levels during the follow-up of chronic liver disease led to tumor detection in 18 of 28 follow-up patients (64.3%). US performed at the time of periodic check-up of patients with liver cirrhosis or abnormal liver function tests, detected tumors in 10 patients (35.7%).

Diagnostic Capability of Various Imaging Modalities: The detection for HCC smaller than 5cm in diameter with US, CT and angiography were shown in Table 1. For small HCC, US had the highest detection rate (90%) compared with CT (66.7%) and angiography (55.6%) (Fig. 1). For group B, differences in detection rate became smaller. All HCC of group C were detected with each imaging modality.

AFP and HBsAg: The frequencies of positive serum AFP and HBsAg of the patients were tabulated in Table 2. In 73% of all cases, the serum AFP value was abnormal, i.e., more than 20ng/ml, and in 28.1% of total cases it was more than 400ng/ml. Only one of the patients with group A had serum AFP levels of more than 400ng/ml, but such levels were detected in 50% and 30.3% of patients with group B and C, respectively.

Serum HBsAg was detected in 31.3% of all patients. As shown in Table 2, 9.1% of patients with group A, 75% with group B, and 23% with group C showed abnormal serum HBsAg.

Pathologic Features

Underlying Liver Diseases: 31 of 32 patients (96.9%) had chronic liver diseases as follow: chronic hepatitis, two cases (6.3%); precirrhosis,

Table 1. Diagnostic Capability of Various Imaging Modalities for Hepatocellular Carcinoma by Tumor Size (<5 cm)

Imaging modality	No. of patients with positive results (%)			
	Tumor size			
	< 2 cm	2-3 cm	3-5 cm	Total
Ultrasonography	9/10 (90.0)	7/8 (87.5)	11/11 (100)	27/29 (93.1)
Computed tomography	6/9 (66.7)	6/8 (75.0)	11/11 (100)	24/29 (82.8)
Angiography	5/9 (55.6)	7/8 (87.5)	13/13 (100)	25/29 (86.2)

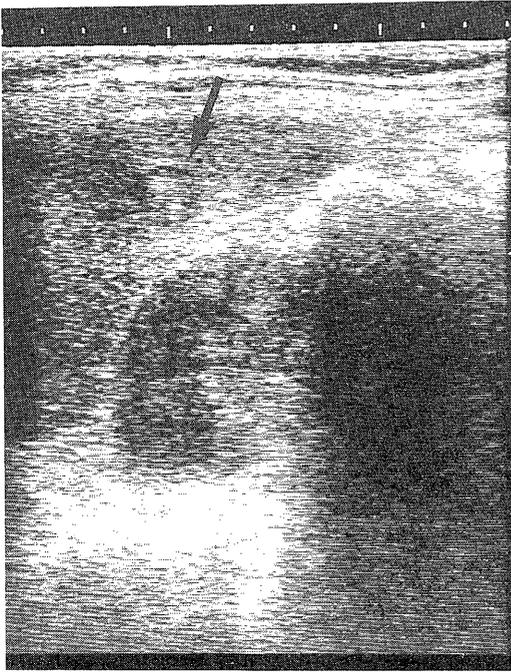


Fig. 1. Preoperative ultrasonogram of small HCC showing 1.5×1.7 cm hypoechoic lesion (arrow) with a sonolucent thin rim or periphery around it.

four cases (12.5%); and liver cirrhosis, 25 cases (78.1%) (Table 3). The presence of advanced liver cirrhosis appeared to be highly associated with group A and B, in which 90.9% and 87.5% of cases had liver cirrhosis, respectively.

Histologic Findings of Tumor: The most frequent histologic type of HCC was the grade II, which was found in 14 tumors from 29 patients excluding three cases with complete tumor necrosis because of TAE (Table 3). One half of small HCC showed low grade differentiation. Tumor size in general tends to increase with tumor anaplasia. The combined type was encountered in only one case, which composed of continuous hepatocellular and ductal carcinoma.

As for gross appearance of tumor, all were nodular or expanding, and none was diffuse. The features of capsule formation and capsule invasion of HCC were shown in Table 4. There were two cases with no capsule formation in small HCC. Grossly these tumors were formed by a cluster of small and contiguous nodules, with fibrous connective tissues evident at the borders of each nodule, often with replacing growth at the periphery. A thin fibrous capsule surrounding the tumor was found in six of all cases (18.8%) (Fig. 2). 12 of 13 cases (92.3%) in group

Table 2. Serum Hepatitis B Surface Antigen (HBsAg) and α -Fetoprotein (AFP)

Tumor size	No. of patients	Status of HBsAg			Level of serum AFP (ng/ml) No. (%)		
		-	+	Positive rate (%)	< 20	20 - 400	400 <
< 2 cm	11	10	1	9.1	4 (36.4)	6 (54.5)	1 (9.1)
2-3 cm	8	2	6	75.0	2 (25.0)	2 (25.0)	4 (50.0)
3-5 cm	13	10	3	23.1	2 (15.4)	7 (53.8)	4 (30.8)

Table 3. Histologic Grade and Underlying Liver Diseases

Tumor size	No. of patients	Grade of differentiation* No. (%)				Histologic finding of noncancerous liver. No. (%)				
		I	II	III	CM	NC	CH	PC	LC	
< 2 cm	11	5 (50.0)	2 (20.0)	3 (30.0)	0	0	1 (9.1)	0	10 (90.9)	
2-3 cm	8	1 (12.5)	4 (50.0)	2 (25.0)	1 (12.5)	0	0	1 (12.5)	7 (87.5)	
3-5 cm	13	0	8 (72.8)	3 (27.3)	0	1 (7.7)	1 (7.7)	3 (23.1)	8 (66.7)	

* Based on evaluation of 29 cases excluding 3 cases with complete tumor necrosis. CM : combined with HCC and cholangioma ; NC : no liver disease ; CH : chronic hepatitis ; PC : precirrhosis ; LC : liver cirrhosis

Table 4. Capsule Formation (fc) and Capsule Invasion (fc-inf) of HCC

Tumor size	No. of patients	Status of fc				Status of fc-inf			
		-	+/-	+	Positive rate (%)	-	+	++	Positive rate (%)
<2 cm	11	2	3	6	54.5	7	4	0	0
2-3 cm	9	0	2	7	77.7	1	0	8	88.8
3-5 cm	13	0	1	12	92.3	2	1	9	69.2

Capsule ; (-) no capsule ; (+/-) the mass is surrounded by fibrous capsule, but incomplete ; (+) the mass is firmly encapsulated with fibrous tissue.

Capsule invasion ; (-) no invasion ; (+) Intracapsule invasion ; (++) cancer invades extending through capsule.

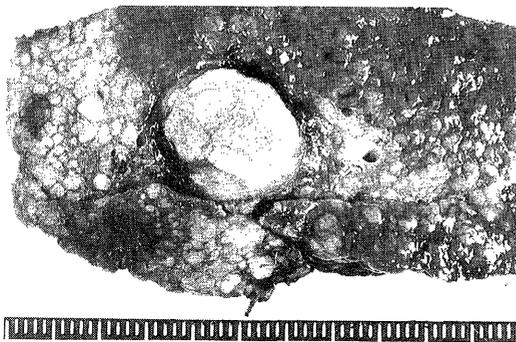


Fig. 2. Cut surface of small HCC showing 1.9 × 1.5 cm gray-white tumor which is incompletely lobulated into several parts.

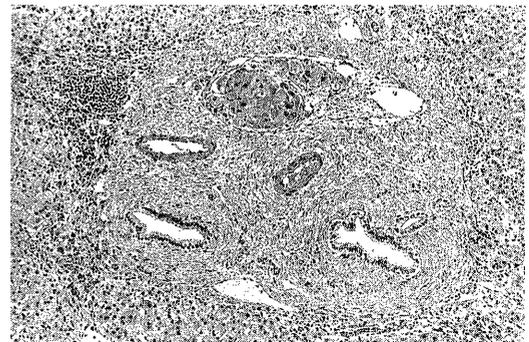


Fig. 3. Histological findings showing portal vein thrombus. (H. E. ×36)

C had the firmly encapsulated tumor which demonstrated expansive growth. Capsule formation appeared to become complete as tumor grew. High incidence of invasion of HCC extending through capsule was noted in group B (88.9%) and group C (69.2%), whereas, there was no evidence of capsule invasion in small HCC excluding one case with intracapsular invasion.

The presence of tumor thrombus in the portal vein was detected in 10 cases (31.3%) (Fig. 3), and satellite tumor adjacent to main mass was

found in four cases (12.5%). Their distribution was shown in Table 5. Small HCC were not associated with tumor thrombus and satellite tumor.

Operative Procedures

All tumors of 32 patients were surgically removed (Table 6). The operations were considered radical in all patients judged by intraoperative findings and postoperative US or CT. Right lobectomy was performed in two cases with precirrhosis and normal liver, respectively.

Table 5. Incidence of Portal Tumor Thrombus and Satellite Tumor

Tumor size	Tumor thrombus			Satellite tumor		
	-	+	Positive rate (%)	-	+	Positive rate (%)
<2 cm	11	0	0	11	0	0
2-3 cm	4	5	55.6	8	1	11.1
3-5 cm	8	5	38.5	10	3	23.1

Table 6. Surgical Procedures in 32 Patients with HCC

Method	No. of patients
Enucleation	2
Partial hepatic resection	7
Subsegmentectomy	12
Segmentectomy	
Posterior	1
lateral	8
right lobectomy	2
Total	32

Limitid hepatic resection which composed of enucleation and partial wedge resection was done in 12 cases with advanced cirrhosis. In recent 21 cases, segmental (Healey's segment) and subsegmental (Couinaud's segment) resections using intraoperative ultrasonography were carried out. In 15 of all cases (46.9%), less than one cm of liver parenchyma surrounding the tumor was removed.

Postoperative Morbidity and Mortality

Five patients had postoperative complications: hepatic failure, postoperative bleeding, postoperative ileus and right hemothorax, respectively. Two patients with right hemothorax were successfully treated by conservative methods, but two patients with postoperative bleeding and one with postoperative ileus died from hepatic failure within one month. Two patients died without discharge from hospital, within three months and four months, because of severe cirrhosis. The operative and in-hospital mortality rates were thus 9.4% and 6.3%, respectively.

Survival

Twenty-seven patients were discharged from hospital. At present, 17 patients are alive with no sign of cancer during the periods from seven months to nine years after operation. Six patients died of tumor recurrence and four from hepatic failure after discharge. Cumulative survival rate (Kaplan-Meier method) of three groups excluding three cases of operative death were shown in Fig. 4. Significant differences ($p < 0.05$) were seen among group A and group B and C, three years after surgery. The 3-year

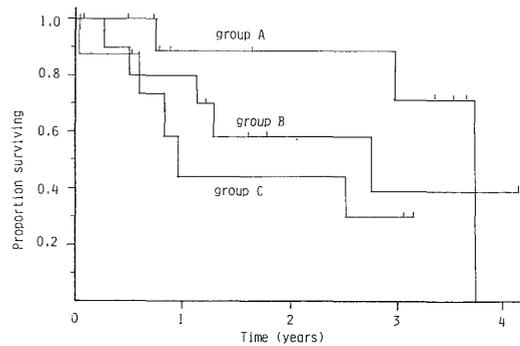


Fig. 4. Cumulative survival rates in 9 patients with small HCC (group A), 7 patients with HCC of 2–3 cm (group B) and 11 patients with HCC of 3–5 cm (group C).

survival rate was 71.7% in group A, 38.9% in group B and 30.0% in group C.

DISCUSSION

Recent advanced imaging modalities and serum AFP measurement in patients at risk made it possible to detect small hepatocellular carcinoma (HCC).^{9,10} This had led to the significant improvement in the management of cirrhotic patients with HCC.^{11,12} In our previous series,⁶ most of the patients have been admitted with tumor-associated symptoms as described by Berman's classification.¹³ In the current series (tumor less than 5cm in diameter), almost all patients had no symptoms or signs, and were diagnosed during periodic follow-up examination for their underlying liver disease. Serum AFP measurement has been the most frequently used screening test for the diagnosis of HCC, even in the group without symptoms.^{9,10} However, 53.1% of our patients had normal or slightly elevated AFP levels below 100ng/ml, and serum AFP levels were the first clue to diagnosis in only 35.7%. AFP levels below 400ng/ml were not specific for HCC, unless a progressive increase has been observed.¹⁴ Therefore, the utility of AFP measurement in the diagnosis of small HCC has some limitation. Serum HBsAg was detected in 31.3% of our patients. The patients with positive HBsAg are the most important high risk groups, but the frequency of positive test for HBsAg was low among the patients of HCC. The positive rates

of HCC in Japan series reported by The Liver Cancer Study Group of Japan was 34.1%.²⁾

In the present series, US, CT and angiography proved to be most useful in the diagnosis of asymptomatic patients. Of these diagnostic modalities available, US has had greater than 90% sensitivity of detection in small HCC, and also can evaluate pathological features of the tumor and its location. Almost all the small HCC were hypoechoic with some weak central echogenicity, reflecting the pathological features such as encapsulation and tumor parenchyma without necrosis. Angiography can provide useful information on the vascular supply of the tumor, and also can be utilized for the therapy of transcatheter embolization for tumor.¹⁵⁾ However, our five patients with tumors less than 3cm in diameter were not detected by angiography. These findings are assumed to reflect the pathological features of small HCC in which tumor encapsulation and vascularity of tumor were feasible. It was reported in Japan series that in 21 of 720 cases (2.9%) hepatic tumors were not visualized on arteriograms and the technical problems of angiography probably account for the non-visualization of these tumors.²⁾

In previous reports, we have identified several important pathological features of the tumor affecting the prognosis after surgery, even when the tumor is diagnosed at an early stage.¹⁶⁾ These include the size of the tumor, the finding of the portal vein tumor thrombus, the presence of satellite tumors, an adequate resection margin and tumor encapsulation. In the current series, we confirmed this fact by an analysis of many patients. In patients with tumor larger than 2cm in size, invasion of the small portal branches, or the presence of satellite tumors were frequently recognized with lower survival rates when compared to that of small HCC. The reported positive rates of several pathological factors of small HCC in large series in Japan were 47.1%-89% in tumor encapsulation, 67%-75% capsule invasion of tumor, 10%-22% portal tumor thrombus and 25%-35.3% satellite tumor.¹⁷⁻²⁰⁾

For hepatic resection of HCC, the important factors are these pathological features and the presence of coexisting cirrhosis. Standard major

liver resection is poorly tolerated in cirrhosis, because of impaired regeneration of residual liver tissues as the results of postoperative hepatic failure. In our previous series, the operative mortality in cirrhotic patients with major hepatectomy were 46.7%, and 75% of follow-up patients died from hepatic failure.⁶⁾ Therefore, in current series, we performed wedge resection or subsegmental resection which were described by MAKUUCHI *et al.*,¹¹⁾ with good results. We also recognized that, survival rates of small HCC were far better than that of the HCC larger than 2cm in diameter, even in the presence of several pathological factors affecting prognosis. It is to be emphasized that early detection of small HCC and an adequate hepatic resection such as subsegmentectomy or segmentectomy, quantitative evaluation of functional reserve of the liver in cirrhotic patients, are most important for the survival of the patients.

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