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Pathological study of small hepatocellular carcinoma: frequency of their invasion*

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Summary. We studied the pathological findings in 28 small hepatocellular carcinomas (less than 5 cm in diameter), especially the mode of invasion. Seventeen of the 28 lesions were encapsulated. Capsular invasion was present in 14 of the 17 encapsulated tumours. Vascular invasion was found in 12 of the 28 tumours. The small hepatocellular carcinoma, even when encapsulated, frequently invaded blood vessels and adjacent liver tissue. in spite of frequent vascular invasion, distant metastasis was seen in only 1 of the 28 tumours.

Key words: Small hepatocellular carcinoma – Hepatoma – Liver neoplasms – Pathology

Introduction

In recent years, because of progress in diagnostic procedures such as ultrasonography, computed tomography etc., small hepatocellular carcinomas have become detectable. It is essential for effective treatment of the tumour to investigate how hepatocellular carcinoma (HCC) grows in its early stages.

The term "small HCC" defines only the tumour's size and does not refer to an early stage of development. We must, however, note that small HCCs may include not only HCCs in their early stages, but also some slow growing HCCs that have a better prognosis than others. In the present study, we define "small HCC" as an HCC whose maximum diameter is less than 5 cm in a solitary tumour, or one whose maximum diameter is less than 4 cm in a case having some daughter nodules.

Materials

For the current study we investigated 21 HCCs from 20 autopsy cases and 7 hepatectomy cases in Osaka University Hospital. Four HCCs between 4 and 5 cm in maximum diameter

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Table 1. HBs-antigen and α-fetoprotein in small HCCs

	HBs-antigen (+)	α-Fetoprotein (>200 ng/ml)
Autopsy cases	2/18	5/18
Hepatectomy cases	2/6	2/6

Table 2. Associated liver disease in small HCCs

	No. of patients	Liver cirrhosis			
		Micro-nodular	Macro-nodular	Incomplete septal	Mixed macronodular and micronodular
Autopsy cases	20	5	12	1	2
Hepatectomy cases	7	2	1	3	1

showing no macroscopic daughter nodules (but which were proven microscopically to have daughter nodules) were included. One autopsy case had 2 HCCs, each which existed as a solitary tumour in each lobe of the liver and had different histological patterns. They appeared to be multi-centric, so we treated them as isolated tumours.

In the two hepatectomy cases, pre-operative transcatheter intra-arterial chemotherapy with Adriamycin (Doxorubicin) or Mytomycin C was given; in the remaining 5 hepatectomy cases no pre-operative therapy was given. Embolization therapy was not used. In most of the autopsy cases HCCs were not diagnosed clinically, most of the patients had died from advanced liver cirrhosis or its fatal complications and HCC was detected incidentally at autopsy.

The autopsy cases consisted of 16 males and 4 females, of ages between 40 and 77 years (mean age of 59). The hepatectomy cases consisted of 5 males and 2 females, ages between 42 and 71 years (mean age of 55).

HBs-antigen (Table 1) was positive in 2 of the 18 autopsy cases and 2 of the 6 hepatectomy cases tested. Serum α-fetoprotein levels higher than 200 ng/ml (Table 1) were seen in 5 of the 18 autopsy cases and 2 of the 6 hepatectomy cases tested.

All cases were associated with liver cirrhosis. According to the classification by the working group sponsored by the WHO (Anthony et al. 1978) in the autopsy cases (Table 2) there are 12 cases of micronodular liver cirrhosis, 5 cases of macronodular liver cirrhosis, 1 case of incomplete septal liver cirrhosis, and 2 cases of mixed macronodular and micronodular liver cirrhosis. The livers weighed between 500 g and 1,700 g (mean of 938 g). In the hepatectomy cases, there were 2 cases of micronodular liver cirrhosis, 1 case of macronodular liver cirrhosis, 3 cases of incomplete septal liver cirrhosis, and 1 case of mixed macronodular and micronodular liver cirrhosis. The fibrous septa in the autopsy cases were thicker than those in hepatectomy cases. The autopsy cases, as a matter of course, showed more advanced liver cirrhosis than the hepatectomy cases.

Methods

In 7 of the autopsy cases and in all 7 of the hepatectomy cases we sliced the liver into thicknesses of about 5 mm (Fig. 1). After macroscopic observation, all of the slices that contained tumours were fixed in 10% formalin and stained with Haematoxylin & Eosin, Azan-Mallory, and Orcein. in the remaining 14 autopsy cases, we reviewed only file specimens.

Results

According to Eggel's classification (1901) the macroscopic appearance of the tumours was nodular in all of the autopsy and hepatectomy cases.

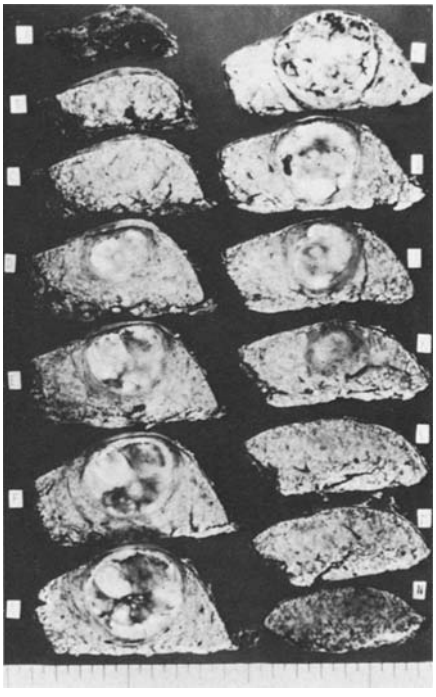

Fig. 1. Cross-sections of a small HCC in 5 mm thicknesses. The tumour is encapsulated and 4.5 cm in maximum diameter

Table 3. Histologic types of small HCCs

	No. of tumours	Trabecular type	Pseudoglandular type	Clear cell type
Autopsy cases	21	19	1	1
Hepatectomy cases	7	5	1	1

Table 4. Differentiation of small HCCs

	No. of tumours	Edmondson's grade			
		I	II	III	IV
Autopsy cases	21	4	14	3	0
Hepatectomy cases	7	0	6	1	0

The predominant histological types (Table 3) in the autopsy cases were: 19 trabecular, 1 pseudoglandular, and 1 clear cell type. In the hepatectomy cases there were 5 trabecular, 1 pseudoglandular, and 1 clear cell type. According to Edmondson and Steiner's classification (1954), the grades of tumour differentiation (Table 4) (classified as the predominant type) were: 4 grade I, 14 grade II, and 3 grade III in the autopsy cases. In the hepatectomy cases there were 6 grade II and 1 grade III.

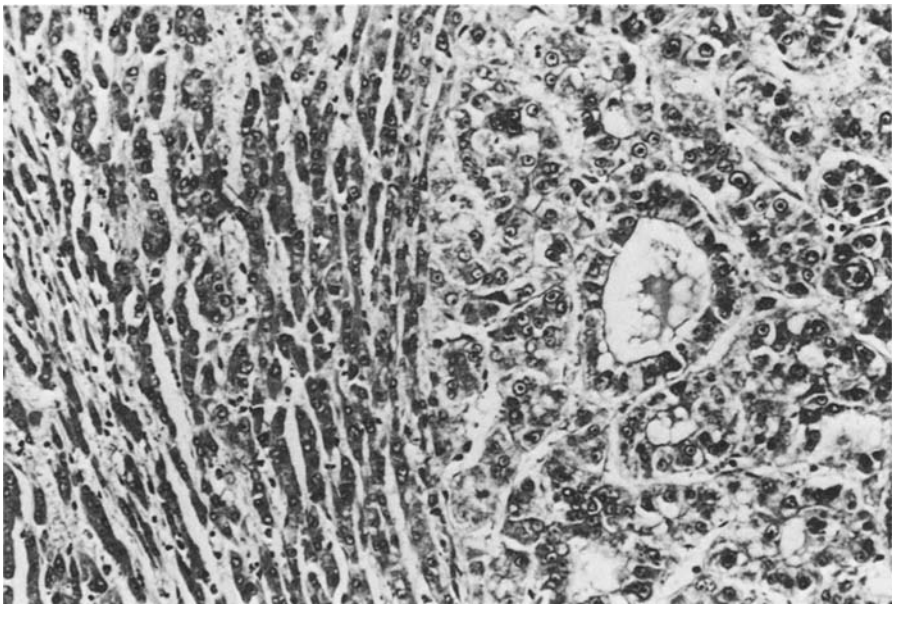

Fig. 2. Pseudoglandular HCC showing expanding growth without capsule. (H & E, ×175)

Table 5. Autopsy cases of small HCCs and their invasion

Case no.	Maximum diameter of tumour	Capsule	Invasion into blood vessel				Intracapsular invasion	Extracapsular invasion	Daughter nodule
			Intracapsular blood vessel	Portal vein		Hepatic vein			
				microscopic	macroscopic				
1	0.3	−		−	−				−
2	0.5	−		−	−	−			−
3	0.8	−		−	−	−			−
4	1.0	−		−	−	−			−
5	1.0	−		−	−	−			−
6	1.5	+	−	−	−	−	−	−	−
7	1.0	−		−	−	−			−
	2.0	−		−	−	−			−
8	2.0	−		−	−	−			−
9*	2.0	+	+	−	−	−	+	+	+
10*	2.0	+	−	−	−	−	+	−	−
11*	2.0	+	−	−	−	−	−	−	−
12*	2.0	+	−	−	−	−	+	−	−
13*	3.0	+	+	−	−	−	+	−	−
14*	3.0	+	−	−	−	−	−	−	−
15	3.0	+	+	−	−	−	+	−	−
16	4.0	+	−	−	−	−	+	−	+
17	4.0	−		+	−	+			+
18*	4.5	+	+	−	+	−	+	−	+
19	5.0	+	−	+	−	−	+	−	+
20	5.0	−		+	−	−			+

*; Cases investigated with 5 mm serial sections

Table 6. Hepatectomy cases of small HCCs and their invasion

Case no.	Maximum diameter of tumour	Capsule	Invasion into blood vessel				Intra-capsular invasion	Extra-capsular invasion	Daughter nodule
			Intra-capsular blood vessel	Portal vein		Hepatic vein			
				microscopic	macroscopic				
1	1.0	+	−	+	−	−	+*	−	+
2	2.3	+	−	−	−	−	+	−	−
3	3.0	+	+	−	−	−	+	+	+
4	3.5	−		−	−	−			−
5	3.5	+	−	+	−	−	+	−	−
6	4.3	+	−	+	−	−	+	+	+
7	4.5	+	+	+	−	−	+	+	−

*; necrotic

Table 7. Frequency of invasion of small HCCs

	Autopsy	Hepatectomy	Total
Intra-capsular invasion	8/11	6/6	14/17
Vascular invasion	7/21	5/7	12/28
Intra-capsular blood vessel	4/11	2/6	6/17
Portal vein (microscopic)	3/21	4/7	7/28
Portal vein (macroscopic)	1/21	0/7	1/28
Hepatic vein	1/21	0/7	1/28
Extra-capsular invasion	1/11	3/6	4/17
Daughter nodule	6/21	3/7	9/28
Intrahepatic metastasis	0/21	0/7	0/28
Extrahepatic metastasis	1/21	0/7	1/28

All of the cases showed expanding growth macroscopically and either replacing growth (Fig. 2) or encapsulation, microscopically. Encapsulated tumours were found in 17 of the 28 cases. In the 21 autopsy cases, 11 tumours were almost entirely encapsulated. In the 7 hepatectomy cases 6 tumours were almost entirely encapsulated.

Invasion and metastasis are summarized in Table 5, 6 and 7. For the definition of daughter nodule (Fig. 3) we refer to Sakurai et al. (1984), "When small tumor nodules were present around the main tumor, we considered these to be daughter nodules. Some were attached and some were located in close proximity". The daughter nodule is clinically significantly different from the distant intrahepatic metastasis. The former is surgically resectable and the latter is not. We designate capsular invasion confined to the inside of a capsule as intra-capsular invasion (Fig. 4), and capsular invasion reaching the outside of a capsule as extra-capsular invasion (Fig. 5).

Vascular invasion was observed in 7 of the 21 autopsy cases. Specifically, there was intra-capsular blood vessel invasion (Fig. 6) in 3 cases; portal vein (microscopic) invasion (Fig. 7) in 2 cases; intra-capsular blood vessel and portal vein (macroscopic) invasion in 1 case; and portal vein (micro-

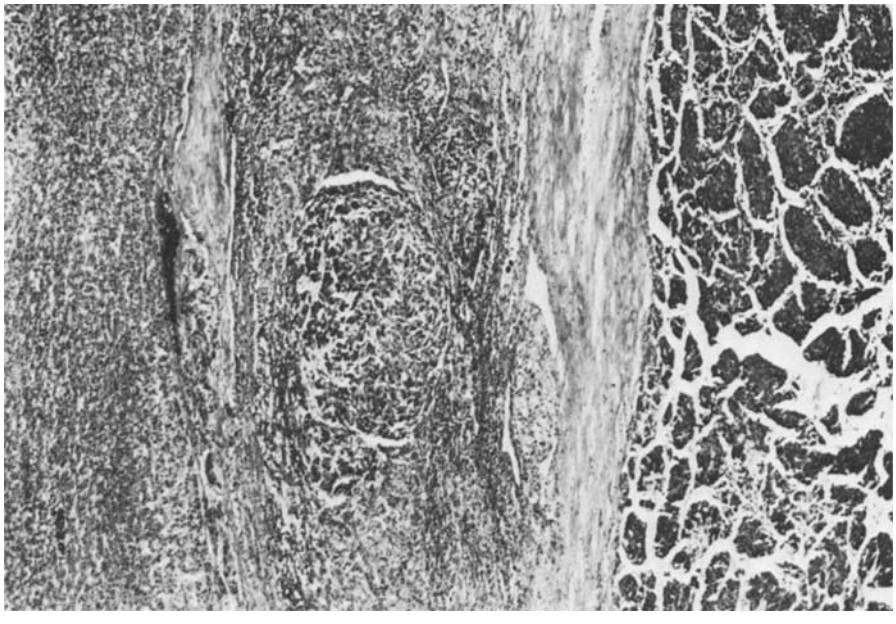

Fig. 3. Daughter nodule (∅ 1 mm) outside of a tumour capsule. (H & E, ×40)

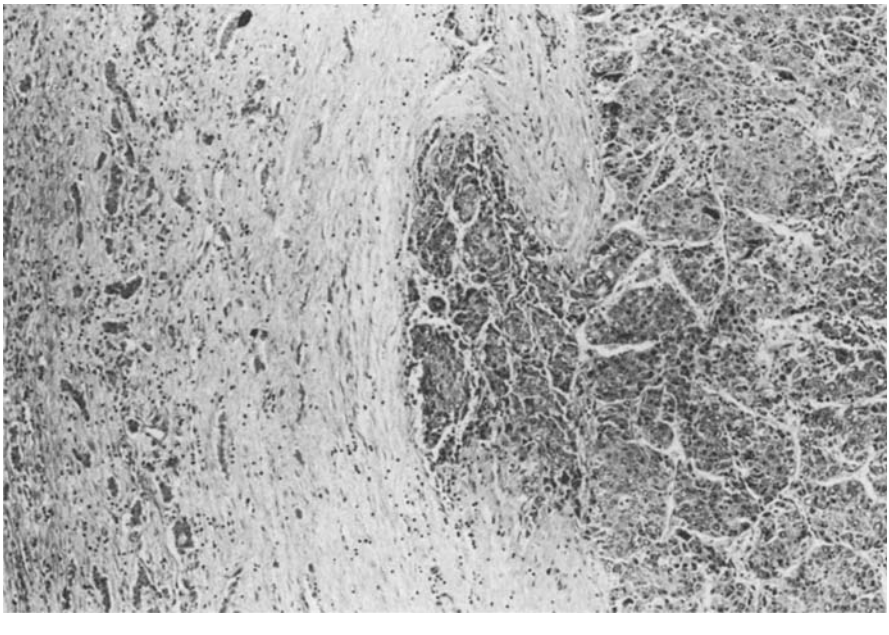

Fig. 4. Intra-capsular invasion limited in a capsule. (H & E, ×70)

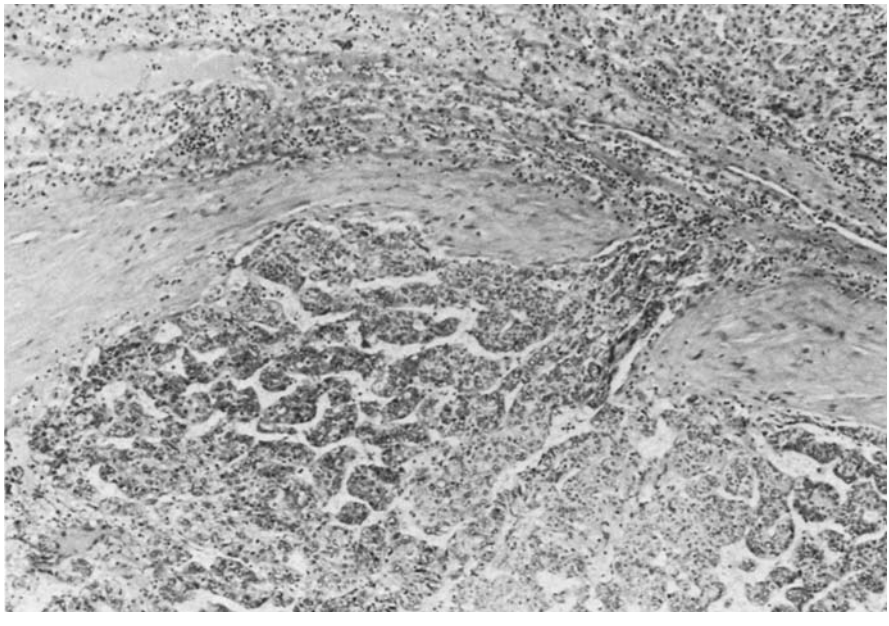

Fig. 5. Extra-capsular invasion permeating a capsule. (H & E, × 70)

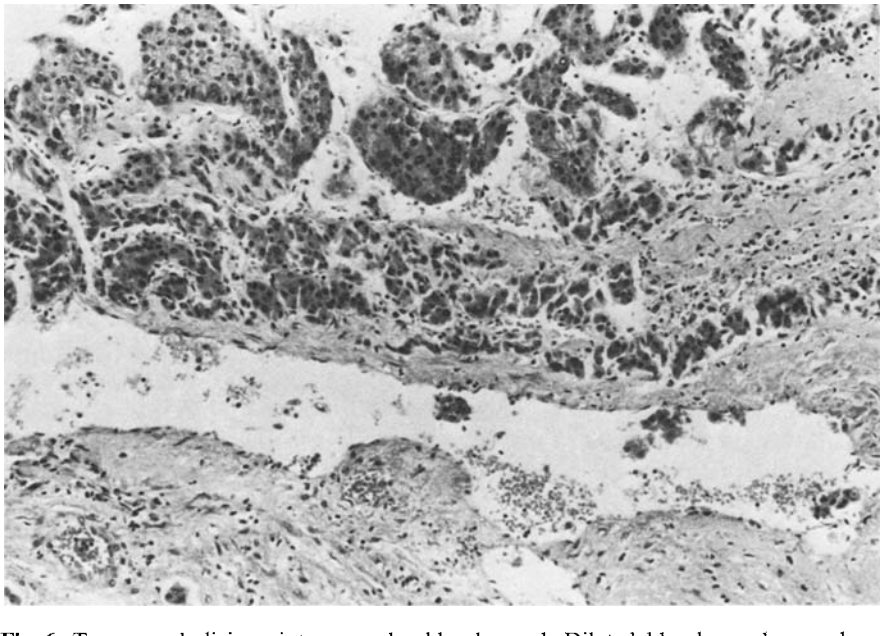

Fig. 6. Tumor emboli in a intra-capsular blood vessel. Dilated blood vessels are abundant in the capsules of the HCCs. (H & E, × 90)

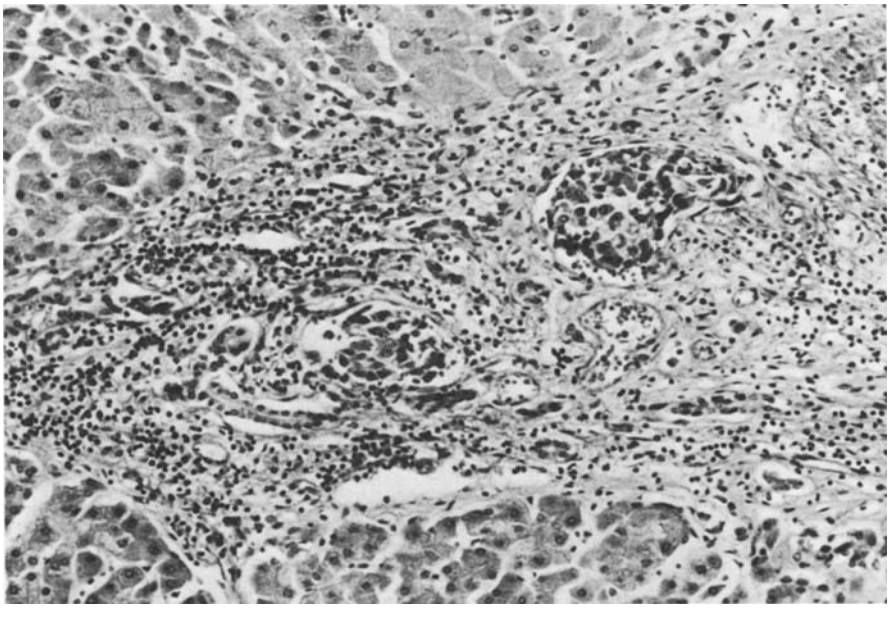

Fig. 7. Tumour emboli in the portal vein. (H & E, ×175)

scopic) and hepatic vein (macroscopic) invasion in 1 case. Intra-capsular blood vessels are considered to be a part of the portal vein, but this has not been proven satisfactorily. We therefore treat them separately. In hepatectomy cases, vascular invasion was found in 5 of the 7 cases. Specifically, there were intra-capsular blood vessel invasion in 1 case; portal vein (microscopic) invasion in 3 cases; and intra-capsular blood vessel and portal vein (microscopic) invasion in 1 case. There was no macroscopic tumour embolus in the portal vein in the hepatectomy cases.

Intra-capsular invasion was seen in 8 of the 11 encapsulated tumours in the autopsy cases and in all 6 of the encapsulated tumours of the hepatectomy cases.

Extra-capsular invasion (Fig. 5) was observed in 1 of the 11 encapsulated tumours of the autopsy cases, and 3 of the 6 encapsulated tumours of the hepatectomy cases. Daughter nodules (Fig. 3) were found in 6 autopsy cases and 3 hepatectomy cases. Metastasis was found in one autopsy case. This case was a tumour of 4 cm maximum diameter, that had a tumour embolus which reached the right atrium via the hepatic vein and then caused multiple pulmonary metastasis.

Discussion

Small HCCs can be regarded as an early stage of HCCs. They must, however, include some slow growing HCCs which may have more chance of

being detected during the time they remain small. Yoshida et al. (1982) reported one case of minute HCC without an appreciable change in size for seven years, but slow growing HCCs can also be of large size. Wakasa (1984) reported one case of slow growing HCC whose maximum diameter was 24 cm. Chen et al. (1984) estimated median doubling time of minute HCCs to be 60–75 days (range 30–223 days).

According to Okuda and the Liver Cancer Study Group of Japan (1980), the mean age is 55.5 years for HCC in Japan. In this study, the mean age was 55 years in the hepatectomy cases, and 59 years in the autopsy cases.

The frequency of positive serum HBs-antigen in HCC is 40.7% (266 out of 654 cases) in Japan (Okuda and the Liver Cancer Study Group of Japan 1980). It varied from 8% (Okuda et al. 1977b) to 38% (Yamasaki et al. 1981) in small HCCs. The cases of minute HCC in Okuda's report consisted of autopsy cases whose tumour sizes were less than 4.5 cm; the cases in Yamasaki's report were hepatectomy cases whose tumour sizes were less than 5 cm. In this study, the frequency is 11% in the autopsy cases and 33% in the hepatectomy cases.

The frequency of positive qualitative tests for α-fetoprotein in HCC was 72.5% (220 out of 304 cases); and the frequency of α-fetoprotein titre above 200 ng/ml by a quantitative test was 77.6% (Okuda and the Liver Cancer Study Group of Japan 1980). The frequency of a high α-fetoprotein titre in minute HCC has varied in previous reports (Watanabe et al. 1984; Shinagawa et al. 1984), and seems to depend on the screening method employed. Generally speaking, in the majority of small HCCs, serum α-fetoprotein is low and not diagnostic. Other examinations, especially by ultrasonography (Shinagawa et al. 1984) and computed tomography, are essential for a follow up in chronic liver disease cases.

The smallest encapsulated HCC was 1 cm in maximum diameter. This tumour, however, was necrotic, and the capsule may have been granulation caused by necrosis, which is thought to be an effect of chemotherapy. The second smallest encapsulated tumour was 1.5 cm in maximum diameter, and showed a thick fibrous capsule of 1 mm thickness. In this study, the smaller the small HCC was, the less tendency there was for encapsulation. If we separate the HCCs into two groups with diameter above or below 2 cm (Table 8) in the 14 tumours of the smaller group ($\leq$2 cm), 6 are encapsulated; and in 14 tumours in the larger group (>2 cm), 11 are encapsulated.

Table 8. Comparison of encapsulation and vascular invasion frequency between the smaller group (diam. $\leq$2 cm) and the larger group (diam. >2 cm)

Tumour size	Encapsulation	Vascular invasion
$\leq$2 cm	6/14	2/14
>2 cm	11/14	10/14

There is no tendency for the capsules to become thicker as the HCCs grow larger.

The small HCCs invaded the adjacent liver tissue and blood vessels with a significantly high frequency. Even when there was a capsule this seemed not to be a barrier against such invasion. Capsular invasion was frequent in the encapsulated autopsy and hepatectomy cases. Vascular invaison was seen in 5 of the 11 encapsulated tumours in the autopsy cases and 5 of the 6 encapsulated tumours in the hepatectomy cases. Of these, invasion into intra-capsular blood vessels was most frequent. Daughter nodules were seen in 4 of the 11 encapsulated tumours in the autopsy cases and 3 of the 6 encapsulated tumours in the hepatectomy cases. Encapsulated HCCs frequently invade intra-capsular blood vessels and extra-capsular blood vessels, and permeate the capsules to make daughter nodules. In this study, it was impossible to compare frequency of invasion between the encapsulated HCCs and the nonencapsulated HCCs because of the difference in their sizes and the limited number of cases.

In this study, the smaller the small HCC was the less tendency it showed for vascular invasion. In the 14 tumours of the smaller group ($\leqq 2$ cm), 2 show vascular invasion; in the 14 tumours of the larger group (>2 cm), 10 show vascular invasion (Table 8). One tumour of 1.0 cm diameter, however, invaded blood vessels.

It has been reported in previous papers (Okuda et al. 1977a; Chen et al. 1982) that small HCCs were often encapsulated and infrequently showed vascular invasion. However, Yamasaki et al. (1981) reported that invasion into the portal vein was seen in 20 of 27 hepatectomy cases of small hepatoma, including one cholangiocarcinoma. Kondo et al. (1983) reported that in 8 cases of small HCC (less than 3.5 cm in diameter) capsular invasion was seen in 7 of 9 tumours; and vascular invasion was seen in 5 of 10. Nakashima et al. (1983) referred to the possibility of early spread via the portal vein system in small HCC.

According to Anthony (1973), in spite of a high frequency of vascular invasion in HCCs, there are many cases having no metastasis. This tendency is more prominent in small HCC cases. One possible explanation is that the HCC more frequently invades the portal vein than the hepatic vein, and the portal vein is an afferent vessel but not an efferent vessel for the liver. If tumour invasion is limited to the periphery of the portal vein, metastasis may be limited to sites around the main tumor. In the present study there was only one case showing distant metastasis, which had a tumour embolus in the hepatic vein. Multi-centric origin was seen in only one case, the others did not display metastasis or distant intrahepatic metastasis. Lymphatic metastasis was not observed. Invasion and metastasis was limited to areas around the main tumour. Accordingly, limited resection of the tumour is a sufficient procedure for most small HCCs. In functional terms a limited resection is favorable, because small HCC frequently complicates advanced liver cirrhosis (Yequin et al. 1980; Tuzuki et al. 1984). After careful examination of autopsy cases advanced liver cirrhosis was complicated by small HCC in an estimated 9% of cases (Köhn 1956).

Sakurai et al. (1984) reported effective clinical results and the pathological findings of transcatheter chemo-embolization through a combination of intra-arterial chemotherapy plus intra arterial embolization of Gelfoam. That makes some main tumours and areas of intra-capsular invasion necrotic and seems to reduce vascular invasion. Multi-disciplinary treatment combining chemotherapy, embolization, and surgical resection is essential to eradicate the small HCC.

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