

Rationale of Surgical Management for Recurrent Hepatocellular Carcinoma

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From 1979 to 1991, 100 patients with hepatocellular carcinoma (HCC) underwent a curative hepatic resection in our institution. Five patients died within 1 month, and four patients died after longer than 1 month hospitalization. The remaining 91 patients were closely followed. Intrahepatic recurrences became obvious in 36 (40%) of these 91 patients during the follow-up period. Second operation was carried out on 22 patients, and the re-extirpation of HCCs was performed on 16 patients. Pure ethanol injection into the tumor associated with implantation of the Infuse-A-Port (Infusaid Inc., Norwood, MA) for intra-arterial infusion of anti-cancer agents was performed on the remaining six patients. Of these 22 patients, 15 are still alive, eight being free of HCC and seven with the disease, for 13 to 92 months after the first operation. The cumulative survival rate of 22 patients with repeated operations was significantly better than that of 14 patients who were treated conservatively ($p < 0.05$). The adequate surgical management of recurrent HCC is considered as most important in achieving better prognosis of HCC.

Hepatocellular carcinoma (HCC) is a common disease in Asian countries and is highly malignant in terms of prognosis. Recent advances in various diagnostic modalities made it possible to detect HCC in earlier phase, which resulted in an increase of patients receiving hepatic resection.¹⁻³ Long-term outlook after the hepatectomy for HCC, however, is not yet satisfactory, mainly because of high incidence of intrahepatic recurrence.

Hepatocellular carcinomas are known to invade the portal vein, and therefore spread easily to the entire liver.⁴ Conversely, the metachronous multicentric carcinogenesis (second primary lesion) also is considered as a frequent cause of intrahepatic recurrence after the hepatectomy. In any case, intrahepatic recurrence is the major cause of death in patients who underwent hepatectomy for HCC.

The surgical treatment of recurrent HCC is usually more arduous than that of primary HCC because of re-

duced hepatic functional reserve and technical difficulties. Nonetheless, repeated operations should be considered in patients with recurrent HCC because conservative treatment usually fail. In the current study, we have investigated the role of repeated operations, including hepatectomy for the recurrent HCC in the residual liver after the resection of the primary lesion, showing a usefulness of aggressive surgical policy.

MATERIALS AND METHODS

One hundred eight hepatic resections for primary HCC were performed from March 1979 to December 1991 at the Surgical Department of Otemae Hospital. One hundred resections were curative, but the other eight were only palliative. Curative resection is defined here as macroscopically complete removal of the tumor tissue. Among 100 patients who underwent curative hepatic resections, five died within 1 month after operation and four died in the hospital later than 1 month. The remaining 91 patients had been closely followed at our outpatient clinic. Serum α -fetoprotein level was measured every 2 months, and ultrasonography was per-

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Accepted for publication April 6, 1992.

Table 1. CLINICAL DATA FOR 22 PATIENTS WHO UNDERWENT REPEAT OPERATIONS FOR RECURRENT HEPATOCELLULAR CARCINOMA

Patient No.	Sex	Age	First Operation	Disease-free Interval (mos)	Repeated Hepatic Resection		Survival Time (mos)
					Second Operation	Third Operation	
1	M	61	Subsegmentectomy	80	El + IP	—	92, alive with disease
2	M	68	Subsegmentectomy	24	Subsegmentectomy	Wedge resection	58, dead
3	M	69	Subsegmentectomy	17	Subsegmentectomy	—	41, dead
4	M	60	Subsegmentectomy	24	El + IP	—	74, alive with disease
5	F	58	Left lobectomy	39	Subsegmentectomy	—	74, alive free of disease
6	M	60	Segmentectomy	21	Wedge resection	—	42, dead
7	M	55	Subsegmentectomy	37	El + IP	—	68, alive with disease
8	M	68	Wedge resection	31	Segmentectomy	Subsegmentectomy	49, dead
9	M	59	Subsegmentectomy	52	El + IP	—	63, alive with disease
10	M	67	Wedge resection	19	Wedge resection	—	26, dead
11	M	74	Subsegmentectomy	53	Subsegmentectomy	—	58, alive free of disease
12	M	64	Subsegmentectomy	13	El + IP	—	26, dead
13	M	72	Subsegmentectomy	15	El + IP	—	37, dead
14	M	55	Wedge resection	38	Right lobectomy	—	46, alive free of disease
15	M	74	Segmentectomy	12	Subsegmentectomy	Subsegmentectomy	45, alive free of disease
16	M	60	Subsegmentectomy	28	Segmentectomy	—	43, alive with disease
17	M	60	Segmentectomy	13	Wedge resection	—	38, alive with disease
18	M	39	Right lobectomy	16	Segmentectomy	—	31, alive free of disease
19	M	60	Subsegmentectomy	12	Subsegmentectomy	—	23, alive free of disease
20	F	68	Subsegmentectomy	9	Subsegmentectomy	—	18, alive free of disease
21	M	54	Subsegmentectomy	2	Wedge resection	Segmentectomy	13, alive free of disease
22	F	79	Segmentectomy	17	Wedge resection	—	18, alive with disease

El + IP, ethanol injection + implantation of a port.

formed every 3 months for the early detection of recurrence. Computed tomography also was done at least once a year. When the recurrence of HCC was suspected, angiography and the enhanced ultrasonography (EU)⁵ with carbon dioxide (CO₂) microbubbles injected into the hepatic artery were added for confirmation. The follow-up period of 91 surviving patients ranged from 1 to 112 months (mean, 31.6 months).

During the follow-up period, 36 patients developed recurrent HCCs in the liver remnant 2 to 81 months (mean, 23.0 months) after the initial hepatectomy. Twenty-two of the 36 patients underwent the second operation and 16 patients of them underwent the hepatic resection (Table 1). There were 19 men and three women, with a mean age of 62.9 years at the time of the second operation (range, 39 to 79 years). All the patients who underwent the second operations had underlying liver cirrhosis. At the first hepatic resection, lobectomies were performed on two patients, segmentectomies on four patients, and partial hepatic resections on 16 patients. At the second hepatic resection, lobectomy was performed on one patient, segmentectomies on three patients, and partial hepatic resections on 12 patients. Second hepatectomies were curative in 13 patients and palliative in the remaining three. Third hepatectomies,

including one segmentectomy and three partial hepatectomies, were performed on four patients. Rehepatectomy was not performed on six patients who underwent the second operation; all of them received injection of pure ethanol into the tumor combined with placement of the catheter of a totally implantable drug delivery systems, Infuse-A-Port (Infusaid Inc., Norwood, MA), into the hepatic artery for intra-arterial infusion, followed by intermittent chemotherapy every 2 weeks.

The second operation was not performed on 14 patients with intrahepatic recurrent HCCs. Nine of them were men, and five were women, with a mean age of 57.8 years (range, 42 to 78 years). The reasons why the second operation was not carried out were as follows: multiple recurrence in the liver in 11; simultaneous extrahepatic recurrence in one; and two patients rejected the second operation. Ten of these patients were treated by various methods. Hepatic arterial embolization with or without intra-arterial infusion of oily contrast medium (Lipiodol, Cedex, France) combined with doxorubicin and mitomycin C was performed on nine patients. Only intra-arterial bolus infusion of doxorubicin and mitomycin C was performed on one patient. Four patients received no specific anti-cancer therapy.

Student's t test, chi square test, and Fisher's exact

Table 2. NUMBER OF INTRAHEPATIC METASTASES AND SECOND OPERATION

Second Operation	No. of Patients	No. of Tumors	
		Solitary	Multiple
Yes	22	11	11
No	14	2	12

method were used for statistical analysis. Survival curves of patients experiencing recurrence were obtained using the Kaplan-Meier method, and survival curves were compared by the log-rank test and the generalized Wilcoxon test. A value of $p < 0.05$ was defined as statistically significant.

RESULTS

Disease-free Interval

Disease-free intervals (Table 1) of 22 patients who underwent the second operation for intrahepatic recurrence of HCC were 793 ± 541 days (mean \pm SD, ranging from 78 to 2417 days), whereas those of 14 patients without the second operation were 514 ± 459 days (ranging from 47 to 1788 days). The former group tended to have a longer disease-free interval than the latter. There was, however, no statistically significant difference between the two groups.

Number of Intrahepatic Recurrence and Second Operation

Intrahepatic recurrence of HCC was observed in 36 (40%) of 91 patients who underwent the curative hepatic resection during the follow-up period. Thirteen (36%) of 36 intrahepatic recurrence were solitary, and the remaining 23 were multiple (Table 2). Of the 22 patients who underwent the second operation, 11 (50%) had solitary intrahepatic recurrence, and the remaining 11 (50%) had multiple recurrence. Twelve (86%) of 14 patients who did not undergo the second operation had multiple intrahepatic recurrence. There was a statistically significant difference in the frequency of multiple recurrence between the two groups ($p < 0.05$).

Morbidity and Mortality Rates

Two patients had postoperative complications; one developed hepatic failure (case 12) and the other bacterial peritonitis (case 16). Both patients were treated conservatively with good success. No patients died within 1

month after the second hepatic resection, and all patients could leave the hospital.

Survival

Fifteen patients are alive, eight being free of tumors and seven with tumors, for 13 to 92 months after the first hepatic resection. Of the seven patients with tumors, six had hepatic tumors and two had lung metastasis. Seven patients have died, five due to HCC, one due to pneumonia and another one due to hepatic failure. Of the four patients who underwent the third hepatic resection, two are still alive, being free of tumors (Table 1). Figure 1 shows the cumulative survival curves after the first operation of 22 patients who underwent the second operation and 14 patients without the second operation for intrahepatic recurrent tumors. In the group of second operation, the survival rate at 1, 3, 5, and 7 years were 100.0%, 83.0%, 51.2%, and 51.2%, and in the other group without the second operation 1-, 3-, 5-, and 7-year survival rate were 78.6%, 48.2%, 48.2%, and 0.0%, respectively. The survival rate of the former group was significantly better than that of the latter group ($p < 0.05$: log-rank test). The survival rate at 1, 2, and 3 years after the diagnosis of recurrence of the former group were 92.9%, 42.9%, and 21.4%, and in the latter group that were 37.6%, 28.2% and 18.8%, respectively. The difference of survival rate of two groups was also statistically significant ($p < 0.05$: generalized Wilcoxon test).

CASE REPORT

A 74-year-old man (case 15) was diagnosed as having chronic hepatitis on the occasion of ophthalmologic sur-

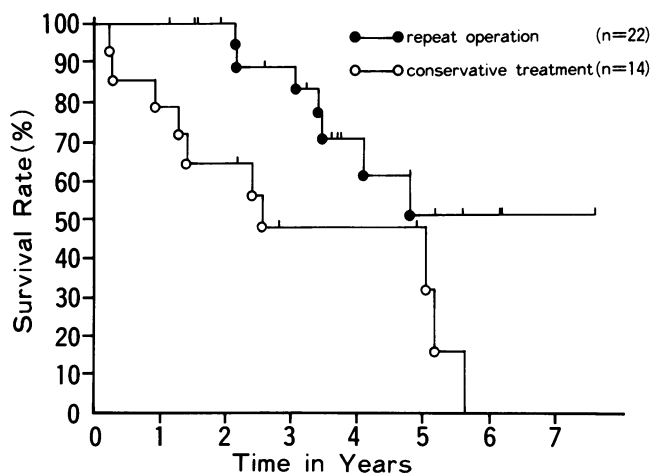


Figure 1. Cumulative survival curves for recurrent hepatocellular carcinoma after the first hepatic resection in 22 patients receiving the repeated operation (group 1, ●) and 14 patients without the repeated operation (group 2, ○). The survival rate of group 1 was significantly better than that of group 2 ($p < 0.05$).

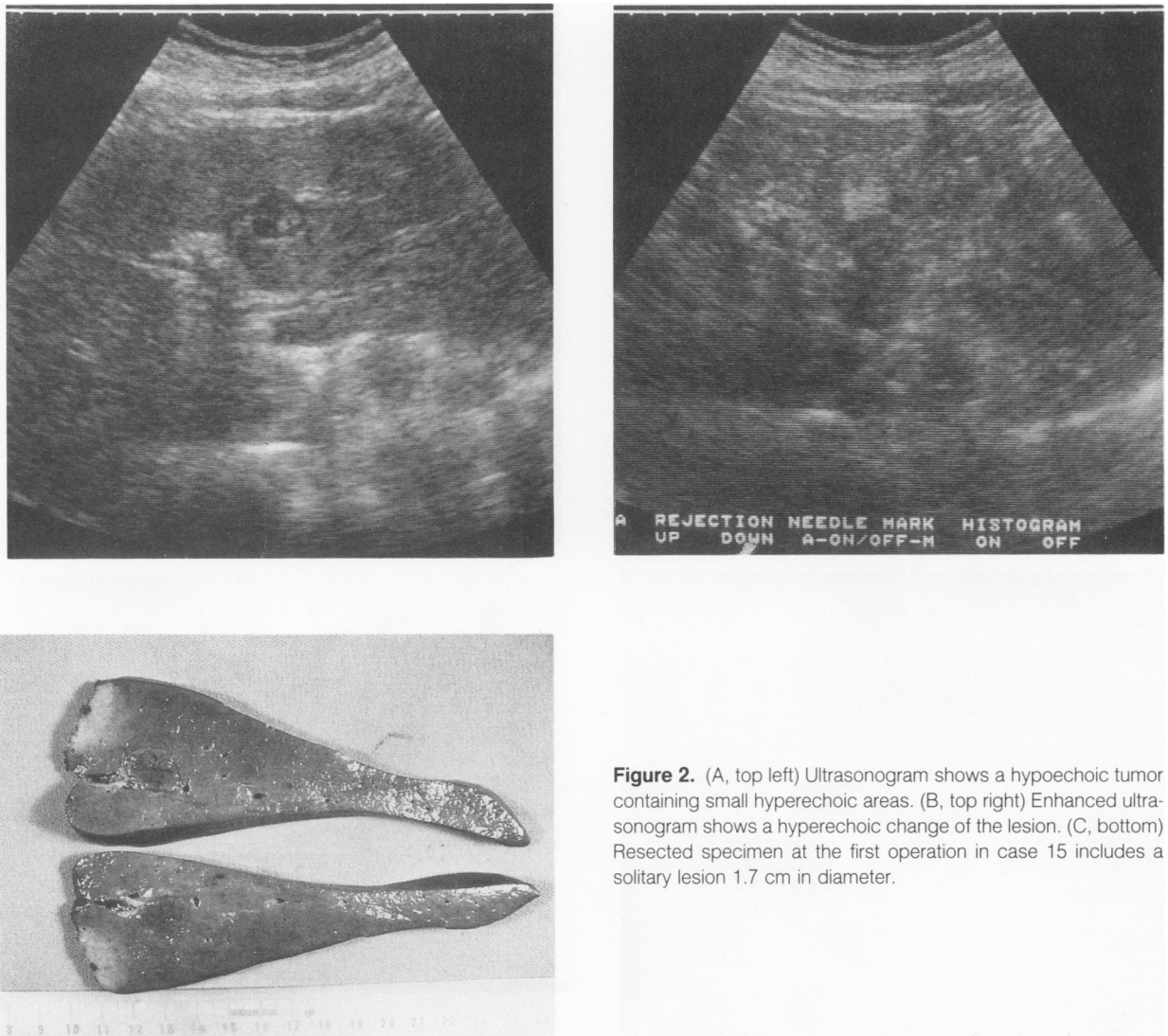


Figure 2. (A, top left) Ultrasonogram shows a hypoechoic tumor containing small hyperechoic areas. (B, top right) Enhanced ultrasonogram shows a hyperechoic change of the lesion. (C, bottom) Resected specimen at the first operation in case 15 includes a solitary lesion 1.7 cm in diameter.

gery. By the routine ultrasonic examination of the liver, a small HCC sized 1.5 cm in diameter was demonstrated in the Couinaud's segment 3 (Fig. 2A). Neither computed tomography nor angiography could detect the tiny lesion, but the EU clearly demonstrated the corresponding tumor as a hyperechoic changed lesion (Fig. 2B). There was no elevation of α -fetoprotein titer. Left lateral segmentectomy was performed. The resected specimen (Fig. 2C) showed a minute HCC sized 1.7 cm in diameter. One year later, the second lesion was discovered in the segment 5 by the follow-up study using the ultrasonic examination (Fig. 3A). This second lesion sized 1.7 cm in diameter was again a tiny lesion demonstrated as a hypervascular lesion by angiography (Fig. 3C) and as a hyperechoic changed lesion by EU (Fig. 3B). Subsegmentectomy was performed at the second operation, and a minute solitary lesion was resected (Fig. 3D). The third lesion, sized 2.0 cm in diameter, was discovered by the ultrasonic examination 6 months after the second

operation (Fig. 4A). This lesion was demonstrated as a hyperechoic changed lesion by EU (Fig. 4B), located in segment 8, but not shown by the angiography and CT. Subsegmentectomy was performed again at the third operation without any complications, and a small solitary lesion was resected (Fig. 4C). This patient is now still alive and free of tumors for 45 months after the first operation. The manner of recurrence of HCC in this patient strongly argues that the metachronous multicentric carcinogenesis should be considered as a frequent cause of intrahepatic recurrence of HCC.

DISCUSSION

Recent advances of surgical techniques and sophisticated postoperative cares have enabled patients with HCC to receive hepatectomy more safely, although they frequently have liver cirrhosis. Currently, the operative mortality rates have been reduced to a few per cent.^{6,7}

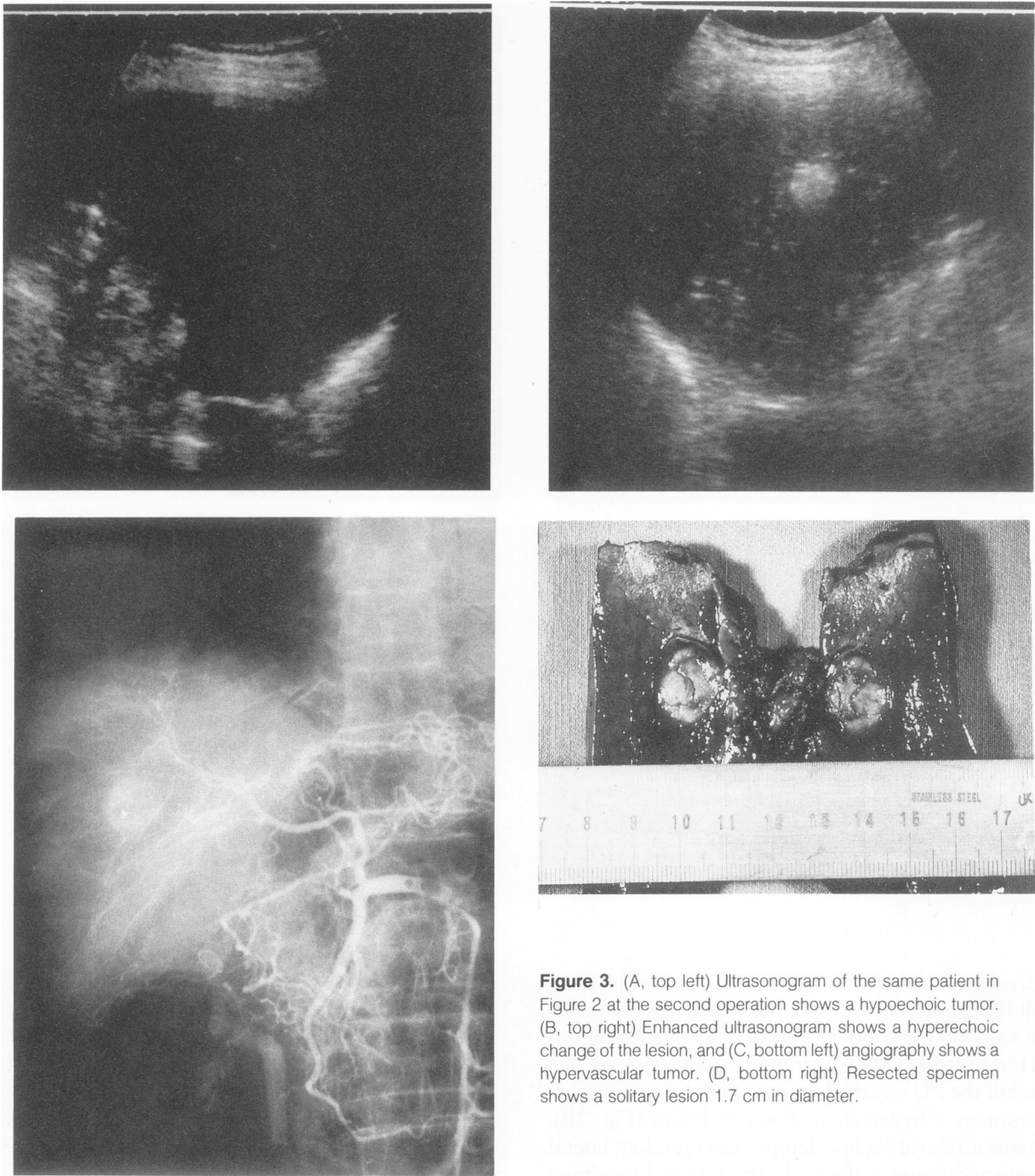


Figure 3. (A, top left) Ultrasonogram of the same patient in Figure 2 at the second operation shows a hypoechoic tumor. (B, top right) Enhanced ultrasonogram shows a hyperechoic change of the lesion, and (C, bottom left) angiography shows a hypervascular tumor. (D, bottom right) Resected specimen shows a solitary lesion 1.7 cm in diameter.

However, long-term results after the hepatectomy for HCC are not yet satisfactory. Most authors have reported a 5-year survival rate of nearly 30%.⁷⁻¹¹ Most causes of deaths after the hepatectomy for HCC are intrahepatic recurrence, far more frequent than the hepatic failure, the variceal hemorrhage or other gastrointestinal tract bleeding resulting from the liver cirrhosis. Recurrences after the extirpation of HCC are not uncommon, particularly in the remnant liver. The incidence of intra-

hepatic recurrence is estimated to be nearly 50%.^{7,10,12-14} In our study, 36 (40%) of 91 patients who could leave the hospital after radical hepatic resection for HCC had intrahepatic recurrences. The incidence was still high, but was slightly better than that reported from other institutions. Thus, prevention and treatment of intrahepatic recurrence after the hepatic resection are the most important factors necessary to obtain better surgical results of HCC.

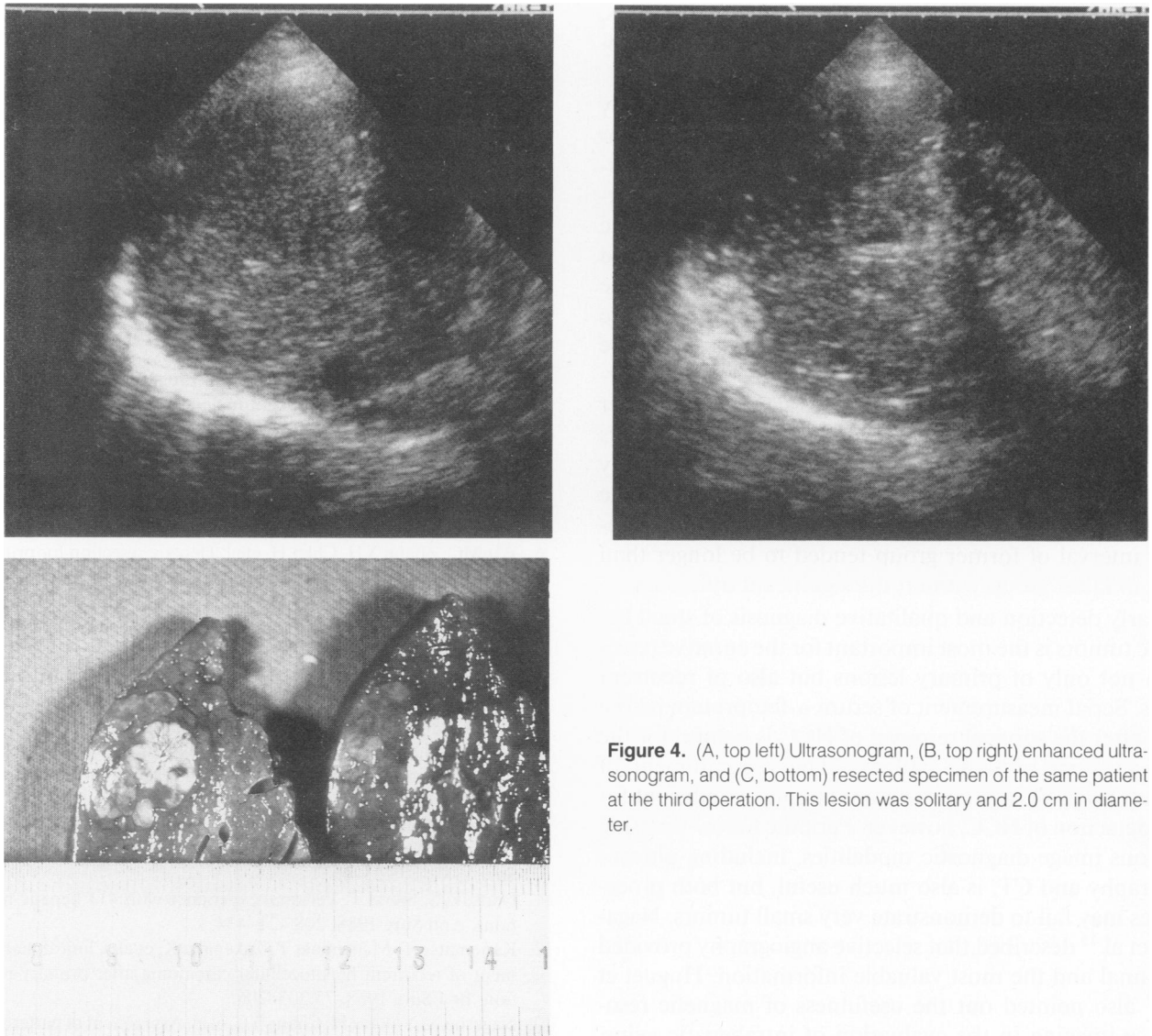


Figure 4. (A, top left) Ultrasonogram, (B, top right) enhanced ultrasonogram, and (C, bottom) resected specimen of the same patient at the third operation. This lesion was solitary and 2.0 cm in diameter.

Two main patterns of intrahepatic recurrence after surgical removal of HCC are conceivable: first, the growth of residual satellite tumors that have not noticed at the initial hepatic resection; second, synchronous and metachronous multicentric carcinogenesis, which may be responsible for late solitary recurrence far from the primary site. In our series, 13 (36%) of 36 intrahepatic recurrence were solitary. Moreover, the clinical course of the patient described in the Case Report is compatible for the metachronous multicentric carcinogenesis. Intrahepatic spread of HCC through the portal vein, possibly facilitated by surgical manipulation, also may be considered as a cause of early recurrence of HCC.

The surgical treatment of recurrent HCC in the remnant liver is usually more difficult than that of primary HCC, because of severe adhesions and anatomic changes due to previous operations. Furthermore, the reduced

reserve of residual liver function is another factor of limitation for repeated hepatectomies. Adhesions may represent a problem responsible for blood loss during mobilization of the liver. Anatomic changes must be exactly explored by various imaging techniques. Further hepatic parenchymal diminution after the first resection of HCC with the liver cirrhosis frequently may cause hepatic failure, which restricts repeated hepatectomies for intrahepatic recurrent tumors. Indeed, the resectability rate of recurrent HCC has been reported to be less than 30%.¹²⁻¹⁴ In our study, 22 (61%) of 36 patients with intrahepatic recurrences were able to receive the second operations, including 16 hepatic resections and six palliative operations. In the latter group, intraoperative pure ethanol injection into the tumors with implantation of the Infuse-A-Port (Infusaid, Inc., Norwood, MA) for intra-arterial infusion were done. If the repeated hepatecto-

mies are not indicated because of severe circumstances, such palliative operation would be a matter to be considered.

The solitary intrahepatic recurrent tumor, which may be due to the synchronous or metachronous multicentric carcinogenesis, can be considered as same as the primary lesion pathologically, especially in terms of its surgical management. Many authors have reported that the repeated hepatectomy for intrahepatic recurrence could prolong the survival time from the first operation or the diagnosis of recurrence, without any significant increase of morbidity and mortality rates.¹²⁻¹⁸ In this study, the survival rate of patients who underwent the second operation for intrahepatic recurrence was significantly better than that of conservatively treated group. These results thus indicate the significance of repeated hepatectomy for the recurrent HCC in the remnant liver, although the background of the two groups may differ and the disease-free interval of former group tended to be longer than that of latter group without the significant difference.

Early detection and qualitative diagnosis of small hepatic tumors is the most important for the curative resection not only of primary lesions but also of recurrent ones. Serial measurement of serum α -fetoprotein before and after the surgical removal of HCC is helpful for the management of these patients. The measurement of serum levels of α -fetoprotein are not always efficient for the detection of HCC, however. Periodic follow-up using various image diagnostic modalities, including ultrasonography and CT, is also much useful, but both procedures may fail to demonstrate very small tumors. Nagasue et al.¹⁵ described that selective angiography provided the final and the most valuable information. Huguet et al.¹⁷ also pointed out the usefulness of magnetic resonance imaging in the evaluation of intrahepatic veins. Recently, we have developed a new method for the contrast enhancement of hepatic tumors using ultrasonography, EU.⁵ We believe that this method is currently the most sensitive for the detection of small HCCs in comparison with all other imaging techniques, as shown in the case report. In our series, all lesions of the patients with HCC were successfully demonstrated by this method, despite frequent failures by other techniques.

Finally, many difficulties still exist in surgical treatment of HCC. Aggressive surgical policy, however, would provide better prognosis, and early detection of HCC by using the EU could support this strategy.

Acknowledgments

The authors thank Dr. S. Tarui, The Director of Otemae Hospital, for reviewing the manuscript.

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