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Selection of therapeutic modalities for hepatocellular carcinoma in patients with multiple hepatic lesions*

Morito Monden[1], Masato Sakon[1], Mitsukazu Gotoh[1], Toshio Kanai[1], Koji Umeshita[1], Kwo-Syin Wang[1], Masami Sakurai[2], Chikazumi Kuroda[3], Jun Okamura[4], and Takesada Mori[1]

[1] Department of Surgery II, Osaka University Medical School, Osaka 553, Japan
[2] Department of Pathology, Osaka University Medical School, Osaka, Japan
[3] Department of Radiology, Osaka University Medical School, Osaka, Japan
[4] Department of Surgery, Osaka Teishin Hospital, Osaka 543, Japan

Summary. In the present study, we compared the survival of patients with multi tumor hepatocellular carcinoma (HCC) following their treatment with liver resection versus TAE. A total of 336 HCC patients were treated at Osaka University Hospital between 1980 and 1989. Of these, 140 patients underwent liver resection in the presence or absence of TAE and 173 subjects were treated with TAE alone. Our TAE protocol consisted of 50 mg Adriamycin, 3–5 ml lipiodol, and Gelfoam. The 1-, 3-, and 5-year survival values found for the liver resection group were 87.4%, 66.0%, and 47.4%, respectively, whereas the values calculated for the TAE group were 64.6%, 29.9%, and 15.8%, respectively. The survival of patients in the resection group was clearly better than that of subjects in the TAE group. Of the 140 patients who underwent resection, 36 cases were proven to have multiple lesions by histopathological examination. The 1- and 3-year survival values determined for this special group were 67.9% and 33.3%, respectively. Of the TAE cases, 113 were diagnosed as having multiple lesions by imaging examination, and their 1- and 3-year survival values were 59.7% and 24.9%, respectively. No significant difference in survival was found between these two different treatment modalities for these multiple-lesion cases. The results of this study indicate that it is unlikely that surgical resection is superior to TAE alone for the treatment of HCC patients with multiple lesions.

Introduction

In the last decade, the results of hepatic resection in patients with hepatocellular carcinoma (HCC) have shown marked improvement [12, 36, 41], probably because of a better understanding of hepatic anatomy due to the use of intraoperative ultrasound [20], improvements in pre- and postoperative management [1], the development of new imaging modalities, and the introduction of transcatheter arterial chemoembolization (TAE) [39]. Overall 5-year survival values of 25%–40% have been reported after resection in many series. Careful analysis of each case of liver resection has revealed some risk factors for early recurrence, which is most frequently observed in patients with intrahepatic metastasis or intraportal invasion [22, 41]. Therefore, it is important to determine the most effective treatment for this special group of patients. In the present study, we compared the survival of HCC patients with multiple lesions in terms of the treatment modality; liver resection or TAE.

Patients and methods

Patients. A total of 336 patients with HCC were treated at Osaka University Hospital between 1980 and 1989. Of these, 140 patients underwent liver resection in the presence or absence of TAE and 173 subjects were treated by TAE alone. Table 1 shows the clinical background of the patients. The two treatment groups did not differ in terms of the distribution of sex, age, or AFP levels; however, a significant difference was found in terms of the number of nodules. In the resection group, the majority of cases involved a solitary nodule, whereas multiple nodules predominated in the TAE group. The resection group also tended to show better liver-function test results. Of the 140 resected patients, 94 (67.1%) were histologically diagnosed as having cirrhosis, whereas the remaining 26 (18.6%) had chronic hepatitis. Therefore, 85.7% of these HCC cases had a diseased liver.

Our first choice of treatment for HCC patients is usually surgical resection. However, if the patient has multiple lesions dispersed in an area too broad for resection or if the liver function is too poor for the patient to survive liver resection, we adopt TAE as our second choice. The resectability was judged on the basis of liver-function test results, including indocyanine green retention (ICGRmax), prothrombin time (PT), and the hepaplastin test (HPT), as well as on the histological findings in the remnant liver and the liver volume to be resected.

TAE method. Our TAE protocol consisted of 40–60 mg Adriamycin (ADM), 3–5 ml lipiodol, and Gelfoam [28]. These materials were intro-

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Correspondence to: M. Monden, Department of Surgery II, Osaka University Medical School 1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan

Table 1. Background of the patients

	Resection (n = 140)	TAE (n = 173)
Sex (M/F):		
M	121	142
F	19	31
Age (years):		
<40	2	2
40–49	10	15
50–59	60	75
60–69	48	54
70–79	12	23
≥80	1	1
Unknown	0	3
Number of tumors:		
Single	104	60
Multiple	36	113
AFP (ng/ml):		
≥10,000	11	11
1,000–9999	15	27
100– 999	20	32
20– 99	30	25
<20	25	27
Unknown	39	55
Serum albumin (g/dl):		
≥3.5	119	90
3.0–3.4	13	23
2.5–2.9	1	3
<2.5	0	1
Unknown	7	56
Total bilirubin (mg/dl):		
<2	132	100
2–2.9	1	13
≥3	0	2
Unknown	7	58
Hepaplastin test (%):		
≥80	61	27
60–79	55	39
40–59	11	24
<40	1	3
Unknown	12	80

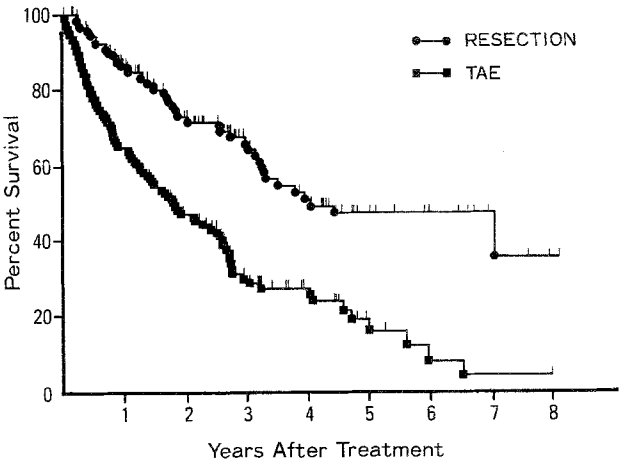

Fig. 1. Cumulative overall survival of HCC patients treated by resection or TAE

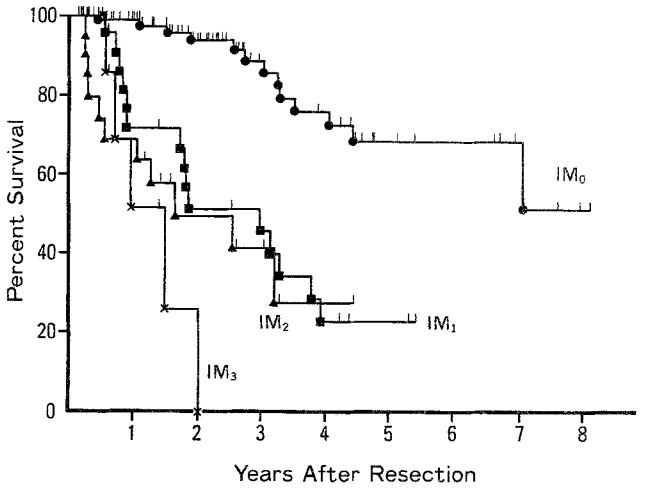

Fig. 2. Cumulative survival of patients after resection as a function of intrahepatic metastasis (*IM*). IM_0 represents the absence of intrahepatic metastasis, whereas IM_1, IM_2, and IM_3 indicate the presence of metastasis in one, two, and three segments of the liver, respectively [18]

duced by the standard Seldinger technique in all cases. We excluded patients whose main truncus of the portal vein was completely obstructed by a tumor thrombus or whose liver function was diagnosed as Child's grade C [30]. After TAE, the tumor markers and imaging were monitored, and TAE was repeated when recurrence was detected. Although 1 patient underwent TAE 7 times, the overall mean was 2.4 times. The tumor was usually less sensitive to the repeated treatment. In these cases, cisplatin (CDDP) or mitomycin C (MMC) was used in place of ADM, but these tumors generally remained resistant to TAE. In some cases, we discontinued TAE treatment because of obstruction of the proper hepatic artery and/or the development of a collateral blood supply that could not be treated by TAE.

Results

Of the 140 patients who underwent liver resection, 2 died within 1 month after resection and another 4 died during the first admission. The 1-month mortality and hospital mortality in our series were 1.4% and 4.3%, respectively. On the other hand, hospital mortality in the TAE group was as low as 0.6%. Figure 1 shows the overall results obtained in both groups. The 1-, 3-, and 5-year cumulative survival values calculated for the liver resection group (excluding hospital mortality) were 87.4%, 66.0%, and 47.4%, respectively, and those determined for the TAE group were 64.6%, 29.9%, and 15.8%, respectively. In all, 13 resection-group patients and 5 TAE-group patients lived for 5 years or longer. The survival of patients in the resection group was obviously better than that of subjects in the TAE group. Of the 140 patients who underwent resection, 36 were demonstrated to have multiple lesions by macro- or microscopic examination. All cases were regarded as involving intrahepatic metastases instead of multicentric foci.

Figure 2 shows the survival of the resection group as a function of the presence of intrahepatic metastases (IM), whereby IM_0 is defined as the absence of intrahepatic metastasis and IM_1, IM_2, and IM_3 indicate the presence of metastasis in one, two, and three segments of the liver, respectively [18]. The 5-year survival of IM_0 cases was

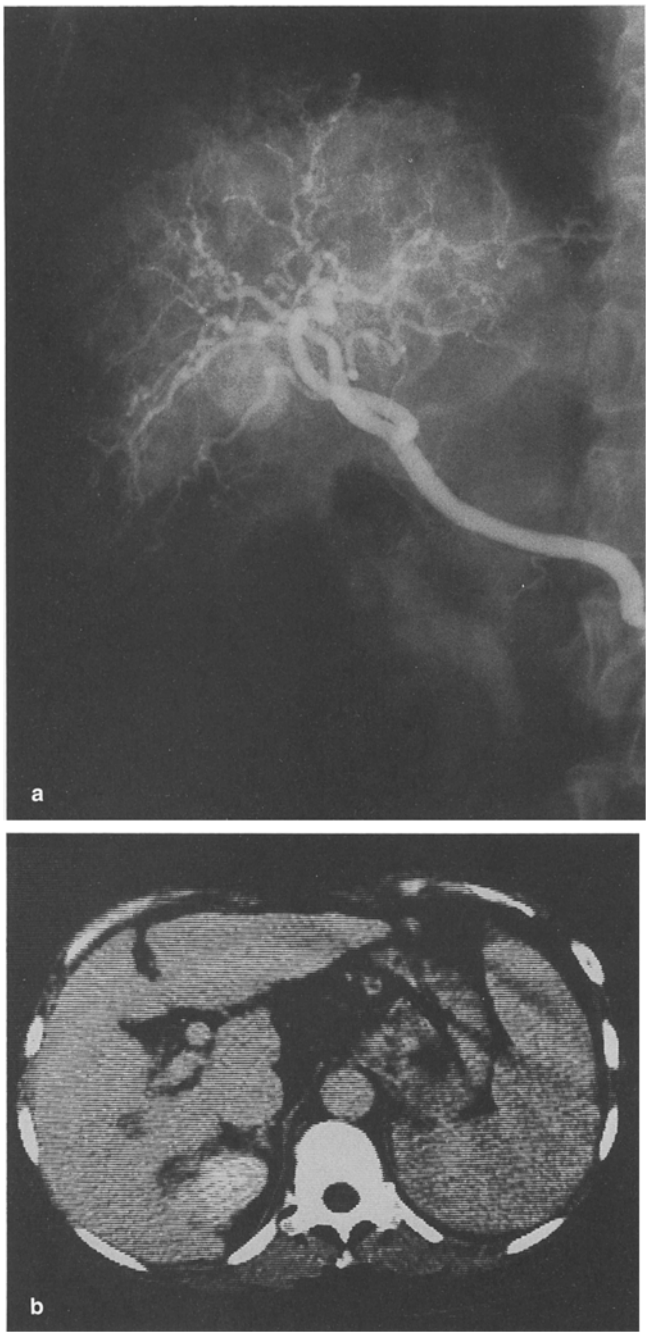

Fig. 3. a Arteriogram of a case treated by TAE alone. A hypervascular tumor is visible in subsegment S6. **b** CT scan of the same patient, showing that the space-occupying lesion has changed to one of low density

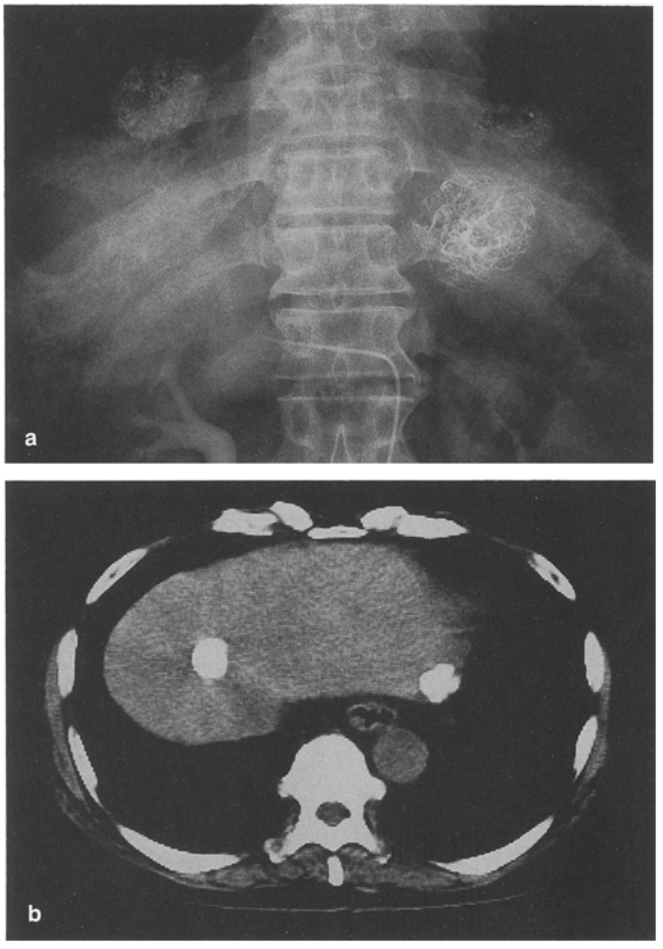

Fig. 4. a X-ray picture taken just after TAE with lipiodol, showing three lipiodol-accumulating nodules. **b** CT scan obtained at 1 month after TAE; lipiodol accumulation is visible in two nodules

69.1%, but that of IM_1 cases was only 22.2%. To date, no patient in the IM_2 or IM_3 groups has survived beyond 5 years. Furthermore, no significant difference was found between the IM_1 group and the IM_2 group.

The TAE-treated patients were also divided into three subgroups on the basis of the imaging examination results: those bearing a single nodule, those bearing a few nodules, and disseminated cases. Multiple nodules were identified in 109 cases and a single nodule was detected in 64 cases. Figure 3a presents the angiogram of a 59-year-old woman with a single nodule who subsequently underwent TAE on June 10, 1982. Figure 3b shows the CT scan obtained at 1 month after angiography. The space-occupying lesion (SOL) became low in density, indicating a good effect of the TAE. Because the patient's liver function was moderately deteriorated, we did not choose surgical treatment. Surprisingly, this patient is now alive and has slight jaundice but shows no sign of tumor recurrence. She is the only patient in our series who has survived for 8 years. Figure 4 illustrates a case involving a few nodules. This X-ray was obtained just after TAE combined with lipiodol injection (Fig. 4a), and three nodules were noted. Figure 4b shows a CT scan obtained in the same patient at 1 month after TAE. Figure 5a presents the pretreatment angiogram of a patient with multiple, disseminated intrahepatic metastases, and Fig. 5b shows a CT scan obtained in the same patient following TAE.

Figure 6 shows the survival of patients treated by TAE alone as a function of the number of nodules. The survival of patients with disseminated metastases was very poor, but the results obtained in the other two groups were quite similar; no statistically significant difference was found between cases involving a single nodule and patients bearing a few nodules.

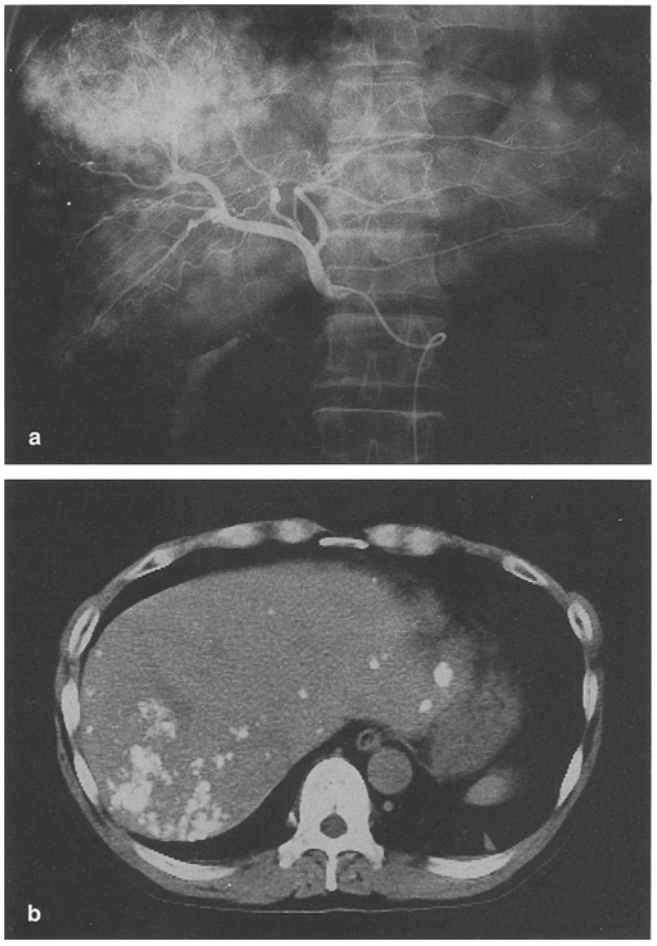

Fig. 5. a Arteriogram of a disseminated case treated by TAE. Multiple hypervascular nodules are visible. **b** CT scan obtained at 1 week after TAE with lipiodol

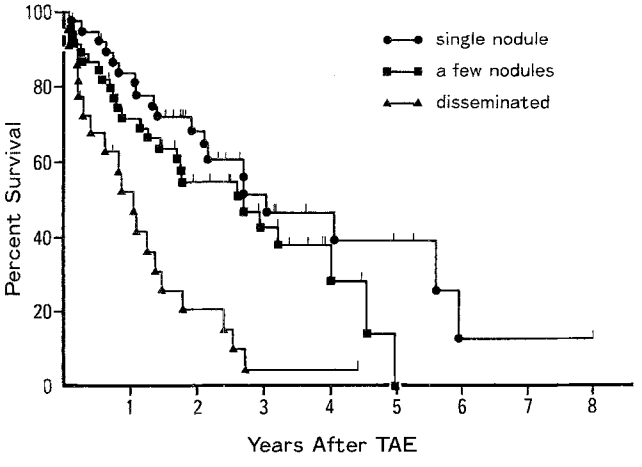

Fig. 6. Cumulative survival of patients treated by TAE alone, plotted as a function of tumor number

Figure 7 compares the survival values determined for single-nodule cases following surgical resection versus TAE. The 3- and 5-year survival values calculated for the resection group were 85.4% and 69.1%, respectively, whereas those found for the TAE group were 38.3% and

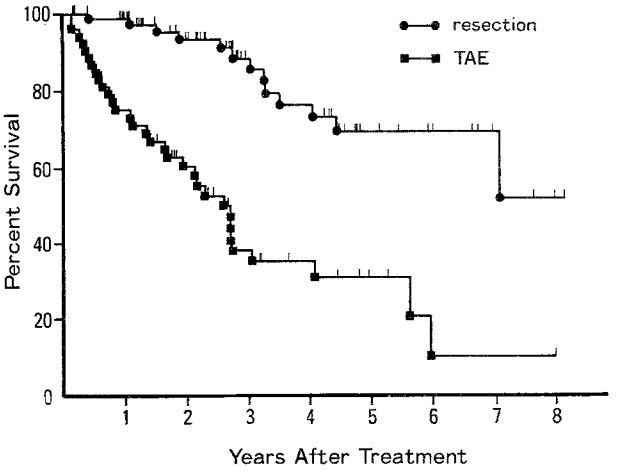

Fig. 7. Cumulative survival of single-nodule cases treated by resection or TAE

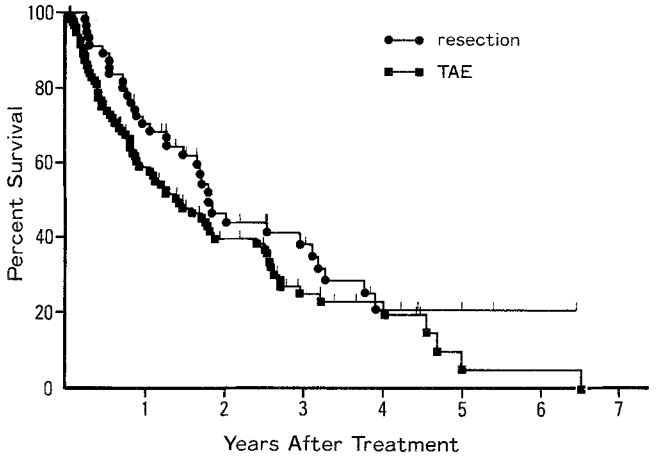

Fig. 8. Cumulative survival of multiple-nodule cases treated by resection or TAE

30.9%, respectively; the differences were highly significant. Similarly, the survival values determined for patients bearing multiple nodules were compared between surgical resection and TAE (Fig. 8), but no significant difference was found.

Discussion

HCC has been considered to be a highly malignant tumor with a poor prognosis [2]. Okuda et al. [29] reviewed the outcome of 600 consecutive patients with HCC, of whom 98 underwent resection, 333 received nonsurgical treatment (158 were treated by intra-arterial chemotherapy; 94, by systemic chemotherapy; 77, by TAE; and 4, by other modalities), and 169 received no treatment. The median survival of the untreated patients was only 1.6 months from diagnosis. The surgically treated patients lived significantly longer than did the nonsurgical patients bearing disease of comparable stages, the median survival being 19.6 months for the former and 2.8 months for the latter.

Although surgical resection offers the only chance for cure, at the time of diagnosis most patients present with tumors that involve both lobes of the liver, insufficient hepatic reserve, or other factors precluding curative surgery. The major problems encountered in many of these cases due to associated cirrhosis and chronic hepatitis make surgery and postoperative management especially difficult. The percentage of patients presenting with cirrhosis at the time of diagnosis averages approximately 80% [19], and the resectability rate is 24%–30% [6, 17]. In the present series, we could not clarify the overall rate of cirrhosis because hardly any of the nonsurgically treated cases were subjected to histological examination. However, of the resected patients, 67.1% were histologically proven to have liver cirrhosis and 18.6% had chronic hepatitis.

In Western countries, some surgeons consider cirrhosis to be a contraindication for resection because of the resultant high mortality [6, 8]. Therefore, alternative therapies have been sought for these patients. In unresectable cases of HCC, systemic anticancer treatment has been used [7, 33], but the results have been very poor. Intra-arterial infusion chemotherapy, which is believed to increase local delivery of drug to the tumor, does not alter the outcome [5, 27]. TAE [11] has been shown to most effective against HCC [16]. Our histopathology study of HCC resected after TAE revealed that 38 of 71 main tumors had become completely necrotic [32]. Yamada et al. [39] have reported the 1- and 2-year survival of patients undergoing TAE to be as high as 44% and 29%, respectively. However, some difficulties are encountered in cases involving intrahepatic metastasis or a tumor thrombus in the portal vein, which are quite commonly found in HCC. Recently, several modifications have been added to the original TAE method to increase its effectiveness, and some success has been reported [14, 25, 26].

As documented earlier, the surgical treatment used for HCC through the 1970s was unsatisfactory because of two major factors: excessively advanced tumors and associated cirrhosis at the time of diagnosis. Therefore, early detection of HCC is the most important requirement for successful treatment. In China, mass screening of people using alpha-feto protein (AFP) has been reported to be helpful in finding early and asymptomatic HCC and has resulted in improvements in both operability and curability rates [38]. Another extremely useful diagnostic modality involves new imaging techniques: echography, computerized tomography (CT), and nuclear magnetic resonance (NMR). Via these procedures, many cases of small and asymptomatic HCC have been diagnosed and referred to surgeons. Since small HCC is usually not associated with intrahepatic metastases, curative resection of the tumor is possible without the need for massive resection.

Cirrhosis associated with HCC increases the operative risk and the postoperative morbidity. Limited hepatic reserve and impaired hemostasis are detrimental factors in cirrhotic patients undergoing resection. The 1-month operative mortality after resection of HCC has been reported to range from 4% to 20% [37]. The mortality and morbidity arising from liver resection is due to intra- or postoperative bleeding, bile leakage, sepsis, and hepatic failure [9]. Various attempts have been made to improve hemostasis; the Pringle maneuver [24] and total hepatic vascular exclusion [4] have been applied with success. Sepsis can reportedly also be prevented either by the use of closed drainage [35] or without drainage [9]. Therefore, these complications can be controlled by technical improvements.

With regard the prevention of hepatic failure, the most important aspect is preoperative management, i.e., precise estimation of the reserve hepatic function. The numerous parameters proposed for this purpose include the indocyanine-green (ICG) retention test [23], determination of the blood-flow rate [21], and the use of a multiple regression model [40]. Their application enables the safer performance of limited hepatic resection, even in cirrhotic livers, which cannot tolerate anatomic hepatic resection. Subsegmentectomy or partial resection as a limited operation [13] is carried out in a majority of these patients. Knowledge of the segmental anatomy of the liver enables the performance of lesser resections via a transparenchymatous technique [3]. Subsegmentectomy guided by intraoperative ultrasound demonstration of the tumor and vessels permits anatomic resection of small tumors as well as minimal parenchymal excision in cirrhotic cases [20]. The prognosis for such patients has been reported to be comparable with that for subjects undergoing anatomic lobectomy [13].

In the present study, we compared the prognosis for HCC patients as a function of the therapeutic modality applied: surgical resection or TAE. The hospital mortality was 4.3% for resection and 0.6% for TAE. The cumulative survival was better in the resection group when all cases were considered. Furthermore, when we compared the survival of patients with a single nodule, the 5-year survival value determined for the resection group was (69.1%) was considerable higher than that found for the TAE group (30.9%); the latter value was also higher than that previously reported by other investigators. However, the outcome of patients with multiple lesions was very poor, regardless of the treatment modality. As a majority of our patients had liver cirrhosis or chronic hepatitis, limited resection rather than massive resection (anatomic resection) was the only surgical modality possible in those cases. Furthermore, resection cannot eradicate all of the lesions involved, even if the lesions are thought to have been completely removed macroscopically. Although extended resection may be capable of eradicating all of the lesions, it increases the resultant mortality, and there is no guarantee that all metastatic lesions will be removed.

TAE is also not very effective against metastatic lesions. Our data indicate that there is no advantage for resection in HCC patients bearing multiple lesions. Because the present investigation was not a randomized study, we could not reach a definitive conclusion. However, many cases in the resection group were diagnosed by microscopic examination. Therefore, there may have been a larger number of advanced cases in the TAE group than in the resection group. These results do not deny the usefulness of surgical resection in the treatment of HCC patients presenting with multiple intrahepatic metastases, as some of these patients survived for a long period. One patient who presented with 15 intrahepatic metastases has sur-

vived for more than 7 years without showing signs of recurrence. Interestingly, at surgery, all but one of the intrahepatic metastases were found to be completely necrotized due to TAE.

It has recently been reported that the prognosis for patients who have undergone hepatic resection is strongly regulated by malignancy showing the ploidy pattern [10] or loss of heterozygosity [34]. This means that the fate of a patient is predetermined by the characteristics of the tumor itself and cannot be changed by the treatment modality. Therefore, it is important to analyze the tumor characteristics before surgery. If the tumor is estimated to have a poor prognosis, other treatments such as chemotherapy, radiotherapy, or immunotherapy should be given.

In more than 80% of cases, HCC is associated with liver cirrhosis or chronic hepatitis. These changes may be a premalignant condition, irrespective of the etiology. It is not difficult to imagine that absolutely new lesions or even multifocal lesions might arise from a cirrhotic liver, although the original tumor has been curatively resected. For complete therapy of such patients, total hepatic resection and liver transplantation may be necessary [15, 31].

In conclusion, the prognosis for HCC patients differs according to the tumor characteristics. In the present study, patients with a single nodule survived significantly longer than those with multiple lesions, regardless of the treatment modality. Among single-lesion cases, the results obtained using liver resection were considerably better than those obtained using TAE. In contrast, the outcome of patients with multiple lesions was very poor, and liver resection did not provide any additional beneficial effect. A restrictive use of resection is indicated in these cases.

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