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Long-term prognosis of surgical patients with hepatocellular carcinoma

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Summary. We reviewed 139 resected patients with hepatocellular carcinoma at our clinic between 1963 and 1987, and using the 118 cases for the period between 1963 and 1986, we analyzed the prognostic factors that influenced the long-term prognosis by comparing the survival curves. Significant differences in the survival patterns were noted when analysed on the basis of the preoperative indocyanine green maximal removal rate (>0.4 mg kg^{-1} min^{-1} versus <0.4 mg kg^{-1} min^{-1}), tumor size (>5 cm versus <5 cm, etc.) and the existence of tumor capsule. The recurrence of carcinoma was the main cause of death of 32 patients (56%), who died after being discharged from hospital. To improve the prognosis of patients with surgically treated hepatocellular carcinoma, postoperative multidisciplinary treatment is mandatory.

Introduction

We have been performing liver surgery for more than 25 years at the First Surgical Department of the University of Tokyo [1, 2]. During that period, we have reviewed 266 patients with hepatocellular carcinoma, including 139 resected cases. In this study, we analyzed the prognostic factors that affected long-term survival.

Material and methods

From January 1963 through December 1987, 266 patients with hepatocellular carcinoma were admitted to our clinic, and 139 of these patients underwent hepatic resection. However, the clinical data of the patients who were treated in 1987 were not complete, so these patients were excluded from this study. We investigated the trend in terms of time of the incidence of hepatocellular carcinoma, the ratio of resection, age and sex distribution, the methods of treatment, coexisting diseases such as liver cirrhosis, the clinicopathological features of the patients and the survival rates.

All the results are shown as means ± SEM, while the Student's *t*-test, χ^2 test and Fisher's exact method were used to make the statistical analysis. The survival curves after treatment were obtained using the Kaplan-Meier method, and the comparison of the survival curves was made using the generalized Wilcoxon test. The value of $P<0.05$ was considered significant.

Results

Since 1963, the number of patients with hepatocellular carcinoma has been increasing, and the mean resectability rate was 52.5%. However, since 1977, the number has been growing even higher, as shown in Fig. 1. The age and sex distribution is shown in Fig. 2.

Of the 233 patients, 118 (50.6%) underwent a hepatic resection, 27 underwent hepatic arterial ligation and/or cannulation (11.6%), and 88 (37.8%) had no operation. Since 1975, it has become possible to detect smaller-sized hepatocellular carcinoma, which is then surgically treated. Fig. 3 shows the ratio of the incidence of these small tumors chronologically. Early detection is due to the recent advances in diagnostic tools such as echography and computerized tomography. As a reflection of this, operative procedures are also changing, that is, minor hepatic resection (sublobectomies, such as segmentectomy and wedge resection) is more often performed than major hepatic resection (hepatic resection of one lobe or more), especially since 1975 (Fig. 4). Table 1 is a summary of the resected cases with the patients divided into two groups, one belonging to the period from 1963 to 1979 and the other to the period from 1980 to 1986. Between these two groups, the only significant difference was the tumor size.

There were 21 hospital deaths after hepatectomy. The operative procedures and operative blood loss were not factors that influenced morbidity and mortality. However, the chronological differences were statistically significant (Table 2). The factors that affected the prognosis of the patients with hepatocellular carcinoma who underwent hepatectomy, survived the operation and were discharged were investigated. No significant differences in the survival patterns were noted when they were analyzed on the basis of a chronological comparison, single versus multiple pattern (Fig. 5), the indices of the liver function such as the indocyanine green 15-min removal rate, and preoperative transarterial embolization (TAE). Significant differences in the survival patterns were noted, however, when the maximal removal rate of indocyanine green (R_{max}) (>0.4 mg kg^{-1} min^{-1} vs <0.4 mg kg^{-1} min^{-1}), operative procedures (major resection versus minor resection), the size of the main tumor and the tumor capsule formation were the variables analyzed. The patients who showed pre-

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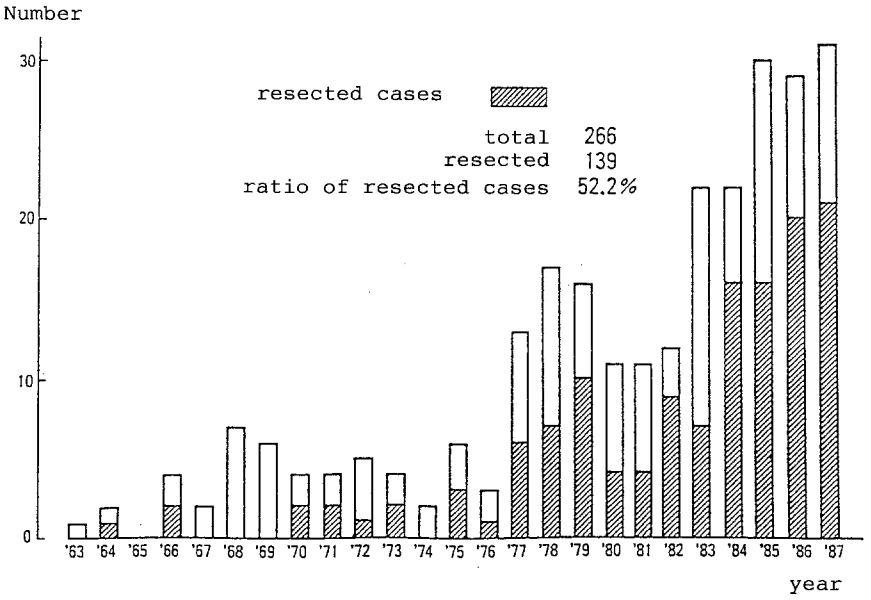

Fig. 1. Performance of patients as a function of time

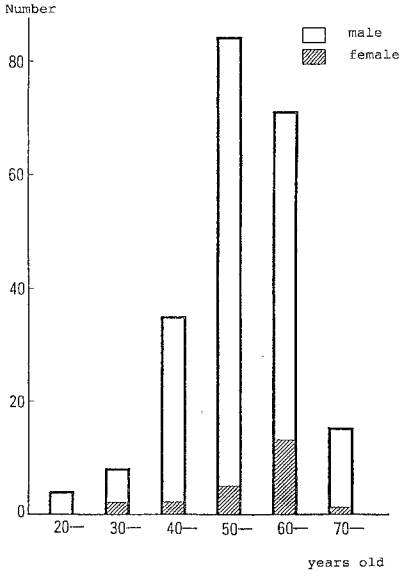

Fig. 2. Age and sex distribution of patients

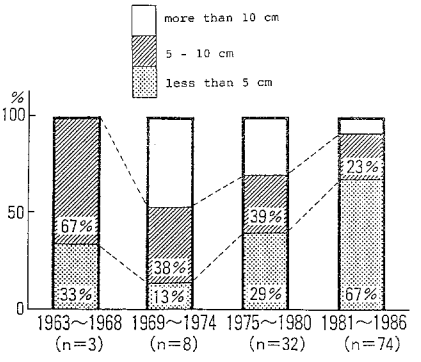

Fig. 3. Chronological change of tumor size

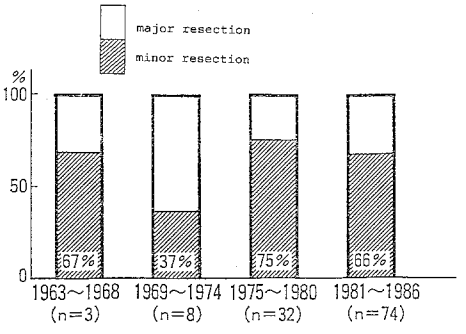

Fig. 4. Hepatic resection. Major resection versus minor resection

operative values of $R_{max} > 0.4$ mg kg^{-1} min^{-1} had a better prognosis than those with $R_{max} < 0.4$ mg kg^{-1} min^{-1} (Fig. 6). The patients who underwent minor resection showed a better survival curve ($P < 0.05$, Fig. 7). The patients with tumors of a maximum diameter of less than or equal to 5 cm had a better prognosis than those with tumors greater than 5 cm ($P < 0.001$, Fig. 8), and when these tumors were classified into three groups, that is, A (less than 5 cm), B (between 5 cm and 10 cm) and C (more than 10 cm), this difference was also clearly demonstrated ($P < 0.05$, A versus B), ($P < 0.001$, A versus C), (Fig. 9). The

Table 1. Comparison of several factors in resected cases

Experimental period	No.	Age (years)	Cirrhosis (%)	Tumor size ≤5 cm (%)	Solitary tumor (%)
(1963–1979)	40	55.2 ± 1.4 (SE)	72.5	37.5	84.6
(1980–1986)	79	57.5 ± 1.0 (SE)	70.9	70.7	86.1
P		NS	NS	$P = 0.001$	NS

Table 2. Hospital death after hepatectomy for hepatocellular carcinoma

Sample and period	Major resection	Operative blood loss ≥5 l	Hospital death
40 (1963–1979)	17/40 (43%)	10/40 (25%)	13/40 (32.5%)
79 (1980–1986)	23/79 (29%)	10/78[a] (13%)	8/79 (10.1%)
			$P = 0.0056$

[a] One case is omitted because of no record of blood loss

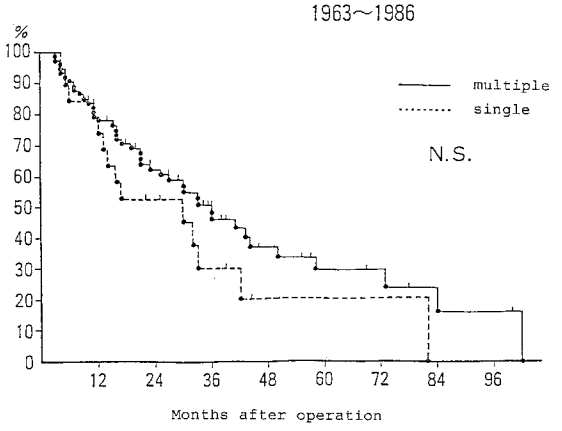

Fig. 5. Survival curves comparing single versus multiple patterns

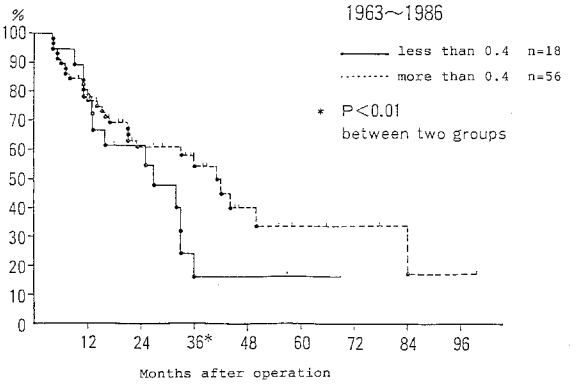

Fig. 6. Survival curves comparing patients with maximum indocyanine green retention ≥ 0.4 mg kg^{-1} min^{-1} versus those showing < 0.4 mg kg^{-1} min^{-1}

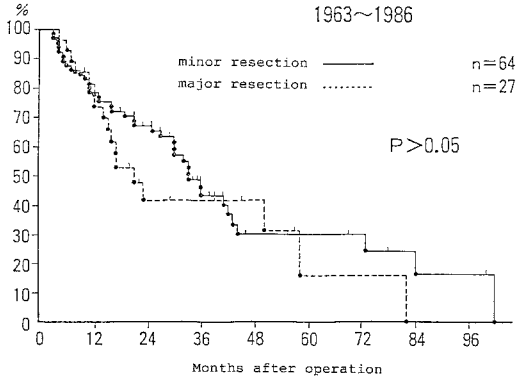

Fig. 7. Survival curves comparing major resection versus minor resection

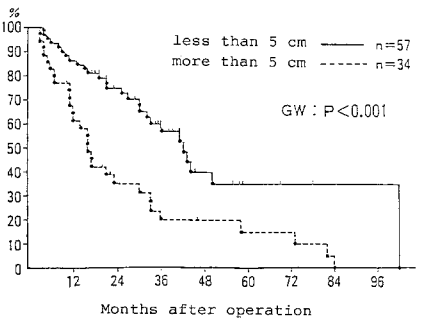

Fig. 8. Survival curves comparing patients with tumor size of more than 5 cm versus those with tumors less than 5 cm

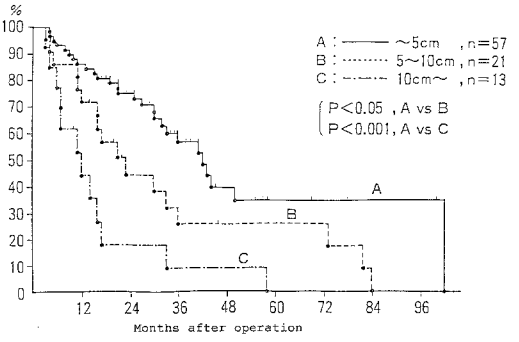

Fig. 9. Survival curves comparing tumor size among groups A, B and C

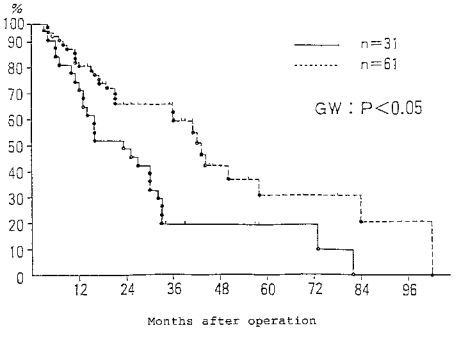

Fig. 10. Survival curves comparing encapsulated tumor versus noncapsulated tumor

existence of a tumor capsule also made a significant difference ($P < 0.05$) to the survival pattern (Fig. 10).

The causes of death of those patients who survived after hepatectomy for hepatocellular carcinoma were as follows: out of the 57 patients, 32 (56%) died from a recurrence of liver cancer, 16 (28%) from liver insufficiency, 7 (12%) from other diseases, and 2 (4%) died of unknown causes.

Discussion

Until a decade ago, the survival period of patients with hepatocellular carcinoma was estimated to be several months at most after diagnosis. However, remarkable advances in diagnosis and operative procedures have led to the early detection of this condition and safer hepatectomy. As a result, the incidence of hepatocellular carcinoma, especially in the form of small tumors (with a maximum

diameter of less than 5 cm) has been increasing year by year in the clinical field. Despite many experimental forms of treatment for this disease, the long-term survival of patients with hepatocellular carcinoma can be expected only if the tumor is surgically removed. The investigation into the prognostic factors revealed that the tumor size, capsule formation and R_{max} were the variables that significantly affected long-term survival. These findings suggest that the long-term prognosis of patients with hepatocellular carcinoma after resection is determined by the biological features of the tumor itself and the hepatic reserve of the patients, as well as the modality of the treatment. According to our data, a minor resection shows a rather better result in the survival curve. However, the stage and state of the tumor in the patients in these two groups were different. For this reason, a simple comparison is meaningless. However, it can at least be said that if the tumor is detected at an earlier stage or when it is still small, it is possible to perform a minor resection.

The main cause of death after discharge from hospital is the recurrence of carcinoma. The postoperative follow-up on the patients should be focused on the prevention and treatment of a recurrence. Since 1980, we have been trying postoperative multidisciplinary treatment, including intra-arterial chemotherapy, immunotherapy and massive reduced glutathione therapy. At present, a proven method for this purpose has not yet been established.

References

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2. Nagao T, Goto S, Kawano N, Inoue S, Mizuta T, Morioka Y, Omori Y (1987) Hepatic resection for hepatocellular carcinoma, clinical features and long-term prognosis. Ann Surg 205: 33