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Clinicopathological features of malignancy in hepatocellular carcinoma

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Summary. The clinicopathological features showing the malignancy of hepatocellular carcinoma were investigated by retrospectively analyzing the postoperative prognosis after hepatic resection. The long-term prognosis was stongly affected by the existence of portal tumor invasion or intrahepatic metastasis as indicated by the following results. The 3-year cumulative survival rates were 61% and 38% for patients in portal vein tumor invasion groups (Vp0 and Vp1 ($P < 0.05$). No patients with Vp2 or Vp3 could survive beyond 3 years after hepatic resection. Similarly, patients with intrahepatic metastasis IM0 showed a better prognosis, compared to those with IM2 or IM3 ($P < 0.05$). In addition, the grade of tumor cell anaplasia to some extent affected the prognosis, but not the tumor growth pattern at the tumor/non-tumor boundary. The tumor growth rate, estimated by the α-fetoprotein doubling time, was not connected with venous invasion or intrahepatic metastasis, but it became shorter at the time of a recurrence. It is concluded that, from the standpoint of a long-term prognosis, the pathological features showing malignancy appear in venous invasion and intrahepatic metastasis.

Introduction

The recent advances in diagnostic modalities, such as ultrasonography and computed tomography, have led to the discovery of an increasing number of resectable hepatocellular carcinoma (HCC). Together with this, a preoperative estimation of the hepatic functional reserve has been made available by using various indices at each institute, preventing the occurrence of a postoperative hepatic failure even in cirrhotic patients [7, 11]. On this basis, one of the main themes of HCC surgery in Japan has moved from the problem of postoperative hepatic failure to the long-term prognosis after hepatic resection.

With respect to the postoperative prognosis of HCC patients, two factors can be considered: the hepatic function according to the possible progress of coexisting liver cirrhosis after hepatic resection, and tumor recurrence. For the latter factor, the diminishing of HCC malignancy may be the most important determinant, as well as the stage of HCC. The present study was aimed at clarifying the clinicopathological features of HCC malignancy evaluated by retrospectively analyzing the postoperative long-term prognosis.

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Patients and methods

From January 1978 to December 1986, a total of 148 patients with histologically proven HCC and capable of undergoing a follow-up study underwent hepatic resection to varying extents. Of these, 23 died of hepatic failure or other diseases without any evidence of a tumor recurrence. These patients were excluded from the present data because the main purpose concerned the malignancy of HCC rather than the hepatic function. Some patients died of hepatic failure with a small recurrent tumor. In this case, these patients were included in the present data solely because of the tumor recurrence. The postoperative cumulative survival rates were determined using Kaplan-Meier's method. A histological study of the resected specimens was made after staining them with hematoxylin/eosin dye. Tumor cell anaplasia was graded according to Edmondson-Steiner's classification [2]. The tumor growth pattern at the tumor/non-tumor boundary was classified into three types, sinusoidal, replacing and pseudocapsular, as described by Nakashima et al. [6]. The staging, grade of portal tumor invasion, intrahepatic metastasis and other definitions were strictly governed by The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, published by The Liver Cancer Study Group of Japan. In cases with serial measurements and a progressive increase in the α-fetoprotein levels, the tumor growth rate was estimated by plotting the α-fetoprotein values on a semilogarithmic table, and the α-fetoprotein doubling time was calculated using the following formula, as developed by Schwartz [9]. Doubling time $= t \times \log 2/\log (c_2/c_1)$, where c_1 and c_2 are the α-fetoprotein values at the different intervals, and t is the time in days between the two measurements. A statistical evaluation was made using Student's t-test with impaired observation, the χ^2 analysis or the general Wilcoxon test for the study on survival. The statistical significance was determined with a P value of less than 0.05.

Results

The overall and stage-dependent cumulative survival rates

The cumulative survival rates for the total number of cases are 72%, 53% and 46% for periods of 1, 3 and 5 years after

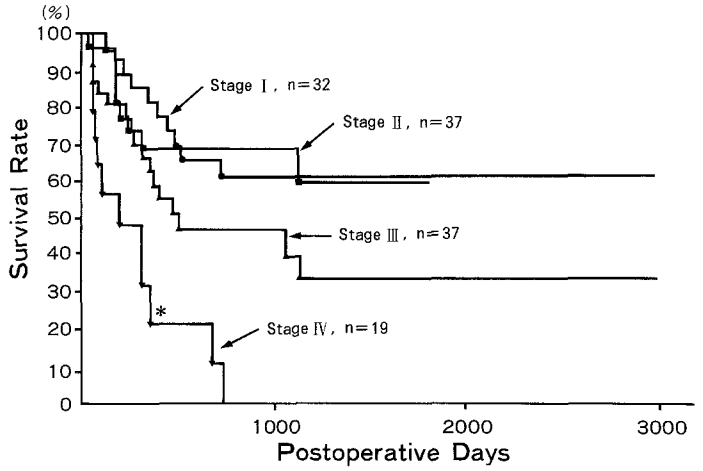

Fig. 1. The stage-dependent cumulative survival rate excluding the cases of death due to hepatic failure. *, $P < 0.05$, compared with stage 1

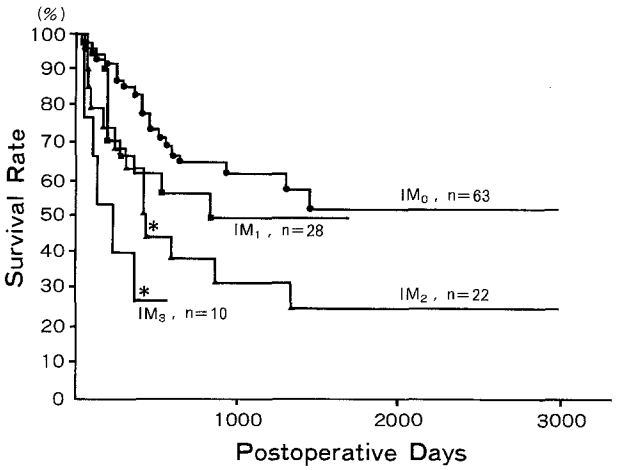

Fig. 3. The cumulative survival rate at different magnitudes of intrahepatic metastasis. *IM0*, no intrahepatic metastasis. *IM1*, metastasis limited to one segment. *IM2, IM3*, found in 2 or 3 segments. *, $P < 0.05$, compared with IM0

hepatic resection respectively. If the survival rates for each stage are referred to, stage 1 and stage 2 patients have a relatively satisfactory prognosis, as indicated by 65% and 66% for a period of 3 years (Fig. 1). However, at the advanced stages of 3 and 4, the survival rates are as low as 46% for a period of 3 years for patients at stage 3, and there were no cases at stage 4 who could survive beyond 3 years after the operation.

The pathological features determining the long-term prognosis

Figure 2 demonstrates the cumulative survival rates with respect to the diminishing of portal tumor invasion (Vp). The 3-year survival rate of the Vp0 cases was 61%, which was significantly higher than the positive portal tumor invasion groups (Vp1, Vp2 and Vp3) ($P < 0.05$). In fact, no patient with Vp2 or Vp3 could survive beyond 3 years after hepatic resection. Similarly, Fig. 3 illustrates the survival rates of the groups with different magnitudes of intrahepatic metastasis (IM). Although there was no significant difference between the IM0 and IM1 groups, the patients with IM2 or IM3 showed significantly lower survival rates compared with the IM0 group ($P < 0.05$).

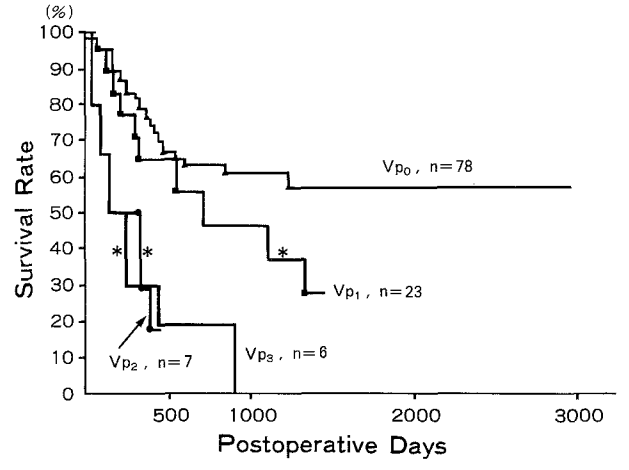

Fig. 2. The cumulative survival rate at the various degrees of portal invasion. *Vp0*, macroscopically negative portal tumor invasion. *Vp1*, portal invasion up to the third branch of the portal vein. *Vp2*, to the second branch. *Vp3*, portal tumor invasion to the first branch or more. *, $P < 0.05$, compared with Vp0

The tumor size and pathological features

Figure 4 indicates the relationship between the tumor size and the pathological features that affect the prognosis. Two groups with different tumor sizes, one with tumor diameters of less than 3 cm and the other with diameters of over 10 cm, were compared, since there was an appropriate number of 40 cases for the former and 30 cases for the latter. Macroscopically, the larger tumor cases were more deeply connected with portal tumor invasion and intrahepatic metastasis ($P < 0.05$), as indicated by 18% versus 60% in Vp and 20% versus 60% in IM at < 3 cm versus > 10 cm, and their histologies showed a higher incidence of poorly differentiated HCC. However, when studied microscopically, even in the smaller cases, a high incidence of portal tumor invasion, intrahepatic metastasis and capsular invasion was observed, as clearly demonstrated by Fig. 5. Histological portal invasion, intrahepatic metastasis and capsular invasion were seen in 53%, 45% and 65% of cases respectively. Such histological features were more predominant in cases with a tumor recurrence, as demonstrated in Fig. 6; that is, portal invasion, capsular invasion and intrahepatic metastasis were noted in 77%, 85% and 85% of cases respectively. In addition, in accordance with Edmondson-Steiner's criteria, the recurrent cases showed a high frequency of more anaplastic tumor cells. Figure 7 indicates the survival rates in reference to Edmondson-Steiner's classification. No cases with type 1 have shown any evidence of a tumor recurrence up to date, while there are no significant differences in the prognosis among the other types. On the other hand, the tumor growth pattern can be classified into three types, sinusoidal, replacing and encapsulated patterns, of which the typical appearances are demonstrated in Fig. 8. Although these patterns seem to play a major role in determining the outcome of the HCC resected patients, there were no significant differences in the long-term prognosis among the three groups (data not shown).

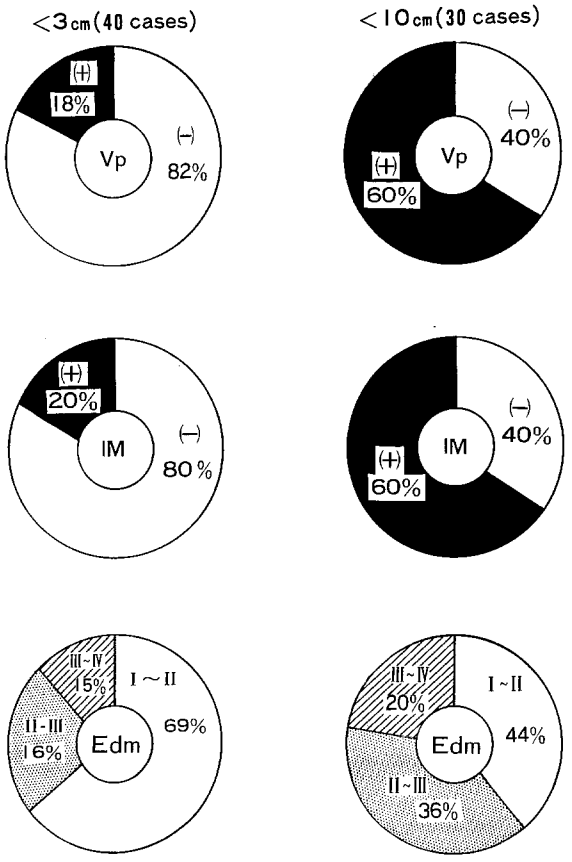

Fig. 4. The frequencies of Vp and IM factors in small tumors (<3 cm in diameter) and larger tumors (>10 cm in diameter). *Vp(−)*, Vp0; *Vp(+)*, Vp1+Vp2+Vp3 (the abbreviations are defined in the legend of Fig. 2. *Edm*, tumor cell anaplasia according to Edmondson-Steiner's classification

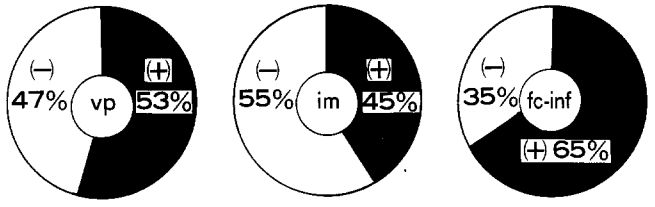

Fig. 5. Microscopical appearances of portal invasion (*vp*), intrahepatic metastasis (*im*) and capsular invasion (*fc-inf*) in the small tumor with a diameter of less than 3 cm

The tumor growth doubling time

Figure 9 illustrates the relationship between the α-fetoprotein doubling time and portal tumor invasion or intrahepatic metastasis in the HCC resected cases. The doubling time had a wide range varying from 9 days to 179 days. With respect to this relationship, there was no statistical significance between the two factors of the tumor growth rate and the invasion potential to the surrounding tissues. On the other hand, it is noteworthy that the doubling time became shorter at the time of recurrence in almost all the cases, as shown in Fig. 10.

Discussion

In general, the pathological features that indicate tumor malignancy can be considered to be the following: (a) vig-

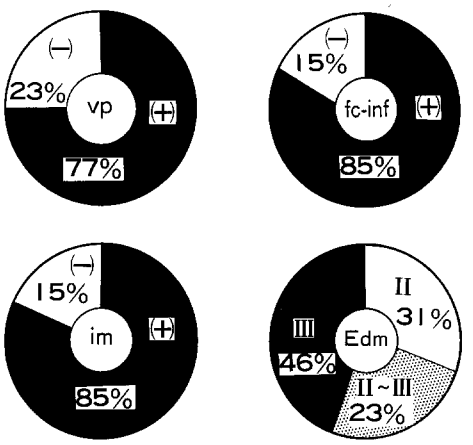

Fig. 6. Histological incidences of vp, im fc-inf and Edmondson's criteria in the recurrent cases of small HCC. Abbreviations are defined in legend to Fig. 5

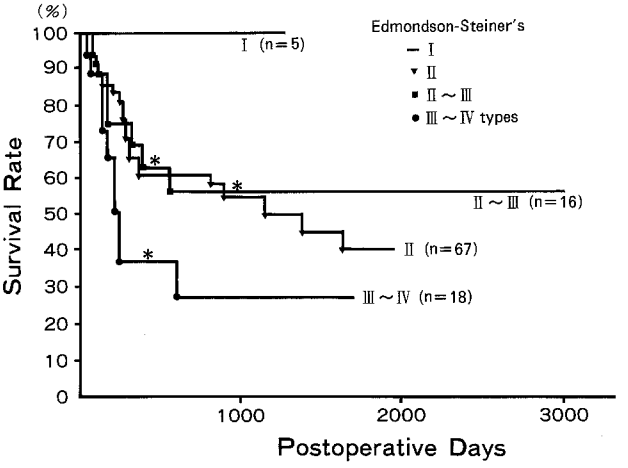

Fig. 7. The cumulative survival rates according to Edmondson-Steiner's classification. *, $P < 0.05$, compared to type 1 cases

orous invasion to the surrounding tissues such as vessels and matrices, (b) rapid tumor growth, (c) frequent recurrence and metastasis to other tissues. Usually the synergic effects clinically result in the prognosis. In HCC patients, portal tumor invasion, intrahepatic metastasis, the tumor size, capsule formation and capsular invasion are considered to play a role in determining the outcome for HCC patients. In particular, portal invasion and intrahepatic metastasis are the most important determinants governing the postoperative prognosis, as clearly indicated in the present results. These factors can thus represent the pathological features that show the malignancy of HCC. Furthermore, from the standpoint of tumor recurrence, portal invasion and intrahepatic metastasis seem likely to indicate malignancy, as suggested by the evidence that cases of small HCC a recurrence have a high incidence of these features. On the other hand, the question arises of whether these characteristic features occur along with the advanced stage of HCC. In one aspect, as suggested by the results indicated in Fig. 5, the portal vein invasion and intrahepatic metastasis are more positive factors in cases of larger tumors; however, on precise histological investigation of small liver cancer, their incidence of seems to be similar to

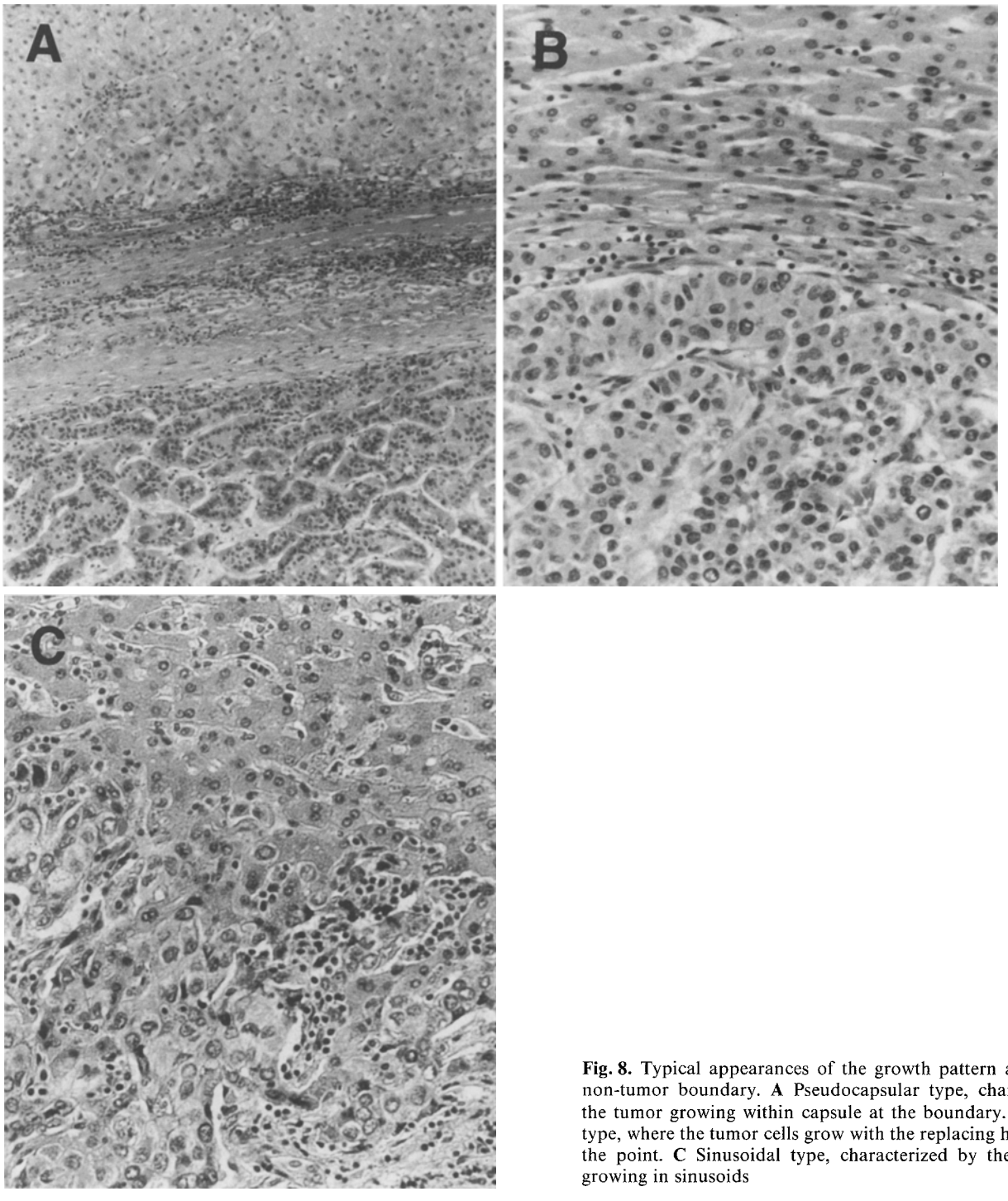

Fig. 8. Typical appearances of the growth pattern at the tumor-non-tumor boundary. **A** Pseudocapsular type, characterized by the tumor growing within capsule at the boundary. **B** Replacing type, where the tumor cells grow with the replacing hepatocytes at the point. **C** Sinusoidal type, characterized by the tumor cells growing in sinusoids

the macroscopical Vp and IM-positive rates seen in the larger tumor cases. This phenomenon may lead to the assumption that the higher frequencies of macroscopical positive portal invasion and intrahepatic metastasis account for the tumor growing. Furthermore, attention should be paid to the phenomenon that even in cases with a large tumor, 40% show Vp(−) or IM(−). These results strongly suggest that the essential potential for vessel invasion or intrahepatic metastasis may be unchanged in each tumor, and is independent of tumor development. In turn, individual tumors may possess their own active mechanisms of attaching themselves to laminine or fibronection and protease, leading to the degradation of a matrix, thereby resulting in vessel invasion [8].

On the other hand, Nakashima et al. [6] have reported that the tumor growth pattern can be classified into three types: sinusoidal, replacing and pseudocapsular patterns, but they did not describe the possible prognosis related to these patterns. Taking into consideration the fact that the invasion potential to the surrounding tissue is indicative of malignancy in other organ cancers, the growth pattern in HCC could be considered to play a certain role in deter-

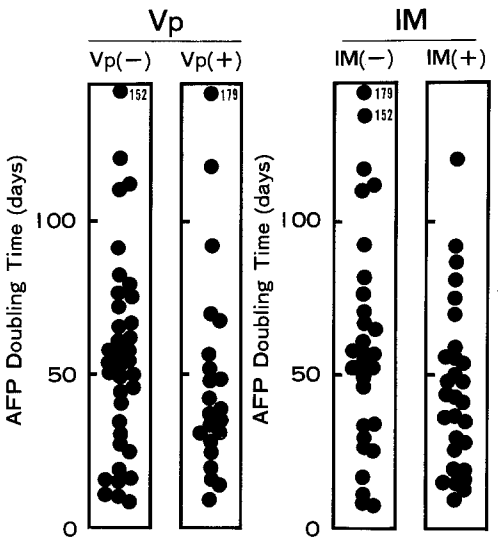

Fig. 9. The relationship between the α-fetoprotein (AFP) doubling time and the portal vein invasion (*Vp*) and intrahepatic metastasis (*IM*) factors

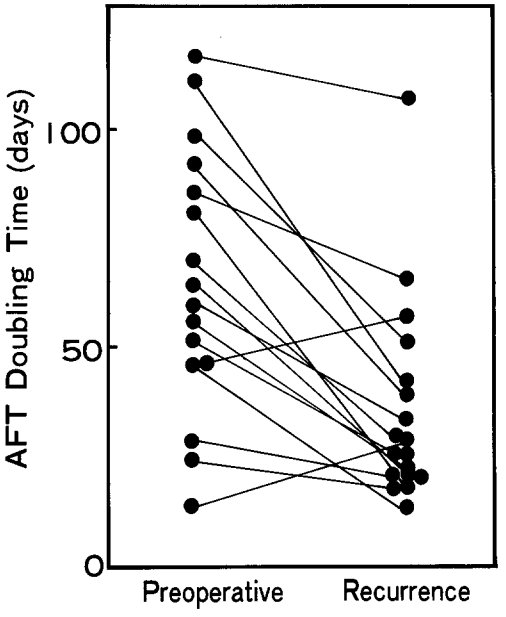

Fig. 10. Changes in the α-fetoprotein (AFP) doubling time at the time of recurrence

mining the outcome. However, there is no significant difference in the long-term prognosis among the three groups. To interprete this, presumably even in such cases of invasion, the tumor cells may not spread so widely, since almost all the parts may be removed by resection. On the other hand, tumor cell anaplasia is also one of the determinants, as indicated by the evidence that no case with the Edmondson 1 type, which is difficult to differentiate from adenoma, has had a recurrence up to date. By contrast, cases with the Edmondson 3–4 types, i.e., poorly differentiated HCC, show a poor prognosis, as indicated in Fig. 7. Thus, tumor cell anaplasia is also representative of the malignancy of HCC.

It has been proposed by Collings et al. [1] that tumor kinetics, in other words, the tumor growth rate, is one of the factors determining the outcome of a tumor-bearing host. In fact, Matsumoto et al. [5] have reported that HCC patients with a rapid increase of α-fetoprotein levels have a shorter survival time than those with a mild elevation. Another report by Shew et al. [10] indicates that the doubling time of the volume change estimated by a computed tomography or ultrasonography has a high correlation with the α-fetoprotein doubling time and varies widely from 29 to 398 days, which is compatible with the present results. From the results demonstrated in Fig. 9, the tumor growth rate is not necessarily concerned with vessel invasion or intrahepatic metastasis, suggesting that both factors may belong to a different category. On the other hand, it is noteworthy that the tumor growth rate became rapid at the time of recurrence, compared with the preoperative status, as demonstrated in Fig. 10. In addition, the frequency of poorly differentiated HCC was high in the larger tumor group. Similar findings of altered tumor characteristics along with the growing of the tumor have been observed; that is, a high ploidy on the DNA histogram, which has been recently recognized as the most effective indicator, occurs in advanced stomach cancer. Thus, the present results and the previous findings suggest that the malignancy of the HCC tumor may alter with the growing of the tumor. It is therefore concluded that the pathological features showing the malignancy of hepatocellular carcinoma appear in venous invasion and intrahepatic metastasis through the retrospective analysis of the postoperative prognosis.

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