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Conditions favoring long-term survival after hepatectomy for hepatocellular carcinomas

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Summary. The present study was aimed at answering the question of what patients with hepatocellular carcinomas could obtain long-term benefits from resectional therapy. The 239 patients hepatectomized from 1973 through 1986, with 33 tumor-free, 3-year survivors, were the subjects of the study. The following criteria for long-term survival were determined. (a) It is essential that there are no macroscopic tumor thrombi in any of the vessels. (b) It is desirable that there is no daughter lesion and a tumor size of less than 5 cm. (c) When there are daughter lesions, they should be confined to the region adjacent to the main tumor and only few in number. (d) Resection should be performed on a large scale within the limit of safety, especially for the tumors with daughter lesions. (e) The surgical margin should be free of tumor though the exposure of the tumor capsule is not always incompatible with long survival.

Introduction

Japan is a country with a high risk of hepatocellular carcinoma (HCC). HCC is the third most common form of malignancy in men and the fifth in women. Such an epidemiological background prompted Japan to conduct a nationwide mass screening of high-risk populations using serum α-fetoprotein tests and ultrasonography. In recent years, resectable small HCCs have increasingly been detected, leading to a rapid increase in potential curative resection.

At the same time, the surgical risk for cirrhotic patients has prompted the development of non-resectional treatments, such as hepatic artery ligation [5], transcatheter arterial embolization [7] and intratumoral ethanol injections [3].

These non-surgical therapies have spread throughout the country with even wider applications for patients with small cancers who have the potential to be cured by resectional treatment.

The purpose of this report is to describe the factors that affect the long-term survival rates following resection and the conditions that promise a tumor-free, 3-year survival.

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Materials and methods

A series of 440 adult patients were surgically treated from 1973 through 1986. The ages of the patients ranged from 22 years to 83 years, the average being 64 years, the male/female ratio was 5.8 to 1. The large majority (78% of the total) had coexisting chronic liver diseases including cirrhosis, chronic hepatitis and fibrosis. The HBsAg-positive patients accounted for 27.6%. The types of treatment are listed in Table 1. The consecutive series was divided into two periods; before (early period) and after (current period) the end of 1980, when an objective guideline on the safe limit of hepatectomy had been established and when smaller-sized HCCs ($\leqq 5$ cm) began to be seen in increasing number in patients admitted to our department. The types of resection are shown in Table 2. Sublobar resections, such as segmentectomy, subsegmentectomy or smaller-scale resections, increased in the latter period accounting for 54% (97/179) of the total compared with 39% (22/56) in the earlier period.

The prognostic factors relating to the long-term survival rates after hepatectomy were investigated using the current 179 hepatectomized series, and the conditions governing 3-year, tumor-free survival were assessed using the hepatectomized patients before the end of 1984. The annual survival rates were expressed as a cumulative survival rate, excluding hospital deaths.

Results

Prognostic factors related to survival

Tumor regional characteristics

Size of the tumor. HCCs less than 5 cm in diameter accounted for 32% (18/56) in the early series, in sharp contrast to the 66% (118/179) in the current series. Focusing on the current period, the 5-year survival rate for patients with small HCCs, less than 5 cm in diameter, was 47%, a much better result than the 10% seen for those with large tumors more than 5 cm in size, as shown in Fig. 1.

Invasion to the vascular and biliary structures. Intraportal invasion occurs much more frequently than intravenous or biliary tumor growth. Tumor thrombi were macroscopically found in 21% of the patients with large HCCs >5 cm (13/61) in the portal vein, 13% (8/61) in the hepatic vein, and 3.2% (2/61) in the biliary system compared with 3.3% (4/118), 0% and 0%, respectively, of the patients with small HCCs less than 5 cm in diameter. The annual survival rate

Table 1. Surgical experiences for HCCs

Treatment	Patients treated during		Total
	Apr 1973 – Dec 1980 (early period)	Jan 1981 – Dec 1986 (current period)	
Hx[a]	56	179	235
Re – Hx	0	6	6
Hx + HAL	2	20	22
HAL	33	95	138
HAC	14	10	24
Others	6	9	15
Total	111	319	440

[a] Hx, hepatectomy; HAL, hepatic arterial ligation; HAC, hepatic arterial cannulation

Table 2. Type of resection

Treatment	Operations performed during the	
	Early period	Current period
Subsegmental or wedge resection	13	64
Segmentectomy	9	44
Lobectomy	29	66
Trisegmentectomy	5	5
Total	56	179

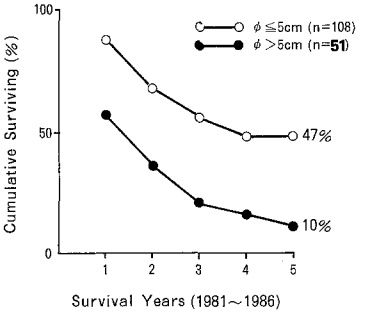

Fig. 1. Survival versus the size of the tumor

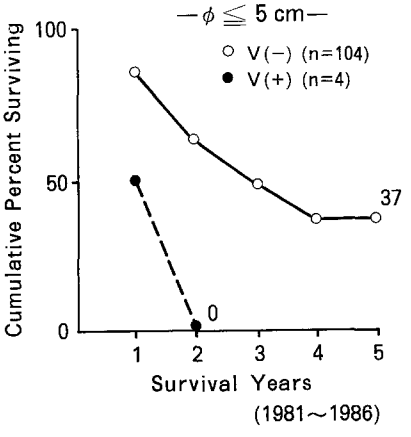

Fig. 2. Survival versus the V factor in cases with tumors of less than 5 cm. V represents the macroscopic tumor thrombi

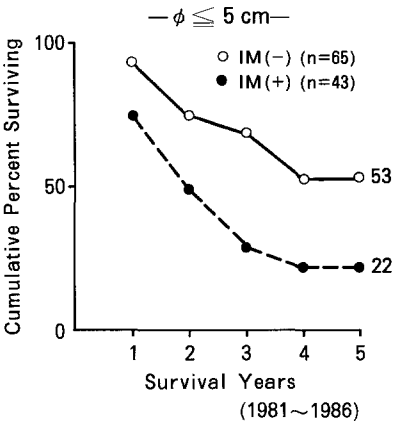

Fig. 3. Survival versus the IM factor in cases with tumors of less than 5 cm. IM represents macroscopic intrahepatic metastasis

of the patients with tumor thrombi in any of the vessels was 0% after 2 years, compared with 37% for 5 years for those without tumor thrombi, as shown in Fig. 2.

Tumor distribution. There were six HCC cases that suggested growth in a multifocal fashion where there were two or three nodules of a similar size in multiple sites distant from each other. The other 171 cases showed unicentric emergences with or without daughter lesions. Single HCCs accounted for 64% (75/118) of the small HCCs versus 29% (24/61) of the large HCCs. The 5-year survival rate was 53% for the cases with single growths, statistically better than the 22% for those with unicentric growths bearing daughter lesions or with multifocal growths in the current series, as shown in Fig. 3.

Resectional factors

Surgical margin. The SM(+) group, referring to patients with a free surgical margin of less than 10 mm from the tumor edge in the resected specimens, had a 27% 5-year survival rate, much worse than the 64% in the SM(−) group, as indicated in Fig. 4a. However, the big difference in survival rate seen between the SM(+) and SM(−) groups disappears, except for the 5-year survival rate, when looking at the HCCs with neither tumor thrombi nor daughter nodules, as demonstrated in Fig. 4b.

Extent of resection. The type of resection performed on cases with small HCCs can be classified into three types, subsegmental or wedge resections, segmentectomies and lobectomies. The lobectomized patients achieved a 5-year survival rate of as high as 64%, in sharp contrast to the approximate value of 16–30% for the patients who underwent sublobar resections, as shown in Fig. 5.

Backgrounds of the 3-year survivors

There were 43 3-year survivors by the end of 1984, and they could be grouped into 33 tumor-free survivors (group NR) and 10 tumor-bearing survivors (group R). Their backgrounds concerning liver function, the extent of resection and the tumor factors were tabulated, comparing the two groups, and are listed in Table 3.

The indocyanine green retention rate at 15 min showed no statistical difference between the two groups. Some difference was found with regard to the extent of resection. Large-scale resections greater than one segment had been performed on 58% (19/33) of group NR as against 40% (4/10) of group R.

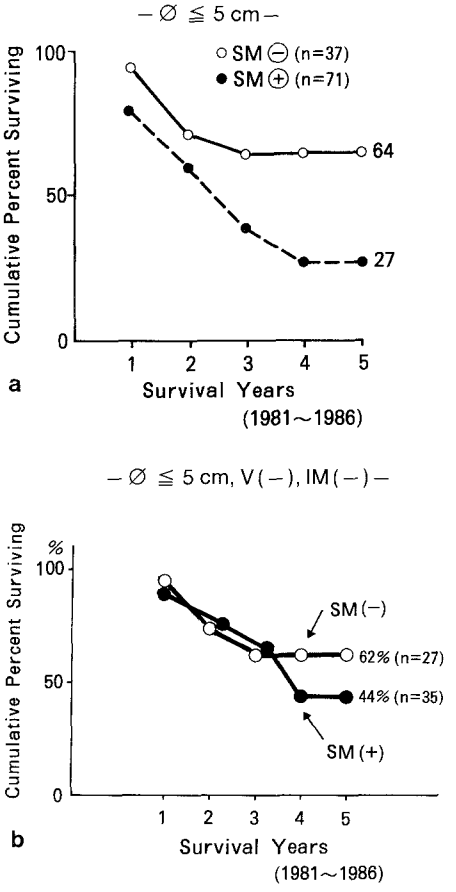

Fig. 4.a Survival versus the SM factor in cases with tumors of less than 5 cm. SM(+) means that the tumor-free tissue from the tumor edge to the surgical plane is less than 10 mm in width. SM(−) means that it is 10 mm or more. **b** Survival versus the SM factor in cases with small tumors (≤5 cm) without tumor thrombi and intrahepatic metastasis

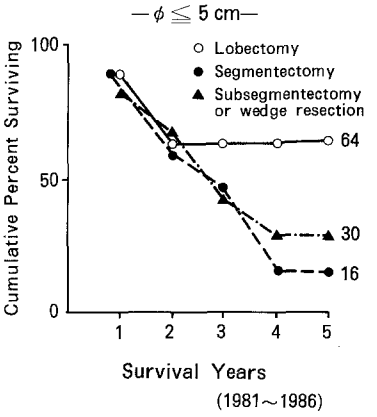

Fig. 5. Survival in contrast to approximate value for patients with sublobar resections

Table 3. Comparison of backgrounds of two groups of 3-year survivors

Characteristic	Tumor-free group NR (n = 33)	Tumor-bearing group R (n = 10)
ICG R15[a] (mean ± SD)	4%–41% (17 ± 11%)	3%–24% (13 ± 6.5%)
Extent of resection		
Lobectomy or CBS[b]	15	4
Segmentectomy	4	3
Subsegmentectomy or less	14	3
Tumor thrombi	0%	0%
Intrahepatic metastasis	9 (27%)	7 (70%)
Tumor size ≤5 cm (mean ± SD)	26 (79%) (4.7 ± 3.3 cm)	5 (50%) (6.1 ± 4.7 cm)
Surgical margin (+)[c]	14 (42%)	8 (80%)
Additional treatment	–	TAE[d] (n = 6) resection (n = 3)

[a] ICG R15, indocyanine green retention rate at 15 min
[b] CBS, central bisegmentectomy
[c] Surgical margin (+), surgical margin of tumor-free <10 mm in width
[d] TAE, transcatheter arterial embolization

The tumor sizes were less than 5 cm in 79% (26/33) of group NR in comparison with 50% (5/10) of group R. Tumor thrombi in the major branches of the vessels were not found in any cases in either group, while there was a distinct difference not only in the incidence of daughter nodules but also in the extent of their spread. They were detected in 70% (7/10) of group R, much more frequently than in the 27% (9/33) of group NR. The distance between the main tumor and the daughter nodules was different between the two groups. The distance was limited to within 2 cm in eight of the nine daughter-positive patients in group NR, all of whom had a lobectomy or bisubsegmentectomy. On the other hand, the distance was as long as 3 cm or more in the six of the seven daughter-positive cases in group R, and lobectomies had been performed in only three of them.

The tumors were located right beneath in liver surface in each of the 3 cases of group R and in 13 of the 14 cases of group NR who had had subsegmentectomies or a lesser resection. The surgical margin was positive in 42% (14/33) of the group NR in contrast to 80% (8/10) of the group R, although there were 8 cases of the 33 in group NR, in whom the tumor edges were partially exposed on the surgical plane.

Regarding additional postoperative treatment, three patients underwent a reresection and six others underwent transcatheter arterial embolization for local recurrences, which occurred 1–2.5 years after the initial resections. They were all alive at the third postoperative year, when two of them who had undergone a reresection returned to a tumor-free state. The group NR and group R patients did not receive any systemic adjuvant immunochemotherapy.

Discussion

Liver failure constitutes the major cause of operative deaths in both Western [1] and Eastern countries [2]. It therefore became a matter of great urgency to establish guidelines on the safe limits of resection prior to an operation, and these were formulated at the end of 1980 by our clinic [4, 8].

Since the introduction of a multiple regression equation defining treatment selection, surgical mortality has dropped drastically from 16% (9/56) for the early series

down to 5.7% (12/209) in the current series. Nowadays, the risk-to-benefit relationship has become a lesser issue, and we are now entering an age where we can discuss exactly what the potential benefits are from resection with regard to a long-lasting, tumor-free state.

Judging from the survival rates and the backgrounds of the 3-year survivors, the most important prognostic factor is the vascular invasion [6]. The patients with tumor thrombi were unable to survive for 3 years. The absence of daughter lesions is a desired factor. If daughter lesions are present, their locations should be confined to the region surrounding the main tumors and removed in a large-scale resection with wide tumor-free tissue. If the metastatic deposits spread over the unilateral lobe, a cancer-free state will not last long enough even with a lobectomy that apparently covers the lesions.

The tumor size is also an important element considering that vascular invasion and daughter lesions develop increasingly as the tumor grows in size [6], but it is not a crucial factor, as was indicated by the fact that the 7 of the 33 cases who could survive for 3 years in a tumor-free state, had HCCs larger than 5 cm.

Obtaining a wide tumor-free surgical margin is a recommendable policy, but it is very likely to be governed by the distance of the tumor from the liver surface and the intrahepatic major vessels, especially when the surgeon is forced to perform a sublobar resection with a limited hepatic reserve [9]. Although a positive surgical margin is a condition compatible with long tumor-free survival, as long as the tumor growth is limited within the tumor-capsular space, the compatibility does not lessen the importance of a wide tumor-free surgical margin, because there is a limit to the image detectability for diagnosing pre- or intra-operatively, the degree of extracapsular invasion and the possible presence of miliary-size daughter lesions.

In conclusion, a long-term complete remission following resection can be expected for cases with HCCs without tumor thrombi and intrahepatic metastases, if any, limited to the region immediately round the main tumors. A tumor location closer to the liver surface and far from the major branches of vessels, when the degree of resection must be limited to the sublobar level, and a tumor size of less than 5 cm are deemed preferable conditions. Patients who well match these conditions should be subject to as large a resection as possible, within the functional limits of safety, as the treatment of first choice.

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