Significance of transcatheter chemoembolization combined with surgical resection for hepatocellular carcinomas*

Morito Monden, Jun Okamura, Masato Sakon, Mitsukazu Gotoh, Kenji Kobayashi, Koji Umeshita, Tsuyoshi Yamada, Chikazumi Kuroda, Masami Sakurai, and Takesada Mori

Departments of Surgery, Radiology and Pathology, Osaka University Medical School, Osaka Teishin Hospital, Osaka, Japan

Summary. In order to improve the survival rate after liver resection for hepatocellular carcinoma (HCC), 71 HCC patients were treated with transcatheter chemoembolization (TCE). In the present study, we analyzed the effects of TCE on the patients' survival rates, as well as on the liver specimens resected in a histopathological study, comparing those not treated with TCE (n = 21). The overall survival rates, including hospital mortality, for 1 year, 3 years and 5 years were 81%, 72% and 54% respectively. However, no differences were observed in the survival rates between the TCE and the non-TCE groups. A histopathological study demonstrated that TCE was quite effective on the main tumor but not on intrahepatic metastasis or on tumor thrombus in the portal vein. However, we found that most of the intrahepatic metastatic lesions were necrotized in 8 of the 30 cases with these lesions. The histopathological study proved that these particular cases had some abnormalities in the portal blood supply. All but one of them are currently alive 3–48 months after resection, although the prognosis of the patients who had intrahepatic metastasis or a tumor thrombus in the portal vein was extremely poor. Preoperative TCE may, therefore, be thought of as a useful modality when it is effective in killing intrahepatic metastases. To control the lesions, portal vein embolization may be a promising technique in the future.

Introduction

Although liver resection has become a standard and safe operative modality these days, the results for hepatocellular carcinoma (HCC) have not been necessarily satisfactory. The 5-year survival rates for patients with primary liver cancer are reported to range from 11% to 46% [6]. Recently the Liver Cancer Study Group of Japan has reported that the 3-year survival rate following liver resection is approximately 30%, having reviewed 809 cases [5]. One of the major factors contributing to these unsatisfactory results might be the early intrahepatic spread via the portal vein.

The high incidence of vascular invasion or extracapsular invasion is well recognized not only in advanced cases, but also in cases of in minute HCC [3, 15]. Extensive excision should therefore be chosen to eradicate all the intrahepatic metastatic lesions. However, when the lesion is combined with liver cirrhosis, as has been reported to be present in more than 80% of the total number of HCC cases [5], a limited resection might be preferable in order to prevent postoperative liver failure [1].

In order to improve the results of liver resection on hepatocellular carcinomas, especially when combined with liver cirrhosis, it is necessary to control intrahepatic metastasis or the tumor thrombus in the portal vein. For this purpose, we performed transcatheter chemoembolization (TCE), which is mainly used for non-resectable hepatic malignancies [13, 14], on patients with resectable hepatic malignancies as preoperative management from October, 1980 [10]. In this study, we have reviewed the results of the HCC patients who underwent a liver resection with or without TCE.

Materials and methods

Since 1980, we have performed 117 liver resections on hepatic malignancies, of which 92 cases were HCC. Out of these 92 patients, 71 patients received preoperative transcatheter chemoembolization (TCE group), while the remaining 21 patients underwent a liver resection without preoperative TCE (non-TCE group). This was not a randomized study. The non-TCE group also underwent one-shot intra-arterial chemotherapy at the time of angiography. For the TCE materials, we infused Gelfoam cubes through a catheter inserted into the hepatic artery following injections of 50 mg adriamycin in the first 25 cases. We then started using 5–10 ml lipiodol (Laboratoire Guerbet, France) in addition to standard TCE (transcatheter lipiodol chemoembolization; TLCE). Forty-six patients were treated with this method.

After resection, all the liver specimens were cut into slices 7–8 mm in thickness following fixation. Each slice containing a tumor was sectioned for histological observation.

Results

Histopathological study

Table 1 summarizes the effect of preoperative TCE examined in a histopathological study. The number of cases

Table 1. Effectiveness of transcatheter chemoembolization observed in histopathological study

Condition	TCE (–) (n=21)	TCE (+)		
		TCE (n=25)	TLCE (n=46)	Total (n=71)
Complete necrosis of main tumor	1 (4.8%)	15 (60.0%)	23 (50.0%)	38 (53.5%)
Incidence of encapsulated tumor	18 (85.9%)	23 (92.0%)	38 (82.6%)	61 (85.9%)
Incidence of capsular invasion	14 (77.7%)	19 (82.6%)	20 (52.6%)	39 (63.9%)
Necrosis of capsular invasion	1 (7.1%)	12 (63.2%)	13 (65.0%)	25 (64.1%)
Incidence of intrahepatic metastasis	10 (47.6%)	9 (36.0%)	21 (45.7%)	30 (42.3%)
Necrosis of intrahepatic metastasis	1 (10.0%)	3 (33.3%)	10 (47.6%)	13 (43.3%)
Incidence of tumor thrombus in the portal vein	4 (19.0%)	5 (20.0%)	8 (17.4%)	13 (18.3%)
Necrosis of tumor thrombus	0 (0.0%)	0 (0.0%)	2 (25.0%)	2 (15.4%)

examined was 21 in the non-TCE group, 25 in the conventional TCE group and 46 cases in the TLCE group. The differences between the TCE and non-TCE groups were observed according to the rate of necrosis of the main tumors, that of the intracapsular invasions and that of the intrahepatic metastasis. As far as the microscopical examination is concerned, preoperative TCE proved effective not only on the main tumor, but also on the metastatic lesions.

Clinical study

The overall operative mortality rates were 2.2% for death within 1 month and 6.5% for total hospital mortality, but no significant difference was observed between the TCE and non-TCE groups. Figure 1 shows the overall cumulative survival rates (Kaplan-Meier method) of the 92 patients including hospital mortalities. The 1-year, 3-year and 5-year survival rates were 81%, 72% and 54% respectively. The actual survival rates of the TCE group, excluding hospital mortalities, were 88.1% (59/67) for 1 year, 62.9% (22/35) for 3 years and 40.0% (6/15) for 5 years.

Figure 2 shows the cumulative survival rates of the TCE and non-TCE groups, excluding hospital mortalities. There is no difference between them. Although the effectiveness was obvious in the histopathological study, the postoperative survival rates of the patients were not found to have improved in the clinical study. In order to elucidate the clinical effects of TCE, further analyses were done using the cases treated with TCE followed by resection, excluding hospital mortalities.
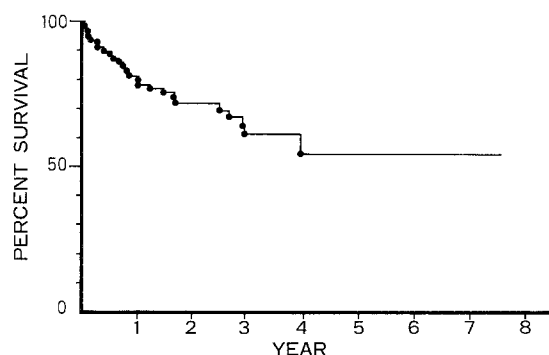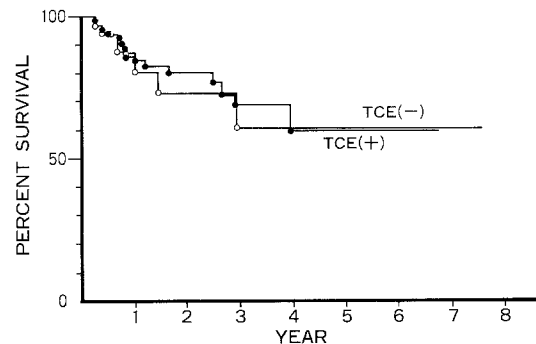

Fig. 2 Cumulative survival rates following liver resection with or without preoperative TCE

Fig. 3 shows the cumulative survival rates by tumor size. The tumors larger than 5 cm in diameter resulted in a poor prognosis, showing 31% for a 3-year survival rate. On the other hand, the prognosis of the cases with tumors smaller than 5 cm in diameter was quite satisfactory. The 5-year survival rate for this group was 73%. We did not see any difference between the two categories when the tumor size was smaller than 5 cm.

The cumulative survival rates of patients with or without a tumor thrombus in the portal vein are shown in Fig. 4. The 5-year survival rate of the patients without a tumor thrombus was 69.6%. On the other hand, for the patients with a portal thrombus, even the 1-year survival rate was only 50.8%, and no one has survived beyond 2 years so far. Figure 5 shows the survival curves for the patients
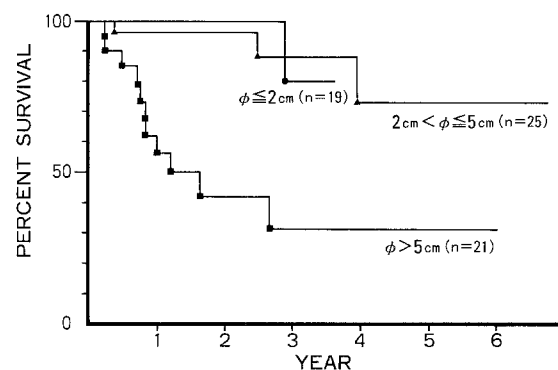

Fig. 1. Cumulative survival rates following liver resection for 92 HCC patients including hospital mortalities (Kaplan-Meier method)

Fig. 3. Cumulative survival rates following liver resection, by tumor size in the TCE group
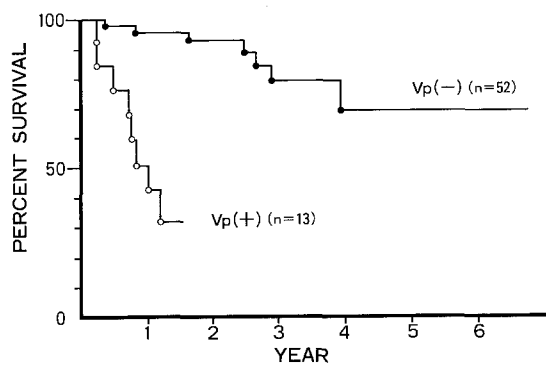
Fig. 4. Cumulative survival rates following liver resection with or without tumor emboli in the portal vein (Vp) in the TCE group
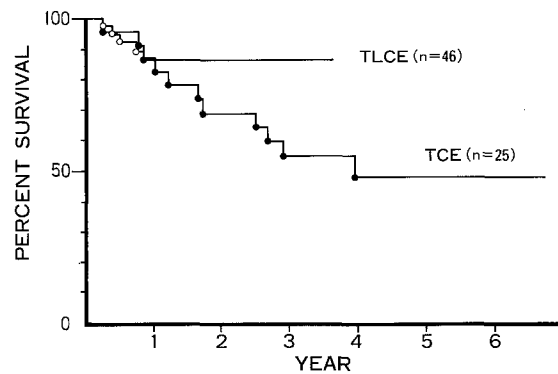

Fig. 6. Cumulative survival rates following liver resection, by TCE method
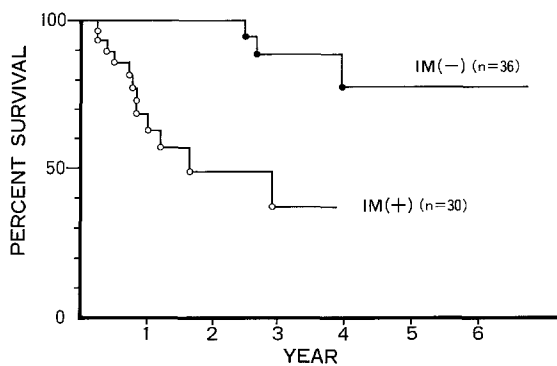

Fig. 5. Cumulative survival rates following liver resection with or without intrahepatic metastases (IM) in the TCE group
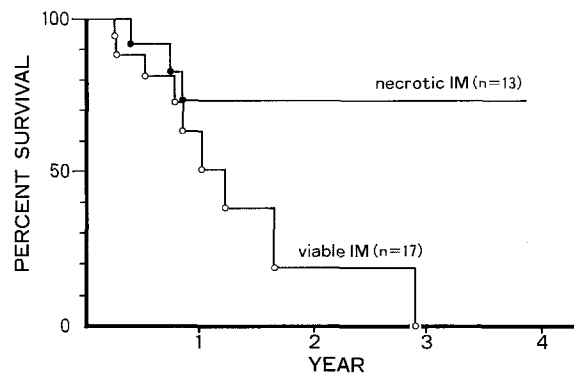

Fig. 7. Cumulative survival rates following liver resection, by necrosis of intrahepatic metastases (IM)

with or without intrahepatic metastasis. The 5-year survival rate for the patients without intrahepatic metastasis was as high as 77.5%. However, the 3-year survival rate for those with metastases was only 36.6%. Figure 6 is a comparison of the two embolization methods. Better results were obtained with lipiodol chemoembolization.

As described above, the survival rates with larger cancers, with a tumor thrombus in the portal vein or with intrahepatic metastasis, were still very low, even though

TCE was performed preoperatively. However, when the survival rates for the cases with intrahepatic metastases were compared between the two groups (one group in which at least one of the metastatic lesions was necrotized, and the other in which no metastasis was necrotized), a marked improvement was observed in the former group (Fig. 7). It can therefore be concluded that preoperative TCE is effective as a HCC therapy, even if improved survival rates have not been obtained so far.

Table 2. Cases in which transcatheter chemoembolization (TCE) was effective on intrahepatic metastases (IM) or tumor thrombi in the portal vein (Vp)

Case	Tumor size (cm)	Necrosis of main tumor	TCE	No. of IM[a]	Vp	Liver histology	Others	Survival (months)
1	5.5	partial	TCE	5 (5)	Vp1 (v)[b]	normal	liver necrosis	10, dead
2	4.0	complete	TCE	16 (15)	–	cirrhosis	liver necrosis	48, alive
3	2.8	complete	TCE	10 (7)	–	cirrhosis	obstruction of the PV[e]	44, alive
4	3.1	partial (99%)	TLCE	12 (12)	–	CIH[c]	liver necrosis	37, alive
5	1.8	complete	TLCE	10 (9)	–	cirrhosis	lipiodol in the liver	24, alive
6	1.8	complete	TLCE	5 (4)	Vp3 (n)	CAH[d]	obstruction of rt PV	16, alive
7	5.0	partial	TLCE	13 (8)	Vp2 (n)	cirrhosis	liver necrosis	15, alive
8	8.5	complete	TLCE	3 (3)	–	normal	liver necrosis	3, alive

[a] Number of necrotic intrahepatic metastases in parentheses
[b] v, viable; n, necrosis
[c] CIH, chronic inactive hepatitis
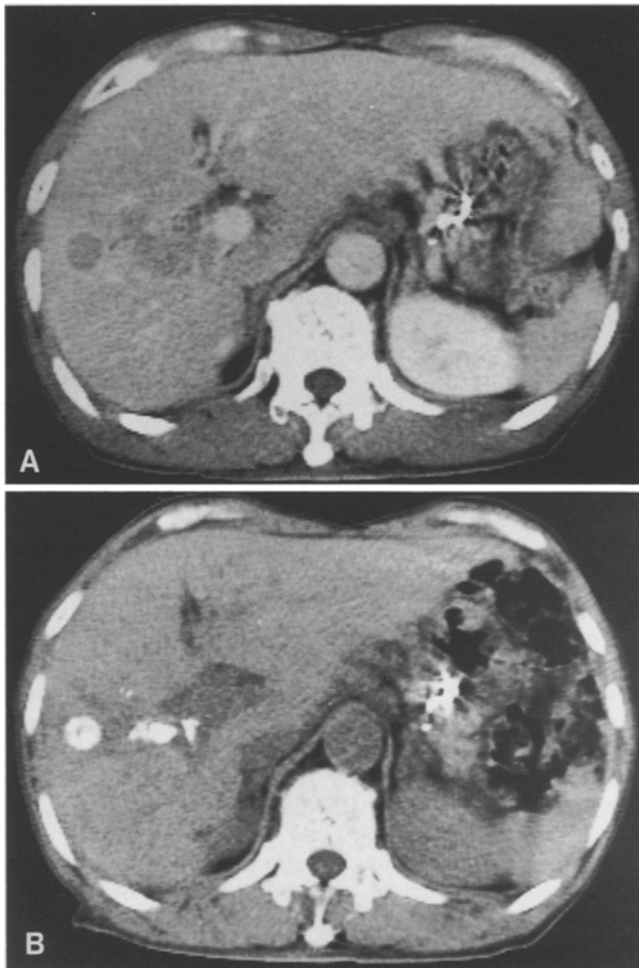[d] CAH, chronic active hepatitis
[e] PV, portal vein

Fig. 8. Computerized tomographic scan of liver pre-TLCE A and post-TLCE B

Fig. 9. Indirect portography showing an obscruction in the right portal vein and a thrombus in the portal vein

vealed a completely necrotized main tumor (1.8 cm in diameter) and tumor thrombus (approximately 1 cm in diameter and 4 cm in length) in the portal vein. Five intrahepatic metastatic lesions were found, of which four were also completely necrotized. The histological diagnosis of hepatocellular carcinoma (Edmondson III) was confirmed by the last viable intrahepatic metastatic lesion (Fig. 11). The patient is doing well without any sign of a recurrence (at the time of writing).

Discussion

The characteristics of HCC easily invading the vascular vessels or growing outside the tumor capsule, resulting in spontaneous intrahepatic metastasis or a tumor thrombus in the portal vein at the early stage of the disease [3, 9, 15], are ascribed to a poor prognosis after a liver resection in HCC patients. The surgical procedure itself might also spread the tumor cells over the liver resulting in multiple recurrences during the early period after resection. In order to avoid this unpleasant outcome, we performed preoperative TCE on patients with resectable HCC. In the present study, we reviewed 92 patients with HCC.

The histopthaological examination clearly demonstrated that TCE was very effective in inducing tumor necrosis especially on the main tumor, with 38 out of the 71 cases having complete necrosis. However, with respect to intrahepatic metastasis or a tumor thrombus in the portal vein, which are believed to be the key factors in determining the prognosis, there was little effect except in a few particular cases as reported elsewhere [11]. The limited effect of TCE on these two lesions may mean that the blood supply to the micrometastasis comes through the portal vein as well as the hepatic artery. If both the arterial and portal blood supplies were therefore controlled, the lesion could be completely necrotized. As shown in Table 2, ne-

Table 2 is a list of the cases in which TCE did have an effect on intrahepatic metastasis or on the portal thrombus. In general, the prognosis of patients who have these lesions is very poor. Interestingly, all but one of the patients are currently alive, 3 months to 4 years after resection.

Case report

The patient was a 72-year-old man who had undergone distal gastrectomy for gastric cancer in our department 5 years previously. In 1986, an increased α-fetoprotein level was first detected. A small low-density area was seen in the right lobe in a computed tomography (CT) scan (Fig. 8 A). We suspected HCC with a tumor thrombus in the portal vein instead of the recurrence of gastric carcinoma.

Angiography revealed a hypervascular tumor in the right lobe and an obstruction in the right branch of the portal vein (Fig. 9). The patient underwent TLCE at the time of angiography. The CT scan carried out 1 month after TLCE showed an accumulation of lipiodol in the main tumor and the tumor thrombus in the portal vein (Fig. 8 B). Right lobectomy was performed for a diagnosis of HCC with a tumor thrombus in the portal vein on July 8, 1986. Fig. 10 shows a slice of the liver specimen resected. A careful histopathological examination of the specimen re-
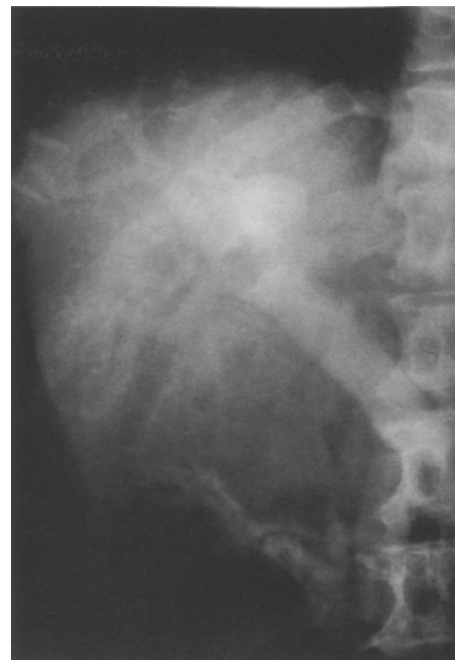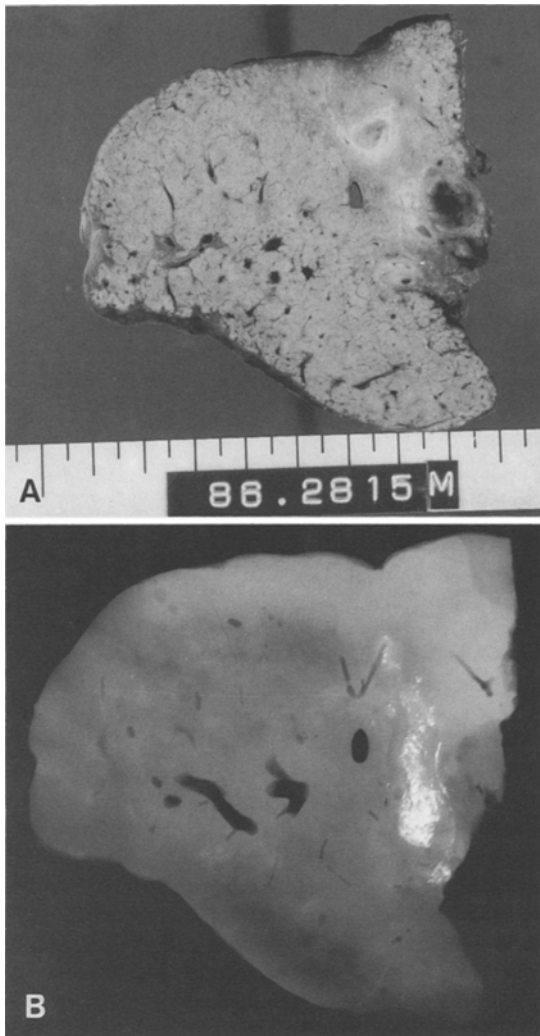
Fig. 10. One slice of surgical specimen **A** and the low-voltage X-ray piture **B**

crosis of intrahepatic metastases or the tumor thrombi in the portal vein was found in several cases in which the portal blood flow was spontaneously excluded from the field where the metastases were located by compression due to the tumor, the tumor thrombus itself or portal embolization, which took place incidentally through the arterioportal shunt. Recently, portal vein embolization has been performed in combination with arterial embolization [2, 8]. When the portal vein was embolized about 2 weeks after arterial embolization, a very high incidence of necrosis of the intrahepatic metastases was observed, but not complete necrosis [2]. Complete necrosis, however, was reported when portal embolization was performed simultaneously with arterial embolization [8]. Thus, it is most important to control the portal blood supply to the tumor area to enhance the effect of arterial embolization.

As demonstrated in Fig. 2, there was no significant difference in the survival rates between the non-TCE and the TCE groups, although this study was not a randomized one. These data could be easily understood because TCE had little effect on intrahepatic metastasis or the tumor thrombus in the portal vein, which should be controlled to improve the results of liver resection in cases of HCC. When the survival data were compared between the two groups treated by conventional TCE and TLCE, better survival rates were obtained with TLCE (Fig. 6). TLCE has a tendency to be effective on intrahepatic metastasis, as shown in Table 2, and these results are compatible with other reports [4, 7, 12]. Although the prognosis of cases with intrahepatic metastases was very poor, the prognosis of cases with necrotic intrahepatic metastasis was significantly better than that of cases with a viable one (Fig. 7, Table 2). Preoperative TCE might, therefore, be effective in improving the prognosis after liver resection in cases with HCC, provided that intrahepatic metastasis can be controlled. The next step would be to devise a more effective method to suppress intrahepatic metastasis, and portal embolization seems to be one of the promising modalities.

Fig. 11. Viable tumor cells in one of the five intrahepatic metastases

References

1. Kanematsu T, Takenaka K, Matsumata T, Furuta T, Sugimachi K, Inokuchi K (1984) Limited hepatic resection effective for selected cirrhotic patients with primary liver cancer. Ann Surg 199: 51
2. Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S (1986) Preoperative portal vein embolization for hepatocellular carcinoma. World J Surg 10: 803
3. Kondo Y, Niwa Y, Akikusa B, Takazawa H, Okabayashi A (1983) A histopathologic study of early hepatocellular carcinoma. Cancer 52: 687
4. Konno T, Maeda H, Iwai K (1983) Effect of arterial administration of high-molecular-weight anticancer agent SMANCS with lipid lymphographic agent on hepatoma: a preliminary report. Eur J Cancer Clin Oncol 19: 1053
5. The Liver Cancer Study Group of Japan (1987) Primary liver cancer in Japan. Cancer 60: 1400
6. Nagrney DM, Adson MA (1987) Major hepatic resections for hepatoma in the West. In: Hepatic and biliary cancer. Marcel Dekker Inc., New York, p 167
7. Nakamura K, Tashirto S, Hiraoka T (1983) Studies on anticancer treatment with an oily anticancer drug injected in the ligated feeding hepatic artery for liver cancer. Cancer 52: 2193
8. Nakao N, Miura K, Takahashi H, Ohnishi M, Miura T, Okamoto E, Ishikawa Y (1986) Hepatocellular carcinoma: Combined hepatic, arterial and portal venous embolization. Radiology 161: 303
9. Nakashima T, Okuda K, Kojiro M, Yamaguchi R, Sakamoto K, Ikara T (1983) Pathology of hepatocellular carcinoma in Japan-232 consecutive cases autopsied in 10 years. Cancer 51: 867
10. Okamura J, Horikawa S, Fujiyama T, Monden M, Kambayashi J, Sikujara O, Sakurai M, Kuroda C, Nakamura H, Kosaki G (1982) An appraisal of transcatheter arterial embolization combined with transcatheter arterial infusion of chemotherapeutic agent for hepatic malignancies. World J Surg 6: 352
11. Sakurai M, Okamura J, Kuroda C (1984) Transcatheter chemoembolization effective for treating hepatocellular carcinoma — a histopathologic study. Cancer 54: 387
12. Sasaki Y, Imaoka S, Kasugai H, Fujita M, Kawamoto S, Ishiguro S, Kojima J, Ishikawa O, Ohigashi H, Furukawa H, Koyama H, Iwanaga T (1987) A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin and gelatin sponge. 60: 1194
13. Wheeler PG, Melia W, Dubbins P, Jones B, Numerleg H, Johnson P (1979) Non-operative arterial embolization in primary liver tumors. Br Med J 2: 242
14. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S (1983) Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 148: 397
15. Yamasaki S, Hasegawa H, Makuuchi M (1981) Clinico pathological observation of the minute liver cancer and the new method of hepatectomy; analysis of 27 resected cases. Acta Hepatol Jpn 22: 1714