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Efficacy of combination treatment – (TAE with Adriamycin and ethanol) – for hepatocellular carcinoma

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Summary. Among 44 patients with hepatocellular carcinoma (HCC), combination treatment with both transhepatic arterial embolization (TAE) and ethanol injection therapy (EIT) was performed in 10 patients. Only two had tumors measuring less than 3 cm in diameter. In all, eight patients had solitary tumors and two had multiple tumors. The tumor was classified as stage I in one patient, stage II in six subjects, stage III in two patients, and stage IV in one subject prior to TAE, but one stage II case was changed to stage III after laparotomy. The clinical stage was I in two patients, II in six subjects and III in two patients. Five patients with tumors of stages I and II achieved either a complete response (CR) or partial response (PR). However, three patients with tumors of stages III and IV showed progressive disease (PD). Thus, the response rate (CR+PR) was 50%. For tumor stages I and II, the 1-, 2-, and 3-year survival values were 100%, 100%, and 83%, respectively. For tumor stages III and IV, the 1- and 2-year survival values were 75% and 25%, respectively. Combination treatment of HCC appears to be efficacious for tumor stages I and II.

Introduction

Hepatocellular carcinoma (HCC) is one of the more common malignancies encountered around the world, particularly in Asian and African countries [23]. Recently, sonography and measurement of serum alpha-fetoprotein (AFP) levels have successfully been used in the detection of HCC. About two-thirds of HCCs found by screening of high-risk groups such as hepatitis B surface-antigen-positive individuals and patients with chronic liver disease are unifocal and measure less than 3 cm in diameter [6, 7]. However, because of the poor functional reserve as judged by liver histology or determination of the ICG Rmax value, only about 20% of HCCs are resectable according to the criteria of the Liver Cancer Study Group of Japan [8]. Most unresectable early HCCs in patients with chronic liver disease are treated by transcatheter arterial embolization (TAE) therapy. However, the value of TAE therapy is limited; indeed, Yamada et al. [24] reported that for 838 HCC patients treated by TAE, the 3- and 5-year survival values were only 12% and 6%, respectively. This appears to be the case because even small HCCs often invade the capsule (intracapsular invasion) and sometimes extend beyond the capsule (extracapsular invasion or satellite formation), and TAE is ineffective against these forms of extension [5, 13].

Sonographically guided percutaneous ethanol injection therapy (PEIT) was first described in 1983 by Sugiura et al. [18]. Ethanol injection therapy (EIT) has recently attracted a great deal of attention in the treatment of liver neoplasms [1, 3, 10, 11, 15, 16, 19, 21]. Because the injected ethanol is distributed in only a limited area, resultant adverse effects and liver dysfunction are also mild and transient. We studied the effects of combination treatment with TAE and EIT in HCC patients grouped according to the tumor-staging classification of the Liver Cancer Study Group of Japan.

Patients and methods

From March 1988 to January 1990, we treated 44 HCC patients at Osaka Teishin Hospital. Combination treatment with both TAE and EIT was given to ten patients (Table 1), including five men and five women whose ages ranged from 40 to 77 years (average, 62 years). TAE was performed at the time of angiography via a catheter placed into the proper (right or left) hepatic artery using the Seldinger technique. Adriamycin (20–50 mg) and ethiodized oil (lipiodol, 2–16 ml) were injected, and embolization of the feeding arteries was performed with particles of gelatin sponge. About 4 weeks after TAE therapy, US-guided EIT was performed percutaneously or transhepatically using a 21-gauge needle (20 cm in length) inserted into both the center of the tumor and sites close to its edge. The volume of injected ethanol was 3–47 ml. Five patients

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Table 1. Combination treatment with doses of Adriamycin and ethanol and subsequent additional procedures

Case number	Age (years)	Sex (M/F)	TAE			EIT (ml)	Subsequent additional procedure
			ADR (mg)	LPD (ml)	GS		
1	40	F	20	6	1/10	10	Resection
2	67	F	50	13	1/10	5	Resection
3	66	F	30	10		3	Laparotomy
4	71	M	40	10	1/10	30	Laparotomy
5	77	M	50	16	3/10	18	–
6	59	F	50	15	1/5	24, 20	AIC
7	60	M	50 (E)	2		10, 26, 9	Laparotomy, TAE
8	64	F	–	7	1/2	38, 20	Laparotomy
9	58	M	50	15	1/3	7, 47	TAE
10	60	M	20	7	1/10	23, 13, 13	

ADR, Adriamycin; E, epirubicin; LPD, ethiodized oil (lipiodol); GS, gelatin sponge; AIC, arterial infusion chemotherapy

Table 2. Classification of tumor stages and clinical stages

Tumor-staging criteria

T1: A single tumor of 2 cm or less in its greatest dimension, without vascular invasion

T2: A single tumor of 2 cm or less in its greatest dimension, with vascular invasion
Multiple tumors with a maximum tumor diameter of 2 cm or less, confined to one lobe
A single tumor with a diameter exceeding 2 cm, without vascular invasion

T3: A single tumor with a diameter exceeding 2 cm, with vascular invasion
Multiple tumors with diameters exceeding 2 cm, confined to one lobe

T4: Multiple tumors in more than one lobe
Associated vascular invasion in the first branch of the portal or hepatic veins

Clinical staging criteria

Findings	Stage		
	I	II	III
Ascites	None	Treatment effective	Treatment ineffective
Serum bilirubin (mg/dl)	<2.0	2.0– 3.0	>3.0
Serum albumin (g/dl)	>3.5	3.0– 3.5	<3.0
ICG R_{15} (%)	<15.0	15 –40	>40.0
Prothrombin activity (%)	>80.0	50 –80	<50.0

underwent repeated EIT. The other additional procedures included resection in two cases, exploratory laparotomy in four cases, and TAE and arterial infusion chemotherapy in one case. The staging of HCC and the clinical stage of liver cirrhosis were determined according to the classification system of the Liver Cancer Study Group of Japan [9] (Table 2).

Results

Table 3 shows the data obtained in the ten patients who received the combination treatment. Four showed elevated AFP levels (>100 ng/ml) before TAE. Only two had tumors measuring less than 3 cm in diameter, and the others had lesions measuring more than 3 cm in diameter. In all, eight patients had solitary lesions and two had multiple tumors. According to the criteria of the Liver Cancer Study Group of Japan, the tumor stage before TAE was I in one patient, II in six subjects, III in two patients, and IV in one subject. Two patients were in clinical stage I; six, in stage II; and two, in stage III. Angiography revealed seven hypervascular tumors, three hypovascular tumors, one lesion of mixed vascularity, and one lesion of fine vascularity.

Table 4 presents the results of the combination treatment. Cases 1 and 2 underwent resection of the tumor; their elevated AFP values decreased to normal levels, and a complete response (CR) was obtained in both cases. Patient 1 is alive at 30 months after TAE, but case 2 died of liver failure after 26 months. Cases 3 and 4 underwent exploratory laparotomy because of poor functional reserve as determined by liver histology. Intraoperative ethanol injection was performed instead of resection. Case 3 showed a PR, whereas patient 4 achieved a CR that lasted for 21 months after TAE (Fig. 1). However, the AFP level increased rapidly at about 24 months after TAE, at which time multiple metastases were detected by CT scanning (case 4). In cases 5 and 6, as liver or renal function was too poor for laparotomy, EIT was performed. Case 5 showed a PR, whereas patient 6 developed PD as revealed by the detection of a daughter nodule; however, this patient remains alive at 33 months after TAE.

In cases 7 and 8, daughter nodules were found during the operation. Intraoperative ethanol injection of the main tumor was performed in both cases. In patient 7, the daughter nodule was not injected with ethanol; the AFP values temporarily decreased to normal levels, but the residual tumor began to grow. In case 8, the daughter nodule also received ethanol injection, and although the tumors showed NC, this patient remains alive at 24 months after TAE. Case 9 had a tumor initially measuring more than 10 cm in diameter and died of liver failure due to massive cancer. Patient 10 had tumors in both lobes; the main tumor was controlled well, but daughter nodules appeared.

Table 5 shows the relationship between the rate of response to the combination treatment and the tumor stage. Five patients with tumors of stages I and II achieved either a CR or a PR, whereas three subjects with tumors of stages III and IV showed PD. The actuarial survival curve

Table 3. Patients' background characteristics

Case number	Age (years)	Sex (M/F)	Initial AFP (ng/ml)	tumor size (mm)	Tumor stage	Clinical stage	Tumor stain on angiogram
1	40	F	800	15 × 15	I	I	Fine vascularity
2	67	F	108	24 × 24	II	II	Hypervascular
3	66	F	34	30 × 30	II	II	Hypovascular
4	71	M	30	31 × 30	II	II	Hypervascular
5	77	M	2	61 × 51	II	I	Hypervascular
6	59	F	46	48 × 38	II	III	Hypervascular
7	60	M	29	46 × 38	II	II	Hypovascular
8	64	F	28	39 × 34	III	II	Hypervascular
				15 × 14			Hypovascular
9	58	M	152	104 × 57	III	III	Mixed vascularity
10	60	M	282	31 × 28	IV	II	Hypervascular
				39 × 33			Hypervascular

Table 4. Results of combination treatment

Case number	Age (years)	Sex (M/F)	Tumor stage prior to operation	Tumor stage at operation	Change in AFP (ng/ml)	Response (CT, Echo)	Outcome	
							Follow-up (months)	Cause of death
1	40	F	I	I	↓	CR	30	Alive
2	67	F	II	II	↓	CR	26	Liver failure
3	66	F	II	II	N	PR	36	Alive
4	71	M	II	II	N	CR → recurrence	30	Alive
5	77	M	II	–	N	PR	32	Alive
6	59	F	II	–	N	PD	33	Alive
7	60	M	II	III	↓↑↓	PD	11	Rupture of EV
8	64	F	III	III	N	NC	24	Alive
9	58	M	III	–	↑	PD	18	Liver failure
10	60	M	IV	–	→	PD	14	Sepsis

EV, Esophageal varices; N, normal

Table 5. Relationship between the response to combination treatment and the tumor stage

Tumor stage	Response			
	CR	PR	NC	PD
I	1	–	–	–
II	2	2	–	1
III	–	–	1	2
IV	–	–	–	1

generated for the ten patients who received combination treatment is shown in Fig. 2. For tumors of stages I and II, the 1-, 2-, and 3-year survival values were 100%, 100%, and 83%, respectively. For tumor stages III and IV, the 1-year survival value was 75% and the 2-year value was only 25%.

Next, we studied the histologic effects of combination treatment. Figure 3 a shows the macroscopic appearance of a formalin-fixed liver specimen; the encapsulated tumor mass together with the surrounding liver parenchyma had become completely necrotic. Figure 3 b shows a microscopic view of the capsule between the necrotic liver parenchyma and the cirrhotic liver tissue. Numerous histiocytes and lymphocytes were seen to have distributed throughout the capsule and infiltrated into the necrotic liver parenchymal tissue.

Discussion

In the present study, we evaluated the efficacy of combination treatment using the tumor-staging classification of the Liver Cancer Study Group of Japan. EIT has quite a good local effect and can serve as an alternative to surgery for the curative treatment of small HCC [19]. We consider that the tumor stage is a better criterion than the tumor diameter for evaluation of the efficacy of treatment. Five of six patients with tumors of stages I and II achieved a CR or PR, whereas three of four subjects with tumors of stages III and IV developed PD. Thus, there was quite a difference between stage II and stage III. In stage II, the tumor diameter is not regarded if the tumor is solitary and has not invaded the vascular system. Stage III represents either a solitary tumor that has invaded the vascular system or multiple tumors that are confined to one lobe. The stage determined by angiography may be different from that determined by observation of the surgical specimen. Surgically unresectable HCC in patients showing poor functional reserve was a good target for combination treatment, and ethanol injection was a good partner for TAE in tumors of stages I and II.

TAE therapy should be performed first, because TAE not only is a good method for evaluating the tumor stage but also treats a wide area of the liver. If EIT were performed prior to TAE, the amount of chemoembolic agent delivered to the tumor would be insufficient due to the

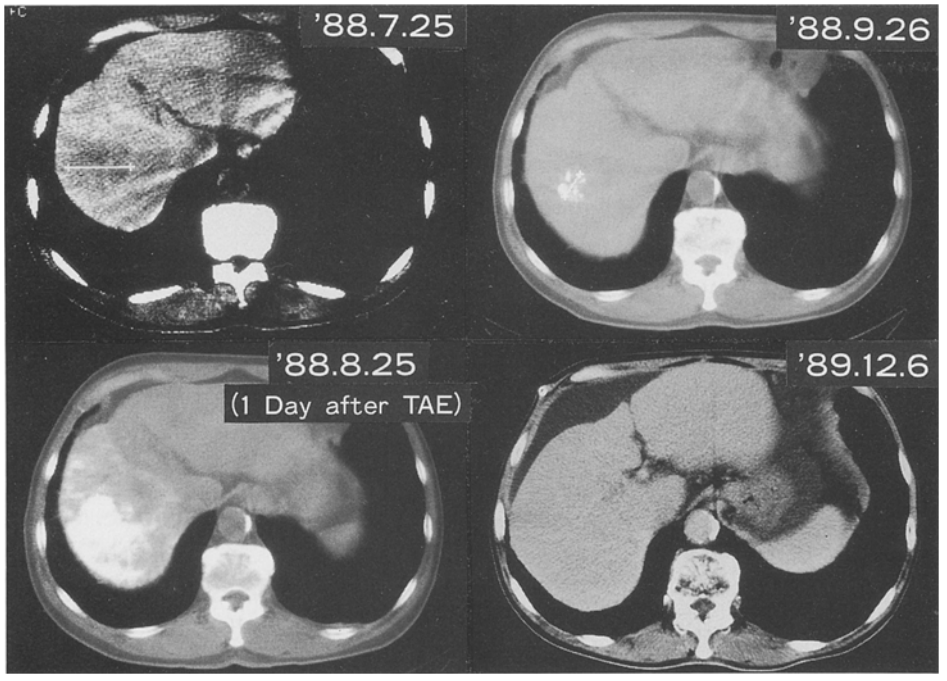

Fig. 1. Computed tomography in a 71-year-old man (case 4). A low-density area was detected in the right hepatic lobe. About 1 month after TAE, the patient showed a PR. During laparotomy on Oct. 6, EIT was performed. About 3 months after TAE, the patient achieved a CR

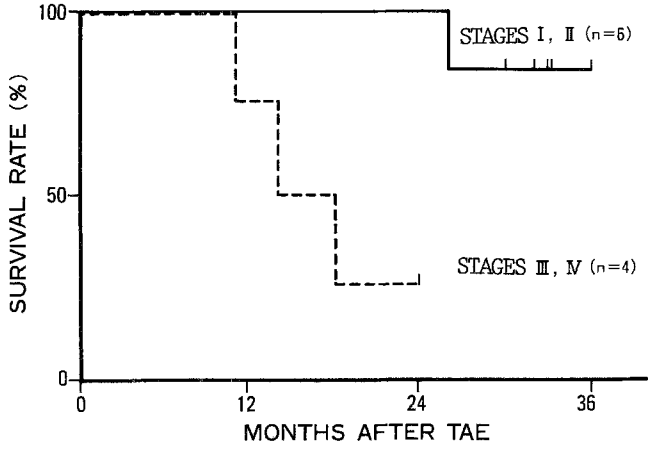

Fig. 2. Actuarial survival curves generated for 10 patients receiving combination treatment

hypovascularity caused by the former procedure. EIT was performed about 4 weeks after TAE because the patients became stable and the necrotic liver tissue could easily be perfused by one-shot ethanol injection. EIT has quite a localized effect, but it can be effective for intercapsular and extracapsular invasion because of ethanol's dehydrating and protein-denaturing effects and partly because of its thromboembolic effect [3]. Therefore, ethanol should be injected not only into the center of the tumor but also into sites close to its edges. The ethanol dose used in our combination regimen was somewhat lower than that usually given for EIT alone [1, 3, 4, 10, 11, 15, 16, 19–21].

The tumors we treated were somewhat larger than those found in the EIT study group. Only two patients had tumors measuring less than 3 cm, but five of six cases in stages I and II achieved a PR or CR. Thus, combination therapy seems quite efficacious if the tumor is solitary, even when its diameter is more than 3 cm. Against multiple tumors, the combination treatment was less effective; apparently, cancer cells persist in the liver in such cases, and other treatments are required.

Although only two cases were resected, histopathologic examination showed that the resected tumors developed complete necrosis. The rate of complete necrosis has been reported to be 15%–50% for TAE [4, 12, 14, 22] and 33%–69% for EIT [2, 3, 17, 20]. As histologic examination revealed numerous histiocytes and lymphocytes distributed throughout the capsule and infiltrating into the necrotic tissue, the injected ethanol may have induced the infiltration of scavenger cells. Some investigators have reported that neutrophils and lymphocytes infiltrate tumors soon after EIT [3].

We also surmise that EIT is a safe procedure, even when the clinical stage of liver cirrhosis is progressive. EIT can be considered even in cases of advanced liver cirrhosis such as Child's class B or C disease [17]. In the present patients who were treated with combination therapy, the disease was so advanced that the clinical stage was I in only two of the ten cases. The common adverse effects of EIT such as pain at the site of injection, transient hypotension, fever, and alcohol intoxication did not require any special treatment. Moreover, the changes in liver function observed after EIT were mild and transient.

We found that for tumors of stages I and II, the 1-, 2-, and 3-year survival values were 100%, 100%, and 83%, respectively, whereas for stages III and IV, the 3-year value was 25%. Although the follow-up period was only 3 years, the results suggest that combination treatment is quite efficacious in tumors of stages I and II. Ebara et al. [1] reported that following EIT, the 3-year survival value was 79% for HCCs with a diameter of 3 cm or less if the number of lesions did not exceed three. Yamada et al. [24] reported a 3-year survival value of 12% for HCC patients treated with TAE.

The follow-up period was not long enough to enable a comparison of the long-term survival of patients receiving

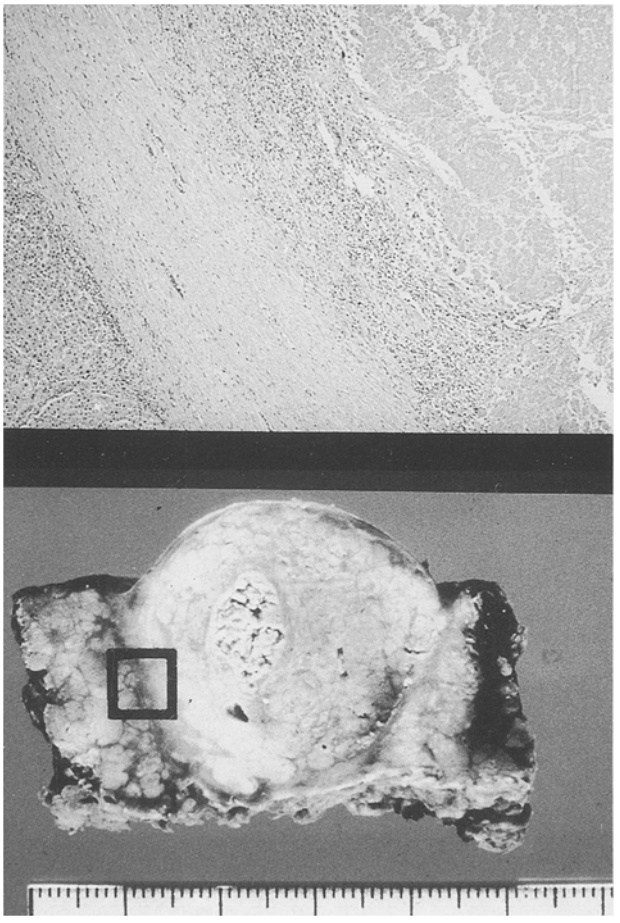

Fig. 3. a Formalin-fixed surgical specimen showing a completely necrotic area, including the HCC. **b** Histologic examination shows many histiocytes and lymphocytes distributed throughout the capsule and infiltrating into the necrotic liver parenchymal tissue

combination treatment with that of patients treated by other techniques. However, we suggest that combination treatment (TAE and EIT) for HCC is efficacious in tumors of stages I or II. Randomized trials comparing the long-term survival of patients receiving combination treatment with that of patients undergoing other therapies should be conducted in the future.

References

1. Ebara M, Nihei T, Ohto M (1988) Intratumoral injection of absolute ethanol for treatment of small hepatocellular carcinoma (in Japanese). Naika 61: 665
2. Ebara M, Kita K, Yoshikawa M, Ohto M (1989) Non-vascular interventional radiology percutaneous ethanol injection (PEI) for hepatocellular carcinoma smaller than 3 cm in diameter. Jpn J Cancer Chemother 16: 3311
3. Fujimoto T (1988) The experimental and clinical studies of percutaneous ethanol injection therapy (PEIT) under ultrasonography for small hepatocellular carcinoma. Acta Hepatol Jpn 29: 52
4. Hirohashi K, Sakai K, Kinoshita H, Igawa S, Matsuoka S, Nagata E, Kubo S (1985) Hepatectomy after transcatheter arterial embolization (TAE) for hepatocellular carcinomas. J Jpn Surg Soc 86: 555
5. Hsu HC, Wei TC, Tsang YM, Wu MZ, Lin YH, Chuang SM (1986) Histologic assessment of resected hepatocellular carcinoma after transcatheter hepatic arterial embolization. Cancer 57: 1184
6. Kubo Y, Okuda K, Musha H, Nakashima T (1978) Detection of hepatocellular carcinoma during a clinical follow-up of chronic liver disease. Observations of 31 patients. Gastroenterology 74: 578
7. Liaw YF, Tai DI, Chu CM, Lin DY, Sheen IS, Chen TJ, Pao CC (1986) Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. Gastroenterology 90: 263
8. Liver Cancer Study Group of Japan (1988) Survey and follow-up study of primary liver cancer in Japan, report 8. Shinko-insatsu, Kyoto, p 63
9. Liver Cancer Study Group of Japan (1989) The general rules for the clinical and pathological study of primary liver cancer. Jpn J Surg 19: 98
10. Livraghi T, Festi D, Monti F, Salmi A, Vettori C (1986) US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. Radiology 161: 309
11. Livraghi T, Salmi A, Bolondi L, Marin G, Arienti V, Monti F, Vettori C (1988) Small hepatocellular carcinoma: percutaneous alcohol injection – results in 23 patients. Radiology 168: 313
12. Nakamura H, Tanaka T, Hori S, Yoshioka H, Kuroda C, Okamura J, Sakurai M (1983) Transcatheter embolization of hepatocellular carcinoma: assessment of efficacy in cases of resection following embolization. Radiology 147: 401
13. 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
14. Ryu S, Yamamoto Y, Yamamoto H, Watanabe Y, Mukai M, Kikuchi T, Ariga T, Nagashima T, Koh Z, Usui S, Odaka M, Sato H (1985) The study on the preoperative transcatheter arterial embolization for hepatocellular carcinoma. Jpn J Gastroenterol Surg 18: 60
15. Sheu JC, Sung JL, Huang GT, Chen DS, Yang PM, Lai MY, Wei TC, Su CT, Tsang YM, Lee CZ, Chen JC, Hsu HC (1987) Intratumor injection of absolute ethanol under ultrasound guidance for the treatment of small hepatocellular carcinoma. Hepatogastroenterology 34: 255
16. Shiina S, Yasuda H, Muto H, Tagawa K, Unuma T, Ibukuro K, Inoue Y, Takanashi R (1987) Percutaneous ethanol injection in the treatment of liver neoplasms. AJR 149: 949
17. Shiina S, Tagawa K, Unuma T, Terano A (1990) Percutaneous ethanol injection therapy for the treatment of hepatocellular carcinoma. AJR 154: 947
18. Sugiura N, Takara K, Ohto M, Okuda K, Hirooka N (1983) Percutaneous intratumoral injection of ethanol under ultrasound imaging for treatment of small hepatocellular carcinoma. Acta Hepatol Jpn 24: 920
19. Suyama Y, Horishi M, Ebisui S, Yorizumi H, Maekawa T, Miyoshi M (1987) US guided intratumoral ethanol injection therapy to small liver cancer – clinical evaluation for twenty cases. J Jpn Soc Cancer Ther 22: 818
20. Suyama Y, Horishi M, Shizumi Y, Ebisui S, Maekawa T, Miyoshi M (1988) Clinicopathological effects of US-guided intratumoral ethanol injection to small liver cancer with special reference to its adequate injected volume. J Jpn Soc Cancer Ther 23: 1727
21. Tagawa K, Muto H, Yasuda H, Unuma T, Shiina S (1987) Therapeutic effects of ultrasonically guided ethanol injection for treatment of hepatocellular carcinoma. Jpn J Med Ultrasonics 14: 743
22. Takayasu K, Moriyama N, Muramatsu Y, Suzuki M, Yamada T, Kishi K, Hasegawa H, Okazaki N (1984) Hepatic arterial embolization for hepatocellular carcinoma. Comparison of CT scans and resected specimens. Radiology 150: 661
23. WHO (1983) Prevention of liver cancer: report of a WHO meeting. WHO Technical Report Series. World Health Organization, Geneva, p 7
24. Yamada R, Kitayama K, Sato M, Kawabata M, Terada M, Maeda M, Shirai S, Tsuda M, Hamachi J, Yoshikawa A, Kishi K, Shioyama Y (1988) Transcatheter arterial embolization in the treatment of primary liver cancer (in Japanese). Nihon Rinsho 46 [Suppl 2]: 161