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Follow-up study of combination treatment (TAE and PEIT) for unresectable hepatocellular carcinoma

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Abstract. The subjects were 35 patients with unresectable hepatocellular carcinoma. The patients were divided into a transcatheter arterial embolization group (TAE group, 18 cases) and a combination therapy group receiving both TAE and percutaneous ethanol injection therapy (TAE+PEIT group, 17 cases). The 50% survival period was 21.1 months for the TAE group and 37.8 months for the TAE+PEIT group ($P < 0.05$). The longest survival period in the TAE group was 89 months. In the TAE+PEIT group, one patient has survived for 59 months. The actuarial 1-, 2-, and 3-year survival rates for the TAE group were 82%, 45%, and 22%, respectively. For the TAE+PEIT group the rates were 83%, 64%, and 64%, respectively. The TAE+PEIT group showed a significantly higher survival rate in the 895- to 1,074-day period as compared with the TAE group ($P < 0.05$). Overall, the survival rate tended to be higher in the TAE-PEIT group ($P < 0.1$). The therapeutic responses of tumors were measured by the maximal reduction rate within 6 months of TAE and PEIT. In the TAE group, a PR was seen in only four cases. In the TAE+PEIT group, CRs and PRs were achieved significantly more frequently than in the TAE group. When the patients were divided into a responder group (CR, PR, and MR) and a nonresponder group (NC and PD), survival was significantly longer in the responder group. The findings of the present study suggest that the combination therapy was useful for improving the survival of patients with unresectable hepatocellular carcinoma.

Introduction

Recent advances in imaging technics have improved the detection of liver neoplasms at an early stage. The resectability of hepatocellular carcinoma (HCC), however, has remained at about 20% due to poor liver function caused mainly by underlying liver cirrhosis and multiple intrahepatic lesions [4]. Treatment of unresectable HCC is a very important problem. Transcatheter arterial embolization (TAE) is an effective nonsurgical modality for treating unresectable HCC, and it is now widely performed [8]. However, by TAE alone it is impossible to achieve complete necrosis of all of the tumor because of the difficulty of controlling intra- and extracapsular invasions and portal vein emboli. The actuarial 5-year survival rate is now just less than 10% [16].

Some additional therapies are urgently needed to improve the survival of patients. Sonographically guided percutaneous ethanol injection therapy (PEIT) was selected as an appropriate therapeutic modality for this purpose [1, 7, 10, 13]. In the preliminary study, the efficacy of PEIT was demonstrated [3]. In the present paper we report the findings of our further analysis of the efficacy of combination therapy with TAE plus PEIT in comparison with therapy with TAE alone.

Patients and methods

A retrospective study was performed on 41 cases of unresectable HCC treated at the Department of Surgery, Osaka Teishin Hospital, from March 1985 to June 1992. In all, 24 of these patients were treated with transarterial chemoembolization alone with Lipiodol (TAE group) and 17 received a combination therapy consisting of TAE and PEIT (TAE++PEIT group). In the TAE group, 6 cases who died within 5 months of TAE were excluded from the present study because they had massive tumors that measured more than 80 mm in diameter; these 6 cases had also been contraindicated for PEIT. Therefore, 30 men and 5 women were entered in this study. The age ranges of the patients were 46–72 years (mean, 57.7 years) in the TAE group and 38–77 years (mean, 60.1 years) in the TAE+PEIT group. All of the patients had liver cirrhosis. The tumor stage of the HCC and the clinical stage of the liver cirrhosis were determined according to the classification systems of the Liver Cancer Study Group of Japan [5]. The background factors of the patients in the two groups are listed in Table 1. No significant difference was found in the age, sex ratio, tumor stage, clinical stage, or amount of Lipiodol used between the two groups.

TAE was performed by injecting a mixture of iodized oil (Lipiodol) and an anticancer drug (doxorubicin hydrochloride, Adriacin; Kyowa

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Table 1. Background factors of the patients

Background factor		TAE	TAE+PEIT	*P*
Number of patients		18	17	NS
Age (years):				
	Mean	57.7	60.1	NS
	Range	46–72	38–77	NS
Sex (M:F)		16:2	14:3	NS
Clinical stage:				
	I	9	7	
	II	8	8	
	III	1	2	NS
Tumor stage:				
	I	2	1	
	II	6	9	
	III	3	3	
	IV	7	4	NS
Lipiodol (ml)	Mean	10.4	9.1	NS
Number of TAE treatments	Mean	1.7	1.7	NS

NS, Not significant

Table 2. Therapeutic responses of HCC after treatment

Treatment group	Number of patients	CR	PR	MR	NC	PD	Unevaluable
TAE	18		4	2	6	3	3
TAE+PEIT	17	1	6	5	2	1	2

Hakko Kogyo Co., Ltd., Japan). TAE was performed 1–4 times (mean, 1.7 times) in both groups. The number of TAE treatments also showed no significant difference between the two groups.

The indications for PEIT were as follows: (1) the tumor was hypovascular and did not stain completely with Lipiodol (6 cases), (2) the artery was occluded because of TAE (2 cases), (3) liver cirrhosis became more advanced during the course of TAE (4 cases), and (4) the tumor was unresectable due to histopathological changes such as active inflammatory changes in the liver leading to postoperative hepatic failure (5 cases) [9].

A 21-gauge, 20-cm PEIT needle (Hakko Co., Ltd.; Tokyo) was used for PEIT. Under sonographic guidance, 99.5% absolute ethanol was injected first into the center (at one or more locations) of the tumor and subsequently into the surrounding tissues. This injection was performed one or two times a week. The total ethanol volume to be injected was calculated as the volume of the tumor; the amount in a single injection ranged from 1 to 50 ml.

The responses to these therapies were evaluated by CT or sonography. The maximal rate of reduction in the tumor size was calculated within 6 months of each therapy, and the efficacy was classified as follows: CR, the tumor had completely disappeared; PR, the reduction rate was 50%–99%; MR, the reduction rate was 25%–49%; NC, the reduction rate was less than 25%; and PD, the tumor had increased in size by at least 25%.

The Kaplan-Meier method was used to calculate the survival rate, the generalized Wilcoxon test was used for statistical analysis, and the *t*-test was used to test for other significant differences. The data provided by the initial angiography were the starting point for the calculations.

Results

Tumor response

The responses of the tumors to the treatments are shown in Table 2. The tumor completely disappeared in only 1 TAE+PEIT patient during the 12 months after treatment. In the TAE+PEIT group, 11 of 17 patients showed a PR or an MR, whereas in the TAE group, a PR or an MR was observed in only 6 patients.

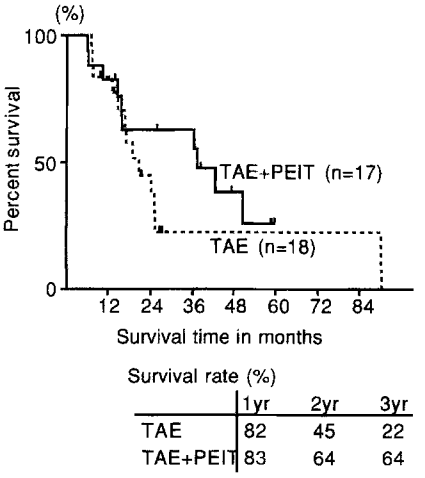

Fig. 1. Survival curves generated for the TAE and TAE+PEIT groups. A significant difference was seen between the two groups in the 895- to 1,074-day period

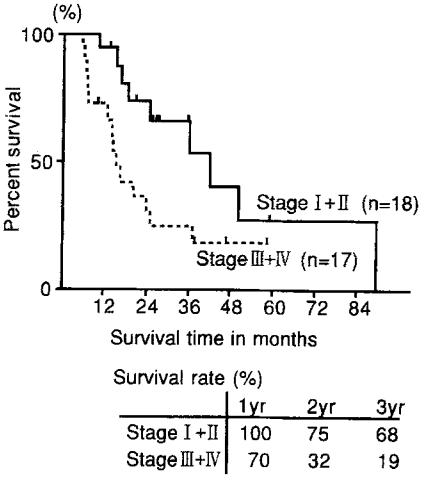

Fig. 2. Survival curves as a function of tumor stage (stage I+II vs stages III+IV). The survival period of the stage I+II cases was significantly longer than that of the stage III+IV cases

Survival

Figure 1 shows the survival curves generated for the TAE and TAE+PEIT groups. The survival rates for the TAE and TAE+PEIT groups were 84% and 83% at 1 year, 45% and 64% at 2 years, and 22% and 64% at 3 years, respectively. A statistically significant difference was found between the two groups in the 895- to 1,074-day period ($P < 0.05$). On the whole, the survival rate tended to be higher for the TAE+PEIT group than for the TAE group ($P < 0.1$).

The survival curves generated as a function of the tumor stage in all cases are shown in Fig. 2. The 1-, 2-, and 3-year survival rates for stage I+II ($n = 18$) were 100%, 75%, and

Table 3. Cumulative survival rate as a function of tumor stage in the TAE and TAE+PEIT groups

Tumor stage	Treatment group	Cumulative survival rate (%)			
		1-year	2-year	3-year	4-year
Stages I+II	TAE (n = 8)	100	71	52	42
	TAE+PEIT (n = 10)	100	79	63	48
Stages III+IV	TAE (n = 10)	70	23	0	
	TAE+PEIT (n = 7)	71	43	43	38

68%, and those for stage III+IV (n = 17) were 70%, 32%, and 19%, respectively. The survival period of the stage I+II cases was significantly longer than that of the stage III+IV cases (P <0.01). Table 3 shows the survival rates obtained in the TAE and TAE+PEIT groups for the same tumor stage. No significant difference was found between the two treatment groups for the stage I+II cases. However, for the stage III+IV cases, the TAE+PEIT group tended to show a higher survival rate as compared with the TAE group (P <0.01).

The survival rates were evaluated with regard to the liver function (Fig. 3). The patients in clinical stage I tended to survive longer than the patients in stage II+III (P <0.1). However, there was no significant difference between the TAE and TAE+PEIT groups for the same clinical stage.

Six patients in the TAE group and seven in the TAE+PEIT group survived until January 1993. The 50% survival period was 21.1 months for the TAE group and 37.8 months for the TAE+PEIT group (P <0.05). The longest survival period in the TAE group was 89.1 months, whereas in the TAE+PEIT group, one patient has survived for 59.0 months.

All of the cases were divided into two groups: a responder group (CR, PR, and MR) and a nonresponder group (NC and PD). Figure 4 shows the survival curves of the responder group and the nonresponder group. The survival rate of the responder group was significantly higher than that of the nonresponders.

Side effects

Almost all of the patients developed a fever after TAE, but the fever decreased within about 10 days of the treatment. No other side effect was detected after TAE.

After ethanol injection, some patients experienced mild alcohol intoxication and pain at the injection site in the liver. The change in liver function after PEIT was mild and transient. Only one patient, who had received a large bolus injection of ethanol (50 ml), developed mild lung edema, but this pulmonary insufficiency disappeared within a few days; the SaO_2 value was decreased. One patient with a tumor located on the liver surface experienced peritonitis-like severe abdominal pain for several days. The SaO_2 value decreased transiently by 6%–8% in some cases during the ethanol injection. However, these symptoms were transient, and no special countermeasures were required.

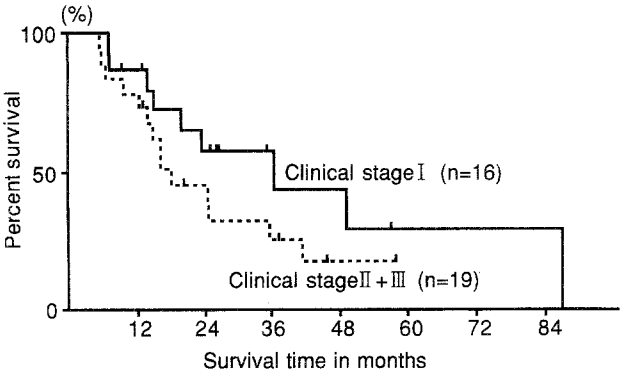

Fig. 3. Survival curves as a function of clinical stage (clinical stage I vs clinical stages II+III). The survival of the clinical stage I cases tended to be higher than that of the stage II+III cases

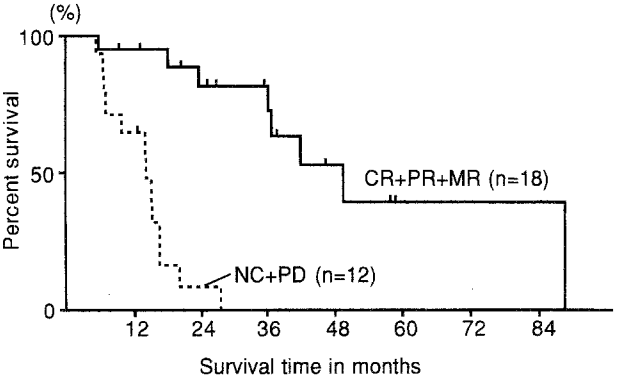

Fig. 4. Survival curves as a function of the response category (CR+PR+MR vs NC+PD). The survival rate of the responder group was significantly higher than that of the nonresponder group

Discussion

In the present study, the survival rate was significantly higher in the 895- to 1,074-day period (P <0.05) and the survival period tended to be longer in the TAE+PEIT group than in the TAE group (P <0.1).

In the 9th Report of the Liver Cancer Study Group of Japan [6], the 1-, 2-, 3-, and 5-year survival rates were 75%, 57%, 46%, and 31% for resected cases and 58%, 34%, 27%, and 8% for TAE group cases, respectively. However, the background factors of the resected and TAE cases were not the same, and a comparison was not justifiable because the resectable cases had a mild degree of liver cirrhosis and a low tumor stage, whereas many of the unresectable cases were more advanced.

Yoshimi et al. [17] performed a prospective randomized study of TAE and hepatectomy for HCC. They reported that no significant difference in survival was found between the two groups. Shiina et al. [11] reported that the survival rates in cases of small HCC (<3 cm) were almost the same for the PEIT and the TAE+PEIT groups. They also concluded that the local effect of PEIT was much stronger than that of TAE for small HCCs. Tanaka et al. [15] compared the

prognosis of patients with large tumors (>3 cm) between TAE and TAE+PEIT groups and reported a significantly higher survival rate for the combination group. Considering the incidence of complications and recurrence in resected cases, TAE+PEIT might be a useful alternative to surgery for large solitary HCCs.

In the present study, survival was significantly longer for the TAE+PEIT group. Although almost all of the HCC patients (in both groups) in this study had tumors measuring 3–5 cm in diameter, the combination therapy was more effective in such cases.

The TAE+PEIT group contained more responders than the TAE group. The survival rate of the responder group was significantly higher than that of the nonresponder group. In many patients in the TAE+PEIT group, we injected ethanol into the same tumor that had received Lipiodol in the TAE procedure. The tumor reduction rate in the TAE+PEIT group was higher than that in the TAE group, perhaps because ethanol was injected directly into lesions that had not responded to the TAE therapy.

When we compared the survival of patients as a function of the tumor stage between the TAE and TAE+PEIT groups, no significant difference was found in the stage I+II cases. For the stage III+IV cases, however, the TAE+PEIT group contained more patients surviving for 24 months after the initial treatment. These results suggest that combination of PEIT with TAE is useful and should be performed even in stage III and IV cases. In the present study, two patients in the TAE+PEIT group had tumors exceeding 8 cm in size. The tumors in these two cases increased in size after treatment using a large amount of ethanol and were evaluated as PD. Many reports have proposed that PEIT is an appropriate therapeutic option for up to three tumors measuring 3 cm or less in diameter [1, 7, 10, 11]. However, in this study, PEIT was carried out mainly in patients with tumors measuring 3–5 cm in diameter and showed that a good effect could be expected when it was used in combination with TAE.

The amount of ethanol injected was 1–50 ml at one time. In an animal study, Takashimizu et al. [14] injected 1 ml of ethanol into the normal liver of rabbits and reported that coagulation necrosis with a maximal diameter of 4 cm became apparent after 5 days. However, in our study, CT and pathology studies revealed necrotic changes with a maximal diameter of about 1 cm when 1 ml of ethanol had been injected and 4 cm when 8 ml had been injected in patients with liver cirrhosis within a few days after the PEIT. In principle, we currently inject an amount of ethanol corresponding to the tumor volume in two or three divided doses.

Pain and intoxication at the time of ethanol injection have been reported as side effects [1, 9]. However, when an SaO_2 monitor was attached at the time of injection, SaO_2 values dropped transiently by 6%–8%. in some cases. The values decreased for only about 30 to 60 s and then immediately recovered to the pretreatment level. Caution is thus required in patients with cardiopulmonary disorders. Although the mechanism of action is not clear, this side effect may be due to apnea at the time of injection or to a reaction to the high concentration of ethanol in the blood vessels of the lung.

It has been reported that the blood flow into the capsule and extracapsular invasion of HCC is supplied by the portal vein system [12], and for this reason, TAE is not likely to kill cancer cells residing in the capsule surrounding the tumor. The effect of PEIT is localized, but PEIT can be effective for intracapsular and extracapsular invasion, mainly because of its dehydrating and protein-denaturing effects and partly because of its thromboembolic effect [2, 18].

In conclusion, we expect that combination therapy with TAE and PEIT will be routinely applied as an effective method for treatment of unresectable HCC cases.

References

1. Ebara M. Ohto M, Sugiura N, Kia K, Yoshikawa M, Okuda K, Kondo F, Kondo Y (1990) Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. J Gastrohepatol 5: 616
2. Fujimoto T (1988) The experimental and clinical studies of percutaneous ethanol injection therapy (PEIT) under ultrasonography for small hepatocellular carcinoma (in Japanese). Acta Hepatol Jpn 29: 52
3. Hasuike Y, Okamura J, Furukawa J, Naoi M, Takata N, Maruyama H, Kinuta M, Yayoi E, Oi H, Okamoto S, Monden M, Mori T, Sakurai M (1992) Efficacy of combination treatment – TAE with Adriamycin and ethanol – for hepatocellular carcinoma. Cancer Chemother Pharmacol 31 [Suppl I]: S30
4. Liver Cancer Study Group of Japan (1988) Survey and follow-up study of primary liver cancer in Japan – 8th report (in Japanese). Shinko-insatsu, Kyoto, p 63
5. 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
6. Liver Cancer Study Group of Japan (1991) Survey and follow-up study of primary liver cancer in Japan – 9th report (in Japanese). Shinko-insatsu, Kyoto, p 104
7. Livraghi T, Salmi A, Bolondi L, Malin G, Arienti V, Monti F, Vettori C (1988) Small hepatocellular carcinoma: percutaneous alcohol injection – results in 23 patients. Radiology 168: 313
8. 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
9. Sakurai M, Okamura J, Kuroda C, Yamada T (1986) Active inflammatory change of the liver as a cause of postoperative hepatic failure. Jpn J Surg 16: 398
10. 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
11. Shiina S, Tagawa K, Unuma T, Fujino H, Uta Y, Niwa Y, Hata Y, Komatsu Y, Shiratori Y, Terano A, Sugimoto T (1990) Percutaneous ethanol injection therapy of hepatocellular carcinoma AJR 155: 1221
12. Sugihara S, Kojiro M, Nakashima T (1985) Ultrastructural study of hepatocellular carcinoma with replacing growth pattern. Acta Pathol Jpn 35: 549
13. 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 (in Japanese). Acta Hepatol Jpn 24: 920
14. Takashimizu I, Yamanaka A, Takenaga T, Yamada M, Sasabe M, Tamura Y, Yamamoto N, Kurosawa H, Fujimoto H, Ohkusa T, Nakamura R, Kuyama Y, Okayasu I (1988) The necrotizing effect of the direct injection of anhydrous ethanol on the liver in the rabbit (in Japanese). Jpn J Gastroenterol 85: 886

15. Tanaka K, Nakamura S, Numata K, Okazaki H, Endo O, Inoue S, Takamura Y, Sugiyama M, Ohaki Y (1992) Hepatocellular carcinoma: treatment with percutaneous ethanol injection and transcatheter arterial embolization. Radiology 185: 457
16. Yamada R, Sato M, Nomura S, Nakatsuka H, Yamada T (1985) Transcatheter arterial embolization in hepatocellular carcinoma. J Jpn Soc Cancer Ther 20: 1627
17. Yoshimi F, Nagao T, Inoue S, Kawano N, Muto T, Gunji T, Ohnishi S, Imawari M (1992) Comparison of hepatectomy and transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma: necessity for prospective randomized trial. Hepatology 16: 702
18. Yune HY, Klatte EC, Richmond BD, Rabe FE (1982) Absolute ethanol in thrombotherapy of bleeding esophageal varices. AJR 138: 1137