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Evaluation of the therapeutic effect of TAE on primary liver cancer

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Abstract. The therapeutic effect of transcatheter arterial chemoembolization (TAE) performed on 31 patients with primary liver cancer was evaluated using the following procedures: (1) the alpha-fetoprotein (AFP) reduction rates and prognoses were analyzed according to the tumor reduction rates (TR), and (2) the AFP reduction rates and prognoses were also analyzed according to the tumor necrosis rates (TN) estimated by regarding every region with Lipiodol retention as being necrotic. The following results were obtained. The AFP level was 400 ng/ml or higher in 15 patients (48%). Their AFP reduction rates were as favorably high as 65.4%–99.8% (mean, 88.1%), and the AFP level was normalized in 3 patients. The cumulative survival rates after the initial treatment were relatively high, i.e., 78.4% in the 1st year, 58.1% in the 2nd year, and 38.7% in the 3rd year. These results suggested the effectiveness of the TAE treatment undertaken in this study. Regarding the TR, the tumor was reduced in size by 50% or more in only 5 patients (16%), and most patients had a TR of less than 25%. On the other hand, the majority, 25 patients (81%), had a TN ranging between 50% and less than 100%, including 7 who had a TN ranging between 50% and less than 90% and 18 who had a TN ranging between 90% and less than 100%. There was no significant correlation between the AFP reduction rate and the TN or TR. Regarding evaluation of the cumulative survival rates by TR and TN, the 1-year survival rate was lower in patients having a TR of less than 25% than in those having a TR of 25% or more. Patients having a TN of less than 50% showed a poor outcome as compared with those having a TN of 50% or more. Although the TR was found to be less than 50% in a majority of the patients when the therapeutic effect of TAE on the liver cancer was evaluated according to the TR, many of these patients showed a good outcome. Thus, the conventional efficacy evaluation, in which a tumor reduction of 50% or more is considered to be effective, should be reconsidered. On the other hand, the TN was found to be 50% or more in most of the patients, suggesting the necessity of a more detailed classification of TN. In relation to the survival rate, patients having a TN of less than 50% showed a poor outcome.

Introduction

It is often difficult to evaluate the therapeutic effect of transcatheter arterial chemoembolization (TAE), a major method of treatment of primary liver cancer (PLC). This is because the necrotized cancer hardly diminishes in size and because TAE is often employed in combination with Lipiodol, resulting in a difficulty in identifying necrosis on images. Since therapeutic effects are categorized according to the tumor reduction rate in the criteria for direct efficacy evaluation of chemotherapy for solid cancers [2], which are being widely employed at present in Japan, such evaluated results are often inconsistent with the actual therapeutic effects of TAE. It has been reported that the regions of Lipiodol retention correspond to necrotic areas following TAE [3, 4, 10]. Thus, it would be more rational if therapeutic efficacy were evaluated by regarding the regions of Lipiodol retention as necrosis.

With this in mind, we carried out efficacy evaluation by regarding every region showing Lipiodol retention for 4 weeks or more as a necrotized region. The results were compared with those obtained by the conventional evaluation performed on the basis of the tumor reduction rate.

Patients and methods

TAE was performed on 93 of 136 patients treated for PLC at Nishi-Gunma Hospital, National Sanatorium, between 1986 and 1992, and 31 of the 93 patients were selected as subjects because they satisfied all of the following conditions.

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Table 1. Patients' characteristics and results of TAE for primary liver cancer

Case	Age (years)	Sex	Tumor size (mm)	TR (%)	TN (%)	AFP		Surviving period (months)	Dead or alive
						Before therapy (ng/ml)	Reduction rate (%)		
1	81	M	19× 19	36.6	100	1,592	93.8	37	Alive
2	51	M	21× 21	23.3	99			9	Dead
3	68	M	22× 22	22.7	99	115	58.8	12	Alive
4	64	F	24× 20	72.5	100			24	Alive
5	75	M	28× 25	28.9	99	833	80.5	34	Dead
6	63	M	29× 27	46.6	80	<20		36	Dead
7	62	M	30× 28	13.5	91	40	Normalized	30	Dead
8	66	M	30× 20	14.3	99	773	Normalized	9	Dead
9	78	M	30× 26	23.1	80	1,697	90.1	23	Alive
10	80	M	31× 25	20.5	99	<20		26	Alive
11	65	M	32× 19	−10.5	99	<20		24	Alive
12	73	F	33× 26	− 3.3	32	126	80.3	5	Alive
13	70	F	35× 33	9.1	90	35	Normalized	16	Alive
14	67	F	38× 33	−15.7	91	6,300	79.4	21	Dead
15	59	M	43× 32	58.4	100	5,081	65.4	13	Dead
16	68	M	49× 35	46.5	90	<20		47	Alive
17	68	M	52× 46	9.7	95	790	93.5	30	Alive
18	66	M	52× 48	15.7	93	<20		29	Alive
19	36	M	55× 45	39.2	99	5,593	81.8	14	Dead
20	67	F	60× 60	5.0	90	190	Normalized	3	Dead
21	63	M	61× 59	42.0	78	430	Normalized	9	Alive
22	56	M	62× 23	41.9	80	9,000	98.1	17	Dead
23	59	M	62× 46	60.0	90	25	Normalized	23	Alive
24	59	M	62× 52	43.4	90	8,470	Normalized	24	Alive
25	61	M	67× 46	54.6	95	45	Normalized	30	Dead
26	60	M	85× 85	19.5	80	129,600	99.8	5	Alive
27	66	M	112× 88	−38.0	70	<20		10	Dead
28	58	M	123×108	14.2	20	540,000	86.3	8	Dead
29	64	M	128× 90	50.6	50	<20		20	Dead
30	50	M	135×125	26.0	90	3,681	97.9	5	Alive
31	44	M	145×110	17.2	40	1,900	90.5	8	Dead

A catheter was inserted up to the right or left hepatic artery or proper hepatic artery using Seldinger's technique, and a solution containing 30 mg/m^2 of doxorubicin (Adriamycin) or 40 mg/m^2 of epirubicin (Farmorubicin) and 5–7 ml of suspended Lipiodol was infused through the catheter (Lipiodol-TAI, L-TAI). After that, the hepatic arteries supplying the cancer were obstructed with gelatin sponge particles soaked in mitomycin C.

The therapeutic efficacy was evaluated by means of computerized tomography (CT) scanning. Namely, CT scans were taken before and at 2 and 6–8 weeks after treatment, the long and short axes of the tumor were measured, and their product was calculated to obtain the area. Then, the ratios of the areas obtained at 2 and 6–8 weeks after treatment to the pretreatment area were calculated, and the larger ratio was used as the tumor reduction rate (TR). A region in which Lipiodol remained for 4 weeks or more on the CT scans was regarded as a necrotized region, and the ratio of the necrotized region to the entire tumor was calculated as the tumor necrosis rate (TN). When more than one measurable lesion was present on CT scans, the three largest lesions were measured, and the TR and TN were calculated from the sum of their areas.

As for the alpha-fetoprotein (AFP) reduction rate, the ratio of the lowest AFP level observed until 8 weeks after treatment to the pretreatment AFP level was calculated.

Results

Table 1 shows the overall results of this study. The patients ranged in age from 36 to 81 years (mean age, 63.4 years). As for the long axis of the main tumor, in 9 cases (29%) it was 3.0 cm or less, in 7 cases (23%) it ranged from 3.1 to 5.0 cm, in 9 cases (29%) it varied from 5.1 to 8.0 cm, and in 6 cases (19%) it exceeded 8 cm. As for the TR, it was higher than 50% in only 5 cases (16%), whereas in 9 cases (29%) it ranged from 25% to 49%, and in 16 cases (52%), which was the largest group, it was within ±25%. In 1 case (3%) a tumor increase rate higher than 25% was noted. As for the TN, in 25 cases (81%), which was the largest group, it ranged from 50% to 99%, whereas 3 cases (10%) showed a rate of almost 100%, 2 cases (6%) showed a rate varying from 25% to 49%, and 1 case (3%) showed a rate lower than 25%. The cases with a long axis of over 10 cm had lower TN values. The pretreatment AFP level was positive in 22 cases (71%), and it was higher than 400 ng/ml in 15 (48%) of these cases. The AFP reduction rate in these cases ranged from 65.4% to 99.8% (mean, 88.1%), and in three cases AFP values became normal. Figure 1 shows the computed tomogram of case 24, which yielded values of 43.4% for TR and 90% for TN. The serum AFP level became normal after TAE (8,470 ng/ml before treatment, and 6.6 ng/ml at 8 weeks after treatment).

The survival rate of all cases from the day of first treatment was calculated using Kaplan-Meier's method (Fig. 2). The 1-, 2-, and 3-year survival rates were 78.4%, 51.8%, and 38.7%, respectively.

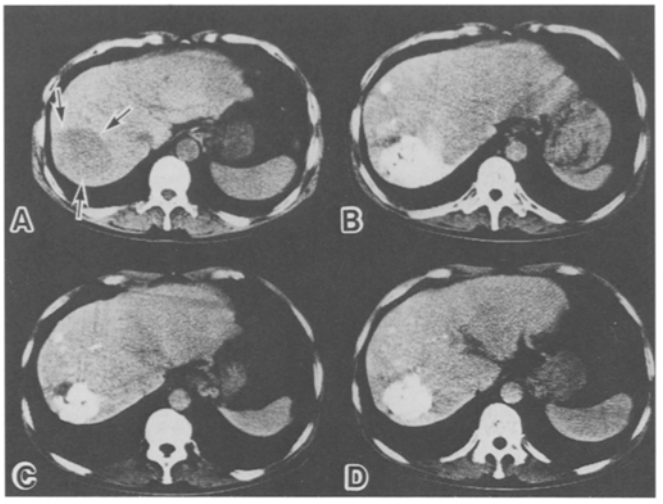

Fig. 1. Computed tomogram of case 24. **A** [before TAE] A low-density space-occupying lesion (*SOL*) is seen in S7 of the liver (*arrow*). Its size is 65×52 mm. **B, C, D** [2 weeks (**B**), 6 weeks after TAE (**C, D**)] Lipiodol retention is visible in the SOL. The size and rate of Lipiodol retention is 52×48 mm (**B**), 48×38 mm (**D**), 90% (**B**), and 85% (**C, D**), respectively. We calculated the TR to be 43.4% and the TN, 90% in this case

Figure 3 shows the correlation between the TR (abscissa) and the AFP reduction rate (ordinate). The cases having a pretreatment AFP level higher than 400 ng/ml were plotted by the size of the tumor. In most cases the reduction rate ranged from 10% to 50%, and particularly those tumors having a diameter larger than 8 cm showed low reduction rates of less than 30%. However, no significant correlation was found between the TR and the AFP reduction rate.

Figure 4 shows the correlation between the TN (abscissa) and the AFP reduction rate (ordinate). Similar the findings shown in Fig. 3, the cases having a pretreatment AFP level higher than 400 ng/ml were plotted by the size of the tumor. Except for some cases having a tumor with a diameter larger than 8 cm, the TN was as high as 80% or more in most cases. However, no significant correlation was found between the TN and the AFP reduction rate.

The survival rate was calculated by Kaplan-Meier's method and plotted versus the TR (Fig. 5). The 1-, 2-, and 3-year survival rates were 0 in all cases with a TR of −25% or less; 64.9%, 55.6%, and 0, respectively in cases with a TR of within ±25%; 100%, 71.4%, and 71.4%, respectively, in cases with a TR ranging from 24% to 49%; and 100%, 60%, and 0 respectively, in cases with a TR ranging from 50% to 99%. The 1-year survival rate of the group showing a TR of within ±25% was poorer than that of the group having a TR of 25% or higher ($P < 0.01$).

The survival rate (Kaplan-Meier's method) was also plotted versus the TN (Fig. 6). The 1-, 2-, and 3-year survival rates were 0 in all cases with a TN of less than 50% and were 82.3%, 62.0%, and 37.2%, respectively, in cases

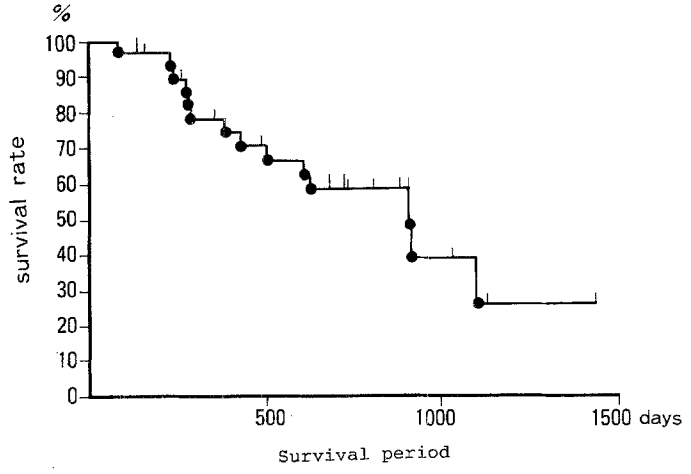

Fig. 2. Cumulative survival curve generated for 31 cases of primary liver cancer treated with TAE

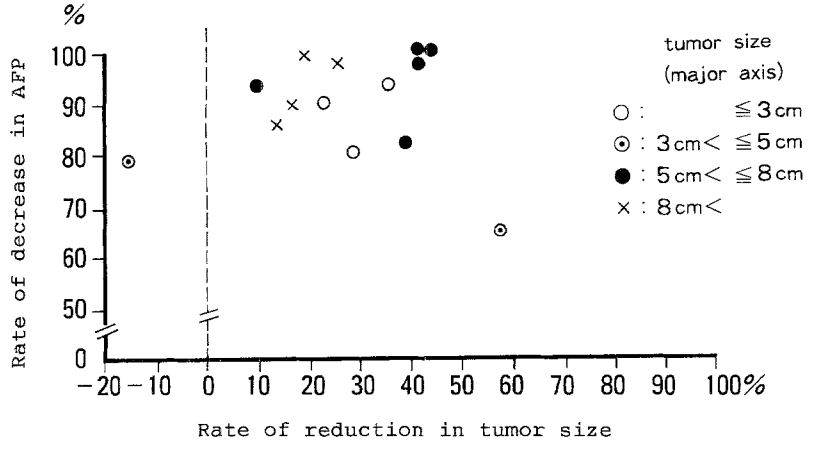

Fig. 3. Relationship between the TR and the AFP reduction rate. We plotted the cases having a pretreatment AFP level higher than 400 ng/ml as a function of the tumor diameter

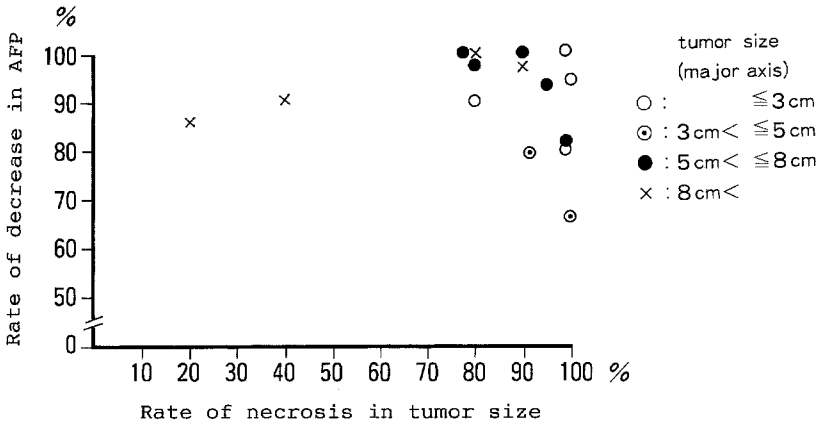

Fig. 4. Relationship between the TN and the AFP reduction rate. We plotted the cases having a pre-treatment AFP level higher than 400 ng/ml as a function of the tumor diameter

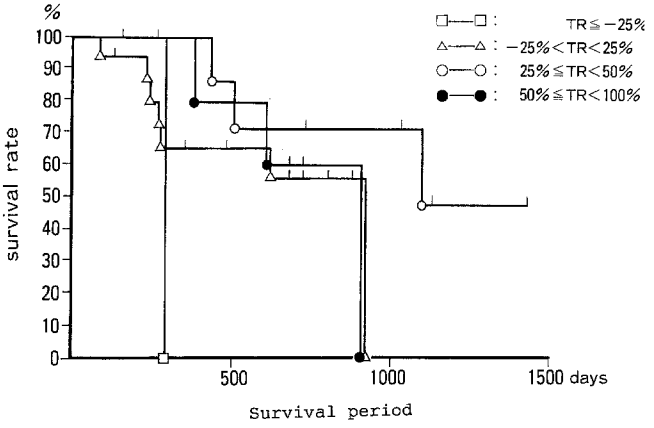

Fig. 5. Cumulative survival curves as a function of the TR

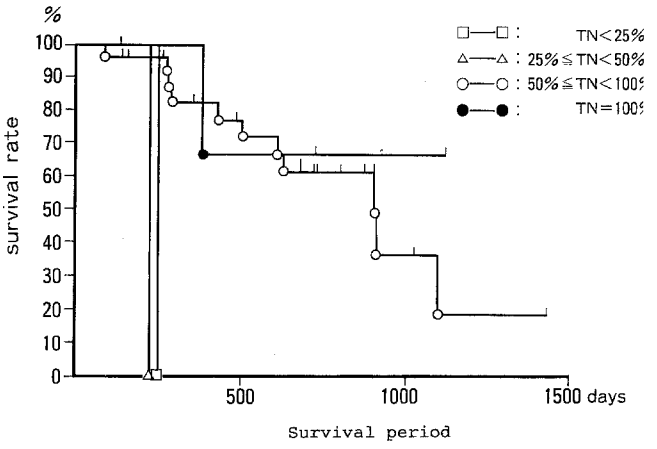

Fig. 6. Cumulative survival curves as a function of the TN

with a TN ranging from 50% to 99%. The 1- and 2-year survival rates were 100% and 66.7%, respectively, in cases with a TN of 100%.

Because the TN ranged from 50% to 99% in almost all of the cases, the results were divided into two groups of TN, i.e., under 90% and 90% or higher. The TN was then plotted against the survival rate (Fig. 7). The 1-, 2-, and 3-year survival rates were 80%, 40%, and 40%, respectively, in cases with a TN ranging from 50% to 89% (7 cases) and 83%, 69%, and 35%, respectively, in cases with a TN ranging from 90% to 99% (18 cases).

Discussion

Hepatocellular carcinoma (HCC), which accounts for the largest portion of PLC in Japan, has the following characteristics. First, although HCC is mainly supplied with nutrition by the hepatic artery, 70%–80% of normal hepatic cells are supplied by the portal vein system [8]. Second, AFP is a useful marker for HCC. Third, HCC often accompanies chronic liver disease such as hepatic cirrhosis [6]. The first observation suggests the usefulness of TAE,

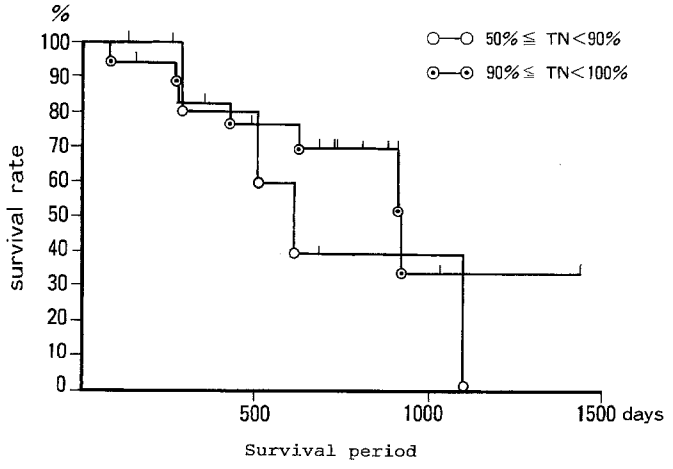

Fig. 7. Cumulative survival curves generated for cases with a TN ranging from 50% to 99%. We divided the cases into two groups of TN: under 90% and 90% or higher

and the third indicates the difficulty of liver resection. Thus, TAE must play a very important role in the treatment of HCC [1].

Yamada et al. [12] reported 1- and 2-year survival rates of 44% and 29%, respectively after TAE. However, recently, TAE performed with a mixture of anticancer agent(s) and Lipiodol has resulted in 1- and 3-year survival rates of 60%–70% and 30%–35%, respectively, revealing an improvement in the prognosis [5, 7]. In the present study, the AFP reduction rates were as high as 65.4%–99.8% (mean, 88.1%), and the AFP level became normal in three patients. The cumulative survival rates after the initial treatment were relatively high, i.e., 78.4% in the 1st year, 58.1% in the 2nd year, and 38.7% in the 3rd year. These results indicate the effectiveness of our TAE procedure.

Although anticancer agents generally manifest their antitumor effects as a diminution or disappearance of tumors, it is difficult to visualize the antitumor effect of TAE as a diminution of the tumor because blood-flow occlusion stops the drainage system in a necrotized tumor region [9]. The long-term retention of Lipiodol in a tumor further magnifies the difficulty of evaluation by means of CT scans. According to the criteria for direct efficacy evaluation of chemotherapy for solid cancers [2], which have been widely used in Japan, "effective" is defined as "the tumor is diminished in size by 50% or more for 4 weeks or longer." This definition is not practical for TAE because of the above-mentioned reasons [11]. There have been many reports that the regions of Lipiodol retention correspond with the regions of necrosis following TAE [3, 4, 10]. Thus, we regarded every region showing Lipiodol retention for 4 weeks or more as being necrotic.

As for the TR, the tumor was found to be reduced in size by less than 50% in a majority of the patients. However, these patients having a TR of less than 50% showed AFP reduction rates as high as 80% or more. Thus, on the basis of the assumption that AFP is a tumor marker, it was surmised that the TR does not reflect the therapeutic effect of TAE.

On the other hand, the TN was found to range from 50% to less than 100% in a majority of the patients and to vary from 90% to less than 100% in as many as 18 (72%) of these 25 patients. These patients also showed a sufficient AFP reduction rate. Since we attempted to increase the retention of Lidiodol within tumors for the purpose of improving the therapeutic effect of TAE, most patients had a TN of 50% or more as well as a sufficient AFP reduction rate. As a result, there was no correlation between the TN and the AFP reduction rate.

Regarding the relationship between the therapeutic effect and the outcome, the 1-year survival rate noted in patients having a TR of less than 25% was lower than that seen in patients having a TR of 25% or more. Since HCC diminishes in size at an extremely slow rate, it seems very rare to observe a reduction by more than 50% at around 8 weeks after treatment, despite the presence of a therapeutic effect. Thus, we think that it is necessary to reconsider the conventional efficacy evaluation criteria, in which a reduction by 50% or more is defined as effective.

The outcome was poor when the TN was less than 50% as compared with a TN of 50% or more. Although three patients having a TN of less than 50% showed a satisfactory AFP reduction rate, their poor outcomes were thought to be partially due to the size of their tumors since the tumor diameter exceeded 10 cm in two cases. When the survival rates were compared between patients having a TN ranging from 50% to less than 90% and those having a TN varying from 90% to less than 100%, the latter group tended to have a better survival rate, although the difference was not significant. Further studies on this point are needed.

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