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Effectiveness of Lipiodol in transcatheter arterial embolization of hepatocellular carcinoma*

Norio Nakao[1], Hideo Uchida[2], Keiji Kamino[1], Yukihiro Nishimura[2], Hajime Ohishi[2], Yukio Takayasu[1], Hironobu Nakamura[3], Chikazumi Kuroda[4], Makoto Fujita[4], Hiroyasu Yoshioka[5], and Osamu Ishida[5]

[1] Department of Radiology, Hyogo College of Medicine, Hyogo, Japan
[2] Department of Radiology, Nara Medical University, Nara, Japan
[3] Department of Radiology, Osaka University Medical School, Osaka, Japan
[4] Department of Radiology, The Center for Adult Diseases, Osaka, Japan
[5] Department of Radiology, Kinki University School of Medicine, Osaka, Japan

Summary. The effectiveness of Lipiodol (iodized oil) in transcatheter arterial embolization (TAE) of hepatocellular carcinoma (HCC) was retrospectively evaluated using statistical analysis. A total of 343 HCC patients who underwent TAE at 5 institutions between 1984 and 1989 were divided into 2 groups: the GS-TAE group underwent TAE with Gelfoam sponge alone, whereas the LP-TAE group was given Lipiodol (LP) immediately before GS-TAE. The statistical T value calculated for the LP-TAE group showed that the administration of LP, the tumor size, intrahepatic metastasis, portal vein infiltration, and serum total bilirubin and alpha-fetoprotein levels significantly ($P < 0.01$) affected the patients' survival. Both the cumulative survival determined using the Kaplan-Meier model and the cumulative hazard calculated using Cox's proportional hazard model differed significantly ($P < 0.01$) between the GS-TAE group and the LP-TAE group (log-rank test). These results confirmed the effectiveness of LP used in combination with Gelfoam sponge for TAE of HCC.

Introduction

Transcatheter arterial embolization (TAE) has been shown to be a very useful therapy for unresectable hepatocellular carcinoma (HCC) [2, 3, 9, 15]. In Japan, Gelfoam sponge (GS) is commonly used as an embolization material. Since the early 1980s, Lipiodol (LP, iodized oil, Laboratoire Guerbert, France; Kodama Ltd., Japan) has been given to patients prior to GS embolization at many institutions, and there have been various reports on its usefulness [1, 12]. However, no report has directly evaluated the use of LP together with GS for TAE of HCC as compared with GS alone [10, 14]. To assess the effect of LP on the outcome of HCC therapy, a retrospective, cooperative multi-institutional study was conducted using multivariate statistical analysis.

Patients and methods

The subjects of this study were 343 patients with HCC who underwent TAE between January 1980 and December 1989 in the Department of Radiology at one of the following 5 institutions: Hyogo College of Medicine; Nara Medical University; Osaka University Medical School; Center for Adult Diseases, Osaka; and Kinki University School of Medicine. The following criteria were used to select patients for this retrospective analysis: (1) a complete follow-up had been performed, (2) there was no tumor infiltration of the main portal trunk or first branch, (3) the serum total bilirubin value was less than 3.0 mg/dl, and (4) the same TAE method was used for both the first and the second procedures in recurrent cases. HCC was diagnosed on the basis of findings characteristic for HCC that were obtained using such diagnostic imaging methods as ultrasonography, CT, and angiography as well as on the basis of a high serum alpha-fetoprotein (AFP) level (20 ng/ml or more).

TAE was performed via the proper hepatic artery or the right or left hepatic artery to all peripheral vessels. TAE was repeated when recurrence was detected after the initial procedure. The second TAE was usually performed at between 6 months and 1 year after the initial procedure. GS 1- × 1- × 2-mm cubes) was used as the embolization material. For the retrospective statistical analysis, the patients were divided into two groups: the GS-TAE group ($n = 87$), which consisted of 75 men and 12 women (62.1 ± 8.5 years) who underwent TAE with GS alone, and the LP-TAE group ($n = 256$), which included 220 men and 36 women (61.6 ± 8.5 years) who were given LP prior to GS-TAE (Table 1).

Both groups contained patients who were given anticancer agents [Adriamycin (ADM) and/or mitomycin C (MMC)] either concurrently with the embolization material or prior to embolization [cisplatin (CDDP)]. ADM [GS-TAE group, 37 ± 13 mg ($n = 37$); LP-TAE group, 38 ± 19 mg ($n = 182$)] and MMC [GS-TAE group, 8 ± 3 mg ($n = 10$); LP-TAE group, 11 ± 4 mg ($n = 66$)] were given to the GS-TAE-group cases after being mixed with GS and were given to the LP-TAE-group cases after being emulsified in LP [10]. CDDP [GS-TAE group, 125 mg ($n = 2$); LP-TAE group, 107 ± 25 mg ($n = 49$)] was given as a single intra-arterial injection prior to TAE.

Compensation for background factors. Both the morphological features of the main tumor and the hepatic function (Table 2) at the time of the

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Correspondence to: N. Nakao, Department of Radiology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya 663, Japan

Table 1. Number of cases in the GS-TAE group and the LP-TAE group

Institution	Number of cases	GS-TAE	LP-TAE
A	201	61	140
B	67	12	55
C	29	4	25
D	38	6	32
E	8	4	4
Totals	343	87	256

A, Hyogo College of Medicine; B, Nara Medical University; C, Osaka University Medical School; D, Center for Adult Diseases, Osaka; E, Kinki University School of Medicine

first embolization were considered to be important background factors that had to be taken into account for accurate statistical analysis. For each background factor, the chi-square test was used to compare the nominal values determined for each group and the *t*-test was employed to compare the numerical values calculated for the two groups.

Estimation of survival. The Kaplan-Meier method was used to estimate the duration of survival, and the log-rank test was employed to compare the survival values determined for the two groups.

Assessment of the usefulness of LP. Cox's regression model was used to determine which of the various background factors affected the patients' prognosis. Using these factors as variables, Cox regression curves were generated. For estimation and statistical analysis, the statistical software packages SYSTAT and SAS were used on personal computers (Apple Macintosh II, Toshiba J3100 SGT).

Results

Evaluation of institutional differences

The differences among the five participating institutions were assessed by comparing the T values obtained using the Cox model. The T value for each institution was approximately 2, suggesting that there was no apparent difference among the institutions.

Investigation of background factors

In all, 18 factors were analyzed for significant difference between the GS-TAE group and the LP-TAE group (Table 2). In regard to tumor morphology, there were significantly more (P <0.05) cases of intrahepatic metastatic foci in the LP-TAE group. With respect to hepatic function, a significant difference (P <0.05) between the two treatment groups was found for total cholesterol and lactic dehydro-

Table 2. Background-factor biases in HCC groups at the time of transcatheter arterial embolization

Background factor		GS-TAE group (n = 87)	LP-TAE group (n = 256)	P
Tumor size (cm)		5.7 ± 3.6 (1.0–16.0)	5.0 ± 3.0 (0.8–14.3)	NS
Type:				
	Nodular	43	153	
	Massive	32	68	NS
	Multinodular	12	35	
H factor:				
	H1	48	168	
	H2	24	60	NS
	H3	15	28	
IM factor:				
	IM0	38	85	
	IM1	9	21	<0.05
	IM2	14	64	
	IM3	26	86	
VP factor:				
	VP0	36	172	
	VP1	29	61	NS
	VP2	22	22	
AFP (log)		2.67 ± 1.11 (0.05–5.05)	2.23 ± 1.06 (0.05–5.96)	NS
Alb	(mg/dl)	3.40 ± 0.46 (2.56–4.60)	3.50 ± 0.47 (2.14–5.40)	NS
Chol	(mg/dl)	149 ± 33 (75–253)	162 ± 44 (42–420)	<0.05
LDH	(U)	310 ± 75 (179–549)	329 ± 99 (123–727)	<0.05
Bil	(mg/dl)	0.95 ± 0.44 (0.27–2.70)	1.07 ± 0.73 (0.23–2.90)	NS
gGlob	(%)	24.8 ± 6.7 (12.4–37.4)	25.3 ± 7.04 (7.8–48.7)	NS
PT	(s)	74.9 ± 25.7 (12.2–119.0)	68.0 ± 33.5 (10.5–143.0)	NS
ICG	(%)	30.0 ± 13.8 (3.0–62.0)	25.9 ± 12.8 (4.0–69.0)	NS
HPT	(%)	68 ± 15 (33–102)	69 ± 17 (27.0–143.0)	NS

Data represent mean values ± SD; range (minimal to maximal values) are shown in parentheses. H factor (tumor extension): H_1, within 1 segment; H_2, within 2 segments; H_3, within 3 segments. IM factor (intrahepatic metastasis): IM_0, no metastasis; IM_1, within 1 segment; IM_2, within 2 segments, IM_3, within 3 segments. VP factor (portal venous infiltration): VP_0, no infiltration; VP_1, infiltration to the 3rd (or more distal) branch; VP_2, infiltration to the 2nd branch. Alb, Albumin; Chol, total cholesterol; LDH, lactic dehydrogenase; Bil, total bilirubin; gGlob, gamma globulin; PT, prothrombin time; ICG, 15-min retention ratio of indocyanine green; HPT, hepaplastin test; NS, not significant

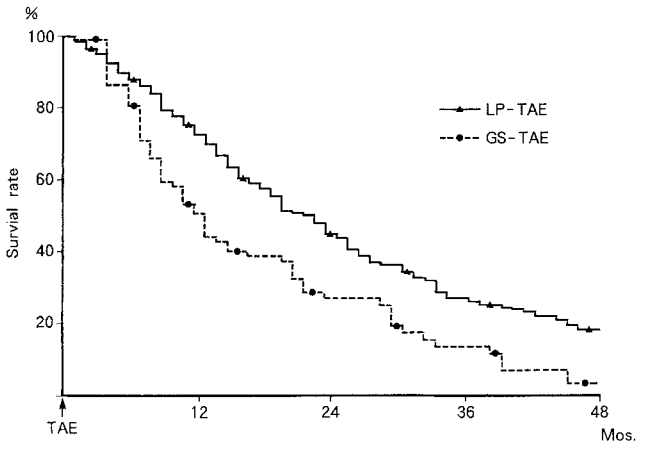

Fig. 1. Cumulative survival of the GS-TAE group and the LP-TAE group after transcatheter arterial embolization (calculated by the Kaplan-Meier method)

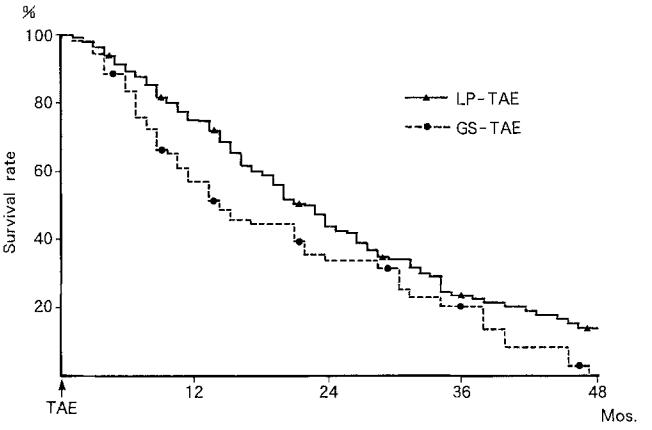

Fig. 2. Survival of patients in the GS-TAE and LP-TAE groups as calculated using Cox's proportional hazard model (parameters: tumor diameter, 5 cm; IM, 1; VP, 1; AFP, 200 ng/ml; Bil, 1.0 mg/dl; MMC, 10 mg)

Table 3. Selection of variables according to Cox's estimation

Covariant	Estimate	SE	*T*-value
LP	–0.529	0.181	–2.915
AFP	0.278	0.067	4.174
IM	0.258	0.063	4.111
SIZE	0.083	0.022	3.743
BIL	0.191	0.075	2.542
VP	0.261	0.111	2.355

LP, Lipiodol; AFP, α-fetoprotein; IM, intrahepatic metastasis; SIZE, tumor diameter; BIL, serum total bilirubin; VP, portal venous infiltration

genase (LDH). No significant intergroup difference was found for any of the other factors, including the doses and types of anticancer agents used.

Cumulative survival: Kaplan-Meier estimation

The cumulative survival values determined using the Kaplan-Meier method are shown in Fig. 1. The respective 1-, 2-, 3-, and 4-year survival values calculated for the GS-TAE group were 53%, 27%, 13%, and 4%, and those found for the LP-TAE group were 75%, 46%, 27%, and 18%. A significant difference ($P < 0.01$) was observed between each of the survival values obtained for the two groups (log-rank test).

Selection of variables

Table 3 shows the results of carrying out stepwise variable selection with 5% addition and 10% deletion criteria using the 18 factors listed in Table 2. Six factors were found to affect the patients' outcome significantly: the administration of LP, the serum alpha-fetoprotein (AFP) level, intrahepatic metastasis (IM), the tumor diameter (SIZE), the serum alpha-fetoprotein (AFP) level, intrahepatic metastasis (IM), the tumor diameter (SIZE), the serum total bilirubin (Bil) level, and portal vein infiltration (VP). Among these six factors, only LP had a minus *T* value, suggesting that LP is an important factor affecting the prognosis.

Estimation using Cox's proportional hazard model

We obtained the survival curves predicted by Cox's estimation in the presence and absence of LP (Fig. 2). These curves were calculated using the following parameters: tumor diameter, 5 cm; IM, 1; VP, 1; AFP, 200 ng/ml; and Bil, 1.0 mg/dl. The predicted 1-, 2-, and 3-year survival values determined for the GS-TAE group were 57%, 34%, and 30%, respectively, whereas the predicted 1-, 2-, 3-, and 4-year values calculated for the LP-TAE group were 75%, 43%, 33%, and 14%, respectively. There was a significant difference ($P < 0.01$, log-rank test) between the survival values found for the two groups. When we calculated the relative risk of patients using the same parameters in the presence and absence of LP, the risk ratio (hazard ratio) obtained was 2.30.

Outcome according to the LP dose

By relating the LP dose to the diameter of the main tumor, we divided the patients into three groups. Group 1 ($n = 33$; LP dose, 26 ± 2.02 ml) received an LP dose (D) expressed in milliliters that was equal to or less than the tumor diameter (d) expressed in centimeters (i.e., about 5 ml LP for a tumor measuring 5 cm in diameter; D = d), group 2 ($n = 69$; LP dose, 6.63 ± 2.98 ml) was given an LP dose that was equivalent to up to twice the main tumor's diameter ($d<D<2d$), and group 3 ($n = 19$; LP dose, 10.13 ± 3.81 ml) received an LP dose that was equivalent to more than twice the main tumor's diameter ($D \geq 2d$). When the prognosis for these three groups was estimated using Cox's regression model (Fig. 3), that of group 1 was found to be significantly better than that of the other two groups after 2 years.

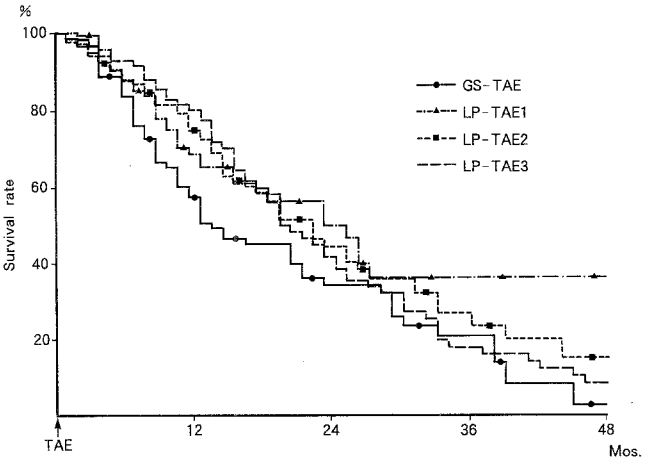

Fig. 3. Cumulative survival plotted as a function of the LP dose after transcatheter arterial embolization (calculated using Cox's proportional hazard model). *LP-TAE1*, group 1 (LP dose ≦d); *LP-TAE2*, group 2 (d<LP dose <2d); *LP-TAE3*, group 3 (LP dose ≧2d)

Discussion

The effectiveness of TAE in HCC has been widely recognized [2, 3, 9, 15]. As an embolization material, LP is generally given prior to embolization with GS, but its effect on the patients' prognosis has not yet been clarified. The present authors thought that a retrospective statistical study would provide the necessary data if all background factors were carefully considered.

The period (1984–1989) from which the TAE cases were selected for this study was limited to 5 years to minimize any historical difference, since during that period there was very little change in postembolic control or in the technique employed for TAE therapy. Although this study was multi-institutional, an analysis of the background factors revealed that there was no difference among the participating institutions.

A significant difference was found between the GS-TAE group and the LP-TAE group for three of the background factors shown in Table 2. To avoid any effect these factors might have on the results, the use of multivariate analysis was necessary to obtain an accurate comparison of the treatments' effectiveness. Althoug statistical methods such as discriminant analysis and factor analysis have been used in previous studies on TAE [11, 16], the present authors considered the proportional hazard model [4, 5, 7, 8] – which incorporates the characteristics of the method of multiple regression analysis reported by Cox in 1972 and the life-table method – to be the most appropriate method for assessing the effectiveness of treatment.

With regard to the effect of LP on the patient's prognosis, when Kaplan-Meier estimation was used to compare the cumulative survival values, a significant difference (P <0.05) was found between the GS-TAE group and the LP-TAE group. A significant difference was also found using Cox's proportional hazard model, which further establishes the usefulness of LP.

However, care must be exercised with regard to the LP dose, since high doses did not yield good long-term results (Fig. 3). On the basis of the results of this study, we recommend the use of an LP dose expressed in milliliters that is approximately equivalent to the diameter of the main tumor expressed in centimeters. It is thought that large doses of LP may damage liver parenchyma afflicted with cirrhosis by entering the portal vein through the arterioportal anastomosis, causing arterial and portal embolization after Gelfoam injection.

The results of stepwise variable selection based on the Cox model showed that the tumor diameter (SIZE), intrahepatic metastasis (IM), and portal vein infiltration (VP) were all morphological tumor factors with a high T value that strongly affected the outcome. This was not unexpected, because all of these factors are directly linked to the degree of tumor extension. Among the factors related to hepatic function, only the total bilirubin level appeared to be related to the prognosis. It was also natural that the AFP level seemed to be an important prognostic factor, since a high AFP value directly reflects the degree of tumor progression.

The anticancer agents ADM, MMC, and CDDP were deleted during the early phase of stepwise variable selection. Despite some reports on their effectiveness [6, 13], no objective assessment has been carried out. One possible reason why these anticancer agents were not shown to affect the outcome in this study may have been that the extensive necrotizing effect of TAE obscured the slighter necrotizing effect that the anticancer agents may have had. The possible usefulness of anticancer drugs should be further clarified through prospective studies, and the possibility that they may have an adverse effect on normal liver parenchyma should always be kept in mind in the consideration of any treatment regimen.

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