Reevaluation of lipiodolized transarterial chemoembolization therapy for intrahepatic recurrence of hepatocellular carcinoma after curative liver resection

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Abstract

Background/Purpose. While lipiodolized transarterial chemoembolization (lip-TACE) is effective for treating unresectable hepatocellular carcinoma (HCC), its effect for recurrent HCC after curative liver resection need to be clarified.

Methods: Of 163 patients who had undergone curative liver resection between 1992 and December 2003, 65 patients (39.8%) had recurrent HCC in the liver without extrahepatic recurrence and were indicated for lip-TACE. Overall survival rate after lip-TACE was calculated, and its correlation with factors such as histology of the primary HCC and background non-cancerous tissue were analyzed.

Results: Survival rates after lip-TACE, namely after detection of the first recurrent HCC, were 82.6%, 44.5%, and 24.8% at 1, 3, and 5 years, respectively. The factors affecting patient survival after lip-TACE were microscopic portal venous involvement of HCC at liver resection, grade of inflammation in non-cancerous liver parenchyma, and recurrence within 1 year after initial liver resection. Multivariate analysis showed that the period between resection and first recurrence had the highest hazard ratio.

Conclusions: Lip-TACE is reasonable procedure for treating recurrent HCC in selected patients who were not eligible for hepatic re-resection. When HCC recurred within 1 year from primary liver resection, the effect of lip-TACE on patient survival was limited.

Key words hepatocellular carcinoma・lipiodolized chemoembolization,・recurrence・resection

Introduction

The troublesome problem of hepatocellular carcinoma (HCC) is the high rate of recurrence even after curative liver resection for primary HCC.[1,2] When a second liver resection is possible, it should be performed to obtain a better prognosis. [3,4] However, since HCCs in Japan mainly develop in cirrhotic liver, re-resection is sometimes hampered by poor remnant liver function even with limited resection as reported previously.[1,5] In addition, recurrence of HCC occasionally occurs multifocally, so neither resection nor ablation therapy are possible for such bi-lobar unresectable disease.[6-8] Systemic chemotherapy is also reported to have limited value in treating HCC recurrence after curative liver resection. [9]

For those cases of recurrent HCC in which re-resection is not considered, lipiodolized transarterial chemoembolization therapy (lip-TACE) could be a treatment of choice. Lipiodol-based chemotherapy has benefit since it can be performed less invasively as compared to the surgery, and can also be repeated as needed. We previously proposed the “lipiodolization” procedure and reported its therapeutic effect in patients with unresectable HCC.[10-12] However, the effect of lip-TACE for recurrent HCC after curative

resection has not been well evaluated in a large case series, and only particle embolization for recurrent HCC was reported recently.[13] In addition, the factors predicting patient survival after lip-TACE have not been analyzed to date. This information could be important for assessing treatment selection and will also be needed for when gaining informed consent of lip-TACE procedure offered by surgeons/oncologists/hepatologist from patients with recurrent HCC that is otherwise untreatable.

The aim of this descriptive study was to clarify the effect of lip-TACE for recurrent HCC after curative liver resection and to identify the factors affecting patient survival after lip-TACE, which we analyzed as a case series identified through a retrospective medical record review in a Japanese single medical center.

Methods

Patients

The medical records from consecutive 163 Japanese patients treated in the Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences between 1992 and 2003 were reviewed. Patients were included if they had undergone a curative liver resection for HCC on the basis of the

histology of the liver. A curative liver resection is defined as a partial hepatectomy with histologically clear margins (R0 resections).

In principle, lip-TACE was indicated if repeated liver resection was not possible, for example, in cases of far advanced recurrent HCC, multiple recurrent HCCs, or poor liver function. Liver function was evaluated by blood chemistry and retention rate of indocyanine green at 15 minutes. The criteria for surgery were almost the same as Makuuchi's criteria, i.e., the presence or absence of ascites, the serum total bilirubin level, and the indocyanine green retention rate at 15 minutes (ICG R15).[14] Usually, lip-TACE was performed as soon as recurrent HCC was assessed to be unresectable.

Serological presence of any hepatitis B antigen was considered as positive evidence of hepatitis B infection. Serologic presence of hepatitis C antibody was considered as positive evidence of hepatitis C infection. The type of hepatic resection performed was classified according to the terminology of the Liver Cancer Study Group of Japan,[14] as follows: Hr0: less than one subsegment (Couinaud's segment), HrS: resection of one subsegment (Couinaud's segment), Hr1: resection of one segment (anterior,

posterior, medial, or left lateral segmentectomy), Hr2: resection of two segments (right or left lobectomy or central bisegmentectomy), Hr3: resection of three segments (right or left trisegmentectomy).

Microscopic vascular invasion to the portal vein was defined as the presence of tumor emboli within the portal vein. The degree was defined as vp0 (no invasion), vp1 (invasion to the third-order portal vein), vp2 (invasion to the second-order portal vein), and vp3 (invasion to the first-order portal vein or main portal trunk) according to the terminology of the Liver Cancer Study Group of Japan.[15] Patients were also stratified according to the TMN classification system.[16] Follow-up of the patients was done, in principle, every 3 months by assessment of serum alpha-fetoprotein (AFP) level and ultrasonography. When recurrence of HCC was suspected, computed tomography scanning was performed. In principal, (neo)adjuvant chemotherapy was not used. To evaluate the degree of chronic hepatitis, we utilized the Staging and Grading categories.[17] Staging indicates the degree of fibrosis, separated into 4 categories, with no fibrotic change expressed as F1 and established cirrhosis shown as F4. Grading means the degree of inflammatory process, with reference to Knodell's histology Activity Index.[18]

Grading was divided into mild (G1), moderate (G2), and severe (G3) activities.

Lip-TACE.

The lip-TACE procedure was performed by specialized interventional radiologists, mainly conducted by one of the co-authors (I. S.). An emulsion consisting of 5 ml lipiodol, 10 mg mytomycin C, and 20 mg epirubicin hydrochloride was infused immediately before embolization with gelform for feeding arteries. If there were multiple recurrent HCCs not suitable for embolization, infusion of above mentioned emulsion was performed from proximal side of hepatic artery. Since lipiodol itself causes fat embolism within cancer tissue, the procedure is also included in lip-TACE.

Usually a combination procedure of embolization for the main HCC and infusion for other multiple small HCCs was used. Also, sometimes same patients had undergone multiple procedures with or without spongel longitudinally.

The median follow-up period after curative liver resection and after lip-TACE was 1593 days (395-8184) and 657 days (135-3755), respectively. The median time to recurrence was 652 days (108-7734).

Statistics. All data were expressed as median values with ranges. Statistical analysis was done with the Mann-Whitney u-test for continuous values and the Chi-square test for categorical values. Survival was measured from the time of resection or the first lip-TACE until death or last follow-up. Survival curves were constructed using the Kaplan-Meier product limit method and compared using the log-rank test. The variables listed in Table 1 were analyzed via univariate analysis. The multivariate analysis was performed by the Cox proportional hazard model. Statistical difference was defined as a p value of less than 0.05. The StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA) was used for all statistical analysis.

Results

Lip-TACE was a procedure of repetition, as shown in Table 1. Forty patients were treated with lip-TACE more than twice. The indication of lip-TACE was multiple recurrent HCCs in fifty patients, while 10 patients were considered to be ineligible for second liver resection due to poor liver function and 5 were unknown.

Of 163 patients, 78 patients had recurrent HCC. Since 13 patients were eligible for liver re-resection, the remaining 65 patients were indicated for lip-TACE. Patient backgrounds are described in Table 2. There were 57 males and 8 females with a median age of 64 years (range 35-79). Fourteen patients were positive for hepatitis B surface antigen, while 42 patients were positive for hepatitis C antibody (5 patients were negative for both hepatitis B surface antigen and hepatitis C antibody; 4 patients unknown). Fifty patients were in Child-Pugh A, while fifteen patients were in Child-Pugh B at the time of primary liver resection. With regard to histology activity index of the resected liver at the time of surgery, Grading (inflammation) was median 9 (range 2-13), while Staging (fibrosis) was median 2 (range 0-4). The factors affecting patient survival after lip-TACE were histological tumor thrombi in the portal vein, the period between resection and recurrence, and histological inflammatory activity (Grading, Table 2). Multivariate analysis showed that the hazard ratio of each variable ranged from 0.063 to 4.226, and the variable of the period between resection and first recurrence had the highest hazard ratio of 4.226 (Table 3).

Overall survival rates after lip-TACE, after detection of the first

recurrent HCC, were 82.6% at 1 year, 44.5% at 3 years, and 24.8% at 5 years (Fig. 1). Almost all patients died of progression of HCC recurrence. The patients treated with lip-TACE were further stratified according to preoperative variables as well as histological findings of the HCCs. There was no significant difference in viral markers, stage of primary HCC, or operative methods after lip-TACE for recurrent HCC. The histological grade of portal venous invasion of the HCC significantly affected patient survival after lip-TACE (Fig. 2). In addition, in the non-cancerous liver, histological activity Grading of inflammation of the liver significantly affected patient survival after lip-TACE, while histological fibrosis staging did not affect survival significantly (Fig. 2). When patients were stratified with the time period of the recurrence (within 1 year or after), patient survival rates after lip-TACE were significantly different (Fig. 2). In Fig. 3, survival after lip-TACE was stratified with indication for lip-TACE with no significant difference.

Discussion

In the present descriptive study, we demonstrated the therapeutic effect of lip-TACE for recurrent HCC after curative liver resection otherwise untreatable. In our series, overall survival after lip-TACE for recurrent HCC was 82.6% at 1 year and 44.5% at 3 years, which almost matches the results reported previously (83.3% at 1 year, 48% at 3 years).[19-22] However, the 24.8% overall survival rate at 5 years in the present study was better than the result of Okazaki et al. and Lee et al., which did not report a 5-year survivor after lip-TACE. This difference might be due to advances in technique and instruments over more than 10 years or heterogeneity of the patient population included in the studies. Poon et al.[23] reported that lip-TACE in patients with postresection recurrent HCC was associated with lowered morbidity and mortality and a better survival outcome compared with patients with primary inoperable HCC, but this was largely related to smaller tumor size and better liver function in the former group at the time of lip-TACE treatment.

Recently, bland particle embolization for recurrent HCC was reported by Covey et al.[13], with a patient survival rate after the therapy for recurrent

HCC reported as 86% at 1 year, 74% at 2 years and 47% at 5 years with a median follow-up of 31 months. Patients with solitary recurrent HCC also had better survival than multiple recurrences, i.e., 92% vs. 75% at 3 years in this cohort. The author's indication of bland hepatic arterial embolization was recurrent HCC in patients with relatively good liver function. Also, since they did not use lipiodolized anti-cancer drugs, the difference at 5 years after therapy should be carefully evaluated with a randomized trial.

Interestingly, there were no significant correlations between survival after lip-TACE and factors such as viral marker, Child-Pugh classification, stage of HCC or operative methods. This means that the state of a primary resected HCC, except for histological portal venous invasion or intrahepatic metastasis, has nothing to do with the effect of lip-TACE on recurrent HCC. In addition, prognosis following lip-TACE was worse in patients whose liver had severe inflammation as compared to that seen in patients with less inflammatory liver. Therefore, when inflammation is severe in the non-cancerous liver tissue, anti-viral /anti-inflammation therapy should be considered in combination with lip-TACE to reduce the chance of recurrence. This finding has never been reported in combination with lip-TACE. Fibrosis

of the liver did not have an impact on postoperative patient survival. Therefore, non-cancerous liver must be carefully checked especially for ongoing inflammation to predict the effect of lip-TACE after recurrent HCC.

Our study cohort was a population that received a variety of treatments for recurrent unresectable HCC with or without embolization. Since we had 45 patients who received multiple lip-TACE procedures, sometimes the same patients had undergone multiple procedures with or without gelform longitudinally. Also, as stated in p8, a patient with multiple recurrent HCCs underwent embolization for main HCC and infusion for other small multiple HCCs. Therefore, it is practically difficult to divide our patients into 2 groups according to the existence of gelform or lack of gelform and compare them. We selected the optimal method of lipiodolized chemotherapy in each case based on the existence of tumor stain, number of HCC, and liver function, even in a single patient longitudinally.

In this study, with regard to recurrent status, multiple recurrence or not was only considered as an independent factor. The individual number, tumor size and distribution of the recurrent HCC were not considered as factors, since lip-TACE is not curative procedure like resection or ablation. Also, since vascular invasion is only

evaluated by imaging study, it was not considered as an independent factor for recurrent HCC. How would the status of recurrent HCC in terms of maximal size or number affect the effectiveness of lip-TACE awaits further investigation.

The present case series in a single medical center demonstrated that lip-TACE was a reasonable treatment modality for patients with recurrent HCC who were not eligible for hepatic re-resection. The procedure was more effective when the resected HCC had no histological portal venous invasion or histological intrahepatic metastasis, and when there was less inflammation in the non-cancerous tissue. When HCC recurred within 1 year from primary liver resection, the effect of lip-TACE on patient survival was limited. Whether lip-TACE should or should not be performed for those patients needs further investigation.

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Figure legends

Fig. 1. Overall survival after initial resection for primary HCC and lip-TACE for recurrent HCC.

A: Overall survival after initial surgery for primary HCC, B: Overall survival after lip-TACE for recurrent HCC

Fig. 2. Patient survival after lip-TACE for recurrent HCC

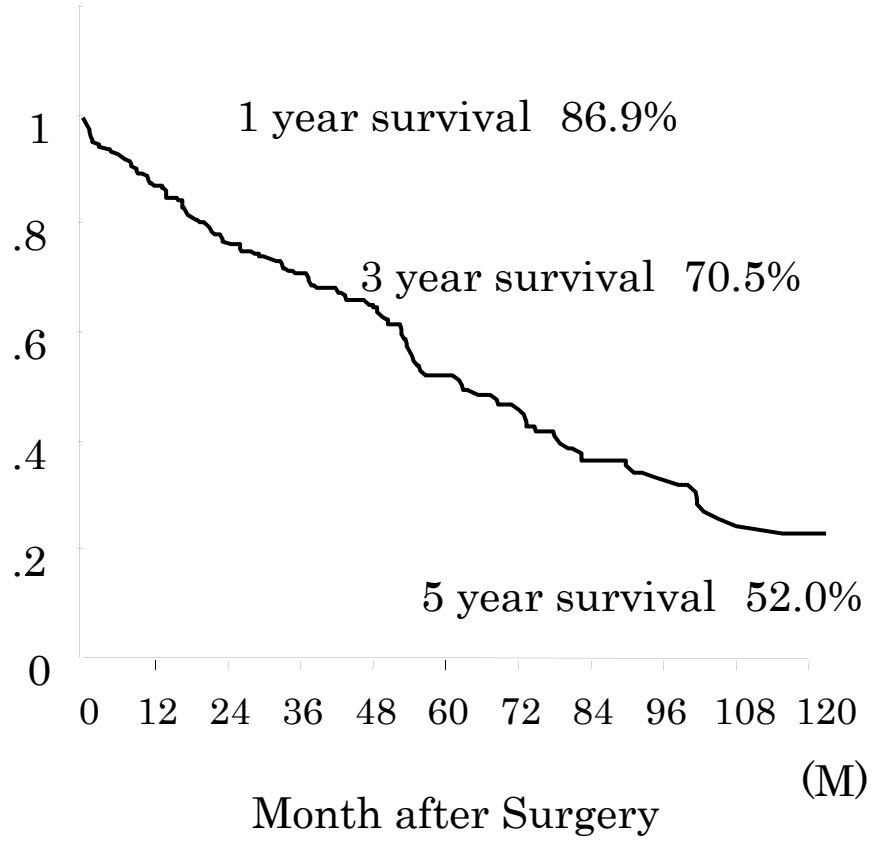
Patient survival after lip-TACE for recurrent HCC were stratified with intraportal involvement, Grading, Staging, and the period between resection and first recurrent HCC, respectively.

Fig. 3. Overall survival after lip-TACE for recurrent HCC according to indication for lip-TACE.

Patient survival after lip-TACE for recurrent HCC were stratified with indication for lip-TACE.

Fig 1. Overall survival after initial resection for primary HCC and lip-TACE for recurrent HCC.

A. Overall survival after initial surgery



B. Overall survival after lip-TACE for recurrent HCC

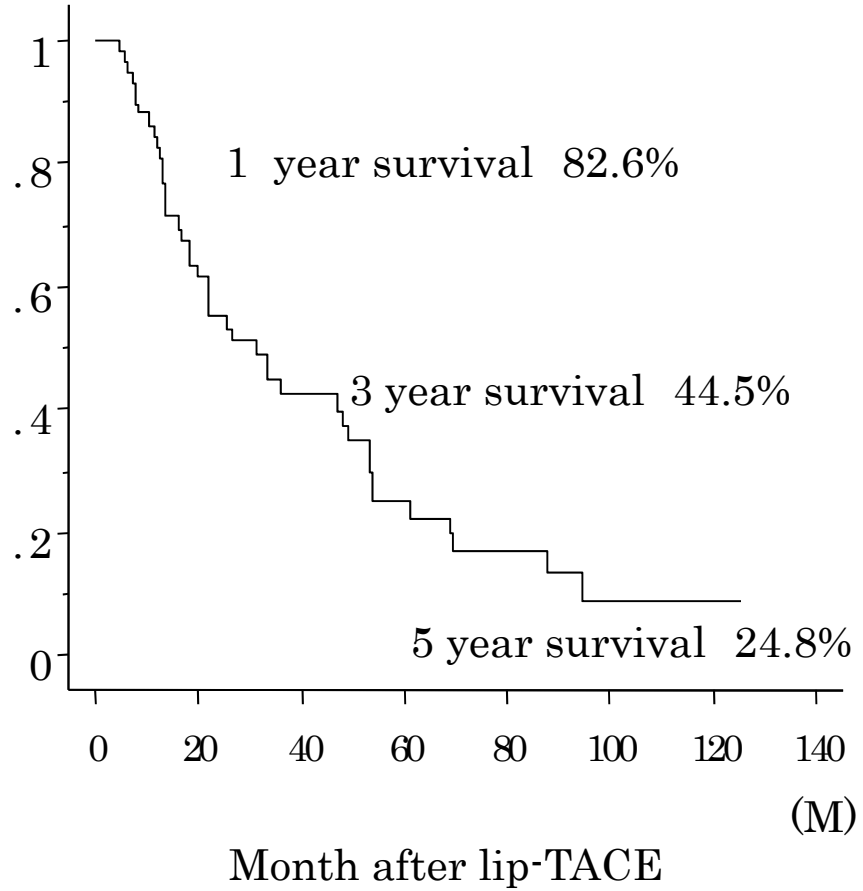
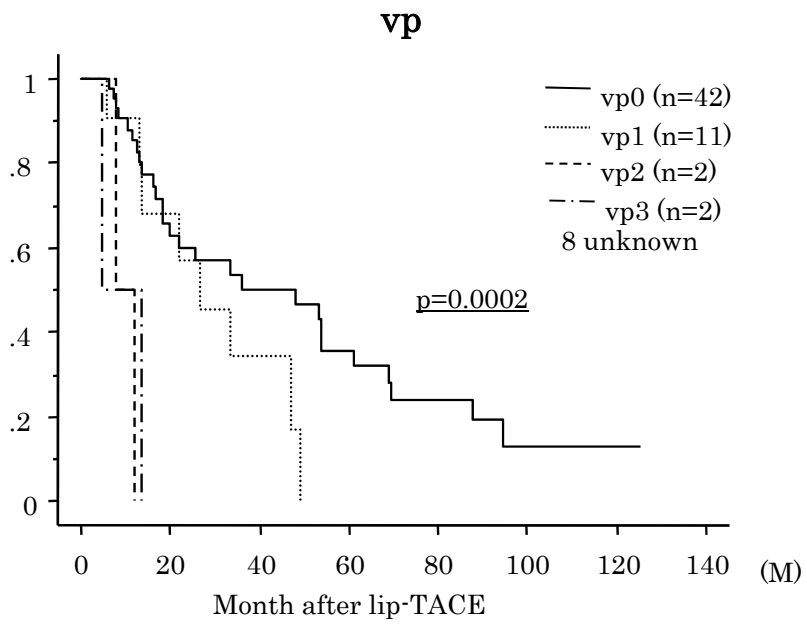
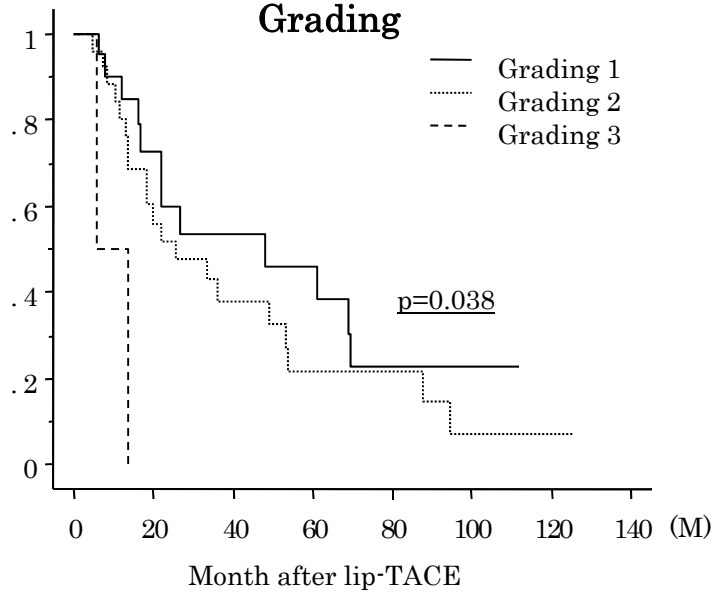
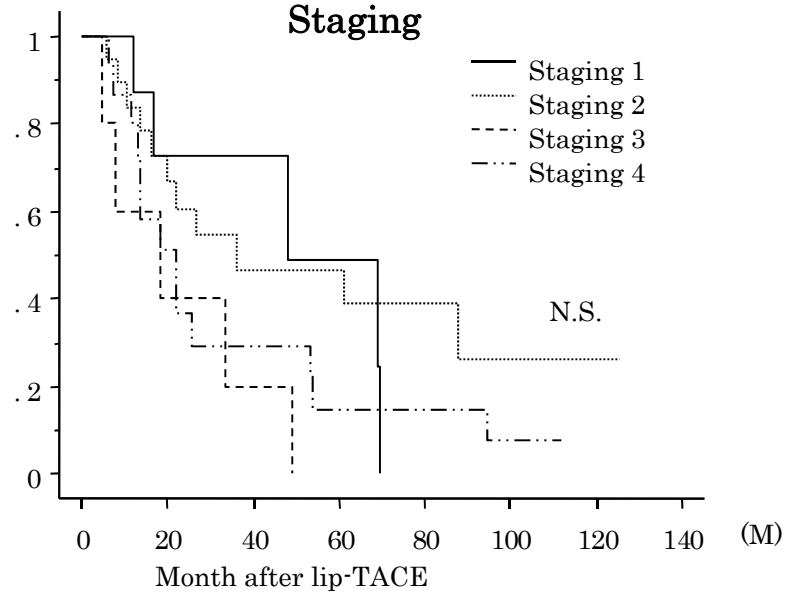


Fig 2. Overall survival after lip-TACE for recurrent HCC







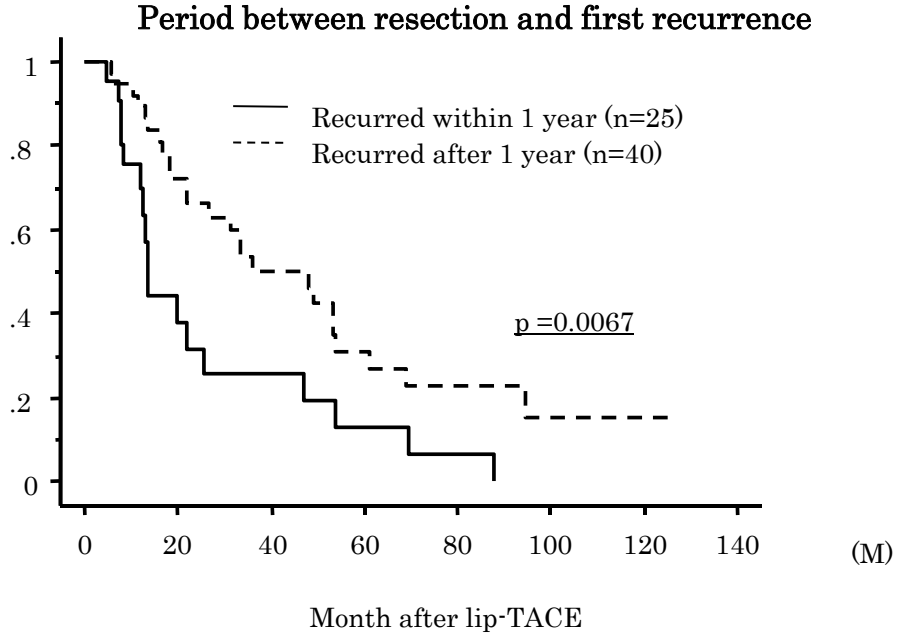


Fig 3. Overall survival after lip-TACE for recurrent HCC according to indication for lip-TACE

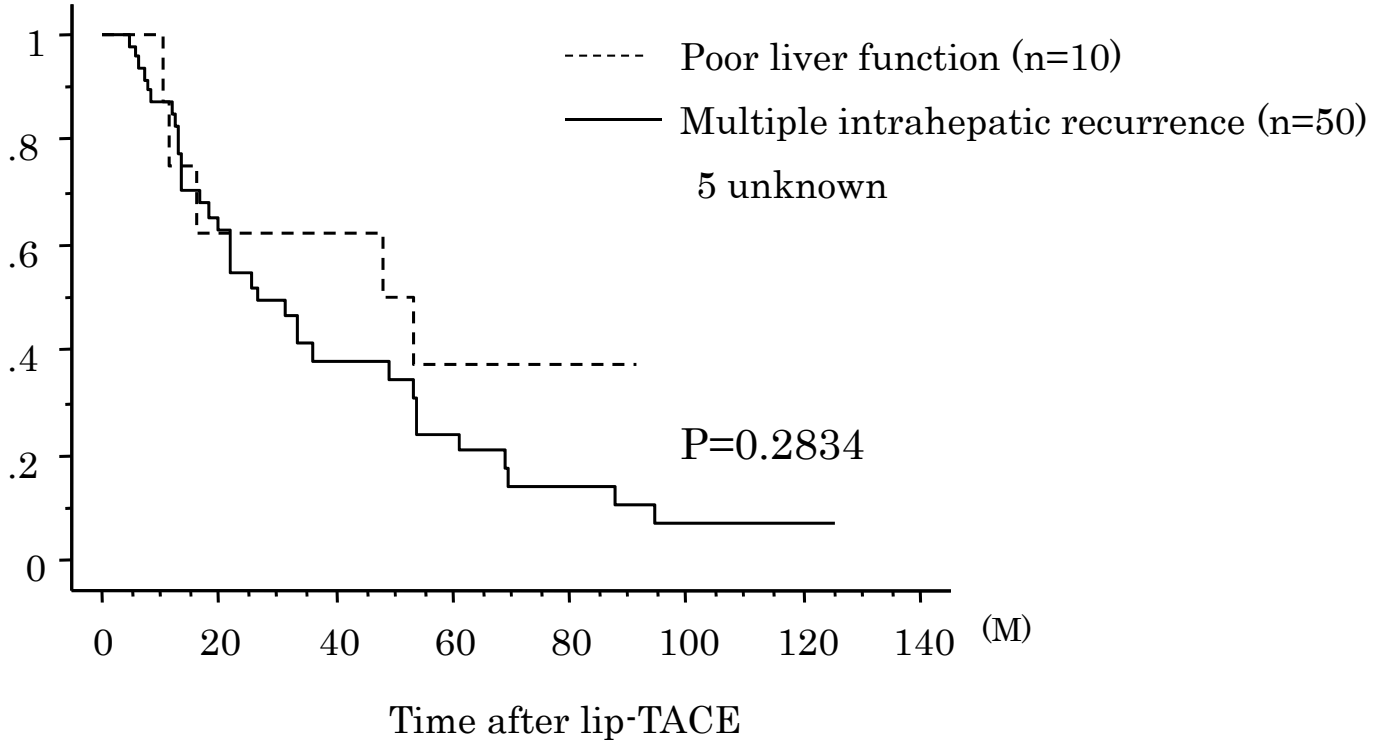


Table 1. Summary of lip-TACE procedure

Number of lip-TACE procedure for recurrent HCC

1	25 patients (38.5%)
2	18 patients (27.7%)
3	7 patients (10.8%)
4	5 patients (7.7%)
5	1 patient (1.5%)
6	6 patients (9.2%)
7	2 patients (3.1%)
12	1 patient (1.5%)
Total	65 patients

Indications of lip-TACE for recurrent HCC

intrahepatic multiple recurrent HCC	50 patients (76.9%)
poor liver function	10 patients (15.4%)
unknown	5 patients (7.7%)

Table 2. Patient demographics and prognostic factors after lip-TACE for recurrent HCC

			Number of patients	Proportion (%)	p value for survival after lip-TACE
Gender		M	57	87.7	0.5586
		F	8	12.3	
Age		Median	64-year-old	(range 35-79)	
Viral markers		HBV	14	21.5	0.4179
		HCV	42	64.6	
		non-B, non-C	5	7.7	
		Unknown	4	6.2	
Child-Pugh classification at liver resection		A	50	76.9	0.9906
		B	15	23.1	
TNM Classification of HCC at at liver resection		Stage I	5	7.7	0.2696
		II	29	44.6	
		III	15	23.0	
		IVA	8	12.3	
		unknown	8	12.3	
Primary operative methods		Hr0	26	40.0	0.5986
		HrS	5	7.7	
		Hr1	12	18.5	
		Hr2	15	23.0	
		Hr3	5	7.7	
		Unknown	2	3.1	
Vascular invasion to the portal vein		vp 0	42	64.6	0.0002
		vp 1	11	16.9	
		vp 2	2	3.1	
		vp 3	2	3.1	
		unknown	8	12.3	
HAI score	Grading	Median	9	(range 2-13)	0.038
	Staging	Median	2	(range 0-4)	0.1316
Recurrence		within 1 year	25	38.5%	0.067
		after 1 year	40	61.5%	

Hr, type of liver resection; vp, vascular invasion of the portal vein; HAI, hepatitis activity index

Table 3. Multivariate analysis of factors affecting survival of the patients who underwent lip-TACE for recurrent HCC

Variables	p value	Hazard ratio	95% C.I.
Vp : 0 vs 3	.0070	.063	.008-.470
: 1 vs 3	.0457	.107	.012 - .958
: 2 vs 3	.5872	2.116	.141 - 31.710
Grading	0.1676	1.090	.965 - 1.231
Recurrence within 1Y	0.0008	4.226	1.820 - 9.813