Manuscript title

Which System is Better to Predict Prognosis of Patients with Hepatocellular Carcinoma Treated by Transcatheter Arterial Chemoembolization as Initial Therapy ? Comparison between CLIP and JIS in a Japanese Population

Abstract

Background:

There has been no consensus which system, either Cancer of the Liver Italian Program (CLIP) or Japan Integrated Staging (JIS) system, is suitable to predict the prognosis of hepatocellular carcinoma (HCC) patients who underwent transcatheter arterial chemoembolization (TACE) as initial therapy.

Purpose:

To retrospectively compare the usefulness of CLIP and JIS system in predicting and stratifying the prognosis of HCC patients treated by TACE.

Materials and Methods:

Between 1995 and 2005, consecutive 728 patients with untreated HCC who underwent TACE in our institute were selected for this study. The survival rate and its prognostic factors were assessed by multivariate analysis. Patients were stratified according to the two systems, and their survival rates between the scores were compared.

Results:

The mean follow-up period was 1689 days. The one-year, 3-year, 5-year, and 10-year survival rates were 83.1%, 55.1%, 34.7%, 12.8%, respectively.

Both systems stratified the prognosis of patients well, but slightly better in CLIP system as compared to in JIS. As for multivariate factor analysis, less severe Child-Pugh classification ($p<.001$), simple tumor morphology ($p<.001$), absence of portal vein invasion ($p<.001$), and lower alpha- fetoprotein (AFP) level ($p<.001$) were suggested to be independent indicators for favorable survival rate. All of these independent factors were included in the CLIP, whereas JIS system lacked AFP level. Furthermore, the likelihood χ^2-test value was higher, and the Akaike information criterion value was lower for CLIP than for JIS system.

Conclusion:

CLIP is more suitable than JIS for predicting prognosis of patients with HCC who would undergo TACE in Japanese population.

Key words:

Abdomen/GI; chemoembolization; liver; neoplasms-primary; outcome analysis

Introduction

Hepatocellular carcinoma (HCC) mainly involves patients already affected with chronic hepatitis or liver cirrhosis due to hepatitis B or C viral infection (1) or alcohol (2). Therefore, the prognostic assessment and choice of therapeutic modalities, such as liver resection, local ablation therapy, transcatheter arterial chemoembolization (TACE), and liver transplantation strongly depends not only on the grade of cancer spread (tumor staging), but also on the grade of residual liver function (liver disease stage) (3).

So far, several integrated staging or scoring systems for HCC have been proposed, including Okuda stage in 1985 (4), Cancer of the Liver Italian Program (CLIP) Scoring System in 1998 (5, 6), Barcelona Clinic Liver Cancer (BCLC) Staging System in 1999 (7), Japan Integrated Stage (JIS) Score in 2004 (8), Tokyo Score in 2005 (9), Modified JIS Score in 2006 (10), and Biomarker Combined JIS Staging Score in 2008 (11), and revised BCLC in 2014 (12).

Generally, TACE has been considered to be indicated for those at BCLC stage B, which is defined as an intermediate-stage disease that consists of heterogeneous patients (13). Furthermore, patients who are not at BCLC stage B, namely stage A or C, are sometimes referred to our department for TACE in actual clinical practice. To adequately determine the indication of TACE, detailed stratification of these patients

based on their respective prognosis would be mandatory, because those actually treated by TACE are highly heterogeneous in terms of tumor staging and liver disease staging as well (14). Among the integrated staging or score systems as mentioned above, CLIP and JIS score systems have detailed stratification, and have been most widely accepted in Japan. The former consists of one patient factor and 3 tumor factors, scoring from 0 to 6 (Table 1), and the latter consists of one patient factor and 5 tumor factors, scoring from 0 to 5 (Table 2). However, there is no worldwide consensus yet regarding which system is more suitable to patients with HCC treated by TACE.

The purpose of this study was to retrospectively compare the usefulness of CLIP and JIS systems in stratifying the prognosis of HCC patients who had undergone TACE as initial therapy in our institute.

Materials and Methods

Our institutional review board waved to obtain informed consent from the patients who were recruited for this study because of its retrospective nature.

Patients and data collections

939 consecutive patients underwent initial TACE for HCC in our institute between January 1995 and April 2005. Indication of TACE was basically in concordance with the "intermediate stage" of BCLC staging system, namely, patients who have Child-Pugh grades A and B liver function, and are considered contraindicated to surgical resection or percutaneous therapies. However, patients who were theoretically indicated for percutaneous therapies but whose HCC were located at difficult sites to access by percutaneous approach, or those who were initially arranged for surgical resection but refused later, or were considered contraindicated for surgery due to poor systemic condition including cardiac or respiratory insufficiency, were also referred to our department for TACE, as an alternative to curative treatments or as a palliative treatment.

Angiographic reports and medical records of these 939 patients were retrospectively reviewed by one of the authors (HU), and CLIP and JIS scores and survival after initial

TACE were recorded. In our institute, the tumor morphology, presence of portal vein thrombosis or bile duct invasion, the liver function reserve to determine Child-Pugh grades, the serum level of alfa-fetoprotein (AFP) before TACE, diameter of the largest HCC treated, and multiplicity of HCC lesions, which are the constituents of CLIP and JIS system, were routinely documented in the angiography records, in addition to usual clinical information. Among all of the patients, those who had been treated with other therapies before initial TACE, including surgical resection and percutaneous therapies, were excluded; those with lymph nodal and distant metastases were also excluded.

After the initial TACE, recurrent diseases were usually treated with additional TACE on demand with or without palliative RFA. Those who underwent hepatectomy after initial TACE were excluded.

TACE procedure

Written informed consent was obtained prior to the procedure, and TACE was performed in a conventional fashion as previously reported (15). After performing diagnostic hepatic angiography, a 2.4 Fr. microcatheter (Micro Feret-18, William Cook, Bjaeverskov, Denmark) using a 0.014 inch microguidewire (Micromate guidewire, Terumo Clinical Supply, Gifu, Japan) was then introduced into the feeding arteries.

TACE was performed for HCCs under superselective catheterization into a peripheral hepatic artery (subsegmental or segmental artery, whenever possible) using a microcatheter according to the distribution of HCC. An oil suspension was prepared by mixing 2-5ml of iodized oil (Lipiodol Ultra-Fluid, Guerbet Japan, Tokyo, Japan）and anticancer agents dissolved in contrast medium (Iopamiron 300 mgI/ml, Bayer Yakuhin, Osaka, Japan) at half the volume of the iodized oil. The anticancer drugs included 10-20 mg of doxorubicin hydrochloride (Adriamycin, Nippon Kayaku, Tokyo, Japan) or 10-30 mg of epirubicin hydrochloride (Farmorubicin, Pfizer Japan, Tokyo, Japan). Just before use, the suspension was shaken by hand for a few minutes for better mixing. The iodized oil suspension was thus injected into hepatic arteries until all parts of the tumor were filled (2-10 ml). Gelatin sponge particles (Spongel, Astellas Pharma, Tokyo, Japan), approximately 500 μm to 1 mm in size, were then introduced until the arterial blood supply to the aimed volume of the tumor was completely stopped. After TACE, patients were followed up by dynamic CT every three to four months at the outpatient clinic.

Assessments and Statistical analysis

728 patients were stratified according to the CLIP or JIS scores, and their survival

rates between the scores were compared using Cox proportional hazard model (16, 17). All patient and tumor factors included in both CLIP and JIS (Table 1) were assessed by univariate and multivariate analyses to clarify significant factors among them. The system, as a whole, was also assessed using multivariate analysis, and also by likelihood χ^2-test and Akaike information criteria (18) for the prognostic stratification and homogeneity assessment for these two systems for comparison, using IBM SPSS software program (version 22, IBM Japan, Tokyo, Japan). All other analyses were performed using the SAS statistical software program (version 9.3, SAS Japan, Tokyo, Japan).

Results

Patients and overall survival

Among these 939 patients, 211 patients were excluded, the details of which are shown in Fig.1, and thus, remaining 728 cases finally formed our patient population.

Table 2 shows the demographic information of the all patients. The follow-up period ranged from 4 to 5093, with a median of 1248 days. The overall survival rates for 1 year, 3 years, 5 years, 7 years, and 10 years were 83.1%, 55.1%, 34.7%, 23.3%, and 12.8%, respectively.

Survival by CLIP and JIS Score systems

There were 150/239/198/80/40/19/2 patients in CLIP scores 0/1/2/3/4/5/6, respectively, and 57/177/266/147/68/13 patients in JIS scores 0/1/2/3/4/5, respectively. Table 3 shows the cumulative survival rates according to CLIP Scores. There were statistically significant differences in survival rates between the score groups except for between scores 5 and 6. Figure 2 shows the survival curves of patients according to CLIP Scores.

Table 4 shows the cumulative survival rates according to JIS Scores. There were

statistically significant differences between the score groups except for between scores 0 and 1 and also between 4 and 5. Figure 3 shows the survival curves of patients according to JIS Scores.

Analysis of prognostic factors and the models

The results of univariate and multivariate analyses of factor analysis were shown in Table 5.

The multivariate analyses revealed less severe Child-Pugh classification ($p<.001$), simple tumor morphology ($p<.001$), absence of portal vein invasion ($p<.001$), and lower AFP level ($p<.001$) as independent indicators for favorable survival rate, all of which are included in CLIP, but not in JIS system.

The univariate and multivariate analyses of CLIP and JIS Score model as a whole were shown in Table 6. Multivariate model analysis suggested CLIP, but not JIS, was an independently significant system to correlate with the survival.

Table 7 shows the prognostic stratification and homogeneity of CLIP and JIS Score model. The likelihood χ^2-test value was higher, and the Akaike information criterion value was lower for the CLIP system than for JIS system, indicating the superiority of CLIP system over JIS in terms of discriminatory ability and homogeneity.

Discussion

There have been several staging systems proposed to predict the prognosis of patients with HCC who undergo particular choice of treatment. Huang et al. (19) reported patients who undergo surgical resection would be best stratified by TNM system. Vauthey et al. (20) concluded that AJCC/UICC system is the best for those treated with transplantation. Guglielmi et al. (21), on the other hand, reported that BCLC system is the best system to predict the prognosis of patients who receive RFA as a treatment of choice. To predict prognosis of patients who undergo TACE, several new staging systems have been proposed (13, 14), but these are rather complicated. We simply applied pre-existing CLIP and JIS systems to see whether these systems can stratify the prognosis of patients who are treated with TACE

1, 3, 5, 7, and 10 year overall survival rates of our study population were 83.1%, 55.1%, 34.7%, 23.3%, and 12.8%, respectively, which are almost comparable to or even better than previously reported data in Western countries (22) or in Japan (23).

We tested all patient and tumor factors which are included in both CLIP and JIS, and found all independently significant factors were included in CLIP but not in JIS (Table 5). We also compared these two systems directly, by multivariate analysis, likelihood χ^2 test, and Akaike information criterion, and successfully showed CLIP is superior to

JIS (Tables 6 and 7). Thus, according to our results of both factor analysis and model analysis, CLIP was suggested to be more suitable to predict prognosis of 783 HCC patients who undergo TACE, rather than JIS. This is reasonable, because JIS Score was originally proposed for evaluation of patients undergoing local therapies, such as PEIT, MCT or RFA (24, 25).

One limitation of this study, other than the retrospective nature, is that we assessed only CLIP and JIS systems, excluding other recently proposed systems, such as Tokyo scores (9) and modified JIS (10, 11). This is because previous cases, typically those before 2000, occasionally lacked relatively newly developed laboratory data, such as prothrombin induced by vitamin K absence or antagonist, or detailed imaging data of these patients were no longer available, both of which are required to assess the patients according to the recently proposed systems. Further investigation including these information may establish better system to assess the prognosis of patients with HCC who undergo TACE as initial therapy. Second, because we recruited patients over 10 years between 1995 and 2005, it is possible that technological improvement during the study period might have biased our results. Third, because we retrospectively recruited all patients treated with TACE, our patient population included those who are not at the intermediate stage according to BCLC classification, as mentioned earlier.

We, therefore, are now conducting a next study in which the role of CLIPS and JIS scoring systems is elucidated in stratifying the patients with HCC who are strictly at BCLC stage B in our patient population. Finally, the etiology of HCC, and its treatment strategies as well, is different in different countries (2), and therefore, our results may not be generalized or directly applicable to patients in other parts of the world.

In conclusion, based on our single center study using Japanese patients who were initially treated with TACE, CLIP system was shown to be more suitable than JIS system for predicting prognosis of patients with HCC who undergo TACE as initial therapy.

References

1) Raza SA, Clifford GM, Franceschi S. Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. British Journal of Cancer 2007; 96: 1127-1134.

2) Bharadwaz A, Bak-Fredslund KP, Villadsen GE, et al. Combination of radiofrequency ablation with transarterial chemoembolization for treatment of hepatocellular carcinoma: experience from a Danish tertiary liver center. Acta Radiologica 2015; 0: 1-8.

3) Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000; 32: 1224-1229.

4) Okuda K, Ohtsuki T, Obata H, et al. Natural History of Hepatocellular Carcinoma and Prognosis in Relation to Treatment. Cancer 1985; 56: 918-928.

5) The Cancer of the Liver Italian Program (CLIP) Investigators. A New Prognostic System for Hepatocellular Carcinoma: A Retrospective Study of 435 Patients. Hepatology 1998; 28: 751-755.

6) The Cancer of the Liver Italian Program (CLIP) Investigators. Prospective Validation of the CLIP Score: A New Prognostic System for Patients with Cirrhosis and Hepatocellular Carcinoma. Hepatology 2000; 31: 840-845.

7) Llovet JM, Bru C, Bruix J. Prognosis of Hepatocellular Carcinoma: The BCLC Staging Classification. Semin Liver Dis 1999; 19: 329-338.

8) Kudo M, Chung H, Haji S, et al. Validation of a New Prognostic Staging System for Hepatocellular Carcinoma: the JIS Score Compared With the CLIP Score. Hepatology 2004; 40: 1396-1405.

9) Tateishi R, Yoshida H, Shiina S, et al. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut 2005; 54: 419-425.

10) Ikai I, Takayasu K, Omata M, et al. A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma. J Gastroenterol 2006; 41: 884-892.

11) Kitai S, Kudo M, Minami Y, et al. A New Prognostic Staging System for Hepatocellular Carcinoma: Value of the Biomarker Combined Japan Integrated Staging Score. Intervirology 2008; 51(suppl 1): 86-94.

12) Forner A, et al. Revised BCLC. Nature Reviews Clinical Oncology 2014; 11: 525-535.

13) Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of Patients with Intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a Subclassification to Facilitate Treatment Decisions. Semin Liver Dis 2012; 32: 348-359.

14) Yamakado K, Miyayama S, Hirota S, et al. Subgrouping of intermediate-stage (BCLC stage B) hepatocellular carcinoma based on tumor number and size and Child-Pugh grade correlated with prognosis after transarterial chemoembolization. Jpn J Radiol 2014; 32: 260-265.

15) Higashihara H, Okazaki M. Transcatheter arterial chemoembolization of hepatocellular carcinoma: A Japanese experience. Hepato-Gastroenterol 2002; 49: 72-78.

16) Kaplan EL, Meier P. Non parametric estimation for incomplete observation. J Am Stat Assoc 1958; 53: 457-481.

17) Cox D. Regression models and life tables. J R Stat Soc 1972; 34: 187-220.

18) Akaike H. A new look at statistical model identification. IEEE Trans Automatic Control 1974; AU-19: 716-722.

19) Huang YH, Chen CH, Chang TT, et al. Evaluation of predictive value of CLIP, Okuda, TNM and JIS staging systems for hepatocellular carcinoma patients undergoing surgery. Journal of Gastroenterology and Hepatology 2005; 20: 765-771.

20) Vauthey JN, Ribero D, Abdalla EK, et al. Outcomes of Liver Transplantation in 490 Patients with Hepatocellular Carcinoma: Validation of a Uniform Staging after Surgical Treatment. Surg 2007; 204: 1016-1028.

21) Guglielmi A, Ruzzenente A, Pachera S, et al. Comparison of Seven Staging Systems in Cirrhotic Patients with Hepatocellular Carcinoma in a Cohort of Patients who Underwent Radiofrequency Ablation with Complete Response. Am J Gastroenterol 2008; 103: 597-604.

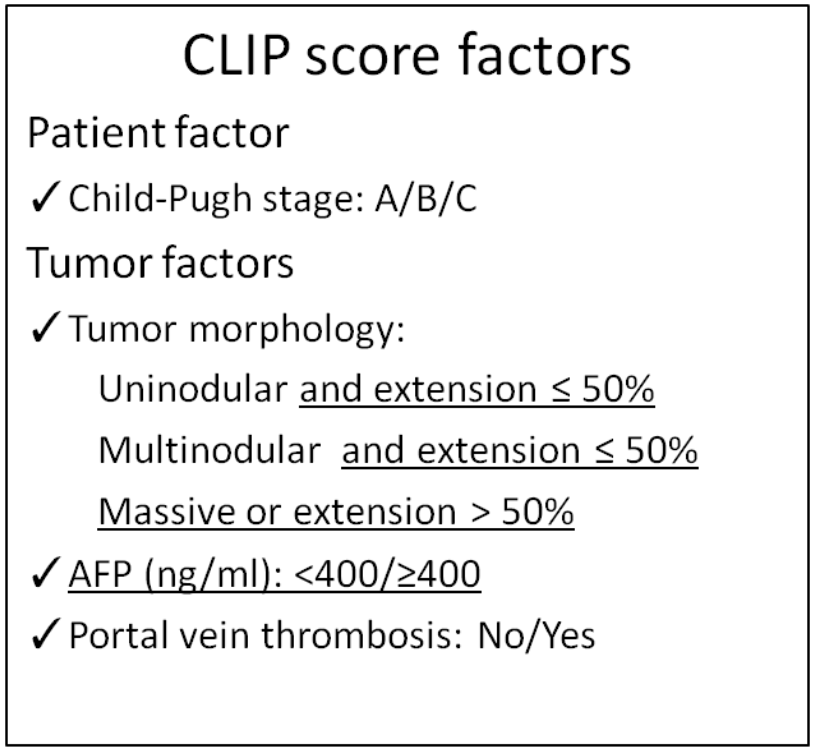
22) Giannini EG, Bodini G, Corbo M, et al. Impact of evidence-based medicine on the treatment of patients with unresectable hepatocellular carcinoma. Aliment Pharmacol Ther 2010; 31: 493-501.

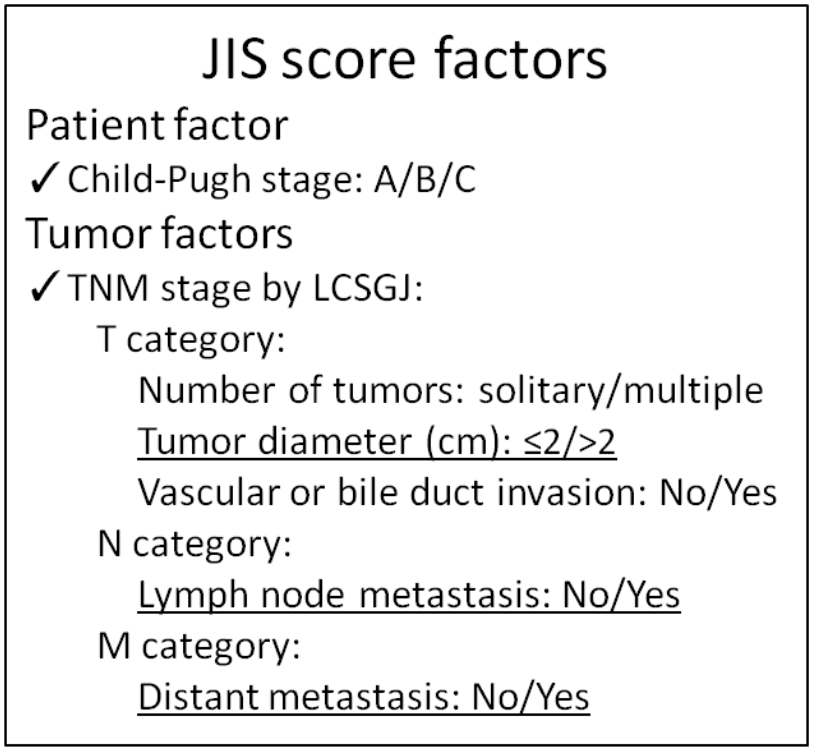
23) Ikai I, Kudo M, Arii S, et al. Report of the 18th follow-up survey of primary liver cancer in Japan. Hepatology Research 2010; 40: 1043-1059.

24) Toyada H, Kumada T, Kiriyama S, et al. Comparison of the Usefulness of Three Staging Systems for Hepatocellular Carcinoma (CLIP, BCLC, and JIS) in Japan. Am J Gastroenterol 2005; 100: 1764-1771.

25) Ueno S, Tanabe G, Sako K, et al. Discrimination Value of the New Western Prognostic System (CLIP Score) for Hepatocellular Carcinoma in 662 Japanese Patients. Hepatology 2001; 34: 529-534.

Table 1 Factors included in Cancer of the liver Italian program (CLIP) and Japan Integrated Staging (JIS) systems





LCSGJ, the Liver Cancer Study Group of Japan

Table 2 Demographic information of the 728 patients

Variable	Value	%
Male/Female	526/202	72.3/27.7
Age (yr)	66.5±8.9 (range 38-93)	
Viral infection B/C/B-C/non B-C/none	76/505/9/100/38	10.4/69.4/1.2/13.7/5.2
Child-Pugh A/B/C	408/260/60	56.0/35.7/8.2
TNM stage by LCSGJ Ⅰ/Ⅱ/Ⅲ/Ⅳ	87/278/260/103	12.0/38.2/35.7/14.1
Max. size of HCC (cm)	4.1±2.5 (range 0.6-18.0)	
Tumor diameter ＜2/≧2 (cm)	105/623	14.4/85.6
Portal vein thrombosis No/Yes	641/87	88.0/12.0
Number of tumors Uninodular/Multinodular	317/411	43.5/56.5
AFP ＜400/≧400 (ng/ml)	543/185	74.6/25.4
Survival Alive/Dead	257/471	35.3/64.7

LCSGJ: the liver cancer study group of Japan

Table 3 Survival according to Cancer of the Liver Italian Program (CLIP) scores

Staging System	n (%)	Cumulative Survival Rate (%) 1 yr	3 yr	5 yr	7 yr	10 yr	Median survival period (day)	
CLIP score								
0	150 (20.6)	93.9	73.9	52.5	39.6	29.5	2088	p=.0040
1	239 (32.8)	91.7	64.9	41.1	28.8	16.1	1466	p=.0006
2	198 (27.2)	85.4	51.8	28.2	13.6	5.2	1133	p=.0007
3	80 (11.0)	68.6	26.6	19.3	13.5	3.4	573	p=.0006
4	40 (5.5)	42.2	14.1	3.8	3.8	3.8	189	p=.0246
5	19 (2.6)	8.3	8.3	0.0			75	N.S.
6	2 (0.3)	50.0	0.0				123	

N.S.: not significant

Table 4 Survival according to Japan Integrated Stage (JIS) score

Staging System	n (%)	Cumulative Survival Rate (%) 1 yr	3 yr	5 yr	7 yr	10 yr	Median survival period (day)	
JIS score								
0	57 (7.8)	98.3	79.2	54.2	43.5	26.4	2310	N.S.
1	177 (24.3)	93.7	69.6	49.5	36.7	24.7	1823	p=.0013
2	266 (36.5)	88.2	61.2	35.8	23.4	11.5	1348	p<.0001
3	147 (20.2)	74.0	34.9	19.3	8.0	3.7	730	p=.0027
4	68 (9.3)	51.0	19.7	10.0	4.0	2.0	368	N.S.
5	13 (1.8)	30.8	23.1	15.4	15.4	0.0	123	

N.S.: not significant

Table 5 Prognostic factor analysis

Factor		Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	*p*	Hazard ratio	95% CI	p
Age		0.99	0.98-1.00	N.S.			
Sex	female vs male	1.19	0.97-1.48	N.S.			
Viral infection				N.S.			
	non B-C	1.00					
	B	1.04	0.71-1.52				
	C	1.02	0.77-1.35				
	B&C	1.42	0.68-2.98				
	none	1.31	0.86-2.01				
Child-Pugh				<.001			<.001
	A	1.00			1		
	B	1.65	1.36-2.00		1.55	1.27-1.89	
	C	2.16	1.59-2.94		1.91	1.38-2.63	
TNM stage by LCSGJ				<.001			N.S.
	Ⅰ	1					
	Ⅱ	1.3	0.93-1.81				
	Ⅲ	2.07	1.49-2.87				
	Ⅳ	5.38	3.75-7.74				
Tumor Morphology				<.001			0.021
	Uninodular	1			1		
	Multinodular	1.57	1.29-1.90		1.29	0.97-1.72	
	Massive	3.92	2.92-5.27		1.76	1.17-2.65	
AFP (ng/ml)	＜400 vs ≧400	1.79	1.47-2.19	<.001	1.45	1.17-1.80	0.001
Portal Vein Thrombosis	No vs Yes	3.6	2.81-4.61	<.001	1.65	1.06-2.56	0.025
Tumor Diameter (cm)	＜2 vs ≧2	1.13	0.74-1.73	N.S.			

LCSGJ: the liver cancer study group of Japan, N.S.: not significant, CI: confidence interval, AFP: alpha-fetoprotein

Table 6 Model analysis

		Univariate analysis			Multivariate analysis		
Factor		Hazard ratio	95% CI	*p*	Hazard ratio	95% CI	p
CLIP				<.001			<.001
	0	1.00			1		
	1	1.48	1.12-1.95		1.13	0.77-1.67	
	2	2.19	1.65-2.90		1.29	0.80-2.08	
	3	3.63	2.60-5.08		1.88	1.08-3.28	
	4	8.22	5.48-12.32		4.16	2.24-7.71	
	5	18.87	11.01-32.33		9.63	4.52-20.54	
	6	3.94	0.97-16.07		1.98	0.40-9.89	
JIS				<.001			N.S.
	0	1.00					
	1	1.31	0.86-2.00				
	2	1.96	1.31-2.93				
	3	3.63	2.39-5.49				
	4	5.90	3.75-9.27				
	5	5.23	2.71-10.10				

CLIP: Cancer of the Liver Italian Program, JIS: Japan Integrated Stage, CI: confidence interval, N.S.: not significant

Table 7 Prognostic stratification and homogeneity analysis

Model	Likelihood Ratio (χ^2)*	Akaike Information Criteria (AIC)**
CLIP Score	147.951	5284.946
JIS Score	119.600	5313.297

CLIP: Cancer of the Liver Italian Program, JIS: Japan Integrated Stage, CI: confidence interval, N.S.: not significant

* Higher $\chi 2$ indicates better model for discriminatory ability, homogeneity, and monotonicity.

** Lower AIC indicates better model for discriminatory ability. Difference in AIC > 2 is considered significant.

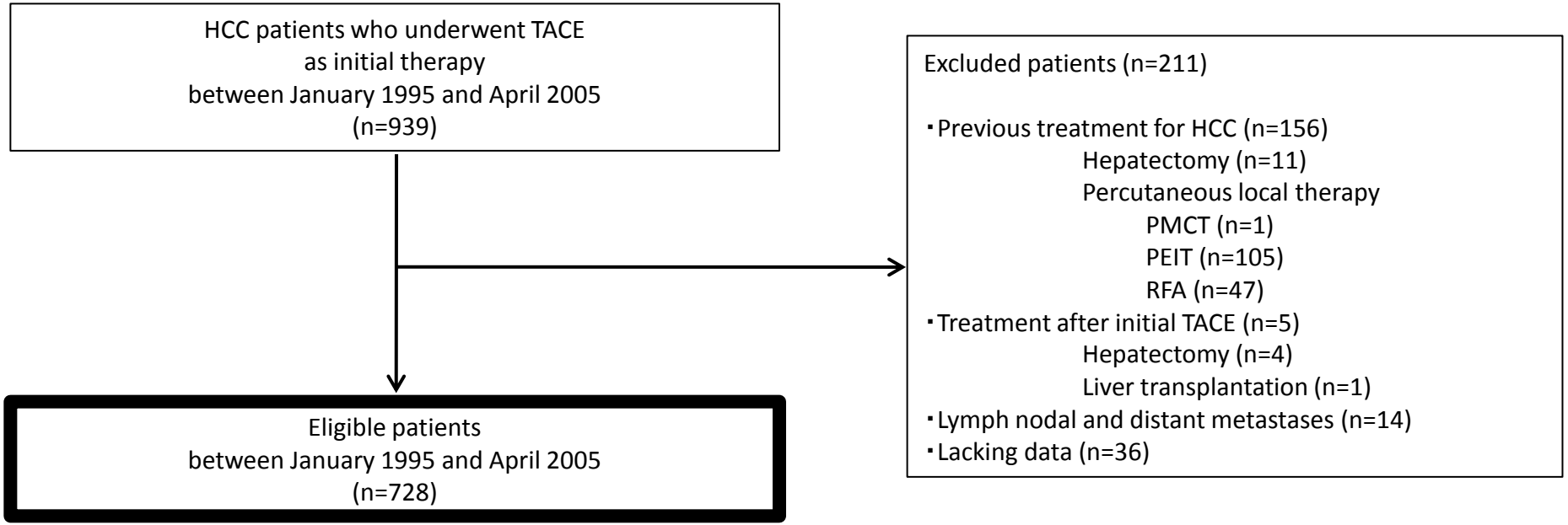
Figure Legends

Fig.1 Flow diagram of patient selection. TACE: transcatheteral arterial chemoembolization, HCC: hepatocellular carcinoma, PMCT: percutaneous microwave coagulation therapy, PEIT: percutaneous ethanol injection therapy, RFA: radiofrequency ablation

Fig.2 Survival stratification according to CLIP score. CLIP: Cancer of the Liver Italian Program, N.S.: not significant

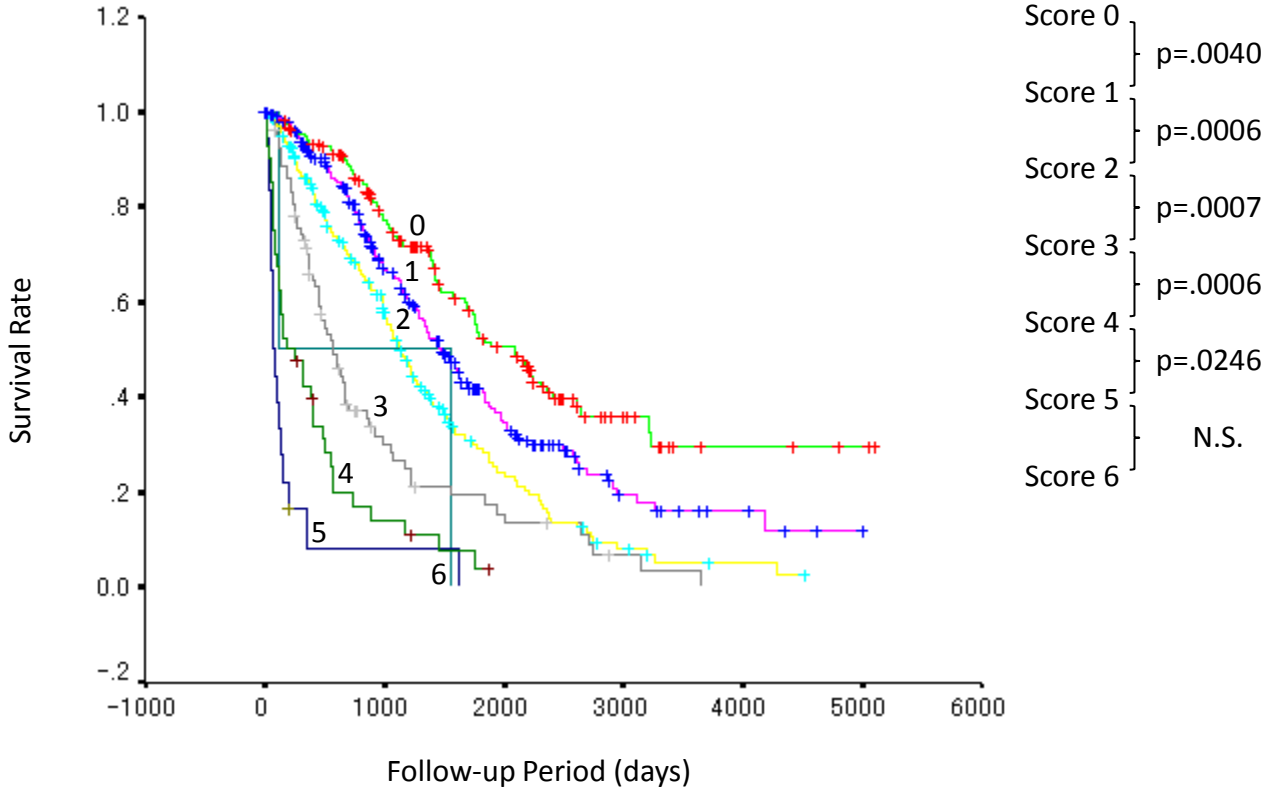
Fig.3 Survival stratification according to JIS score. JIS: Japan Integrated Stage, N.S.: not significant

Figure 1 Flow diagram of patient selection



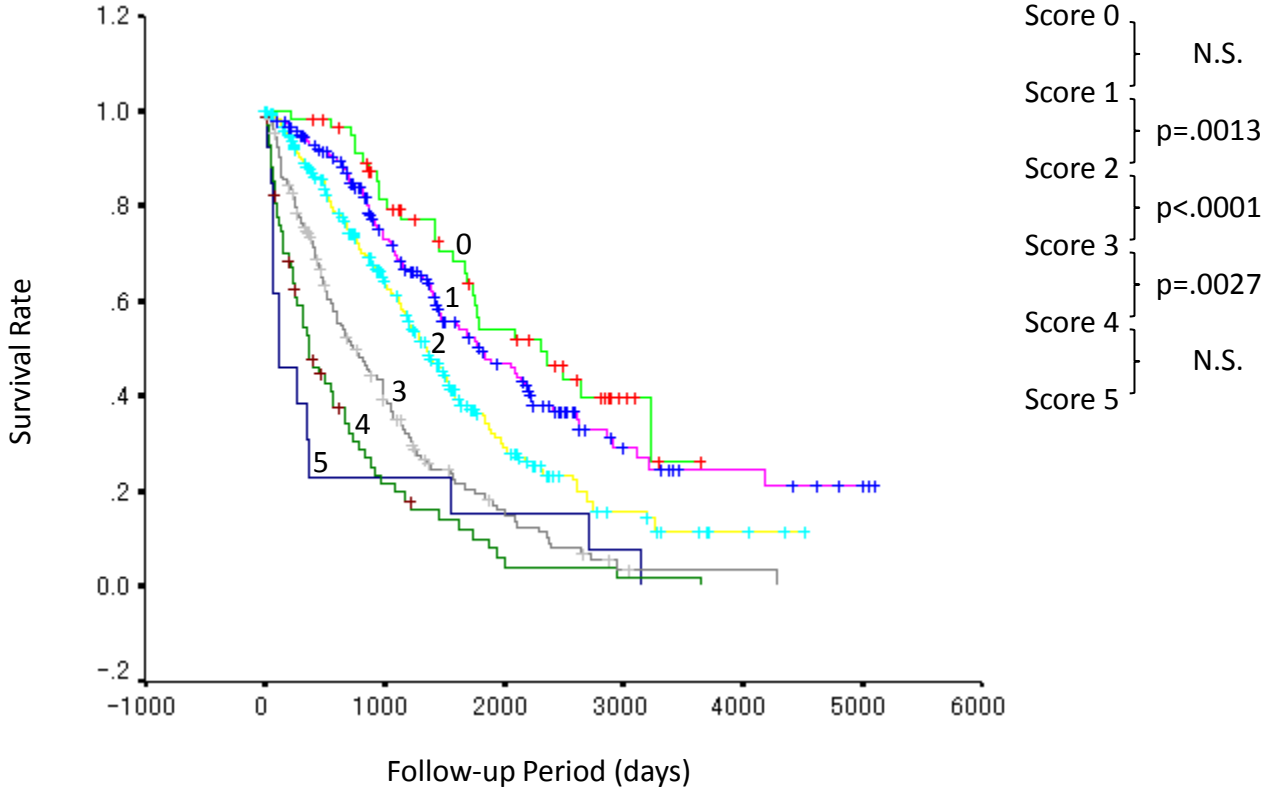
Flow diagram of patient selection. TACE: Transcatheter arterial chemoembolization , HCC: hepatocellular carcinoma, PMCT: Percutaneous microwave coagulation therapy, PEIT: percutaneous ethanol injection therapy, RFA: radiofrequency ablation

Figure 2 Survival stratification according to CLIP scores



Survival stratification according to CLIP score. CLIP: Cancer of the Liver Italian Program, N.S.: not significant

Figure 3 Survival stratification according to JIS scores



Survival stratification according to JIS score. JIS: Japan Integrated Stage, N.S.: not significant