Table 3
Estimation of effects of covariates following selection of regressor in Cox regression model

Category	Hazard ratio	95% Confidence interval (CI)	p-Value
Lamivudine therapy			
No	1		
Yes	0.49	0.31–0.77	0.002
Gender			
Male	1		
Female	0.42	0.28–0.62	<0.001
Family clustering of hepatitis B			
No	1		
Yes	1.44	1.08–1.94	0.015
Age at liver biopsy			
<40 y.o.	1		
≧40 y.o.	2.09	1.77–2.48	<0.001
Stage of liver fibrosis			
F0 or F1	1		
F2, F3, or F4	1.43	1.24–1.64	<0.001
Serum albumin level			
<4.0 g/dL	1		
≧4.0 g/dL	0.58	0.43–0.79	0.001
Platelet count			
<150 × 1000/μL	1		
≧150 × 1000/μL	0.53	0.38–0.73	<0.001

In the analysis of retrospective studies, great precautions are required in order to eliminate any bias between lamivudine-treated and non-treated groups. To minimize inter-group bias, we conducted with the cooperation of multiple medical institutions and a large number of patients ($n=2795$). The effect of lamivudine on HCC was ultimately analyzed in a matched case-controlled study. Because the time of liver biopsy was used as the starting point in our analysis, the analytical results were not expected to appropriately reflect lamivudine's effect if the therapy was started a long time after the biopsy. Therefore, from among the 657 patients who received lamivudine therapy, we selected 377 patients who started lamivudine therapy within 2 years after biopsy. For a control group, the same number of patients ($n=377$) without lamivudine therapy was selected from the 2138 subjects.

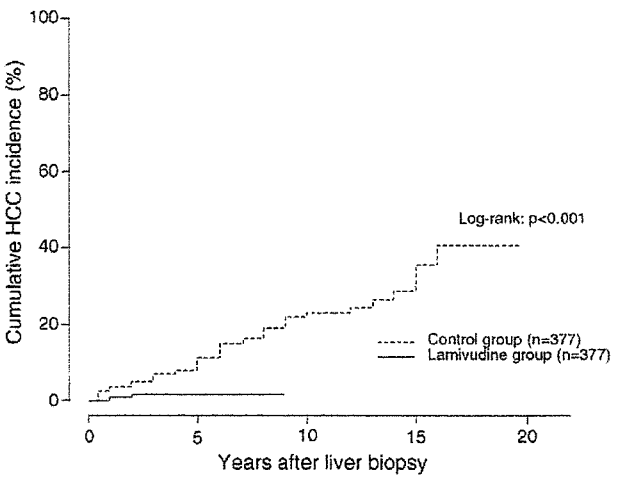

Fig. 1. Comparison of the cumulative HCC incidence between the lamivudine group (solid line) and the control group (broken line) by the Kaplan–Meier method in a case-matched control study. A significant difference was seen between the two groups ($p<0.001$, log-rank test).

The regimen was not the same in all patients who have been treated by lamivudine. It was transiently discontinued before being recommenced later in some patients, whereas it was uninterrupted throughout the follow-up period in the majority (63%) of subjects in the matched case-controlled study. The duration of lamivudine regimen was not taken into account in the design of our study. Some patients received lamivudine for relatively short periods to improve acute exacerbation of their clinical course in chronic hepatitis B. On the other hand, some patients received lamivudine for the long-term to suppress the development of HCC. In the analysis by a multivariate Cox regression model in all unmatched patients, lamivudine therapy was selected as one of the factors inhibiting the occurrence of HCC. In the matched case-controlled study, the annual occurrence rate of HCC was significantly lower (0.4%/(patient/year)) in the lamivudine group than in the control group (1.8%/(patient/year)), suggesting that lamivudine treatment is effective for inhibiting the occurrence of HCC.

Recently, Liaw et al. conducted a multicenter, centrally randomized, double-blind, placebo-controlled, parallel group study to evaluate the effects of lamivudine on the progression of chronic hepatitis B to hepatic cancer [21]. They randomized 651 patients with histologically confirmed (F3 and F4), compensated hepatic cirrhosis to receive either lamivudine or a placebo at a ratio of 2:1 and continued the treatment for up to 5 years. The study was terminated after a median treatment duration of 32.4 months (range 0–42) owing to a significant difference between the groups in the number of end points reached. The end points were reached by 7.8% of the patients receiving lamivudine and 17.7% of those receiving placebo (hazard ratio for disease progression, 0.45; $p=0.001$). The Child–Pugh score increased in 3.4% of the patients receiving lamivudine and in 8.8% of those receiving placebo (hazard ratio, 0.45; $p=0.02$), whereas HCC occurred in 3.9% of those in the lamivudine group and in 7.4% of those in the placebo group (hazard ratio, 0.49: $p=0.047$). The results of our analysis, which included patients with F0 through F2 hepatic fibrosis, were similar to those of Liaw et al. [21]. Thus, two studies demonstrated that the use of potent anti-viral agents such as lamivudine represents a major advance in the treatment of chronic hepatitis B and slows the progression of severe liver disease to liver cirrhosis as well as HCC.

Both hepatitis B and C are caused by persistent infection with hepatitis viruses, and both have a high probability of resulting in HCC. For this reason, these two diseases have a number of common traits, but some differences have been noted in their relationships with HCC. Among both

Table 4
Comparison of background factors between lamivudine group and control group assessed at the time of liver biopsy (matched case-controlled study)

Parameter	Lamivudine group ($n=377$)	Control group ($n=377$)	p-Value
Gender[a]			
Male	276 (73.2%)	273 (72.4%)	0.806
Female	101 (26.8%)	104 (27.6%)	
Age (years)[b]	41.5 ± 12.0	41.4 ± 12.2	0.950
Follow-up period (years)[b]	2.7 ± 2.1	5.3 ± 4.7	<0.001
Family clustering of hepatitis B[a]			
Yes	238 (63.1%)	242 (64.2%)	0.762
No	139 (36.9%)	135 (35.8%)	
Drinking during the course of the study (>ethanol 80 g/day)[a]			
Yes	38 (10.1%)	62 (16.4%)	0.007
No	333 (88.3%)	314 (83.3%)	
Unknown	6 (1.6%)	1 (0.3%)	
IFN therapy[a]			
Yes	129 (34.2%)	143 (37.9%)	0.046
No	236 (62.6%)	231 (61.3%)	
Unknown	12 (3.2%)	3 (0.8%)	
Liver histology			
Grade of inflammation[a]			
A0	6 (1.6%)	18 (4.8%)	0.001
A1	110 (29.2%)	101 (26.8%)	
A2	157 (41.6%)	186 (49.3%)	
A3	98 (26.0%)	72 (19.1%)	
Unknown	6 (1.6%)	0 (0.0%)	
Stage of fibrosis[a]			
F0	7 (1.9%)	6 (1.6%)	0.647
F1	103 (27.3%)	117 (31.0%)	
F2	95 (25.2%)	97 (25.7%)	
F3	107 (28.4%)	90 (23.9%)	
F4	65 (17.2%)	67 (17.8%)	
HBeAg[a]			
+	193 (51.2%)	220 (58.4%)	0.005
−	178 (47.2%)	141 (37.4%)	
Unknown	6 (1.6%)	16 (4.2%)	
HBeAb[a]			
+	126 (33.4%)	121 (32.1%)	0.030
−	245 (65.0%)	237 (62.9%)	
Unknown	6 (1.6%)	19 (5.0%)	
Albumin (g/dL)[b]	4.00 ± 0.51	4.00 ± 0.52	0.989
AST (IU/L)[b]	118.5 ± 155.4	95.5 ± 126.4	0.031
ALT (IU/L)[b]	191.7 ± 234.8	151.5 ± 180.5	0.009
Platelet count ($\times 1000/mm^3$)[b]	161.7 ± 52.7	164.3 ± 59.5	0.523

[a] Data are expressed as positive numbers (%).
[b] Data are expressed as means ± S.D.

hepatitis B patients and hepatitis C patients, HCC occurs mainly in those with advanced hepatic fibrosis, but the incidence of liver cirrhosis as a background of liver disease is lower in patients with B than in those with C. Furthermore, among hepatitis C patients HCC occurs mainly in those 60 years or older, while among hepatitis B patients it occurs mainly in those under 60 [22–24]. Studies on the cumulative incidence of HCC in hepatitis B patients showed that the HCC incidence increases linearly during the initial 12 years, plateaus, and then increases again in the 17th or 18th year [24,25]. In hepatitis C patients, on the other hand, the HCC incidence shows a continuous, linear increase [26,27]. Various findings obtained to date suggest that these clinical differences are related not only to differences in the hepatitis viral infection route and the timing of infection but also to differences in the mechanisms underlying cancer associated with hepatitis B and C. HCV is an RNA virus, and viral genes are not integrated into the host's genes, whereas HBV is a DNA virus with reverse-transcriptase activity. Thus, HBV genes are often integrated into the host's chromosomes

Table 5
Comparison of distribution of background factors between patients who developed HCC and those who did not in the lamivudine group (matched case-controlled study)

Parameter	Patients with HCC ($n=4$)	Patients without HCC ($n=373$)	p-Value
Gender[a]			
Male	3 (75.0%)	273 (73.2%)	1.000[c]
Female	1 (25.0%)	100 (26.8%)	
Age (years)[b]	55.0 ± 19.5 ($n=4$)	41.3 ± 11.9 ($n=373$)	0.024
Follow-up period (years)[b]	1.5 ± 0.6 ($n=4$)	2.7 ± 2.1 ($n=373$)	0.236
Family clustering of hepatitis B[a]			
Yes	2 (50.0%)	236 (63.3%)	0.628[c]
No	2 (50.0%)	137 (36.7%)	
Drinking during the course of the study (>ethanol 80 g/day)[a]			
Yes	1 (25.0%)	37 (9.9%)	0.393[c]
No	3 (75.0%)	330 (88.5%)	
Unknown	0 (0.0%)	6 (1.6%)	
IFN therapy[a]			
Yes	0 (0.0%)	129 (34.6%)	0.387[c]
No	4 (100.0%)	232 (62.2%)	
Unknown	0 (0.0%)	12 (3.2%)	
Liver histology			
Grade of inflammation[a]			
A0	0 (0.0%)	6 (1.6%)	0.458[c]
A1	0 (0.0%)	110 (29.5%)	
A2	3 (75.0%)	154 (41.3%)	
A3	1 (25.0%)	97 (26.0%)	
Unknown	0 (0.0%)	6 (1.6%)	
Stage of fibrosis[a]			
F0	0 (0.0%)	7 (1.9%)	0.918[c]
F1	1 (25.0%)	102 (27.3%)	
F2	1 (25.0%)	94 (25.2%)	
F3	2 (50.0%)	105 (28.2%)	
F4	0 (0.0%)	65 (17.4%)	
HBeAg[a]			
+	3 (75.0%)	190 (50.9%)	0.648[c]
−	1 (25.0%)	177 (47.5%)	
Unknown	0 (0.0%)	6 (1.6%)	
HBeAb[a]			
+	2 (50.0%)	124 (33.2%)	0.632[c]
−	2 (50.0%)	243 (65.1%)	
Unknown	0 (0.0%)	6 (1.6%)	
Albumin (g/dL)[b]	4.23 ± 0.45 ($n=4$)	4.00 ± 0.51 ($n=373$)	0.384
AST (IU/L)[b]	47.0 ± 22.8 ($n=4$)	119.4 ± 156.2 ($n=326$)	0.356
ALT (IU/L)[b]	46.3 ± 24.2 ($n=4$)	193.2 ± 235.5 ($n=372$)	0.213
Platelet count ($\times 1000/mm^3$)[b]	141.0 ± 27.0 ($n=4$)	161.9 ± 52.9 ($n=373$)	0.431

[a] Data are expressed as positive numbers (%).
[b] Data are expressed as means ± S.D.
[c] Fisher's exact test.

and play an important role in hepatic carcinogenesis [28,29]. It is known that the repeat of necrosis and regeneration of liver might accelerate the mutation of oncogenes. In addition, de novo carcinogenesis is thought to be promoted in hepatitis B patients as a result of the increased genetic instability caused by the integration of the HBV genome into the host's chromosomes. When administered to patients with hepatitis B, lamivudine decreases the blood HBV-DNA concentration and markedly improves ALT levels, with consequent improvement of liver histological findings [7,11,13,14]. An early in vitro study showed that lamivudine decreases the amount of free HBV-DNA in hepatocytes but does not affect integrated HBV genes [30]. Therefore, lamivudine is thought to inhibit HCC by abating hepatitis and not by inhibiting viral gene integration. In fact, as shown in the matched case control study, all four patients who developed HCC in the lamivudine group had non-cirrhotic liver disease, whereas 23 (46%) of 50 patients who developed HCC had liver cirrhosis. Due to the small number of patients included, however, further studies are necessary to confirm this finding.

Table 6
Comparison of distribution of background factors between patients who developed HCC and those who did not in the control group (matched case-controlled study)

Parameter	Patients with HCC ($n=50$)	Patients without HCC ($n=327$)	p-Value
Gender[a]			
Male	40 (80.0%)	233 (71.3%)	0.236[c]
Female	10 (20.0%)	94 (28.7%)	
Age (years)[b]	50.6 ± 10.1	40.0 ± 11.9	<0.001
Follow-up period (years)[b]	5.3 ± 4.3	5.2 ± 4.8	0.951
Family clustering of hepatitis B[a]			
Yes	29 (58.0%)	213 (65.1%)	0.345[c]
No	21 (42.0%)	114 (34.9%)	
Drinking during the course of the study (>ethanol 80 g/day)[a]			
Yes	14 (28.0%)	48 (14.7%)	0.050[c]
No	36 (72.0%)	278 (85.0%)	
Unknown	0 (0.0%)	1 (0.3%)	
IFN therapy[a]			
Yes	16 (32.0%)	127 (38.8%)	0.578[c]
No	34 (68.0%)	197 (60.2%)	
Unknown	0 (0.0%)	3 (0.9%)	
Liver histology			
Grade of inflammation[a]			
A0	2 (4.0%)	16 (4.9%)	0.026[c]
A1	6 (12.0%)	95 (29.1%)	
A2	27 (54.0%)	159 (48.6%)	
A3	15 (30.0%)	57 (17.4%)	
Stage of fibrosis[a]			
F0	0 (0.0%)	6 (1.8%)	<0.001[c]
F1	7 (14.0%)	110 (33.6%)	
F2	8 (16.0%)	89 (27.2%)	
F3	12 (24.0%)	78 (23.9%)	
F4	23 (46.0%)	44 (13.5%)	
HBeAg[a]			
+	26 (52.0%)	194 (59.3%)	0.564[c]
–	22 (44.0%)	119 (36.4%)	
Unknown	2 (4.0%)	14 (4.3%)	
HBeAb[a]			
+	20 (40.0%)	101 (30.9%)	0.319[c]
–	27 (54.0%)	210 (64.2%)	
Unknown	3 (6.0%)	16 (4.9%)	
Albumin (g/dL)[b]	3.63 ± 0.59	4.06 ± 0.49	<0.001
AST (IU/L)[b]	96.9 ± 100.8	95.3 ± 130.0	0.934
ALT (IU/L)[b]	132.8 ± 165.5	154.4 ± 182.7	0.431
Platelet count ($\times 1000/mm^3$)[b]	126.8 ± 50.7	170.0 ± 58.7	<0.001

[a] Data are expressed as positive numbers (%).
[b] Data are expressed as means ± S.D.
[c] Fisher's exact test.

Seven HBV genotypes (A–G) have been identified to date, and their distribution shows regional variations [31–36]. In Japan, genotypes C, B, and the other five account for 85, 12, and 3% of hepatitis B patients [36]. The virological differences between HBV genotype B and genotype C might influence not only on the natural course of hepatitis B but also the efficacy by lamivudine. The patients with HBV genotype B are frequently negative for HBeAg, have lower ALT levels and a better prognosis. In contrast, the patients with HBV genotype C tend to remain HBeAg-positive for a longer duration and tend to have elevated ALT levels and more advanced liver disease, such as liver cirrhosis and HCC. This indicates that the analysis of HBV genotypes will be needed in this study.

In conclusion, our multicenter, retrospective, matched case study indicated that lamivudine treatment might suppress the risk of HCC in patients with chronic hepatitis B. However, the study has several limitations, such as the relatively short duration of treatment and the lack of virological analyses (HBV genotype, YMDD mutation, and HBV-DNA volume). To relief these limitations, further long-term observation should be continued to clarify the conclusion.

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Appendix A

The Inuyama Hepatitis Study Group consists of the following 30 institutions and members: Dr. Sumio Watanabe (Akita University School of Medicine, Akita, Yamagata), Dr. Sumio Kawada (Yamagata University School of Medicine, Yamagata), Dr. Osamu Yokosuka (Chiba University, Graduate School of Medicine, Chiba), Dr. Kunihiko Hino (Delta Clinic, Tokorozawa), Dr. Hiromasa Ishii (Keio University, School of Medicine, Tokyo), Dr. Hiromitu Kumada (Toranomon Hospital, Tokyo), Dr. Gotaro Toda (Jikei University School of Medicine, Tokyo), Dr. Yasuyuki Arakawa (Nihon University School of Medicine, Tokyo), Dr. Nobuyuki Enomoto (Yamanashi University, School of Medicine, Kofu), Dr. Kendo Kiyosawa (Shinshu University School of Medicine, Matsumoto), Dr. Takafumi Ichida (Niigata University, Graduate School of Medical and Dental Science, Niigata), Dr. Tomoteru Kamimura (Niigata Saiseikai Hospital Dai-2, Niigata), Dr. Masashi Mizogami (Nagoya City University Graduate School of Medical Science, Nagoya), Dr. Shinichi Kakumu (Aichi Medical University, Nagoya), Dr. Hisataka Moriwaki (Gifu University School of Medicine, Gifu), Dr. Shuichi Kaneko (Kanazawa University, Graduate School of Medical Science, Kanazawa), Dr. Takeshi Okanoue (Kyoto Prefectural University, Graduate School of Medical Science, Kyoto), Dr. Norio Hayashi (Osaka University Graduate School of Medicine, Osaka), Dr. Masatoshi Kudo (Kinki University School of Medicine, Sayama), Dr. Yasushi Shiratori (Okayama University, Graduate School of Medicine and Dentist[r]y, Okayama), Dr. Gotaro Yamada (Kawasaki Hospital, Kawasaki Medical School, Okayama), Dr. Kazuaki Chayama (Hiroshima University, Graduate School of Biomedical Science, Hiroshima), Dr. Kiwamu Okita (Yamaguchi University, School of Medicine, Ube), Dr. Shigeki Kuriyama (Kagawa Medical University, Takamatsu), Dr. Morikazu Onji (Ehime University School of Medicine, Juushin-cho), Dr. Saburo Ohnishi (Kochi University School of Medicine, Nangoku), Dr. Michio Sata (Kurume University School of Medicine, Kurume), Dr. Shigetoshi Fujiyama, and Dr. Hiroshi Sasaki (Kumamoto University, Faculty of Medical and Pharmaceutical Science, Kumamoto), Dr. Hirohito Tsubouchi (Miyazaki University School of Medicine, Miyazaki), and Dr. Hiromi Ishibashi and Dr. Hiroshi Yatsuhashi (Nagasaki Medical Center, Omura).

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Prospective Cohort Study of Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma in 8510 Patients

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Background & Aims: To elucidate the survival of the patients with unresectable hepatocellular carcinoma (HCC) who underwent transcatheter arterial lipiodol chemoembolization (TACE) and to analyze the factors affecting the survivals. *Methods:* During the last 8 years, a nationwide prospective cohort study was performed in 8510 patients with unresectable HCC who underwent TACE using emulsion of lipiodol and anticancer agents followed by gelatin sponge particles as an initial treatment. Exclusion criteria were extrahepatic metastases and/or any previous treatment prior to the present TACE. The primary end point was survival. The survival rates were calculated by the Kaplan–Meier method. The multivariate analyses for the factors affecting survival were evaluated by the Cox proportional hazard model. The mean follow-up period was 1.77 years. *Results:* For overall survival rates by TACE, median and 1-, 3-, 5-, and 7-year survivals were 34 months, 82%, 47%, 26%, and 16%, respectively. Both the degree of liver damage and the tumor-node-metastasis (TNM) system proposed by the Liver Cancer Study Group of Japan demonstrated good stratification of survivals ($P = .0001$). The multivariate analyses showed significant difference in degree of liver damage ($P = .0001$), α-fetoprotein value ($P = .0001$), maximum tumor size ($P = .0001$), number of lesions ($P = .0001$), and portal vein invasion ($P = .0001$). The last 3 factors could be replaced by TNM stage. The TACE-related mortality rate after the initial therapy was .5%. *Conclusions:* TACE showed safe therapeutic modality with a 5-year survival of 26% for unresectable HCC patients. The degrees of liver damage, TNM stage, and α-fetoprotein values were independent risk factors for patient survival.

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and is responsible for 500,000 deaths globally every year.[1] The prognosis still remains poor because of the advanced stage of cancer and associated hepatic impairment at diagnosis and because of the high intrahepatic recurrence rate at 5 years of 79%–80% after hepatic surgery[2,3] and of 83% after percutaneous ethanol injection (PEI),[4] resulting from either intrahepatic metastases from the primary tumor or multicentric occurrence. With regard to treatment, surgical resection and PEI or radio-frequency ablation (RFA) are considered to be curable treatments of choice.[5] Whereas transcatheter arterial embolization irrespective of with and without anticancer agent and lipiodol has been controversial in the survival benefit,[6–10]2 randomized controlled trials recently elucidated that TACE showed a survival benefit compared with control.[11,12]

Transcatheter arterial embolization was initially used to treat HCC by Doyon et al[13] in 1974 and was applied to most inoperable HCC using gelatin sponge particles and anticancer agents in Japan.[14] In the mid-1990s, lipiodol was newly introduced to enhance mainly the therapeutic effect.[15–18] Transcatheter arterial lipiodol chemoembolization (TACE) is now the mainstay of treatment of choice for noncurative HCC.[19–32]

The latest nationwide report registered every 2 years by the Liver Cancer Study Group of Japan[33] showed the frequency of treatment for HCC as an initial therapy: transcatheter arterial embolization including TACE and transcatheter arterial injection of emulsion of lipiodol and anticancer agent (without gelatin sponge) accounted

Abbreviations used in this paper: HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; RFA, radio-frequency ablation; TACE, transcatheter arterial lipiodol chemoembolization; TNM, tumor-node-metastasis.

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for 36.4% of 16,941 patients; surgical resection for 31.3%; local ablation therapy such as PEI, microwave coagulation therapy, and RFA for 26.8%; and others for 5.5%. Moreover, TACE serves for treatment of intrahepatic recurrent foci in 52% of patients who developed after previous treatments.[33]

To date, the long-term survival rate and analysis of predictor affecting the survival rate of TACE for more than 8000 patients with HCC have not yet been reported. Thus, we conducted a study to elucidate them using a list of patients registered nationwide.

Materials and Methods

Patients

During the last 8 years from January 1994 to December 2001, a total of 72,866 patients with primary liver cancer were newly registered biannually by the Liver Cancer Study Group of Japan throughout some 800 medical institutions using a registration/questionnaire sheet with more than 180 questions. HCC patients occupied 95% (69,182/72,866) of primary liver cancer. Of these, 8542 patients were assigned in the current prospective cohort study, who underwent TACE as an initial treatment for unresectable HCC and did not receive any other therapy during the first investigation period of no more than 2 years and fulfilled the following inclusion criteria. First, the hepatic lesion was clinicopathologically diagnosed as HCC. Other primary hepatic lesions such as intrahepatic cholangiocarcinoma, sarcoma, and other benign lesions were excluded. Second, there was neither extrahepatic metastasis to lymph nodes and/or other organs nor any treatment prior to the present TACE. Finally, 8510 patients were enrolled, with the exclusion of 32 patients whose replies for the questionnaire were incomplete.

The diagnosis of HCC was made mainly based on the reliable imaging modalities using ultrasonography, dynamic computed tomography (CT), magnetic resonance imaging (MRI), and angiography and/or pathologically by biopsy specimens (4.5%). Abnormal elevation of tumor markers was also referred: α-fetoprotein more than 400 ng/mL (normal, <20 ng/mL) and des-γ-carboxyl prothrombin more than 100 mAU/mL (normal, <40 mAU/mL). Typical HCC was depicted as hyperattenuation in arterial phase and hypoattenuation or washout in delayed phase (approximately 3 minutes after the contrast injection) of dynamic CT[34] and on dynamic MRI, as was shown a hypervascular lesion on hepatic arteriography. The extrahepatic metastases were routinely examined by ultrasonography, CT, and chest x-ray.

The distribution of background factors was tabulated in Table 1. The study population consisted of 6122 males and 2386 females with a mean age of 66.2 years (standard deviation (SD), 9.15). The number of patients in grades A, B, and C of degree of liver damage was 4008 (51%), 3053 (39%), and 766 (10%), respectively. The degree of liver damage proposed by the Liver Cancer Study Group of Japan was classified as grades

Table 1. Distribution of Background Factors and Results of the Univariate Analysis in 8510 Patients With Unresectable Hepatocellular Carcinoma Who Underwent Transcatheter Arterial Lipiodol Chemoembolization

Background factors	Number of patients	Proportion (%)	Survival (%) 1 y	3 y	5 y	*P* value
Age, *y*						
<60	1871	22	78	44	29	.07
≥60	6639	78	83	47	25	
Sex						
Male	6122	72	81	46	25	.002
Female	2386	28	84	50	28	
Degree of liver damage						
A	4008	51	87	56	33	
B	3053	39	80	41	21	.0001
C	766	10	63	23	8	
HBV and HCV						
HCV Ab positive	6063	74	84	48	25	
HBs Ag positive	900	11	73	39	24	.0001
Both positive	211	3	80	50	32	
Both negative	971	12	78	45	28	
Maximum tumor size (*cm*)						
≤2	1989	24	93	63	39	
2.1–3	1981	24	90	52	28	.0001
3.1–5	2318	28	83	43	23	
≥5.1	2076	25	63	30	16	
No. of lesions						
1	3648	44	87	57	33	
2–3	2675	32	84	45	24	.0001
4</=	2066	25	72	33	16	
Degree of portal vein invasion (Vp)						
Vp0	6881	88	87	51	28	
Vp1	323	4	64	23	12	.0001
Vp2	306	4	51	22	11	
≥Vp3	347	4	35	10	—	
Degree of hepatic vein invasion (Vv)						
Vv0	7246	97	85	49	27	.0001
≥Vv1	244	3	48	15	—	
Alpha-Fetoprotein (*ng/mL*)						
≤20	2745	34	90	59	34	
21–200	2807	35	87	49	27	
201–400	591	7	82	38	19	.0001
401–1000	603	7	72	30	19	
≥1001	1399	17	60	27	15	
Des-γ carboxy-prothrombin (*mAU/mL*)						
≤100	3557	54	90	56	33	
101–299	811	12	85	45	23	
300–499	339	5	82	42	20	.0001
500–999	406	6	77	33	24	
≥1000	1478	22	64	28	14	
TNM stage						
I (T1N0M0)	927	13	96	72	47	
II (T2N0M0)	2934	40	90	57	32	.0001
III (T3N0M0)	2949	40	80	39	20	
IV A (T4N0M0)	501	7	49	16	10	

Vp, vascular invasion of the portal vein; Vv, vascular invasion of the hepatic vein.

Table 2. Degree of Liver Damage Classified by the Liver Cancer Study Group of Japan

Item	Degree of liver damage		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (*mg/dL*)	<2.0	2.0–3.0	>3.0
Serum albumin (*g/dL*)	>3.5	3.0–3.5	<3.0
ICGR15 (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

NOTE. If 2 or more items scoring the same grade occurred in the 2 grades, the higher grade is adopted as the degree of liver damage. ICGR15 (%), indocyanine green retention rate at 15 minutes.

A, B, and C based on the highest grade containing at least 2 findings such as ascites, serum bilirubin, serum albumin, indocyanine green retention rate at 15 minutes (ICG R15), and prothrombin activity (Table 2).[35,36] This classification is closely related to the Child–Pugh class.

Seventy-four percent of patients were positive for hepatitis C virus antibody, 11% were positive for hepatitis B virus surface antigen, 3% were positive for both, and 12% were negative for both. Regarding the maximum tumor size, 24% of patients each had lesion(s) no larger than 2 cm in diameter and lesion(s) measured from 2.1 to 3 cm, 28% of patients had lesion(s) from 3.1 to 5 cm, and 25% had lesion(s) larger than 5.1 cm. The number of lesions was 1 in 44% of patients, 2 or 3 in 32% of patients, and more than 4 in 25% of patients. The degree of vascular invasion to the portal vein was Vp0 (no invasion) in 88% of patients, and in the remaining 12% of patients, Vp1 (invasion to the third order or more peripheral branch) in 4%, Vp2 (the second order portal vein) in 4%, and more than Vp3 (the first portal vein or main portal trunk) in 4% of patients. Meanwhile, the degree of hepatic vein invasion was Vv0 (no invasion) in 97% of patients and more than Vv1 (any hepatic vein invasion including the main hepatic veins and/or inferior vena cava) in 3% of patients. Normal AFP value was seen in 34% of patients, 21–200 ng/mL in 35%, 201–400 ng/mL in 7%, and more than 401 ng/mL in 25%. The des-γ-carboxyl prothrombin value of more than 101 mAU/mL was recognized in 46% of patients.

The tumor-node-metastasis (TNM) staging adopted in the present study was revised by the Liver Cancer Study Group of Japan in 2000 (Table 3)[35,36] and was proposed as a new concordant TNM classification of the primary liver cancer by the International Hepato-Pancreato-Biliary Association.[37] Namely, T category consists of 3 factors such as a single lesion, no larger than 2 cm in diameter, and no vascular or bile duct invasion. T stage is determined based on the factors that are fulfilled from zero to 3. Each stage of I, II, III, and IV-A corresponds to the T factor. Stage IV-B is excluded because of the inclusion criterion. The present study showed 13% of patients in stage I, 40% each in stages II and III, and 7% in stage IV-A.

The catheter tip was advanced at the nearest site of the feeding artery as possible. The emulsion of anticancer agent and lipiodol followed by gelatin sponge particles was carefully injected in the x-ray monitoring. The dose of emulsion of anticancer agent and lipiodol and the pieces of embolic materials used for TACE were determined based on the tumor size and extension of the lesions. The patients were followed by dynamic CT or MRI every 3 to 4 months, and repeated TACE was determined when the local recurrence, intrahepatic metastases, and/or second primary HCC was found.

The survival rate of patients who underwent TACE was calculated from the date of diagnosis of HCC and the follow-up was ended on December 31, 2001. All patient deaths were the end point irrespective of cause of death. The mean follow-up period was 1.77 years (range, 0.003–7.99). TACE-related death was designated as death within 30 days of the initial therapy.

Statistical Analysis

The 11 variables listed in Table 1 were analyzed via univariate analysis. The multivariate analysis was performed by the Cox proportional hazard model. The survival rates were obtained by the Kaplan–Meier method and compared by the log-rank test. All variables with a P value less than .05 by univariate analysis were subjected to multivariate analysis. All significance tests were 2-tailed, and a P value less than .05 was considered statistically significant. All statistical analyses were performed with the Statistical Analysis System (SAS) version 8.02 (SAS Inc, Cary, NC).

Results

During an 8-year follow-up period, the total numbers of patient deaths and censored cases were 3605 and 4905, respectively. The number of patients who died and were censored annually was as follows: 1316 and 1939 during year 1, 1067 and 1258 from 1 to 2 years, 630 and 764 from 2 to 3 years, 341 and 454 from 3 to 4 years, 148 and 216 from 4 to 5 years, 72 and 145 from 5 to 6 years, 23 and 81 from 6 to 7 years, and 8 and 48 from 7 to 8 years, respectively.

Table 3. Definitions of TNM Stage Proposed by the Liver Cancer Study Group of Japan

T factor	
T1	Fulfilling 3 factors
T2	Fulfilling 2 factors
T3	Fulfilling 1 factor
T4	Fulfilling 0 factor
Stages	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
Stage IV-A	T4 N0 M0, or any T N1 M0
Stage IV-B	Any T N0-1 M1

T factor consists of I, Single; II, <2 cm; III, no vascular involvement

Table 4. The Survival of Overall Patients Who Underwent Transcatheter Arterial Lipiodol Chemoembolization, Based on Degree of Liver Damage, TNM Stage, and Combination of Degree of Liver Damage and TNM Stage

		Survival (%)							
Grading/staging	n	1 y	2 y	3 y	4 y	5 y	7 y	Median (*mo*)	*P* value
Overall survival	8510	82	63	47	34	26	16	34	
Degree of liver damage (n = 7827)									
A	4008	87	71	56	42	33	21	41	
B	3053	80	59	41	29	21	12	30	.0001
C	766	63	37	23	15	8	—	17	
TNM stage by Liver Cancer Study Group of Japan (n = 7311)									
I	927	96	86	72	57	47	30	56	
II	2934	90	73	57	43	32	22	42	.0001
III	2949	78	56	39	26	20	11	29	
IV-A	501	49	27	16	10	10	—	12	
Combination of degree of liver damage and TNM stage									
Liver damage A (n = 3499)									
I	489	98	92	78	64	52	38	62	
II	1439	94	80	66	52	39	26	50	.0001
III	1358	84	64	47	33	27	14	35	
IV-A	213	59	34	24	12	10	—	15	
Liver damage B (n = 2667)									
I	309	92	82	67	50	43	16	47	
II	1068	88	70	52	38	28	16	38	.0001
III	1116	79	54	32	22	15	8	26	
IV-A	174	45	21	13	10	10	—	11	
Liver damage C (n = 648)									
I	59	94	69	52	37	24	—	39	
II	224	72	49	29	19	11	—	24	.0001
III	282	66	30	23	14	9	—	17	
IV-A	83	27	16	3	—	—	—	6	

Survival Rates

For overall survival of the 8510 patients who underwent TACE, the median and 1-, 3-, 5-, and 7-year survival rates were 34 months, 82%, 47%, 26%, and 16%, respectively (Table 4) (Figure 1). With the degree of liver damage classification, 5-year survival rates of grades A, B, and C were 33%, 21%, and 8%, respectively, with statistical significance (P = .0001) (Figure 2). According to the TNM staging system, 5-year survival rates in stages I, II, III, and IV-A were 47%, 32%, 20%, and 10%, respectively, with significant difference among them (P = .0001) (Figure 3).

Next, the survival rates of patients were estimated using a combination of degree of liver damage and the TNM staging system. In the degree of liver damage grade A, 5-year survival rates in stages I, II, III, and IV-A were 52%, 39%, 27%, and 10%, respectively, with significant differences among 4 subgroups (P = .0001). The well-stratified survival curves were obtained (not shown). The same tendency as grade A was recognized in liver damage grades B and C (P = .0001). On the other hand, 5-year survival rates in TNM stage I through liver damage grades A, B, and C were 52%, 43%, and 24%, respectively, with significant differences (P = .0001). The same results were recognized in stages II, III, and IV-A through the liver damage grades A, B, and C (P = .0001).

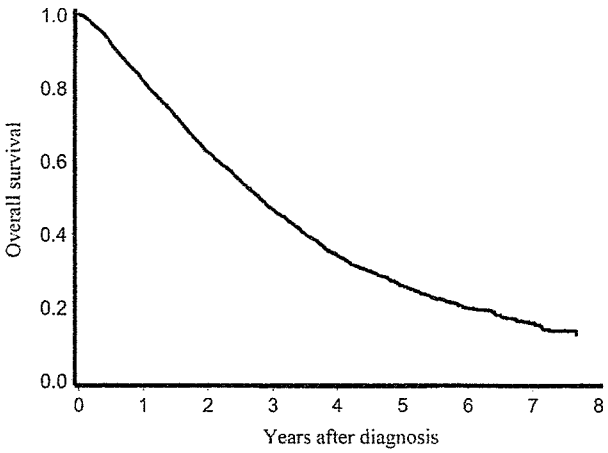

Figure 1. Overall survival rates of 8510 patients with unresectable HCC treated by transcatheter arterial lipiodol chemoembolization between 1994 and 2001. The 1-, 3-, and 5-year survival rates were 82%, 47%, and 26%, respectively.

Analysis of Factors Affecting the Survival of Patients

The univariate analysis revealed the following 11 factors as independent prognostic variables: gender, degree of liver damage, hepatitis B virus surface antigen, hepatitis C virus antibody, maximum tumor size, number of lesions, portal vein invasion, hepatic vein invasion, α-fetoprotein (AFP) value, des-γ carboxyl prothrombin

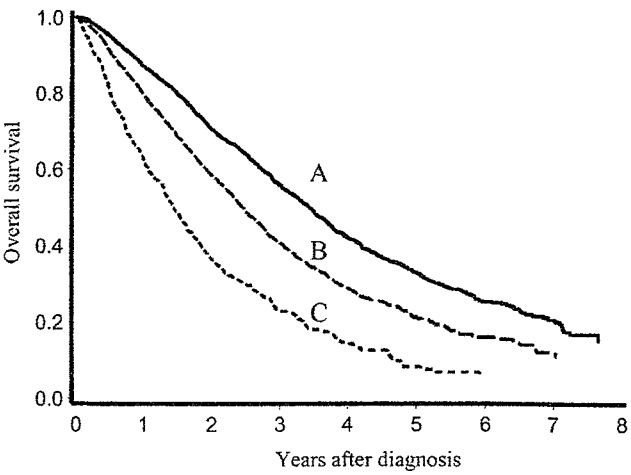

Figure 2. Comparison of survival rates stratified by degrees of liver damage A, B, and C with statistical significance (P = .0001).

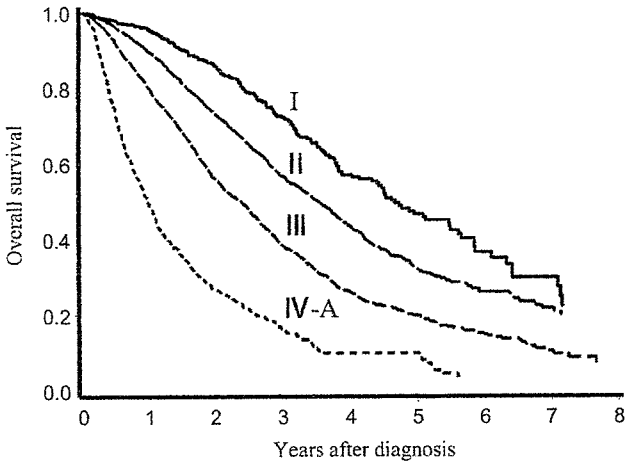

Figure 3. Comparison of survival rates stratified by TNM stages I, II, III, and IV-A with statistical significance ($P = .0001$).

value, and TNM stage (Table 1). The multivariate analysis showed the following 5 factors as an independent prognostic factor: degree of liver damage, maximum tumor size, number of lesion(s), degree of portal vein invasion, and AFP value in trial 1 (Table 5). The hazard ratio of each variable ranged from 1.48 to 2.52, among which the degree of liver damage between grades A and C followed by portal vein invasion had the highest hazard ratio of 2.52 and 2.27, respectively.

Provided 3 factors of maximum tumor size, number of lesions, and portal vein invasion as seen in trial 1, were replaced by 1 factor of TNM stage in trial 2, finally, 3 variables of degree of liver damage, TNM stage, and AFP value were statistically independent risk factors for patient survival with high hazard ratio ranging from 1.49 to 5.07 in trial 2 than from 1.49 to 2.52 in trial 1 (Table 5). TNM stage between stages I and IV-A and degree of liver damage between grades C and A had a high hazard ratio of 5.07 and 2.56, respectively. The des-γ-carboxyl prothrombin was not evaluated because of incomplete data acquisition in the questionnaire, despite a significant factor by univariate analyses.

TACE-Related Mortality Rate

Forty-four (.5%) of 8510 patients developed treatment-related death after the initial TACE. The breakdown of the cause of death consisted of hepatic failure in 18 patients, cancer death in 8, intraperitoneal rupture of HCC in 7, rupture of esophago-gastric varices in 4, gastrointestinal bleeding in 1, and other causes in 6. The degree of liver damage in these 44 cases was grade A in 7 patients, grade B in 14, grade C in 17, and unknown in 6.

Discussion

As the background of causal factor of HCC in the current study, hepatitis C virus infection was more prevalent than hepatitis B virus (74% to 11%, respectively). The ratio of hepatitis C virus to hepatitis B virus was

Table 5. Multivariate Analysis of Factors Affecting Survival of Patients Who Underwent Transcatheter Arterial Lipiodol Chemoembolization Using Cox Proportional Hazard Model in Trials 1 and 2

	Trial 1		Trial 2	
Variables	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)
Age, *y*, ≥60 vs <60	.42	1.04 (.95–1.14)	.36	1.05 (.95–1.15)
Sex, Male vs female	.16	1.07 (.98–1.16)	.19	1.06 (.97–1.16)
Degree of liver damage				
B vs A	.0001	1.49 (1.37–1.61)	.0001	1.49 (1.37–1.62)
C vs A	.0001	2.52 (2.24–2.85)	.0001	2.56 (2.28–2.89)
HCV+ve vs HCV−ve/HBsAg−ve[a]	.39	.95 (.84–1.07)	.26	.93 (.82–1.05)
HBsAg+ve vs HBsAg−ve/HCV−ve[b]	.1	1.15 (.97–1.35)	.1	1.15 (.97–1.35)
HBsAg+ve and HCV+ve vs HBsAg−ve and HCV−ve	.84	1.03 (.79–1.34)	.99	1 (.77–1.30)
Maximum tumor size, >2.1 cm vs <2 cm	.0001	1.55 (1.40–1.71)		
No. of lesions, multiple vs solitary	.0001	1.48 (1.37–1.61)		
Portal vein invasion (Vp), present vs absent	.0001	2.27 (2.02–2.55)		
Hepatic vein invasion (Vv), present vs absent	.1	1.18 (.97–1.44)		
TNM				
II vs I			.0001	1.51 (1.29–1.77)
III vs I			.0001	2.4 (2.06–2.80)
IVA vs I			.0001	5.07 (4.21–6.10)
α-Fetoprotein (ng/mL), >401 vs ≤400	.0001	1.8 (1.65–1.96)	.0001	1.82 (1.68–1.99)

[a]HBsAg −ve and HCV +ve vs HBsAg −ve and HCV −ve.
[b]HBsAg +ve and HCV −ve vs HBsAg −ve and HCV −ve.

almost similar to that reported by a Spanish paper[11] and was different from that from Hong Kong where hepatitis B virus was predominant[12] and from France where alcohol abuse was the main cause of HCC.[8] In relation to the tumor size, small HCC no larger than 2 cm in diameter was found in 24% of patients and less than 5 cm in 75% of patients. By contrast, in the countries outside Japan,[11,12] TACE was performed for larger HCCs—approximately 7 cm—than in those we performed. Regarding the number of lesions, solitary lesions were in 44% of patients, which was similar in incidence to that of 24%–43% reported by other studies.[11,12] The patients without portal vein invasion (88%) showed better survival rate than those with it, especially those with lobar or main portal tumor thrombus (portal vein trunk) of 0% at 5 years. The normal AFP value of no more than 20 ng/mL was in 34% of patients, and the abnormal elevation of more than 400 ng/mL was only in 24% of patients. These findings suggest that most HCC lesions were found as asymptomatic by periodical screening system with ultrasonography and AFP measurement for high-risk population, whereas the degree of liver function was 51% of patients in grade A and only 10% in grade C (Table 1).

The nationwide study showed that the overall survival rates of the 8510 patients who underwent TACE as an initial treatment were 47% at 3 years, 26% at 5 years, and 16% at 7 years. The previous papers reported that TACE with lipiodol showed 3-year and 5-year survival rates to be 26%–29%[11,12] and 16%–20%,[28,31] respectively, whereas other papers reported that TACE without lipiodol demonstrated various 5-year survival rates from 6% to 23%.[38,39] Our previous national study in 9363 patients who received TACE without lipiodol registered from 1980 to 1993 showed the 5-year survival rate to be 9%.[40] The marked difference of survivals between 2 different decades might depend in part on the introduction of lipiodol and the technique of super selective catheterization with the advent of the microcatheter system and in part on the lead time bias because of the advance of diagnostic modalities.

Both the degree of liver damage and the TNM staging system could stratify the survival rates with statistically significant difference ($P = .0001$). The same significant differences were also recognized among TNM stages I, II, III, and IV-A in 3 different degrees of liver damage grades A, B, and C ($P = .0001$). In the group with liver damage grade C, no survival remained at 7 years. By contrast, the patients with liver damage grade A and TNM stage I, the longest survival expected, demonstrated a much better 5-year survival rate of 52% than those in other subgroups. Namely, the lower the degree of liver damage and TNM stage, the better the survival rate of patients.

Multivariate analyses revealed the following 5 variables to be independent predictor of patient prognosis such as degree of liver damage, maximum tumor size, number of lesion(s), portal vein invasion, and AFP value.[41] Portal vein invasion showed much higher hazard ratio than the other 4 variables. A similar result was elucidated from the study of surgical resection.[42] The TNM stage could replace the 3 factors of maximum tumor size, number of lesions, and portal vein invasion. The TNM staging system proposed by the Liver Cancer Study Group of Japan[35,36] is more accurate to classify the HCC patients in Japan than the new TNM stage proposed by the American Joint Committee on Cancer, in which a cut-off value of 5 cm is adopted as the T factor.[43] In general, tumor burden, hepatic functional reserve, performance status, and response to treatment have been given as prognostic factors.[44–47] In the current study, tumor response of TACE was not assessed because the consensus of therapeutic effectiveness of TACE with lipiodol is not still obtained.

The degree of liver damage proposed by the Liver Cancer Study Group of Japan adopts the indocyanine green 15-minute retention rate instead of hepatic encephalopathy in Child–Pugh classification and is slightly different in the cut-off value among total albumin and prothrombin activity values in 2 classifications (Table 2). The degree of liver damage could more precisely discriminate the patients with Child–Pugh class A, good candidate for surgical resection,[48] to grades A or B.

The policy to determine the repeated TACE seems extremely different between Japan and Western countries. We have routinely performed repeated TACE based on the findings of follow-up CT; after confirmation of whether local recurrence, intrahepatic metastases, and/or de novo evolution of HCC developed or not.[39] However, most randomized controlled trials designed mainly in Western countries determined repeated TACE periodically at specific intervals ranging from 2 to 3 months.[8,11,12] The procedure in a randomized controlled trial appears scientific to elucidate the efficacy of TACE for HCC; however, some possible drawbacks could be considered, such as the deterioration of hepatic function because of multiple procedures of TACE for a short interval and to the proximal embolization of the right, left, or proper hepatic artery.[8,10,12] One paper reported that hepatic failure occurred in up to 60% of patients,[8] whereas Ernst et al[49] retrospectively demonstrated that the efficacy of TACE increased when it was repeated only when necessary on follow-up CT or MRI rather than on

scheduled intervals. To our knowledge, there was no trial to assess what was better during the follow-up.

As another important factor to obtain good survival of TACE, super selective catheterization using a 2.7F to 3.0F microcatheter has been developed to maximize the therapeutic effect for targeted lesion and to minimize the unnecessary injury to the noncancerous hepatic portion.[22,23,32] In addition, this technique is indispensable to avoid adverse complication such as necrosis of the gallbladder or refractory gastroduodenal ulcer secondary to the embolization for nontargeted organs.[29] According to the latest report of the national study of the primary liver cancer,[33] chemoembolization was carried out by super selective catheterization: in those more peripheral to the segmental artery in 29% of 7567 patients, in 1 or 2 segmental arteries in 42%, in the right or left hepatic artery in 20%, and in the proper hepatic artery only in 9%.

TACE-related mortality rate was .5% (40/8510 patients) after the initial treatment. The previous study reported that TACE-related mortality rate was 10% (3/30 patients) in 1991,[50] 9.4% (12/127 patients) in 1994,[26] and, recently, 1.1% (2/182 patients) in 1999,[31] the last paper that reported the event occurred after multiple therapeutic procedures. The incidence of TACE-related deaths tended to decrease year by year. In the current study, hepatic failure (40.1%) ranked first, followed by cancer death (18.2%) and rupture of HCC (15.9%). Forty-five percent of 38 patients whose degree of liver damage was mentioned were in liver damage grade C. One study reported hepatic failure as the main adverse event of this therapy.[26] The postembolization rupture of HCC was uncommon but is life-threatening.[51]

As a limitation of this study, we did not analyze the relationship between the survival and dosage of the anticancer agent and lipiodol administered for TACE because of lack of items in the questionnaire sheet. It was presumed that doxorubicin[20,21,23,28,32,52] and epirubicin[32] analog of doxorubicin followed by cisplatin[20,28] were mainly used. The dose of lipiodol used was speculated to be approximately 5 mL/body and at maximum no more than 10 mL/body to prevent deterioration of hepatic function, which were mainly based on the recommended safety dose of lipiodol of 0.1 mL/kg[53] and 0.4 mL/kg[54] that were studied in normal animal liver combined with and without gelatin sponge particles, respectively. We failed to clarify which agent was more effective and how much of lipiodol was optimal.

As a main cause of a short mean follow-up period of 1.77 years, the following 2 factors can be given. One was early death of patients and the other was early increase of censored cases. During the first 2 years of follow-up, 66.1% (2383/3605) patients died, and 65.2% (3197/4905) patients were censored. The reason why the censored cases were high could be speculated as follows: the patients would frequently change hospitals to seek more specialized therapy, which was optimized to their stage of HCC and liver function. If these censored patients were low in frequency, the survival rates of TACE would have been probably lower than those of the current study because the majority of HCC patients has a poor prognosis. The high incidence of censored cases might reflect the limitation of the large scale of the current registration system. A new registration system has just started in which the drawbacks are improved, and the more precise and flexible information would be transmitted to the world.

In conclusion, the current study revealed that TACE demonstrated a high 5-year survival rate of 26% and a low TACE-related mortality rate of .5% in 8510 patients with unresectable HCC. The measurements of hepatic function (degree of liver damage proposed by the Liver Cancer Study Group of Japan), tumor characteristics (size, number, and presence of portal vein tumor thrombus evaluated by TNM staging), and AFP value were independent predictors of survival of patients. We hope these results will aid in predicting prognosis of a candidate patient who will be treated with the current procedure of TACE, in comparing the effectiveness with newly designed transarterial therapy, and in constructing a more practical new treatment algorism.

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A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma

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Background. For patients with hepatocellular carcinoma (HCC), the selection of effective therapeutic options depends on a reliable prognostic assessment of both the tumor characteristics and liver impairment. This study sought to provide a modified Japan Integrated Stage (m-JIS) score to predict more accurately the survival of patients with HCC. ***Methods.*** We analyzed the records of 42269 patients diagnosed with HCC that were registered between 1992 and 1999 in a nationwide Japanese database. The m-JIS score was calculated from the tumor-node-metastasis stage and the grade of liver damage as defined by the Liver Cancer Study Group of Japan. The predictive accuracy for patient survival based on the m-JIS score was compared with that determined by the modified Cancer of the Liver Italian Program (m-CLIP) score using the cross-validation method. ***Results.*** Patients were divided randomly into two groups, a training sample for construction of prediction models ($n = 21127$ patients with 8458 deaths) and a validation sample for assessment of those prediction models ($n = 21142$ patients with 8434 deaths). Both the m-JIS score and the m-CLIP score showed good discriminatory ability in the training sample. In the validation sample, the residuals of prediction based on the m-JIS score were smaller than those of the m-CLIP score ($P < 0.0001$). ***Conclusions.*** The m-JIS scoring system had better predictive accuracy than the m-CLIP score system for survival of Japanese patients with HCC.

Key words: TNM Stage, degree of liver damage, nationwide survey database, Liver Cancer Study Group of Japan, CLIP score

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. For HCC patients, several effective treatment modalities exist, including liver resection, local ablation therapy, transcatheter arterial chemoembolization, and liver transplantation. However, the efficacy of these modalities is limited by both tumor status and liver dysfunction, because most HCC patients present with chronic hepatitis or liver cirrhosis due to hepatitis B or C viral infection.[1] In Japan, more than 85% of HCC patients have hepatitis B or C viral infection.[2] Therefore, a reliable prognostic assessment based on tumor characteristics and the grade of liver impairment is required to predict outcome in patients.

During the last decade, better screening of high-risk populations with hepatitis virus B or C infection has led to increases in the early detection of HCC. Several advances in diagnostic techniques and therapeutic modalities have significantly improved the prognosis of patients with HCC.[3–5] In Japan, the 5-year survival rate of patients with HCC who underwent liver resection increased from less than 40% during the 1980s to greater than 50% during the 1990s.[6] We have reported that age, degree of liver damage, α-fetoprotein (AFP) levels, maximum tumor diameter, number of tumors, presence of portal vein or hepatic vein invasion, extrahepatic metastasis, surgical curability, and surgical free margin are independent prognostic factors for HCC

patients who undergo liver resection.[6] These findings prompted the revision of the tumor-node-metastasis (TNM) staging system by the Liver Cancer Study Group of Japan (LCSGJ).[7] In this system, tumor status is determined by maximum tumor diameter, total number of tumors, and the presence of vascular or bile duct invasion. To evaluate liver function precisely, the LCSGJ also proposed a classification of the degree of liver damage to replace the Child-Pugh classification system.[7] Both TNM staging and the LCSGJ degree of liver damage classification are useful for predicting the prognosis of patients with HCC.

Staging systems are created to predict the outcome of patients and to evaluate the efficacy of therapeutic modalities. Such systems are important research tools, permitting comparison of different groups and trials.[8] Recently, to predict outcome in patients with HCC, new HCC staging systems combining tumor status with the degree of liver damage, namely, the Cancer of the Liver Italian Program (CLIP) score,[9] the Barcelona Clinic Liver Cancer (BCLC) staging classification,[10] the Chinese University Prognostic Index (CUPI),[11] and the Japan Integrated Stage (JIS) score,[12,13] have been proposed.

In this study, we propose a new staging system, defined by the LCSGJ TNM stage and the LCSGJ degree of liver damage classification. This staging system is a modified JIS score that incorporates the degree of liver damage classification, instead of the Child-Pugh classification, to evaluate liver function more precisely. We calculated the modified JIS (m-JIS) score of patients in a nationwide HCC survey database and compared the predictive accuracy of the m-JIS score for the survival of patients with that of a modified CLIP (m-CLIP) score.

Patients and methods

In a nationwide follow-up survey of primary liver cancer conducted by the LCSGJ, patients from approximately 800 institutions in Japan with primary malignant liver tumors diagnosed by imaging studies, preoperative clinical data, or histopathological studies were registered every 2 years. Registered patients were followed up prospectively. In this study, we collected the records of HCC patients who were registered in the database between January 1992 and December 1999 and for whom complete information on six tumor characteristics in imaging studies (maximum tumor diameter, number of tumors, portal and hepatic vein invasion, and lymph node or distant organ metastasis) for determination of the TNM stage, degree of liver damage, and AFP levels at diagnosis was available.

TNM stage and the degree of liver damage classification are defined by the LCSGJ in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, second English edition (Tables 1 and 2).[7] In this study, the TNM stage was determined by tumor characteristics in imaging studies, not from resected specimens, even when hepatic resection was performed. Bile duct invasion in imaging studies was excluded from our determination of TNM stage owing to the lack of a corresponding item in the database. The m-JIS score was calculated using the TNM stage and the grade of liver damage (Table 3). The original CLIP score was determined from tumor morphology, AFP levels, portal vein invasion, and liver function. Unfortunately, the Child-Pugh classification and tumor morphology with "extent >50% of the liver" for calculating the original CLIP score were not included in our database. In the m-

Table 1. The TNM classification proposed by LCSGJ

Factors	Factor score	Determination
T factor		
1. Solitary tumor	T1	Meets all of the criteria
2. Maximum tumor diameter ≤2 cm	T2	Meets two of the three criteria
3. No vascular invasion (to PV, HV, or BD)	T3	Meets one of the three criteria
	T4	Does not meet any of the criteria
N factor		
Lymph node metastasis	N0	Absent
	N1	Present
M factor		
Distant metastasis	M0	Absent
	M1	Present
Stage		
I		T1 N0 M0
II		T2 N0 M0
III		T3 N0 M0
IV-A		T4 N0 M0; any T N1 M0
IV-B		Any T or N M1

TNM, tumor-node-metastasis; LCSGJ, Liver Cancer Study Group of Japan; PV, portal vein; HV, hepatic vein; BD, bile duct

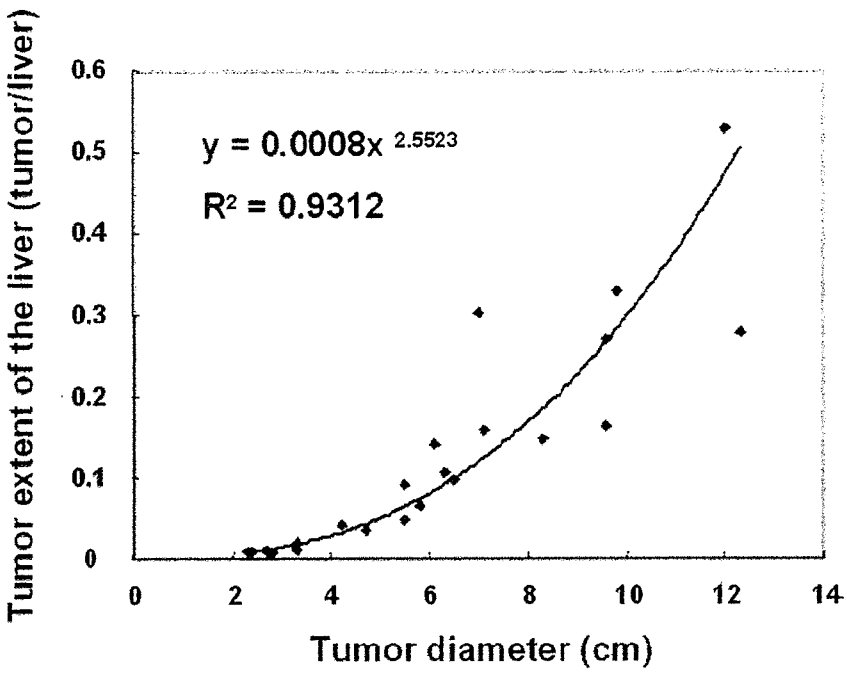

Fig. 1. Relationship between maximum tumor diameter and tumor extent in 23 patients with hepatocellular carcinoma

Table 2. Degree of liver damage classification by LCSGJ

Item	Liver damage grade		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dl)	>3.5	3.0–3.5	>3.0
$ICGR_{15}$ (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

The highest grade with at least two items meeting the criteria for that grade is adopted as the degree of liver damage
$ICGR_{15}$, indocyanine green retention rate at 15 min

Table 3. The modified Japan Integrated Stage (m-JIS) scoring system

Liver damage grade	TNM stage	Value assigned
A	I	0
B	II	1
C	III	2
	IV	3

m-JIS score = (liver damage grade) + (TNM stage)

CLIP score, the grade of liver damage, indicated in Table 2, was applied for liver function, instead of the Child-Pugh classification. In a preliminary study, we examined the relationship between maximum tumor diameter and tumor extent in 23 patients with HCC who underwent computed tomography at Kyoto University Hospital. "Extent >50% of the liver" corresponded to a tumor diameter of approximately 12 cm (Fig. 1). In the nationwide database, maximum tumor diameter groups were 0–2, 2–3, 3–5, 5–10, 10–15, 15–20, 20–25, and more than 25 cm. In this study, tumor morphology with "extent >50% of the liver" was changed to maximum tumor diameter >10 cm (Table 4). In the original CLIP score, 400 ng/dl was defined as the cutoff level for AFP;[9] we used 400 ng/ml as the cutoff level in the m-CLIP score, as only 6.2% of patients had AFP levels above 10 000 ng/ml.

Overall cumulative survival rates were obtained with the Kaplan-Meier method. To calculate survival times, the starting point was the date of admission and the end point was the date of either death or the last follow-up information. Follow-up ended on 31 December 1999. The mean follow-up period was 23.2 months (range, 1–96 months). Differences in survival between groups were compared by a log rank test. To evaluate the m-JIS

Table 4. The modified Cancer of the Liver Italian Program (m-CLIP) scoring system

Degree of liver damage	Tumor morphology	AFP (ng/ml)	Portal thrombosis	Value assigned
A	Uninodular and maximum tumor diameter ≤10 cm	≤400	No	0
B	Multinodular and maximum tumor diameter ≤10 cm	>400	Yes	1
C	Maximum tumor diameter >10 cm			2

AFP, α-fetoprotein

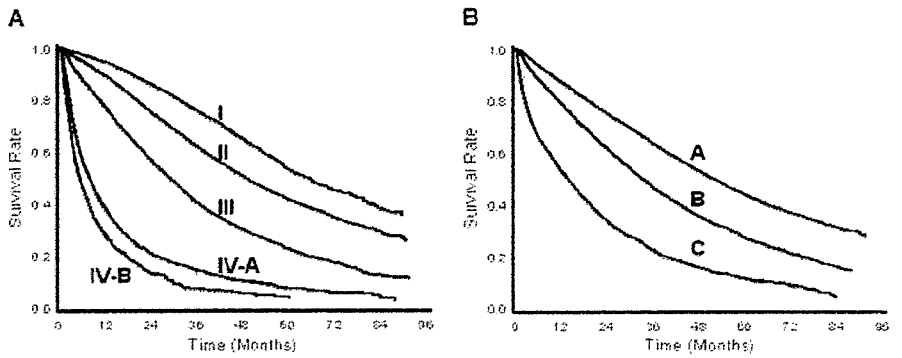

Fig. 2. Survival curve of patients with hepatocellular carcinoma according to the tumor-node-metastasis (TNM) stage (**A**) and degree of liver damage classification (**B**) by the Liver Cancer Study Group of Japan. We observed statistically significant differences among groups (stages or liver damage grades) for both TNM stage and the degree of liver damage classification ($P < 0.0001$)

score as a predictor, independent variables [m-JIS score, age, sex, hepatitis B virus surface antigen (HBsAg), anti-hepatitis C virus antibody (HCVAb), tumor size, number of tumors, portal and hepatic vein invasion, extrahepatic metastasis, and AFP level] were used in a multivariate analysis by Cox's proportional hazard model.

The predictive accuracies of the m-JIS score and the m-CLIP score for the survival of patients were compared using the cross-validation method. For cross validation, patients were divided randomly into two groups: a training sample and a validation sample. In the training sample, two predictive models that included either the m-JIS or the m-CLIP score as a covariate were constructed using Cox's proportional hazards model. In the validation sample, each estimated model from the test sample was applied to predict the survival of each patient. The predicted survival curves, plotted for each model, were compared to the observed survival curves of the validation sample, plotted by the Kaplan-Meier method. The predictive accuracy was compared in terms of the residual, the difference between the observed survival time and the predicted survival time in the validation sample. Small absolute values of the residuals indicate accurate prediction of the survival of patients. The estimated absolute values of the residuals were compared between the m-JIS and m-CLIP scores by the analysis of variance (ANOVA) method. For the ANOVA, the generalized estimating equation (GEE) approach was used to account for the correlation between the two residuals in each patient.[14]

P values less than 0.05 were considered statistically significant. Statistical analysis was carried out with SAS ver. 8.02.

Results

Records of a total of 42269 registered patients were collected from the database. The patients' profiles are shown in Table 5. The average patient age was 64.1 ± 9.3 (mean ± SD), and the ratio of men to women was 2.9:1. Among total patients, 15.4% tested positive for HBsAg and 74.6% were positive for HCVAb. According to the imaging studies, 27.0% of the patients had tumor(s) with a maximum diameter of 2 cm or less, and 76.9% of 5 cm or less. Only 7.6% of the patients had a tumor with maximum diameter greater than 10 cm. More than half of the patients had a solitary tumor. Portal and hepatic vein invasions were observed in 12.4% and 4.7% of the patients, respectively. In 3.7% of all patients, extrahepatic metastasis, including lymph node and distant organ metastases, was observed. As the initial treatment for HCC, 13119 patients underwent liver resection, 11302 received local ablation therapy, 13868 underwent transcatheter arterial chemoembolization, and 3980 patients received other treatments or best supportive therapy. Up through 1999, no patients who underwent

Table 5. Patient profiles and tumor characteristics

	n	(%)
Age (mean ± SD)		
64.1 ± 9.3		
Sex		
Male	31537	74.6
Female	10732	25.4
HBsAg		
Negative	34627	81.9
Positive	6523	15.4
NR	1119	2.7
HCVAb		
Negative	9956	23.6
Positive	31548	74.6
NR	765	1.8
Tumor size		
Diameter ≤2 cm	11426	27.0
2 cm < diameter ≤3 cm	10683	25.3
3 cm < diameter ≤5 cm	10412	24.6
5 cm < diameter ≤10 cm	6552	15.5
10 cm < diameter	3196	7.6
Number of tumors		
Solitary	24044	56.9
Multiple	18225	43.1
Portal vein invasion		
Absent	37013	87.6
Present	5256	12.4
Hepatic vein invasion		
Absent	40299	95.3
Present	1970	4.7
Extrahepatic metastasis		
Absent	40693	96.3
Present	1576	3.7
AFP (ng/ml)		
≤400	32421	76.7
>400	9848	23.3
TNM Stage		
I	7439	17.6
II	17998	42.6
III	12571	29.7
IV-A	3023	7.2
IV-B	1238	2.9
Degree of liver damage		
A	22732	53.8
B	15152	35.9
C	4385	10.4
m-JIS score		
0	4698	11.1
1	12475	29.5
2	13265	31.4
3	7591	18.0
4	3133	7.4
5	1107	2.6
m-CLIP score		
0	10775	25.5
1	13838	32.7
2	9733	23.0
3	4690	11.1
4	1997	4.7
5	897	2.1
6	339	0.8

HBsAg, hepatitis B virus surface antigen; HCVAb, anti-hepatitis C virus antibody; NR, not recorded

liver transplantation for HCC were registered in our database.

The cumulative survival curves of patients according to the TNM stage indicated that the 5-year survival rates were 53.0%, 41.3%, 22.1%, 7.0%, and 3.2% in patients with stage I (n = 7439), stage II (n = 17998), stage III (n = 12571), stage IV-A (n = 3023), and stage IV-B (n = 1238) disease, respectively (Fig. 2A). The 5-year survival rates were 43.4% for liver damage grade A (n = 22732), 26.7% for grade B (n = 15152), and 11.2% for grade C (n = 4385) (Fig. 2B). There were statistically significant differences in survival among groups, whether calculated for TNM stages or the degree of liver damage ($P < 0.0001$).

Multivariate analysis with Cox's proportional hazard model indicated that the m-JIS score, patient age, HBsAg, tumor size, number of tumors, portal vein invasion, hepatic vein invasion, extrahepatic metastasis, and AFP level were independent prognostic predictors for HCC patients (Table 6). Among these variables, the m-JIS score had the highest hazard ratio. Therefore, the predictive accuracy for patient survival based on the m-JIS score was compared with that determined by the m-CLIP score by using the cross-validation method.

The 42269 patients were divided randomly into two groups: a training sample (n = 21127 patients with 8458 deaths) and a validation sample (n = 21142 patients with 8434 deaths). Tables 7 and 8 show the prediction models constructed by Cox's proportional hazards method from the training sample based on the m-JIS and the m-CLIP score, respectively. In the training sample, both of these models had a good discriminating ability. Figure 3 shows the results of the application of each predictive model to the validation sample. The residual sum of squares was 17.49 for models based on the m-JIS score (Fig. 3A) and 21.81 for those based on the m-CLIP score (Fig. 3B) ($P < 0.0001$). Table 9 details the results of the GEE analysis adjustment of the score values. The negative parameter estimate for the scoring method (m-JIS vs m-CLIP) indicates that the residuals based on the m-JIS score were smaller than those based on the m-CLIP score ($P < 0.0001$).

Discussion

To distinguish patients with a curable disease from those with more advanced disease, it is important to be able to assess the prognosis of HCC patients using imaging studies and clinical data, without a histopathological review of a resected specimen. The Okuda staging classification proposed in the 1980s is a simple staging system combining tumor characteristics with liver function.[15] In this staging system, however, tumor character is evaluated only by whether the tumor has extended