Nationwide Study of 4741 Patients With Non-B Non-C Hepatocellular Carcinoma With Special Reference to the Therapeutic Impact

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Objective: To examine the prognostic factors and outcomes after several types of treatments in patients with hepatocellular carcinoma (HCC) negative for hepatitis B surface antigen and hepatitis C antibody, so-called "non-B non-C HCC" using the data of a nationwide survey.

Background: The proportion of non-B non-C HCC is rapidly increasing in Japan.

Methods: A total of 4741 patients with non-B non-C HCC, who underwent hepatic resection (HR, n = 2872), radiofrequency ablation (RFA, n = 432), and transcatheter arterial chemoembolization (TACE, n = 1437) as the initial treatment, were enrolled in this study. The exclusion criteria included extrahepatic metastases and/or Child-Pugh C. Significant prognostic variables determined by a univariate analysis were subjected to a multivariate analysis using a Cox proportional hazard regression model.

Results: The degree of liver damage in the HR group was significantly lower than that in the RFA and TACE groups. The HR and TACE groups had significantly more advanced HCC than the RFA group. The 5-year survival rates after HR, RFA, and TACE were 66%, 49%, and 32%, respectively. Stratifying the survival rates, according to the TNM stage and the Japan Integrated Staging (JIS) score, showed the HR group to have a significantly better prognosis than the RFA group in the stage II and in the JIS scores "1" and "2." The multivariate analysis showed 12 independent prognostic factors. HR offers significant prognostic advantages over TACE and RFA.

Conclusions: The findings of this large prospective cohort study indicated that HR may be recommended, especially in patients with TNM stage II and JIS scores "1" and "2" of non-B non-C HCC.

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths and fifth most common cancer worldwide.[1,2] Moreover, the incidence and mortality rate have been increasing in the United States and other countries.[3,4] The prominent etiological factors associated with HCC include chronic infection of hepatitis B virus (HBV) and hepatitis C virus (HCV), and chronic alcohol consumption. Although HCV-related HCC is responsible for the greatest proportion of HCC patients in Japan,[5,6] many hepatologists note that the proportion of HCC negative for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb), so-called "non-B non-C HCC," is rapidly increasing.[7,8] Indeed, a nationwide follow-up survey by the Liver Cancer Study Group of Japan (LCSGJ) found the proportions of HBV- and HCV-related HCC to have decreased over the previous decade, possibly thanks to the promotion of antiviral therapy, whereas the number of other HCC patients (mostly non-B non-C HCC) have more than doubled during the same period from 6.8% to 17.3%.[9] The exact background or molecular mechanisms for such a sharp increase in the incidence of non-B non-C HCC remain unclear at this point; however, nonalcoholic steatohepatitis (NASH) and metabolic syndrome are suggested to be important risk factors.[10] Nonetheless, it is crucial to elucidate clinicopathological characteristics including the prognostic factors of such patients with non-B non-C HCC at this moment.

Several studies, most of which enrolled around 100 patients or less, have investigated the clinical features of non-B non-C HCC to date.[11–16] However, the impact of the treatment, such as surgical treatment, local ablative therapy, and hepatic arterial embolization, for these patients has not been thoroughly examined. On the contrary, many studies have compared the outcomes after several therapeutic modalities for patients with HCC, and the results have been controversial because of the different therapeutic designs and small sample sizes.[17–21] All these findings prompted a study, clarifying the prognostic factors and the therapeutic impact of several types of treatment for the patients with non-B non-C HCC based on the data of the nationwide follow-up survey by the LCSGJ.

METHODS

A total of 62,321 patients with primary liver cancer were prospectively registered biannually from January 2000 to December 2005 by the LCSGJ using a registration/questionnaire sheet with more than 180 questions. They included 57,450 patients who were clinically diagnosed with HCC using multiple imaging modalities, clinical data, such as tumor markers, and/or histopathological

studies at each institution. Radiofrequency ablation (RFA) began to be more widely used in Japan in 2000. In addition, the data of the Child-Pugh class were requested on the form from the 16th survey. Therefore, the current study used the data from 2000 (16th survey) to 2005 (the latest 18th survey). In this study, 3447 patients for whom the data of hepatitis viral infection status of HBsAg and HCVAb were not available were excluded (Fig. 1), and 9307 of the remaining 54,003 patients with HCC (17.2%) were negative for both HBsAg and HCVAb (defined as "non-B non-C HCC").

The main purpose of this study was to compare the outcomes after hepatic resection (HR), RFA, and transcatheter arterial chemoembolization (TACE) in the non-B non-C HCC patients. The treatment algorithm for HCC proposed by Japanese guideline[22] indicates these 3 types of therapeutic modalities for patients without extrahepatic metastasis in the degree of liver damage A or B. The treatment algorithm[22] is based on 3 factors: "degree of liver damage" defined by the LCSGJ,[23] "number of tumors," and "tumor diameter." However, Child-Pugh class was adopted instead of the degree of liver damage because the former is globally used to evaluate liver function. Accordingly, the patients with extrahepatic metastasis (n = 944) and those in Child-Pugh C (n = 1028) were excluded. The study also excluded the 2192 patients who underwent the treatment other than the 3 types of therapeutic modalities described earlier. In addition, patients lacking outcome data were excluded (n = 402). Finally, 4741 non-B non-C HCC patients were selected in the current cohort study (Fig. 1) and classified according to the primary treatment into the HR group (n = 2,872), the RFA group (n = 432), and the TACE group (n = 1,437). In fact, the majority of Japanese patients with HCC are treated with 1 of the 3 types of treatment modalities, including surgical treatment, local ablative therapy, and hepatic arterial embolization. The questionnaire sheet of LCSGJ subclassified "Surgical treatment" into HR, liver transplantation, and others. "Local ablative therapy" includes RFA, ethanol injection therapy, microwave coagulation therapy, and others. "Hepatic arterial embolization" is subdivided into TACE (anticancer agents and lipiodol followed by gelatin sponge particles; this method was defined as "TACE" in this study), anticancer agents and lipiodol alone, anticancer agents and gelatin sponge particles alone, and others. The current investigation strictly selected HR, RFA, and TACE as the most frequently adopted and well-standardized therapeutic strategy from each type of treatment modality in Japan. Indeed, the 18th survey of LCSGJ found that approximately 97% of "Surgical treatment" was HR, 72% of "Local ablative therapy" was RFA, and 76% of "Hepatic arterial embolization" was TACE.

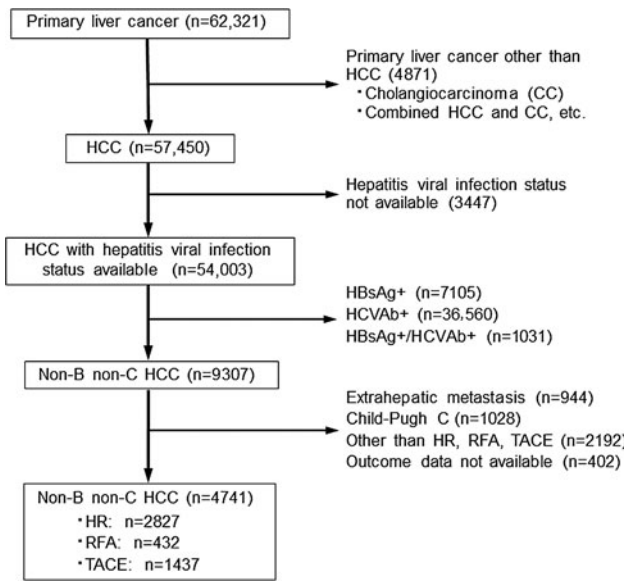

FIGURE 1. Flow chart of the patients with non-B non-C hepatocellular carcinoma (HCC) analyzed in this study.

The patients were prospectively followed up at each institution. Most of the patients have been traditionally observed according to the protocol, similar to the Japanese guidelines,[22] in which ultrasonography and measurement of the tumor markers every 3 or 4 months and enhanced computed tomography or magnetic resonance imaging every 6 or 12 months is recommended. The final prognosis of these registered patients was followed until confirmation of death at every survey.

The clinical characteristics among the 3 treatment groups were summarized in Table 1. All of the 19 variables were significantly different among the groups. Particularly, for the patients in the HR group, the positive percent of habitual alcohol consumption, defined as 86 g or more of ethanol per day over a 10-year period, was significantly lower than that in the RFA and TACE groups. The results of liver function tests, such as indocyanine green retention rate at 15 minutes (ICGR15) and prothrombin activity in this group, were significantly better than those in the RFA and TACE groups. These findings were well coordinated with the status of Child-Pugh class among the 3 groups. On the contrary, the HR and TACE groups had significantly more advanced HCC based on the most of tumor factors, such as the tumor size, tumor markers, and portal venous invasion, than the RFA group. However, the number of tumors in the HR group was the smallest, whereas that in the TACE group was largest. Liver-related deaths, such as those due to liver failure, in the RFA group were more frequently observed, whereas HCC-related deaths were more common in the HR and TACE groups (Table 1).

Statistical Analysis

The clinical characteristics among the 3 treatment groups were compared by either the chi-square test or the Kraskul-Wallis test. The survival rate after each treatment was calculated by the Kaplan–Meier method and then was compared by the log-rank test. The Bonferroni correction was applied for the multiple comparisons. Nineteen clinical variables, including type of treatment were evaluated by univariate analysis using a log-rank test to determine the prognostic factors in the patients with non-B non-C HCC. The survival rates after each treatment were stratified according to the TNM staging system defined by the LCSGJ (Table 2 and Table 3)[23] and the Japan Integrated Staging (JIS) score (Table 4).[24] Because the patients in Child-Pugh C were excluded in this study, JIS score "2" indicated either Child-Pugh class A/stage III or Child-Pugh class B/stage II, JIS score "3" indicated either Child-Pugh class A/stage IVA or Child-Pugh class B/stage III, and JIS core "4" indicated Child-Pugh class B/stage IVA.

Continuous variables were divided into 2 groups according to the median value. Significant variables with a P value less than 0.05 by the univariate analysis were subjected to multivariate analysis using a Cox proportional hazard regression model with backward elimination method.[25] All significance tests were 2-tailed, and a P value less than 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Analysis System (SAS) version 9.1.3 (SAS Inc, Cary, NC).

RESULTS

The follow-up periods after the treatment of HR, RFA, and TACE were 1.9 ± 1.6 years, 2.3 ± 1.4 years, and 1.5 ± 1.4 years, respectively. The 1-, 3-, and 5-year survival rates of the 4741 patients with non-B non-C HCC were 89%, 70%, and 55%, respectively.

TABLE 1. Clinical Characteristics in the Non-B Non-C HCC Patients Who Underwent 3 Types of Therapeutic Strategies

Variables	HR (n = 2872)	RFA (n = 432)	TACE (n = 1437)	*P*
Age (yr)	67 (50, 79)	68 (53, 81)	69 (53, 83)	<0.001
Sex				<0.001
Male	2332 (81%)	315 (73%)	1124 (78%)	
Female	540 (19%)	117 (27%)	313 (22%)	
Alcohol				<0.001
None	1,652 (58%)	209 (48%)	689 (48%)	
Positive*	874 (30%)	178 (41%)	619 (43%)	
Unknown	346 (12%)	45 (10%)	129 (9%)	
Serum albumin (g/dL)	4.0 (3.2, 4.7)	3.8 (2.9, 4.6)	3.7 (2.8, 4.5)	<0.001
Serum total bilirubin (mg/dL)	0.8 (0.4, 1.5)	1.1 (0.4, 2.4)	1.1 (0.4, 2.3)	<0.001
ICG R15 (%)	15 (4, 32)	26 (8, 52)	25 (5, 56)	<0.001
Prothrombin activity (%)	89 (65, 114)	80 (54, 104)	82 (55, 106)	< 0.001
Esophageal varices				<0.001
None	2231 (78%)	195 (45%)	740 (52%)	
Positive	276 (10%)	152 (35%)	489 (34%)	
Unknown	365 (13%)	85 (20%)	208 (15%)	
Degree of liver damage†				<0.001
A	2368 (83%)	224 (52%)	808 (56%)	
B	409 (14%)	132 (31%)	399 (28%)	
C	10 (0.3%)	14 (3%)	39 (3%)	
Unknown	85 (3%)	62 (14%)	191 (13%)	
Child-Pugh class				<0.001
A	2679 (93%)	316 (73%)	1068 (74%)	
B	193 (7%)	116 (27%)	369 (26%)	
Alpha-fetoprotein (ng/mL)	3491 (15, 16368)	215 (15, 927)	3177 (15, 13605)	<0.001
PIVKA-II (AU/mL)‡	2198 (40, 10000)	501 (40, 10000)	1905 (40, 10000)	<0.001
Tumor number				<0.001
1	2193 (76%)	293 (68%)	679 (47%)	
2	323 (11%)	85 (20%)	256 (18%)	
>3	126 (4%)	28 (7%)	126 (9%)	
Tumor size (mm)	5.8 (1.8, 14)	3.0 (1.1, 6)	5.0 (1.4, 13)	<0.001
Gross classification§				<0.001
Type 1	2362 (82%)	407 (94%)	1181 (82%)	
Type 2	199 (7%)	9 (2%)	160 (11%)	
Type 3	21 (0.7%)	2 (0.5%)	39 (3%)	
Unknown	290 (10%)	14 (3%)	57 (4%)	
Portal venous invasion				<0.001
Negative	2336 (81%)	403 (93%)	1218 (85%)	
Positive	342 (12%)	8 (2%)	179 (10%)	
Unknown	194 (7%)	21 (5%)	76 (5%)	
TNM stage†				<0.001
I	251 (9%)	119 (28%)	160 (11%)	
II	1489 (52%)	189 (44%)	550 (38%)	
III	707 (25%)	75 (17%)	517 (36%)	
IVA	321 (11%)	4 (1%)	74 (5%)	
Unknown	85 (3%)	45 (10%)	136 (10%)	
JIS score				<0.001
0	233 (8%)	87 (20%)	116 (8%)	
1	1423 (50%)	173 (40%)	466 (32%)	
2	732 (26%)	103 (24%)	514 (36%)	
3	374 (13%)	23 (5%)	184 (13%)	
4	25 (1%)	1 (0.2%)	21 (2%)	
Unknown	85 (3%)	45 (10%)	136 (10%)	
Cause of death				<0.001
HCC-related	302 (63%)	41 (38%)	271 (62%)	
Liver-related	69 (14%)	31 (29%)	94 (22%)	
Treatment-related	15 (3%)	2 (2%)	1 (0.2%)	
Others	96 (20%)	34 (32%)	68 (16%)	
Median follow-up period (yr)	1.9 (0.1, 5.1)	2.3 (0.1, 4.7)	1.5 (0.1, 4.3)	<0.001

Data are shown as the median (5 percentile, 95 percentile) unless specified.
*Eighty-six gram of alcohol daily for more than 10 years.
†By the Liver Cancer Study Group of Japan.
‡Questionnaire sheet requested the actual value when it was between 40 and 10,000 AU/mL.
§Type 1, simple nodular type; Type 2, simple nodular type with extranodular growth; Type 3, confluent multinodular type.

TABLE 2. TNM Stage by the Liver Cancer Study Group of Japan

	T Category	N Category	M Category
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	T1, T2, T3, T4	N1	M0
Stage IVB	T1, T2, T3, T4	N0, N1	M1

The grade for each category is determined individually, and the staging of the disease is determined according to the aforementioned chart.

M1 indicates presence of distant metastasis; N1: presence of lymph node metastasis.

TABLE 3. T Category of the TNM Stage by the Liver Cancer Study Group of Japan

	T1		T2		T3		T4	
No. tumor: multiple	−	+	−	−	+	+	−	+
Tumor diameter: >2 cm	−	−	+	−	+	−	+	+
Vascular and/or bile duct invasion	−	−	−	+	−	+	+	+

The T category is determined on the basis of the "number," "size," and "vascular and/or bile duct invasion" by the tumor. All multiple tumors, including multicentric tumors and intrahepatic metastatic tumors, are counted.

TABLE 4. Definition and Criteria for the JIS Score

	0	1	2	3
Child-Pugh class	A	B	C	
TNM stage*	I	II	III	IV

JIS score = Child-Pugh class + TNM stage.
*By the Liver Cancer Study Group of Japan.

Prognostic Factors and Survival Rates

Nineteen clinical variables were screened as prognostic factors using a univariate analysis (Table 5). Sex and habitual alcohol intake were not selected as prognostic factors, whereas the remaining 17 variables, including age, serum albumin, serum total bilirubin, ICGR15, prothrombin activity, esophageal varices, degree of liver damage, Child-Pugh class, alpha-fetoprotein, protein induced by Vitamin K absence-II (PIVKA-II), tumor number, tumor size, gross classification, portal venous invasion, TNM stage, JIS score, and type of treatment, were significant prognostic factors. With the Child-Pugh class, 5-year survival rates of grades A and B were 58% and 31%, respectively, with statistical significance ($P < 0.001$; Fig. 2A). The TNM staging system by the LCSGJ[23] revealed that 5-year survival rates in stages I, II, III, and IVA were 66%, 64%, 46%, and 19%, respectively. A good separation, except stage I vs II, was observed (Fig. 2B). The 5-year survival rates based on a JIS score of 0, 1, 2, 3, and 4 were 70%, 67%, 44%, 23%, and 0%, respectively. There was a good separation, except JIS score "0" vs "1" (Fig. 2C). The 5-year survival rates after HR, RFA, and TACE were 66%, 49%, and 32%, respectively (Fig. 2D). There was no significant difference between the HR group and the RFA group ($P = 0.101$).

However, when the survival rates were stratified according to the TNM staging system (Fig. 3), the HR group showed a significantly better prognosis than the TACE group in all 4 stages (stage I to IVA). The RFA group had a significantly better prognosis than the TACE group only in the stage II and III. A comparison between the HR group and the RFA group showed that the HR group had a significantly better prognosis than the RFA group in stage II (Fig. 3B). However, there were no statistically significant differences between the 2 groups in stages I, III, and IVA. The survival rates in the stage II patients were further stratified according to each T category (Table 3) on the basis of the "number of tumors: multiple," "tumor diameter > 2 cm," and "vascular and/or bile duct invasion" by the tumor (Fig. 4). The HR group had a significantly better prognosis than the RFA group in all 3 T categories. The effectiveness of RFA was almost identical to that of TACE in the stage II patients with multiple tumors (Fig. 4A) and only HR could provide long-term survival in the stage II patients with vascular and/or bile duct invasion (Fig. 4C).

Similarly, stratifying survival rates according to the JIS score (Fig. 5) showed that the HR group had a significantly better prognosis than the TACE group in all the 4 scores (JIS score "0" to "3"). The RFA group had a significantly better prognosis than the TACE group only in the JIS score "1" and "3." A comparison between the HR group and the RFA group revealed that the former had a significantly better prognosis than the later in the JIS scores "1" and "2" (Figs. 5B, C). In contrast, the RFA group had an even better prognosis than the HR group in the JIS score "3" (Fig. 5D). The survival rates in the JIS scores "1," "2," and "3" were further stratified according to each criterion (Table 4) on the basis of the "Child-Pugh class" and "TNM stage" (Supplemental Figs 1–3, available at http://links.lww.com/SLA/A388, http://links.lww.com/SLA/A389, and http://links.lww.com/SLA/A390).

Analysis of the Factors Independently Affecting the Survival of Patients

The multivariate initial model provided 11 variables as independent prognostic factors: age, serum albumin, ICGR15, esophageal varices, Child-Pugh class, alpha-fetoprotein, PIVKA-II, tumor size, gross classification, TNM stage, and type of treatment (Supplemental Table 1, available at http://links.lww.com/SLA/A387). Consequently, the multivariate final model showed 12 variables as independent prognostic factors: the 11 variables described earlier and portal venous invasion (Table 6). The stage IVA and gross classification type 3 (confluent multinodular type) had the highest hazard ratio of 3.83 and 2.86, respectively. In particular, the univariate analysis showed no significant difference between the HR group and the RFA group (Table 5), but the multivariate analysis revealed a statistically significant difference (hazard ratio: 1.54, $P = 0.014$) between the 2 groups.

DISCUSSION

In general, it is theoretically difficult to clarify the prognostic factors and therapeutic outcomes after treatments for patients with HCC due to the diversities of tumor stage, degree of chronic liver damage, and therapeutic design, as well as variable etiologic factors of HCC. The present study focused on a relatively small proportion of patients with non-B non-C HCC in Japan, which were further restricted to the patients without extrahepatic metastasis in the Child-Pugh A or B, and which principally met the indications for HR, RFA, and TACE based on the treatment guideline.[22] It was obvious that such strict selection of patients requires huge number of patients to be analyzed. Therefore, the present study used the data of a nationwide follow-up survey by the LCSGJ.

The study first compared the clinical backgrounds among the patients who underwent HR, RFA, or TACE as the initial therapy (Table 1). The degree of liver damage in the HR group was significantly lower than those in the RFA and TACE groups. On the contrary, the HR and TACE groups had significantly more advanced HCC than the RFA group. These findings seem to be consistent with

TABLE 5. Prognostic Factors Determined by the Univariate Analysis in the Patients with Non-B Non-C Hepatocellular Carcinoma

Variables	No. Patient	Survivals (%)			*P*
		1-yr	3-yr	5-yr	
All	4741	89	70	55	
Age (yr)					
<69	2289	88	72	58	Reference
≥69	2438	90	69	50	0.046
Sex					
Male	3771	88	71	56	Reference
Female	970	91	66	51	0.312
Alcohol					
None	2550	89	69	56	Reference
Positive*	1671	89	72	52	0.907
Serum albumin (g/dL)					
<3.9	2004	85	61	42	Reference
≥3.9	2645	92	76	63	<0.001
Serum total bilirubin (mg/dL)					
<0.8	2004	90	74	61	Reference
≥0.8	2645	88	67	48	<0.001
ICGR15 (%)					
<14	1809	90	75	75	Reference
≥14	1896	89	68	68	<0.001
Prothrombin activity (%)					
<87	2177	88	66	48	Reference
≥87	2239	89	73	61	<0.001
Esophageal varices					
None	3166	90	74	60	Reference
Positive	917	85	58	32	<0.001
Degree of liver damage†					
A	3400	90	90	60	Reference
B	940	85	85	39	<0.001
C	63	68	68	–	<0.001
Child-Pugh class					
A	4063	90	73	58	Reference
B	678	81	51	31	<0.001
Alpha-fetoprotein (ng/mL)					
<15	2638	95	80	63	Reference
≥15	1915	81	57	43	<0.001
PIVKA-II (AU/mL)					
<148	2069	94	79	66	Reference
≥148	2074	84	62	45	<0.001
Tumor number					
1	3165	91	76	62	Reference
>2	1461	84	56	38	<0.001
Tumor size (mm)					
<40	2128	94	77	58	Reference
≥40	2455	85	65	53	<0.001
Gross classification‡					
Type 1	3950	91	73	57	Reference
Type 2	368	70	41	32	<0.001
Type 3	62	55	32	0	<0.001
Portal venous invasion					
Negative	3957	91	73	57	Reference
Positive	493	67	41	24	<0.001
TNM stage†					
I	530	96	83	66	Reference
II	2228	93	78	64	0.121
III	1299	87	62	46	<0.001
IVA	399	64	35	19	<0.001
JIS score					
0	436	97	85	70	Reference
1	2062	94	81	67	0.208
2	1349	87	62	44	<0.001
3	581	71	41	23	<0.001
4	47	49	9	0	<0.001
Type of treatment					
HR	2872	91	77	66	Reference
RFA	432	93	73	49	0.101
TACE	1437	83	55	32	<0.001

*Eighty-six gram of alcohol daily for more than 10 yrs.
†By the Liver Cancer Study Group of Japan.
‡Type 1, simple nodular type; Type 2, simple nodular type with extranodular growth; Type 3, confluent multinodular type.

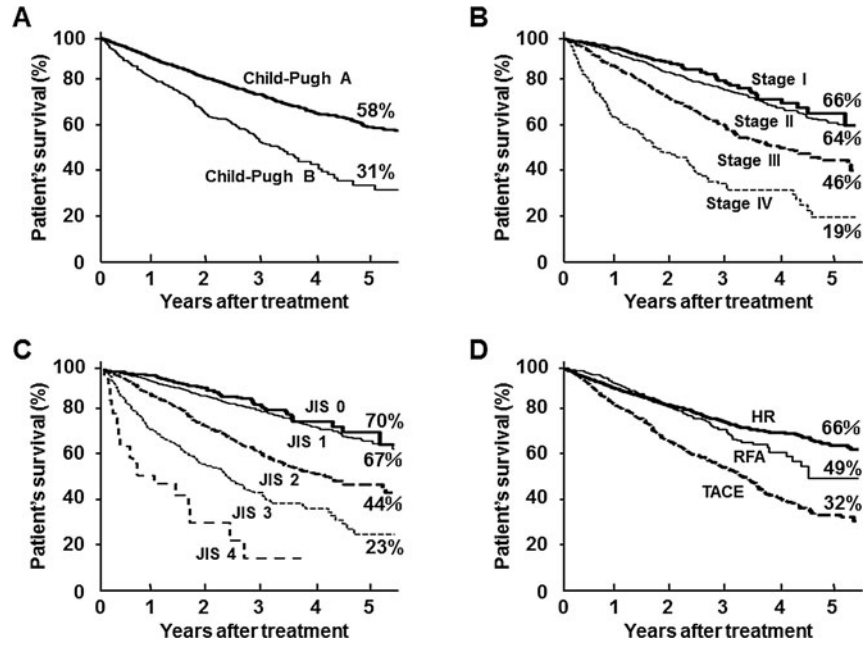

FIGURE 2. Comparisons of the survival rates among liver function, tumor stage, and type of treatment. Survival rates stratified by Child-Pugh A and B (A), staging system according to the Liver Cancer Study Group of Japan (B), JIS score (C), and type of treatment (D). HR vs RFA, $P = 0.30$; HR vs TACE, $P < 0.001$; RFA vs TACE, $P < 0.001$. All comparisons were made the log-rank test with Bonferroni correction.[24]

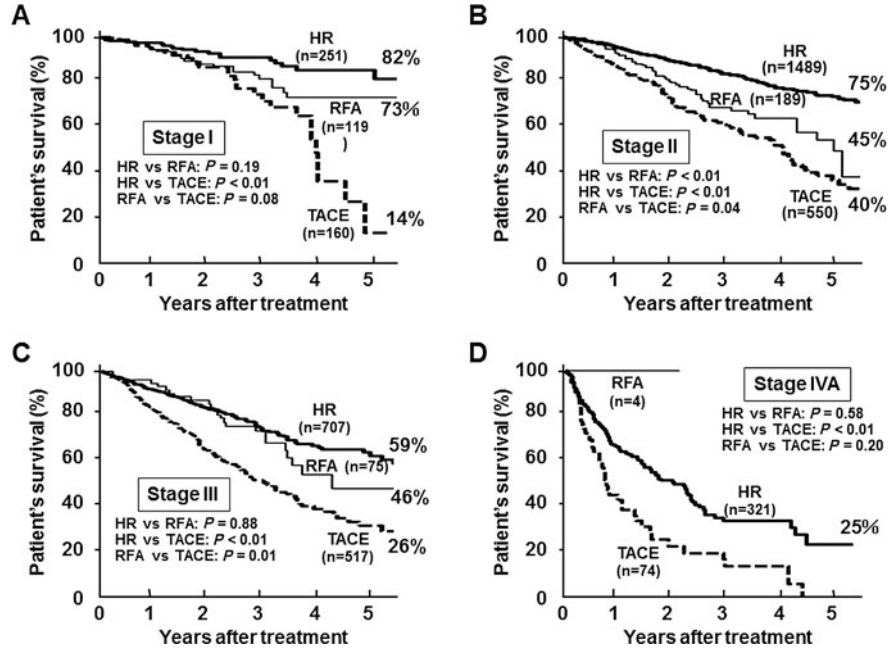

FIGURE 3. Comparisons of the survival rates among the type of treatment. Survival rates were stratified by stage I (A), stage II (B), stage III (C), and stage IVA (D). All comparisons were made by the log-rank test with Bonferroni correction.

those in other studies that included the patients with HCC of varied etiologies of liver disease. However, none of the previous studies have compared the prognostic factors and therapeutic outcomes after the 3 types of treatment modalities with taking such differences in the clinical backgrounds into consideration, possibly due to the limited number of patients.

The study then analyzed the prognostic factors and found that 17 variables, including types of treatment, were significant prognostic factors. Sex and alcohol abuse were not selected as prognostic factors. Although the synergic action of alcohol and HCV infection on hepatocarcinogenesis has been suggested,[26] alcohol consumption alone may not always affect the progression of HCC. The 5-year survival rate in the TACE group (32%) was significantly poorer, whereas there was no significant difference between the RFA group (49%) and the HR group (66%) in the univariate analysis. The 5-year survival rate after TACE in this series (32%) was almost identical to that (34%) based on the data of same nationwide survey (LCSGJ) during the same periods (January 2000–December 2005) but not restricted to the patients with non-B non-C HCC.[27] Hasegawa et al[18] also used the data of the nationwide survey by LCSGJ and compared the prognosis after surgical resection, RFA, and percutaneous ethanol injection. Their evaluation of more than 7000 HCC patients revealed that the time-to-recurrence rate of surgical resection was significantly better than that of RFA or percutaneous ethanol injection. However, the median follow-up period was only 10.4 months, and they did not provide the 5-year survival rate in their study.

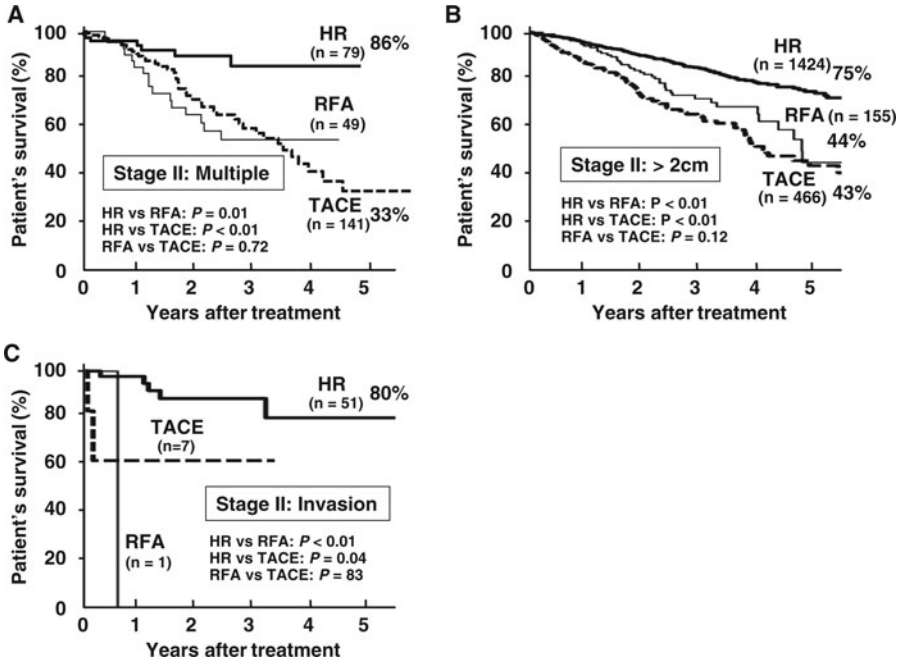

FIGURE 4. Comparisons of the survival rates based on the type of treatment. The survival rates in the stage II were further stratified by number of tumor (A), tumor size (B), and vascular and/or bile duct invasion (C). All comparisons were made by the log-rank test with Bonferroni correction.

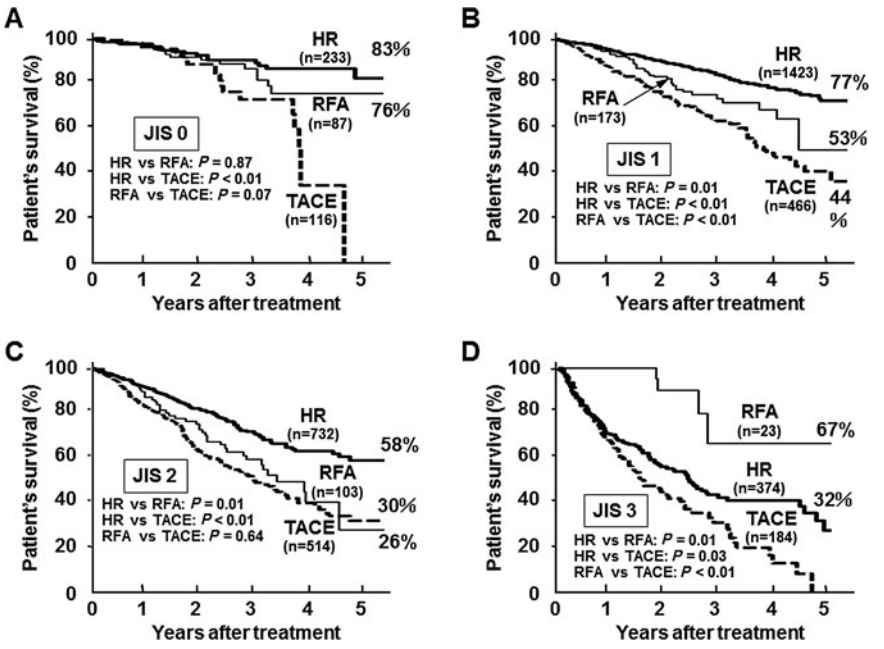

FIGURE 5. Comparisons of the survival rates among the type of treatment. Survival rates were stratified by JIS score "0" (A), JIS score "1" (B), JIS score "2" (C), and JIS score "3" (D). All comparisons were made by log-rank test with Bonferroni correction. [24]

The patients in the TACE group had poorer liver functional reserve and more advanced stage of HCC, thus it would be quite natural that overall survival rate in this group had a poorer prognosis. Because the degree of chronic liver damage and the tumor stage were markedly different among the HR, RFA, and TACE groups, the patients were stratified according to the TNM stage. The study also stratified the patients on the basis of the JIS score.[24] Particularly, the HR group had a significantly better prognosis than the TACE group in all 4 stages and the 4 JIS scores even after the stratifications. On the contrary, the prognosis for the patients in the RFA group did not differ significantly in comparison with those in the TACE group in stages I and IVA and JIS scores "0 and 2." The comparison between the HR group and the RFA group showed the HR group to have a significantly better prognosis than the RFA group only in stage II and in JIS scores "1" and "2." These findings suggest that the HR may not offer prognostic advantages over RFA in the early or far advanced stage of non-B non-C HCC patients. Because the stage II patients included the 3 different types of T categories (Table 3), the survival rates were further stratified on the basis of the T categories (Fig. 4). The HR group had a significantly better prognosis than the RFA group, especially for the patients with multiple tumors and with vascular and/or bile duct invasion. Long-term survival could be expected only after HR in the stage II patients with vascular and/or bile duct invasion (Fig. 4C). Similarly, the survival rates in the

TABLE 6. Independent Prognostic Factors Determined by the Cox Proportional Hazard Regression Analysis With the Backward Elimination Method (Multivariate Final Model)

Variables	No. Patient	Hazard Ratio (95% CI)	*P*
Age (yr)			
<69	1125	Reference	—
≥69	1174	1.37 (1.13, 1.66)	0.001
Serum albumin (g/dL)			
<3.9	939	Reference	—
≥3.9	1360	0.81 (0.66, 0.99)	0.047
ICGR15 (%)			
<14	1129	Reference	—
≥14	1170	1.29 (1.04, 1.59)	0.021
Esophageal varices			
None	1844	Reference	—
Positive	455	1.71 (1.34, 2.17)	<0.001
Child-Pugh class			
A	2032	Reference	—
B	267	1.46 (1.10, 1.92)	0.008
Alpha-fetoprotein (ng/mL)			
<15	1354	Reference	—
≥15	945	1.46 (1.20, 1.79)	<0.001
PIVKA-II (AU/mL)			
<148	1149	Reference	—
≥148	1150	1.60 (1.28, 1.99)	<0.001
Tumor size (mm)			
<40	1015	Reference	—
≥40	1284	1.36 (1.07, 1.74)	0.013
Gross classification*			
Type 1	2105	Reference	—
Type 2	171	1.59 (1.18, 2.12)	0.002
Type 3	23	2.86 (1.48, 5.51)	0.002
Portal venous invasion			
Negative	2068	Reference	—
Positive	231	1.41 (1.04, 1.91)	0.025
TNM stage†			
I	257	Reference	—
II	1168	1.51 (0.97, 2.33)	0.062
III	677	1.96 (1.25, 3.05)	0.003
IVA	197	3.83 (2.27, 6.47)	<0.001
Type of treatment			
HR	1644	Reference	—
RFA	167	1.54 (1.09, 2.19)	0.014
TACE	488	1.56 (1.23, 1.97)	< 0.001

*Type 1, simple nodular type; Type 2, simple nodular type with extranodular growth; Type 3, confluent multinodular type.
†By the Liver Cancer Study Group of Japan.

patients with JIS scores of "1" and "2" were further stratified (Supplemental Figs. 1, 2, available at http://links.lww.com/SLA/A388 and http://links.lww.com/SLA/A389). The effect of HR was observed only in the patients with Child-Pugh class A. Interestingly, the patients in the RFA group (n = 23) in the JIS score "3" subgroup had a significantly better prognosis than the HR group (n = 374). However, after further stratification (Supplemental Fig. 3, available at http://links.lww.com/SLA/A390), there was no statistically significant difference between the 2 groups, possibly because of the small number of patients. A possible therapeutic advantage of RFA in the JIS score "3" patients remains to be confirmed.

Surgical hepatectomy provides better survival and lower recurrence rates than RFA for patients with HCC conforming to the Milan criteria in a randomized clinical trial.[19] The authors considered that segment-based anatomic hepatectomy with at least 1 cm of the rim of nontumor parenchyma eradicates both the primary tumor and intrahepatic micrometastasis. There are 2 types of HCC recurrence; one is "early recurrence" due to intrahepatic metastasis and the other is "late recurrence" due to multicentric hepatocarcinogenesis.[28] Recurrence in non-B non-C HCC are mainly dependent on the advanced tumor factors, such as lager tumor size and portal venous invasion, and thus local control of microscopic intrahepatic metastases is required.[29] The importance of an adequate surgical margin for the non-B non-C HCC has also been reported.[14] Therefore, HR, if a segment-based anatomic hepatectomy is deemed to be possible, should be recommended especially for the patients with stage II or the JIS scores "1" and "2" of non-B non-C HCC. Anatomic hepatectomy with adequate surgical margin may decrease the risk of "early recurrence" of non-B non-C HCC due to intrahepatic metastasis. However, the prediction and prevention of "late recurrence" of non-B non-C HCC due to de novo hepatocarcinogenesis may be difficult, because the background liver diseases can be multifactorial and non-B non-C HCC may develop without displaying any features of severe underlying fibrosis.[29–32] In fact, 13,572 patients underwent HR among the 54,003 total patients for whom the data regarding the hepatitis viral infection status were available (Fig. 1). The incidence of liver cirrhosis based on

the histological examination of resected specimens was 1130 of 2495 patients (45%) with HBV-related HCC, 3666 of 7783 patients (47%) with HCV-related HCC, and 788 of 3040 patients (26%) with non-B non-C HCC, indicating that there was a markedly lower incidence of cirrhosis in the non-B non-C HCC patients. Information regarding the possible etiologies of non-B non-C HCC, such as NASH, diabetes mellitus, autoimmune hepatitis, primary biliary cirrhosis, aflatoxin-B1-contaminated food consumption, and hemochromatosis was not available because of lack of inclusion in the questionnaire sheet of this survey. However, according to the reports describing the recent trend of clinical features in Japanese patients with HCC,[10,33] it is conceivable that a nonnegligible proportion of patients in this study met the criteria for the metabolic syndrome. Potential carcinogenic mediators related to NASH in metabolic syndrome are insulin, lipid peroxidation, free radical oxidative stress, and proinflammatory cytokines.[34–36] Because HCC associated with metabolic syndrome can often develop without significant liver fibrosis,[31,32] metabolic syndrome per se may have a direct oncogenic effect, and it may follow a specific molecular pathway of tumorigenesis different from the usual multistep process: fibrosis-cirrhosis-HCC.[31] In this context, specific strategies for screening "late recurrence" may be required for patients with HCC related to metabolic syndrome, even when underlying chronic liver damage is only minimal.

The molecular mechanisms underlying the individual predisposition to non-B non-C HCC may be different, and a better understanding of these mechanisms will lead to improvements in the prevention and early diagnosis of "late recurrence."[9] Because the number of patients with each etiology is limited, a prospective accumulation of non-B non-C HCC patients including information regarding the possible etiologies is essential, and a nationwide multi-institutional study would be desirable.

Finally, 12 independent prognostic factors, including the type of treatment, were identified by using the Cox proportional hazard regression analysis. There was a significant prognostic advantage of HR not only to TACE but also to RFA. Many studies have compared the outcomes after several therapeutic modalities for patients with HCC,[17–21] most of which compared HR versus RFA, whereas a few studies compared HR versus TACE or RFA versus TACE. This is the first study to compare the prognostic factors and outcomes after 3 types of therapeutic modalities at once. All these findings regarding the non-B non-C HCC patients in Japan may be applicable to the HCC patients in the United States and Western countries where the prominent etiological factors are NASH and metabolic syndrome rather than chronic infection of hepatitis viruses.

Limitations of this study include that the data of TNM staging system of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) were not available to directly apply the current data to the HCC patients in other countries. However, both the TNM stage by the LCSGJ and the AJCC/UICC were developed on the basis of a survival analysis of patients who underwent HR. Therefore, the applicability of these surgical staging systems to other therapies, such as RFA and TACE, has been a matter of controversy.[37] Comparisons of clinicopathological features and prognostic factors between the non-B non-C HCC and HCC caused by other etiological factors, such as HBV- and HCV-related HCC, are beyond the scope of this study. Because the current study was not prospectively randomized, the treatment polices were not regulated and the effectiveness of each treatment might not be comparable among the different institutions. In addition, although this study used a multivariate analysis to assess the impact of diverse background on outcomes, there are limits to such a statistical approach.

CONCLUSIONS

This large prospective study based on data derived from a nationwide follow-up survey suggested that HR offers prognostic advantage over RFA and TACE although such advantage may depend upon the degrees of chronic liver damage and the tumor stage.

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