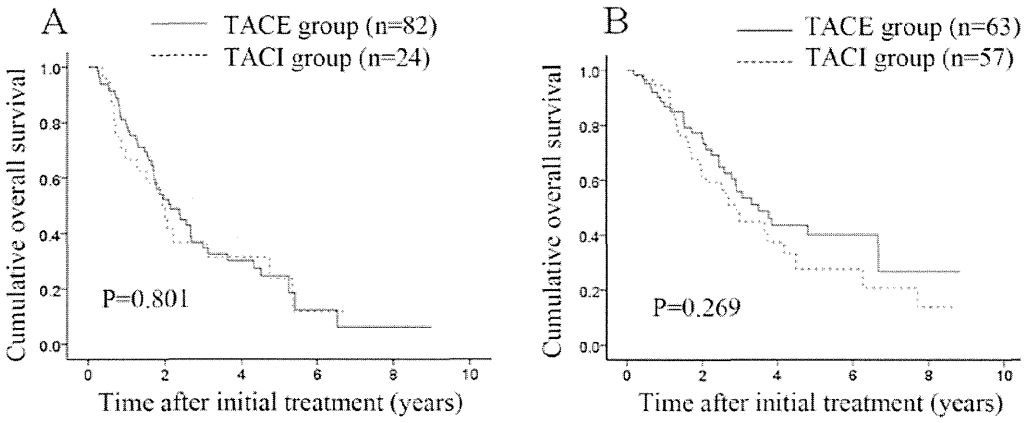

Figure 3. Subgroup analysis according to maximum tumor size. (A) There were 82 patients with a maximum tumor size >4 cm in the TACE group and 24 in the TACI group. The MST was 2.15 years for patients in the TACE group and 1.93 years for patients in the TACI group. There was no significant difference (P=0.801) between the two groups in terms of overall survival (OS). (B) There were 63 patients with maximum tumor size ≤4 cm in the TACE group and 57 in the TACI group. The MST was 3.51 years for patients in the TACE group and 2.92 years for patients in the TACI group. There was no significant difference in the two groups in terms of OS (P=0.269).

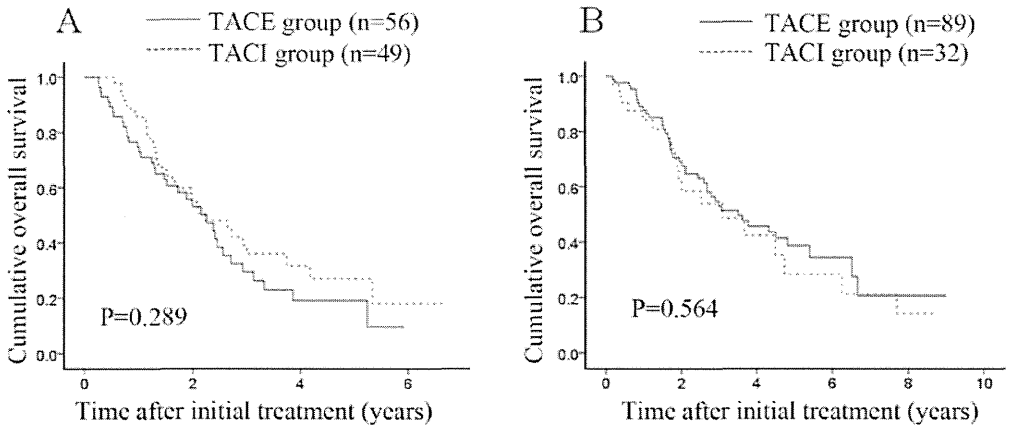

Figure 4. Subgroup analysis according to tumor distribution. (A) There were 56 patients with bilobar disease in the TACE group and 49 in the TACI group. The MST was 2.25 years for patients in the TACE group and 2.23 years for patients in the TACI group. No significant difference (P=0.289) was observed in the two groups in terms of overall survival (OS). (B) There were 89 patients with unilobar disease in the TACE group and 32 in the TACI group. The MST was 3.51 years for patients in the TACE group and 3.09 years for patients in the TACI group. No significant difference was observed between the two groups in terms of OS (P=0.564).

Discussion

Okusaka *et al* (29) conducted an RCT that compared clinical outcomes between unresectable HCC patients treated with TACE using zinostatin stimalamer (n=79) and those treated with TACI using zinostatin stimalamer (n=82). They concluded that treatment intensification involving the addition of embolization did not improve survival over TACI with zinostatin stimalamer. Similarly, Ikeda *et al* (30) carried out a retrospective comparative study regarding clinical outcomes between HCC patients treated with TACE using cisplatin suspended in lipiodol (n=74) and patients treated with TACI using cisplatin suspended in lipiodol (n=94). They reported that TACE using cisplatin suspended in lipiodol had a higher treatment efficacy than TACI using cisplatin suspended in lipiodol, but that it did not significantly improve the survival of patients with HCC. However, it remains unclear as to whether or not TACE using an EML emulsion can deliver a survival benefit over TACI using an EML emulsion; hence the reason for the present comparative study. To the best of our knowledge, this is the first study to compare clinical outcomes in intermediate-stage HCC patients using TACE and TACI, both with an EML emulsion.

In the present study, the MST was 2.68 years for patients in the TACE group and 2.64 years for patients in the TACI group. Takayasu *et al* (12) reported that the MST was 2.83 years in 8510 HCC patients who underwent TACE. Our findings were similar to theirs, although their study population analysis included patients with early-, intermediate- and advanced-stage HCC (12). Here, in all cases and in all subgroup analyses, the difference between the TACE and the TACI group did not reach statistical significance in terms of OS. Our results suggest that TACI using an EML emulsion could achieve a comparable survival benefit to TACE using an EML emulsion, although the treatment efficacy after initial therapy in the TACE group was significantly higher than that in the TACI group. Intermediate-stage HCC includes heterogeneous patient populations with varying tumor size, tumor distribution, tumor number and liver function (31). Thus, all patients with intermediate-stage

HCC might not derive a similar survival benefit from TACE. In fact, in patients with Child-Pugh class B disease, the MST in the TACI group was longer than that in the TACE group in the present study. In patients where TACE was technically impossible for anatomical reasons, or in patients with poor liver function whose liver function was expected to deteriorate if TACE was performed, TACI using an EML emulsion was an acceptable alternative.

Epirubicin and doxorubicin are anthracycline-based anticancer drugs (18). Both drugs have been conventionally used in TACE or TACI for the treatment of patients with HCC (18). Since epirubicin can easily undergo glucuronidation, it is less toxic than doxorubicin (18). Furthermore, TACE or TACI using cisplatin may cause renal dysfunction or a hypersensitivity reaction, and TACE or TACI using zinostatin stimalamer causes severe vascular endothelial damage and loss of the hepatic artery for infusion (18,32). This is the reason why we have routinely used an epirubicin containing regimen in transcatheter arterial chemotherapy for HCC.

In our multivariate analysis, Child-Pugh classification, tumor number and DCP value were revealed as being significant predictors linked to OS. As mentioned earlier, Takayasu *et al* (12) conducted a large nationwide prospective cohort study in 8,610 HCC patients treated with TACE. Their multivariate analysis revealed that the degree of liver damage, tumor marker, maximum tumor size, tumor number and portal vein invasion were significantly associated with OS (12); our results were consistent with those reported in that study. Preserving liver function in HCC patients treated with transcatheter arterial therapies may be one of the key factors for optimizing clinical outcome (33). However, it is of interest that objective tumor response after initial therapy was not a significant predictor linked to OS in the present study. Even if treatment response after initial therapy was poor, performance of the most appropriate therapy at disease progression may be associated with favorable clinical outcomes.

In the present study, molecular targeted therapies were performed (sorafenib was approved for its use in 2009 in Japan) in 14 patients (9.7%) in the TACE group and in 3 patients (3.7%) in the TACI group. In practice, the point at which transcatheter arterial therapies should be replaced by targeted molecular therapy in patients with HCC refractory to transcatheter arterial therapies is a critical issue (34). We did not examine this issue in the present study; future studies will therefore be required.

In this study, TACE or TACI-related mortality was 0% in both groups. TACE-related mortality has been reported to range from 0.5 to 7% (12,35,36). Relative to these other studies, our transcatheter arterial therapy procedure was safe.

The present study had several limitations. First, it was a retrospective study. Second, the choice of TACE or TACI in the treatment of HCC was mainly based on the decision of the attending physicians, leading to bias. Third, patient characteristics in the two groups were not well balanced for analysis, also leading to bias. Future prospective studies with well-balanced cohorts are, therefore, required to overcome these limitations. However, our results demonstrated that patients in the TACI group had a similar prognosis to patients in the TACE group. In conclusion, TACI using an EML emulsion can be considered as one of the therapeutic options for the treatment of intermediate-stage HCC.

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Comparison of standard-dose and half-dose sorafenib therapy on clinical outcome in patients with unresectable hepatocellular carcinoma in field practice: A propensity score matching analysis

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Abstract. The aims of the present study were to examine whether unresectable hepatocellular carcinoma (HCC) patients treated with initial dose of sorafenib of 400 mg/day (half-dose group) had comparable treatment efficacy, safety and survival merit as compared with those treated with initial dose of sorafenib of 800 mg/day (standard-dose group) in a multicenter large study. For reducing the bias in patient selection, we compared clinical outcomes of these two groups using propensity score matching analysis. A total of 465 patients were treated with sorafenib at fourteen hospitals in Japanese Red Cross Liver Study Group from 2008 to 2013. After propensity score matching, 139 matched HCC patients were selected for analysis in both groups. We retrospectively compared overall survival (OS), progression-free survival (PFS), best treatment response and sorafenib related serious adverse events (SAEs) in the two groups. There were no relevant differences in terms of OS (median OS intervals: 9.2 months in the standard-dose group and 9.7 months in the half-dose group, P=0.350), PFS (median PFS intervals: 3.4 months in the standard-dose group and 3.2 months in the half-dose group, P=0.729) and best treatment efficacy (objective response rate: P=0.416; disease control rate: P=0.719). Grade 3 or more SAEs were observed in 37 patients (26.6%) in the standard-dose group and 33 patients (23.7%) in the half-dose group (P=0.580). Furthermore, in all subgroup analyses according to Child-Pugh classification and Barcelona Clinic Liver Cancer stage, there were no significant differences in the two groups. In conclusion, unresectable HCC patients treated with initial half-dose sorafenib had comparable prognosis compared with those treated with initial standard-dose sorafenib.

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Key words: hepatocellular carcinoma, sorafenib, standard dose, half dose, clinical outcomes

Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related mortality worldwide in terms of incidence with 626,000 new cases per year, accounting for 5.7% of all new cancer cases (1-5). Annual incidence rates of HCC are highest in Sub-Saharan Africa and East Asia, where ~85% of all cases occur (1-5). The vast majority of HCC cases occur in the context of hepatitis virus or alcohol related chronic liver disease and consequently many patients with HCC present with liver dysfunction and experience a high rate of comorbidity (1-5). Thus, HCC is a heterogeneous disease with regard to etiology as well as clinical presentation, presenting challenges for disease management. The therapies of HCC have significantly changed in the last few decades (1,2,5). With these changes and advances in medical technology such as diagnostic imaging and surveillance programs for detecting earlier stage HCC, survival in patients with HCC has markedly improved (4,5). However, unfortunately, <20% of HCC patients are amenable to curative therapy such as liver transplantation, surgical resection or ablative therapies. Furthermore, HCC

often recurs even after curative therapy and survival in HCC patients with advanced stage remains poor (5,6).

Sorafenib is a multi-kinase inhibitor that blocks tumor growth and cell proliferation (7,8). Although systemic chemotherapy such as doxorubicin was not demonstrated to be effective for the treatment of advanced HCC for several decades, two randomized phase III studies, namely the Sorafenib HCC Assessment Randomised Protocol (SHARP) study and the Asian Pacific study, showed that sorafenib therapy obtained survival benefit over placebo group for patients with unresectable HCC, and molecular targeted therapy with sorafenib is currently approved for use as first-line systemic chemotherapy in these patients (7,8). Furthermore, results with regard to the treatment efficacy and safety of sorafenib therapy for HCC in clinical practice were demonstrated by several field practice experiences, including the SOraFenib Italian Assessment (SOFIA) study and the Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib (GIDEON) study (9-12). However, to the best of our knowledge, few studies compared the clinical outcomes and safety between different initial doses of sorafenib administered to HCC patients (10,13). In Japan, the investigations for optimal initial dose of sorafenib for unresectable HCC are still underway, although two pivotal studies recommended initial dose of sorafenib of 800 mg/day (7,8).

The aims of the present study were thus to examine whether HCC patients treated with initial dose of sorafenib of 400 mg/day (half-dose) had comparable treatment efficacy, safety and survival merit as compared with those treated with initial dose of sorafenib of 800 mg/day (standard-dose) in a multicenter large study. For reducing the bias in patient selection, we compared clinical outcomes of these two groups using propensity score matching analysis.

Patients and methods

Patients. A total of 465 consecutive HCC patients have been treated with sorafenib at fourteen hospitals in Japanese Red Cross Liver Study Group from January 2008 to July 2013. Sorafenib therapy was indicated in patients with unresectable HCC determined by dynamic computed tomography (CT); i) existence of extrahepatic metastases; or ii) refractory to previous HCC therapies such as transcatheter arterial chemoembolization (TACE); or iii) unsuitability for TACE for anatomical reasons; or iv) vascular invasion such as tumor thrombus in the portal vein (14-16). Patients with a performance status (PS) of 3 or 4 according to the Eastern Cooperative Oncology Group (ECOG) classification were excluded (14,15). Since the aim of the current analysis was to compare clinical outcomes of HCC patients treated with initial dose of sorafenib of 800 mg/day and those treated with initial dose of sorafenib of 400 mg/day, patients treated with initial dose of sorafenib of 600 or 200 mg/day (n=22) were excluded from the current analysis. Patients with Barcelona Clinic Liver Cancer (BCLC)-A or D (n=6) were also excluded. Thus, a total of 437 patients (n=184 in the standard-dose group and n=254 in the half-dose group) were analysed in the present study (Fig. 1). We retrospectively compared overall survival (OS), progression-free survival (PFS), treatment response and sorafenib related adverse events in the two groups.

The present study comprised a retrospective analysis of patient records and all treatments were conducted in an open-label manner. The ethics committees of all facilities that participated in this study approved the present study protocol and this study protocol complied with all of the provisions of the Declaration of Helsinki.

HCC diagnosis and sorafenib therapy. HCC was diagnosed as described previously (14,15). Briefly, dynamic CT or magnetic resonance imaging of the liver was undertaken prior to sorafenib therapy in all analysed patients. In some patients who presented with atypical liver tumors, we conducted ultrasound-guided tumor biopsy. HCC was diagnosed by radiological or histological method according to European Association for the Study of Liver guideline (17).

As for initial dose of sorafenib, for patients with no risk factors, we introduced the recommended initial dose 400 mg twice a day of sorafenib (800 mg/day). The initial dose was reduced according to factors such as body weight, age, ECOG-PS and liver function. During sorafenib treatment, each attending physician decided to reduce daily dose of sorafenib according to the grades of adverse events or ECOG-PS. In patients treated with half-dose sorafenib with good tolerance, dose escalation of sorafenib was allowed. Temporary interruption was maintained until the symptoms resolved to grade 1 or 2. We assessed the treatment response of sorafenib every 4-8 weeks after the initiation of sorafenib therapy by modified Response Evaluation Criteria in Solid Tumors (mRECIST) and/or tumor markers (14,15,18,19). Sorafenib therapy continued until disease progression, unacceptable drug-related toxicity, or the patient's wish to discontinue treatment. After discontinuation of sorafenib therapy for any reason, any other therapies such as TACE or systemic chemotherapy were permitted according to the tumor status or the general status of each patient (14,15).

Evaluation of treatment efficacy. Best treatment efficacy of sorafenib during treatment was assessed in accordance with the mRECIST criteria and/or tumor marker levels as mentioned above (14,15,18). The treatment efficacy was classified as: i) complete response (CR), ii) partial response (PR), iii) stable disease (SD) and progressive disease (PD). CR was defined as disappearance of any arterial enhancement within all target tumors. PR was defined as ≥30% decrease in tumor size as determined by evaluation of the sum of the diameters of the target tumors, whose size was estimated using unidirectional measurement. PD was defined as ≥20% increase in tumor size as determined by evaluation of the sum of the maximal dimensions of the target tumors. SD was defined as the absence of either PR or PD (15,18). The objective response rate (ORR) was defined as the percentage of patients who had a best response rate of CR and PR. The disease control rate (DCR) was defined as the percentage of patients who had a best response rate of CR, PR and SD.

Safety evaluation of sorafenib therapy. Sorafenib related toxicities, including hand foot skin reaction (HFSR), rash, diarrhea, hypertention, fatigue, liver injury, gastrointestinal bleeding and lung injury were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

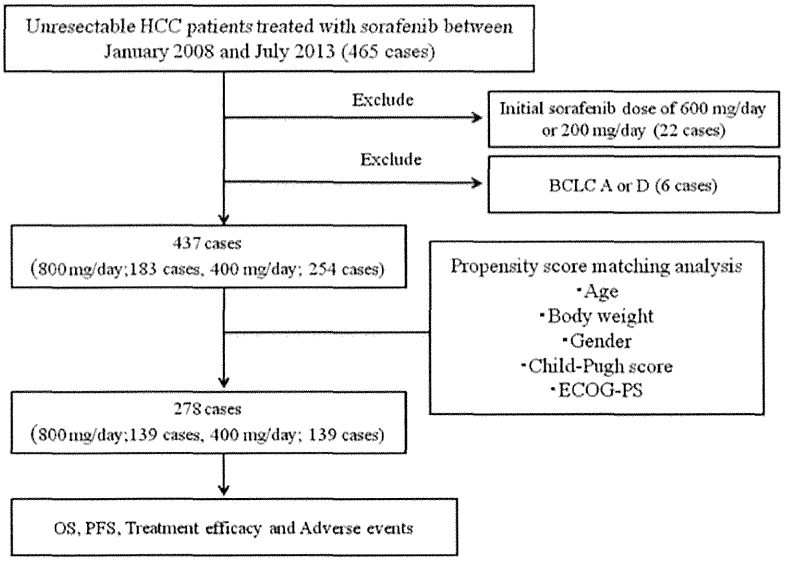

Figure 1. Study design. HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; PFS, progression-free survival.

Table I. Baseline characteristics between patients treated with initial dose of sorafenib of 800 mg/day (standard-dose group) and those treated with initial dose of sorafenib of 400 mg/day (half-dose group) before propensity score matching.

	Standard-dose group (800 mg/day, N=183)	Half-dose group (400 mg/day, N=254)	P-value
Age (years)	67.2±9.9	71.7±10.2	<0.001[a]
Gender, male/female	156/27	200/54	0.104[b]
Height (cm)	162.4±8.2	159.2±16.7	0.020[a]
Body weight (kg)	60.8±12.1	57.8±12.1	0.012[a]
Cause of liver disease			
B/C/B and C/non-B and non-C	43/96/1/43	24/155/4/71	0.001[b]
HCC stage, II/III/IV	4/69/110	15/89/150	0.168[b]
ECOG PS, 0/1/2	143/36/4	190/55/9	0.626b
Child-Pugh score, 5/6/7/8/9	84/76/21/2/0	87/111/32/22/2	0.002[b]
Serum albumin (g/dl)	3.59±0.48	3.49±0.52	0.043[a]
Total bilirubin (mg/dl)	0.89±0.43	0.94±0.51	0.230[a]
AST (IU/l)	65.9±64.9	68.0±64.1	0.740[a]
ALT (IU/l)	53.2±43.1	44.1±37.6	0.019[a]
Cholinesterase (IU/l)	176.8±70.6	157.8±71.1	0.010[a]
AFP (ng/ml)	5,491±18,113	18,973±108,883	0.054[a]
DCP (mAU/ml)	11,347±38,474	23,672±130,183	0.155[a]
BCLC stage, B/C	64/119	93/161	0.762[b]

Data are expressed as number or mean ± standard deviation. B, hepatitis B virus; C, hepatitis C virus; HCC, hepatocellular carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; BCLC, Barcelona Clinic Liver Cancer. [a]Unpaired t-test; [b]Fisher's exact test.

Statistical analyses. Categorical variables were analyzed by Fisher's exact test. Continuous variables were analyzed by unpaired t-test. OS curves were generated using the Kaplan-Meier method and compared using the log-rank test. OS was calculated from the initial date of sorafenib therapy until death from any cause or the last follow-up. PFS was calculated from the initial date of sorafenib treatment until the date of progression disease or death from any cause (14,15). Data were analyzed using SPSS (Chicago, IL, USA). Two-tailed probability values of $P<0.05$ were considered significant.

Table II. Baseline characteristics between patients treated with initial dose of sorafenib of 800 mg/day (standard-dose group) and those treated with initial dose of sorafenib of 400 mg/day (half-dose group) after propensity score matching.

	Standard-dose group (800 mg/day, N=139)	Half-dose group (400mg/day, N=139)	P-value
Age (years)	70.0±8.5	70.1±9.1	0.903[a]
Gender, male/female	114/25	111/28	0.760[b]
Height (cm)	161.4±8.3	159.7±21.0	0.362[a]
Body weight (kg)	60.1±12.1	59.1±14.0	0.528[a]
Cause of liver disease B/C/B and C/non-B and non-C	28/76/1/34	16/75/2/46	0.121[b]
HCC stage, II/III/IV	4/58/77	7/49/83	0.438[b]
ECOG PS, 0/1/2	107/30/2	106/29/4	0.803[b]
Child-Pugh score, 5/6/7/8	58/60/19/2	59/66/11/3	0.445[b]
Serum albumin (g/dl)	3.56±0.48	3.59±0.48	0.616[a]
Total bilirubin (mg/dl)	0.88±0.43	0.91±0.51	0.551[a]
AST (IU/l)	58.2±32.3	65.9±62.2	0.198[a]
ALT (IU/l)	46.5±32.0	44.9±36.2	0.695[a]
Cholinesterase (IU/l)	171±71.6	167±73.0	0.703[a]
AFP (ng/dl)	3,593±10,551	10,384±37,885	0.043[a]
DCP (mAU/ml)	8,851±33,057	20,797±96,248	0.168[a]
BCLC stage, B/C	53/86	51/88	0.901[b]

Data are expressed as number or mean ± standard deviation. B, hepatitis B virus; C, hepatitis C virus; HCC, hepatocellular carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; BCLC, Barcelona Clinic Liver Cancer. [a]Unpaired t-test; [b]Fisher's exact test.

Propensity score analysis. For reducing the bias in patient selection, a propensity score matching analysis was performed to examine causal relationships between initial dose of sorafenib (800 or 400 mg/day) and clinical outcomes in a retrospective study other than a randomized controlled trial (RCT). Clinical variables entered into the propensity model were age, body weight, gender, Child-Pugh score and ECOG-PS, which indicated variables we frequently take into account in daily clinical practice when we decide initial dose of sorafenib (20). Subsequently, a one-to-one match between the standard-dose group (800 mg/day of sorafenib) and the half-dose group (400 mg/day of sorafenib) was obtained by using the nearest-neighbor matching method (21,22).

Results

Baseline characteristics before propensity score matching. Baseline characteristics in the standard-dose group (n=183) and the half-dose group (n=254) prior to sorafenib therapy before propensity score matching are demonstrated in Table I. There were no relevant differences among two groups with respect to gender (P=0.104), HCC stage (P=0.168), BCLC stage (P=0.762), ECOG-PS (P=0.626), total bilirubin (P=0.230), aspartate aminotransferase (P=0.740), α-fetoprotein (AFP) (P=0.054) and des-γ-carboxy prothrombin (P=0.155), whereas in terms of age (P<0.001), height (P=0.020), body weight (P=0.012), cause of liver disease (P=0.001), Child-Pugh score (P=0.002), serum albumin (P=0.043), alanine aminotransferase (P=0.019) and cholinesterase (P=0.010), significant differences were found in the two groups. The most frequently performed previous therapy for HCC was TACE in both groups.

Comparison of OS and PFS rates in the two groups before propensity score matching. The median follow-up periods after sorafenib therapy before propensity score matching were 6.9 months (range, 0.5-46.2 months) in the standard-dose group and 7.9 months (range, 0.3-41.4 months) in the half-dose group. The median OS intervals were 8.8 months [95% confidence interval (CI), 6.9-10.7 months] in the standard-dose group and 9.4 months (95% CI, 7.6-11.1 months) in the half-dose group (P=0.913) (Fig. 2). The median PFS intervals were 3.4 months (95% CI, 3.0-3.7 months) in the standard-dose group and 3.3 months (95% CI, 2.9-3.7 months) in the half-dose group (P=0.875) (Fig. 3).

Baseline characteristics, OS and PFS after propensity score matching. Baseline characteristics in the two groups prior to sorafenib therapy after propensity score matching (139 pairs) are shown in Table II. The median follow-up periods after propensity score matching were 7.1 months (range, 0.5-46.2 months) in the standard-dose group and 9.0 months (range, 0.7-41.4 months) in the half-dose group. In baseline characteristics, there were no relevant differences among two groups except for AFP-value (P=0.043). The median OS intervals were 9.2 months (95% CI, 7.3-11.0 months) in the

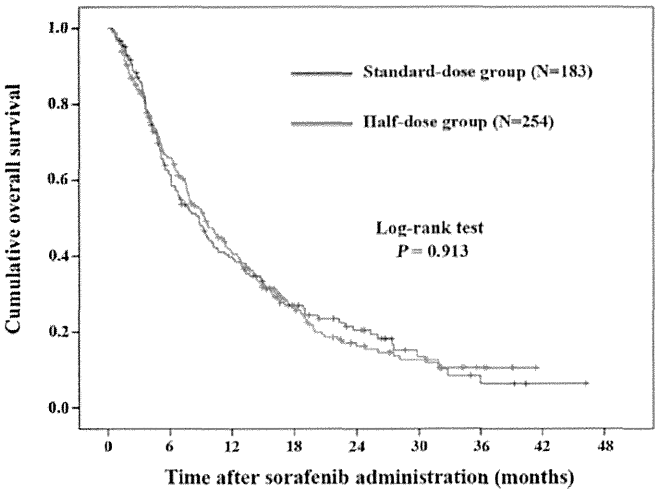

Figure 2. Cumulative overall survival (OS) in the standard-dose group (n=183) and the half-dose group (n=254) before propensity score matching. The median OS intervals were 8.8 months [95% confidence interval (CI)], 6.9-10.7 months) in the standard-dose group and 9.4 months (95% CI, 7.6-11.1 months) in the half-dose group (P=0.913).

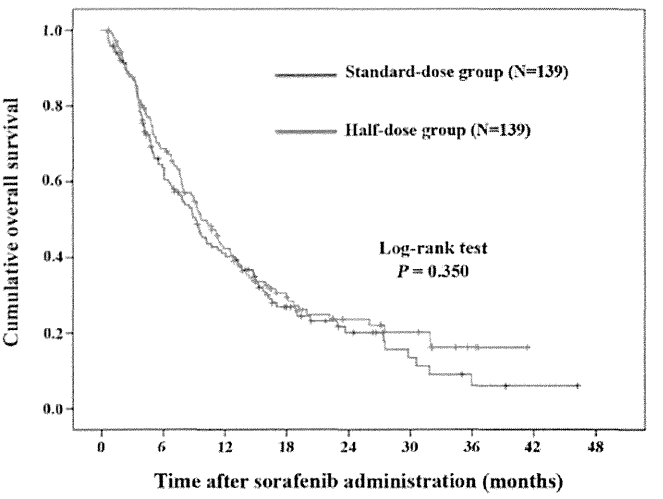

Figure 4. Cumulative overall survival (OS) in the standard-dose group (n=139) and the half-dose group (n=139) after propensity score matching. The median OS intervals were 9.2 months (95% CI, 7.3-11.0 months) in the standard-dose group and 9.7 months (95% CI, 7.8-11.7 months) in the half-dose group (P=0.350).

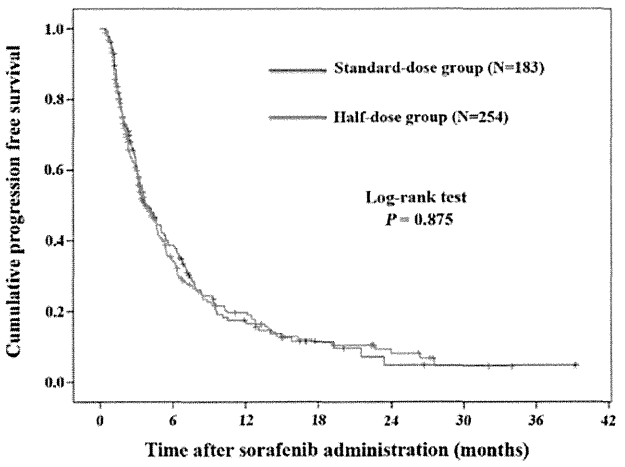

Figure 3. Cumulative progression-free survival (PFS) in the standard-dose group (n=183) and the half-dose group (n=254) before propensity score matching. The median PFS intervals were 3.4 months (95% CI, 3.0-3.7 months) in the standard-dose group and 3.3 months (95% CI, 2.9-3.7 months) in the half-dose group (P=0.875).

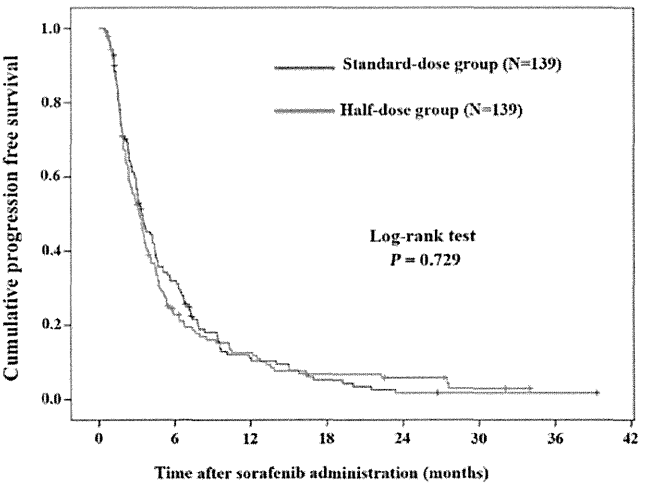

Figure 5. Cumulative progression-free survival (PFS) in the standard-dose group (n=139) and the half-dose group (n=139) after propensity score matching. The median PFS intervals were 3.4 months (95% CI, 2.6-4.2 months) in the standard-dose group and 3.2 months (95% CI, 2.5-3.9 months) in the half-dose group (P=0.729).

standard-dose group and 9.7 months (95% CI, 7.8-11.7 months) in the half-dose group (P=0.350) (Fig. 4). The median PFS intervals were 3.4 months (95% CI, 2.6-4.2 months) in the standard-dose group and 3.2 months (95% CI, 2.5-3.9 months) in the half-dose group (P=0.729) (Fig. 5).

Treatment duration, treatment discontinuation rate and dose reduction or escalation rate in the two groups after propensity score matching. In the standard-dose group, the median treatment duration period of sorafenib after propensity score matching was 3.1 months (range, 0.1-39.3 months). Sorafenib treatment was discontinued in 127 patients (91.4%) and sorafenib dose was reduced in 85 patients (61.2%) the sorafenib dose was not escalated in any patient during the follow-up period. The mean administered sorafenib dose per day was 628 mg (missing data for some patients). In the half-dose group, the median treatment duration period of sorafenib after propensity score matching was 3.9 months (range, 0.1-32.1 months). Sorafenib treatment was discontinued in 121 patients (87.1%) and sorafenib dose was reduced in 44 patients (31.7%) and sorafenib dose was escalated in 36 patients (25.9%) during follow-up period. The mean administered sorafenib dose per day was 395 mg (missing data for some patients). Most patients in the two groups discontinued sorafenib therapy due to progressive disease or sorafenib related SAEs.

Cause of death in the two groups after propensity score matching. During follow-up period, 101 patients (72.7%) in the standard-dose group died. The causes of death in the standard-dose group were HCC progression in 73 patients, liver failure

Table III. Sorafenib related adverse events in the standard-dose group and the half-dose group after propensity score matching.

	Standard-dose group (N=139)		Half-dose group (N=139)		P-value[a]	
	Any grade n (%)	Grade 3 or more n (%)	Any grade n (%)	Grade 3 or more n (%)	Any grade	Grade 3 or more
Overall	127 (91.4)	37 (26.6)	127 (91.4)	33 (23.7)	>0.999	0.580
HFSR	77 (55.4)	8 (5.8)	62 (44.6)	7 (5.0)	0.092	>0.999
Rash	27 (19.4)	7 (5.0)	24 (17.3)	6 (4.3)	0.757	>0.999
Diarrhea	43 (30.9)	2 (1.4)	44 (31.7)	1 (0.7)	>0.999	>0.999
Hypertension	26 (18.7)	2 (1.4)	19 (13.7)	3 (2.2)	0.328	>0.999
Fatigue	69 (49.6)	5 (3.4)	69 (49.6)	4 (2.9)	>0.999	>0.999
Liver injury	60 (43.2)	15 (10.8)	61 (43.9)	16 (11.5)	>0.999	>0.999
Gastrointestinal bleeding	9 (6.5)	3 (2.2)	5 (3.4)	0 (0.0)	0.206	0.247
Lung injury	4 (2.9)	3 (2.2)	8 (5.8)	3 (2.2)	0.255	>0.999

HFSR, hand foot skin reaction. [a]Fisher's exact test.

in 16, sorafenib related SAEs in 2 and miscellaneous causes in 10. On the other hand, 98 patients (70.5%) in the half-dose group died during follow-up period. The causes of death in the half-dose group were HCC progression in 81 patients, liver failure in 10 and miscellaneous causes in 7.

Best tumor response in the two groups after propensity score matching. In the standard-dose group, regarding the best tumor response, CR was obtained in 2, PR in 23, SD in 45, PD in 44 and not evaluated (NE) in 25. Thus, ORR was 18.0% (25/139) and DCR was 50.4% (70/139) in the standard-dose group. In the half-dose group, regarding best tumor response, CR was obtained in 2, PR in 18, SD in 54, PD in 45 and NE in 20. Thus, ORR was 14.4% (20/139) and DCR was 53.2% (74/139) in the half-dose group. There was no relevant difference in the two groups in terms of best treatment efficacy (ORR: P=0.416, DCR: P=0.719).

Serious adverse events (SAEs) after propensity score matching. Any grade SAEs as defined by CTCAE were found in 127 patients (91.4%) in the standard-dose group and 127 patients (91.4%) in the half-dose group (P>0.999). The most frequently observed SAE (any grade) was HFSR (55.4%) in the standard-dose group and fatigue (49.6%) in the half-dose group. On the other hand, grade 3 or more SAEs as defined by CTCAE were observed in 37 patients (26.6%) in the standard-dose group and 33 patients (23.7%) in the half-dose group (P=0.580). The most frequently observed SAE (grade 3 or more) was liver injury (10.8%) in the standard-dose group and liver injury (11.5%) in the half-dose group (Table III).

Subgroup analyses according to BCLC stage and Child-Pugh classification after propensity score matching. We also performed subgroup analyses according to BCLC stage and Child-Pugh classification after propensity score matching as these variables are well known prognostic factors in HCC patients.

In patients with BCLC-B HCC (n=53 in the standard-dose group and n=51 in the half-dose group), the median survival times (MSTs) (95% CIs) were 13.3 months (9.1-17.6 months) in the standard-dose group and 14.7 months (10.6-18.7 months) in the half-dose group (P=0.522), whereas in patients with BCLC-C HCC (n=86 in the standard-dose group and n=88 in the half-dose group), the MSTs (95% CIs) were 6.5 months (4.1-8.9 months) in the standard-dose group and 7.8 months (5.8-9.8 months) in the half-dose group (P=0.418).

In patients with Child-Pugh A HCC (n=118 in the standard-dose group and n=125 in the half-dose group), the MSTs (95% CIs) were 10.7 months (6.9-14.4 months) in the standard-dose group and 10.4 months (8.3-12.5 months) in the half-dose group (P=0.910), while in patients with Child-Pugh B HCC (n=21 in the standard-dose group and n=14 in the half-dose group), the MSTs (95% CIs) were 4.2 months (3.0-5.3 months) in the standard-dose group and 5.1 months (2.4-7.9 months) in the half-dose group (P=0.058), indicating that there was trend for better survival in HCC patients with Child-Pugh B treated with initial sorafenib dose of 400 mg/day.

Discussion

There have been few studies comparing the clinical outcome and safety between different initial doses of sorafenib administered to HCC patients (10,13). HCC patients enrolled in RCTs do not necessarily represent the field practice owing to the absence of potential confounding factors such as comorbid diseases. In addition, the results of clinical studies of sorafenib therapy for HCC performed in Japan revealed that >80% of enrolled patients treated with initial standard-dose sorafenib (800 mg/day) required dose reduction (23). Thus, there is urgent need for investigating the usefulness of initial reduced dose of sorafenib therapy in HCC patients in field practice. Hence, we aimed to conduct this multicenter comparative study using propensity score matching analysis for reducing selection biases. The major strengths of the

current analyses were the large sample size (n=278 after propensity score matching), the consecutive enrollment of Japanese HCC patients with broad eligibility criteria reflecting the diversity and complexity of our field practice for HCC and the involvement of 14 centers with well-referenced expertise in HCC diagnosis and treatment for HCC.

In the present study, there were no significant differences in terms of OS, PFS, best treatment response and SAEs in the standard-dose and the half-dose groups after propensity score matching or in the subgroup analyses after propensity score matching, no significant difference was observed in the two groups. Our results suggest that initial half-dose sorafenib therapy for HCC can be a treatment option for some patients. While the interim analysis in the GIDEON study demonstrated a trend toward more evident clinical benefits for initial standard-dose sorafenib as compared with the initial half-dose sorafenib and patients who initiated standard-dose sorafenib tended to discontinue treatment later than patients who initiated half-dose sorafenib (12.3 vs. 9.7 weeks) and present a longer OS (9.3 vs. 7.1 months) and time to progression (4.5 vs. 3.6 months) (10,11,24). On the other hand, a recent comparative study reported from Japan showed that using propensity score matching, HCC patients treated with the initial half-dose sorafenib therapy (n=58) led to a comparable survival benefit compared with those treated with the standard-dose sorafenib therapy (n=58), which are in line with our present study results (13). Furthermore, the results in the SOFIA study confirmed the safety and treatment effectiveness of sorafenib in a real-life clinical setting even with a reduced dose (9). The authors in the SOFIA study demonstrated that the median OS was 10.5 months in the overall cohort (n=296) [8.4 months in BCLC-C vs. 20.6 months in BCLC-B patients (P<0.0001)], and 21.6 months in the 77 patients treated for ≥70% of the time with a half-dose sorafenib vs. 9.6 months in the 219 patients with standard-dose sorafenib or half-dose sorafenib <70% treatment period (P=0.0006) (9). The discrepancies for these study results may be attributed to different baseline characteristics such as race, age, body weight, extension of liver disease and background liver disease in these studies (1,2,4,5,25,26). For instance, the mean age in our current analysis was ~70 years, while that in the GIDEON study was 62 years (several Japanese HCC patients were included in the GIDEON study), which is 8 years younger than our study population (10,11,24). Further well defined comparative studies will thus be needed in the future to confirm these results.

It is of note that in our subgroups analyses in patients with Child-Pugh B (n=21 in the standard-dose group and n=14 in the half-dose group), the median OS tended to be longer in the half-dose group than the standard-dose group (5.1 vs. 4.2 months, P=0.058) and the median duration of sorafenib therapy was 3.3 months in the half-dose group and 1.6 months in the standard-dose group (data not shown). Available evidence suggests that the safety profile of sorafenib therapy is comparable in HCC patients with Child-Pugh A and B, however, half-dose sorafenib therapy can be recommended in HCC patients with poor liver function of Child-Pugh B for avoiding treatment discontinuation due to SAEs considering our results of subgroup analyses (10,11).

In our analyses of sorafenib related SAEs, grade 3 or more sorafenib related SAEs in the standard-dose and half-dose groups were found in 37 patients (26.6%) and 33 patients (23.7%), whereas in the GIDEON study, grade 3 or more sorafenib related SAEs in the standard-dose and half-dose groups were found in 274 out of 1,161 patients (24%) and 84 out of 347 patients (24%), which are similar to our results (11). On the other hand, in the present study, sorafenib treatment was discontinued in 127 patients (91.4%) in the standard-dose group and 121 patients (87.1%) in the half-dose group, which are higher than the discontinuation rate of sorafenib in the SHARP study [226 out of 297 patients (sorafenib arm), 76.9%] (7). The higher prevalence of patients with Child-Pugh B in this study (15.1% in the standard-dose group and 10.1% in the half-dose group) compared with that in the SHARP study (5%, sorafenib arm) could in part account for high rates of treatment discontinuation of our present study (7).

In our propensity score matching, clinical variables including age, body weight, gender, Child-Pugh score and ECOG-PS were entered. All these variables are key factors when deciding initial dose of sorafenib in field practice. After propensity score matching, the distributions of all confounding factors except for AFP-value in the two groups were well balanced for statistical analyses and we believe that this difference in the two groups after propensity score matching did not affect for interpreting our study results.

Our study included several limitations. Firstly, this is a retrospective study although propensity score matching analysis for reducing selection biases was performed. Secondly, various therapies for HCC were performed after discontinuation of sorafenib, potentially leading to bias for evaluating OS. Thirdly, in this study, dose adjustment of sorafenib during treatment was decided mainly based on the decision of each attending physician, also leading to bias. Fourthly, our study cohort included only Japanese HCC patients, who in general had lower body weight than populations in Western countries (25,26). Hence, caution should be exercised for interpreting our results. However, our study results demonstrated that HCC patients treated with half-dose sorafenib had comparable clinical outcomes compared with those treated with standard-dose sorafenib. In conclusion, reduced initial dose of sorafenib may not affect clinical outcomes for patients with unresectable HCC especially in Japanese HCC patients with relatively lower body weight.

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Clinical implication of the preoperative GSA index in ^{99m}Tc-GSA scintigraphy in hepatitis C virus-related hepatocellular carcinoma

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Abstract. We aimed to examine the relationship between the preoperative GSA index [uptake ratio of the liver to the liver plus heart at 15 min (LHL15) to uptake ratio of the heart at 15 min to that at 3 min (HH15) ratio] calculated from ^{99m}Tc-labeled diethylene triamine pentaacetate-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy and background liver fibrosis and to investigate whether the GSA index can be a useful predictor in hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) patients treated with surgical resection (SR). A total of 213 HCV-related HCC patients were analyzed. Receiver operating characteristic (ROC) curve analysis was performed for calculating the area under the ROC (AUROC) for nine noninvasive parameters including GSA index, indocyanine green retention at 15 min, aspartate aminotransferase (AST) to platelet ratio index, FIB-4 index, AST to alanine aminotransferase ratio, serum albumin, total bilirubin, platelet count and prothrombin time for cirrhosis. We also examined predictive factors associated with overall survival (OS) and recurrence-free survival (RFS) after SR in univariate and multivariate analyses. There were 153 males and 60 females with the mean age of 69.9 years. The median observation periods were 2.8 years. The mean maximum tumor size was 4.1 cm. HH15 ranged from 0.452 to 0.897. LHL15 ranged from 0.669 to 0.982. The mean value of the GSA index was 1.41. Among the nine parameters, the GSA index yielded the highest AUROC for cirrhosis with a level of 0.786 at an optimal cut-off value of 1.37 (sensitivity, 65.9%; specificity, 79.0%). In multivariate analyses, the GSA index was an independent predictor (P<0.001) linked to RFS and it had a marginal significance in terms of OS (P=0.074). In conclusion, the preoperative GSA index can be a useful predictor in HCV-related HCC patients treated with SR.

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Key words: hepatocellular carcinoma, HCV, surgical resection, ^{99m}Tc-GSA scintigraphy, GSA index, diagnostic accuracy, prognostic factor

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer-related death (1-3). In Japan, most HCC cases are due to chronic hepatitis C virus (HCV) infection (3). Curative therapies for HCC consist of liver transplantation, surgical resection (SR) and radiofrequency ablation (RFA) (1-3). The clinical outcome of HCC patients undergoing these therapies has improved substantially in recent years due to treatment advances. However, HCC often recurs even after curative therapies, leading to high mortality, and the pattern of HCC recurrence is frequently ectopic as well as local. The identification of predictive factors and effective management of HCC recurrence are essential for improving survival, even after curative treatment (1-5).

^{99m}Tc-labeled diethylene triamine pentaacetate-galactosyl human serum albumin (^{99m}Tc-GSA) is a radiopharmaceutical that binds specifically to the hepatic asialoglycoprotein receptor (ASGP-R). Expression of ASGP-R has been reported to be decreased in patients with chronic liver damage and thus it has been widely used to assess liver functional reserve in various pathological and pharmacological states (6-8). In clinical field practice, receptor index (uptake ratio of the liver to the liver plus heart at 15 min; LHL15) and blood clearance index (uptake ratio of the heart at 15 min to that at 3 min; HH15) characteristics are frequently used for this purpose (6,7,9,10). On the other hand, indocyanine green retention at 15 min (ICG15) is an easy and convenient method for obtaining parameters to determine the appropriate and safe extent of liver resection (11). However, in patients with jaundice or when a porto-systemic shunt is present, the results of ICG15 are not reliable. In addition, discrepancies between ICG clearance and the extent of liver fibrosis are occasionally noted in such cases (8,12). ICG mainly reflected hepatic blood flow, while GSA was associated with both the amount of functional hepatocytes and blood flow (6,7,9-11).

Recently, Yoshizumi *et al* demonstrated the clinical significance of blood appearance corrected hepatic uptake ratio (LHL15 to HH15 ratio; GSA index) as an index of liver functional reserve in patients treated with living donor liver

transplantation (13). However, to the best of our knowledge, there have been no reports regarding GSA index on clinical outcome in HCV-related HCC patients treated with SR. Furthermore, although there has been a substantial drive to noninvasive assessment of liver fibrosis particularly for the grading of severity of chronic hepatitis C (CHC), the relationship between GSA index and the extent of liver fibrosis in patients with CHC is unclear. The aims of the present analysis were thus to examine the relationship between preoperative GSA index calculated from ^{99m}Tc-GSA scintigraphy and background liver fibrosis in non-tumor parts obtained from extracted surgical specimens and to investigate whether the preoperative GSA index can be a useful predictor in HCV-related HCC patients treated with SR.

Patients and methods

Patients. Between March 2004 and April 2014, a total of 213 treatment-naïve HCV-related HCC patients in whom preoperative ^{99m}Tc-GSA scintigraphy was performed received SR at our institution with curative intent and they were thus analyzed. Curative surgery was defined as resection of all tumors detectable using imaging modalities. HCV-related HCC was defined as HCC positive for HCV antibody and negative for hepatitis B surface antigen. A diagnosis of diabetes mellitus was based on past medical history or 75-g oral glucose tolerance test results (14). We examined predictive factors associated with overall survival (OS) and recurrence-free survival (RFS) after SR in univariate and multivariate analyses.

Written informed consent was obtained from all patients prior to SR, and the study protocol complied with all of the provisions of the Declaration of Helsinki. The present study was approved by the Ethics Committee of Osaka Red Cross Hospital, Japan. The present study comprised a retrospective analysis of patient records registered in our database, and all treatments were conducted in an open-label manner.

^{99m}Tc-GSA scintigraphy and calculated scores. Three milligrams of Tc-GSA (185 MBq; Nihon Medi-Physics, Nishinomiya, Japan) was injected as a bolus into an antecubital vein. Dynamic imaging was performed in the supine position under a gamma camera with a large-field-of view. Digital images were acquired at a rate of 30 sec/frame. Static anterior abdominal images were obtained at 5, 10, 15, 20, 25 and 30 min after injection of Tc-GSA (15). LHL15 was calculated by dividing the radioactivity of the region of interest (ROI) of the liver by the radioactivity of the ROI of the liver and the heart 15 min after injection, and HH15 was calculated by dividing the radioactivity of the ROI of the heart 15 min after injection by that 3 min after injection (6). LHL15 to HH15 ratio (GSA index) was also calculated.

The aspartate aminotransferase (AST) to platelet ratio index (APRI) score was calculated using Wai's formula: (AST/upper limit of normal)/platelet count (expressed as platelets x 10^9/l) x 100 (16). The FIB-4 index was calculated using Sterling's formula as: age (years) x AST (IU/l)/platelet count (x10^9/l) x alanine aminotransferase (ALT) (IU/l)^{½} (17).

HCC diagnosis. HCC was diagnosed using abdominal ultrasound and dynamic CT scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase) and/or magnetic resonance imaging (MRI), based mainly on the recommendations of the American Association for the Study of Liver Diseases (18). Arterial- and portal-phase dynamic CT images were obtained at ~30 and 120 sec, respectively, after the injection of the contrast material. HCC stage was determined using the Liver Cancer Study Group of Japan staging system (19). All HCC was confirmed pathologically except for 19 cases with complete necrosis due to the preoperative transcatheter arterial chemoembolization (TACE).

Hepatectomy and surgical procedure. All surgical procedures were performed by one of four surgeons with at least 10 years experience of SR. Anatomical SR was defined as a resection in which tumors are completely removed anatomically on the basis of Couinaud's classification (segmentectomy, sectionectomy, and hemihepatectomy or extended hemihepatectomy). Non-anatomical partial SR was carried out as a limited resection or tumor enucleation. Anatomical SR was performed in 100 patients (46.9%) and non-anatomical SR was performed in 113 patients (53.1%) in the present study. Conventional open hepatectomy was performed in 166 patients (77.9%) and laparoscopic hepatectomy was performed in 47 patients (22.1%) in the present study.

Histological evaluation of extracted liver specimens. All extracted liver specimens were reviewed by a single pathologist in our hospital. Background liver fibrosis was staged as F0-F4: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and a few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. The degree of differentiation of HCC in each resected specimen was determined as well-differentiated HCC, moderately differentiated HCC, poorly differentiated HCC or combined type of HCC and cholangiocellular carcinoma (CCC) (20).

Follow-up. Follow-up after each therapy consisted of periodic blood tests and monitoring of tumor markers, including α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), using chemiluminescent enzyme immunoassays (Lumipulse PIVKAII Eisai, Eisai, Tokyo, Japan). Dynamic CT scans and/or MRI were obtained every 2-4 months after each therapy. Chest CT, whole abdominal CT, brain MRI, and bone scintigraphy were performed when extrahepatic HCC recurrence was suspected. When HCC recurred, the most appropriate therapy for HCC recurrence was performed considering tumor status, liver function or performance status of patients.

Statistical analysis. Data were analyzed using univariate and multivariate analyses. Continuous variables were compared between groups by the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed for calculating the area under the ROC (AUROC) for GSA index, ICG15, APRI, FIB-4 index, AST to ALT ratio, serum albumin, total bilirubin, platelet count and prothrombin time (PT) selecting the optimal cut-off value that maximized the sum of sensitivity and specificity for cirrhosis (F4). Time to recurrence was defined as the interval between initial therapy

Table I. Baseline characteristics of the patients with HCV-related hepatocellular carcinoma (N=213).

Variables	N=213
Age (years)	69.9±7.9
Gender, male/female	153/60
Body mass index (kg/m^2)	22.8±3.6
Diabetes mellitus, yes/no	47/166
HCC stage, I/II/III/IV	18/113/63/19
Maximum tumor size (cm)	4.1±2.3
Tumor number, single/multiple	123/90
AST (IU/l)	61.0±36.7
ALT (IU/l)	56.0±41.6
ALP (IU/l)	346.6±151.9
GGT (IU/l)	97.0±110.8
LHL15	0.898±0.058
HH15	0.657±0.094
GSA index	1.41±0.28
Serum albumin (g/dl)	3.8±0.5
Total bilirubin (mg/dl)	0.9±0.5
Prothrombin time (%)[a]	88.6±14.8
Platelets (x10^4/mm^3)	12.8±5.7
AFP (ng/ml)	2,180±11,580
DCP (mAU/ml)[b]	3,484±14,865
Histological findings (extracted surgical specimen)	
Background liver fibrosis, F4/3/2/1/0	132/34/19/27/1
Tumor-differentiation Well/moderate/poor/combined/necrosis	19/100/73/2/19

Data are expressed as number or mean ± standard deviation. HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; LHL15, uptake ratio of the liver to the liver plus heart at 15 min; HH15, uptake ratio of the heart at 15 min to that at 3 min; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; [a]missing data, n=1; [b]missing data, n=3. Combined means the combined type of HCC and cholangiocellular carcinoma. Necrosis means complete necrosis.

and first confirmed recurrence. For analysis of RFS, follow-up ended at the time of first recurrence; other patients were censored at their last follow-up visit or the time of death from any cause without recurrence. For analysis of OS, follow-up ended at the time of death from any cause, and the remaining patients were censored at the last follow-up visit. The cumulative OS and RFS rates were calculated using the Kaplan-Meier method, and tested using the log-rank test. Factors with a P-value <0.05 in univariate analysis were subjected to multivariate analysis using the Cox proportional hazards model. These statistical methods were used to estimate the interval from initial treatment. Data were analyzed using SPSS software (SPSS, Inc., Chicago, IL, USA) for Microsoft Windows. Data are expressed as means ± standard deviation (SD). Values of P<0.05 were considered to indicate a statistically significant result.

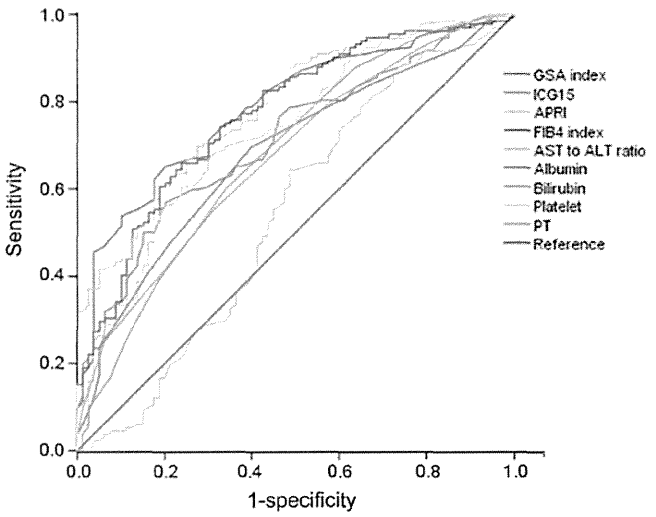

Figure 1. Correlation between GSA index and serum markers including indocyanine green retention at 15 min (ICG15), FIB-4 index, aspartate aminotransferase (AST) to platelet ratio index (APRI), AST to alanine aminotransferase (ALT) ratio, platelet count, serum albumin, total bilirubin and prothrombin time (PT) and cirrhosis (F4). GSA index yielded the highest AUROC with a level of 0.786 at an optimal cut-off value of 1.37 (sensitivity, 65.9%; specificity, 79.0%).

Results

Baseline characteristics. The baseline characteristics of the analyzed subjects (n=213) are shown in Table I. There were 153 males and 60 females with the mean (± SD) age of 69.9±7.9 years. The median observation periods were 2.8 years (range, 0.1-10.5 years). The mean maximum tumor size was 4.1±2.3 cm. HH15 ranged from 0.452 to 0.897. LHL15 ranged from 0.669 to 0.982. Thus, the mean value of the GSA index was 1.41±0.28. As for histological findings, in terms of the degree of liver fibrosis in the non-tumor portion, F4 was observed in 132 patients, F3 in 34, F2 in 19, F1 in 27 and F0 in 1, whereas in terms of HCC histology, well-differentiated HCC was observed in 19 patients, moderately differentiated HCC in 100, poorly differentiated HCC in 73, combined type of HCC and CCC in 2 and complete necrosis due to preoperative TACE in 19.

Comparison of area under receiver operating curves for GSA index and serum markers for cirrhosis. We evaluated the correlation between the GSA index and serum markers including ICG15, FIB-4 index, APRI, AST to ALT ratio, platelet count, serum albumin, total bilirubin and PT and cirrhosis (F4). Receiver operating curves of the serum markers used for predicting cirrhosis are demonstrated in Fig. 1. GSA index, ICG15, FIB-4 index, APRI and platelet count exhibited reliable discriminative ability for predicting cirrhosis. Among these, the GSA index yielded the highest AUROC with a level of 0.786 at an optimal cut-off value of 1.37 (sensitivity, 65.9%; specificity, 79.0%) (Table II). The GSA index in patients with cirrhosis (F4, n=132) was significantly lower than that in those with non-cirrhosis (F0-3, n=81) (P<0.001, Mann-Whitney U test) (Fig. 2). Between patients with F0 or 1 (n=28) and F4 (P<0.001), F2 (n=19) and F4 (P<0.001), F3 (n=34) and F4 (P<0.001), F0 or 1 and F2 (P=0.005) and F0 or 1 and F3

Table II. Comparison of the area under receiver operating curves (AUROCs) for the GSA index, ICG15, APRI, FIB-4 index, AST to ALT ratio, serum albumin, total bilirubin, platelet count and prothrombin time for cirrhosis.

Variables	AUROC	95% CI	P-value
GSA index	0.786	0.724-0.847	<0.001
ICG15	0.713	0.644-0.782	<0.001
APRI	0.761	0.693-0.828	<0.001
FIB-4 index	0.771	0.706-0.835	<0.001
AST to ALT ratio	0.542	0.458-0.627	0.304
Serum albumin	0.683	0.610-0.755	<0.001
Bilirubin	0.681	0.606-0.756	<0.001
Platelet	0.755	0.692-0.819	<0.001
Prothrombin time	0.676	0.603-0.749	<0.001

CI, confidence interval; ICG15, indocyanine green retention at 15 min; APRI, aspartate aminotransferase (AST) to platelet ratio index; ALT, alanine aminotransferase.

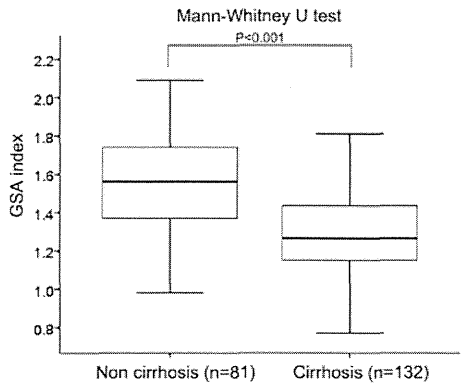

Figure 2. Box plots of the GSA index between patients with non-cirrhosis (F0-3) and those with cirrhosis (F4). The GSA index in patients with cirrhosis (n=132) was significantly lower than that in those with non-liver cirrhosis (n=81) (P<0.001, Mann-Whitney U test).

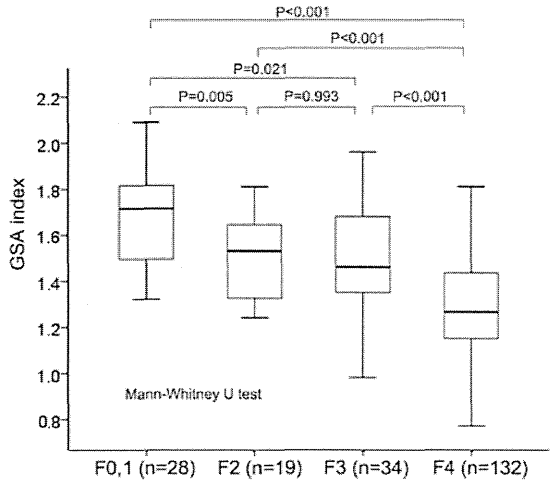

Figure 3. Box plots of the GSA index between patients with various stages of liver fibrosis [F0 or 1 (n=28), F2 (n=19), F3 (n=34) and F4 (n=132)]. GSA index had well discriminative ability between the various stages of liver fibrosis except for the relationship between F2 and F3.

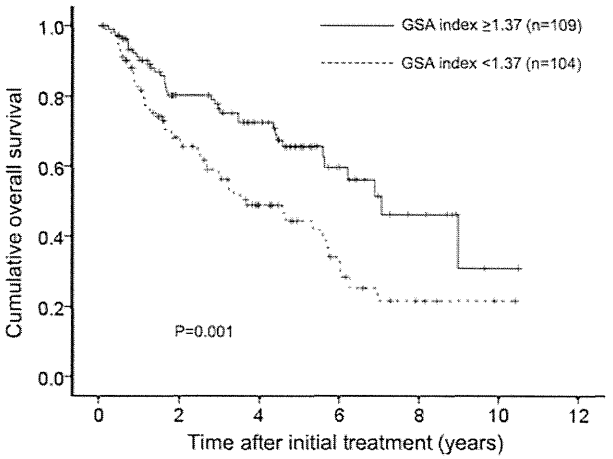

Figure 4. Cumulative overall survival (OS) rates according to the GSA index. The 1-, 3- and 5-year cumulative OS rates in patients with GSA index ≥1.37 (n=109) were 91.3, 76.5 and 65.6%, respectively, and the corresponding cumulative OS rates in patients with GSA index <1.37 (n=104) were 82.8, 57.6 and 44.5%, respectively (P=0.001).

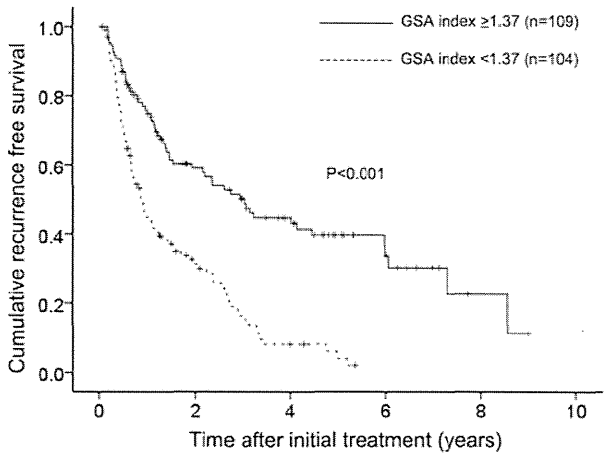

Figure 5. Cumulative recurrence-free survival (RFS) rates according to the GSA index. The 1-, 3- and 5-year cumulative RFS rates in patients with GSA index ≥1.37 (n=109) were 74.9, 50.2 and 39.7%, respectively, and the corresponding cumulative RFS rates in patients with GSA index <1.37 were 44.9, 16.3 and 4.1%, respectively (P<0.001).

(P=0.021), significant differences were observed in terms of the GSA index (Fig. 3).

Cumulative OS and RFS rates according to GSA index. The 1-, 3- and 5-year cumulative OS rates in patients with GSA index ≥1.37 (optimal cut-off value) (n=109) were 91.3, 76.5 and 65.6%, respectively, and the corresponding cumulative OS rates in patients with GSA index <1.37 (n=104) were 82.8, 57.6 and 44.5%, respectively (P=0.001) (Fig. 4). The 1-, 3- and 5-year cumulative RFS rates in patients with GSA index ≥1.37 were 74.9, 50.2 and 39.7%, respectively, and the corresponding cumulative RFS rates in patients with GSA index <1.37 were 44.9, 16.3 and 4.1%, respectively (P<0.001) (Fig. 5).

Univariate and multivariate analyses of factors contributing to OS. Univariate analysis identified the following factors

Table III. Univariate and multivariate analysis of factors contributing to overall survival.

Variables	n	Univariate analysis	Multivariate analysis	
			Hazard ratio (95% CI)	P-value[a]
Gender, male vs. female	153/60	0.639		
Age (years), ≥70 vs. <70	119/94	0.296		
Tumor number, single vs. multiple	123/90	0.001	0.715 (0.452-1.131)	0.152
Maximum tumor size (cm), ≥3.5 vs. <3.5	109/104	0.010	0.906 (0.554-1.483)	0.696
Microscopic vascular invasion, yes vs. no	72/141	0.020	0.660 (0.414-1.052)	0.081
AST (IU/l), ≥50 vs. <50	109/104	0.025	0.824 (0.523-1.300)	0.406
ALT (IU/l), ≥50 vs. <50	91/122	0.459		
ALP (IU/l), ≥320 vs. <320	109/104	0.008	0.906 (0.566-1.452)	0.683
GGT (IU/l), ≥70 vs. <70	104/109	0.482		
GSA index ≥1.37, yes vs. no	109/104	0.001	1.594 (0.957-2.658)	0.074
Serum albumin level (g/dl), ≥3.9 vs. <3.9	112/101	0.005	1.642 (0.996-2.705)	0.052
Total bilirubin (mg/dl), ≥1.0 vs. <1.0	67/146	0.002	0.647 (0.409-1.024)	0.063
Platelet count ($x10^4/mm^3$), ≥12 vs. <12	105/108	0.475		
Prothrombin time (%), ≥88 vs. <88[b]	105/107	0.113		
Diabetes mellitus, yes vs. no	47/166	0.475		
Body mass index (kg/m^2), ≥23 vs. <23	99/114	0.562		
Serum AFP (ng/ml), ≥100 vs. <100	62/151	<0.001	0.623 (0.385-1.007)	0.053
DCP (mAU/ml), ≥100 vs. <100[c]	129/81	0.001	0.451 (0.259-0.788)	0.005

CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ glutamyl transpeptidase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin. [a]Cox proportional hazard model; [b]missing data, n=1; [c]missing data, n=3.

as significantly associated with OS for all cases (n=213): tumor number (P=0.001); maximum tumor size ≥3.5 cm (P=0.010); microscopic vascular invasion (MVI) (P=0.020); AST ≥50 IU/l (P=0.025); alkaline phosphatase (ALP) ≥320 IU/l (P=0.008); GSA index ≥1.37 (P=0.001); serum albumin ≥3.9 g/dl (P=0.005); total bilirubin ≥1.0 mg/dl (P=0.002); AFP ≥100 ng/ml (P<0.001); and DCP ≥100 mAU/ml (P=0.001) (Table III). The hazard ratios (HRs) and 95% confidence intervals (CIs) calculated using multivariate analysis for the 10 factors with P<0.05 in univariate analysis are detailed in Table III. Only the DCP value was found to be a significant predictor linked to OS in the multivariate analysis (P=0.005).

Univariate and multivariate analyses of factors contributing to RFS. Univariate analysis identified the following factors as significantly associated with RFS for all cases: tumor number (P<0.001); MVI (P=0.002); AST ≥50 IU/l (P=0.010); ALP ≥320 IU/l (P=0.008); GSA index ≥1.37 (P<0.001); serum albumin ≥3.9 g/dl (P=0.016); total bilirubin ≥1.0 mg/dl (P=0.001); and PT ≥88% (P=0.023) (Table IV). The HRs and 95% CIs calculated using multivariate analysis for the eight factors with P<0.05 in univariate analysis are detailed in Table IV. Tumor number (P=0.002), MVI (P=0.002), ALP ≥320 IU/l (P=0.039) and GSA index (P<0.001) were found to be significant prognostic factors linked to RFS.

Causes of death. In patients with preoperative GSA index ≥1.37 (n=109), 35 patients (32.1%) died during the follow-up period. The causes of death were HCC recurrence in 26 patients, liver failure in 6 patients and miscellaneous causes in 3 patients, while in patients with preoperative GSA index <1.37 (n=104), 54 patients (51.9%) died during the follow-up period. The causes of death were HCC recurrence in 34 patients, liver failure in 10 patients and miscellaneous causes in 10 patients.

HCC recurrence. In patients with preoperative GSA index ≥1.37, 59 patients (54.1%) had HCC recurrences during the follow-up period. Nineteen patients (17.4%) had late first confirmed HCC recurrence (≥2 years after initial SR). The patterns of HCC recurrence after initial treatment were: single HCC recurrence in the liver in 23 patients; multiple HCC recurrences in the liver in 27 patients; multiple HCC recurrences in the liver with lung metastases in 2 patients; multiple bone metastases in 2 patients; multiple HCC recurrences in the liver with lymph node metastases in 2 patients; multiple HCC recurrences in the liver with peritoneal dissemination in one patient; multiple HCC recurrence in the liver with right atrium invasion in one patient; and local tumor progression (recurrence in the SR site) in one patient. Treatment methods for the first HCC recurrence were: SR in 7 patients; RFA in 23 patients; percutaneous ethanol injection (PEI) in one patient; TACE in 19 patients; systemic chemotherapy such as sorafenib in 2 patients; radiation therapy in 2 patients and no specific treatment in 5 patients.

In patients with preoperative GSA index <1.37, 87 patients (83.7%) had HCC recurrences during the follow-up period. Twenty patients (19.2%) had late first confirmed HCC

Table IV. Univariate and multivariate analyses of the factors contributing to recurrence-free survival.

Variables	n	Univariate analysis	Multivariate analysis	
			Hazard ratio (95% CI)	P-value[a]
Gender, male vs. female	153/60	0.733		
Age (years), ≥70 vs. <70	119/94	0.560		
Tumor number, single vs. multiple	123/90	<0.001	0.581 (0.410-0.823)	0.002
Maximum tumor size (cm), ≥3.5 vs. <3.5	109/104	0.251		
Microscopic vascular invasion, yes vs. no	72/141	0.002	0.567 (0.395-0.815)	0.002
AST (IU/l), ≥50 vs. <50	109/104	0.010	0.945 (0.663-1.345)	0.753
ALT (IU/l), ≥50 vs. <50	91/122	0.141		
ALP (IU/l), ≥320 vs. <320	109/104	<0.001	0.683 (0.475-0.982)	0.039
GGT (IU/l), ≥70 vs. <70	104/109	0.483		
GSA index ≥1.37, yes vs. no	109/104	<0.001	2.379 (1.594-3.550)	<0.001
Serum albumin level (g/dl), ≥3.9 vs. <3.9	112/101	0.016	1.056 (0.730-1.529)	0.771
Total bilirubin (mg/dl), ≥1.0 vs. <1.0	67/146	0.001	0.840 (0.587-1.203)	0.342
Platelet count ($x10^4/mm^3$), ≥12 vs. <12	105/108	0.050		
Prothrombin time (%), ≥88 vs. <88[b]	105/107	0.023	1.064 (0.751-1.508)	0.727
Diabetes mellitus, yes vs. no	47/166	0.664		
Body mass index (kg/m^2), ≥23 vs. <23	99/114	0.662		
Serum AFP (ng/ml), ≥100 vs. <100	62/151	0.201		
DCP (mAU/ml), ≥100 vs. <100[c]	129/81	0.118		

CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ glutamyl transpeptidase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin. [a]Cox proportional hazard model; [b]missing data, n=1; [c]missing data, n=3.

recurrence (≥2 years after initial SR). The patterns of HCC recurrence after initial treatment were: single HCC recurrence in the liver in 37 patients; multiple HCC recurrences in the liver in 43 patients; multiple HCC recurrences in the liver with lung metastases in 3 patients; multiple bone metastases in one patient; multiple lung metastases in one patient; multiple HCC recurrences in the liver with lymph node metastases in one patient; and local tumor progression (recurrence in the SR site) in one patient. Treatment methods for the first HCC recurrence were: SR in 3 patients; RFA in 38 patients; PEI in 2 patients; TACE in 29 patients; systemic chemotherapy such as sorafenib in 4 patients; radiation therapy in one patient and no specific treatment in 10 patients.

Discussion

To the best of our knowledge, this is the first reported study to examine the relationship between preoperative GSA index calculated from ^{99m}Tc-GSA scintigraphy and liver fibrosis and clinical outcomes in HCV-related HCC patients treated with SR. Although several noninvasive serum markers such as ICG15, FIB-4 index and APRI are associated with clinical outcomes in HCV-related HCC patients, no reports have assessed the impact of preoperative GSA index on clinical outcomes in HCV-related HCC patients treated with SR (21-24). Hence, we conducted the current analysis.

In the present study, the GSA index yielded the highest AUROC for cirrhosis and in multivariate analyses, GSA index was an independent predictor (P<0.001) linked to RFS and it had a marginal significance in terms of OS (P=0.074). Our results suggest that the preoperative GSA index well reflects hepatic functional reserve and is a useful predictor of clinical outcomes in HCV-related HCC patients treated with SR. Yoshizumi *et al* demonstrated that the 6-month survival probability was improved in the group with a GSA index ≥1.3 in patients who underwent liver transplantation, whereas our optimal cut-off value of the GSA index according to ROC analysis was 1.37 (13). Our results were consistent with their results. As mentioned earlier, ICG mainly reflected hepatic blood flow, while GSA was related to the amount of functional hepatocytes as well as blood flow. As shown in our results, the GSA index can reflect the liver fibrosis more accurately than ICG15.

On the other hand, FIB-4 index and APRI exhibited highly discriminative ability for predicting cirrhosis in our analysis. Several investigators demonstrated that FIB-4 and ARPI are useful noninvasive serum markers for predicting liver fibrosis in patients with CHC (25-28). In addition, a recent meta-analysis regarding diagnostic accuracy of FIB-4 and APRI in patients with chronic hepatitis B infection showed that the mean AUROCs of FIB-4 and APRI for predicting cirrhosis were 0.78 and 0.72, while our data of FIB-4 and APRI were 0.771 and 0.761. Although the causes of liver diseases were different between their data and ours, our results were similar to their reports (29).

In our analysis, as demonstrated in Fig. 3, the GSA index had well discriminative ability between various stages of liver fibrosis except for the relationship between F2 and F3. The

reason why the GSA index did not show well discriminative ability between patients with F2 and F3 is unclear, however, the small sample size in patients with F2 (n=19) may be attributed to our current results.

Liver biopsy, which has been considered as the 'golden standard' for assessing the extent of liver fibrosis, carries some drawbacks: sampling error and interobserver variability, which have raised questions on its value, whereas in our present analyses, we investigated the impact of the preoperative GSA index on cirrhosis using non-tumor parts of extracted surgical specimens, which had sufficient amount of liver specimens for exact evaluation of the degree of liver fibrosis (30-32). Thus, our data are highly reliable and this is a major strength of the present study.

The presence of MVI was a significant factor linked to RFS and it had a tendency toward poorer OS in our multivariate analyses. Postoperative factors as well as preoperative factors may be essential for predicting survival. Indeed, Lim *et al* reported that MVI is a better predictor of HCC recurrence and OS after SR for HCC (33). On the other hand, it is of interest that a higher ALP value was significantly linked to higher HCC recurrence in multivariate analysis. Cumulative evidence derived from Asian populations with HCC revealed that a higher ALP level was associated with poor outcomes, which is in line with the present study results (34).

We acknowledge several limitations to the present study. First, the present study was a retrospective observational study with heterogeneous HCC patients with various HCC stages. Second, postoperative therapy such as interferon was not included in our analysis, leading to bias. Third, subjects in whom ^{99m}Tc-GSA scintigraphy prior to surgery was not performed were excluded from our analysis (data not shown) and whether ^{99m}Tc-GSA scintigraphy was performed or not before SR mainly depends on the decision of attending surgeons in our hospital, also leading to bias. Thus, a well characterized study will be needed in the future. However, the present study results demonstrated that the preoperative GSA index well reflected the extent of liver fibrosis and it is closely associated with clinical outcomes in patients with HCV-related HCC treated with SR.

In conclusion, the preoperative GSA index calculated from ^{99m}Tc-GSA scintigraphy can be a useful predictor for patients with HCV-related HCC treated with SR.

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Clinical significance of the FIB-4 index for non-B non-C hepatocellular carcinoma treated with surgical resection

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Abstract. The aims of the present study were to examine the relationship between the preoperative FIB-4 index and background liver fibrosis in non-tumor parts obtained from surgical specimens and to investigate whether the FIB-4 index can be a useful predictor for non-B non-C hepatocellular carcinoma (NBNC-HCC) patients treated with surgical resection (SR). A total of 118 patients with NBNC-HCC treated with SR with curative intent were analyzed. Receiver operating characteristic (ROC) curve analysis was performed for calculating the area under the ROC (AUROC) for the FIB-4 index, aspartate aminotransferase (AST) to platelet ratio index, AST to alanine aminotransferase ratio, serum albumin, total bilirubin and platelet count for cirrhosis. We also examined predictors linked to overall survival (OS) and recurrence-free survival (RFS) after SR. The mean patient age was 68.9±9.0 years (93 males and 25 females) with a median observation period of 3.2 years. In extracted surgical specimens, background liver cirrhosis (F4) was observed in 39 patients (33.1%). The mean maximum tumor size was 5.7±3.2 cm. The mean body mass index was 24.3±3.9 kg/m^2. The FIB-4 index yielded the highest AUROC for cirrhosis with a level of 0.887 at an optimal cut-off value of 2.97 (sensitivity, 92.3; specificity, 69.6%). In the multivariate analysis, serum α-fetoprotein >40 ng/ml (P=0.026) was the only significant independent predictor linked to OS, while tumor number (P=0.002) and FIB-4 index >2.97 (P=0.044) were significant factors linked to RFS. In conclusion, preoperative FIB-4 index can be a useful predictor for NBNC-HCC patients who undergo SR.

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Key words: non-B non-C hepatocellular carcinoma, liver fibrosis, FIB-4 index, overall survival, recurrence-free survival

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer-related death (1-3). Although most cases of this malignancy are associated with viral infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, a substantial proportion of HCC patients are negative for markers of HBV surface antigen (HBsAg) and HCV antibody (HCVAb) [non-B non-C HCC (NBNC-HCC)]. The frequency of NBNC-HCC has been reported to range from 5 to 15%, and the number of NBNC-HCC patients in Japan has recently been gradually increasing (4-7). It is noteworthy that the proportion of NBNC-HCC patients was ~30% in 2011, 2012 and 2013 in our hospital (1).

Curative therapies for HCC consist of liver transplantation, surgical resection (SR) and radiofrequency ablation (RFA) (1-7). The clinical outcome of HCC patients undergoing these therapies has improved substantially in recent years due to their advances. However, HCC often recurs even after curative therapies, leading to high mortality. Recurrence only occurs at intrahepatic sites in 68-96% of patients (1,8-10). Hence, the identification of predictive factors and effective management of HCC recurrence are essential for improving survival, even after curative treatment.

Recently, several noninvasive tools have been introduced to evaluate the degree of hepatic fibrosis in patients with chronic liver disease; these include serum markers such as aspartate aminotransferase to platelet ratio index (APRI), FIB-4 index, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio or modalities such as acoustic radiation force impulse, transient elastography and magnetic resonance elastography (11-18). Serum markers and developed scores are of rising significance in noninvasive diagnosis of liver fibrosis owing to the easy availability in field practice. Among these tools, the FIB-4 index is a simple formula used for predicting liver fibrosis based on standard biochemical values (platelet count, AST and ALT) and age, and is demonstrated to be highly helpful for predicting advanced liver fibrosis (19-22). However, this test has seldom been applied for the evaluation