Original Article

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PEG-IFNα/RBV Combination Therapy for Chronic Hepatitis C Patients Increases Serum Ferritin Level while It Improves Sustained Viral Response Rate

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Key Words

Alanine aminotransferase · Chronic hepatitis C · Combination therapy · Hemolytic anemia · Hepatic iron overload · Pegylated interferon · Ribavirin · Serum ferritin · Sustained viral response

Abstract

Objectives: We investigated the significance of serum ferritin levels in pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy for chronic hepatitis C (CHC) and examined its correlation with serum alanine aminotransferase (ALT) levels during therapy and response to the therapy. ***Methods:*** A total of 175 patients with CHC received the combination therapy. Correlations between serum ferritin levels and serum ALT levels at 12 and 24 weeks of therapy were examined. Differences in serum ferritin levels during therapy between patients with sustained viral response (SVR) and non-SVR were also examined. ***Results:*** Only 24 (13.7%) and 20 (11.4%) patients showed elevated serum ALT levels (≥70 IU/l) at 12 and 24 weeks of therapy, respectively. There was no correlation between serum ferritin levels and ALT levels. Ninety-five (54.3%) of 175 patients achieved SVR. Serum ferritin levels increased dramatically in both SVR and non-SVR groups after starting the therapy and were significantly higher in the SVR group throughout the therapy. ***Conclusions:*** Serum ferritin level increases during PEG-IFN and RBV combination therapy; however, it did not correlate with either serum ALT level or the total dose of RBV. Higher serum ferritin levels during combination therapy appear to be associated with favorable therapeutic response.

Introduction

Pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy is the current standard treatment for chronic hepatitis C (CHC) infection, demonstrating an improved sustained viral response (SVR) rate even in patients infected with hepatitis C virus (HCV) genotype 1 and who had a high viral load [1, 2]. Several host and viral factors contribute to SVR in the combination treatment for Japanese patients infected with HCV genotype 1 with high viral load [3–7]. The host factors include younger age, male gender, mild liver fibrosis, platelet count, LDL cholesterol values and γ-glutamyl transpeptidase values. The viral factors include amino acid substitutions in the IFN sensitivity-determining region of the HCV nonstructural 5A (NS5A) protein and in the HCV core region.

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Hepatic iron overload is frequently observed in patients with HCV infection and has been considered to be associated with disease progression and hepatocarcinogenesis [8, 9]. However, the association between hepatic iron overload and therapeutic response to IFN therapy for CHC remains controversial [10–12]. We previously reported that elevation of serum alanine aminotransferase (ALT) levels during PEG-IFNα-2a monotherapy for CHC seems to be caused by hepatic iron overload which may be induced by the therapy itself [13].

In this study, we investigated the correlation between serum ferritin levels and serum ALT levels during PEG-IFN and RBV combination therapy for CHC, and also investigated whether the elevated serum ferritin level during therapy is associated with a therapeutic response.

Patients and Methods

Patients

This retrospective study was conducted at the Kinki University of Medical Science. Eligible subjects were: CHC patients who had received weekly injections of PEG-IFNα-2a or -2b for 24–72 weeks; who had been followed for more than 24 weeks after treatment, and who had been examined serially for quantitative and qualitative HCV RNA, serum ferritin, serum iron, ALT and complete blood cell counts.

Patients with a high load (≥100 kIU/ml) of HCV genotype 1 were treated for 48–72 weeks, those with a low load (<100 kIU/ml) of genotype 1 for 24–48 weeks and those with genotype 2 were treated for 24 weeks. PEG-IFNα-2a was administered once a week at a daily dose of 90 or 180 μg, PEG-IFNα-2b was administered once a week at a daily dose of 1.5 μg/kg body weight. RBV was orally administered daily in 2 divided doses. The doses of RBV were adjusted based on the subject's body weight (600 mg for ≤60 kg, 800 mg for 60–80 kg, 1,000 mg for ≥80 kg). Doses were adjusted during therapy according to standard indications.

Patients with hepatitis B virus infection, HIV infection, autoimmune hepatitis, primary biliary cirrhosis, alcoholic liver disease, non-alcoholic steatohepatitis, hemochromatosis, Wilson's disease and hemoglobinopathy were excluded. Patients were classified as responders if they achieved SVR (defined as undetectable HCV RNA at 24 weeks after the completion of therapy). The remaining patients were categorized as non-SVR. Written informed consent was obtained from all patients before treatment and the protocol was approved by the ethics committee of the Kinki University School of Medicine.

Biochemical and Virological Assay

Laboratory tests including serum ALT levels, serum iron, serum ferritin and complete blood cell counts were assessed in a centralized laboratory using automated methods.

Quantitative HCV testing was performed using the Cobas® Amplicor HCV Monitor Test v.2.0 (Roche Diagnostics, Australia) on the Roche Cobas Amplicor Analyzer (Roche Diagnostics) according to the manufacturer's instructions. HCV RNA qualitative determination was performed by real-time PCR on a Cobas TaqMan 48 Analyzer or by Cobas Amplicor HCV Test, v.2.0 (Roche Diagnostics) on the Roche Cobas Amplicor Analyzer with a sensitivity limit of at least 50 IU/ml. Laboratory tests and HCV RNA were analyzed before treatment and at 4, 12 and 24 weeks after initiation of therapy, at the end of the treatment period and 4, 12, 24 and 48 weeks following completion of therapy.

Statistical Analysis

Data were expressed as the means ± standard errors. Differences between groups were determined by Wilcoxon's signed rank test and confirmed by the non-parametric Mann-Whitney U test between groups. Correlation between data was tested using the non-parametric Spearman rank correlation analysis. Differences were considered statistically significant at $p < 0.05$. Statistical calculations were performed using the commercially available software SPSS v.11.5 (SPSS, Chicago, Ill., USA).

Table 1. Demographics and baseline characteristics

Patients, n	175
Age	60.2 ± 0.8
Sex (male/female), n	85/90
BMI, kg/m^2	22.9 ± 0.3
Genotype, n	
1	151 (86.3%)
2	24 (13.7%)
Viral load, kIU/ml	2,200 ± 200
WBC, ×10^3/μl	4.9 ± 0.1
Hb, g/dl	13.8 ± 0.1
PLT, ×10^4/μl	16.3 ± 0.5
Serum ferritin, ng/ml	115.6 ± 12.5
ALT, IU/l	71.5 ± 4.3
PEG-IFN, n	
α-2a	42 (24%)
α-2b	133 (76%)

BMI = Body mass index; WBC = white blood cell count; Hb = hemoglobin; PLT = platelets.

Results

Demographics and Baseline Features

Of the 187 patients, 12 discontinued treatment due to adverse events. The remaining 175 patients, consisting of 90 (51.4%) women and 85 men (48.6%), who met the requirements were enrolled in the study. HCV genotype 1 was prevalent in 151 (86.3%) patients with the remaining 24 (13.7%) positive for type 2. PEG-IFNα-2b was administered to 133 (76%) of the patients (table 1).

Table 2. Univariate analysis for SVR

	SVR	Non-SVR	p value
Patients, n	95	80	
Age, years	60.2 ± 1.2	60.1 ± 9.0	0.418
Sex (male/female), n	50/45	35/45	0.243
BMI, kg/m^2	22.6 ± 4.4	23.2 ± 0.3	0.173
Genotype			<0.05
1	74 (49.0%)	77 (51.0%)	
2	21 (87.5%)	3 (12.5%)	
Viral load, kIU/ml	1,700 ± 200	2,700 ± 400	<0.05
WBC, $\times 10^3/\mu l$	5.1 ± 0.2	4.6 ± 0.2	<0.05
Hb, g/dl	14.0 ± 0.1	13.6 ± 0.2	<0.05
PLT, $\times 10^4/\mu l$	17.8 ± 0.6	14.6 ± 0.7	<0.05
Serum ferritin, ng/ml	135.9 ± 14.6	174.1 ± 19.9	0.214
ALT, IU/l	73.6 ± 6.5	69.0 ± 5.3	0.494
PEG-INF			0.321
α-2a	20 (47.6%)	22 (52.4%)	
α-2b	75 (56.4%)	58 (43.6%)	

BMI = Body mass index; WBC = white blood cell count; Hb = hemoglobin; PLT = platelets

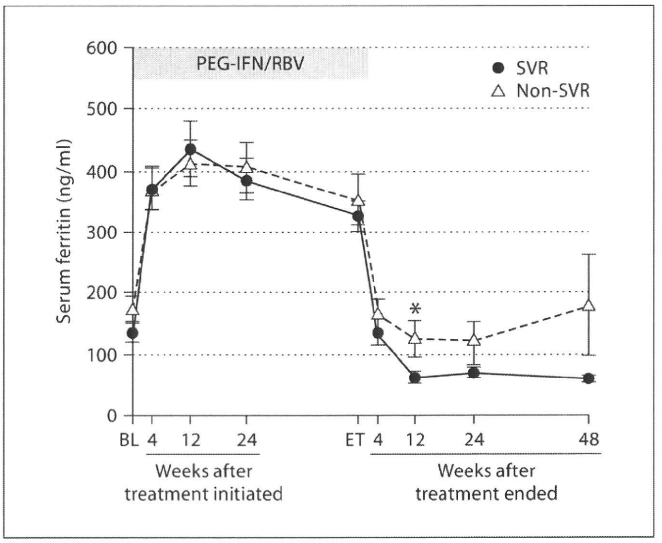


Fig. 1. Serum ferritin levels during and after treatment in patients with or without a SVR. Changes over time of serum ferritin levels in SVR and non-SVR patients after antiviral therapy are displayed. BL = Baseline; ET = end of treatment. * $p < 0.05$, comparing between groups at each time point.

Viral Response

SVR was achieved by 95 (54.3%) of the 175 patients, with the remaining 80 patients not responding even at 24 weeks after completion of the treatment. Of the 95 patients achieving SVR, 50 (52.6%) were male and 45 (47.4%) were female. There were no significant differences in the rate of SVR between the 2 sexes ($p = 0.243$). For HCV genotype 2, 21 (87.5%) of 24 patients exhibited SVR. Only 74 (49.0%) of 151 patients infected with HCV genotype 1 demonstrated SVR. Univariate analysis showed that factors significantly associated with SVR were low viral load, elevated white blood cell count, high hemoglobin and high platelet count. Serum ferritin levels tended to be lower in patients with SVR. There was no significant difference in age, sex, body mass index, serum ferritin level and serum ALT level between SVR and non-SVR patients (table 2).

Correlation between Serum ALT and Serum Ferritin Level

Only 24 (14%) and 20 (11%) patients showed elevated serum ALT levels (≥70 IU/l) at 12 and 24 weeks of the therapy, respectively. Among the subjects whose ALT levels were ≥70 IU/l at weeks 12 and 24, the relationship between the serum ALT and ferritin levels was investigated using Pearson's correlation coefficient test. There was no significant relation between serum ALT and ferritin levels at each time point ($p = 0.838$, $r = -0.049$ at week 12; $p = 0.142$, $r = 0.340$ at week 24).

Dynamics of Serum Ferritin Level during and after Treatment

Serum ferritin levels increased and peaked between 4 and 12 weeks after commencement of therapy, remained high until the end of the treatment period, and returned to baseline levels after completion of the treatment. If SVR did not occur, serum ferritin levels increased again following completion of therapy (fig. 1). The 'increasing ratio of serum ferritin' was calculated as the ratio of serum ferritin level to baseline serum ferritin level. The increasing ratio of serum ferritin in patients with a SVR was significantly higher than that in non-SVR individuals during treatment (fig. 2).

Correlation between Dosage of PEG-IFN or RBV and Increasing Ratio of Serum Ferritin

We analyzed the relationship between administered doses and serum ferritin during the first 4 and 12 weeks of treatment by Pearson's correlation coefficient test. There was no significant correlation between the administered dose of RBV and increasing ratio of serum ferritin ($p = 0.110$, $r = 0.166$ during the first 4 weeks; $p = 0.071$,

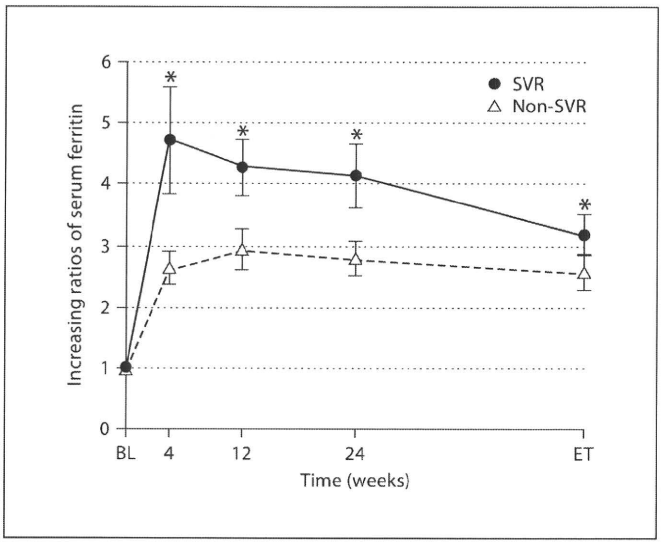
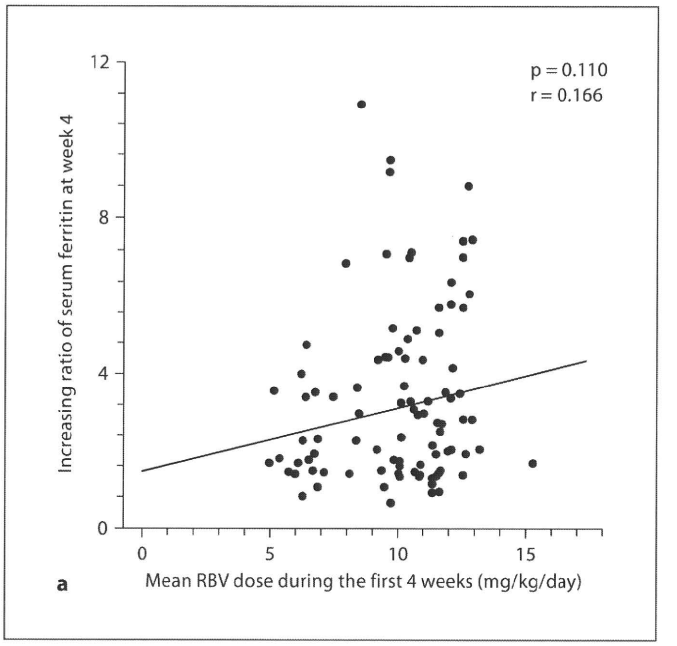


Fig. 2. Increasing ratios of serum ferritin during treatment in patients with or without a SVR. The 'increasing ratio of serum ferritin' was calculated as the ratio of serum ferritin level to baseline serum ferritin level. BL = Baseline; ET = end of treatment. * $p < 0.05$, comparing between groups at each time point.



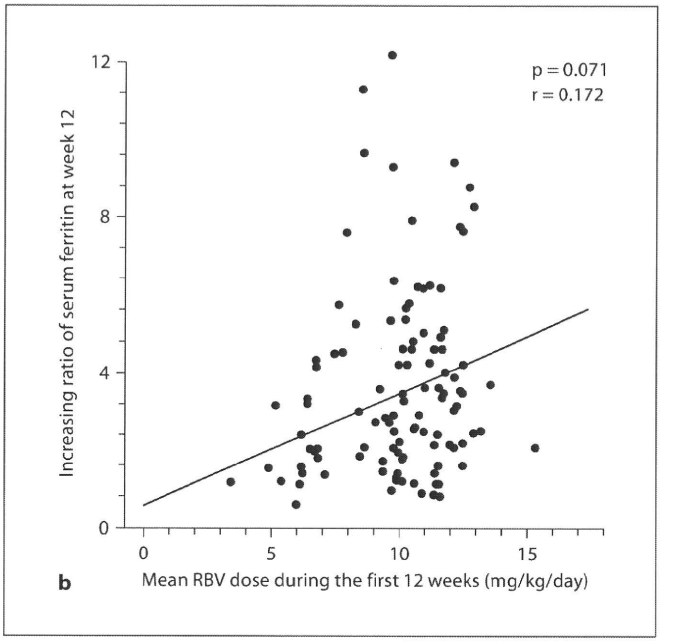


Fig. 3. Correlation between administered doses of RBV and increasing ratio of serum ferritin. The 'increasing ratio of serum ferritin' was calculated as the ratio of serum ferritin level to baseline serum ferritin level. **a** Correlation between the mean dose of RBV and increasing ratio of serum ferritin at week 4. **b** Correlation between the mean dose of RBV and increasing ratio of serum ferritin at week 12.

r = 0.172 during the first 12 weeks; fig.3). There was also no correlation between PEG-IFNα-2a or -2b and increasing ratio of serum ferritin (PEG-IFNα-2a: p = 0.856, r = 0.037 at week 4; p = 0.752, r = −0.58 at week 12; PEG-IFNα-2b: p = 0.692, r = 0.049 at week 4; p = 0.243, r = 0.132 at week 12).

Discussion

We previously reported that elevation of serum ALT levels correlated to serum ferritin levels during PEG-IFNα-2a monotherapy for CHC seems to be caused by hepatic iron overload, which may be induced by the therapy itself [13]. In this paper, 28 (44.4%) of 63 patients exhibited elevated ALT levels (≥70 IU/l). Also, serum ALT levels were elevated (≥70 IU/l) in 24 (13.7%) of 175 patients at week 12, and in 20 (11.4%) of 175 patients at week 24. In our present study, during PEG-IFN and RBV combination therapy, there was no elevation of serum ALT level in almost all patients, and there was no significant correlation between serum ferritin and ALT levels.

RBV, a guanosine analogue which has a broad antiviral spectrum, is known as an immunomodulator inhibiting the viral RNA polymerase, balancing Th1 and Th2 cell responses and acting by direct cytoprotection [14, 15].

Although HCV RNA levels and hepatic fibrosis scores did not change significantly in patients with CHC who were treated by RBV alone, serum ALT levels and inflammatory features of liver histology were improved [16, 17]. One possible reason why the correlation between serum ALT and serum ferritin levels was not seen in PEG-IFN and RBV combination therapy, distinct from PEG-IFNα-2a monotherapy, is the efficacy of RBV to improve inflammation of the liver as described above.

In this study, whether SVR was reached or not, serum ferritin levels significantly increased after initiation of therapy, peaked at an early stage (4–12 weeks) after initiation and decreased slowly. In SVR patients, serum ferritin levels after treatment were lower than the initial baseline. In non-SVR patients, serum ferritin levels increased again after completion of therapy with a corresponding increase of HCV-RNA load (data not shown). The increased ratio of serum ferritin (serum ferritin/baseline ferritin ratio) in SVR subjects was significantly higher than in non-SVR individuals. A similar report has been previously published, and its results correspond with what we are reporting here [18].

In general, it is thought that an adequate dose of RBV in the first stages of treatment correlates to SVR [19]. It is expected that the more RBV is administered, the more strongly hemolysis occurs and serum ferritin levels rise. In this study, there was no significant correlation between dose of RBV and serum ferritin levels. Even if the same dose of RBV was administrated, metabolism and concentration of RBV differ between individuals. Though we did not investigate parameters involving hemolysis or RBV concentration, the correlation between rising levels of ferritin and the rate of SVR may be related to RBV-induced hemolysis and/or RBV concentration. Ferrara et al. [18] considered that the rise of serum ferritin correlated to RBV-induced hemolysis at earlier phases of treatment, but the correlation between serum ferritin levels and hemolysis is lost at later phases of treatment. Therefore, they considered that elevated serum ferritin at a later phase might be caused by a reactive response from activated macrophages to interferon [18]. Their hypothesis that elevation of serum ferritin level during the PEG-IFN and RBV combination therapy might be caused not only by RBV-induced hemolysis but also by IFN is quite reasonable, because elevation of serum ferritin levels is also observed in PEG-IFNα-2a monotherapy [13]. Further studies are necessary to confirm these hypotheses.

In conclusion, serum ferritin levels increase during PEG-IFN and RBV combination therapy; however, this did not correlate with either serum ALT levels or the total dose of RBV administered. Higher serum ferritin levels during combination therapy appeared to be associated with favorable therapeutic response.

Disclosure Statement

The authors declare that they have no financial conflict of interest.

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Original Article

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Non-Invasive Evaluation of Hepatic Fibrosis for Type C Chronic Hepatitis

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Key Words

Biopsy, liver · FibroScan · Fibrosis, liver · Real-time tissue elastography

Abstract

Objective: The aim of this study was to investigate liver fibrosis using non-invasive Real-time Tissue Elastography® (RTE) and transient elastography (FibroScan®) methods. ***Methods:*** RTE, FibroScan and percutaneous liver biopsy were all performed on patients with chronic liver disease, particularly hepatitis C, to investigate liver fibrosis. ***Results:*** FibroScan and RTE were compared for fibrous liver staging (F stage), which was pathologically classified using liver biopsy. In FibroScan, significant differences were observed between F1/F3 and F2/F4, but no such differences were observed between F1/F2, F2/F3 and F3/F4. In RTE, significant differences were observed between F1/F2, F2/F3 and F2/F4. But for F3/F4, no significant differences were observed. ***Conclusion:*** FibroScan and RTE correlated well with F staging of the liver. In particular RTE was more successful than FibroScan in diagnosing the degree of liver fibrosis.

Introduction

Currently, percutaneous liver biopsy is considered to be the gold standard for determining the index of the liver fibrosis in a patient with chronic liver disease including hepatitis type C. However, liver biopsy is associated with risks of complications, lacks accuracy due to sampling error, and is physically and psychologically uncomfortable for the patient. Transient elastography (FibroScan®) and Real-Time Tissue Elastography® (RTE) have been developed as non-invasive methods to evaluate the degree of liver fibrosis, potentially providing alternatives to liver biopsy. FibroScan detects the propagation speed of a shear wave transmitted from a probe through the liver and calculates the shear modulus of the liver to evaluate the degree of liver fibrosis [1–3]. On the other hand, RTE visualizes a 2-dimensional strain image induced by external freehand compression with the probe or by internal heartbeats. To evaluate the degree of liver fibrosis, it is reported that the pattern of strain image induced by compression becomes patchy as fibrosis progresses [4]. To increase objectivity,

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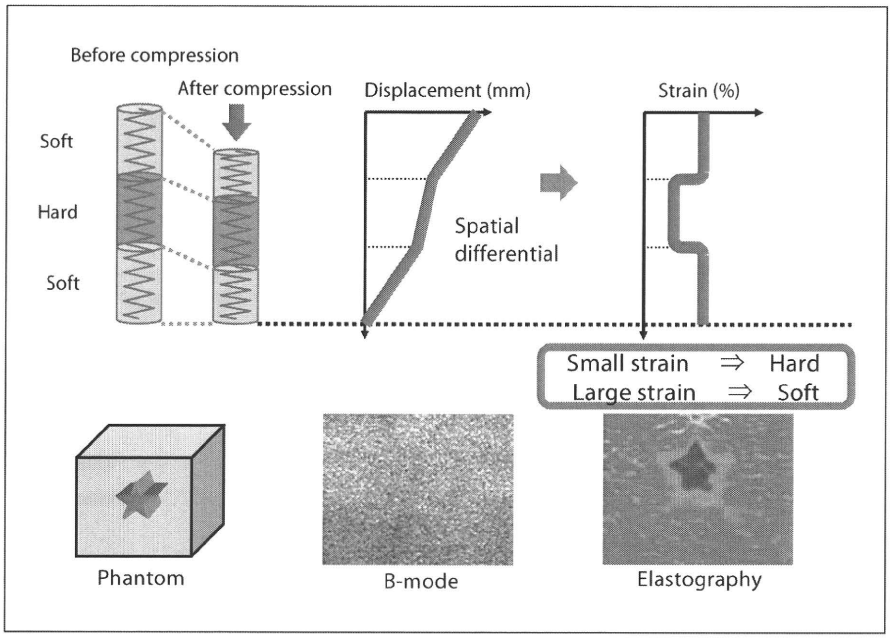

Fig. 1. Principle of elasticity imaging.

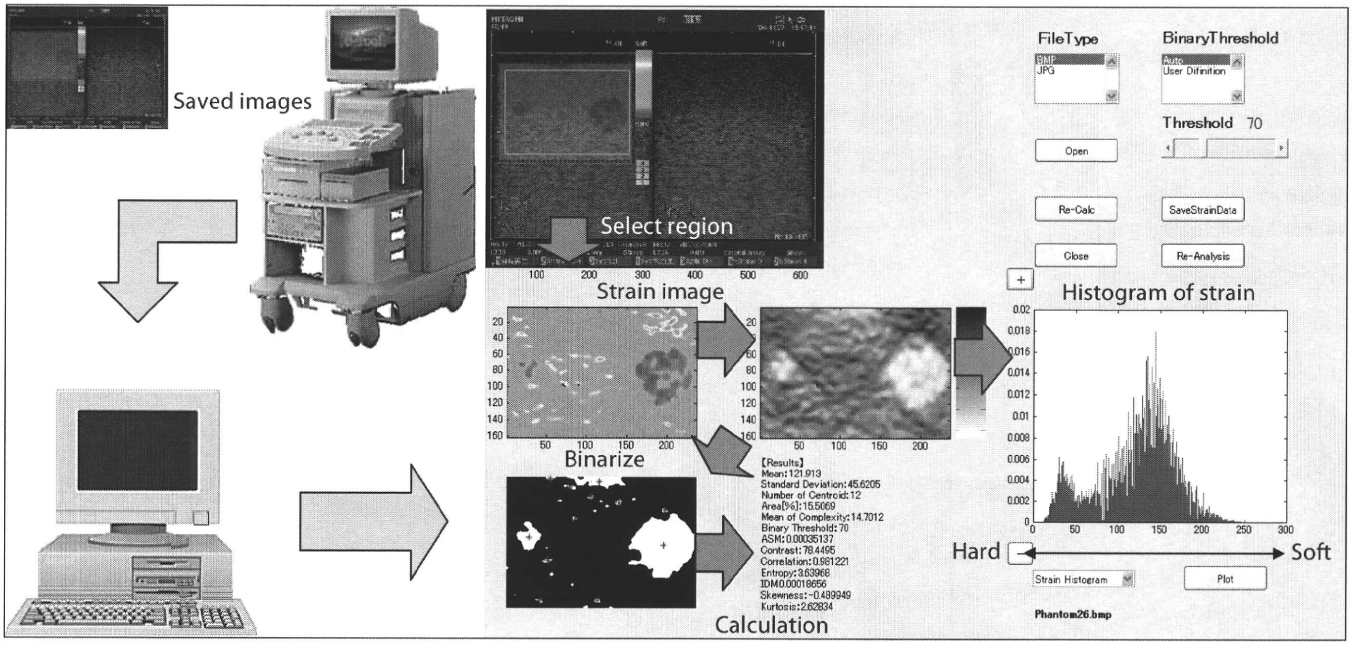

Fig. 2. Analysis tool. Mean = Mean of relative strain value; SD = standard deviation of relative strain value; area[%] = ratio of blue area in the analyzed region; complexity = complexity of blue area [calculated as $(\text{boundary length})^2/\text{area}$].

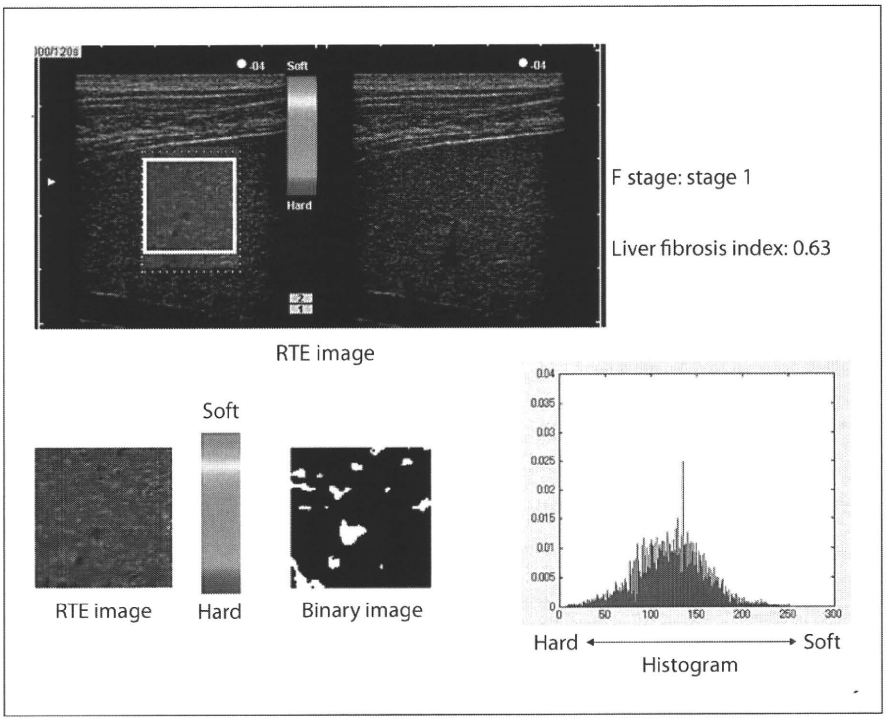

Fig. 3. Example of liver RTE image and result of liver fibrosis index (F stage 1).

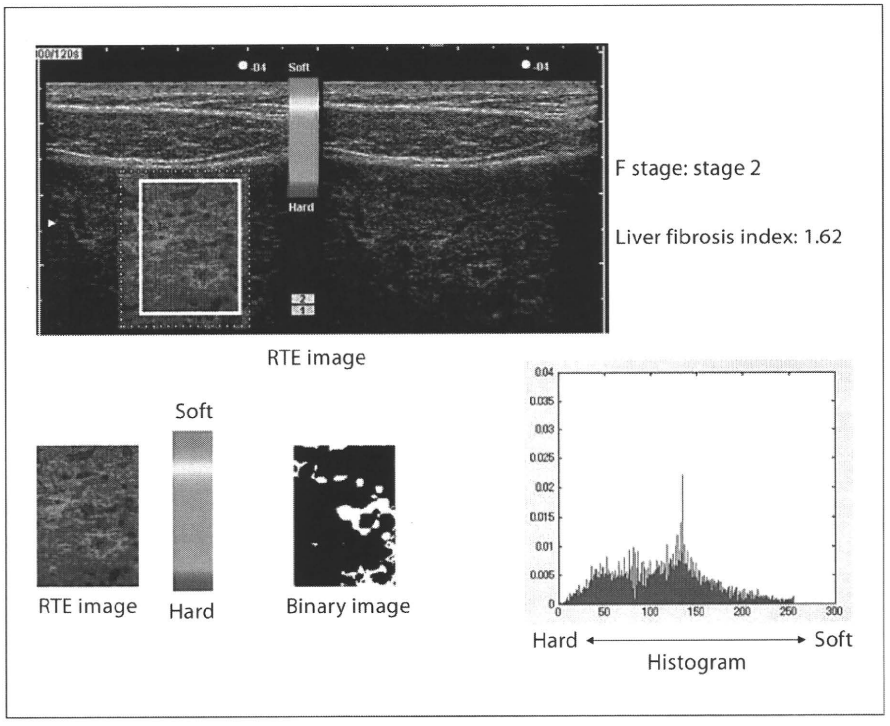

Fig. 4. Example of liver RTE image and result of liver fibrosis index (F stage 2).

we proposed an image analysis method to evaluate strain image features [5]. In this paper, we propose a new algorithm for RTE to deliver an index which corresponds to the liver fibrosis stage (F stage), and report our clinical experience.

Methods

Before IFN treatment, percutaneous liver biopsy, FibroScan and RTE examinations were performed on 44 patients with chronic hepatitis C. All patients gave their consent for this study. Of these 44 patients, 12 had F1, 9 had F2, 10 had F3, and 13 had F4, all diagnosed pathologically using percutaneous liver biopsy. FibroScan and RTE were performed before the liver biopsy for comparison with the F stage of the liver biopsy specimen. Measurements with FibroScan (EchoSens, Paris, France) were performed on the right lobe of the liver through intercostal spaces. The mean of 10 valid measurements was used as the index of liver stiffness. RTE was performed with EUB-8500 (Hitachi Medical Corp., Tokyo, Japan) through the right intercostal spaces to obtain the elastography images of the liver.

RTE displays elastic information of the tissue calculated from the tissue displacement. The tissue displacement is caused either by manual compression and relaxation of the probe or by the internal compression and relaxation with the heart. The principles underlying RTE are shown in figure 1 using a spring model with the hard and soft springs connected in series. When the spring is compressed, a hard spring is displaced to a lesser extent than a soft spring, thus the strain calculated from the displacement is small in hard springs and large in soft springs. RTE visualizes the relative strain using color gradations, similar to ultrasound color Doppler imaging. RTE is being clinically used and studied in various regions, such as breast, [6], thyroid gland, and prostate [7]. As discussed in the previous study, the RTE image shows a patchy pattern of colors as liver fibrosis progresses from hepatitis to cirrhosis [4, 5]. This is because the fibrotic region is harder than the normal liver parenchyma and does not spread uniformly. For evaluation of liver, the strain induced by heartbeats (diastole) is used to perform RTE to reduce interobserver variability by compressing with an external probe. Six RTE images were collected for each patient and analyzed with the prototype analysis software shown in figure 2 to calculate 9 image features: mean of relative strain value; standard deviation of relative strain value; ratio of blue area in the analyzed region; complexity of blue area; kurtosis of strain histogram; skewness of strain histogram; entropy; inverse difference moment, and angular second moment. Multiple regression analysis was then performed with these 9 image features to quantify the index of liver fibrosis. Examples of liver RTE images and index of liver fibrosis results are shown in figures 3–6. As can be seen from these figures, as F stage progresses, the liver fibrosis index increases.

Results

FibroScan and RTE findings were compared against pathologically classified F-staged patients using liver biopsy. In FibroScan, significant differences were observed between F1/F3 and F2/F4, but no significant differences were observed between F1/F2, F2/F4 and F3/F4 (fig. 7).

In RTE, significant differences were observed between F1/F2, F2/F3 and F2/F3, but no significant differences were recognized between F3/F4 (fig. 8).

Discussion

The percutaneous liver biopsy is most reliable but it is invasive and cannot be performed frequently to study the progress of fibrosis. Thus non-invasive techniques, such as FibroScan and RTE, are more desirable.

FibroScan is simple and easy to use and displays the results on a monitor immediately. The result is based on 1-dimensional information (1-line) only. In the case of RTE, it visualizes 2-dimensional elastic information in real time and can be used in most patients.

FibroScan has many limitations. It cannot be used in patients with ascites, thick subcutaneous fat, narrow intercostal spaces, and hepatic atrophy. RTE does not have such limitations and it can be used in almost all patients, including those with the conditions mentioned above. However, RTE requires training to scan patients to obtain reproducible images and to analyze the data. To address these issues in RTE, we are investigating easy-to-use acquisition techniques to reduce interobserver variability and also to simplify RTE image acquisition.

FibroScan and RTE both correlate highly with the F staging of the liver using biopsy. In particular RTE is very useful for the differential diagnosis and staging of the liver fibrosis.

In future, we plan to study more cases to evaluate FibroScan and RTE for liver fibrosis staging and to establish guidelines to minimize unnecessary liver biopsies, which will significantly benefit patients with chronic liver diseases.

Disclosure Statement

The authors declare that they have no financial conflict of interest.

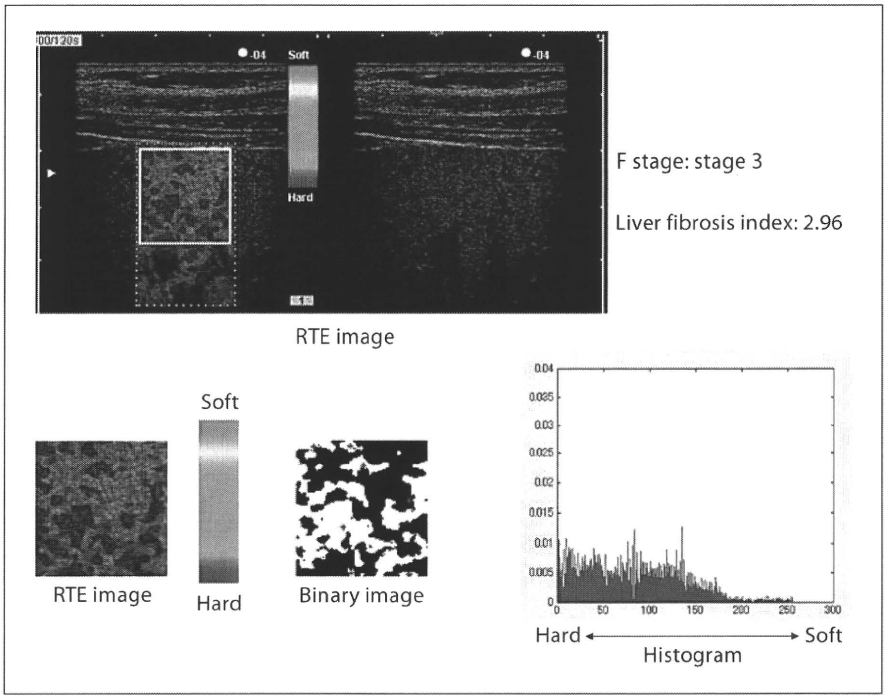

Fig. 5. Example of liver RTE image and result of liver fibrosis index (F stage 3).

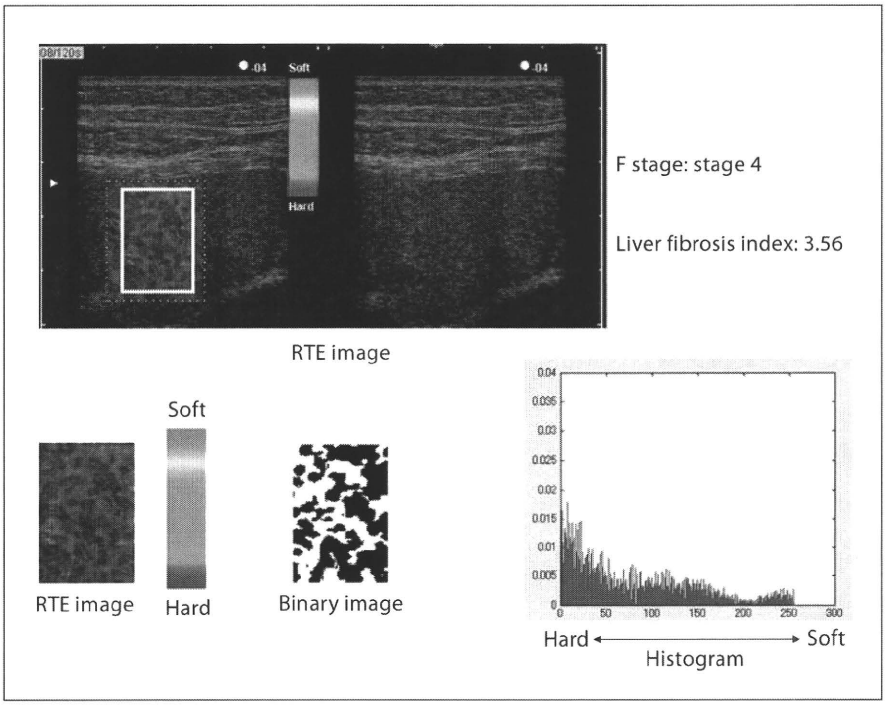

Fig. 6. Example of liver RTE image and result of liver fibrosis index (F stage 4).

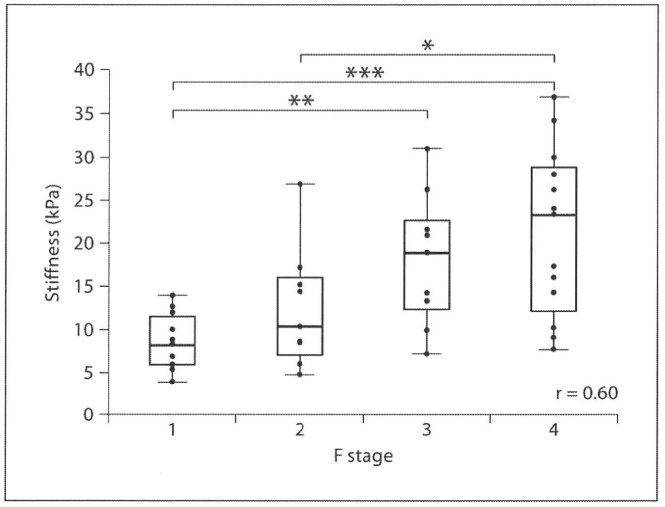

Fig. 7. FibroScan and F stage. * $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$.

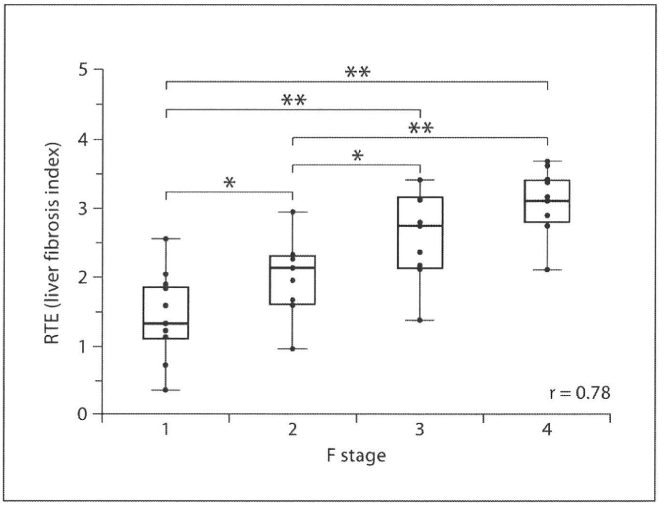

Fig. 8. RTE (liver fibrosis index) and F stage. * $p < 0.05$; ** $p < 0.001$.

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Overall Survival After Transarterial Lipiodol Infusion Chemotherapy With or Without Embolization for Unresectable Hepatocellular Carcinoma: Propensity Score Analysis

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OBJECTIVE. Although iodized oil transarterial chemoembolization (TACE) has been found to have survival benefit in the care of patients with unresectable hepatocellular carcinoma, iodized oil infusion chemotherapy without embolization has not been clearly found inferior to or equal to TACE. The purpose of this study was to determine whether one of these therapies is superior to the other or the two are equal in survival benefit and whether embolization with gelatin sponge particles is indispensable to prolonging survival.

SUBJECTS AND METHODS. A prospective nonrandomized observational cohort study was conducted over 8 years. Among 11,030 patients with unresectable hepatocellular carcinoma, 8,507 underwent TACE, and 2,523 underwent transarterial infusion therapy with an emulsion of iodized oil and an anticancer agent as initial treatment. Patients with extrahepatic metastasis or any previous treatment were excluded. The primary end point was all-cause mortality. To minimize selection bias, propensity score analysis was used to compare the two groups.

RESULTS. During the follow-up period, 5,044 patients (46%) died. In the analysis of all patients, TACE was associated with a significantly higher survival rate than infusion therapy without embolization (hazard ratio, 0.60; 95% CI, 0.56–0.64; $p = 0.0001$). The propensity score analysis showed that the hazard ratio for death in the TACE group ($n = 1,699$ patients) compared with the group who underwent infusion therapy without embolization ($n = 1,699$) was 0.70 (95% CI, 0.63–0.76; $p = 0.0001$). The median survival time of the TACE group was 2.74 years, and the 1-, 3-, and 5-year survival rates were 81%, 46%, and 25%. The corresponding values for the group who underwent transarterial infusion therapy without embolization were 1.98 years and 71%, 33%, and 16%.

CONCLUSION. Propensity score analysis showed that in the treatment of patients with unresectable hepatocellular carcinoma, TACE was associated with significantly better overall survival rates than was transarterial infusion therapy without embolization. TACE can be recommended as initial treatment of these patients.

Keywords: chemotherapy, hepatocellular carcinoma, iodized oil infusion, propensity analysis, transarterial chemoembolization

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Hepatocellular carcinoma (HCC) is the fifth most common type of cancer and the third most common cause of cancer mortality in the world [1]. The incidence of HCC is increasing in Japan [2], the United States [3], and other Western countries [4]. However, the number of patients who can undergo curative therapy such as resection, transplantation, and percutaneous ablation remains low. A 2005 report by the Liver Cancer Study Group of Japan showed transarterial chemotherapy, including transarterial chemoembolization with iodized oil and gelatin sponge particles (TACE) and transarterial iodized oil infusion chemotherapy without embolization, accounted for the initial treatment of 36.4% of 16,941 patients with HCC [5].

Randomized controlled trials [6, 7] and meta-analyses [8, 9] have shown that TACE is widely performed and recognized as having survival benefit in the treatment of patients with unresectable HCC accompanied by well-compensated cirrhosis. However, TACE is not always indicated, especially for patients with poor liver function and those with cancer in an advanced stage, because of the risk of hepatic failure and death after treatment [10, 11]. Instead, transarterial infusion therapy with an emulsion of iodized oil and an anticancer agent, also known as lipiodolization [12], has been performed for patients in poor condition [13–19].

A few reports have appeared on comparisons of the survival associated with transarterial iodized oil infusion therapy without

embolization and that associated with TACE, but no consensus has been reached. Two studies [18, 19] showed no significant difference between the two therapies, another study [14] showed infusion without embolization was associated with better survival than was TACE in a subgroup of patients at high risk, and another study [16] showed the reverse. We conducted a prospective nonrandomized observational cohort study to determine whether one of the therapies is superior to the other or whether the therapies are equal in survival benefit. We also evaluated whether gelatin sponge particles are indispensable to prolonging survival.

Subjects and Methods

Patient Characteristics

During the 8 years January 1994–December 2001, the Liver Cancer Study Group of Japan prospectively collected and biannually registered clinicopathologic data on 72,836 patients with primary liver cancer at nearly 800 medical institutions. Data were collected with a registration and questionnaire sheet with more than 180 questions. From that population, 11,030 patients (15.1%) with unresectable HCC were assigned to the current study cohort. Among these patients, 8,507 (77%) underwent TACE and 2,523 (23%) underwent iodized oil transarterial infusion therapy without embolization as initial treatment. These patients did not receive any other therapy during the first investigation period of no more than 2 years. Exclusion criteria were extrahepatic metastasis to lymph nodes and other organs and any previous treatment before the one studied. The 8,507 patients who underwent TACE in the current study were among 8,510 patients who participated in another study [20].

The diagnosis of HCC was based mainly on findings with imaging techniques such as sonography, dynamic CT, MRI, and angiography or on findings at pathologic study of biopsy specimens (4.7%). Abnormal elevation of levels of tumor markers also was found: α-fetoprotein greater than 400 ng/mL (normal, < 20 ng/mL) and des-γ-carboxyl prothrombin more than 100 mAU/mL (normal, < 40 mAU/mL). Typical HCC was visualized as high attenuation or signal intensity in the arterial phase and low attenuation or signal intensity or washout in the delayed phase (≈ 3 minutes after the initiation of contrast injection) of dynamic CT [21, 22] and dynamic MRI and as a hypervascular lesion at hepatic arteriography. Extrahepatic metastatic lesions were routinely examined with sonography, CT, and chest radiography.

The baseline characteristics of the 11,030 patients who underwent TACE (n = 8,507) and transarterial infusion therapy without embolization (n = 2,523) are shown in Table 1. The hepatic functional reserve was evaluated as liver damage in grade A, B, or C in the classification proposed by the Liver Cancer Study Group of Japan in 2000 and published in English in 2003 [23] (Table 2). This classification consists of five clinical and laboratory findings: ascites, serum bilirubin concentration, serum albumin concentration, indocyanine green retention rate at 15 minutes, and prothrombin activity. The severity of each clinical finding is evaluated separately. Degree of liver damage is based on the highest grade that contains at least two findings. This classification is closely related to the Child-Pugh classification and is more precise for discriminating whether patients with Child-Pugh A disease, that is, good candidates for surgical resection, have liver damage grade A or B [5, 24]. Concerning hepatitis B and C virus infection, four groups were categorized: negative result for hepatitis B virus surface antigen and positive result for hepatitis C virus antibody, positive result for hepatitis B virus surface antigen and negative result for hepatitis C virus antibody, positive results for both, and negative results for both. Maximum tumor size had four subgroups, and number of tumors had three subgroups.

Tumor Characteristics

The degree of vascular invasion of the portal vein consisted of the following four categories: Vp0, no invasion; Vp1, invasion to a third-order branch; Vp2, invasion to a second-order or segmental portal vein; and greater than Vp3, first-order portal vein including Vp4, main portal trunk. The degree of hepatic vein invasion was Vv0, no invasion, and greater than Vv1, any hepatic vein invasion, including the main hepatic veins and the inferior vena cava.

The TNM staging adopted in this study was proposed and revised by the Liver Cancer Study Group of Japan in 2000 (Table 3) and published in English in 2003 [23]. This revised TNM system was proposed as a new concordant TNM classification of primary liver cancer by the International Hepato-Pancreato-Biliary Association [25]. Namely, the T category is determined on the basis of the following three criteria: single lesion, tumor diameter 2 cm or less, and no vascular or biliary invasion (Table 3). Category T1 is determined when three criteria are fulfilled; T2, two criteria; T3, one criterion; and T4, no criteria. Stages I–IVA are determined mainly by the corresponding T category from T1 to T4.

Technique

A 5-French catheter was advanced to the superior mesenteric artery to confirm the patency of the portal vein trunk at postmesenteric portography. Common hepatic or celiac arteriography was performed to discern the number and location of lesions, tumor size, feeding artery, and presence of anatomic variation. A coaxial microcatheter (2.7 or 3.0 French) was selectively inserted through a 5-French catheter into the feeding artery as close to the lesion as possible. For multiple foci occupying the hepatic lobes, the right or left or both hepatic arteries were treated. For transarterial infusion therapy without embolization, an emulsion of iodized oil and an anticancer agent dissolved in contrast medium was injected with a three-way stopcock. For TACE, the emulsion was followed by injection of 0.5- to 1-mm-diameter gelatin sponge particles until cessation of blood flow was recognized under radiographic monitoring.

The following anticancer agents, in order of frequency used, were administered mostly as single agents but in some instances as part of multiple-drug therapy: doxorubicin (20–40 mg/m^2), epirubicin (30–60 mg/m^2), analogue of doxorubicin, mitomycin C, cisplatin, or zinostatin stimalamer (4–6 mg/kg body weight) [26]. The common dose of iodized oil was 5 mL/kg body weight (range, 3–10 mL). The entire dose of iodized oil and gelatin sponge particles was based on tumor size and the extent of the tumor. Follow-up consisted of dynamic CT or MRI with measurement of a tumor marker such as α-fetoprotein or des-γ-carboxyl prothrombin every 3–4 months. Therapy was repeated on demand when local recurrence (regrowth of the treated tumor), intrahepatic metastasis, or a second primary HCC was found and the patient would tolerate the therapy.

Statistical Analysis

The survival rates of patients who underwent TACE or transarterial infusion therapy without embolization were calculated from the date of diagnosis of HCC. Follow-up was ended on December 31, 2003. The primary end point was all-cause mortality. For the analysis of the patient characteristics of the TACE and therapy without embolization groups, chi-square or Mantel Trend chi-square tests were used. All-cause mortality was analyzed with univariate and multivariate Cox proportional hazards regression models.

Because this study was nonrandomized and observational, potential confounding (selection) bias was accounted for with propensity score analysis [27–29] and a multivariate Cox proportional hazards model. The propensity score is the probability that a patient with specific prognostic factors will receive treatment. It is a scalar summary of all observed prognostic factors. Within propensity score strata, prognostic factors in treated and control groups are similarly distributed, so that stratifying on propensity score strata removes overt selection bias due to the prognostic factors. We computed the propensity

TABLE 1: Baseline Characteristics of Patients With Unresectable Hepatocellular Carcinoma Who Underwent Transarterial Chemoembolization With Iodized Oil and Transarterial Iodized Oil Infusion Chemotherapy Without Embolization (n = 11,030)

Background Factor	Transarterial Chemoembolization With Iodized Oil (n = 8,507)		Transarterial Iodized Oil Infusion Chemotherapy Without Embolization (n = 2,523)		p
	No. of Patients	%	No. of Patients	%	
Age (y)					0.0144
< 60	1,845	22	604	24	
≥ 60	6,645	78	1,908	76	
Sex					0.4076
Men	6,120	72	1,836	73	
Women	2,385	28	686	27	
Degree of liver damage					< 0.0001
A	4,000	51	1,046	45	
B	3,052	39	964	41	
C	768	10	332	14	
Hepatitis B and C virus status					0.664
Hepatitis B surface antigen negative, hepatitis C virus antibody positive	6,063	74	1,795	74	
Hepatitis B surface antigen positive, hepatitis C virus antibody negative	895	11	266	11	
Both positive	212	3	58	2	
Both negative	972	12	311	13	
Maximum tumor size (cm)					0.0004
< 2	1,986	24	597	24	
2.1–3	1,980	24	577	24	
3.1–5	2,319	28	584	24	
> 5.1	2,072	25	684	28	
No. of tumors					0.0016
1	3,645	43	1,040	42	
2–3	2,676	32	689	28	
≥ 4	2,065	25	722	29	
Degree of portal vein invasion					< 0.0001
Vp0	6,881	88	1,777	77	
Vp1	322	4	90	4	
Vp2	305	4	130	6	
≥ Vp3	347	4	297	13	
Degree of hepatic vein invasion					< 0.0001
Vv0	7,246	97	1,936	95	
≥ Vv1	243	3	106	5	
α-Fetoprotein level (ng/mL)					< 0.0001
< 20	2,745	34	724	30	
21–400	3,393	42	994	41	
> 401	2,001	25	700	29	
TNM stage					< 0.0001
I (T1N0M0)	915	12	280	13	
II (T2N0M0)	2,908	39	719	34	
III (T3N0M0)	2,972	40	775	37	
IVA (T4N0M0)	639	9	318	15	

Note—Numbers in the sections do not equal those in the number columns because of missing values on the questionaire. Some percentages do not total 100 due to rounding.

TABLE 2: Degree of Liver Damage According to the Classification of the Liver Cancer Study Group of Japan

Clinical or Laboratory Finding	Grade of Liver Damage		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin concentration (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin concentration (g/dL)	>3.5	3.0–3.5	<3.0
Indocyanine green retention rate at 15 minutes (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

Note—Degree of liver damage is based on the highest grade containing at least two findings. For example, grade C applies if a patient has three clinical findings, one in column B and two in column C.

TABLE 3: Definitions of TNM Stage Proposed by the Liver Cancer Study Group of Japan

Classification	Criteria
T category	Single lesion, tumor diameter 2 cm or less, and no vascular or biliary invasion
T1	Fulfilling 3 criteria
T2	Fulfilling 2 criteria
T3	Fulfilling 1 criterion
T4	Fulfilling no criteria
TNM stage	
I	T1N0M0
II	T2N0M0
III	T3N0M0
IVA	T4N0M0, any T N1M0
IVB	Any T, N0–1M1

score by using multiple logistic regression with the dependent variable receiving TACE. The independent variables (prognostic factors) were the first nine variables (all but TNM stage) in Table 1.

To provide optimal control for confounding, propensity-based matching was used to select control patients similar to patients undergoing TACE. Using a macro (available at http://www2.sas.com/proceedings/sugi26/p214-26.pdf), we used propensity scores to match TACE patients to unique patients undergoing transarterial infusion therapy without embolization. We tried to match the background characteristics of the patient in the two groups by using propensity scores identical to five digits. If we could not make the match, we proceeded to four-, three-, two- and one-digit matches. We were able to match 1,699 TACE patients to 1,699 patients undergoing transarterial therapy without embolization.

For the 3,398-patient propensity score–matched sample, the survival curves were obtained with the Kaplan-Meier method and compared by log-rank test. Although performed with a nonrepresentative sample of patients undergoing treatment, matched analyses may yield a more valid estimate of treatment effect because patients with similar observed characteristics are compared, all of whom are candidates for selection of the treatment. All significance tests were two-tailed, and a value of $p < 0.05$ was considered statistically significant. All analyses were performed with statistical software (SAS version 9.1.3, SAS).

Results

Patient Characteristics in the Whole Sample

In the baseline characteristics of patients with unresectable HCC who underwent TACE ($n = 8,507$) and those who underwent iodized oil infusion chemotherapy without embolization ($n = 2,523$) (Table 1), there was a significant difference between the two groups in the following variables: age ($p = 0.0144$), liver function ($p < 0.0001$), maximum tumor size ($p = 0.0004$), number of tumors ($p = 0.0016$), portal and hepatic vein invasion ($p < 0.0001$), α-fetoprotein value ($p < 0.0001$), and TNM stage ($p < 0.0001$).

Crude Survival of TACE Patients and Patients Undergoing Therapy Without Embolization

During an 8-year follow-up period, 3,671 patients (43%) in the TACE group died, and data on the other 4,836 (57%) were censored; 1,373 patients (54%) in the therapy without embolization group died, and the data on 1,150 patients (46%) were censored. The median follow-up period was 1.39 years (range, 0.003–7.99 years) for the TACE group and 0.95 year (range, 0.003–7.97 years) for the therapy without embolization group. The median time and overall survival rates at 1-, 2-, 3-, 4-, 5-, and 7-years were 2.76 years and 82%, 62%, 46%, 34%, 25%, and 15% for the TACE group and 1.69 years and 66%, 45%, 31%, 23%, 15%, and 7% for the therapy without embolization group. There was a significant difference between two therapies (hazard ratio [HR], 0.60; 95% CI, 0.56–0.64; $p = 0.0001$).

Multivariate analysis of factors affecting time to death of patients who underwent TACE and iodized oil infusion chemotherapy without embolization showed that the following seven covariates were independent factors (Table 4): treatment (HR, 0.63; 95% CI, 0.59–0.68; $p = 0.0001$), degree of liver damage ($p = 0.0001$), maximum tumor size ($p = 0.0001$), number of tumors ($p = 0.0001$), portal vein invasion ($p = 0.0001$), hepatic vein invasion ($p = 0.001$), and α-fetoprotein value ($p = 0.0001$).

Survival of TACE Patients and Patients Undergoing Therapy Without Embolization Matched by Propensity Score

The baseline characteristics of 1,699 patients treated with TACE and 1,699 treated with transarterial iodized oil infusion chemotherapy without embolization matched by propensity score are shown in Table 5. Unlike the population as a whole, these two propensity-matched groups were well balanced. Regarding portal vein invasion, a significant difference seen among four subgroups was not seen in two subgroups categorized as Vp0–Vp1 and greater than Vp3.

The median follow-up periods for the TACE and infusion chemotherapy without embolization groups were 1.82 and 1.06 years, respectively. The patients with TACE had a lower risk of death than those who underwent treatment without embolization (HR, 0.70; 95% CI, 0.63–0.76; $p = 0.0001$). The median survival time and overall survival rates at 1-, 2-, 3-, 4, 5-, and 7-years were 2.74 years and 81%, 62%, 46%, 34%, 25%, and 15% for TACE versus 1.98 years and 71%, 49%, 33%, 23%, 16%, and 7% for therapy without embolization (Fig. 1).

Discussion

Infusion therapy of an emulsion of iodized oil and an anticancer agent without gelatin

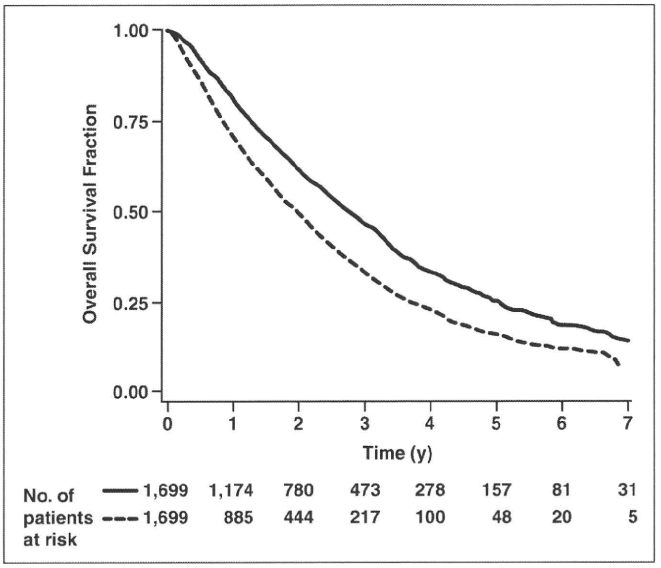

Fig. 1—Graph shows comparison of survival rates among patients with unresectable hepatocellular carcinoma treated with iodized oil transarterial chemoembolization (TACE) (n = 1,699 patients) (*solid line*) and those treated with iodized oil transarterial infusion therapy without embolization (n = 1,699) (*dotted line*) and matched by propensity score. TACE had significantly higher survival rate than therapy without embolization (hazard ratio, 0.70; 95% CI, 0.63–0.76; p = 0.0001).

TABLE 4: Results of Cox Proportional Hazards Model Multivariate Analysis of Factors Affecting Time to Death (n = 11,030)

Variable	Estimate	Standard Error	p	Hazard Ratio	
				Ratio	95% CI
Treatment (TACE vs no embolization)	−0.4556	0.0385	0.0001	0.63	0.59–0.68
Sex (male vs female)	0.0731	0.0383	0.056	1.08	0.99–1.16
Age (y) (≥ 60 vs < 60)	0.0551	0.0386	0.15	1.06	0.98–1.14
Liver damage					
Grade B vs A	0.3711	0.0358	0.0001	1.45	1.35–1.56
Grade C vs A	0.8566	0.0508	0.0001	2.36	2.13–2.60
Maximum tumor size (cm)					
2.1–3 vs ≤ 2	0.2076	0.0523	0.0001	1.23	1.11–1.36
3.1–5 vs ≤ 2	0.3802	0.0499	0.0001	1.46	1.33–1.61
≥ 5.1 vs ≤ 2	0.6689	0.0533	0.0001	1.95	1.76–2.17
No. of tumors					
2–3 vs 1	0.2593	0.0396	0.0001	1.30	1.20–1.40
≥ 4 vs 1	0.4990	0.0416	0.0001	1.65	1.52–1.79
Vascular invasion					
Vp1–≥ 3 vs Vp0	0.6137	0.0520	0.0001	1.85	1.67–2.05
≥ Vv1 vs Vv0	0.2649	0.0806	0.001	1.30	1.11–1.53
α-Fetoprotein (ng/mL)					
21–400 vs ≤ 20	0.2562	0.0412	0.0001	1.29	1.19–1.40
≥ 401 vs ≤ 20	0.7338	0.0454	0.0001	2.08	1.91–2.28

Note—TACE = transarterial iodized oil chemoembolization; no embolization = transarterial iodized oil infusion chemotherapy without embolization.

sponge particles was developed as a variation of TACE in the mid-1980s in Japan mainly to prevent posttherapeutic hepatic failure and to delay death among patients with poorer liver function and a more advanced stage of cancer than would be managed with TACE. Therapy without embolization continues to account for approximately one fourth of transarterial chemotherapeutic procedures [5].

The survival of patients who have undergone TACE and transarterial infusion therapy without embolization has stood in delicate balance between therapeutic effect against HCC and inadvertent injury to the noncancerous hepatic parenchyma. Pathologic study of resected specimens of HCC managed with TACE and with therapy without embolization revealed that TACE was associated with significantly more extensive tumor necrosis than was therapy without embolization [30, 31], whereas injury to noncancerous hepatic parenchyma has seldom been reported pathologically and clinically. An animal study [32] showed that intraarterial injection of iodized oil followed by gelatin sponge particles caused necrosis in the normal hepatic parenchyma that occurred in parallel with an increased dose of iodized oil, whereas injection of iodized oil alone did not induce necrosis. These findings are consistent with our impression of these therapies. TACE causes postembolization syndrome more frequently than does iodized oil infusion chemotherapy without embolization [19]. One serial clinical study of emulsion of iodized oil and zinostatin stimalamer, a lipophilic chemotherapeutic agent, with and without gelatin sponge particles showed that the former induced a higher response rate for HCC and more frequent impairment of hepatic function [33] than did the latter [34].

In our study of crude survival, TACE had a significantly higher overall survival rate than did therapy without embolization (HR, 0.60; 95% CI, 0.56–0.64; p = 0.0001). The median survival time and overall survival rates of therapy without embolization at 1-, 2-, 3-, and 5 years were 1.69 years and 66%, 45%, 31%, and 15%. The results in the literature are widely different from one series to another: a median survival time of 45 days [35], a 1-year survival rate of 25–82% [15, 19], a 2-year survival rate of 6–54% [15, 17], a 3-year survival rate of 24–40% [13, 19], and a 5-year survival rate of 18% [16]. The 1- to 5-year survival rates in our study were not inconsistent with those in other studies. In our study, patients who underwent TACE had better survival rates than patients in European [10, 11] and other Asian [7] series. The results may be due to the more preferable patient characteristics in our study for undergoing either transarterial therapy than was found in the other studies. More than 40% of patients in our study had a solitary HCC, and one fourth of them had HCCs smaller than 2 cm in diameter (Table 1).

Adjustment with multivariate analysis and the Cox proportional hazards model showed that TACE was associated with a better survival rate than was therapy without embolization (HR, 0.63; 95% CI, 0.59–0.68). We

TABLE 5: Baseline Characteristics of Patients in Two Groups Matched by Propensity Score (n = 3,398)

Background Factor	Transarterial Chemoembolization With Iodized Oil (n = 1,699)		Transarterial Iodized Oil Infusion Chemotherapy Without Embolization (n = 1,699)		p
	No. of Patients	%	No. of Patients	%	
Age (y)					0.75
< 60	422	25	414	24	
≥ 60	1,277	75	1,285	76	
Sex					0.52
Men	1,232	73	1,215	72	
Women	467	27	484	28	
Degree of liver damage					0.81
A	782	46	778	46	
B	696	41	694	41	
C	221	13	227	13	
Hepatitis B and C virus status					0.95
Hepatitis B surface antigen negative, hepatitis C virus antibody positive	1,282	75	1,269	75	
Hepatitis B surface antigen positive, hepatitis C virus antibody negative	165	10	172	10	
Both positive	36	2	39	2	
Both negative	216	13	219	13	
Maximum tumor size (cm)					0.59
< 2	475	28	463	27	
2.1–3	431	25	422	25	
3.1–5	394	23	413	24	
≥ 5.1	399	24	401	24	
No. of tumors					0.77
1	772	45	754	44	
2–3	472	28	494	29	
≥ 4	455	27	451	27	
Degree of portal vein invasion					0.03
Vp0	1,432	84	1,428	84	
Vp1	91	5	47	3	
Vp2	81	5	68	4	
≥ Vp3	95	6	156	9	
Degree of hepatic vein invasion					0.25
Vv0	1,630	96	1,616	95	
≥ Vv1	69	4	83	5	
α-Fetoprotein level (ng/mL)					0.19
< 20	560	33	533	31	
21–400	724	43	720	42	
> 401	415	24	446	26	
TNM stage					0.44
I (T1N0M0)	259	15	252	15	
II (T2N0M0)	636	37	628	37	
III (T3N0M0)	616	36	626	37	
IVA (T4N0M0)	188	11	193	11	

Note—Some percentages do not total 100 due to rounding.

compared the survival rates by performing patient-to-patient matching and computing the propensity score by logistic regression of the independent prognostic factors with all of the variables in Table 1 except TNM stage. As a result, the hazard ratio for death in the TACE compared with the therapy without embolization group was 0.70 (95% CI, 0.63–0.76; $p = 0.0001$), suggesting that TACE significantly reduced the overall risk of death 30%. This finding means embolization may be indispensable to better survival among patients with unresectable HCC. That is, the more intensive therapeutic effect of TACE may take precedence over the lower risk of inadvertent liver injury associated with therapy without embolization. Caturelli et al. [36] reported that the worsening of liver function expected in the long term with TACE did not occur. Results of phase 2 studies of transcatheter arterial therapy for HCC with drug-eluting beads with doxorubicin [37] and ^{90}Y-microspheres [38] and a cohort study of bland embolization with trisacryl gelatin microspheres without an anticancer agent and iodized oil [39] have been reported.

There were limitations to our study. The propensity score analysis might have matched the background of patients to have the same possibility of receiving one of the two therapies. This method, however, includes factors for insufficiency of treatment protocol among institutions and laboratory data that might affect survival. Another limitation was incomplete information about the doses of anticancer agents and iodized oil used, the total number of treatments, and Child-Pugh class because questions were overlooked on the questionnaire of the registration sheet.

Although a randomized controlled trial remains the reference standard, our analysis of an entire sample and of matched patients with a propensity score showed that in the care of patients with unresectable HCC, the survival rate associated with TACE was significantly higher than that associated with iodized oil infusion chemotherapy without embolization. These results may enhance or change decision-making about the strategy for transcatheter arterial therapy for HCC.

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