

症例④ 胃GIST多発肝転移(図5)

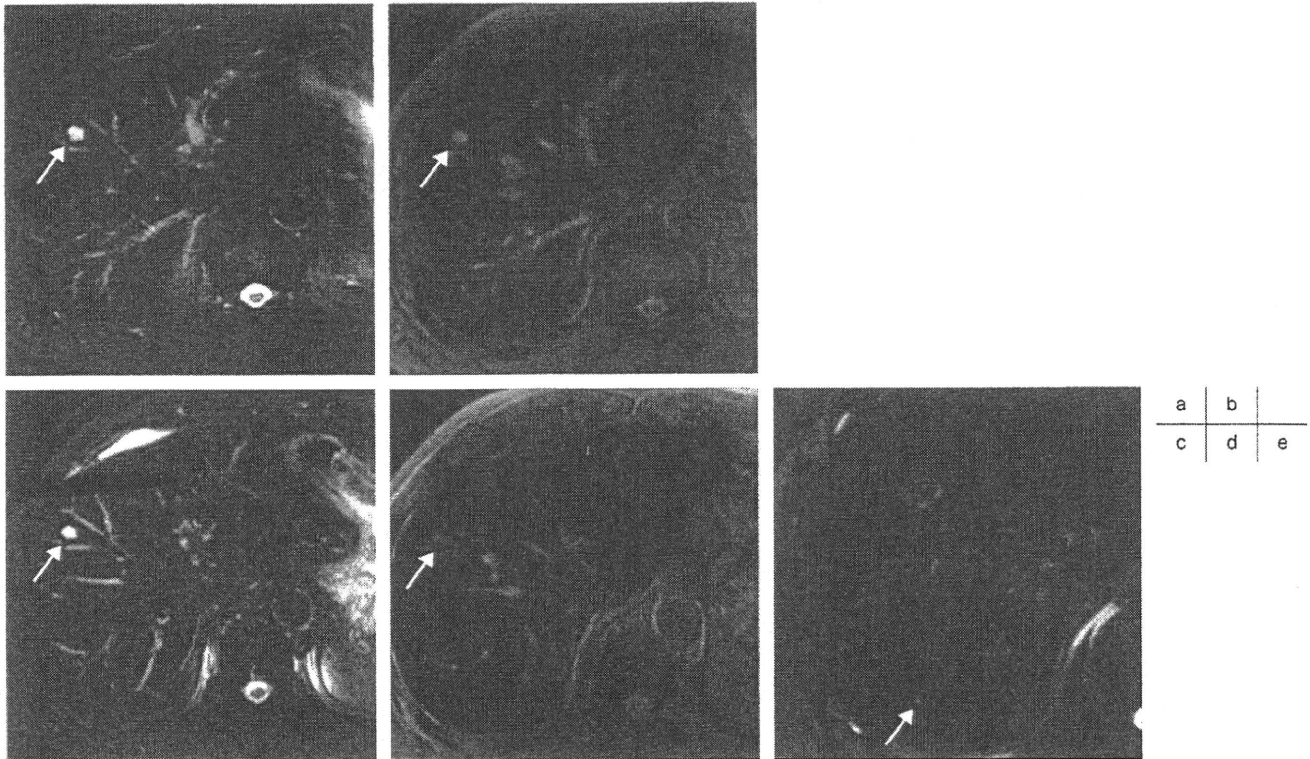


図5 症例4: 1.5T MRIと3T MRIによるSPIO造影MRI

- a: 1年前に撮像された1.5T MRIによるSPIO造影後脂肪抑制T2*強調横断像。肝S₈に高信号を呈する結節を認める(↑)。
 - b: 1年前に撮像された1.5T MRIによるSPIO造影後T2*強調横断像。肝S₈病変は高信号を呈している(↑)。
 - c: 3T MRIによるSPIO造影後脂肪抑制T2*強調横断像。aと比較して背景肝の磁化率効果による低信号化が強く、肝S₈の病変とのコントラストが明瞭である(↑)。
 - d: 3T MRIによるSPIO造影後脂肪抑制T2*強調横断像。bと比較して背景肝の磁化率効果による低信号化が強く、肝S₈の病変とのコントラストが明瞭である(↑)。
 - e: 3T MRIによるSPIO造影後SPACEを用いたT2強調横断像。肝S₇に高信号を呈する微小な結節を認める(↑)。
- 3T MRIは、1.5T MRIより磁化率効果が増強され、SPIOを取り込む背景肝の信号低下はより顕著となるため、病変とのコントラストは高くなる。しかし、aとc、bとdを比較すると、胃と近接する肝左葉外側区では、磁化率アーチファクトとRF不均一性の影響による無信号域が3T MRIの方で顕著に認められる。また、eでは微小な病変が背景肝と高いコントラストを有して描出されている。3T MRIのSPACE(2mm厚)はSNRを保ったまま高い空間分解能を有していると言える。



3T MRIでは、細胞外液性Gd造影剤、あるいはGd-EOB-DTPA、SPIOなどの肝特異性造影剤のいずれを使用しても高いSNRとCNRを有し、空間分解能を上げても1.5T MRIより良好なコントラストを有する画像が得られる。これにより、微小な病変の検出や詳細な病変内部の性状評価が可能となっている。しかし、患者の状態や撮像方法によっては、3T MRI独特の画像劣化が顕著となり、診断に支障を来す恐れがある。造影MRIが患者にとって有益な検査となるためには、3T MRIの利点と欠点を熟知しておく必要があることを改めて強調したい。

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Liver / Other

SE-083

Hepatic venous phase of the liver is already affected by hepatobiliary uptake of Gd-EOB-DTPA: comparison between Gd-EOB-DTPA and Gd-DTPA in dynamic MRI on 3.0-T apparatus

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Purpose: To reveal the difference in contrast enhancement of the liver in comparison to other abdominal structures on dynamic contrast-enhanced MRI (DCE-MRI) using gadoteric acid (Gd-EOB-DTPA: EOB) and gadobutrol acid (Gd-DTPA) in the same patients.

Material and Methods: DCE-MRI on a 3.0-T apparatus using EOB and Gd-DTPA was performed in the same 17 patients. Precontrast and DCE-MRI images [arterial phase (AP), portal venous phase (PP), hepatic venous phase (HP)] were acquired before and after bolus injection of each contrast agent. Signal intensity ratio of organ-to-muscle [liver (L/M), spleen (S/M), aorta (A/M), portal vein (P/M) and hepatic vein (H/M)] were calculated at each phase and statistically analyzed.

Results: Between EOB and Gd-DTPA, there were no significant differences in the means of L/M, S/M, A/M, P/M or H/M on precontrast images, L/M at AP, or L/M at PP. At all phases, the mean S/M (AP, 2.06, 2.70, $p < 0.01$; PP, 1.97, 2.33, $p < 0.001$; HP, 1.80, 2.09, $p < 0.01$), A/M (AP, 2.78, 3.50, $p < 0.01$; PP, 2.36, 2.82, $p < 0.001$; HP, 2.15, 2.61, $p < 0.001$), P/M (AP, 1.98, 2.47, $p < 0.01$; PP, 2.65, 2.96, $p < 0.05$; HP, 2.30, 2.65, $p < 0.01$) and V/M (AP, 1.11, 1.23, $p < 0.05$; PP, 2.65, 2.84, $p < 0.001$; HP, 2.22, 2.67, $p < 0.001$) with EOB were all lower than the respective values with Gd-DTPA. On HP, the mean L/M (1.99, 1.88, $p < 0.05$) with EOB was higher than that with Gd-DTPA.

Conclusion: On DCE-MRI on 3.0-T using EOB, contrast enhancement of all organs except for the liver was lower than that of other organs on DCE-MRI using Gd-DTPA, but that of the liver at HP was already affected by the hepatobiliary uptake of EOB.

Mesentery and Peritoneum

SE-084

Spontaneous hemoperitoneum: a diagnostic challenge
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Purpose: Spontaneous hemoperitoneum is an emergency condition, the diagnosis of which is usually difficult to be made only by clinical criteria.

Material and Methods: A review of our institution cases, for the last 5 years, was carried out. Examinations were performed in a 16x MDCT before and after IV contrast administration and scans were taken at arterial, portal venous and delayed phase. The presence of active bleeding and the cause of the bleeding were assessed.

Results: Ten cases of spontaneous hemoperitoneum were found. Active extravasation was present in 5 patients. In 9 cases, there were direct (active bleeding) or indirect (sentinel clot) signs that implicated the exact cause of the bleeding. In 3 circumstances, the origin of the bleeding was the liver (2 HCCs, 1 metastases from choriocarcinoma), in 2 a ruptured ovary cyst, in 1 spontaneous bleeding of the spleen, in 1 the splenic artery which had been eroded because of pancreatitis, in 1 the small intestine and in 1 cirrhotic patient a dilated portosystemic shunt. In 1 patient, the cause of bleeding was not determined initially, although sentinel clots were present in the epigastrium. Three days later, a second CT revealed an abnormal vessel at the greater curvature of the stomach, which was considered the cause of bleeding.

Conclusion: CT is the examination of choice in the diagnosis of spontaneous hemoperitoneum. In the majority of cases, it can reliably determine the cause of the bleeding.

Other / Acute and Post-Traumatic Abdomen

SE-085

Focused assessment with sonography for trauma as screening method in trauma patients with blunt abdominal injuries: a prospective study
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Purpose: Blunt abdominal trauma is a diagnostic challenge to the emergency radiology. The aim of the study is to determine FAST (focused assessment with sonography for trauma) as screening method in trauma patients with blunt abdominal injuries.

Material and Methods: From March 2008 to April 2009, we examined in our department with ultrasonography (FAST) according to protocol 756 hemodynamically stable trauma patients with suspected blunt abdominal injuries. In most of these cases, a CT scan was necessary to be performed.

Results: Ultrasonography examination was positive in 72 patients. The results of FAST were compared with findings of CT scan, diagnostic peritoneal lavage, laparotomy and clinical course when the FAST was positive or followed by a period of clinical observation when the FAST was negative.

Conclusion: The FAST examination is a routine component of the initial work-up of trauma patients with high sensitivity to detect free fluid which would lay a suspicion for a parenchyma lesion. We must remember that a negative ultrasonography does not exclude an abdominal injury. In this case, another imaging procedure such as CT should be performed.

Other / Radiologic-Pathologic Correlation

SE-086

Optimization of b value in diffusion MRI for detection and characterization of abdominal benign and malignant lesions
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Purpose: To determine the optimal b value in diffusion-weighted imaging (DWI) for detection and differentiation of benign and malignant abdominal lesions.

Material and Methods: Routine abdomen MRI and single shot echo planar DWI were prospectively performed using seven b values (50, 200, 400, 500, 600, 800, 1000 s/mm²). 66 lesions in 58 patients who had pathologically proven diagnosis of the malignant or benign diseases obtained after MRI examinations were included. The image quality was analyzed on a five-point scale and by measurement of the signal-to-noise ratio (SNR). The lesion detectability was analyzed by measurement of the contrast-to-noise ratio (CNR). The lesions were analyzed for benignity/malignancy on a 5 point scale, and by measurement of the apparent diffusion coefficient (ADC) values and lesion ADC/normal parenchyma ADC.

Results: Significant differences were found in visual scores between different b values ($p < 0.01$). Lower b values correlated with better DW image quality and lesion detectability. The SNR and CNR with b values of 50 and 200 s/mm² were significantly high from that with b400 and higher b values. Differentiation of malignant from benign abdominal lesions using visual scoring was found successful with 600 and higher b values. The mean ADC values of malignant lesions inversely correlated with b values. The mean ADC values with a b value of 200 s/mm² and ADC ratio for b200 and ADC with all b values of malignant lesions were significantly lower than those of benign lesions on DWI ($p < 0.05$).

Conclusion: Image quality and lesion detectability are better with low b values around 50 and 200 s/mm². The lesion ADC/normal parenchyma ADC are more accurate for differentiation of malignant and benign abdominal lesions.

SE-087

Abdominal lesions in post-mortem non-enhanced CT-scan: correlations with forensic autopsy

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Purpose: To investigate the interest of post-mortem non-enhanced CT for abdominal damages in a forensic context of suspect death.

Material and Methods: 30 cadavers have been submitted to a body CT-scan without injection of contrast material. CT exams were reviewed by two independent radiologists and radiological findings were compared with forensic autopsy data.

Results: False negative CT findings included small contusions, vascular thromboses, acute infarcts foci, and non-radioopaque foreign bodies. False positive CT findings included physiological post-mortem transudates misdiagnosed with intra-abdominal bleedings and putrefaction gas misdiagnosed with gas embolism, aeroperity, aerobily, digestive parietal pneumatosis. Incidentalomas without any role in death process were also reported. CT could diagnose solid organ fractures, digestive perforations, hematomas and massive hemorrhages, metallic foreign bodies, advanced tumors, aortic dissections (when the flap was calcified). CT was helpful to guide autopsy and to show knife and ballistic trajectories. CT showed postoperative scars (on vascular map, biliary tree, digestive tract or solid organs) which were anatomical arguments during identification process. CT images constituted an useful numerical memory of the cadaver for cross-examination.

Conclusion: The radiologist should be familiar with the normal abdominal post-mortem features to avoid misdiagnoses and detect informative lesions which can help and guide the forensic practitioner. This study shows the interest of a radiological examination of cadavers by CT (even without any injection of contrast material) before forensic autopsy.

Effect of Aging on Risk for Hepatocellular Carcinoma in Chronic Hepatitis C Virus Infection

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An increase in the aging population is an impending problem. A large cohort study was carried out to determine the influence of aging and other factors on hepatocarcinogenesis in patients treated with interferon. Biopsy-proven 2547 chronic hepatitis C patients registered at our referral center since 1992 were included. Of these, 2166 were treated with interferon-based therapy. Incidences of hepatocellular carcinoma (HCC) associated with interferon were analyzed by Kaplan-Meier and person-years methods for an average follow-up of 7.5 years. Factors associated with HCC risk were determined by Cox proportional hazard analysis. HCC developed in 177 interferon-treated patients. The risk for HCC depended on age at primary biopsy and increased more than 15-fold after 65 years of age. Even when stratified by stage of fibrosis, the cumulative and annual incidences of HCC were significantly higher in older patients than in younger patients ($P < 0.001$) at the same stage of fibrosis, except for cirrhosis. Progression of fibrosis over time was significantly accelerated in older patients. The impact of viral eradication on HCC prevention was less significant in older patients than in younger patients. Multivariate analysis confirmed that age, gender, liver fibrosis, liver steatosis, total cholesterol level, fasting blood sugar level, baseline and postinterferon alpha-fetoprotein level, and virological response to interferon were independent risk factors associated with HCC. Aging was the strongest risk factor for a nonvirological response to interferon-based antiviral therapy. **Conclusion:** Elderly patients are at a higher risk for HCC. Hepatitis C viral eradication had a smaller effect on hepatocarcinogenesis in older patients. Patients should therefore be identified at an earlier age and treatment should be initiated. (HEPATOLOGY 2010;52:518-527)

Primary liver cancer is the third most common cause of cancer mortality worldwide,¹ and hepatocellular carcinoma (HCC) is one of the most frequent primary liver cancers.^{2,3} Infection with hepatitis C virus (HCV) is a common cause of chronic hepatitis, which progresses to HCC in many patients.⁴ The prevalence of older patients has been increasing in

Japan, and this is an impending problem in other countries where viral spread has occurred more recently.⁵ The number of Americans older than 65 years is expected to double by the year 2030.⁶ In Western Europe, people older than 65 years already constitute 15%-18% of the population⁷; thus, aging patient who is chronically infected with HCV is

Abbreviations: AFP, alpha-fetoprotein; HBe, hepatitis B core; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; SVR, sustained virological response.

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Received December 4, 2009; accepted March 15, 2010.

Supported by grants from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, and the Japanese Ministry of Welfare, Health, and Labor.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.23691

Potential conflicts of interest: Nothing to report.

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one of the most important issues confronted by physicians.

Viral eradication with interferon-based therapy for chronic hepatitis C has been shown to prevent HCC by studies conducted in Japan and Italy.⁸⁻¹¹ However, this finding is controversial according to another study conducted in Europe and Canada,¹² in which viral eradication did not significantly reduce the risk for HCC in 479 consecutively treated patients. The likelihood of development of HCC among interferon-treated patients is difficult to determine because of the paucity of adequate long-term cohort studies. Moreover, in patients who are treated with interferon the effect of certain factors, including aging, on the risk for HCC remains unclear. Furthermore, the benefit of viral eradication with interferon-based therapy, including pegylated interferon and ribavirin combination therapy, in older patients remains unknown. To further clarify this, we conducted a large-scale, long-term cohort study and analyzed the influence of aging and other host and virological factors in patients treated with interferon.

Patients and Methods

Patients. Consecutive patients (n = 2547) chronically infected with HCV who underwent liver biopsy between 1992 and January 2008 at our referral center were enrolled. Of these, 2166 patients were treated with interferon-based antiviral therapy, whereas 381 patients did not receive interferon treatment (Fig. 1). All patients had histologically proven chronic hepatitis or cirrhosis. HCV infection was proven in all patients by identification of HCV RNA. Patients with a history of HCC, autoimmune hepatitis, or primary biliary cirrhosis were excluded. We also excluded patients who had a history of excessive alcohol consumption (50 g/day) and confirmed alcohol abstinence during follow-up. No patient was positive for hepatitis B surface antigen or antihuman immunodeficiency virus antibody. Written informed consent was obtained from all patients. The study was approved by the Ethical Committee of Musashino Red Cross Hospital in accordance with the Declaration of Helsinki.

Histological Evaluation. A liver biopsy specimen was obtained laparoscopically using 13G needles. When laparoscopy was impossible, ultrasound-guided liver biopsy was performed with 15G needles (n = 254). The mean length of the specimen was 18 mm (range 12-40 mm), and the mean number of portal tracts was 17 (range 8-34). Liver biopsy specimens

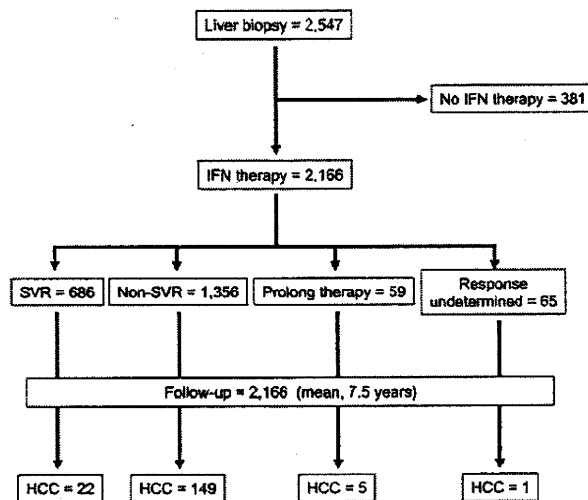


Fig. 1. Clinical outcomes of the patients enrolled in the present study. HCC, hepatocellular carcinoma; SVR, sustained virological response.

were scored by board-certified pathologists for stage of fibrosis and grade of inflammatory activity according to the classification of Desmet et al.¹³ Additional macroscopic pathological information was obtained from laparoscopic findings. The percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis. In this study, superimposed nonalcoholic steatohepatitis (NASH) was defined as a central pattern of colocalization of hepatic steatosis and hepatocyte ballooning with pericellular/perisinusoidal fibrosis or Mallory hyaline.

Interferon Treatment. Among the 2166 patients treated with interferon-based antiviral therapy, 1062 patients received interferon-alpha or beta monotherapy either for 24 weeks (n = 1003) or for 2 to 5 years (n = 59); 386 patients received interferon-alpha and ribavirin combination therapy for 24 weeks; 306 received pegylated interferon-alpha monotherapy for 48 weeks; and 412 received pegylated interferon-alpha and ribavirin combination therapy for 48 weeks. All interferon treatment was initiated within 48 weeks after liver biopsy.

Definitions of Response to Interferon Therapy. A patient negative for serum HCV RNA after the first 6 months of completion of interferon-based therapy was defined as a sustained viral responder. HCV RNA was determined by the qualitative Amplicor or TaqMan HCV assay (Roche Molecular Diagnostics, Tokyo, Japan).

Data Collection and Patient Follow-up. Data on patient characteristics, biochemical data, hematological

data, virological data, histological data, and treatment details were collected at enrollment. Age was determined at primary liver biopsy. Patients were examined for HCC with abdominal ultrasonography, dynamic computed tomography, and/or magnetic resonance imaging every 3-6 months. Serum alpha-fetoprotein (AFP) levels were measured every 1-2 months. This screening program constitutes the standard of care in Japan. To evaluate the effect of interferon-induced AFP reduction on hepatocarcinogenesis, the average AFP level after interferon treatment was calculated in each patient. HCC diagnosis was confirmed with needle biopsy, surgically resected specimens, or typical radiological findings diagnosed by board-certified radiologists. Figure 1 shows the schema for patient follow-up and clinical outcomes.

The start date of follow-up was the date of primary liver biopsy and the endpoint of follow-up was the development of HCC or the latest medical attendance until January 2009. The mean follow-up period was 7.5 years (range 0.5-17 years). The factors associated with development of HCC were retrospectively analyzed.

Change in Fibrosis Staging Over Time. To evaluate change in fibrosis staging over time, 271 patients who had not achieved a sustained virological response (SVR) with interferon therapy underwent a sequential biopsy after the initial biopsy. The interval between the paired biopsies was on average 4.8 years (range 0.7-14 years). The yearly rate of progression of fibrosis was calculated as the change in fibrosis staging divided by the time between paired biopsies.

Statistical Analysis. Categorical data were compared by the chi-square test and Fisher's exact test. Distributions of continuous variables were analyzed with Student's *t* test or the Mann-Whitney *U* test for two groups. All tests of significance were two-tailed and a *P* value of <0.05 was considered statistically significant. The cumulative incidence curve was determined with the Kaplan-Meier method and differences among groups were assessed using the log-rank test. Factors associated with HCC risk and virological response to interferon therapy were determined by the Cox proportional hazard model and logistic regression analysis, respectively. To depict the role of aging in developing risk for HCC, the multivariate Cox proportional hazard model was used after adjusting for stage of liver fibrosis, steatosis, and virological response to interferon. A polynomial regression was used to fit risk ratios for segments of the age distribution. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 11.0 (SPSS, Chicago, IL).

Results

Patient Characteristics. Patient characteristics at the time of enrollment are shown in Table 1. The distribution of stages of liver fibrosis differed between younger and older patients, indicating the need to adjust for stage of liver fibrosis when comparing the two subgroups.

Response to Interferon Therapy. The response to interferon therapy was determined in 2042 (97.2%) of the interferon-treated patients, excluding those who received prolonged interferon treatment at the endpoint. SVR rates are shown in Table 1. The percentage of patients showing SVR was significantly lower in older patients (≥ 65 years) than in younger patients (< 65 years) ($P < 0.001$). Overall response rates to the different types of interferon therapy were as follows: interferon monotherapy, 31.5% (312/992); interferon-alpha and ribavirin combination therapy, 28.6% (108/378); pegylated interferon-alpha monotherapy, 37.9% (108/285); and pegylated interferon-alpha and ribavirin combination therapy, 41.1% (159/387). Response rates in genotype-1 patients ($n = 1347$) were 20.6% (114/554), 17.9% (29/162), 18.9% (56/297), and 36.8% (123/334), and those in nongenotype-1 patients ($n = 565$) were 52.2% (163/312), 63.1% (77/122), 65.0% (52/80), and 70.6% (36/51). Overall response rates of interferon and pegylated interferon monotherapy seem to be high because of the high response rates in the nongenotype-1 patients treated with these regimens.

Overall Cumulative Incidence of HCC. During follow-up, HCC developed in 177 interferon-treated patients (Fig. 1). The cumulative incidence of HCC 5, 10, and 15 years after interferon therapy was 4.7%, 11.6%, and 15.5%, respectively. The cumulative incidence in SVR patients was 2.1%, 4.3%, and 4.3%, respectively, which was significantly lower than that in non-SVR patients (5.8%, 14.9%, and 20.2%, respectively; log-rank test, $P < 0.001$).

Effect of Aging on Risk for HCC. The risk ratio determined by multivariate Cox proportional hazards analysis after adjustment for stage of liver fibrosis, degree of liver steatosis, and virological response to interferon demonstrated that the risk for HCC after interferon treatment was age-dependent and increased predominantly when the age at primary liver biopsy was > 65 years (Fig. 2A). Hence, we defined older patients as those ≥ 65 years of age at primary liver biopsy and younger patients as those aged < 65 years. As shown in Fig. 2B, the cumulative incidence of HCC was significantly higher in older patients than in younger patients (log-rank test, $P < 0.001$).

Table 1. Characteristics of Patients Enrolled in the Present Study

Characteristics	Total	<65 year	≥65 year	P Value*
Patients, n	2166	1614	552	
Sex, n (%)				<0.001†
Male	1080 (49.9)	840 (52.0)	240 (43.6)	
Female	1086 (50.1)	774 (48.0)	312 (56.4)	
Age (SD), year	55.4 (12.1)	51.1 (10.8)	68.4 (2.9)	<0.001‡
BMI (SD), kg/m ²	23.3 (3.1)	23.4 (3.0)	23.3 (3.1)	0.9‡
Fibrosis stage, n (%)				<0.001†
F0	27 (1.3)	24 (1.5)	3 (0.5)	
F1	860 (39.7)	704 (43.6)	156 (28.2)	
F2	733 (33.8)	515 (31.9)	218 (39.5)	
F3	444 (20.5)	301 (18.6)	143 (25.9)	
F4	102 (4.7)	70 (4.3)	32 (5.8)	
%Severe steatosis (≥10%)	27.6	27.1	29.3	0.4†
ALT level (SD), IU/L	95 (18)	101 (119)	76 (58)	<0.001‡
HCV load (SD), KU/mL	880 (1046)	861 (1016)	924 (1116)	0.2‡
HCV genotype, n (%)				<0.001†
1a	7 (0.3)	5 (0.3)	2 (0.4)	
1b	1414 (69.6)	1036 (68.9)	378 (71.3)	
2a	373 (18.3)	273 (18.2)	100 (18.9)	
2b	211 (10.4)	164 (10.9)	47 (8.9)	
Others	28 (1.4)	25 (1.7)	3 (0.6)	
Duration (SD), year	7.5 (4.4)	8.1 (4.4)	5.8 (3.7)	<0.001†
IFN regimen, n (%)				<0.001†
IFN mono	1062 (49.0)	833 (51.6)	229 (41.5)	
PEG-IFN mono	306 (14.1)	200 (12.4)	106 (19.2)	
IFN + RBV	386 (17.8)	291 (18.0)	95 (17.2)	
PEG-IFN + RBV	412 (19.0)	290 (18.0)	122 (22.1)	
SVR, n (%)	686 (33.6)§	565 (36.6)¶	121 (24.3)¶¶	<0.001‡

Unless otherwise indicated, data are given as the mean (SD).

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; N/A, not applicable; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

*Comparison between <65 years and ≥65 years.

†Chi-squared test.

‡Student t test.

§Virological responses were determined in 2042 patients.

¶Virological responses were determined in 1545 patients.

¶¶Virological responses were determined in 497 patients.

As shown in Fig. 2C-E, even when stratified by stage of fibrosis the cumulative incidences among patients at stages F0/F1, F2, and F3 were significantly greater in older patients than in younger patients (log-rank test, $P < 0.001$). These differences were not significant among patients with cirrhosis (Fig. 2F, log-rank test, $P = 0.7$).

The annual incidence of HCC after interferon treatment was calculated by the person-years method (Table 2); it increased with the degree of liver fibrosis from 0.2% (F0 or F1) to 4.6% (F4) and was higher among older patients at the same stage of liver fibrosis.

Among the 177 patients with HCC, 92 showed evidence of a single blood transfusion. We analyzed the relationship between duration of infection and age in these 92 patients. A significant and strong negative correlation was found between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion ($r =$

-0.74 , $P < 0.001$) (Fig. 3A). The mean duration of chronic infection was 22.0 years in patients who had received blood transfusion at >40 years of age, which was significantly shorter than that in patients who received it at ≤40 years of age (40.6 years, $P < 0.001$).

The presence of cirrhosis at the time of development of HCC, which was defined as having any of the following criteria, was evaluated: (1) histological evidence for cirrhosis, (2) findings of cirrhosis in any radiological study, or (3) presence of marked portal hypertension (i.e., presence of esophagogastric varices). Following this, 142 of the 177 with HCC (80.2%) were diagnosed as having cirrhosis, of which 42 were diagnosed histologically, 69 radiologically, and 31 based on the presence of marked portal hypertension. No significant difference was found in the proportion of patients with cirrhosis between older and younger patients, at the rate of 78.3% (94/120) in older

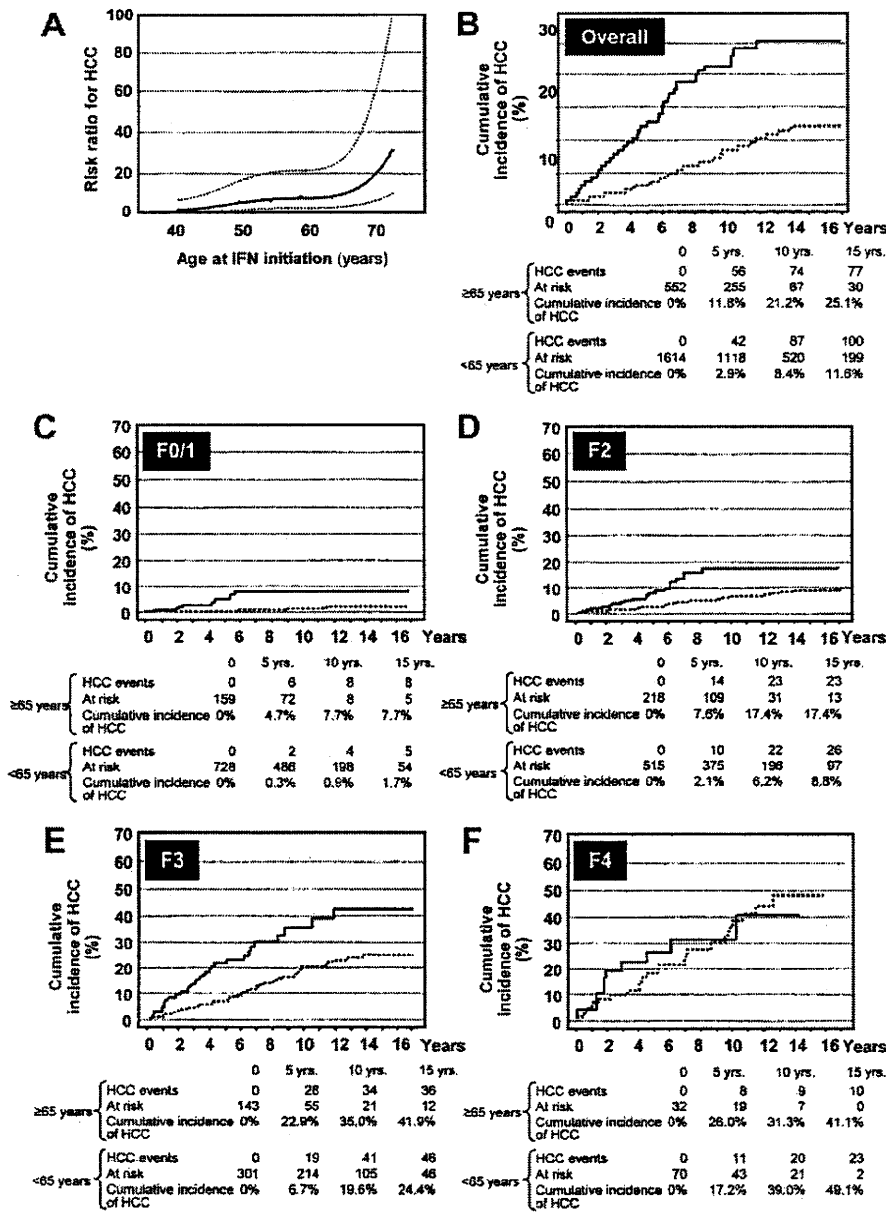


Fig. 2. Effect of aging on the risk for HCC. (A) Risk ratio (solid line) and 95% CI (dotted lines) for the risk of HCC according to age. To show the age-dependent relationship, a multivariate Cox proportional hazard model was used after adjustment for gender, stage of liver fibrosis, body mass index, and virological response to interferon therapy. Curves were fitted using polynomial regression. (B-F) Cumulative incidence of HCC after interferon therapy among younger (<65 years, n = 552, dotted line) and older patients (≥65 years, n = 1614, solid line). (B) Overall data, P < 0.001. (C) Patients with stage F0 or F1 liver fibrosis (no or mild fibrosis with portal expansion), P < 0.001. (D) Patients with stage F2 liver fibrosis (bridging fibrosis without architectural distortion), P < 0.001. (E) Patients with stage F3 liver fibrosis (bridging fibrosis with architectural distortion), P < 0.001. (F) Patients with stage F4 liver fibrosis (cirrhosis), P = 0.7. All P values were obtained by the log-rank test. The numbers of HCC events and patients at risk at each timepoint are shown below the graphs.

patients and 84.2% (48/57) in younger patients (P = 0.36, comparison at the age of HCC development).

Influence of Aging on Progression in Fibrosis Staging Over Time. In 271 patients who underwent paired biopsies, fibrosis staging progressed in 69 patients (25.5%), remained unchanged in 154 (56.8%), and regressed in 48 patients (17.7%). The overall rate of progression of fibrosis in these patients was 0.06 ± 0.02 fibrosis stages per year. Progression of fibrosis over time was significantly accelerated in older patients than in younger patients (0.21 ± 0.10 versus 0.03 ± 0.21 fibrosis stages per year, P = 0.03, Mann-Whitney U test) (Fig. 3B).

Effect of Viral Eradication on Risk for HCC in Older Patients. As shown in Fig. 4, the effect of viral eradication on the prevention of HCC was less significant in older patients than in younger patients. The annual incidence was higher among older patients than among younger patients with the same virological response (Table 2).

Influence of Liver Steatosis on Risk for HCC. The cumulative incidence of HCC after interferon therapy was significantly higher in patients with severe steatosis (≥10%) than in those with milder steatosis (at 5, 10, and 15 years: 8.6%, 19.1%, 32.0% versus 1.8%, 4.8%, 7.0%, respectively, log-rank test, P < 0.001).

Table 2. Annual Incidence of HCC After IFN Treatment

Factors	Total	<65 Years	≥65 Years
Fibrosis stage			
F0/F1	0.2%	0.1%	0.9%
F2	0.8%	0.6%	1.7%
F3	2.5%	1.8%	4.6%
F4	4.6%	4.4%	5.1%
Total	1.1%	0.8%	2.4%
Degree of liver steatosis			
<10%	0.5%	0.2%	1.4%
≥10%	2.0%	1.8%	3.0%
Virological response			
SVR	0.4%	0.2%	1.3%
Non-SVR	1.4%	1.0%	2.9%

Data were calculated by the person-years method. IFN, interferon; SVR, sustained virological response.

The annual incidence was higher in older patients than in younger patients with the same degree of liver steatosis (Table 2). In patients with severe steatosis (≥10%), superimposed NASH was diagnosed in 6.0% (26/435). Overall, superimposed NASH was significantly associated with hepatocarcinogenesis on univariate analysis (risk ratio, 4.1; 95% confidence interval [CI], 1.8-9.4; $P < 0.001$), but not on multivariate analysis. Superimposed NASH was significantly associated with high body mass index ($27.2 \pm 4.6 \text{ kg/m}^2$ versus $23.0 \pm 3.1 \text{ kg/m}^2$, $P < 0.001$), hyperglycemia ($186 \pm 67 \text{ mg/dL}$ versus $115 \pm 39 \text{ mg/dL}$, $P < 0.001$), and advanced fibrosis (F3) (risk ratio, 2.9; 95% CI, 1.4-6.0; $P = 0.005$).

Factors Associated with Hepatocarcinogenesis After Interferon Therapy. Univariate analysis demonstrated factors that increase the risk ratio for the development of HCC (Table 3). Multivariate analysis using Cox proportional hazards regression confirmed that aging was one of the most significant independent factors associated with the development of HCC after interferon therapy. In this analysis, advanced fibrosis, presence of steatosis, male gender, lower total cholesterol level, higher fasting blood sugar level, higher baseline AFP level, insignificant improvement of mean AFP level after interferon therapy, and nonresponse to interferon therapy were also significantly associated with risk for HCC (Table 3).

We identified 22 patients in whom HCC developed even after achieving SVR. Univariate and multivariate logistic regression analyses indicated that both liver steatosis and aging were independently associated with the development of HCC among patients who achieved SVR ($n = 686$) (Table 4). Anti-HBc was detected in only 4 out of 22 patients and the age distribution was similar among anti-HBc-positive and anti-HBc-negative patients.

Response to Interferon Therapy in Older Patients.

Multivariate logistic regression analysis confirmed that aging, female gender, severe liver fibrosis, extremely severe liver steatosis, genotype-1, high HCV load, and nonuse of pegylated interferon and ribavirin were independent risk factors for non-SVR (Supporting Table 1). The odds ratio, determined by multivariate logistic regression analysis after adjustment for these factors, demonstrated that the risk for non-SVR was age-dependent (Supporting Fig. 1). It was also ≈2.5 times higher in patients aged ≥65 years than in those aged <35 years.

In patients with genotype-1b and a high viral load who were treated with pegylated interferon and ribavirin combination therapy, the SVR rate was significantly lower in older patients than in younger patients (<49 years, 59.3%; 50-59 years, 50.5%; 60-65 years, 27.3%; ≥65 years, 25.2%; intention-to-treat analysis). Multivariate logistic regression analysis showed that

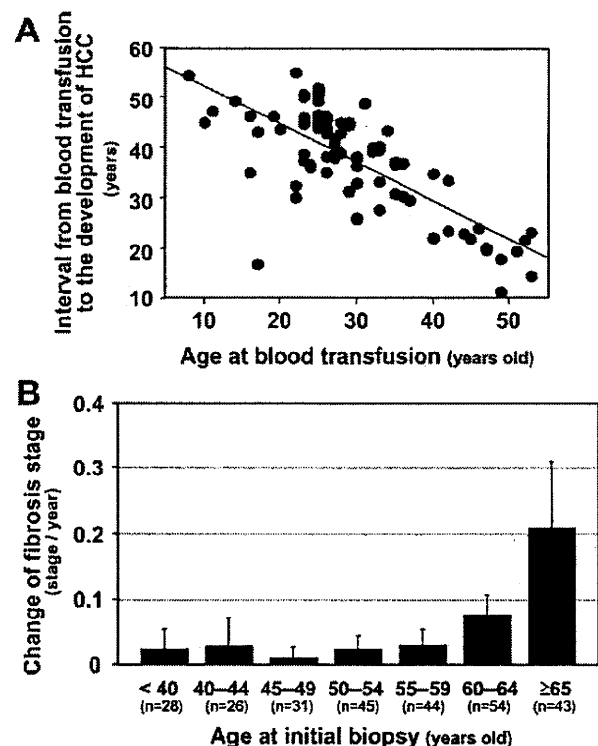


Fig. 3. (A) Relationship between the interval from blood transfusion to development of HCC and the age at blood transfusion ($n = 92$). A significant and strong negative correlation was observed ($r = -0.74$, $P < 0.001$). (B) Change in fibrosis staging over time. A total of 271 patients who had not achieved SVR by interferon therapy underwent a sequential biopsy after the initial biopsy. The yearly rate of progression of fibrosis was calculated as the change in fibrosis stage divided by the time between the paired biopsies. The yearly rate of progression of fibrosis was significantly higher in older patients (≥65 years) than in younger patients (<65 years) ($P = 0.03$, Mann-Whitney U test).

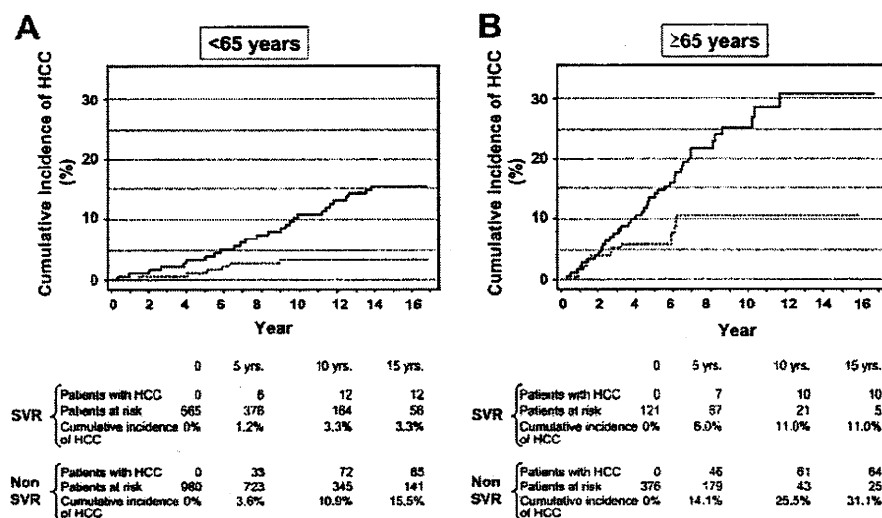


Fig. 4. Cumulative incidence of HCC after interferon therapy among SVRs (dotted lines) and non-SVRs (solid lines) according to age. (A) Younger patients (<65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P < 0.001$). (B) Older patients (≥ 65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P = 0.02$). However, the difference between SVR and non-SVR was less in older patients than in younger patients. The number of HCC events and patients at risk at each timepoint are shown below the graphs.

aging was the strongest independent factor contributing to SVR in these patients (data not shown). The odds ratio for the risk of non-SVR was 1.8 for each additional 10 years of age (95% CI, 1.5-2.3, $P < 0.001$).

Discussion

In this large cohort study we demonstrated that aging is significantly associated with the development of HCC in patients treated with interferon. The risk ratio increased predominantly in patients older than 65 years, which was more than 15 times that in patients in their 20s. Aging is becoming the most critical risk factor for the development of HCC. Although liver fibrosis was also an important risk factor, we clearly demonstrated that the risk for hepatocarcinogenesis after interferon treatment was significantly higher in older patients at each stage of liver fibrosis except for cirrhosis. Hence, physicians should be aware that older patients can develop HCC regardless of the stage of fibrosis.

Because the present study included a large cohort, it was difficult to determine the duration of infection in all patients, and this might have affected the risk determination for HCC development. Therefore, we analyzed the relationship between duration of chronic infection and HCC development in patients who underwent a single blood transfusion. We found a significant and strong negative correlation between the

interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion. Consistent with our results, a previous report with posttransfusion HCV demonstrated that the age of patients, rather than the duration of HCV infection, was more significant for HCC development.¹⁴⁻¹⁶ Therefore, older age and not duration of infection is more likely to influence hepatocarcinogenesis. Moreover, our analysis of sequential biopsy specimens demonstrated that the progression rate of liver fibrosis significantly accelerated in patients aged >65 years. Hence, the progression of fibrosis along with aging may also contribute to the increased risk for hepatocarcinogenesis in older patients.

We further demonstrated that liver steatosis was an independent risk factor for the development of HCC, which was not mentioned in previous reports.⁸⁻¹¹ The presence of steatosis is related to both viral (genotype-3 or HCV core protein) and host metabolic factors.^{17,18} In our cohort, most superimposed NASH was associated with host metabolic factors such as high body mass index and hyperglycemia, whereas infection of genotype-3 was only noted in two patients. In vitro experiments have suggested an association between liver steatosis induced by HCV core protein and hepatocarcinogenesis,¹⁹ and have proposed virus-associated steatohepatitis as a new aspect of chronic hepatitis C.^{20,21} Because steatosis was likely to be related to hepatocarcinogenesis, patients with chronic hepatitis C, whose liver histology shows superimposed NASH,

Table 3. Factors Associated with HCC After IFN Therapy

Risk Factor Value	Univariate Analysis		Multivariate Analysis	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Age (by every 10 year)	2.2 (1.8-2.7)	<0.001	3.0 (1.9-4.8)	<0.001
Sex				
Female	1		1	
Male	1.2 (0.9-1.6)	0.2	2.0 (1.0-3.8)	0.04
BMI (by every 10 kg/m ²)	2.0 (1.2-1.3)	0.005	1.1 (0.4-3.5)	0.8
Fibrosis stage				
F0/F1/F2	1		1	
F3/F4	5.4 (3.9-7.5)	<0.001	2.5 (1.2-4.9)	0.01
Degree of steatosis				
<10%	1		1	
≥10%	4.5 (3.0-6.9)	<0.001	3.5 (1.9-6.4)	<0.001
Esophagogastric varices				
No	1		1	
Yes	3.3 (2.0-5.3)	<0.001	1.6 (0.6-4.4)	0.3
Virological response				
SVR	1		1	
Non-SVR	3.3 (2.1-5.2)	<0.001	2.6 (1.2-5.5)	0.001
Genotype				
Non-1	1		1	
1	1.7 (1.2-2.5)	0.006	1.0 (0.5-2.3)	0.9
Albumin (by every 1 g/dL)	0.2 (0.1-0.3)	<0.001	0.6 (0.2-2.2)	0.3
ALT (by every 100 IU/L)	1.0 (0.9-1.0)	0.8	0.4 (0.1-1.8)	0.6
AST (by every 100 IU/L)	1.2 (1.1-1.3)	0.001	1.1 (0.6-1.8)	0.8
γ-GTP (by every 100 IU/L)	1.3 (1.1-1.6)	0.009	0.6 (0.3-1.6)	0.3
ALP (by every 100 IU/L)	1.3 (1.2-1.5)	<0.001	0.6 (0.3-1.2)	0.2
Total bilirubin (by every 1 mg/dL)	1.6 (1.3-2.1)	<0.001	1.2 (0.6-2.7)	0.6
Total cholesterol (by every 100 mg/dL)	0.3 (0.2-0.6)	<0.001	0.2 (0.1-0.6)	0.006
Triglyceride (by every 100 mg/dL)	0.8 (0.5-1.1)	0.2	0.1 (0.02-1.1)	0.08
Fasting blood sugar (by every 100 mg/dL)	1.8 (1.5-2.2)	<0.001	1.1 (1.0-1.1)	0.04
WBC (by every 100/ μ L)	0.1 (0.03-0.3)	<0.001	0.1 (0.01-2.2)	0.2
RBC (by every 10 ⁶ / μ L)	0.5 (0.4-0.7)	<0.001	1.8 (0.7-4.4)	0.2
Platelet counts (by every 10 ⁹ / μ L)	0.3 (0.2-0.4)	<0.001	0.6 (0.3-1.5)	0.3
Baseline AFP (by every 10 ng/mL)	1.0 (0.9-1.1)	0.2	1.3 (1.0-1.7)	0.04
Post IFN AFP (by every 10 ng/mL)	1.2 (1.1-1.3)	<0.001	1.9 (1.5-2.4)	<0.001
HCV load (by every 100 KIU/mL)	1.0 (0.9-1.0)	0.4	1.0 (1.0-1.1)	0.06
IFN regimen				
IFN monotherapy	1		1	
IFN + RBV (24 W)	1.2 (0.8-1.8)	0.4	1.5 (0.7-3.2)	0.3
PEG-IFN monotherapy (48 W)	1.1 (0.6-1.9)	0.8	1.5 (0.4-5.5)	0.6
PEG-IFN + RBV	0.4 (0.2-0.9)	0.03	1.0 (0.3-3.1)	0.9

Risk ratios for development of HCC were calculated by Cox proportional hazards regression analysis. AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; γ-GTP, gamma-glutamyltranspeptidase; HCC, hepatocellular carcinoma; IFN, interferon; PEG, pegylated; RBC, red blood cell counts; RBV, ribavirin; SVR, sustained virological response; WBC, white blood cell count.

may be at a higher risk of developing HCC. Further study is necessary to confirm this association in a clinical situation. Because several developed countries are in the midst of a growing obesity epidemic, the risk related to obesity cannot be ignored in patients with chronic hepatitis C who are treated with interferon.

Several retrospective cohort studies have been conducted to evaluate the effect of interferon on the incidence of HCC among patients with chronic hepatitis C.⁶⁻¹¹ Our results, obtained from one of the largest cohort studies, confirm the efficacy of viral eradication in preventing HCC. In one study conducted in a Western population, no statistically significant reduc-

tion was found in the development of HCC among patients with SVR compared with those without SVR (adjusted hazard ratio, 0.46; 95% CI, 0.12-1.70; $P = 0.25$).¹² Because relatively few occurrences of HCC were observed in this cohort, and the duration of follow-up was shorter, the differences in HCC development between patients with and without SVR might be less pronounced.

Interestingly, our results demonstrated that the risk for HCC remains even after achieving SVR in older patients, confirming the findings of previous studies conducted with a smaller number of patients.^{22,23} The cumulative incidence of HCC during the first 5 years

Table 4. Factors Associated with Development of HCC After Achieving SVR

Risk Factor	Odds Ratio (95% CI)	P-value
Univariate analysis		
Age (by every 10 year)	3.2 (1.8-5.5)	<0.001
Sex		
Female	1	
Male	3.0 (1.0-8.8)	0.04
Fibrosis stage		
F0/F1/F2	1	
F3/F4	5.9 (2.5-14.0)	<0.001
Degree of steatosis		
<10%	1	
≥10%	5.5 (2.0-15.2)	0.001
BMI (by every 10 kg/m ²)	3.2 (0.8-12.6)	0.09
ALT (by every 10 IU/L)	0.9 (0.7-1.3)	0.7
AST (by every 10 IU/L)	1.1 (0.9-1.4)	0.3
Genotype		
Non-1	1	
1	1.2 (0.6-3.0)	0.5
HCV load (by every 100 KU/mL)	0.9 (0.8-1.0)	0.2
IFN regimen		
IFN monotherapy	1	
IFN + RBV (24 W)	0.7 (0.2-2.3)	0.5
PEG-IFN monotherapy (48 W)	0.8 (0.2-3.6)	0.8
PEG-IFN + RBV	0.3 (0.03-2.0)	0.2
Multivariate analysis		
Age (by every 10 year)	2.7 (1.5-5.1)	0.002
Sex		
Female	1	
Male	4.1 (0.9-18.9)	0.06
Fibrosis stage		
F0/F1/F2	1	
F3/F4	2.6 (0.9-7.5)	0.08
Degree of steatosis		
<10%	1	
≥10%	5.6 (1.9-16.5)	0.002

Odds ratios for SVR were calculated by logistic regression analysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; HCC, hepatocellular carcinoma; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

after completion of interferon therapy was similar between SVR and non-SVR patients in the older age group, and the risk for HCC remained for 9 years after eradication of HCV in our patients. Therefore, HCC patients with SVR who have a risk factor should be screened for at least 5-10 years after the completion of interferon therapy.

It has been reported that coffee consumption has a protective effect against hepatocarcinogenesis^{24,25} and liver disease progression in patients with chronic HCV infection.²⁶ Because we could not review coffee consumption in all the patients and fewer data were available in the previous literature as to whether a habitual change of reducing coffee consumption occurs in older patients, it is unclear whether increased risk for HCC in older patients is an effect of this habitual change in older patients. However, the majority (68%) of Japa-

nese patients who have HCV (n = 1058) drink less than 1 cup of coffee per day, and only 7.6% consume more than 3 cups of coffee per day.²⁷ Therefore, it is unlikely that a habitual change in older patients affects the increased risk for hepatocarcinogenesis in older patients.

Recently, it was reported that interferon therapy might be less effective in preventing HCC among patients with chronic hepatitis C who are positive for anti-HBc antibody,²⁸ but this finding is still controversial.^{29,30} In the present study, anti-HBc was only detected in 4 of 22 patients in whom HCC developed after viral eradication, and age distribution was similar among anti-HBc-positive and anti-HBc-negative patients. Because no significant difference in mean age was found between anti-HBc-positive and anti-HBc-negative patients in the recent study conducted in Japan,²⁸ it is unlikely that previous exposure to hepatitis B virus or occult hepatitis B virus infection is responsible for the difference in risk for HCC between younger and elderly patients found in the present study.

In conclusion, aging has become one of the most important risk factors for HCC. Even after stratification by stage of fibrosis, the risk for HCC after antiviral treatment was significantly higher in older patients, and HCV eradication had a smaller effect on HCC-free survival in older patients. Patients with HCV should therefore be identified at an earlier age and antiviral treatment should be initiated. The present results have potentially important clinical implications for physicians that may influence their decisions about the treatment strategy in individual patients.

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Diagnostic and Treatment Algorithm of the Japanese Society of Hepatology: A Consensus-Based Practice Guideline

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Key Words

Hepatocellular carcinoma · Radiofrequency ablation · Surgical resection · Child-Pugh · JIS score

Abstract

In Japan, more than 70% of hepatocellular carcinomas (HCC) develop from hepatitis C virus infections and 15% are derived from hepatitis B infections. Since most have received close observation with e.g. ultrasound or enhanced computed tomography (CT) scan every 3–6 months before development of HCC, the HCC nodule was detected in the early stage in more than 60% of the patients. An algorithm for the HCC surveillance was shown as a Japanese clinical guideline of a scientific-based research group. At the joint symposium with JSH and the International Liver Cancer Association (ILCA), the algorithm of diagnosis and treatment for HCC was discussed using Answerpad. Several important discussions are described in this article.

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Diagnosis of Early Hepatocellular Carcinoma

A consensus symposium of diagnosis and treatment for hepatocellular carcinoma (HCC) was held at the Annual Meeting of the Japanese Society of Hepatology (JSH) on June 4–5, 2009. This consensus-based practice guideline was a revision from that reported at the 2005 JSH Annual Meeting. More than 400 hepatologists including surgeons, radiologists and pathologists joined the symposium and consensus statements and recommendations were discussed using Answerpad. When more than 67% of the participants agreed with the statement, the statement was defined as established and described as a JSH consensus statement. More than 40 statements were discussed, which remain to be published.

In Japan, more than 70% of HCCs develop from hepatitis C virus infection and 15% are derived from hepatitis B infection. Since most had received close observation with e.g. ultrasound, enhanced computed tomography (CT) scan or enhanced magnetic resonance imaging (MRI) every 3–6 months before development of HCC, the HCC nodule was detected in the early stage in more than 60% of the patients. An algorithm for the HCC surveillance was shown as a Japanese clinical practice guideline of a scientific evidence-based research group supported

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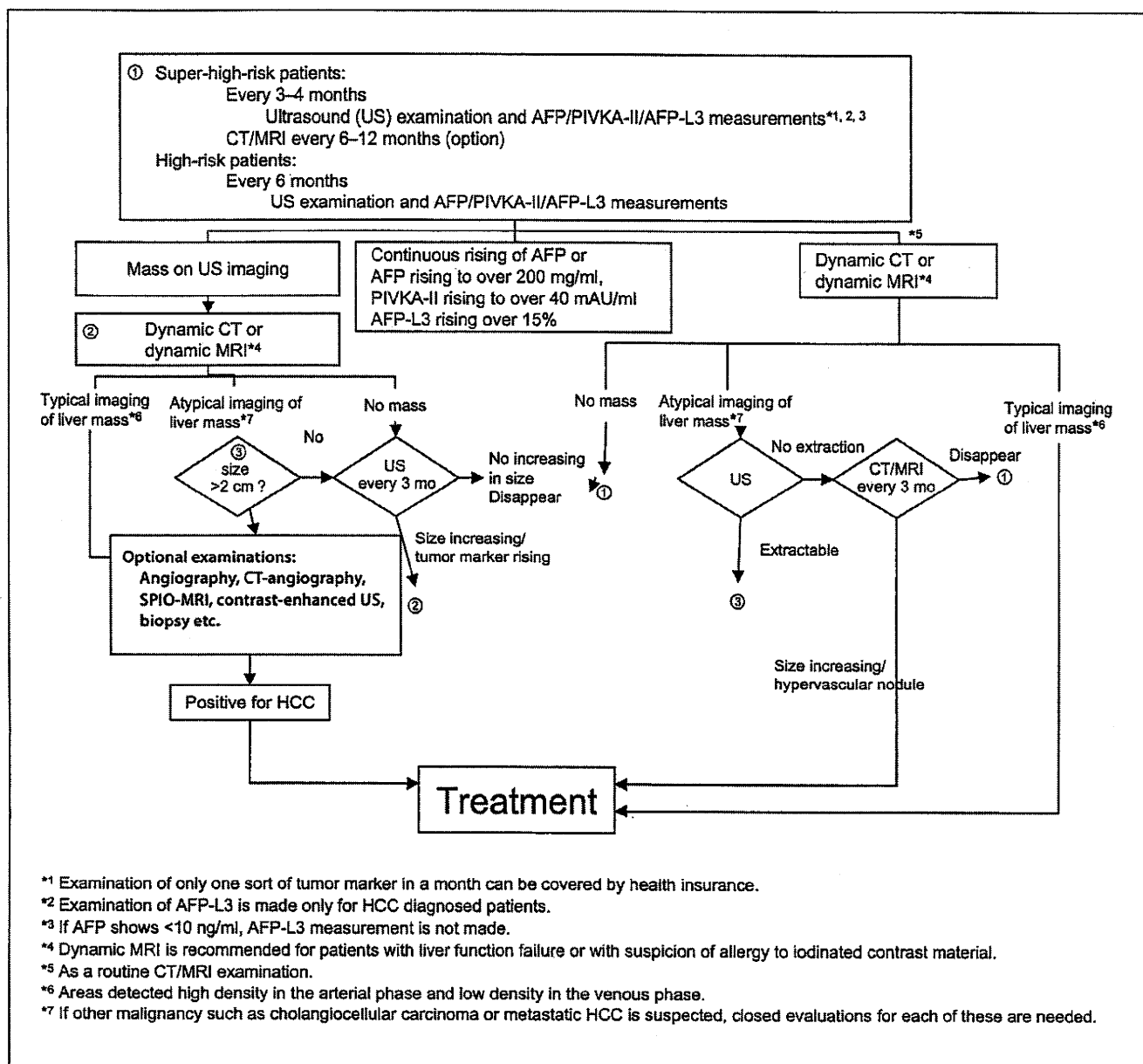


Fig. 1. Algorithm for the HCC surveillance 2005 (Japanese clinical practice guideline of a scientific evidence-based research group supported by the Japanese Ministry of Health, Labor and Welfare [taken from 1]).

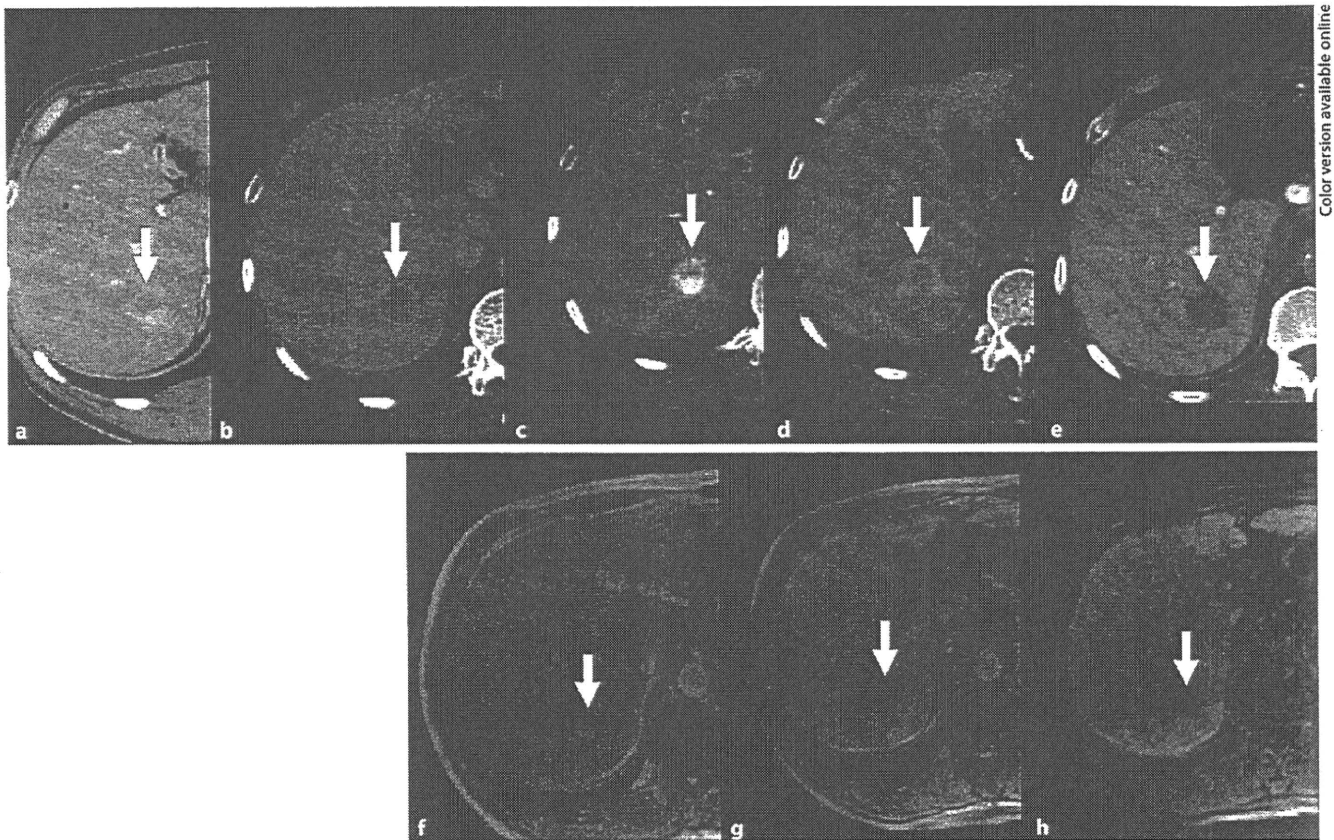
by the Japanese Ministry of Health, Labor and Welfare (Head: M. Makuuchi) [1] in 2005 (fig. 1).

At the joint symposium with JSH and the International Liver Cancer Association (ILCA), the algorithm of diagnosis and treatment for HCC was discussed using Answerpad. Forty-five hepatologists, surgeons, radiologists and pathologists participated in this meeting and voted

the statement. Eight important statements were discussed and voted by Answerpad. The results described compare them with those of the JSH consensus meetings.

Statement 1

A needle biopsy of the hypervascular HCC nodule with 1.5 cm should not be done.



Color version available online

Fig. 2. Representative case of hypervascular early HCC in a 64-year-old male. There is a hypervascular nodule 1.8 cm in diameter in segment 7 during the arterial phase in the dynamic CT scan (a) which becomes a low-density area during the equilibrium phase (b). CTHA revealed a hypervascular region (c) which becomes a ringed enhancement, a so-called 'corona enhancement'

in the late phase of CTHA (d). This nodule becomes a low-density area during CTAP (e). Gd-EPB-DTPA-enhanced MRI revealed a high-intensity area during the arterial phase (f) and a low-intensity area during the portal phase (g). Importantly, this nodule showed a low-intensity area in the T₁ hepatobiliary phase by Gd-EOB-DTPA-enhanced MRI (h).

A typical case is shown in figure 2. A hypervascular nodule was observed at the arterial phase in a contrast-enhanced CT scan with a diameter of 1.8 cm in segment 7, which becomes a hypovascular region in the equilibrium phase. This nodule was defined as a hypervascular region during CT during hepatic arteriography (CTHA) and low-density area during CT during arteriportography (CTAP). Gadolinium (Gd)-EOB-DTPA MRI was carried out and the nodule of segment 7 became a low-intensity area in the hepatobiliary phase. A needle biopsy gives important information concerning pathological differentiation grade and biomarker expression; however, implantation of neoplastic cells to the tract or seeding has been reported [2, 3].

This statement was agreed on by 78% of the participants, but 22% disagreed. At the JSH consensus meeting,

91% of the participants agreed with this statement, and only 9% disagreed. Thus, most of the hepatologists who participated in both consensus meetings did not agree to undergo needle biopsy of the nodule when the nodule is hypervascular.

Biopsy of the nodule was done under guided ultrasound, which revealed moderately differentiated HCC (fig. 3). This nodule was treated by radiofrequency ablation (RFA), and complete necrosis was obtained.

Statement 2

A needle biopsy of the nodule should be done to the arterial hypovascular nodule with 1.0 cm when the nodule becomes a low-intensity area in the hepatobiliary phase by Gd-EOB-DTPA-enhanced MRI.

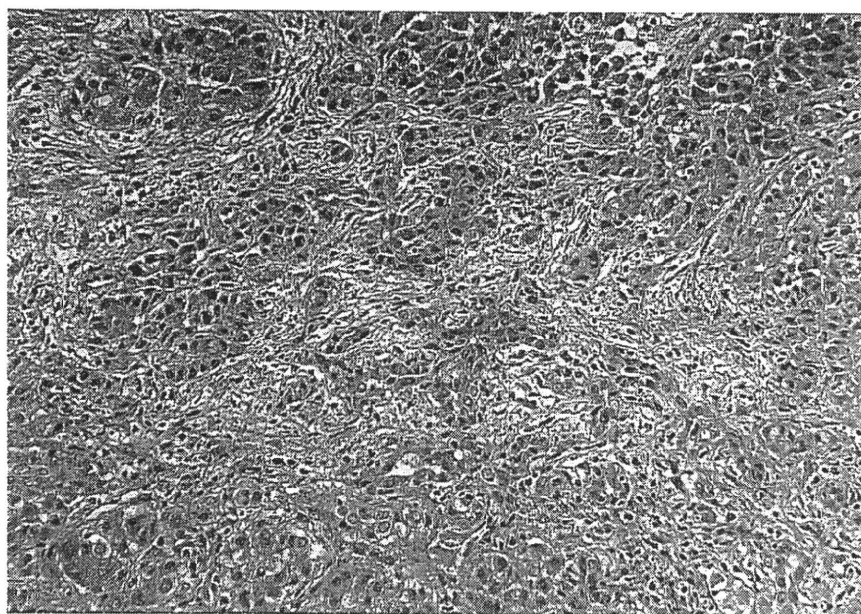


Fig. 3. A needle biopsy of the nodule was done which revealed moderately differentiated HCC. HE. 200×.

Table 1. The JIS (Japan Integrated Score) was defined by adding the tumor TMN stage and Child-Pugh score

	Variable			
	0	1	2	3
Tumor stage (TMN) ¹	1	2	3	4
Child-Pugh score	A	B	C	

¹ Liver Cancer Study Group of Japan.

A typical case is shown in figure 4. The hypovascular nodule was detected at the arterial phase in a contrast-enhanced CT scan with a diameter of 1.5 cm in segment 8, which becomes also a hypovascular region in the equilibrium phase. This nodule was defined as a hypovascular region during CTHA and low-density area during CTAP. Gd-EOB-DTPA MRI was carried out, and the nodule of segment 8 became a low-intensity area in the hepatobiliary phase.

This statement was agreed on by 57% of the consensus meeting participants, but 43% disagreed with the statement. At the JSH consensus meeting, 47% of the participants agreed with this statement, and only 53% disagreed. Both of the voting results were similar.

A needle biopsy of the nodule was done which revealed well-differentiated HCC (fig. 5). When the hypovascular

nodule was detected, it was difficult to obtain an accurate diagnosis without a needle biopsy and the strategy that was reported [4]. Since hypovascular nodules sometimes converted from malignant progression to overt HCC [5], it seems necessary to undertake a needle biopsy of the nodule.

Statement 3

For estimating the prognosis of patients with HCC, the most reliable staging system is the Japan Integrated Score (JIS).

The JIS scoring system was proposed by Kudo et al. [6] and was defined as adding the tumor TMN stage of the Japan Hepatocellular Cancer Study Group and Child-Pugh score as shown in table 1. In Japan, screening systems for the early detection of HCC have been established, e.g. periodic ultrasound, enhanced CT scan including measuring α -fetoprotein and prothombin induced by vitamin K deficiency. Thus, most HCC nodules were detected in the early stage. The JIS score has been validated in Japanese patients [7] and approved to be the best prognosis estimation of patients with HCC in Japan.

This statement was agreed on by 63% of the participants, but 37% disagreed at the ILCA consensus meeting. At the JSH consensus meeting, 71% of the participants agreed with this statement, and 29% disagreed.

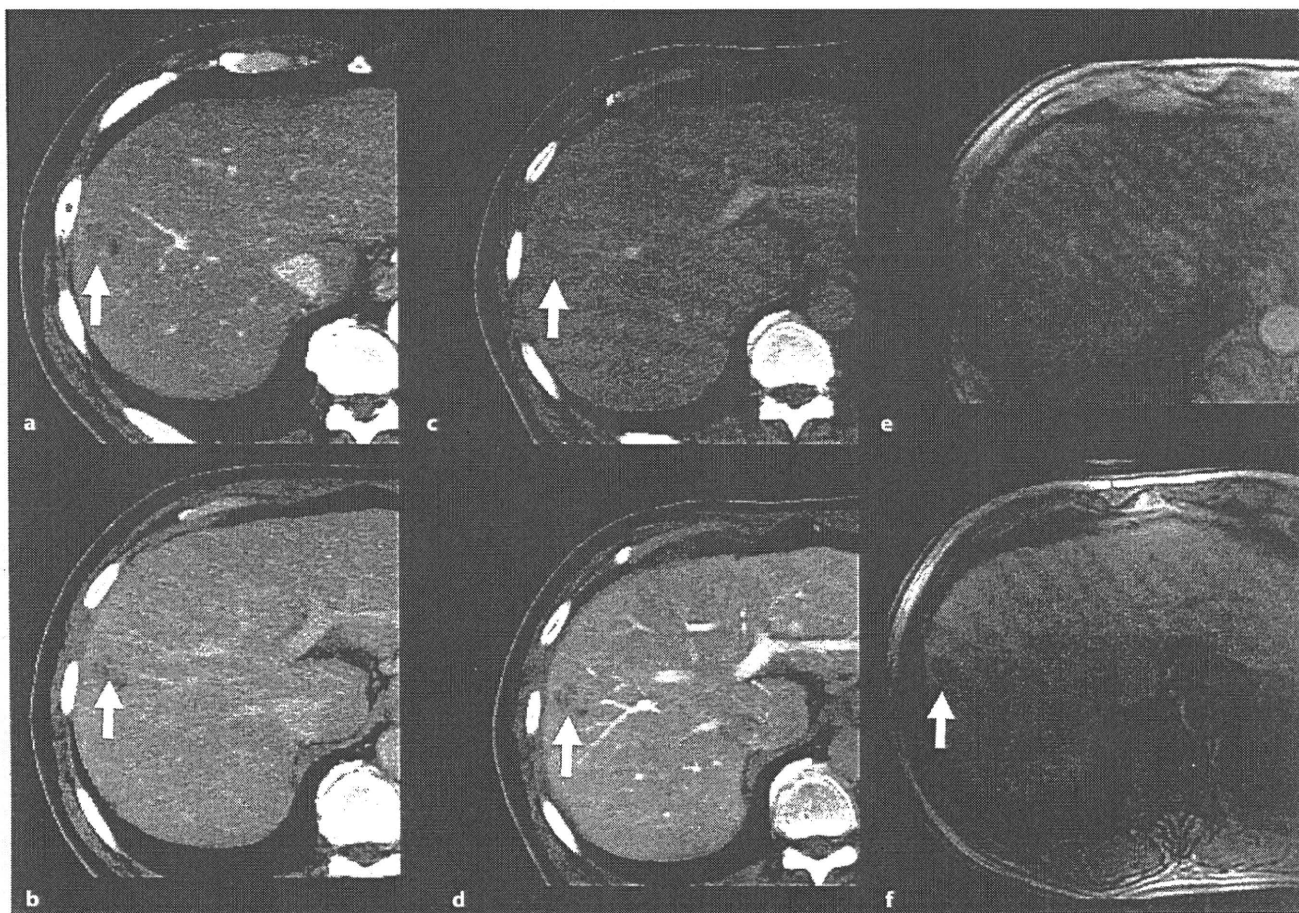


Fig. 4. A representative case of hypovascular early HCC in a 75-year-old male. There is a hypovascular nodule with a diameter of 1.5 cm in segment 8 during the arterial phase in the dynamic CT scan (a) which becomes a low-density area during the equilibrium phase (b). CTHA also revealed a hypovascular region (c).

This nodule becomes a low-density area during CTAP (d). Superparamagnetic iron oxide-enhanced MRI was carried out, but a nodular region was not detected in the T_2^* MRI image (e). Gd-EPB-DTPA-enhanced MRI showed a low-intensity area in the T_1 hepatobiliary phase by Gd-EOB-DTPA-enhanced MRI (f).

Treatment Algorithm of HCC

The treatment algorithm was discussed at the JSH consensus meeting in 2005. At this meeting the treatment algorithm was established by initially dividing the patients according to extrahepatic spread, Child-Pugh score, and vascular invasion (fig. 6). Next, they were divided by the nodule number and the vascularity of the nodule. When the single nodule was identified as being hypovascular, intensive follow-up or ablation was recommended. When the patient had 1–3 hypervascular nodules <3 cm in diameter, they should be treated by surgical resection or RFA. When the nodules are >3 cm, they should be treated by surgical resection or transarterial

chemoembolization (TACE). When the patients have 4 or more HCC nodules, they should be treated by TACE or transarterial embolization (TAE). If the patients have 3 or less nodules <3 cm or a single nodule <5 cm which are divided within the Milan criteria, liver transplantation should be considered if the patients are younger than 65 years of age. If invasion to the portal or hepatic vein was observed, they should be treated by surgical resection, TAI or TACE.

When the patients were classified as having poor liver function with Child-Pugh C and the HCC nodules are within the Milan criteria, liver transplantation should be considered. Otherwise, palliative care should be chosen.

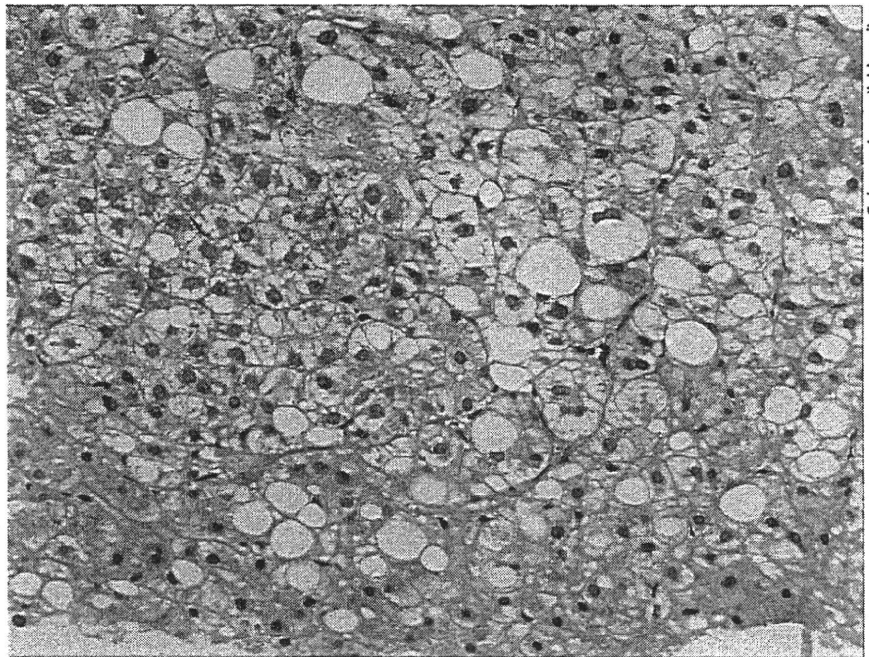


Fig. 5. A needle biopsy of the nodule was done which revealed a well-differentiated HCC. HE. 200×.

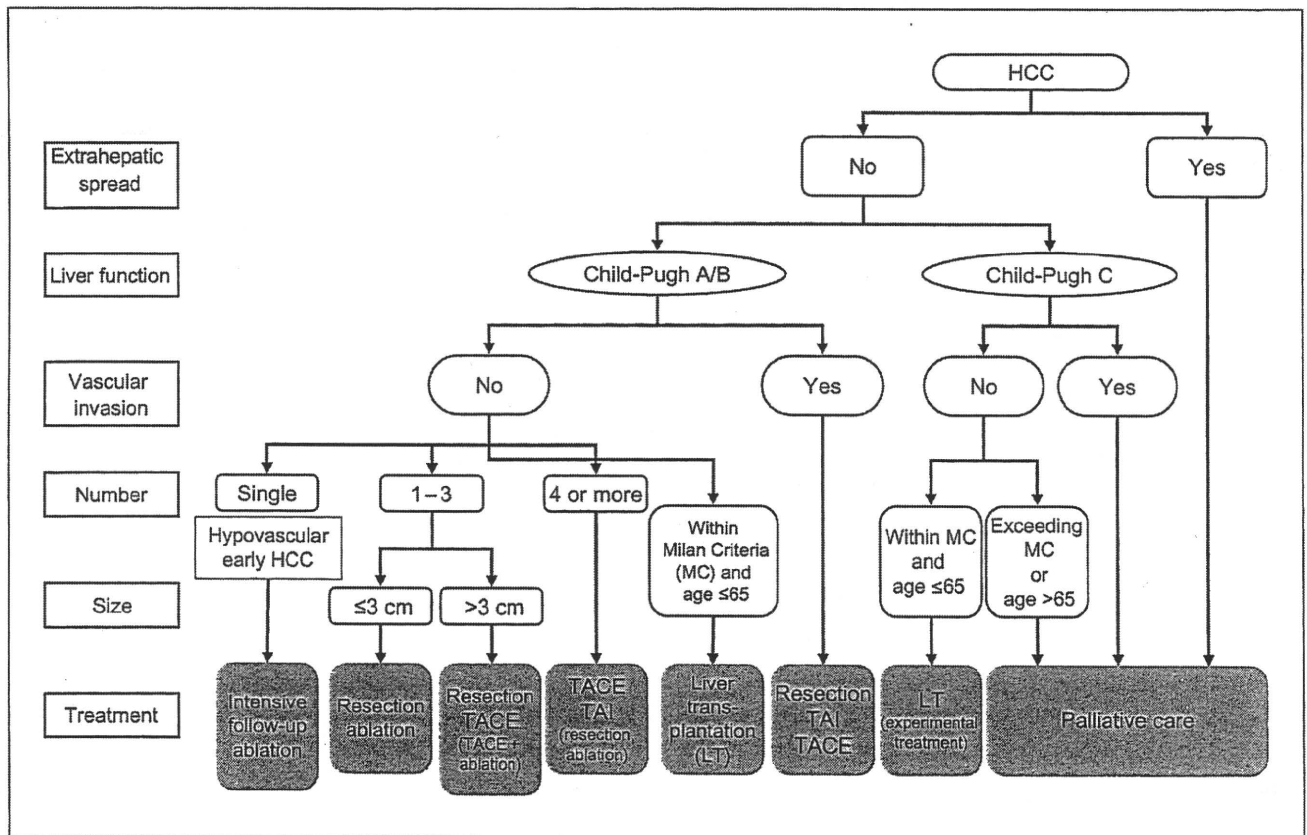


Fig. 6. Treatment algorithm for HCC (JSH consensus-based 2007).

Fig. 7. A representative case with a hypervascular nodule by CTHA in segment 8 with a diameter of 1.8 cm (a). This nodule became a low-density area by CTAP (b). This patient has good liver function classified as Child-Pugh A.

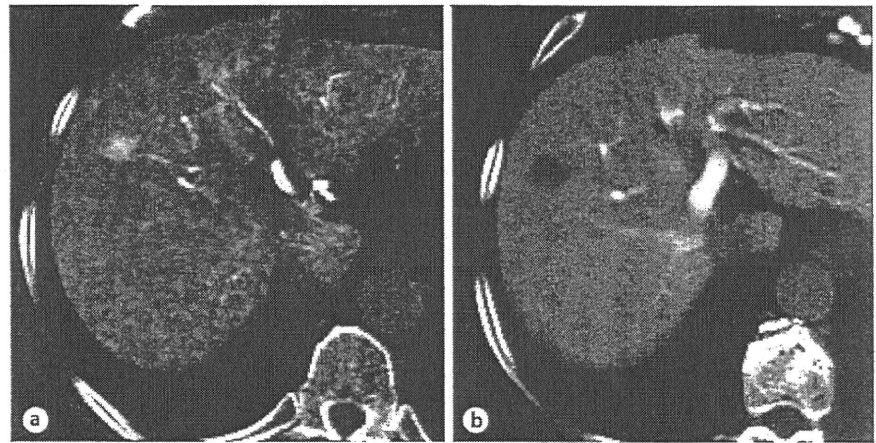
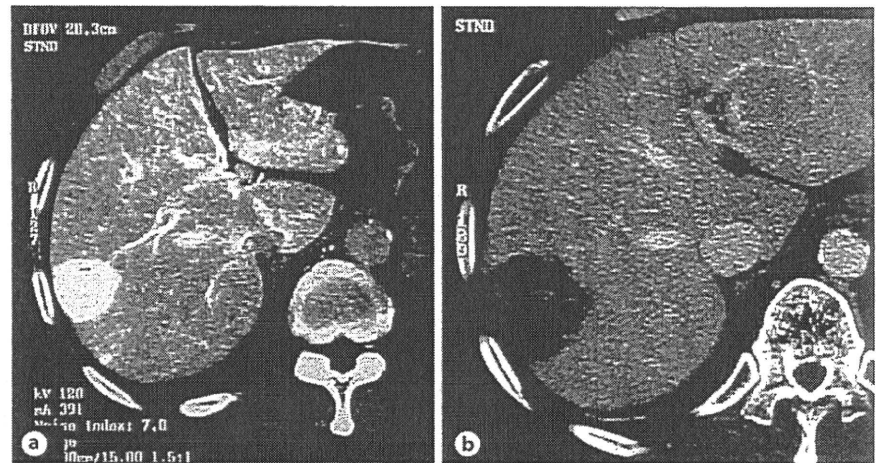


Fig. 8. A representative case with a hypervascular nodule by CTHA in segment 7 with a diameter of 3.0 cm (a). Locally complete curative necrosis was achieved by RFA (b).



Statement 4

Which treatment do you choose for the patient having a single HCC nodule <2 cm with Child-Pugh A?

A typical case of a 62-year-old male is shown in figure 7. A hypervascular small nodule was observed by CTHA at segment 8 with a diameter of 1.8 cm, which became a low-intensity area by CTAP. His liver function was classified as Child-Pugh A.

38% of the participants chose surgical resection, but 62% chose RFA. At the JSH consensus meeting, 44% of the participants chose surgical resection, but 56% chose RFA. When only surgeons were asked the same question, 80% of them chose surgical resection, but 20% chose RFA. This question was asked to only physicians at the JSH consensus meeting, and 32% chose surgical resection, and 68% chose RFA.

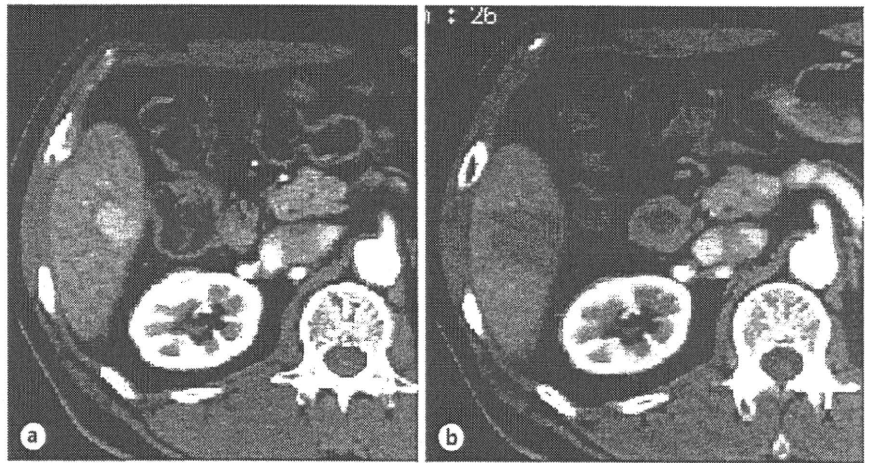
Overall survival was compared after surgical resection with RFA [8], in which no apparent difference was observed between the two groups. Thereafter, several reports including a large number of patients with HCC compared the survival or recurrence, but they are not randomized [9–11]. This is an important issue that needs to be clarified. Thus, randomized controlled trials are necessary including a large number of patients to clarify which treatment is superior between surgical resection and RFA.

Statement 5

Which treatment do you choose for a patient having a single HCC nodule <3 cm with Child-Pugh A?

A representative case of a 75-year-old male is shown in figure 8a. He had a single hypervascular nodule defined by CTHA at segment 7 with a diameter of 3 cm. His liver

Fig. 9. A typical case with a single hypervascular HCC nodule in segment 6 with a diameter of 1.4 cm. He has a good liver function of Child-Pugh A (a). He was treated by RFA alone, and complete necrosis was obtained (b).



function was well preserved and he was classified as Child-Pugh A. The participants were asked this question. 74% of the participants chose surgical resection, but 26% chose RFA by the ILCA. At the JSH consensus meeting, 80% of the participants chose surgical resection, but 20% chose RFA as the first-line treatment.

Interestingly enough, most of the participants chose surgical resection when the nodule was as large as 3 cm. This hypervascular HCC nodule was treated by percutaneous RFA, and locally complete curative necrosis was obtained (fig. 8b).

Statement 6

RFA should be done after TACE to the hypervascular HCC nodule with a diameter of 2 cm.

A typical 62-year-old male with a 1.6-cm single hypervascular HCC nodule in segment 6 is shown in figure 9a. He has a good liver function with Child-Pugh A.

This statement was agreed on by 36% of the participants at the ILCA consensus meeting, but 64% disagreed. However, at the JSH consensus meeting, 51% of the participants agreed with this statement, but 49% disagreed.

This hypervascular HCC nodule was completely ablated by RFA alone (fig. 9b). It has been reported that TACE before RFA increased the ablated area, suggesting that overall survival will improve [12–14]; however, TACE may increase the adverse events by RFA. Whether TACE before RFA is beneficial for the patients should be examined by analyzing the overall survival of patients and comparing them to receiving TACE before RFA or without TACE before RFA.

Statement 7

Do you prescribe sorafenib as the first-line treatment option for the patients with advanced HCC in whom surgical resection, RFA or TACE is not indicated?

As sorafenib was approved in Japan in May 2009 [15], only a few hepatologists have experienced prescribing the medicine. Its usefulness after TACE in patients with advanced HCC is under investigation in the USA and Japan [16]. It will be included in the therapeutic algorithm for HCC, but it is still unclear to hepatologists to which patients the medicine should be prescribed.

At the ILCA consensus meeting, 61% of the participants agreed with this statement, but 30% disagreed. 9% of them did not have any opinion on the statement because they have no experience with sorafenib. At the JSH consensus meeting, 35% of the participants agreed with this statement, but 29% disagreed. 36% of the participants did not have any opinion because they have no experience with sorafenib.

The best indication for sorafenib should be investigated in the near future [17].

Statement 8

Overall survival should be the endpoint for the assessment of efficacy comparing ablation with surgical resection.

The recurrence rate after surgical resection or RFA was reported including a large number of patients, and the incidence of intrahepatic recurrence was higher after RFA than surgical resection [11]. However, overall survival was not different between the two groups. Thus, the problem is how to evaluate the outcome of surgical resection and RFA, and this question was proposed by hepatologists.