frequently present with glucose intolerance which is referred to as hepatogenous diabetes with insulin resistance and hyperinsulinemia. The prevalence of glucose intolerance in HCV-related chronic liver disease is higher than in other liver diseases[12] and it has been suggested that HCV directly causes hepatic insulin resistance and hyperinsulinemia.[13,14] Previous studies have shown that the incidence of HCC has been increased 2–4-fold in patients with diabetes mellitus (DM)[15,16] and some reports have indicated that insulin resistance may be involved in cell growth and the carcinogenesis of HCC.[17,18] Meanwhile, several recent studies have reported that obesity increases the risk of malignancy,[19] including HCC.[20] In human obesity, intra-abdominal visceral fat content is strongly correlated with glucose intolerance.[21] In the obese state, adipose tissue promotes inflammation and macrophages migrating into adipose tissue secrete adipocytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1). Enlarged adipose cells also secrete these adipocytokines and free fatty acids (FFA). These adipocytokines and FFA can induce insulin resistance in the whole body.[22–24]

Adiponectin is an adipose tissue-specific plasma protein and is specifically secreted from fat tissue. Hypoadiponectinemia may be implicated in the pathogenesis of the various disorders which comprise metabolic disease,[25] and may be related to the pathogenesis of liver disease through cells expressing the adiponectin receptor in the liver.[26] Leptin is another circulating hormone secreted by adipocytes which acts as an important signaling molecule in energy regulation and food intake,[27] and modulates multiple physiological and pathophysiological states.[27,28]

Meanwhile, adiponectin is thought to be involved in the carcinogenesis of several cancers.[29,30] Adachi *et al.* showed that an adiponectin receptor, T-cadherin, was selectively expressed in intratumoral capillary endothelial cells in HCC, suggesting a positive role for T-cadherin in mediating angiogenesis in HCC.[31] In addition, leptin may also play an important role in the processes of initiation and progression of various human cancers.[32,33] Chen *et al.* reported that leptin induced proliferation and inhibited apoptosis in human HCC cells.[34] Zhou *et al.* showed that leptin stimulated Hep G2 cell proliferation through increased DNA synthesis and the enhancement of mitotic activity.[35] Ribatti *et al.* have reported an involvement of leptin and the leptin receptor in angiogenesis in human HCC.[36]

In this study, we investigated whether obesity, insulin resistance, leptin and adiponectin were involved in the development of HCC in patients after SVR undergoing IFN treatment for chronic hepatitis C (CH-C).

METHODS

Patients

THE SUBJECTS IN this study were nine patients who were diagnosed with HCC at Kurume University Hospital after being treated with IFN therapy for CH-C between 1993 and 2003 and exhibiting SVR. Seven patients were treated with IFN at Kurume University Hospital or affiliated hospitals, and two were treated with IFN at other hospitals. The diagnosis of HCC was based on histological examination for eight patients and on computed tomography (CT), magnetic resonance imaging (MRI) and elevation of tumor markers in one patient. One thousand one hundred and forty-three patients received IFN therapy for CH-C and 308 patients achieved SVR between 1993 and 2003 at Kurume University Hospital. Out of these patients, we selected 27 patients who met the following requirements as control: (i) periodically observed at our hospital after SVR and had no evidence of HCC for over 5 years from the time of SVR until the last outpatient visit; (ii) blood samples before IFN treatment and at following outpatient visit were stored; and (iii) hepatitis B virus surface antigen (HBsAg) was negative in the serum. All control patients and six HCC patients were followed up after SVR. These patients received ultrasonography (US), computed tomography (CT) and examination of tumor markers at least once per year. HCC were detected 1 year or later after SVR regarding six patients developing HCC with periodic observation. Another three patients developing HCC did not undergo periodic observation from the time of SVR to the detection of HCC. Intervals from SVR until detection of HCC regarding these three patients were 106, 156 and 108 months, respectively. SVR was defined as being serum HCV RNA negative for more than 6 months after the termination of IFN therapy. Serum HCV RNA was measured using the COBAS AmpliPrep/COBAS TaqMan HCV Test (Roche Molecular Systems, Branchburg, NJ, US). This newly established technique has excellent sensitivity for the detection of HCV RNA and is more sensitive than conventional methods of detection.[37]

We had less information prior to their IFN therapy about the two HCC patients treated with IFN at other hospitals. Upon detection of their HCC, both patients

were seropositive for anti-HCV antibodies, seronegative for HBsAg and negative for serum HCV RNA as determined by the COBAS AmpliPrep/COBAS TaqMan HCV Test. The other seven HCC patients and 27 control patients were all seropositive for anti-HCV antibodies, positive for serum HCV RNA and seronegative for hepatitis B antigen prior to IFN therapy. The HCV RNA load was quantitated by competitive reverse-transcription polymerase chain reaction, a branched-DNA probe assay, or by the Amplicor-HCV monitor assay.[38–40] HCV genotype was determined according to previously described methods.[41] We excluded patients who had a coexisting liver disease, such as autoimmune hepatitis or primary biliary cirrhosis. Past occurrence of HCC and treatment history for HCC were also part of the exclusion criteria. Informed consent was obtained from each patient and the study was approved by the Ethical Committee of Kurume University. The study was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki.

Metabolic parameters

We compared the clinical characteristics of the nine HCC patients and 27 control patients just before the start of IFN therapy. Body mass index (BMI) was calculated as weight in kilograms/height in meters squared. We obtained BMI values prior to IFN therapy from seven HCC patients treated with IFN in Kurume University Hospital or affiliated hospitals, and from 23 out of 27 control patients. We obtained BMI values for nine HCC patients at the time of HCC diagnosis, and for 22 of the control patients more than 5 years after SVR. The high molecular weight (HMW) form of adiponectin, leptin, insulin and glucose were measured from blood samples stored at −80 °C. Blood samples were obtained from five HCC patients and all control patients within 9 months before the start of IFN therapy. Additional samples were obtained within 9 months after the time of SVR in three patients who developed HCC and from all control patients. Blood was also collected later as the last time point sample at the time of HCC diagnosis for nine HCC patients and more than 5 years after SVR for all the control patients. All samples were obtained at fasting time.

Serum insulin levels were measured using an enzyme-linked immunoassay kit (Lumipulse Presto Insulin; Fujirebio, Tokyo, Japan). Plasma glucose levels were measured using the hexokinase-glucose-6-phosphate dehydrogenase method. Insulin resistance was calculated from fasting levels of glucose and insulin using the Homeostatic Model of Assessment (HOMA) method. The formula for the HOMA model is: insulin resistance (HOMA-IR) = fasting glucose (mg/dL) × fasting insulin (μU/mL) / 405. Adiponectin is present in serum in a number of forms, and often exists as a trimer or hexamer of HMW.[42] Adiponectin in the HMW form has been reported to play a primary role in hepatic and whole-body insulin sensitivity and to have significant anti-inflammatory effects.[43] For this reason, we measured serum HMW adiponectin in this study. The levels of HMW adiponectin were determined using a HMW adiponectin assay kit (Fujirebio). Leptin levels were determined using a human leptin RIA kit (Linco Research, St Charles, MO, USA). Values of each metabolic parameter at each time point were compared between the HCC patients and controls.

Histopathology

We compared the histological features of liver tissue before IFN therapy in HCC patients and controls and also compared these with liver tissue at the time of detection of HCC. Liver biopsies were performed on 32 patients treated with IFN at Kurume University Hospital or at affiliated hospitals less than 1 year before the start of IFN therapy. One HCC patient underwent a biopsy 8 years before IFN therapy and showed cirrhosis at that point, and no biopsy was performed on one of the control patients. Assessment of the histological diagnosis was made according to the classifications of Desmet *et al.*[44] Hepatic steatosis was also graded by a modification of the Brunt scoring system as described[45,46] using the following categories: steatosis less than 5%, 5–33%, 33–66% and patients with over 66% steatosis were categorized as grades 0, 1, 2 and 3, respectively. All tissue samples were evaluated by two independent hepatologists. We also examined non-cancerous hepatic lesions resected with HCC from seven patients. These seven cases were assessed for histological tumor differentiation[47] in the resected specimen and one other case was examined using a specimen obtained by aspiration tumor biopsy.

Statistical analysis

Statistical analysis was performed using SPSS ver. 12.0J. Fisher's exact probability test was used to compare categorical data. Differences between two groups were measured using the Mann–Whitney *U*-test. A relationship between different continuous variables was measured by linear regression analysis. $P < 0.05$ was considered statistically significant.

Table 1 Characteristics of nine patients with HCC after sustained virological response

Age at detection of HCC (years)†	61 (54–75)
Maximal tumor diameter (mm)†	26.8 (16–43)
No. of tumors (1/2/3)	7/1/1
Tumor stage (I/II/III)‡	1/5/3
Differentiation (well/moderately)	3/5§
Child–Pugh score (at detection of HCC)¶	A5 for all
Therapy (resection/RFA/radiation)	7/1/1
Periodic observation	
Before detection of HCC (yes/no)	6/3

†Mean (range).
‡Based on the tumor–node–metastasis (TNM) classification.[48]
§Tumor histology was not available for one case.
¶Classified according to Child–Pugh classification.[49]
HCC, hepatocellular carcinoma; RFA, radiofrequency ablation.

RESULTS

Characteristics of nine patients with HCC after SVR

THE CHARACTERISTICS OF nine SVR patients who developed HCC are summarized in Table 1. Eight patients underwent curative therapy, including resection for seven patients and percutaneous radiofrequency ablation for one patient. Another patient was evaluated for resection, but ultimately received radiation therapy due to dementia.

Table 2 shows the clinical and histological profiles of HCC patients. Histological fibrosis worsened in three patients and did not change in one patient out of the six in whom we could compare liver histology at both time points. Four out of five alcohol consumers with HCC continued drinking alcohol after IFN therapy, and only patient 6 stopped drinking after IFN therapy. Four patients developed HCC within 5 years after SVR and five patients developed HCC more than 5 years after SVR. Three of four patients in the former group showed liver cirrhosis when HCC was diagnosed, and no patient showed liver cirrhosis in the latter group although histological data of two patients were not available.

Comparison of baseline characteristics of SVR patients with and without HCC after SVR

A comparison of the baseline characteristics of SVR patients with and without HCC is summarized in Table 3. Patients with regular smoking were significantly more in the HCC group than in the control group ($P = 0.046$). Before the start of IFN therapy, four out of nine HCC patients and none of the controls were diagnosed with type 2 DM, a significant difference between the two groups ($P = 0.002$). The average observation period from the time of SVR to the detection of HCC for the HCC group was 81.7 months (range

Table 2 Clinical and histological profiles of SVR patients with HCC

	Before IFN therapy			At the detection of HCC			DM	Alcohol (23 g/day)	Interval (months)§
	G/S†	Steatosis‡	BMI	G/S†	Steatosis‡	BMI			
Patient 1	2/2	1	23.4	1/4	0	23.7	−	−	22
Patient 2	2/4	2	26.5	1/4	1	28.9	+	−	38
Patient 3	2/1	0	19.3	1/4	1	23.1	−	−	42
Patient 4¶	2/2	1	27.8	1/1	0	29.6	−	+	48
Patient 5	2/2	0	20.2	N/A	NA	24.1	−	+	80
Patient 6	2/2	1	29.8	2/1	0	27.6	+	+	106
Patient 7¶	NA	NA	NA	NA	NA	24.5	+	−	108
Patient 8¶	1/1	2	23.3	1/2	1	24.9	−	+	135
Patient 9¶	NA	NA	NA	1/1	1	26.9	+	+	156

†G and S refer to hepatic inflammatory grading (A0–3) and fibrotic staging (F0–4), respectively.
‡Graded 0–3.
§Interval from SVR until detection of HCC.
¶Adiponectin, leptin, insulin and HOMA-IR prior to IFN therapy could not be acquired for patients 4 and 8. Detailed information for IFN therapy, laboratory and histological data, and metabolic parameters prior to IFN therapy could not be acquired for patients 7 and 9.
BMI, body mass index; DM, type 2 diabetes mellitus; HOMA-IR, Homeostatic Model of Assessment of Insulin Resistance; HCC, hepatocellular carcinoma; IFN, interferon; NA, not available; SVR, sustained virological response.

Table 3 Comparison of baseline characteristics between SVR patients with and without HCC after SVR

	HCC group	Control group	*P*-value†
Age at IFN induction (years)‡	53.0 (44–65)	51.3 (23–74)	NS
Sex (male/female)	5/4	11/16	NS
Alcohol (≥23 g/day) (+/−)	5/4	6/21	NS
Smoking (+/−)	6/3	7/20	0.046
Type 2 diabetes mellitus (+/−)	4/5	0/27	0.002
HBcAb (+/−)	5/4	11/16	NS
HCV viral load before IFN (high/low)§	2/5	8/18	NS
Virus genotype (1/2)	3/3	15/12	NS
IFN (a/b/a + b/consensus)	5/2/0/0	19/4/2/2	NS
(with RBV¶: PEG IFN††)	(3:0)	(4:1)	
Total IFN amount ($\times 10^4$) (mean)	59 800	56 392	NS
Observation period after SVR (months)‡	81.7 (22–156)	102 (61–149)	NS
AST (IU/L)‡‡	75.9 ± 49.9	62.2 ± 44.7	NS
ALT (IU/L)‡‡	69.3 ± 40.7	78.3 ± 70.4	NS
Total bilirubin (mg/dL)‡‡	1.0 ± 0.6	0.8 ± 0.2	NS
Albumin (g/dL)‡‡	3.7 ± 0.3	4.0 ± 0.2	NS
Prothrombin time (%)‡‡	93.2 ± 12.4	97.8 ± 16.4	NS
Platelet ($\times 10^4$/mL)‡‡	12.3 ± 3.4	15.4 ± 5.3	NS
Hyaluronic acid (ng/mL)‡‡	187.5 ± 153.4	122.9 ± 212.6	0.045
α-Fetoprotein (ng/mL)‡‡	42.4 ± 81.4	11.0 ± 29.2	NS
Child–Pugh score (5/6/7)	5/0/1	24/1/0	NS

All data were based on the patients from whom it was available for each characteristics.
†Comparison between patients with HCC (HCC group) and without HCC (control group) after SVR. *P*-values were calculated with Fisher's exact probability test and the Mann–Whitney *U*-test.
‡Mean (range).
§When the serum HCV RNA level was more than 1 Meq/mL by branched DNA assay, more than 10^6 copies/mL by competitive reverse transcription polymerase chain reaction, or more than 10^5 copies/mL by the Amplicor-HCV monitor assay, it was determined to be a high viral load.
¶Number of the patients in whom Ribavirin was used in combination.
††Number of patients in whom pegylated interferon was used.
‡‡Means ± standard deviation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBcAb, hepatitis B core antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; NS, not significant.

22–156), and the average time from SVR to the outpatient visit when we obtained the last follow-up results for the control group was 102 months (range 61–149). There was no significant difference in the length of the observation period between the two groups. Serum levels of hyaluronic acid prior to IFN therapy were significantly higher in the HCC group than in the control group ($P = 0.045$).

Changes in adipocytokines during the observation period

Our findings on metabolic parameters are summarized in Table 4. Prior to IFN therapy and at the time of SVR, serum levels of adiponectin and leptin were not significantly different between the HCC group and the control group. However, adiponectin was significantly lower in the HCC group upon HCC detection than in the controls at their follow-up visit more than 5 years after SVR ($P = 0.030$), and leptin was significantly higher in HCC patients than in controls at that time ($P = 0.036$). When we only analyzed patients for whom we had data both prior to IFN therapy and at the last time point, percentage of change per year in adiponectin level was significantly lower ($P = 0.046$) and that in leptin level was significantly higher ($P = 0.003$) in the HCC patients than in controls. Figure 1(A) shows changes in adiponectin and Figure 1(B) shows changes in leptin in both groups during the observation period.

In all cases in both the HCC group and control group, serum leptin levels were positively correlated with serum insulin levels and HOMA-IR but not with adiponectin levels or BMI at the last time point (data not

Table 4 Metabolic parameters of the study population

	Adiponectin (μg/mL)		
	Before IFN Tx	at SVR	Last Time point†
HCC group	10.8 ± 8.6 (5)	8.8 ± 4.0 (3)	5.0 ± 2.7 (9)
Control group (27)‡	8.5 ± 4.1	8.0 ± 4.2	8.1 ± 4.0
P-value§	NS	NS	0.03
	Leptin (ng/mL)		
	Before IFN Tx	At SVR	Last Time point†
HCC group	8.9 ± 2.9 (5)	8.4 ± 2.1 (3)	11.1 ± 6.9 (9)
Control group (27)‡	6.4 ± 4.7	6.5 ± 5.7	7.0 ± 6.8
P-value§	NS	NS	0.036
	BMI		
	Before IFN Tx		Last Time point†
HCC group	24.3 ± 3.9 (7)		25.9 ± 2.4 (9)
Control group	21.7 ± 2.6 (23)		21.9 ± 2.5 (22)
P-value§	NS		0.001
	Insulin (μU/mL)		
	Before IFN Tx	At SVR	Last Time point†
HCC group	16.4 ± 10.6 (5)	9.3 ± 1.3 (3)	11.5 ± 6.9 (9)
Control group (27)‡	8.9 ± 6.6	8.7 ± 9.8	6.3 ± 6.8
P-value§	0.022	NS	0.03
	HOMA-IR		
	Before IFN Tx	At SVR	Last Time point†
HCC group	5.0 ± 4.9 (5)	1.6 ± 0.6 (3)	2.9 ± 2.1 (9)
Control group (27)‡	1.8 ± 1.7	1.7 ± 1.7	1.3 ± 0.9
P-value§	0.014	NS	0.004

Data are shown as the means ± standard deviation.
P-values were calculated with the Mann–Whitney *U*-test.
†Data at the time of HCC diagnosis in the HCC group and at an outpatient visit more than 5 years after SVR for control group. Number in parenchyma means the number of cases involved in the analysis.
‡The number of control group cases was 27 except BMI analysis.
§Comparison between patients with HCC (HCC group) and without HCC (Control group) after SVR.
HCC, hepatocellular carcinoma; HOMA-IR, Homeostatic Model of Assessment of Insulin Resistance; IFN, interferon; NS, not significant; SVR, sustained virological response; Tx, therapy.

shown). In addition, adiponectin levels were inversely correlated with serum insulin and HOMA-IR but not with BMI at the last time point (data not shown). Prior to IFN therapy, leptin and adiponectin levels were not correlated with other metabolic parameters (data not shown). At the time of SVR, serum leptin levels were positively correlated with serum insulin levels and HOMA-IR, however, serum adiponectin levels were not correlated with these parameters and leptin levels (data not shown).

Variation in BMI and insulin resistance during the period of observation

Prior to IFN therapy, the BMI of HCC patients and control patients were not significantly different (Table 4). However, at the last time point, the BMI of HCC patients was significantly higher than that of control patients ($P = 0.001$). Figure 1(C) shows the changes in BMI during the period of observation. For six out of seven HCC patients, BMI was higher at the time of HCC detection compared to before IFN therapy. When we only analyzed patients for whom we had data both prior to IFN therapy and at the last time point, percentage of change per year in BMI values was significantly higher in the HCC patients than in controls ($P = 0.048$). Prior to IFN therapy, serum insulin and HOMA-IR were significantly higher in HCC patients than in controls ($P = 0.022$ and $P = 0.014$, respectively) (Table 4). In addition, serum insulin and HOMA-IR were significantly higher in HCC patients than in controls at the last time point ($P = 0.003$ and $P = 0.004$, respectively). Percentage of change per year in the insulin level or HOMA-IR in the HCC patients were not significantly different from those in the controls (data not shown). At the time of SVR, there was no significant difference in serum insulin and HOMA-IR between these two groups.

Histological features of the study population

Table 5 shows the histological features of the study population. When patients were divided into the hepatic inflammation groups A0–1 and A2–3, the histological activity grade at HCC detection was significantly improved compared to that before IFN therapy ($P = 0.029$). The histological activity grade prior to IFN therapy was not significantly different between the HCC group and the control group. When patients were divided into the fibrosis groups F0–1 and F2–4, the histological fibrotic stage at HCC detection was not significantly improved compared to that before IFN therapy, and fibrotic stage prior to IFN therapy was not significantly different between the HCC group and the control group. When patients were divided into the hepatic steatosis groups grade 0–1 and grade 2–3, there was no significant difference in the two groups before IFN therapy. Hepatic steatosis at the time of HCC detection was not significantly different from before IFN therapy in the HCC group.

DISCUSSION

FOR OUR STUDY, we selected patients who had been followed for more than 5 years after SVR with no detectable HCC as a control group because we wanted to be sure to exclude patients who developed HCC from the control group as much as possible. When we divide the patients in the HCC group into two groups – one group in which patients developed HCC within 5 years after SVR and another group in which patients developed HCC more than 5 years after SVR – three of four patients in the former group showed liver cirrhosis when HCC was diagnosed. This observation suggests that liver cirrhosis is tightly related to the development of HCC with a relatively short interval after SVR.

Insulin is known to be an important factor not only for a variety of metabolic pathways, but also for cell proliferation.[17] One of the major functions induced by elevated serum insulin is the activation of the mitogen-activated protein kinase cascade which has effects on cell proliferation.[50] Saito *et al.* reported that hyperinsulinemia activated the growth of human HCC cells from patients with liver cirrhosis.[18] Insulin resistance has also been shown to induce fibrotic progression in the liver with CH-C.[51] Advanced hepatic fibrosis is known to be a major risk factor for the occurrence of HCC in patients with CH-C,[52] even after SVR.[6–10] In our study, liver fibrosis was not significantly improved at the time of detection of HCC compared with before IFN therapy, and had progressed in three patients and was unchanged in another one out of the seven patients for whom we were able to compare the histological findings at both time points, although previous studies had shown an improvement of hepatic fibrosis after SVR to IFN therapy.[53] Kawaguchi *et al.* have reported that clearance of HCV improves insulin resistance.[14] In this study, both the HCC group and control group also showed a decline in serum insulin levels and HOMA-IR after SVR, and significant differences in these parameters between the two groups were not found once at the time of SVR; however, the values in the HCC group were still relatively high at the time of detection of HCC (normal

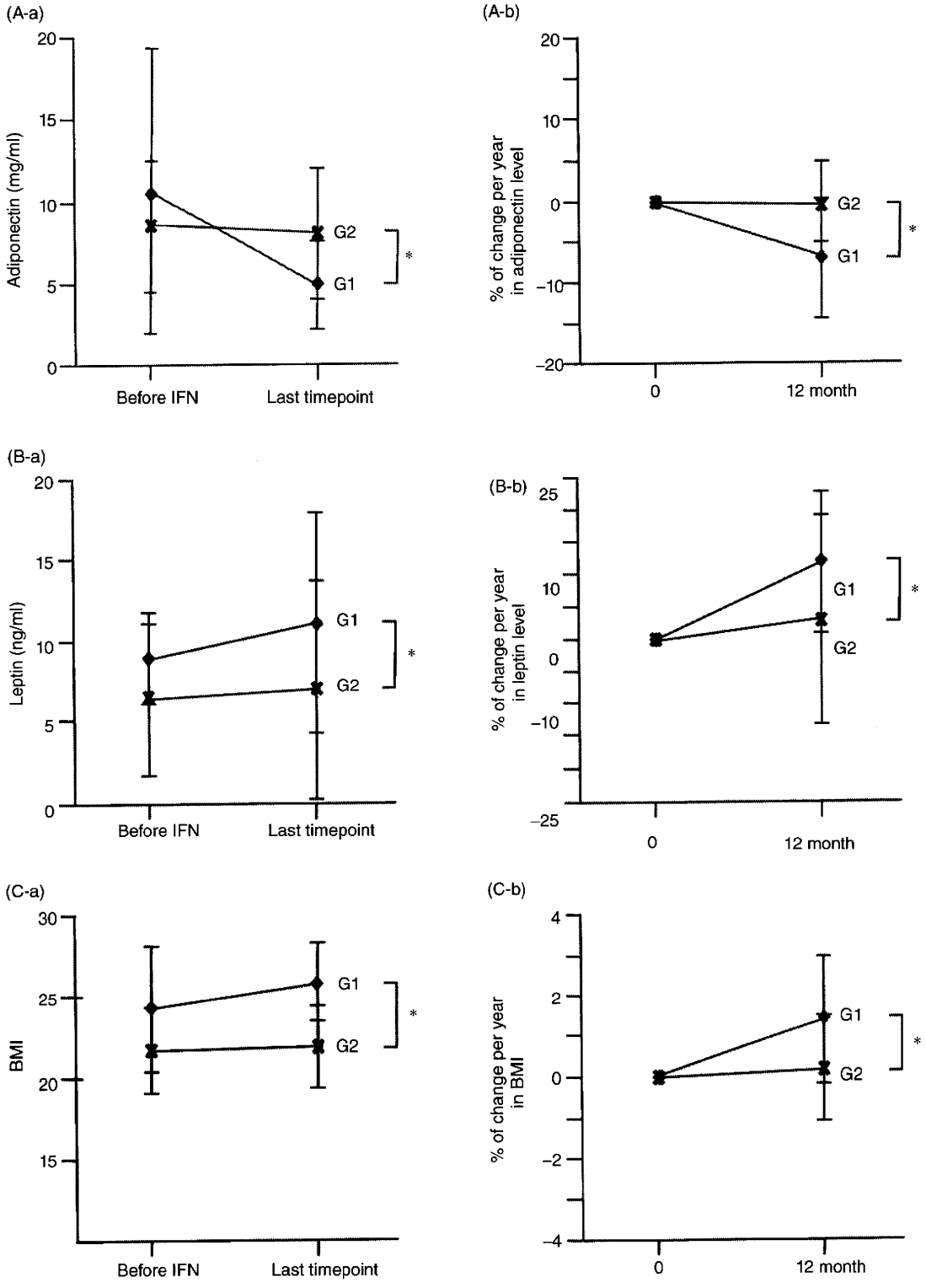

Figure 1 Changes in metabolic parameters during the period of observation in sustained virological response (SVR) patients. Hepatocellular carcinoma (HCC) group (G1) comprised SVR patients who developed HCC, and control group (G2) comprised those who did not develop HCC. (A-a) Changes in the high molecular weight form of adiponectin in the serum (B-a) changes in serum leptin and (C-a) changes in body mass index (BMI). Serum samples were collected and BMI values were obtained before the start of interferon (IFN) therapy. Serum samples and BMI values were also obtained as the last time point sample when HCC was diagnosed in the HCC group and at an outpatient visit more than 5 years after SVR for the control group. Percentages of change per year in the level of the high molecular weight form of adiponectin (A-b), leptin level (B-b) and BMI value in each group were shown. We only included patients for whom both time points were available in this analysis. The data represent means ± standard deviation. *Statistically significant differences between the indicated groups ($P < 0.05$).

range: insulin 1.84–12.2 μU/mL, HOMA-IR ≤1.6) and were significantly different from those of the control group at the last time point. Hyperinsulinemia might be one of the reasons why hepatic fibrosis was not shown to improve in the SVR patients developing HCC.

Adiponectin has been reported to increase insulin sensitivity[54] and to inhibit hepatic fibrosis,[55] however, adiponectin paradoxically decreases with the accumulation of visceral fat.[56] Therefore, hypoadiponectinemia resulting from obesity can cause insulin resistance and accelerate hepatic fibrosis. Two out of three HCC patients in which histological fibrosis worsened showed very low ratio of adiponectin at the last time point to that before IFN therapy (0.2 and 0.51), and another one case that lacked the data before IFN therapy showed very low value of adiponectin at HCC detection (2.7 μg/mL).

Serum leptin levels are positively correlated with BMI as fat tissue increases.[57] Leptin has inhibitory effects on insulin resistance,[58] however, the risk of insulin resistance rises with obesity and in these patients, increased leptin may not be sufficient to improve insulin resistance. It is conceivable that the serum level of leptin is simply a reflection of the degree of insulin resistance.[59] Leptin facilitates hepatic fibrosis through the induction of TNF-α, the proliferation of hepatic stellate cells and stimulation of the sympathetic nervous system.[55,60] In addition, leptin have been reported to be associated with proliferation of HCC.[31,34–36] Taken together, bodyweight gain leads to insulin resistance, increased leptin and decreased adiponectin, and these metabolic alternations may induce the initiation and progression of HCC, in part by promoting hepatic fibrosis in the HCC group.

Serum leptin levels have been reported to decrease after the end of IFN therapy for hepatitis C and then to recover to pretreatment levels after a long follow up.[61] One study reported that serum adiponectin was increased at 6 months after IFN therapy,[62] but another reported decreased adiponectin at 12 weeks after IFN therapy.[63] Thus, the influence of IFN on the levels of serum adiponectin for an extended period is unclear.

Fibrotic stage prior to IFN therapy was not significantly different between the HCC group and the control group ($P = 0.106$), although the number of patients in both groups was very low. Serum levels of hyaluronic acid prior to IFN therapy were significantly higher in the HCC group than in the control group ($P = 0.045$), therefore, we could not disclaim an association between hepatic fibrosis prior to IFN therapy and the occurrence of HCC after SVR.

Table 5 Histological features of the study population

	Inflammatory grading A 0/1/2/3		Fibrotic staging F 0/1/2/3/4		Steatosis Grade 0/1/2/3	
	HCC group	Control group	HCC group	Control group	HCC group	Control group
Before IFN	0/1/6/0	2/11/13/0	0/2/4/0/1	3/14/7/2/0	2/3/2/0	11/13/1/1
At HCC detection	*0/6/1/0	–	0/3/1/0/3	–	3/4/0/0	–

*$P = 0.029$ when A0–1 and A2–3 were compared between the two time points of the HCC group using the Mann–Whitney *U*-test. Prior to IFN therapy, the activity grade was not significantly different between the HCC group and control group. When divided into F0–1 and F2–4 groups for hepatic fibrosis, and when divided into grade 0–1 and grade 2–3 for hepatic steatosis, there was no significant difference between the two groups before IFN therapy and between the two time points of HCC group.
HCC, hepatocellular carcinoma; IFN, interferon.

An association between smoking and hepatic fibrosis, and also an association between smoking and HCC were reported previously.[64,65] Ratio of patients with smoking was significantly higher in the HCC group than in the control group. Therefore, smoking might facilitate hepatic fibrosis and increase the risk of HCC synergistically with the other risk factors in our study.

It is possible that undetectable HCC may have already developed in patients in this study before IFN therapy, based on information about the estimated doubling time of HCC.[52] Even so, abnormalities in metabolic factors prior to IFN therapy and alterations of these factors after IFN therapy might affect the progression of HCC.

This study was conducted at a single medical center and the number of enrolled patients was limited. As a result, the number of patients developing HCC after SVR and of controls was fairly low, and thus the accuracy of our statistical analysis was limited. A large-scale study and careful analysis are needed to confirm our results, which indicate the importance of metabolic factors in the hepatocarcinogenesis process after SVR.

In conclusion, hepatic fibrosis may be tightly related to the emergence of HCC after SVR, and insulin resistance and adipocytokine disorders may be implicated in hepatocarcinogenesis after SVR, in part by promoting hepatic fibrosis. This study is the first to report the correlation between the development of HCC after SVR and metabolic factors including insulin resistance, obesity and adipocytokine levels.

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Special Report

Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009)

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Hepatocellular carcinoma (HCC) is responsible for approximately 600 000–700 000 deaths worldwide. It is highly prevalent in the Asia–Pacific region and Africa, and is increasing in Western countries. The evidence-based guideline for HCC in Japan was published in 2005 and revised in 2009. Apart from this guideline, a consensus-based practice manual proposed by the HCC expert panel of the Japan Society of Hepatology (JSH), which reflects widely accepted daily practice in Japan, was published in 2007. At the occasion of the 45th Annual meeting of the JSH in Kobe 4–5 June 2009, a consensus meeting of HCC was held. Consensus statements were created based on 67% agreement of 200 expert members.This article describes the up-to-date consensus statements which largely reflect the real world HCC practice in Japan. We believe readers of this article will gain the newest knowledge and deep insight on the management of HCC proposed by consensus of the HCC expert members of JSH.

Key words: hepatocellular carcinoma, Japan Society of Hepatology, staging system, surveillance, treatment algorithm, consensus-based guideline

INTRODUCTION

THE LAST EVIDENCE-BASED guideline for hepatocellular carcinoma (HCC) for Japan was published in 2005,[1] and has prevailed nationwide. This document was developed by a committee composed of 14 experts (Chairman: Professor Masatoshi Makuuchi) and was based on a critical review of 7118 English reports published between 1966 and 2002. This guideline includes 58 research questions regarding important issues for the prevention, diagnosis, surveillance and treatment of HCC. The utility of this guideline is recognized by many Japanese clinicians and has provided a great contribution to clinical practice. However, there are several issues in which solid evidence is still lacking; thus, clear recommendations for clinical practice cannot be stated. In fact, 45% of the research questions are of grade C recommendation level, representing a lack of adequate evidence. These issues are left to the clinician's discretion within the clinical setting. Furthermore, because the guidelines did not include the most up-to-date articles, no recommendation or statements were made regarding newly established evidence. In addition, the clinical practices that follow these guidelines are considered to account for 70–80% of general practice institutions.

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As mentioned above, Congress President, Professor Masatoshi Kudo, at the 45th Annual Meeting of the Japan Society of Hepatology organized the Consensus Meeting of Hepatocellular Carcinoma. The program was chaired by Professors M. Sata and S. Arii and covered the updated problems and clarified some controversial issues. Eight experts were selected to contribute to the meeting and they were assigned the following topics based on their specialties. Professor M. Sakamoto presented recommendations regarding diagnostic problems for small-sized HCC from the clinicopathological point of view. Professor M. Shimada discussed the utility of clinical staging and prognosis. Dr T. Kumada reviewed the current status of diagnostic imaging and tumor markers. Dr S. Shiina discussed important issues on ablative treatment. Dr Yamashita reviewed transarterial chemoembolization and chemotherapy. Professor N. Kokudo discussed surgical treatment, including liver transplantation. Dr M. Tanaka presented a treatment algorithm from the point-of-view of hepatologists. Finally, Professor T. Takayama comprehensively discussed the appropriateness of the present treatment algorithm.

In each presentation, the speakers raised clinical questions regarding the remaining problems that needed to be clarified in the present guidelines, and the HCC specialists (a total of 200 physicians: hepatologists, 70%; surgeons, 24%; radiologists, 2%; and pathologists, 4%) answered these questions using a question and answer analyzer system. Recommendations were approved when at least 67% of the HCC experts reached agreement. For instances where agreement was between 50% and 67%, the statements were considered informative, and are cited here as "informative statements".

In this consensus paper, each presenter has provided a summary of the recommendations and consensus. It is highly expected that this Consensus Statement established by the Japan Society of Hepatology (JSH)will provide valuable insight, and will greatly contribute to the future improvement of the guidelines and appropriate clinical practices for patients with HCC worldwide.

PATHOLOGICAL ASSESSMENT

PATHOLOGICAL ASSESSMENT OF HCC is described in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.[2] It focuses on macroscopic typing and tumor grading based on tumor differentiation and reflects the aggressiveness of the tumors; differential diagnosis between multicentric development and intrahepatic metastasis of multiple tumors; and diagnosis of early HCC and precancerous lesions. Historically, careful and detailed histological evaluation of surgical specimens enabled us to understand the clinicopathological features of HCC development and extension, and to establish the above-mentioned diagnostic criteria. However, the recent increase in non-surgical treatments for HCC, such as radiofrequency ablation (RFA), is rapidly changing the role and position of pathological diagnosis. Thus, we discussed the indications for liver tumor biopsy for the diagnosis and treatment of HCC.

When we consider the indications for liver biopsy, the risk and benefit of this procedure must be considered.[3–8] The risk includes complications caused by the procedure itself, such as hemorrhage by needle insertion, and by tumor seeding. The incidence of tumor seeding has been reported in approximately 1–5% of cases. Certainly, we have to note that the incidence depends on the characteristics of the tumor such as tumor size and tumor differentiation. Liver biopsy is important in terms of tumor diagnosis, assessment of prognosis and decision making for treatment. For example, for a typical HCC larger than 2 cm in size with a typical vascular pattern on imaging, and elevated tumor markers such as α-fetoprotein (AFP) and/or des-γ-carboxy prothrombin (DCP), the benefit of performing tumor biopsy to confirm the diagnosis of HCC seems minimal. In contrast, only liver biopsy can be used to confirm the diagnosis of cancer in cases with suspected HCC or borderline lesions on clinical and imaging diagnosis. However, controversy remains because of the inconsistent treatment strategy for suspected lesions, particularly in cases with poor liver function.

Previous follow-up data of suspected HCC and borderline lesions showed that the tumors grow slowly during the precancerous or early HCC stages, but grow rapidly in some early HCC cases or in progressed HCC.[9] The transition from slow growing to rapidly growing tumors was supposed to take place once the tumor reaches approximately 1.5 cm in size. Therefore, the proposed recommendations for liver biopsy are as follows.

Recommendation 1. Liver biopsy should be discouraged in cases with a typical HCC over 1.5 cm in size, which shows typical pattern on imaging.

Recommendation 2. Liver biopsy should be considered in cases with a suspected HCC or borderline lesions/early HCC of 1.5 cm in size or less, which does not show typical pattern on imaging.

In addition to these recommendations, the requirement of liver biopsy should increase if the detection and diagnostic ability of imaging techniques increases for

smaller lesions. The emergence of new contrast agents such as gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) are expected to reveal suspected HCC nodules, including early HCC at approximately 1 cm in size. Tumor biopsy should then be performed to confirm the diagnosis of early cancer before it can progress to overt HCC. It is also expected that the increase in therapeutic options will increase the need for more detailed information of the tumor characteristics, such as tumor differentiation and immunophenotype reflecting tumor aggressiveness, which can only be determined by tumor biopsy.

PROGNOSTIC STAGING SYSTEM

IN TERMS OF estimating the prognosis of HCC, there are currently insufficient evidence-based data; therefore, no definite recommendations can be made, unlike other fields of HCC management. It is well known that the prognosis of HCC is defined by the behavior of the HCC itself, and by host factors such as hepatic functional reserve. The major questions that still need to be answered in terms of estimating the prognosis of HCC are: (i) whether an integrated staging system is necessary for the management of HCC; (ii) what is the best integrated staging system; and (iii) should the integrated staging system be included in the algorithm for HCC treatment?

Tumor staging (TNM staging)

There are two major classifications used for tumor staging of HCC. One is the tumor–node–metastasis (TNM) stage, developed by the American Joint Committee on Cancer (AJCC). This classification can also be applied to liver transplant recipients. However, the cut-off value for tumor diameter of 5 cm is too large to define small HCC, which are frequently found in Japan.

The other is the TNM stage proposed by the Liver Cancer Study Group of Japan (LCSGJ). The cut-off of 2 cm is very appropriate for patients in countries such as Japan, where small HCC are often found in an established nationwide screening system. However, in this system, the weighting of the strongest prognostic factor, vascular invasion, is equal to that of other factors used to estimate prognosis, which might not be adequate.

Staging for hepatic functional reserve

There are two major classifications for estimating liver functional reserve. One is the Child–Pugh classification, which is widely used worldwide, but is difficult to apply for decision making for hepatectomy. The other is the Liver Damage Classification scheme proposed by the LCSGJ, which is useful for hepatectomy. However, this scheme is not widely accepted because of the need to perform the indocyanine green retention at 15 min test ($ICGR_{15}$).

Integrated staging system for HCC

The combined classification of TNM stage and liver function stage, namely, an integrated staging system, is extremely important to estimate patient prognosis and guide decision making for patient management. The integrated staging system contributes to: (i) estimate patient prognosis; (ii) select the best treatment option for each patient; (iii) compare different treatment modalities; and (iv) compare treatment outcomes among different institutions.

Since the Okuda classification in 1985,[10] several integrated staging systems have been reported, including the Cancer of the Liver Italian Program (CLIP) score,[11] the Barcelona Clinic Liver Cancer (BCLC) stage[12] and the Japan Integrated Staging (JIS) score.[13] The Okuda classification scheme is simple and has been found to be suitable in the past, but does not seem to be suitable at the present time, now that relatively small HCC can be detected. The CLIP score is popular in Western countries, but its discriminating power is weak for small HCC, particularly at higher scores of 4–6, and over 50% of Japanese HCC patients are classified as score 0. The BCLC staging is thought to be useful as an integrated staging system and for guiding treatment. Therefore, it is recommended as an integrated treatment algorithm by the European Association for the Study of the Liver and the American Association for the Study of Liver Disease (AASLD). However, it is not suitable for the estimation of patient prognosis, and a large number of variables are used. In contrast, the JIS score essentially consists of the Child–Pugh score and the LCSGJ TNM stage, and is widely accepted in Japan. The discriminating power for relatively small HCC is excellent, and is particularly suitable for countries such as Japan, where many small HCC are detected.

In terms of a comparison of these integrated staging systems, Cillo *et al.*[14] reported that the BCLC was the best system among the Okuda, CLIP, BCLC and French classifications. Meanwhile, Tateishi *et al.*[15] reported that the Tokyo score was superior to BCLC staging and comparable to the CLIP score in predicting prognosis after hepatectomy and ablation. Kudo *et al.*[16] reported that the JIS score was better than the CLIP score, particularly in terms of discriminating power for each subgroup. Similarly, Chung *et al.*[17] reported that the JIS score was

the most excellent staging system among the BCLC, Tokyo and JIS staging systems. Therefore, JIS score is currently considered to be the best integrated staging system in Japan. Regarding other integrated staging systems, modified JIS score has been reported[13,18] to be useful for patients undergoing hepatectomy. Biomarker combined JIS score has also been reported to be useful in discrimination in patients with good prognosis.[19] However, the usefulness of these new staging systems will remain unclear until they are assessed in a range of patient sets with HCC.

Regarding the estimation of HCC prognosis, most hepatologists recognize the importance of an integrated staging system rather than applying the TNM stage and hepatic functional reserve scales individually. Furthermore, the JIS score is considered to be the best integrated staging system for current clinical practice. However, it is still difficult to incorporate the integrated staging systems, such as the JIS score, into algorithms for HCC treatment.

Recommendation 3. Integrated staging system should be used to assess the prognosis of patients with HCC, instead of individually applying scales for TNM stage and liver function stage.

Recommendation 4. The JIS score is the best staging system to estimate the prognosis of patients with HCC.

Informative Statement 1. Integrated staging systems, such as the JIS score, are not yet suitable for inclusion in algorithms for HCC treatment.

SURVEILLANCE AND DIAGNOSIS

Surveillance programs

IT IS WELL known that HCC mainly occurs in cases with chronic liver disease, particularly cirrhosis. Several cohort studies have shown that the surveillance of high-risk patients with hepatitis B virus (HBV)- or hepatitis C virus (HCV)-related chronic liver disease improves the rate of early detection and the rate of curative treatments.[20–27] For this reason, UK[28], European[29] and American[3] practice guidelines for HCC recommend routine surveillance of HCC among individuals with viral hepatitis or cirrhosis. Almost all gastroenterologists in Japan conduct surveillance programs using a combination of tumor markers such as AFP, the *lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3%) and DCP, and by ultrasound (US).[30] However, no consensus has been reached in terms of the optimal surveillance strategy. Thompson *et al.* calculated the number of people who need to be under surveillance to prevent either a single death from HCC or a single premature death (defined as death before the age 75 years) and showed the effectiveness of surveillance programs.[31] In the absence of surveillance, approximately 20% of the mixed etiology cohort died as a result of HCC.

Recommendation 5. Surveillance with US and three tumor markers including AFP, DCP and AFP-L3 should be performed for early detection of HCC in patients with HBV- and HCV-related chronic liver disease, particularly cirrhosis.

Tumor markers

In Japan, AFP, AFP-L3 and DCP are widely and routinely used as serological tumor markers for the surveillance, diagnosis and prognostic estimation of HCC. The Evidence-Based Clinical Practice Guidelines of HCC published in 2005[1] recommended that AFP, AFP-L3 and DCP should be measured at intervals of 3–4 months for very high-risk patients (defined as HBV- or HCV-related liver cirrhosis), and at 6-month intervals for high-risk patients (defined as HBV- or HCV-related chronic liver disease or other causes of liver cirrhosis).[32] Although AFP is the most widely used tumor marker for HCC, the levels of AFP are also increased in patients with liver diseases other than HCC, including viral hepatitis, with a prevalence of 10–42%.[33–35] In contrast, AFP-L3 and DCP are very specific for HCC, compared with AFP alone. The combination assay for AFP, AFP-L3 and DCP should be performed for the early detection of HCC.[36,37] The specificity and sensitivity of the combination assay of AFP and DCP were 83% and 84%, respectively, to detect small HCC of less than 3 cm in diameter.[38] The specificity and sensitivity of the combination assay of DCP and AFP-L3 were 41.7–66.7% and 89.5–89.8%, respectively, to detect small HCC of less than 3 cm in diameter.[39,40]

Recommendation 6. Periodical measurement of more than two kinds of tumor markers (particularly AFP and DCP) is recommended for the early detection of HCC in high-risk and very high-risk patients.

Recommendation 7. The surveillance interval needs to be shorter in very high-risk patients than in high-risk patients.

Imaging modalities

Periodic follow-up of chronic liver disease by US, multidetector row computed tomography (MDCT) and magnetic resonance imaging (MRI) allows relatively

easy detection of small HCC.[41–43] However, it is sometimes difficult to characterize small hepatic nodular lesions detected by these imaging modalities. Definitive diagnosis requires invasive methods such as US-guided liver biopsy. Hemodynamic evaluation of the nodule is also important to assess the biological behavior of HCC. The recent advances in MRI and computed tomography (CT) procedures, such as CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP), have enabled the detailed hemodynamic evaluation of small hepatic nodules.

Recently, liver-specific contrast agents such as superparamagnetic iron oxide particles (SPIO), which are taken up by Kupffer cells, and Gd-EOB-DTPA, which is taken up by hepatocytes, are frequently used in MRI for early diagnosis of HCC. Gd-EOB-DTPA is a superb agent because it provides dynamic and liver-specific MR images.[44–46] This contrast agent is highly liver specific; approximately 50% of the injected dose is taken up by functioning hepatocytes and is excreted in bile, compared with just 3–5% for gadobenate dimeglumine.[46] Early studies comparing Gd-EOB-DTPA-enhanced dynamic MRI with dynamic MDCT showed that Gd-EOB-DTPA-enhanced MRI is significantly more accurate, sensitive and specific than dynamic MDCT for the diagnosis of HCC in patients with cirrhosis.[47,48] In addition, Gd-EOB-DTPA-enhanced MRI has a high detection rate for early stage HCC nodules that are not enhanced in dynamic studies. However, although the differentiation of early HCC from dysplastic nodule by hepatobiliary phase images of Gd-EOB-DTPA MRI is promising, more data are still needed.

Informative statement 2. Gd-EOB-DTPA-enhanced MRI provides dynamic and hepatocyte-specific images and is more accurate than dynamic MDCT or SPIO-MRI for the detection and characterization of small HCC, including early HCC.

ABLATION THERAPIES

IMAGE-GUIDED PERCUTANEOUS ablation therapies have long played important roles in the treatment of HCC. Percutaneous ethanol injection has been used for unresectable, small HCC since the early 1980s[49–51] and offers us the potential to treat HCC using non-surgical means. Percutaneous microwave coagulation therapy became popular in Japan in the late 1990s.[52] However, since the introduction of radiofrequency ablation (RFA) into clinical practice around 1999, there has been a dramatic shift from ethanol injection or microwave coagulation to RFA.[53] RFA for HCC has been covered by public health insurance since April 2004 in Japan. Although more than 1700 institutions have experienced RFA in Japan, RFA is estimated to be performed routinely in approximately 1000 institutions throughout Japan at the present.

Radiofrequency ablation often seems to be performed with less than adequate treatment planning or preparation compared with surgical resection. RFA appears to be a very simple procedure. Thus, some physicians may perform RFA without adequate training or experience. In addition, RFA does not require expensive equipment. Thus, several hospitals have introduced RFA into clinical practice without high-performance US and CT.

However, RFA is indicated for malignant tumors and inadequate outcome should be avoided. Thus, only physicians with sufficient experience and appropriate skill should perform the procedure. Furthermore, only well-equipped hospitals should perform RFA because the outcomes of RFA are strongly influenced by the performance of the CT and US equipment available at each institution. It is crucial to offer consistent outcomes for RFA at all institutions and for all operators.

More importantly, before commencing RFA, the tumors should be evaluated by US, contrast-enhanced CT or MRI to determine tumor size, shape, number, presence or absence of extracapsular invasion, presence or absence of satellite lesions, location relative to Glisson's capsule or other critical structures, and to determine the optimal route to approach the tumor.

Within 1–3 days after RFA, contrast-enhanced CT or MRI is essential to objectively assess the treatment response. If the tumor is completely ablated with a sufficient safety margin, the treatment may be considered complete. However, if there is any residual cancer tissue or an insufficient safety margin, RFA should be repeated until complete tumor destruction with a sufficient ablative margin is achieved. The following recommendation was supported by 94% of the experts.

Recommendation 8. Imaging should be performed within 1–3 days after RFA to evaluate treatment response. It is essential that RFA is repeated until entire tumor destruction with a sufficient ablative margin is achieved.

For accurate tumor evaluation, CT and MRI performed before and after RFA should be done using a thin slice interval. The following recommendation was agreed by 94% of the experts.

Recommendation 9. CT and MRI before and after RFA should be done using a slice thickness and interval of 5 mm or less; slice thickness and interval of 10 mm or more is not adequate.

A histopathological study has revealed that, in cases with incomplete necrosis, viable cancer tissue remains around the main tumor, in portions isolated by the septa, or along the edge of the tumor after ablation therapies.[54] There may also be extranodular growth, satellite nodules or portal vein invasion, which cannot be detected by imaging modalities.[55,56] The incidence of satellite nodules and portal vein invasion is associated with the gross appearance of the main tumor. The single nodular type with extranodular growth and the confluent multinodular type both show satellite lesions more frequently than early HCC (vaguely nodular-type HCC showing preservation of the preexisting liver structure) and the single nodular type. Thus, it is important to determine the gross appearance of the tumor by imaging. It is also essential to ablate beyond the tumor border to achieve complete tumor necrosis and prevent local tumor progression (ablative margin or safety margin). Sonazoid-enhanced US in the Kupffer phase is useful to determine the gross tumor appearance.[57] The width of the safety margin should be modified based on the gross appearance of the tumor, the number of tumors, the initial tumor or recurrent tumor, the duration of time between the previous treatment and recurrence in recurrent cases, tumor location (particularly in relation to the Glisson's capsule), liver function, comorbid conditions and the patient's age.

Furthermore, the accuracy of contrast-enhanced CT or MRI for evaluating the extent of necrosis is limited because of the partial volume effect.[58] The following recommendation was agreed by 94% of the experts.

Recommendation 10. A safety margin completely surrounding the lesion should be achieved in cases in which RFA is performed as a locally curative treatment (level 6, grade A).

Ablation therapies, including RFA, are widely accepted as the preferred treatment for unresectable small HCC. On the other hand, it has been strongly debated whether ablation therapies can provide a treatment option for resectable HCC since the introduction of ethanol injection. Although the number of patients treated by RFA has steadily increased, the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan recommends surgery rather than ablation.[1] Their scientific statement recommends the following: "(i) if only one tumor is present, liver resection is recommended irrespective of the diameter of the tumor. Ablation therapy may also be selected if the severity of liver damage is class B and the diameter of the tumor is no more than 2 cm; (ii) if two to three tumors with diameters of no more than 3 cm are present, liver resection or local ablation therapy is recommended". This scientific statement is based on a cohort study of patients at clinical stage I (fair liver function), with a solitary tumor of less than 2 cm in diameter, patients across all clinical stages with a solitary tumor greater than 2 cm, and patients of clinical stage II (moderately impaired liver function) with two tumors greater than 2 cm. In that cohort, those who underwent hepatic resection showed higher survival rates than those who received non-surgical interventions.[59]

However, those findings were not based on randomized controlled trials (RCT) and the different survival rates may be subject to bias arising from the background characteristics of the patients. Of note, the hepatic resection group was younger than the ethanol injection group. Furthermore, even among patients at clinical stage I, most patients with normal liver or chronic hepatitis seemed to undergo resection while many with cirrhosis seemed to receive ethanol injection. This might reduce the recurrence rate because of multicentric carcinogenesis and less frequent development of liver failure in the resection group. Moreover, the trend that patients with severe comorbid conditions, such as cardiopulmonary diseases and others, received ethanol injection rather than resection might explain some of the disparity in survival. By contrast, in one RCT the recurrence and survival rates were comparable between surgical resection and ethanol injection.[60] In addition, other non-randomized trials have reported similar or better overall survival after ethanol injection than after resection.[61–63]

In addition, the findings described above only compared resection with ethanol injection. For example, our RCT showed that RFA had higher survival and lower recurrence rates than ethanol injection while the adverse events were similar between the two therapies.[64] Similarly, other RCT have shown that RFA is superior to ethanol injection in terms of treatment outcomes for HCC.[65–67] Another RCT has shown that there was no difference between resection and RFA in terms of overall and disease-free survival, while post-treatment complications occurred more frequently and were more severe after surgery.[68]

Hence, it is inappropriate to generalize the findings for ethanol injection to other percutaneous local ablation therapies such as RFA, and it should not be concluded that hepatectomy is recommended over percutaneous local ablation.

Further trials are needed to determine whether RFA can become a preferred treatment for "resectable HCC". In such trials, the primary end-point should be overall

survival.[69] The AASLD practice guideline clearly states the following: "although a treatment might be less active against the tumor than another treatment and thus result in a higher recurrence rate after initial treatment, the overall survival might not differ or may even be better".[3]

Recurrence-free survival can be misleading and should not be considered as a surrogate end-point for overall survival. In HCC, unlike other solid tumors, recurrence can still be treated, and the first recurrence does not cause death in most cases. Furthermore, surgery theoretically offers better disease-free survival than RFA because it removes larger liver tissue. However, the better curability associated with hepatectomy could be cancelled out by the surgical invasion and the potential deterioration in liver function. The following recommendation was agreed by 84% of the experts.

Recommendation 11. Overall survival should be the end-point to compare results between ablation and hepatectomy.

SURGICAL TREATMENT: RESECTION AND TRANSPLANTATION

A NATIONWIDE SURVEY by the Japanese Liver Transplantation Society found that a total of 4725 cases of living-donor liver transplantations (LDLT) were reported in Japan as of the end of 2007 since its initiation in 1989. By contrast, during the same period, only 46 cases of deceased-donor liver transplantation (DDLT) were documented. At the end of 2006, 778 patients with HCC had undergone an LDLT in Japan.[70] Because of the severe shortage of brain-dead donors and the extremely long waiting time for such organs, DDLT is not a realistic treatment option for HCC patients in Japan.

Algorithm for the treatment of patients with HCC in Japan

Figure 1 shows the treatment algorithm presented in the Japanese evidence-based guideline for the diagnosis and treatment of HCC.[1] Liver transplantation is recommended for HCC patients with liver damage C (similar to Child–Pugh C), but only when the patients meet the Milan criteria proposed by Mazzaferro.[71] In the revised version of the guidelines published at the end of 2009, an age limit of 65 years was added to the criteria for liver transplantation.

Can the indications for liver transplantation be expanded beyond the Milan criteria?

Until the mid-1990s, HCC was considered a contraindication for liver transplantation because of the extremely poor outcome of early series.[72,73] This pessimistic view was reversed by Mazzaferro *et al.* who conducted a prospective cohort study to identify subgroups of HCC patients who may benefit from DDLT. They presented clear eligibility criteria for transplantation, as follows: the presence of a solitary tumor of 5 cm or less in diameter and no more than three tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors, and the absence of vascular invasion or extrahepatic disease. In their series, the overall and recurrence-free survival rates

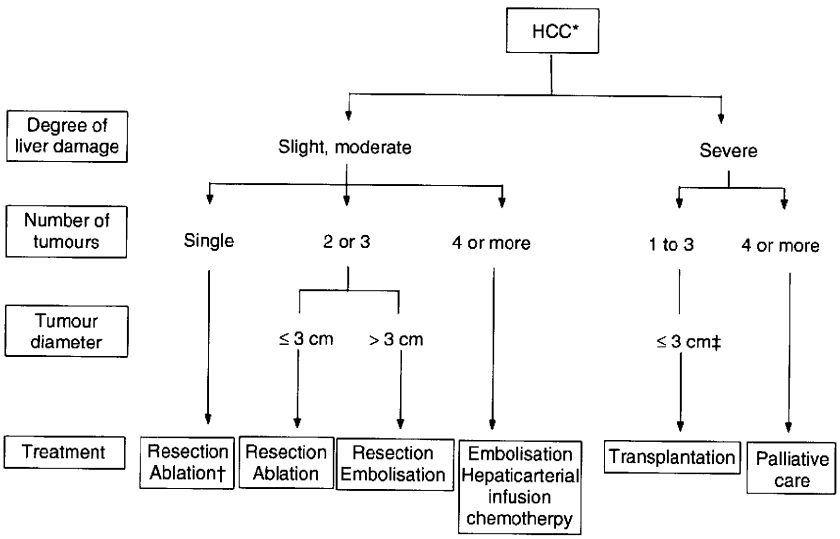

Figure 1 Japanese evidence-based treatment algorithm. HCC, hepatocellular carcinoma.

at 4 years for 35 patients who met the above criteria were as high as 85% and 92%, respectively. These criteria were named the "Milan criteria" and became the gold standard for patient selection for liver transplantation. The Milan criteria were also validated for LDLT using data from a nationwide survey in Japan.[74] Since 2004, LDLT for HCC has been covered by social medical insurance in Japan when the preoperative imaging studies indicate that the patient's condition meets the Milan criteria.

The Milan criteria have encouraged transplant surgeons to increase the number of liver transplantations performed in HCC patients, and the United Network for Organ Sharing (UNOS) has incorporated the Milan criteria as conditions for listing HCC patients. During the extensive application of liver transplantation for HCC, transplant surgeons have noticed that the outcomes of some patients who slightly exceeded the Milan criteria were also favorable. To expand the indications for liver transplantation, several groups from different countries have challenged these restrictive criteria (Table 1).[75–79] Yao *et al.* at the University of California at San Francisco (UCSF) proposed criteria consisting of a single tumor of less than 6.5 cm in diameter or two lesions of less than 4.5 cm in diameter, with a total tumor diameter of less than 8 cm; these criteria are known as the "UCSF criteria".[76] The utility of the UCSF criteria was subsequently confirmed by the University of California at Los Angeles.[80]

Regarding the indications for LDLT in HCC patients, several proposals from Asian centers have extended the eligibility criteria (Table 1). For example, a group at the University of Tokyo proposed the "5-5 rule", which allows up to five nodules with a maximum diameter of 5 cm.[77] The 3-year recurrence-free rate of 72 patients who met the Tokyo 5-5 rule was as high as 94%, which was comparable with that of patients within the Milan criteria. A group at the University of Kyoto subsequently proposed a further expansion of the criteria, increasing the upper limit of the number of tumors to 10.[79]

Because LDLT is not governed by an organ-sharing system, some authors have argued that the indications for LDLT in patients with HCC could be further extended. One might say that "If the patient (recipient) and his/her family (donor) strongly wish to undergo LDLT even in cases of very advanced HCC with full knowledge of potential for poor outcomes, there is no reason for transplant surgeons to reject their wish. The family members may accept the poor outcome after LDLT without doing any harm to the community." However, we should always remember that, while LDLT does not require a donor from the community, it does require extensive medical resources, including a large workload for surgeons and other hospital staff members, medical supplies, drugs and blood products. Furthermore, the premature death of the recipient is well known to cause severe emotional trauma to the living donors and their family members.

Based on an answer-pad vote at the consensus meeting of 45th JSH congress, 84% of the experts supported keeping the Milan criteria for DDLT, but only 25% supported keeping these criteria for LDLT. Although any expansion of the criteria should be modest, no consensus exists as to the extent to which the criteria can be extended.

Recommendation 12. For DDLT, the HCC status of the recipients should meet the Milan criteria.

Recommendation 13. For LDLT, the HCC status of the recipients does not need to be within the Milan criteria.

Which is better, liver resection or transplantation, for HCC patients who are eligible for either treatment?

Because liver transplantation replaces the whole liver, removing the highly carcinogenic background and the cirrhotic liver can avoid multicentric or de novo cancer recurrence.[80] In contrast, liver resection is associated with a very high risk of tumor recurrence. Even after curative liver resection in patients with good liver function, the 5-year recurrence rate is as high as 70–79%.[80] Roughly half of these recurrences are multicentric or de novo recurrences. For this reason, liver transplantation

Table 1 Summary of proposed criteria for indication of liver transplantation for HCC

Criteria	Conditions	References
Milan criteria	Up to 5 cm for single nodule or up to 3 nodules with a maximum diameter of 3 cm	70
UCSF criteria	Up to 6.5 cm for single nodule or up to 3 nodules with a maximum diameter of 4.5 cm	76
Tokyo 5-5 rule	Up to 5 nodules with a maximum diameter of 5 cm	77
Asan criteria	Up to 6 nodules with a maximum diameter of 5 cm	78
Kyoto criteria	Up to 10 nodules with a maximum diameter of 5 cm and PIVKA-II <400 mAU/mL	79
Up-to-seven criteria	Up to seven as the sum of the size of the largest tumor [in cm] and the number of tumors	75

may be recommended for HCC patients with good liver function who are also eligible for liver resection, as in Western countries.

Another issue is the operative risk of the two treatments. In Japan, the operative mortality rates for LDLT and liver resection are estimated to be 4–10% and 0.8–1.2%, respectively. This striking difference in operative mortality rates might preclude LDLT for patients with good liver function.

Using two databases at the National Cancer Center Hospital in Japan and the University of Pittsburgh Medical Center in the USA, Yamamoto *et al.* compared the long-term outcome of liver resection and transplantation in cirrhotic patients with HCC.[81] The overall survival of Child–Pugh A patients who underwent liver resection was similar to that of the patients without vascular invasion or lymph node metastases who underwent transplantation (most cases with Child-Pugh C). The recurrence rate was significantly lower in the transplantation group. For cases in which either treatment can be performed, the outcome of liver transplantation might be better than that of hepatic resection, particularly in cases with only a few small lesions.[81,82] In cases with large lesions, superior outcomes are achieved with hepatectomy. Because some patients may withdraw from treatment during the pre-transplantation period,[83] the outcomes with resection are better than those for liver transplantation based on intention-to-treat analysis of patients who meet the criteria for resection.

The evidence-based guideline[1] recommends the following: considering the occurrence of dropouts during the pre-transplantation period, the outcome of resection is better than that of liver transplantation among patients who meet the criteria for resection (grade B).

According to a question and answer-analyzer vote at this consensus meeting, 83% of the HCC experts selected LDLT for Child–Pugh C patients meeting the Milan criteria, whereas only 15–19% of the audience selected LDLT for Child–Pugh A or B patients.

Recommendation 14. LDLT should not be recommended for HCC patients with Child–Pugh A or B liver function.

PALLIATIVE TREATMENTS: TRANSARTERIAL CHEMOEMBOLIZATION AND CHEMOTHERAPY

PALLIATIVE TREATMENTS FOR HCC include transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC) and systemic chemotherapy.

Transarterial embolization/TACE

Transcatheter arterial embolization (TAE)/TACE is one of the treatment options to treat hypervascular HCC. The theoretical basis of embolization is to induce ischemic tumor necrosis by acute arterial occlusion in hypervascular classical HCC. Embolization may be done alone (TAE) or in combination (TACE) with antineoplastic agents such as doxorubicin, epirubicin or cisplatin and a contrast agent, lipiodol. TACE is more effective and, thus, more widely used than embolization alone.

The technique for TACE is well established. The subsegmental artery or a peripheral artery near the target tumor is selected by a micro-catheter technique, followed by selective injection of antineoplastic agents mixed with lipiodol (lipiodol emulsion). The artery is then selectively obstructed with gelatin sponge particles. For bi-lobular multiple HCC with moderately impaired hepatic function (Child–Pugh B), TACE might need to be performed twice with an interval of several weeks to avoid hepatic decompensation.

The survival benefit of TAE/TACE was controversial until the publication of two RCT in 2002, which showed that TACE improved the survival of selected patients (Child–Pugh A with no vascular invasion) compared with conservative treatment.[84,85] A subsequent meta-analysis of seven RCT comparing TAE/TACE as a primary treatment for HCC in comparison with conservative management and/or suboptimal therapies showed a significant improvement in the 2-year survival, favoring TAE/TACE (odds ratio [OR] = 0.53; 95% confidence interval [CI] = 0.32–0.89, $P = 0.017$).[86,87]

According to the Nationwide Follow-up Survey of Primary Liver Cancer in Japan, one-third of all patients with primary HCC were treated by TAE/TACE (Fig. 2). Thus, TAE/TACE, hepatic resection and local ablation therapy are commonly used in Japan. TAE/TACE is the most widely used treatment for unresectable HCC.

In two Japanese treatment guidelines for HCC, evidence-based[1,30,88] and consensus-based guidelines,[89] TACE is recommended for patients with the severity of the liver damage categorized into A or B, in whom there are two or three tumors with a diameter greater than 3 cm, or four or more tumors.

In early stages of HCC, TACE is not indicated as first-line treatment because the outcome review of the Nationwide Follow-up Survey by the LCSGJ reported worse results for TACE than surgery or percutaneous ablation. This survey revealed that the 5-year survival rates for resection, ablation and TACE were 59.2%,