This statement was agreed on by 89% of the participants at the ILCA consensus meeting, but 11% disagreed with this statement. At the JSH consensus meeting, 84% of the participants agreed with this statement, and 16% disagreed. The outcome should be evaluated by both overall survival and incidence of recurrence.

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Disclosure Statement

The author declares that he has no financial conflict of interest.

References

1 Kokudo N, Makuuchi M: Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: the J-HCC guidelines. J Gastroenterology 2009;44:119–121.
2 Silva MA, Hegab B, Hyde C, et al: Needle tract seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systemic review and meta-analysis. Gut 2008;57:1592–1596.
3 Stigliano R, Marelli L, Yu D, et al: Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 2007;33:437–447.
4 Suzuki M, Maeyama S, Takahashi H, et al: Strategy for hepatic hyperplastic nodules in heavy drinkers. Alcohol Clin Exp Res 2004; 28:153S–158S.
5 Golfieri R, Coppola F, Fusco F, et al: Malignant progression of a small nodule: hypovascular 'early HCC' converted to hypervascular 'small HCC' within six months. Dig Liver Dis 2007;39:883–890.
6 Kudo M, Chung H, Osaki Y: Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score. J Gastroenterol 2003;38:207–215.
7 Kudo M, Chung H, Haji S, et al: Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. Hepatology 2004;40: 1396–1405.
8 Vivarelli M, Guglielmi A, Ruzzenente A, et al: Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg 2004;240:102–107.
9 Ueno S, Sakoda M, Kubo F, et al: Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within Milan criteria. J Hepatobiliary Pancreat Surg 2009;16:359–366.
10 Hiraoka A, Horiike N, Yamashita Y, et al: Efficacy of radiofrequency ablation therapy compared to surgical resection in 164 patients in Japan with single hepatocellular carcinoma smaller than 3 cm along with report of complications. Hepatogastroenterology 2008;55:217–214.
11 Hasegawa K, Makuuchi M, Takayama T, et al: Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: a preliminary report of the Japanese nationwide survey. J Hepatol 2008;49:589–594.
12 Kirikoshi H, Saito S, Yoneda M, et al: Outcome of transarterial chemoembolization monotherapy, and combination with percutaneous ethanol injection, or radiofrequency ablation therapy for hepatocellular carcinoma. Hepatol Res 2009;39:553–562.
13 Yang W, Chen MH, Wang MQ, et al: Combination therapy of radiofrequency ablation and transarterial chemoembolization in recurrent hepatocellular carcinoma after hepatectomy compared with single treatment. Hepatol Res 2009;39:231–240.
14 Kurokohchi K, Hosomi N, Yoshitake A, et al: Successful treatment of large-size advanced hepatocellular carcinoma by transarterial chemoembolization followed by the combination therapy of percutaneous ethanol-lipiodol injection and radiofrequency ablation. Oncol Res 2006;16:1067–1070.
15 Llovet JM, Bruix J: Molecular targeted therapies in hepatocellular carcinoma. Hepatology 2008;48:1312–1327.
16 Hoffmann K, Glimm H, Radeleff B, et al: Prospective, randomized double-blind, multicenter, phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation – HeiLivCa. BMC Cancer 2008;26:349.
17 Kudo M: Hepatocellular carcinoma 2009 and beyond: from the surveillance to molecular targeted therapy. Oncology 2008;75:1–12.

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Original Article

Hepatic steatosis in chronic hepatitis C is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage and response to interferon therapy

Masayuki Kurosaki,[1] Takanori Hosokawa,[1] Kotaro Matsunaga,[2] Itsuko Hirayama,[1] Tomohiro Tanaka,[1] Mitsuaki Sato,[1] Yutaka Yasui,[1] Nobuharu Tamaki,[1] Ken Ueda,[1] Kaoru Tsuchiya,[1] Teiji Kuzuya,[1] Hiroyuki Nakanishi,[1] June Itakura,[1] Yuka Takahashi,[1] Yasuhiro Asahina,[1] Nobuyuki Enomoto[3] and Namiki Izumi[1]

Divisions of [1]Gastroenterology and Hepatology, and [2]Pathology, Musashino Red Cross Hospital, Tokyo, and [3]First Department of Internal Medicine, University of Yamanashi, Yamanashi, Japan

Aim: Hepatic steatosis is linked to development of hepatocellular carcinoma (HCC) in non-viral liver disease such as non-alcoholic steatohepatitis. The present study aimed to assess whether hepatic steatosis is associated with the development of HCC in chronic hepatitis C.

Methods: We studied a retrospective cohort of 1279 patients with chronic hepatitis C who received interferon (IFN) therapy between 1994 and 2005 at a single regional hospital in Japan. Of these patients, 393 had a sustained virological response (SVR) and 886 had non-SVR to IFN therapy. After IFN therapy, these patients were screened for development of HCC every 6 months. The average period of observation was 4.5 years.

Results: HCC developed in 68 patients. The annual incidence of HCC was 2.73% for patients with a steatosis grade of 10% or greater and 0.69% for patients with a steatosis grade of 0–9%. On multivariate analysis, higher grade of steatosis was a significant risk factor for HCC independent of older age, male sex, higher body mass index (BMI), advanced fibrosis stage and non-SVR to IFN therapy. The adjusted risk ratio of hepatic steatosis was 3.04 (confidence interval 1.82–5.06, $P < 0.0001$), which was higher than that of older age (1.09), male sex (2.12), non-SVR to IFN (2.43) and higher BMI (1.69).

Conclusion: Hepatic steatosis is a significant risk factor for development of HCC in chronic hepatitis C independent of other known risk factors, which suggest the possibility that amelioration of hepatic steatosis may prevent hepatocarcinogenesis.

Key words: hepatocellular carcinoma, interferon, steatosis, virological response.

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common cancers worldwide and its incidence has been increasing. This recent increase in HCC incidence may likely be attributed to the higher prevalence of non-alcoholic fatty liver disease (NAFLD) and hepatitis C virus (HCV) infection.[1]

Non-alcoholic fatty liver disease is characterized by hepatic steatosis with or without inflammation in the absence of excessive alcohol consumption. Several studies have indicated the etiological association between NAFLD and development of HCC.[2–4] Other studies have shown that obesity or diabetes, a common etiology of non-alcoholic hepatic steatosis, is associated with development of HCC.[5–7] Although the mechanism of carcinogenesis in NAFLD has not been determined, an animal model showed that obesity-related hepatic steatosis leads to the development of hepatic

Correspondence: Dr Namiki Izumi, Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital, 1-26-1 Kyonan-cho, Musashino-shi, Tokyo 180-8610, Japan. Email: nizumi@musashino.jrc.or.jp

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hyperplasia, suggesting the possibility that hepatic steatosis is a pre-malignant condition.[8]

Another important etiological agent for HCC is HCV infection. Because steatosis is a common pathological feature of HCV-infected patients,[9] the important question is whether steatosis influences the progression of liver disease in hepatitis C, by analogy with NAFLD. Several studies, including ours[10] indicated that hepatic steatosis promotes the progression of hepatic fibrosis.[11–15] The association between hepatic steatosis and the development of HCC in chronic hepatitis C has been proposed[16] and was confirmed in two studies[17,18] while another study failed to show such an association.[19] The present study was conducted to analyze the association between hepatic steatosis and development of HCC in a large cohort of chronic hepatitis C patients, which enabled to adjust for known risk factors for HCC.

METHODS

Patients

A TOTAL OF 1437 chronic hepatitis C patients were treated with interferon (IFN) at Musashino Red Cross Hospital between October 1994 and October 2005. Among them, 1279 patients who fulfilled the following inclusion criteria were enrolled in this study: (i) positive for HCV RNA by reverse-transcription polymerase chain reaction before IFN therapy; (ii) absence of other causes of liver disease, such as co-infection with hepatitis B virus, autoimmune hepatitis or primary biliary cirrhosis; (iii) had undergone liver biopsy within the 12 months prior to IFN treatment; (iv) were followed for more than 1 year after the completion of IFN therapy; and (v) absence of HCC during and within 1 year after the completion of therapy. A total of 158 patients were excluded: two patients who were positive for hepatitis B surface antigen, 97 patients lacking liver biopsy, 53 patients with less than 1 year's duration of follow up, and six patients who developed HCC within 1 year of the completion of IFN therapy. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional ethics review committee.

Patients were followed up by regular visits to our hospital every 1–3 months. Six patients died of liver-unrelated disease (two patients with gastric cancer and one patient each with lung cancer, colon cancer, pancreatic cancer and leukemia). There were 122 patients who were lost to follow up because of relocation. We included their data in the analysis, censored at the time of their last visit. The start of follow up was defined as the date of completion of first IFN therapy and the end of follow up was defined as the date of diagnosis of HCC or the date of the last visit. The average period of follow up was 4.5 years.

Clinical characteristics and laboratory data were collected at the most recent time point before liver biopsy. Diabetes mellitus was diagnosed based on a fasting plasma glucose concentration that exceeded 126 mg/dL, a casual plasma glucose concentration that exceeded 200 mg/dL, or the need for insulin or oral antihyperglycemic drugs. Information regarding alcohol consumption was obtained through an interview. Body mass index (BMI) was calculated using the following formula: weight in kilograms/height in meters squared. The baseline clinical features of patients at enrollment are summarized in Table 1.

Histological examination

Liver biopsy specimens were obtained from all patients before therapy. The median length of liver biopsy specimens was 13 mm (range 10–42 mm) and median number of portal tracts was 11 (range 4–30). Histological findings were re-evaluated recently by three independent pathologists who were blinded to the clinical details to ensure consistency over time. Fibrosis and activity were scored according to the METAVIR scoring system.[20] Fibrosis was staged on a scale of 0–4: F0 (no fibrosis); F1 (mild fibrosis: portal fibrosis without septa); F2 (moderate fibrosis: few septa); F3 (severe fibrosis: numerous septa without cirrhosis); and F4 (cirrhosis). Activity of necroinflammation was graded on a scale of 0–3: A0 (no activity); A1 (mild activity); A2 (moderate activity); and A3 (severe activity). Percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis and graded on a scale of 0%, 1–9%, 10–29% and 30% or greater as reported previously.[10] All three pathologists assigned the same scale in 85% of cases for fibrosis staging, 87% for inflammation grading and 95% for steatosis grading. If there was discordance, the scores assigned by two pathologists were used for the analysis.

Screening for HCC

At enrollment, no patient had HCC or any suspicious lesion on abdominal ultrasonography or computed tomography. Patients were examined for HCC by abdominal ultrasonography or computed tomography at least every 6 months. Suspicious lesions were examined further by a triphasic contrast-enhanced computerized tomography or magnetic resonance imaging,

Table 1 Clinical characteristics of patients

Male, *n* (%)	643 (50%)
Age (years)	54.2 ± 11.9
BMI (kg/m^2)	23.4 ± 3.1
Alcohol consumption ≥20 g/day, *n* (%)	44 (3%)
Diabetes Mellitus, *n* (%)	197 (15%)
AST level (IU/L)	68.9 ± 45.3
ALT level (IU/L)	92.9 ± 75.9
GGT level (IU/L)	41.2 ± 38.2
Platelet count (×10^{10}/L)	16.4 ± 5.2
HCV genotype, *n* (%)	
1b	873 (68.2%)
2a	236 (18.4%)
2b	139 (10.9%)
3	2 (0.2%)
Not determined	29 (2.3%)
Histological findings	
Grade of activity, *n* (%)	
A0	154 (12%)
A1	574 (45%)
A2	441 (34%)
A3	110 (9%)
Stage of fibrosis, *n* (%)	
F0	24 (2%)
F1	591 (46%)
F2	378 (30%)
F3	242 (19%)
F4	44 (3%)
Grade of steatosis, *n* (%)	
0%	384 (30%)
1–9%	543 (42%)
10–29%	215 (17%)
≥30%	137 (11%)
SVR to interferon therapy, *n* (%)	393 (31%)
Development of HCC, *n* (%)	68 (5%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, γ-glutamyltransferase; HCC, hepatocellular carcinoma; SVR, sustained virological response.

angiography or tumor biopsy to confirm the diagnosis. Diagnostic criteria of HCC on radiological findings were hyper-vascularity at angiography or hyper-attenuation at triphasic contrast-enhanced computerized tomography or magnetic resonance imaging during the hepatic arterial phase.

Statistical analysis

The SPSS software package ver. 15.0 was used for statistical analysis. Categorical data were analyzed using Fisher's exact test. Continuous variables were compared with Student's *t*-test. The time for the development of HCC was defined as the time from the completion of IFN therapy to the time of diagnosis. Annual incidence of HCC was calculated using the person-years method. Effect of hepatic steatosis on time to development of HCC was analyzed by the Kaplan–Meier method and log-rank test, after stratification by age, sex, BMI, degree of fibrosis and response to IFN therapy, as well as multivariate analysis using Cox proportional hazards regression analysis. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Background factors for steatosis

PATIENTS WITH A steatosis grade of 10% or greater were older (53.6 ± 12.6 vs 56.0 ± 9.8, $P = 0.001$), had a higher BMI (23.0 ± 3.0 vs 24.6 ± 3.3, $P < 0.0001$), higher frequency of diabetes (12% vs 24%, $P < 0.0001$), higher serum levels of aspartate aminotransferase (AST) (66 ± 46 vs 75 ± 43, $P = 0.002$), γ-glutamyltransferase (GGT) (37 ± 52 vs 52 ± 33, $P < 0.0001$), total cholesterol (173 ± 32 vs 179 ± 33, $P = 0.005$), triglycerides (123 ± 56 vs 145 ± 68, $P < 0.0001$), and a lower serum level of albumin (4.2 ± 0.3 vs 4.1 ± 0.3, $P = 0.005$) and lower platelet counts (16.6 ± 5.2 vs 15.7 ± 5.1, $P = 0.007$). Histological grade of activity (A2–3: 39% vs 54%, $P < 0.0001$), and stage of fibrosis (F3–4: 18% vs 34%, $P < 0.0001$) were higher. The proportion of non-sustained virological response (SVR) to IFN also was higher (35% vs 19%, $P < 0.0001$). These results indicate that hepatic steatosis in hepatitis C is related to metabolic factors and associated with other risk factors for the development of HCC such as older age, advanced stage of fibrosis, and non-SVR to IFN therapy.

Factors associated with the development of HCC

Hepatocellular carcinoma developed in 68 patients during follow up. An overall annual incidence of HCC development was 1.19% by person-years. The annual incidence of HCC development by person-years was higher in patients with higher grade of steatosis: 0.45% for patients without steatosis, 0.78% for patients with 1–9% of steatosis, 2.30% for patients with 10–29% of steatosis, and 3.56% for patients with 30% of steatosis. The relative risk of hepatic steatosis (grade of ≥10%) for HCC development was 4.39 (95% confidence interval 2.66–7.26, $P < 0.0001$). The difference remained significant, even after stratification for other risk factors such as IFN therapy, stage of fibrosis, age, sex and BMI (Fig. 1). When analyzed by the multivariate Cox proportional hazards regression method, a higher grade of steatosis,

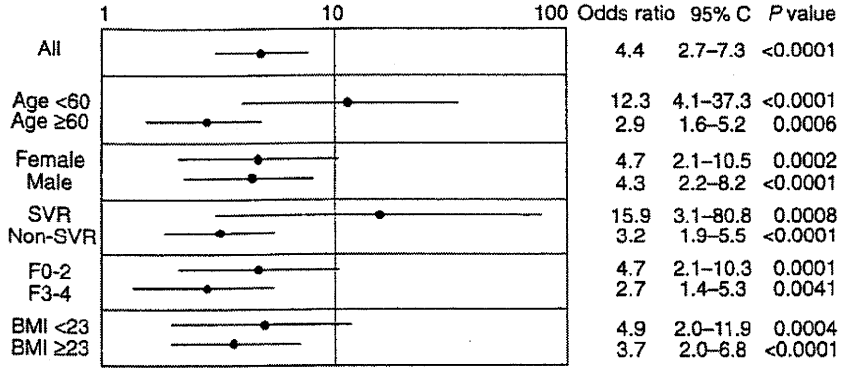


Figure 1 Relative risk differences of hepatocellular carcinoma (HCC) among patients with and without steatosis. The relative risk of hepatic steatosis (grade ≥10%) for HCC development was analyzed, after stratification for other risk factors such as interferon (IFN) therapy, stage of fibrosis, age, sex and body mass index (BMI). SVR, sustained virological response.

older age, male sex, higher BMI, an advanced stage of fibrosis and non-SVR to IFN therapy were independent risk factors associated with the development of HCC (Table 2). The adjusted risk ratio of hepatic steatosis was 3.04 (95% confidence interval 1.82–5.06, $P < 0.0001$). The presence of diabetes and consumption of ethanol were not significant. Figure 2(a) shows the Kaplan–Meier curve of the time to development of HCC in the entire cohort. The cumulative incidence of HCC was significantly higher with hepatic steatosis of 10% or greater. To adjust for other risk factors, patients were stratified according to response to IFN therapy, stage of fibrosis, age, sex and BMI. The difference remained significant, even after stratification for these confounding factors (Fig. 2b–f). Three patients died after the development of HCC. All were over 60 years old, and had significant steatosis. The impact of hepatic steatosis on the survival rate could not be analyzed due to the small number of death.

DISCUSSION

IN THIS STUDY, we have shown that the presence of significant steatosis is an independent risk factor for the development of HCC in chronic hepatitis C. Our study involved the largest number of patients, compared to previous reports, and this enabled us to adjust for other known risk factors for HCC. The impact of steatosis on HCC development remained significant even after adjusting for other risk factors such as older age, male sex, higher BMI, advanced fibrosis and non-SVR to IFN therapy. These findings indicate the need of intensive surveillance for HCC in patients with significant steatosis and provide an argument for therapeutic interventions aimed at reducing steatosis, in order to reduce the risk of HCC.

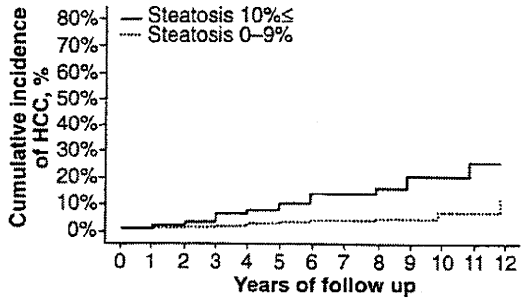
The association between hepatic steatosis and the development of HCC in chronic hepatitis C has been proposed and the possible mechanism has been discussed.[16] There are several cohort studies on this topic but their results are conflicting. The first report included 20 patients with SVR to IFN, 51 patients with non-SVR to IFN and 90 patients who did not receive IFN therapy.[17] In this cohort of 161 patients, older age, absence of IFN therapy, cirrhosis and steatosis were associated with HCC development. Another study involved 25 patients with HCC and an equal number of patients who did not develop HCC, matched for

Table 2 Multivariate analysis of risk factors for hepatocellular carcinoma

Predictor		Odds ratio (95% CI)	*P*-value
Age	By every 10 years	1.09 (1.05–1.13)	<0.0001
Sex	Male vs female	2.12 (1.28–3.51)	0.004
Stage of fibrosis	F3–4 vs F0–2	4.30 (2.59–7.14)	<0.0001
Grade of steatosis	≥10% vs <10%	3.04 (1.82–5.06)	<0.0001
Response to IFN	Non-SVR vs SVR	2.43 (1.13–5.23)	0.023
Diabetes	Present vs absent	0.75 (0.42–1.33)	0.319
Ethanol consumption (g/day)	≥20 vs <20	0.50 (0.07–3.60)	0.478
BMI (kg/m2)	≥23 vs <23	1.69 (1.02–2.86)	0.043

BMI, body mass index; CI, confidence interval; IFN, interferon; SVR, sustained virological response.

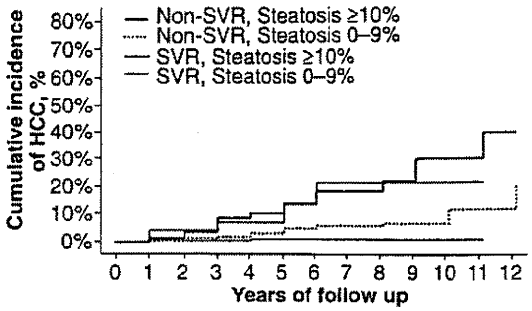
(a) **Entire cohort**



Number of patients at risk

Steatosis 0–9%	927	824	620	503	320	227	161	117	77	49	27	10
Steatosis ≥10%	352	271	207	157	113	83	54	48	32	17	9	1

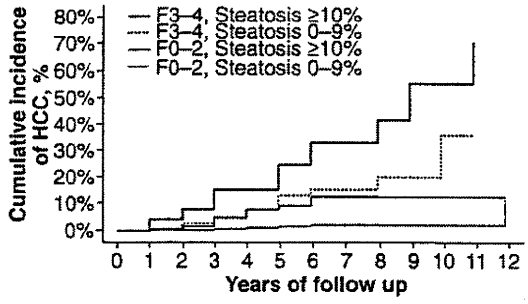
(b) **Stratified by response to IFN therapy**



Number of patients at risk

SVR												
Steatosis 0–9%	326	254	204	153	81	55	33	21	15	10	5	0
Steatosis ≥10%	67	50	34	22	14	10	4	4	4	2	2	0
Non-SVR												
Steatosis 0–9%	601	507	416	350	239	172	128	96	62	39	22	10
Steatosis ≥10%	285	221	173	135	99	73	50	44	28	15	7	1

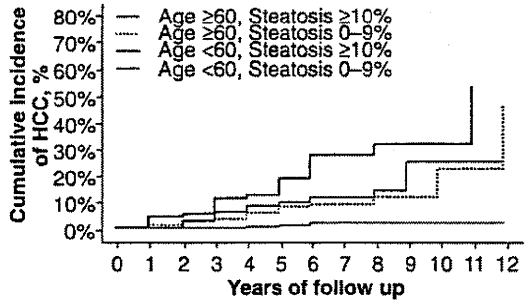
(c) **Stratified by stage of fibrosis**



Number of patients at risk

F0–2												
Steatosis 0–9%	759	623	509	415	266	188	137	99	64	39	25	10
Steatosis ≥10%	234	190	146	107	77	55	37	32	19	11	6	1
F3–4												
Steatosis 0–9%	118	81	61	50	36	28	17	16	13	6	3	0
Steatosis ≥10%	168	138	111	88	54	39	23	18	13	10	2	0

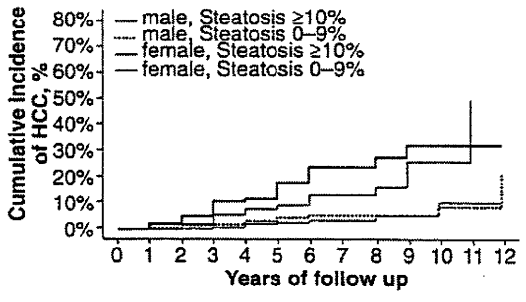
(d) **Stratified by age**



Number of patients at risk

Age <60												
Steatosis 0–9%	549	457	367	298	188	148	111	83	53	33	19	7
Steatosis ≥10%	193	154	111	83	61	48	34	31	23	12	6	1
Age ≥60												
Steatosis 0–9%	378	304	253	205	132	79	50	34	24	16	8	3
Steatosis ≥10%	159	117	96	74	52	35	20	17	9	5	3	0

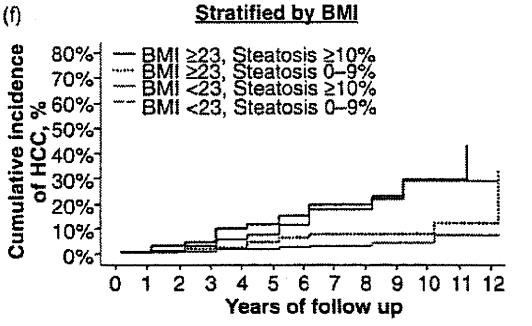
(e) **Stratified by gender**



Number of patients at risk

Male												
Steatosis 0–9%	470	389	319	265	169	126	90	65	46	30	17	7
Steatosis ≥10%	173	134	98	73	54	40	21	21	15	8	6	1
Female												
Steatosis 0–9%	457	372	301	238	151	101	71	52	31	19	10	3
Steatosis ≥10%	179	137	109	84	59	43	33	27	17	9	3	0

(f) **Stratified by BMI**



Number of patients at risk

BMI ≥23												
Steatosis 0–9%	417	346	269	213	129	94	66	49	31	19	8	4
Steatosis ≥10%	226	176	137	101	71	55	34	33	20	10	5	0
BMI <23												
Steatosis 0–9%	510	415	351	290	191	133	95	68	46	30	19	6
Steatosis ≥10%	126	95	70	56	42	28	20	15	12	7	4	1

Figure 2 Cumulative incidence of hepatocellular carcinoma (HCC) among patients with steatosis (solid line) and without steatosis (dotted line), stratified by other risk factors. The cumulative incidence of HCC was (a) significantly higher in patients with a steatosis grade of 10% or greater ($P < 0.0001$ by the log-rank test), even after (b) stratification by the response to interferon therapy ($P < 0.0001$ for sustained virological response [SVR] and non-SVR by the log-rank test), (c) stratification by the stage of fibrosis ($P < 0.0001$ for F0–2 and $P = 0.0036$ for F3–4 by the log-rank test), (d) stratification by age ($P = 0.0001$ for age ≥60 and $P < 0.0001$ for age <60 by the log-rank test), (e) stratification by sex ($P < 0.0001$ for men and women by the log-rank test), and (f) stratification by body mass index (BMI) ($P < 0.0001$ for BMI ≥23 kg/m^2 and <23 kg/m^2 by the log-rank test). The number of patients at risk is shown below each graph.

age, sex, HCV genotype and stage of fibrosis.[19] In this study, only ALT and albumin were identified as predictors of HCC and steatosis was not. The authors acknowledged the small size of the cohort as a limitation and emphasized the need for larger cohort studies. The third study analyzed explanted liver from cirrhotic patients who underwent liver transplantation and included 32 patients with HCC and 62 patients without HCC.[18] The authors found that older age, higher α-fetoprotein levels and steatosis were significantly associated with HCC. The major advantage of this study was the standardization of fibrosis stage to cirrhosis. On the other hand, a limitation was the retrospective nature of the study; steatosis was evaluated after the diagnosis of HCC, when cirrhosis already was present (fibrosis stage F4). Because steatosis has been reported to decrease once cirrhosis has developed, this study may have underestimated the grade of steatosis present prior to the development of HCC. Thus, we cannot simply apply their findings to a clinical setting where biopsies are usually obtained before the development of cirrhosis and years before the development of HCC. Based on that background, the principal aim of this study was to analyze the association between hepatic steatosis and the development of HCC in chronic hepatitis C patients, adjusting for known risk factors. We found that steatosis was an independent risk factor by the multivariate Cox proportional hazards regression analysis and by the Kaplan–Meier method and log-rank test after stratification by other risk factors. To our surprise, the adjusted risk ratio of hepatic steatosis was higher than that of older age, male sex, non-SVR to IFN and higher BMI.

How steatosis contributes to the development of HCC remains unclear. Several studies including ours,[10] indicated that hepatic steatosis promotes the progression of hepatic fibrosis,[11–15] which potentiates the risk of HCC indirectly. On the other hand, the ob/ob mouse model of NAFLD showed that hepatic neoplasia developed in the absence of advanced fibrosis, supporting the concept that metabolic abnormalities related to obesity initiate the neoplastic process.[8] Leptin, an adipocytokine related to steatosis in chronic hepatitis C,[21] was shown recently to be mitogenic in human liver[22] and thus may be a link between steatosis and HCC development. Otherwise, steatosis may be responsible for increased lipid peroxidation and reactive oxygen species which induce genetic damage.[23–25] Another study showed that mice transgenic for the HCV core gene developed hepatic steatosis early in life and thereafter HCC which indicates that the HCV core protein has a chief role in the development of both steatosis and HCC development.[26] The precise mechanism of the association between steatosis and carcinogenesis needs further investigation.

The higher incidence of HCC in patients with significant steatosis has important clinical implications. The most important question is whether therapeutic interventions aimed at reducing steatosis could reduce the risk of HCC in chronic hepatitis C. Because the adjusted risk ratio of hepatic steatosis was higher than that of older age, male sex, non-SVR to IFN and higher BMI, we hypothesize that modification of lifestyle and the amelioration of hepatic steatosis may efficiently prevent hepatocarcinogenesis in patients having concomitant risk factors. Apparently, further prospective studies focusing on this point are necessary. Weight reduction may provide an important treatment strategy because one study indicated that weight reduction in chronic hepatitis C leads to a reduction in steatosis and an improvement in fibrosis despite the persistence of HCV infection.[27] Alternatively, insulin resistance may be another target of therapy because a study showed that the administration of pioglitazone led to metabolic and histological improvement in subjects with non-alcoholic steatohepatitis.[28] A limitation of the present study was that data for the plasma insulin concentration was not available and thus insulin resistance could not be assessed. Whether insulin resistance plays a role in hepatocarcinogenesis or its amelioration could improve steatosis and ultimately prevent development of HCC in chronic hepatitis C awaits future investigation.

Another important finding of the present study was that steatosis was a significant risk factor for the development of HCC in patients with SVR to IFN therapy. Thus, steatosis may play a role in carcinogenesis in patients who have cleared HCV. Several studies have shown that the incidence of HCC is reduced but not eliminated in those with SVR to IFN.[29–31] Because the predictors of HCC development in SVR patients have not been established to date, steatosis may be used to identify patients who need intensive surveillance and long-term follow up, even after the clearance of HCV. In conclusion, we showed that hepatic steatosis is significantly associated with the development of HCC in chronic hepatitis C independent of age, sex, BMI, degree of fibrosis and response to previous IFN therapy. Steatosis may be a useful marker for identifying patients at higher risk for HCC. Further studies are needed to evaluate the hypothesis that therapeutic interventions aimed at reducing steatosis may prevent hepatocarcinogenesis.

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REFERENCES

1 El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; 132: 2557–76.
2 Shimada M, Hashimoto E, Taniai M *et al.* Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J Hepatol* 2002; 37: 154–60.
3 Bugianesi E, Leone N, Vanni E *et al.* Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; 123: 134–40.
4 Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 2002; 36: 1349–54.
5 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; 348: 1625–38.
6 El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; 126: 460–8.
7 Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005; 54: 533–9.
8 Yang S, Lin HZ, Hwang J, Chacko VP, Diehl AM. Hepatic hyperplasia in noncirrhotic fatty livers: is obesity-related hepatic steatosis a premalignant condition? *Cancer Res* 2001; 61: 5016–23.
9 Lefkowitch JH, Schiff ER, Davis GL *et al.* Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. The Hepatitis Interventional Therapy Group. *Gastroenterology* 1993; 104: 595–603.
10 Kurosaki M, Matsunaga K, Hirayama I *et al.* The presence of steatosis and elevation of alanine aminotransferase levels are associated with fibrosis progression in chronic hepatitis C with non-response to interferon therapy. *J Hepatol* 2008; 48: 736–42.
11 Hourigan LF, Macdonald GA, Purdie D *et al.* Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999; 29: 1215–19.
12 Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; 33: 1358–64.
13 Westin J, Nordlinder H, Lagging M, Norkrans G, Wejstal R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002; 37: 837–42.
14 Fartoux L, Chazouilleres O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology* 2005; 41: 82–7.
15 Leandro G, Mangia A, Hui J *et al.* Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006; 130: 1636–42.
16 Koike K. Hepatitis C virus contributes to hepatocarcinogenesis by modulating metabolic and intracellular signaling pathways. *J Gastroenterol Hepatol* 2007; 22 (Suppl 1): S108–11.
17 Ohata K, Hamasaki K, Toriyama K *et al.* Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; 97: 3036–43.
18 Pekow JR, Bhan AK, Zheng H, Chung RT. Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. *Cancer* 2007; 109: 2490–6.
19 Kumar D, Farrell GC, Kench J, George J. Hepatic steatosis and the risk of hepatocellular carcinoma in chronic hepatitis C. *J Gastroenterol Hepatol* 2005; 20: 1395–400.
20 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; 24: 289–93.
21 Romero-Gomez M, Castellano-Megias VM, Grande L *et al.* Serum leptin levels correlate with hepatic steatosis in chronic hepatitis C. *Am J Gastroenterol* 2003; 98: 1135–41.
22 Ramani K, Yang H, Xia M, Ara AI, Mato JM, Lu SC. Leptin's mitogenic effect in human liver cancer cells requires induc-

tion of both methionine adenosyltransferase 2A and 2beta. *Hepatology* 2008; 47: 521–31.
23 Okuda M, Li K, Beard MR *et al.* Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002; 122: 366–75.
24 Cai D, Yuan M, Frantz DF *et al.* Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 2005; 11: 183–90.
25 Arkan MC, Hevener AL, Greten FR *et al.* IKK-beta links inflammation to obesity-induced insulin resistance. *Nat Med* 2005; 11: 191–8.
26 Moriya K, Fujie H, Shintani Y *et al.* The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med* 1998; 4: 1065–7.
27 Hickman IJ, Clouston AD, Macdonald GA *et al.* Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. *Gut* 2002; 51: 89–94.
28 Belfort R, Harrison SA, Brown K *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; 355: 2297–307.
29 Yoshida H, Shiratori Y, Moriyama M *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999; 131: 174–81.
30 Nishiguchi S, Shiomi S, Nakatani S *et al.* Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet* 2001; 357: 196–7.
31 Shiratori Y, Ito Y, Yokosuka O *et al.* Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005; 142: 105–14.

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Single HCC smaller than 2 cm: surgery or ablation?

Surgeon's perspective

Tadatoshi Takayama · Masatoshi Makuuchi · Kiyoshi Hasegawa

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Abstract
Purpose For hepatocellular carcinoma (HCC), surgical resection and radiofrequency ablation (RFA) are accepted as effective treatments. To clarify the long-term outcome in patients with small HCC, we analyzed data from a nationwide survey of Japan.
Methods Between 2000 and 2003, a total of 2,550 patients who had undergone resection ($n = 1,235$) or RFA ($n = 1,315$) for single small HCC (≤2 cm) were registered to the database of the Liver Cancer Study Group of Japan (LCSGJ).
Results After a median follow-up period of 37 months, disease-free survival after resection was significantly better than after RFA (1-year, 91 vs. 87%; 2-year, 46 vs. 25%; $P = 0.001$), but overall survival after resection and RFA were similar (98 vs. 99%; 94 vs. 95%, $P = 0.28$). In the patients of Child–Pugh class A, disease-free survival was significantly better after resection ($n = 1,056$) than after RFA ($n = 965$) ($P = 0.001$), while overall survival was not significantly different ($P = 0.16$). In the patients of Child–Pugh class B, both disease-free and overall survival were almost similar ($P = 0.63$ and $P = 0.66$) after resection ($n = 136$) and RFA ($n = 303$).
Conclusions For single small HCC (≤2 cm), surgical resection provides better disease-free survival than does RFA. Longer follow-up is needed to regard this indication as conclusive.

For the Liver Cancer Study Group of Japan.

T. Takayama (✉)
Department of Digestive Surgery,
Nihon University School of Medicine,
30-1 Oyaguchikami-machi, Itabashi-ku,
Tokyo 173-8610, Japan
e-mail: tadtak@med.nihon-u.ac.jp

M. Makuuchi
Department of Hepato-Biliary-Pancreatic Surgery,
Japanese Red Cross Medical Center, Tokyo, Japan

K. Hasegawa
Department of Surgery, Faculty of Medicine,
University of Tokyo, Tokyo, Japan

Introduction

Recent progress in imaging modalities has facilitated recognition of small hepatocellular carcinoma (HCC), which seems to be curable by surgery or ablation, in high-risk patients who undergo regular medical check-ups for chronic viral hepatitis or cirrhosis [1]. Based on the accumulating information on small HCC, Japanese researchers proposed to define the pathological concept of early HCC (carcinoma in situ) [2], which was proved to be the earliest clinical entity, with a high cure rate (stage 0 HCC) [1]. To clarify survival in patients with single HCC smaller than 2 cm, we compared long-term outcomes after surgical resection and radiofrequency ablation (RFA) based on data obtained in the latest Japanese survey [3].

Methods

The patients with primary liver cancer in about 800 institutions have been registered every 2 years and followed prospectively in a nationwide survey conducted by the Liver Cancer Study Group of Japan (LCSGJ). Between 2000 and 2003, a total of 2,550 patients who had undergone resection ($n = 1,235$) or RFA ($n = 1,315$) for single HCC smaller than 2 cm were registered to the database of the LCSGJ [3].

Relevant clinical data were collected and analyzed. Regarding liver function, the resection group had significantly higher proportions of Child–Pugh class A (88 vs. 75%, $P = 0.001$) and better indocyanine clearance rate [15% (10–22%) vs. 23% (15–34%), $P = 0.001$] than did the RFA group. Regarding tumor-related factors, maximum tumor diameter was larger in the resection group than in the RFA group [18 (15–20) mm vs. 16 (14–20) mm, $P = 0.001$]. The level of alpha-fetoprotein was not significantly different between the two groups [16 (15–83) ng/ml vs. 18 (15–59) ng/ml, $P = 0.44$]. Overall and recurrence-free survival curves were made by the Kaplan–Meier method and compared by the log-rank test. The therapeutic impact of surgical resection and RFA was estimated using a Cox proportional-hazards model, including the variables associated with HCC.

Results

After a median follow-up period of 37 months, disease-free survival after resection was significantly better than that after RFA (1-year, 91 vs. 84%; 2-year, 70 vs. 58%; $P = 0.001$) (Fig. 1), but overall survival after resection and RFA were similar (98 vs. 99%; 94% vs. 95%, $P = 0.28$). Using multivariate analyses, we found three independent prognostic factors for recurrence of HCC: alpha-fetoprotein, therapy, and Child–Pugh class. The relative risk for recurrence in resection was 0.71 [95% confidence interval (CI) 0.56–0.90; $P = 0.004$], as compared with ablation. In the patients of Child–Pugh class A, disease-free survival was significantly better after resection ($n = 1{,}045$) than after RFA ($n = 946$) ($P = 0.001$), while overall survival was not significantly different ($P = 0.16$). In the patients of Child–Pugh class B, both disease-free and overall survivals were almost similar ($P = 0.28$ and $P = 0.66$) after resection ($n = 132$) and after RFA ($n = 301$).

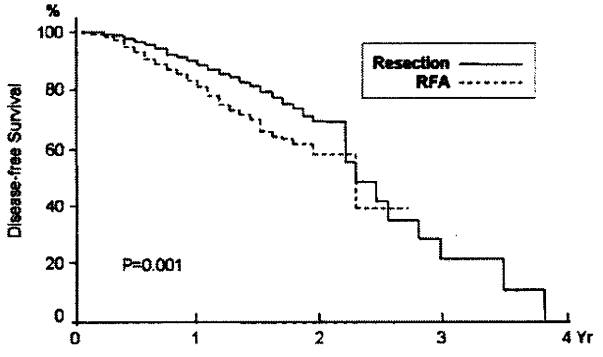

Fig. 1 Disease-free survival in single HCC smaller than 2 cm. The resection group ($n = 1.235$) had significantly better disease-free survival than the RFA group ($n = 1{,}315$) ($P = 0.001$)

Discussion

For single HCC smaller than 2 cm, hepatic resection provides better disease-free survival than RFA, although overall survival at 1 and 2 years were similar for both treatments [3]. A larger Japanese study demonstrated a similar outcome in patients with no more than 3 tumors ($\leq$3 cm) [4]. Whether the improvement in recurrence-free survival seen with resection will translate into better overall survival more that 2 years out following therapy remains unanswered at present.

Current imaging modalities have high sensitivity and positive predictive value for diagnosing overt HCC, but they are less sensitive for detecting early HCC, missing tumors smaller than 2 cm or that are well differentiated [5]. Computed tomography (CT) and magnetic resonance (MR) imaging perform poorly for detection and characterization of precursor lesions, but the use of intravenous contrast material with multiphasic imaging can enhance their ability to characterize such early focal lesions accurately [6, 7]. The chance of diagnosing and treating small HCC will increase in due time.

From the treatment perspective, data from the East and West indicates that single small HCC has a high chance for cure by resection [3], ablation [8] or transplantation [9]. However, interpretation of these outstanding outcomes should be cautious, as the results are probably affected by potential sources of lead-time bias and length bias. Whether resection or RFA is the better treatment for small HCC has been debated. A recent randomized trial concluded that the therapeutic impact in both options would be similar [10]. However, the trial had some drawbacks in terms of study design, small sample size, and high conversion rates from RFA to resection. Whether increased recognition of early HCC in clinical practice will contribute to improved patient survival will require further study.

References

1. Takayama T, Makuuchi M, Hirohashi S, et al. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology. 1998;28:1241–6.
2. Kojiro M, Roskams T. Early hepatocellular carcinoma and dysplastic nodules. Semin Liver Dis. 2005;25:133–47.
3. Takayama T, Makuuchi M, Kojiro M, et al. Early hepatocellular carcinoma: pathology, imaging, and therapy. Ann Surg Oncol. 2008;15:972–8.
4. Hasegawa K, Makuuchi M, Takayama T, et al. Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: a preliminary report of the Japanese nationwide survey. J Hepatol. 2008;49:589–94.
5. Matsui O, Kadoya M, Kameyama T, et al. Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. Radiology. 1991;178:493–7.

6. Burns PN, Wilson SR. Focal liver masses: enhancement patterns on contrast-enhanced images, concordance of US scans with CT scans and MR Imaging. Radiology. 2006;242:162–74.
7. Holland AE, Hecht EM, Hahn WY, et al. Importance of small (≤20-mm) enhancing lesions seen only during the hepatic arterial phase at MR imaging of the cirrhotic liver: evaluation and comparison with whole explanted liver. Radiology. 2005;237: 938–44.
8. Livraghi T, Meloni F, Morabito A, et al. Multimodal image-guided tailored treatment of early and intermediate hepatocellular carcinoma: long-term survival in the experience of a single radiologic referral center. Liver Transpl. 2004;10:S98–106.
9. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg. 2004;240:451–61.
10. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for hepatocellular carcinoma. Ann Surg. 2006;243:321–8.

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Current Approaches to the Treatment of Early Hepatocellular Carcinoma

SHENG-LONG YE,[a] TADATOSHI TAKAYAMA,[b] JEFF GESCHWIND,[c] JORGE A. MARRERO,[d] JEAN-PIERRE BRONOWICKI[e]

[a]Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China; [b]Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan; [c]Vascular and Interventional Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [d]Multidisciplinary Liver Tumor Program, University of Michigan, Ann Arbor, Michigan, USA; [e]Department of Gastroenterology and Hepatology, INSERM U954, University Hospital of Nancy, University Henri Poincaré, Vandœuvre-lès-Nancy, France

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ABSTRACT

For patients with early-stage hepatocellular carcinoma (HCC), potentially curative treatment options exist, including liver transplantation, surgical resection, and ablation therapy. These treatments are associated with survival benefits, and outcomes are optimized by identification of appropriate patients. However, further studies are needed to definitively confirm optimal treatment approaches for all patients.

Treatment patterns vary in different parts of the world as a result of geographic differences in the incidence and presentation of the disease. In particular, because of successful screening programs, a high proportion of tumors that are identified in Japan are amenable to curative treatments, which are appropriate in a smaller proportion of patients in the west, although screening is now widely carried out in industrialized countries. Differences in the applicability of transplantation are also evident between the west and Asia.

Although existing treatments for early-stage HCC are supported by considerable evidence, there remain significant data gaps. For example, further data, ideally from randomized controlled trials, are needed regarding: the use of neoadjuvant and adjuvant therapy to decrease the rate of recurrence after resection or ablation, further investigation of the role of chemoprevention following resection, and prospective analysis of outcomes of living donor compared with deceased donor liver transplantation. *The Oncologist* 2010;15(suppl 4):34–41

Correspondence: Sheng-Long Ye, M.D., Ph.D., Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China. Telephone: 86-21-6443-1055; Fax: 86-21-6443-1055; e-mail: slye@shmu.edu.cn Received January 21, 2010; accepted for publication July 20, 2010. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2010-S4-34

INTRODUCTION

Hepatocellular carcinoma (HCC) is an increasingly prevalent clinical problem worldwide and is the third most common cause of cancer-related death [1, 2]. The presence of cirrhosis is a key risk factor [3]. HCC is a complex disease involving many factors, and HCC staging systems can be very complicated [4]. The widely used, comprehensive Barcelona Clinic Liver Cancer staging system takes into account variables related to tumor stage, liver function, physical status, and cancer-related symptoms to generate a treatment algorithm [5].

Treatment is most effective in the early stages of disease, but diagnosing early-stage HCC is difficult because the diagnosis of cirrhosis is often not made before the emergence of HCC. Patients at high risk for developing HCC (e.g., those with cirrhosis, hepatitis B virus, or hepatitis C virus) should be entered into surveillance programs using ultrasound and serum α-fetoprotein (AFP) [3, 6, 7]. Based mainly on observational data on tumor-volume doubling time, a screening interval of 6 months is commonly used by physicians in the West, in contrast to the Far East, where a 3-month screening interval is generally implemented [8]. In a recent meta-analysis, a significantly higher sensitivity for early HCC was observed with a 6-month interval than with annual surveillance [9]. Because of the high rates of false-positive and false-negative results in patients with chronic liver disease, the American Association for the Study of Liver Diseases (AASLD) does not recommend the use of AFP alone as a screening method, unless ultrasound is not available. Information from a recent meta-analysis demonstrated that AFP provided no additional benefit to ultrasound, further supporting this guidance [9]. In contrast, abdominal ultrasonography combined with measurements of tumor markers is recommended for HCC screening, and assessments of AFP, protein induced by vitamin K absence or antagonist-II, or AFP lectin fraction are routinely performed in Japan [10].

Individuals with abnormal screening results require further investigation (e.g., with computed tomography scanning, magnetic resonance imaging, or liver biopsy) to confirm a diagnosis of HCC. Although surveillance programs can lead to detection of HCC at early stages when the tumors are amenable to curative treatment, guidelines are not always followed and are not always reproducible from large hospitals to nontertiary hospitals. Further studies are warranted to determine the optimal surveillance methods, which may also involve evaluation of novel biomarkers in the future.

Treatments for early-stage HCC include hepatectomy, liver transplantation, and local ablation therapy (Fig. 1) [6, 10–13]. However, there are no large randomized controlled trials (RCTs) comparing these treatments directly, nor are there any studies comparing these treatments with best supportive care [6]. In an intent-to-treat analysis in cirrhotic patients with HCC, early findings suggested similar survival rates in a comparison of resection with transplantation [14]. However, patient dropouts from waiting lists significantly impacted the longer-term findings in the transplantation group, and the authors concluded that resection may provide a better outcome for properly selected candidates. Further research is needed to confirm the optimal strategy based on the currently available treatments, and careful selection of patients is important in all approaches. Applicability of these treatments varies according to geographic distribution, with 50%–70% of cases in Japan (where there is widespread surveillance and a broad application of treatments) being suitable for curative treatment, compared with 25%–40% of cases in Europe and the U.S., and <10% in Africa [15]. Data from a nationwide survey in Japan indicate that a single early HCC patient has a high chance of prolonged survival with resection, ablation, or transplantation [16]. The aim of this article is to review the therapeutic options and associated outcomes for the management of patients with early HCC.

OUTCOMES AND TOLERABILITY OF EARLY-STAGE HCC TREATMENTS

Resection

Patients with early-stage HCC are those most likely to benefit from curative interventions. In a study of patients diagnosed with HCC in 1988–1998 in the Surveillance, Epidemiology, and End Results database, 417 of the 4,008 patients were candidates for surgical resection. The study showed that surgery was associated with longer survival in patients with unifocal, nonmetastatic HCC tumors <5 cm. In patients receiving surgery, the 5-year overall survival (OS) rate was 33%, compared with 7% without surgery [17].

Surgical resection is recommended as treatment for early HCC in noncirrhotic patients, or in patients with cirrhosis who have a single lesion and well-preserved liver function, normal bilirubin, and no portal hypertension [6, 13]. However, there are data that suggest that portal hypertension may not necessarily be a contraindication for resection. Patients with the same model for end-stage liver disease score and extent of hepatectomy had similar outcomes, whether or not they had portal hypertension [18], whereas several other studies found that resection can be performed safely in selected patients even in the presence of portal hypertension [19, 20]. Patients with multiple tumors may also be suitable for resection, although tumor multiplicity is an independent risk factor for postoperative recur-

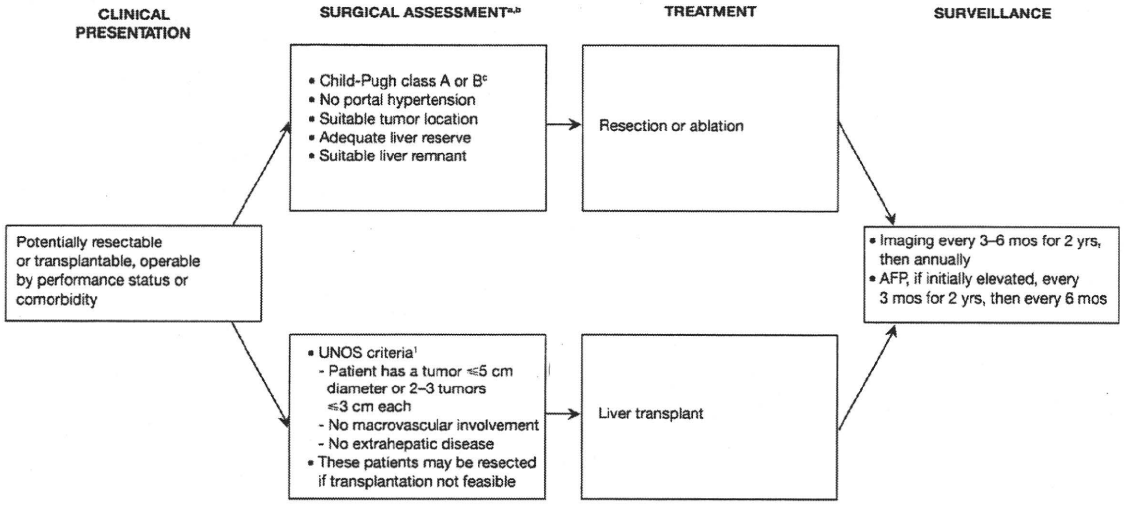

Figure 1. National Comprehensive Cancer Network guidelines for the treatment of potentially resectable disease.

[a]Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

[b]Patients with Child-Pugh class A liver function who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

[c]In highly selected Child-Pugh class B patients with limited resection.

[1]Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–700.

Abbreviations: AFP, α-fetoprotein; UNOS, United Network for Organ Sharing.

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rence, and the OS time is shorter in these patients [20]. However, among patients with both multiple tumors and better liver function (Child-Pugh class A), an absolute 5-year survival rate of 58% was achieved. Although there is no limitation on tumor size for resection, the risk for vascular invasion and dissemination increases with size. The amount of liver that can be resected depends on the degree of cirrhosis, the functional liver reserve, and the regenerative capacity of the liver [7]. Strict selection criteria are required in order to avoid treatment-related complications such as liver failure. Survival rates of ~70% at 5 years have been achieved in patients with a normal bilirubin concentration and no clinically significant portal hypertension [6]. In Japan, the indocyanine green retention rate, a marker of hepatic clearance, is commonly used to predict the safe limit of liver resection and posthepatectomy liver failure [21]. Preoperative portal vein embolization (PVE) has been used to evaluate the regenerative abilities of the liver, with lack of hypertrophy following PVE indicating an inability of the liver to regenerate, therefore contraindicating major liver resection [22]. Furthermore, preoperative PVE has been shown to improve outcomes following major hepatectomy [23]. In patients with very early HCC (carcinoma in situ) undergoing surgery, the best 5-year survival rate so far, 93%, was demonstrated [24]. Only 10%–30% of HCC cases are suitable for "curative" surgical resection at the time of diagnosis, and recurrent HCC has been reported in 50%–80% of patients 5 years after resection [7]. Key predictors of recurrence are the presence of microvascular invasion and/or further tumor sites in addition to the primary lesion. Preoperative transcatheter arterial chemoembolization (TACE) has been evaluated but has shown no benefit in this setting [7]. AASLD and Japanese guidelines conclude that there is currently no preoperative or postoperative adjuvant therapy that can be recommended for improving prognosis after hepatic resection [6, 10]. Further investigation is required for neoadjuvant and adjuvant therapies that may decrease the incidence of recurrence following resection.

Transplantation

Liver transplantation as a treatment for early-stage HCC is well established in the U.S. and Europe and is associated

with 5-year survival rates of ~70% [6], comparable with those of noncancer liver recipients. In most centers, candidates for transplantation are deemed not resectable. In some parts of the world, transplantation is not available or has very limited applicability [6]. The benefits of liver transplantation over resection include removal of the tumor and the underlying diseased liver and also improvement in portal hypertension. Because of the limited supply of donor organs, identification of the patients most likely to receive maximum benefit from a transplant is of utmost importance. For over a decade, the Milan criteria for HCC (one lesion ≤5 cm or two to three lesions ≤3 cm) have been widely used for the selection of candidates for liver transplantation. However, there is an ongoing debate on whether expanded criteria may be adopted, to enable patients with slightly more advanced HCC to also benefit from liver transplantation [25]. A 5-year survival rate of ~50% was described in patients selected with such expanded criteria, but there are currently no clear data to define the new limits [6]. In addition, expanding the criteria may cause harm to other patients without cancer who need a transplant, as a result of fewer donors being available [26]. Because the waiting time for an organ to become available may exceed 12 months in some western countries [27], the dropout rate is high (up to 50%). Most centers administer adjuvant treatments to prevent tumor progression while patients are on the waiting list, but these are often chosen based on observational studies, because robust data from RCTs are not available. Such bridging therapy before transplantation may include locoregional therapy such as chemoembolization, which has been investigated as a means of downstaging tumors to facilitate liver transplantation [25]. Information from a liver transplant waiting list in the U.S. showed that HCC patients who received pretransplant ablation treatments had a higher adjusted 3-year post-transplant survival rate than HCC transplant patients who did not (79% versus 75%; $p = .03$) [28]. However, in another retrospective cohort study in the U.S., using data from a liver transplant waiting list, the authors concluded that the effects of downstaging with neoadjuvant treatment were difficult to evaluate [29]. It has also been suggested that resection can be used as a bridging therapy for patients who have already been enlisted for liver transplant [30]. There is no definitive evidence confirming that the use of bridging therapies confers an advantage post-transplantation in terms of survival and recurrence rates, and no specific recommendations in relation to bridging strategies (for either TACE or local ablation therapy) are currently made in the guidelines [7, 13].

An alternative strategy to increase the pool of available donor livers is the use of live donor transplantation, which originated in Asia as a result of the legal and societal constraints on cadaveric liver transplantation [27, 31]. The results appear to be comparable with those from cadaveric donation [7, 32]; however, this is a complex intervention and may not have wide applicability.

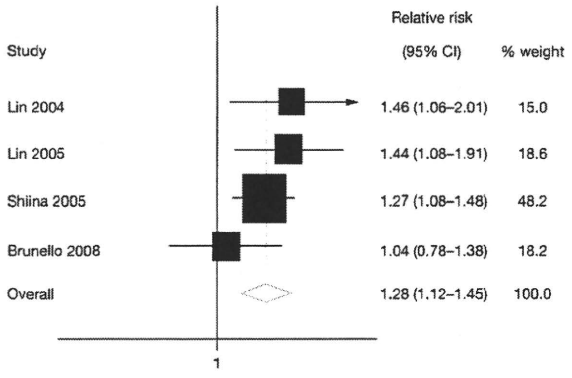

Figure 2. Radiofrequency ablation versus percutaneous ethanol injection: results of the meta-analysis on overall survival at 3 years. All based on random-effects meta-analysis.

Abbreviation: CI, confidence interval.

From Bouza C, López-Cuadrado T, Alcázar R et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol 2009;9:31, with permission. Originally published by BioMed Central.

Ablation

Local ablation therapy, with either radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), is commonly used to treat small HCCs confined to the liver that may be unresectable because of the poor general condition or compromised liver function of the patient. In an RCT comparing RFA with PEI for early HCC, the 1-year complete response rate was better with RFA than with PEI, although no clear survival advantage was observed in cirrhotic patients [33]. However, other RCTs [34–36] and a recent meta-analysis [37] have shown evidence of the superiority of RFA over PEI, in terms of longer survival and better local control of disease, in patients with relatively preserved liver function and early-stage nonsurgical HCC (Fig. 2). At 3 years, the pooled analysis showed an OS rate of 73% in the RFA group, compared with 58% in the PEI group ($p < .001$) [37]. However, RFA was associated with a statistically significant higher rate of adverse events ($p < .001$), with 19% of patients (95% confidence interval [CI], 15%–23%) experiencing complications, compared with 10.5% of those treated with PEI (95% CI, 7%–13.5%) [37]. The most frequent complication observed in that study was severe pain, which was more common with RFA than with PEI [37]. For studies that reported major complications, the

incidence in RFA-treated patients was 4.1% (95% CI, 1.8%–6.4%), including hemothorax requiring thoracostomy drainage, gastric bleeding, hemoperitoneum, transitory icterus, liver infarction, cutaneous burn, and tumoral cell seeding, and in PEI-treated patients it was 2.7% (95% CI, 0.4%–5.1%), including liver abscess, hemoperitoneum, tumoral cell seeding, and one procedure-related death; however, this difference was not statistically significant. This safety profile should be taken into consideration as part of the overall risk–benefit profile in each individual case. Further support for the benefit of RFA was provided by a different meta-analysis, which was more selective in the studies that it included and showed a higher 3-year OS rate with RFA than with PEI (odds ratio, 0.47; 95% CI, 0.340–0.670; $p < .001$) in patients with small HCCs [38].

Local ablation therapy has been compared with resection in a number of retrospective studies and clinical trials. Long-term outcomes in 87 patients with single-nodule HCCs treated with either surgical resection or RFA were similar [39]. Similarly, 5-year survival rates were comparable in a study of 224 patients with Child-Pugh class A cirrhosis treated with either resection (70.4%) or RFA (76.8%) ($p = .561$) [40]. A study of 186 patients with small (<5 cm) HCCs found that the choice of treatment should be based on local factors, such as the availability of resources and expertise [41]. In contrast to these findings, a study of 149 patients with HCCs ≤4 cm comparing resection with percutaneous ablation found that resection provided better local control and better long-term survival (median survival time, 122 months after hepatectomy compared with 66 months after ablation; $p = .0123$) [42]. A nationwide survey in Japan generated data on survival following resection or RFA [16]. In 2000–2003, 1,235 patients with a single early HCC (<2 cm) underwent resection and 1,315 patients received RFA. Although, with a median follow-up of 37 months, the disease-free survival rate was significantly better after resection than after RFA (1 year, 91% versus 84%; 2 years, 70% versus 58%; $p = .001$), there was no significant difference in the OS rate between the two groups (98% versus 99%; 94% versus 95%; $p = .28$). However, it is currently unknown whether the better disease-free survival seen with resection will translate into longer survival over a longer time period following therapy. Local ablation therapy was compared with resection in two RCTs in patients with small HCCs, with comparable survival results [43, 44]. Based on a trial of 180 patients, Chen et al. [43] concluded that RFA was as effective as surgical resection in the treatment of solitary and small HCCs, with the advantage of being less invasive. In a smaller study of 76 patients, Huang et al. [44] reported that PEI appeared to be as safe and effective as resection. Recent studies have shown that, in some centers, RFA is regarded as the first-line treatment for small, operable HCCs (≤2 cm), with 68.5% of patients surviving at 5 years [45]. Furthermore, in a simulated randomized trial comparing hepatic resection with RFA for very early HCCs (<2 cm), the OS times were similar for resection and RFA followed by resection for cases of initial local failure, suggesting that RFA could be considered as a primary treatment for very early HCC [46]. Given these equivocal results, larger RCTs are needed before there is any change in the recommended treatment of patients with good surgical risk and before ablation therapy is confirmed as an alternative to surgery for potentially resectable HCC.

TACE

Embolization procedures are used in patients with inoperable or unresectable disease. However, the place of TACE for the treatment of early HCC is not clear, and official guidelines do not currently recommend it. Caution should be exercised regarding the use of TACE for early HCC, and it should be considered only when curative treatment (e.g., transplantation, resection, or RFA) is contraindicated.

Differences in the Treatment of Early HCC and Outcomes Between Populations

As described above, well-defined treatment options for early HCC exist; however, there are inevitable differences in the treatment received, and hence the outcome achieved, in different populations worldwide. There are geographic variations in the incidence and etiology of HCC, and a difference in tumor size at presentation. Japanese patients have been shown to present with smaller tumors than patients in the U.S. and Europe, likely as a result of the more widespread screening carried out in Japan [47]. This, together with differences in hepatitis B or C virus status, has resulted in more limited surgical resections being necessary in Japan, compared with more extended resections in the U.S.

In a more recent comparison, analysis of the medical records of 353 patients subject to surgical resection for HCC at two referral centers in China and Japan highlighted differences between populations [48]. As well as demographic differences in age of incidence, serum examination, and history of viral infection, differences in outcome were observed. Patients in Japan were diagnosed earlier, were subject to more standard treatment, and had better prognoses than those in China. However, these results were based only on HCC at each center and not on HCC detected in a surveillance program. In addition, the demographic disparities in survival in patients with localized HCC in the U.S. were investigated in a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results

population-based cancer registry [49]. That study found substantial and significant disparities by race/ethnicity in the 3-year survival rate, therapy administered, and stage-specific survival rate for individual therapies. These differences were not explained by age, date of diagnosis, or geography, but may have resulted from differences in treatments received by different demographic groups or variations in treatment response, which may be influenced by compliance or differences in disease biology. However, these patients were not identified through a surveillance program, but were patients diagnosed with HCC, which may be associated with lead-time bias. In a prospective cohort study in Europe, hepatic resection performed under strict intraoperative ultrasonographic guidance had low mortality and acceptable morbidity, even in patients with intermediate and advanced HCC [50].

Improving Treatment Options

There remains a considerable number of unanswered questions in the recommendations for treatment of early-stage HCC, many of which require a definitive answer to be provided through robust data from RCTs. Key areas for consideration include: the use of neoadjuvant or adjuvant therapy to decrease or delay recurrence after resection or ablation, chemoprevention after resection or ablation, and the use of molecular profiling of HCC to provide additional tools to define those patients most at risk for recurrence following resection. Indeed, a number of clinical trials are ongoing in these areas. Three ongoing phase IV trials are investigating radiotherapy (ClinicalTrials.gov identifier, NCT00557024), TACE (ClinicalTrials.gov identifier, NCT00556803), and lamivudine or entecavir (ClinicalTrials.gov identifier, NCT00555334) as adjuvant therapies after RFA, and are due to complete in 2010. Furthermore, sorafenib (Nexavar®; Onyx Pharmaceuticals, Inc., Emeryville, CA; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ; Bayer Schering Pharma AG, Berlin, Germany) is being investigated as adjuvant treatment in the prevention of recurrence of HCC following either surgical resection or local ablation, in the large phase III randomized, double-blind, placebo-controlled Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial (ClinicalTrials.gov identifier, NCT00692770), due to complete in 2011. With regard to liver transplantation, bridging therapy before transplantation, including the questions of which treatment to give and when [7], and prospective analysis of outcomes of living donor compared with deceased donor transplantation are areas that warrant further study.

Important considerations in future trials include analysis of the cost-effectiveness of the treatments under investigation and also the use of genomics- and proteomics-based technologies [51], in order to add to the body of information on the biologic behavior and natural history of HCC, which should help guide the diagnosis and management of HCC.

Conclusions

Early diagnosis remains a key goal in order to improve the prognosis of HCC patients. Surgical resection and liver transplantation are usually considered as first-line options because they offer the possibility of prolonged survival in patients with early disease and have excellent outcomes in well-selected patients. Local ablation therapy, using RFA or PEI, also has a role to play. Further improvements in the outcome of patients with early HCC may be achieved once outstanding questions have been answered by prospective RCTs.

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Author Contributions

Conception/Design: Sheng-Long Ye, Tadatoshi Takayama, Jeff Geschwind, Jorge A. Marrero, Jean-Pierre Bronowicki
Data analysis and interpretation: Sheng-Long Ye, Tadatoshi Takayama, Jeff Geschwind, Jorge A. Marrero, Jean-Pierre Bronowicki
Manuscript writing: Sheng-Long Ye, Tadatoshi Takayama, Jeff Geschwind, Jorge A. Marrero, Jean-Pierre Bronowicki
Final approval of manuscript: Sheng-Long Ye, Tadatoshi Takayama, Jeff Geschwind, Jorge A. Marrero, Jean-Pierre Bronowicki

References

1 Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.

2 Venook et al. The incidence and epidemiology of hepatocellular carcinoma: A global and regional perspective. ***The Oncologist*** 2010;15(suppl 4):5–13.

3 Sanyal et al. The etiology of hepatocellular carcinoma and consequences for treatment. ***The Oncologist*** 2010;15(suppl 4):14–22.

4 Marrero JA, Kudo M, Bronowicki JP. The challenge of prognosis and staging for hepatocellular carcinoma. ***The Oncologist*** 2010;15(suppl 4): 23–33.

5 Lencioni R, Chen XP, Dagher L et al. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: How can outcomes be improved? ***The Oncologist*** 2010;15(suppl 4):42–52.

6 Bruix J, Sherman M; Practice Guidelines Committee, American Associa-

tion for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.

7 Lau WY, Lai ECH. Hepatocellular carcinoma: Current management and recent advances. Hepatobiliary Pancreat Dis Int 2008;7:237–257.

8 Colombo M. Screening and diagnosis of hepatocellular carcinoma. Liver Int 2009;29(suppl 1):143–147.

9 Singal A, Volk ML, Waljee A et al. Meta-analysis: Surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37–47.

10 Makuuchi M, Kokudo N, Arii S et al. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. Hepatol Res 2008;38:37–51.

11 Llovet JM, Di Bisceglie AM, Bruix J et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698–711.

12 Ryder SD; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003; 52(suppl 3):iii1–iii8.

13 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers V. 1.2010. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp, accessed January 7, 2010.

14 Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. Hepatology 1999;30:1434–1440.

15 Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005;40:225–235.

16 Takayama T, Makuuchi M, Kojiro M et al. Early hepatocellular carcinoma: Pathology, imaging, and therapy. Ann Surg Oncol 2008;15:972–978.

17 Liu JH, Chen PW, Asch SM et al. Surgery for hepatocellular carcinoma: Does it improve survival? Ann Surg Oncol 2004;11:298–303.

18 Cucchetti A, Ercolani G, Vivarelli M et al. Is portal hypertension a contraindication to hepatic resection? Ann Surg 2009;250:922–928.

19 Capussotti L, Ferrero A, Viganò L et al. Portal hypertension: Contraindication to liver surgery? World J Surg 2006;30:992–999.

20 Ishizawa T, Hasegawa K, Aoki T et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 2008;134:1908–1916.

21 Nakayama H, Takayama T, Hemmi A. Postoperative complications of hepatectomy for hepatocellular carcinoma in relation to liver fibrosis. Hepatogastroenterology 2005;52:587–590.

22 Farges O, Belghiti J, Kianmanesh R et al. Portal vein embolization before right hepatectomy: Prospective clinical trial. Ann Surg 2003;237:208–217.

23 Palavecino M, Chun YS, Madoff DC et al. Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: Perioperative outcome and survival. Surgery 2009;145:399–405.

24 Takayama T, Makuuchi M, Hirohashi S et al. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology 1998;28: 1241–1246.

25 Yao FY. Liver transplantation for hepatocellular carcinoma: Beyond the Milan criteria. Am J Transplant 2008;8:1982–1989.

26 Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant 2008;8:839–846.

27 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362:1907–1917.

28 Freeman RB Jr, Steffick DE, Guidinger MK et al. Liver and intestine transplantation in the United States, 1997–2006. Am J Transplant 2008;8:958–976.

29 Pelletier SJ, Fu S, Thyagarajan V et al. An intention-to-treat analysis of liver transplantation for hepatocellular carcinoma using organ procurement transplant network data. Liver Transpl 2009;15:859–868.

30 Belghiti J. Resection and liver transplantation for HCC. J Gastroenterol 2009;44(suppl 19):132–135.

31 Ng KK, Lo CM. Liver transplantation in Asia: Past, present and future. Ann Acad Med Singapore 2009;38:322–331.

32 Liu CL, Fan ST, Lo CM et al. Operative outcomes of adult-to-adult right lobe live donor liver transplantation: A comparative study with cadaveric whole-graft liver transplantation in a single center. Ann Surg 2006;243: 404–410.

33 Brunello F, Veltri A, Carucci P et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. Scand J Gastroenterol 2008;43:727–735.

34 Lencioni RA, Allgaier HP, Cioni D et al. Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228:235–240.

35 Lin SM, Lin CJ, Lin CC et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005;54:1151–1156.

36 Shiina S, Teratani T, Obi S et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129:122–130.

37 Bouza C, López-Cuadrado T, Alcázar R et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol 2009;9:31.

38 Cho YK, Kim JK, Kim MY et al. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology 2009;49:453–459.

39 Ogihara M, Wong LL, Machi J. Radiofrequency ablation versus surgical resection for single nodule hepatocellular carcinoma: Long-term outcomes. HPB (Oxford) 2005;7:214–221.

40 Takahashi S, Kudo M, Chung H et al. Outcomes of nontransplant potentially curative therapy for early-stage hepatocellular carcinoma in Child-Pugh stage A cirrhosis is comparable with liver transplantation. Dig Dis 2007;25:303–309.

41 Farinati F, Gianni S, Marin G et al. Does the choice of treatment influence survival of patients with small hepatocellular carcinoma in compensated cirrhosis? Eur J Gastroenterol Hepatol 2001;13:1217–1224.

42 Wakai T, Shirai Y, Suda T et al. Long-term outcomes of hepatectomy vs percutaneous ablation for treatment of hepatocellular carcinoma ≤4 cm. World J Gastroenterol 2006;12:546–552.

43 Chen MS, Li JQ, Zheng Y et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243:321–328.

44 Huang GT, Lee PH, Tsang YM et al. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: A prospective study. Ann Surg 2005;242:36–42.

45 Livraghi T, Meloni F, Di Stasi M et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008;47:82–89.

46 Cho YK, Kim JK, Kim WT et al. Hepatic resection versus radiofrequency

ablation for very early stage hepatocellular carcinoma: A Markov model analysis. Hepatology 2010;51:1284–1290.

47 Pawlik TM, Esnaola NF, Vauthey JN. Surgical treatment of hepatocellular carcinoma: Similar long-term results despite geographic variations. Liver Transpl 2004;10(suppl 1):S74–S80.

48 Yuan P, Tang W, Kokudo N et al. Demographic and clinical characteristics of resectable hepatocellular carcinoma in China and Japan. Hepatogastroenterology 2007;54:2343–2347.

49 Wong RJ, Corley DA. Survival differences by race/ethnicity and treatment for localized hepatocellular carcinoma within the United States. Dig Dis Sci 2009;54:2031–2039.

50 Torzilli G, Donadon M, Marconi M et al. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: Results of a prospective analysis. Arch Surg 2008;143:1082–1090.

51 Pei Y, Zhang T, Renault V et al. An overview of hepatocellular carcinoma study by omics-based methods. Acta Biochim Biophys Sin (Shanghai) 2009;41:1–15.