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

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

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

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

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

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

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

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

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

Subjects and Methods

Patient Characteristics

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

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

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

Tumor Characteristics

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

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

Technique

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

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

Statistical Analysis

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

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

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

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

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

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

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

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

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

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

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

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

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

Results

Patient Characteristics in the Whole Sample

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

Crude Survival of TACE Patients and Patients Undergoing Therapy Without Embolization

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

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

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

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

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

Discussion

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

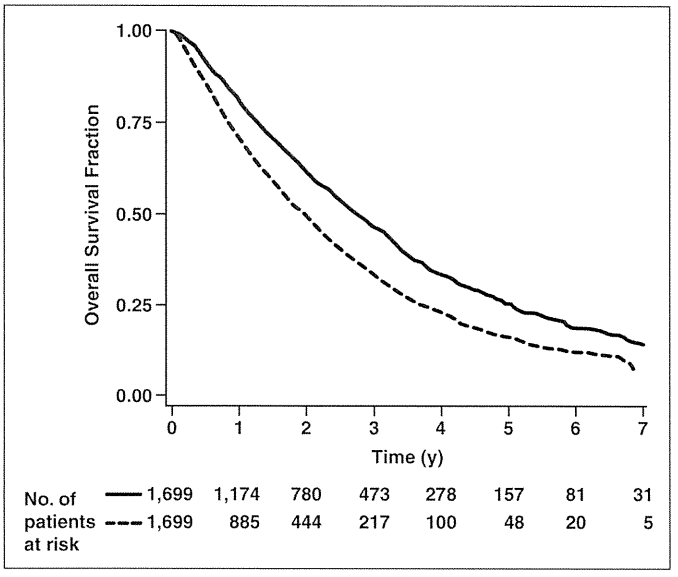

Fig. 1—Graph shows comparison of survival rates among patients with unresectable hepatocellular carcinoma treated with iodized oil transarterial chemoembolization (TACE) (*n* = 1,699 patients) (*solid line*) and those treated with iodized oil transarterial infusion therapy without embolization (*n* =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

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

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

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

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

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

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

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

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

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

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

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

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

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

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GUIDELINES

Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma

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Abstract
Introduction The Asian Pacific Association for the Study of the Liver (APASL) convened an international working party on the management of hepatocellular carcinoma (HCC) in December 2008 to develop consensus recommendations.
Methods The working party consisted of expert hepatologist, hepatobiliary surgeon, radiologist, and oncologist from Asian-Pacific region, who were requested to make drafts prior to the consensus meeting held at Bali, Indonesia on 4 December 2008. The quality of existing evidence and strength of recommendations were ranked from 1 (highest) to 5 (lowest) and from A (strongest) to D (weakest), respectively, according to the Oxford system of evidence-based approach for developing the consensus statements.

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Results Participants of the consensus meeting assessed the quality of cited studies and assigned grades to the recommendation statements. Finalized recommendations were presented at the fourth APASL single topic conference on viral-related HCC at Bali, Indonesia and approved by the participants of the conference.

Keywords Hepatocellular carcinoma · Consensus statements · Recommendations · Epidemiology · Diagnosis · Treatment algorithm

Abbreviations

AASLD	American Association for Study of Liver Diseases
AFP	α-Fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive fraction of AFP
APASL	Asian Pacific Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
CI	Confidence interval
CEUS	Contrast-enhanced US
CSF-1	Colony-stimulating factor 1
CTAP	CT during arterial portography
CTHA	CT hepatic arteriography
DCP	Des-γ-carboxyprothrombin
DN	Dysplastic nodule
EASL	European Association for the study of the liver
FNH	Focal nodular hyperplasia
Gd-EOB-DTPA	Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid
GPC3	Glypican-3
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGDN	High-grade dysplastic nodules
HH	Hereditary hemochromatosis
IFN	Interferon
LAM	Lamivudine
LGDN	Low-grade dysplastic nodules
LR+	Positive likelihood ratio
MDCT	Multidetector-row CT
MTT	Molecular targeted therapy
NASH	Nonalcoholic steatohepatitis
PDGFR	Platelet-derived growth factor receptors
PIVKA-II	Prothrombin induced by vitamin K absence-II
RCT	Randomized controlled trial
RD	Risk difference
SPIO	Superparamagnetic iron oxide
TACE	Transarterial chemoembolization
US	Ultrasonography
VEGFR	Vascular endothelial growth factor receptors

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of death from cancer. Approximately three-fourth of cases occur in Asian countries because of a high prevalence of chronic infection with HBV. HCC is undoubtedly a great health threat in Asian region.

The Asian Pacific Association for the Study of the Liver (APASL) convened an international working party on the management of HCC in December 2008 to develop consensus recommendations. The working party consisted of expert hepatologists, hepatobiliary surgeons, radiologists, and oncologists from Asian-Pacific region, who were requested to make drafts prior to the consensus meeting, held at Bali, Indonesia, on 4 December 2008. The consensus statements consisted of recommendations and scientific comments based on comprehensive review of the literature on each topic. The quality of existing evidence and strength of recommendations were ranked from 1 (highest) to 5 (lowest) and from A (strongest) to D (weakest), respectively, according to the Oxford system of evidence-based approach for developing the consensus statements [1]. Participants of the consensus meeting assessed the quality of cited studies and assigned grades to the recommendation statements. Finalized recommendations were presented at the fourth APASL single topic conference on viral-related HCC at Bali, Indonesia, and approved by the participants of the conference.

Epidemiology and risk factors

Recommendations
Patients with cirrhosis due to HBV or HCV are at the highest risk for HCC (2a).
The incidence of HCC was significantly higher in those who were HBeAg positive or have HBV DNA with high loads (>10^4 copies/mL) and older than 40 years (2a).
Coinfection with HBV and HCV may have synergistic effect on the development of HCC (2b).
Male sex, aging, and familial history are independent risk factors for HCC (2a).
Chronic and heavy alcohol intake, high body mass index (BMI > 25) and diabetes mellitus leading to liver disease increases the risk for HCC (2b).

Geographical distribution

The prevalence of HCC worldwide parallels that of viral hepatitis, and the majority of cases are associated with HBV and HCV. Chronic HBV infection is a leading cause of HCC in most African and Asian countries except Japan. HCV predominantly contributes to HCC in some southern European countries (e.g., Italy and Spain) and Japan.

HCC has large variation in incidence according to geographic locations [2]. High-incidence regions include sub-Saharan Africa, East Asia, and South-East Asia (i.e., China, Hong Kong, Taiwan, Korea, and Japan). The distribution of HCV-related HCC also differs among ethnic groups within the same country and among regions within the same country. In contrast, HBV-related HCC is evenly distributed, except in high aflatoxin exposure areas.

Hepatitis B infection

Chronic infection with HBV is the strongest risk factor for HCC in Asian countries. A landmark study by Beasley et al. [3] indicated that the relative risk of HCC in these HBsAg carriers was 223 times that of the normal population. Tsukuma et al. [4] also reported that the relative risk of HBsAg was 6.9 among 917 Japanese patients with cirrhosis or chronic hepatitis.

Some authors indicated that active viral replication of HBV increases the risk of HCC in subjects with chronic HBV infection [5–9]. Yang et al. [6] reported that the incidence of HCC was significantly higher in those who were HBsAg and HBeAg positive than in those who were HBsAg positive only. Recently, this was confirmed by showing a correlation between baseline HBV DNA levels in asymptomatic adult HBsAg carriers and the risk of HCC [10–13].

Studies have now shown that HBV genotype correlates with the risk for HCC and that genotype C carries two- to threefold higher risk than genotype B in developing HCC [10, 14–19]. Other HBV variants, such as precore, basal core, and pre-S deletion mutants, may also influence the development of HCC in carriers [15, 19–25].

The impact of genetic background of patients with chronic viral hepatitis, especially those with a family history of HCC, may need further investigation.

Hepatitis C infection

Chronic HCV infection is also strongly associated with HCC [4, 26–29]. The increased incidence of HCC in the developed world is likely to be a direct result of the HCV epidemic occurring some 20–30 years ago in the target population.

There is no clear evidence of the association between HCV genotype and HCC [30–34]. The significance of HCV viral titers in determining HCC risk needs further investigation.

HBV and HCV coinfection, HIV coinfection with HBV or HCV

A few studies have supported the synergistic effect of HBV–HCV coinfection in the development of HCC [35–40], although the mechanism of this synergy is still unknown.

HIV coinfection in HBV or HCV patients has increased in Asia. The liver disease progresses faster in patients with HIV coinfection [41, 42].

Cirrhosis

Cirrhosis is present in the majority of patients with HCC, especially in those with HCV infection [28]. It is unclear whether cirrhosis itself is biologically important in the hepatocarcinogenesis, or whether clonal expansion/tumor development and fibrogenesis take place concurrently.

Male sex

Males are more likely to develop HCC than females. Male-to-female ratios are around 3 in high-risk countries [43], and they tend to be higher in patients with HBV than in those with HCV [44–46].

Age

Age-specific incidence rates are strongly affected by the etiology of the background liver disease. Old age is an independent risk factor for HCC, especially in areas where HCV infection is endemic [2, 47]. On the other hand, the incidence rates increase after 20 years of age in countries where HBV-related carcinogenesis is dominant.

Tobacco and alcohol intake

It is still controversial whether cigarette smoking is a risk factor for HCC [37, 48, 49]. Many authors now support the supposition that heavy alcohol intake is strongly associated with HCC [37, 49–51]. Alcohol also increases the risk for HCC in chronic hepatitis B and C [52].

Aflatoxin

Aflatoxin exposure has been associated with HCC [53–57]. Aflatoxin is produced from fungi, which is a common contaminant in the food items such as corn, peanuts, and soy beans in areas such as Qidong, The People's Republic of China. Chen et al. [54] conducted a community-based

cohort study including 6,487 residents of the Penghu Islets in Taiwan and reported that patients with aflatoxin exposure had a high risk for HCC with an odds ratio of 5.5 as compared with those without aflatoxin exposure. It has also been shown that a synergistic effect exists between chronic HBV infection and aflatoxin exposure for hepatocarcinogenesis [53, 55, 56].

Metabolic factors

Recently, it has been shown that both obesity and diabetes are independent risk factors for HCC, depending on HBV and HCV infection status [58]. As both obesity and diabetes have rapidly increased in Asia, their contributions to HCC should be closely watched.

Family history

Family history of HCC is associated with a moderately increased risk of HCC [59–61]. In a cohort study, HBV carriers with a family history of HCC had a multivariate-adjusted rate ratio for HCC of 2.41 compared with HBV carriers without a family history of HCC. Risk of HCC increased as the number of affected relatives increased. For carriers with two or more affected relatives, the ratio increased to 5.55 [95% confidence interval (CI) 2.02–15.26] [61]. This factor needs to be incorporated into risk evaluation.

Hemochromatosis

Patients affected with hereditary hemochromatosis (HH), a genetic disease of iron overload, were found to lead to cirrhosis and eventually an increased risk of HCC [62–64].

Prevention

Prevention of HBV-related HCC

Recommendations
Universal hepatitis B vaccination should be implemented in the countries where HBV infection is endemic or hyperendemic (2a, A).
Interferon (IFN) therapy in adult with active hepatitis may be effective in reducing the incidence of HBV-related HCC (2b, B).
Maintained HBV suppression by oral antiviral agent(s) can reduce the risk of HCC (1b, A).

HBV vaccination (primary prevention of HCC)

About 350 million people are chronic carriers of HBV worldwide. The infection can cause acute and chronic liver diseases including cirrhosis and HCC globally. The efficacy of universal immunization has been shown in different countries to strikingly reduce the prevalence of HBV carrier in children. A nationwide vaccination program against HBV launched in Taiwan [65, 66] has drastically reduced the HBsAg carrier rate in the younger population [67]. More important, follow-up results from the Taiwan vaccination programs have shown a significant reduction in the incidence of HCC in children. The average annual incidence of HCC in children 6–14 years of age declined from 0.70/100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and further to 0.36/100,000 between 1990 and 1994 ($P < 0.01$) [68]. An 80–85% decrease of HCC in the Taiwanese adults 3–4 decades later is anticipated. The decrease of HCC after the implementation of universal vaccination against HBV not only represents a practical approach to primary prevention of a human cancer by vaccination for the first time in history but also firmly establishes HBV as the cause of HCC in human beings [69]. These data prove that preventing HBV infection leads to a reduction in HBV-related morbidity and mortality and justify advocacy for universal hepatitis B vaccination programs worldwide.

Interferon therapy (secondary prevention of HCC)

It is evident that IFN therapy reduces the risk of HCC in chronic hepatitis B with/without cirrhosis. In HBeAg-positive patients with chronic hepatitis B, several long-term follow-up studies following 4–6 months of conventional IFN therapy have shown that sustained seroclearance of HBeAg was associated with a significant increase in survival and decreased liver decompensation, especially in patients with preexisting cirrhosis [70–75]. Among these studies, there was one randomized controlled trial (RCT) that involved 101 Taiwanese men with chronic hepatitis B, 67 of whom received IFN therapy and 34 of whom received placebo [75]. During 1.1–11.5 years of follow-up after completion of therapy, the incidence of HCC in untreated patients was higher than that in IFN-treated patients (12 vs. 1.5%, $P = 0.043$). The cumulative incidence of HCC was also higher in untreated patients than in treated patients ($P = 0.013$). However, the beneficial effect of HCC prevention was not observed in another nonrandomized study comparing 208 Chinese patients with chronic hepatitis B who were treated with IFN against 203 untreated patients [76]. These contradictory results were due to nonrandomization, patients of younger age (median 27 vs. 32 years), patients with low or normal alanine aminotransferase (ALT) (median 46 vs. 163 U/L), and associated low response rates (22 vs. 34% at 24 months, 45 vs. 82% at 132 months) in the Hong Kong study [76] compared with the Taiwan study [71]. The beneficial effect of HCC reduction was also supported by another study of

165 HBeAg-positive patients who were treated with IFN-alfa, as reported by van Zonneveld et al. [74]. On multivariate time-dependent analysis, adjusting for baseline factors that included cirrhosis, responders were found to have a significantly lower risk of HCC than nonresponders ($P = 0.027$). Because the long-term benefit of IFN therapy occurs only in patients with HBeAg loss, the actual benefit is difficult to prove when the HBeAg loss rate in untreated patients is not high enough, especially if the sample size is not big [71, 74]. Addressing these problems, a recent study comparing 233 IFN-treated patients with 233 matched, untreated controlled patients (matched for age, sex, baseline ALT, HBV DNA, and follow-up period) by Lin et al. showed a long-term significant benefit in preventing HCC development (2.7 vs. 12.5%, $P = 0.011$) [77]. This study had the superiority of including more patients with appropriate disease characteristics (active hepatitis), well-matched parameters, and a longer follow-up.

A meta-analysis of 11 randomized studies comparing IFN-treated versus untreated patients with HBV-related cirrhosis showed that IFN seemingly decreased the rate of HCC [92]. The pooled estimate of the HCC preventive effect of treatment was significantly in favor of patients undergoing IFN therapy [risk difference −4.1, 95% CI −0.8 to −7, $P < 0.013$]. However, these trials showed significant inconsistency if assessment did not take ethnicity of patients into account (European vs. Oriental studies). Consistent results were only observed when assessing data pooled from European reports, which did not show a preventive effect of HCC with treatment. Meta-analysis of longitudinal studies with prolonged follow-up showed no differences in the rate of HCC development between treated patients (1.9%, 95% CI 0.8–3.0) and controls (3.16%, 95% CI 1.8–4.5) [78].

In HBeAg-negative patients, Papatheodoridis et al. [72] studied a cohort of 209 IFN treated and 195 untreated patients and showed that the rate of HCC development was significantly reduced in IFN responders than in IFN non-responders (1.8 vs. 10.5%, $P = 0.027$), or in untreated patients (7.7%, $P = 0.048$). Another study by Lampertico et al. [73] in 101 HBeAg-negative patients showed no difference in HCC development in responders and nonresponders. The low response rate or relatively small number of patients may be one of the reasons for failure to show significant long-term benefits of IFN therapy in HBeAg-negative patients.

Lamivudine (secondary prevention of HCC)

Lamivudine (LAM) produces marked viral suppression, reduction of hepatic necroinflammatory activity, and histologic improvement of liver fibrosis [79], as well as improved liver function even in patients with decompensation [80]. However, it is still undetermined whether LAM or other oral antiviral drugs can suppress HBV-related hepatocarcinogenesis. To date, only one RCT suggests that LAM treatment of chronic hepatitis B and advanced liver disease does reduce the incidence of HCC, but with marginal significance (hazard ratio 0.49, 95% CI 0.25–0.99, $P = 0.047$) [81]. A multicenter retrospective study of 2,795 patients (657 treated with LAM, 2,138 not treated with LAM) was reported from Japan [82]. Of these, a controlled study including 377 LAM-treated patients and 377 untreated patients were selected on the basis of the propensity score. The mean follow-up period was 2.7 years in LAM-treated group and 5.3 years in the control group. In the LAM group, HCC occurred in four patients with an annual incidence rate of 0.4% per patient per year, whereas in the control group HCC occurred in 50 patients (13.3%) at a rate of 2.5% per patient per year. The cumulative HCC incidence was significantly lower in LAM group ($P < 0.001$). These findings suggest that LAM effectively reduces the incidence of HCC in patients with chronic hepatitis B. Another study including 59 patients of HBeAg-positive or HBeAg-negative cirrhosis treated with long-term LAM (median 44 months, range 15–78 months) showed that the cumulative event-free (decompensation or HCC) survival rate is significantly higher ($P = 0.001$) in patients with maintained virologic suppression than in those who did not have a complete virologic response or suffered a breakthrough [83]. On the basis of these studies, LAM was effective in HCC prevention in patients with chronic hepatitis B. Since drug resistance after long-term LAM therapy is likely to reverse or halt clinical benefit, long-term effects of HCC prevention after longer therapy with other antiviral agents with fewer drug resistance rates need to be studied.

Prevention of HCV-related HCC

Recommendations
The control of transfusion-related, iatrogenic, and illicit drug use-related viral transmission is of paramount importance (2a, A).
Efficient screening for HCV infection would find patients who require treatment (2b, B).
Interferon therapy is indicated in acute hepatitis C to prevent chronicity (1b, A)
Sustained virologic response to an IFN-based therapy reduces the risk of HCV-related HCC in patients with compensated chronic hepatitis C (1a, A).

Prevention of viral transmission

It is well known that HCV infection may be transmitted, though not commonly, by mother to neonate or by sexual transmission. In Egypt, intravenous tartar emetic injection

to prevent schistosomiasis is reported to cause an endemic of HCV infection in the country [79]. In United States, the peak of HCV viral spread coincided with the peak of injecting drug abuse from 1960s to 1980s [80]. In Japan, the peak of viral spread in 1950s and 1960s accompanied the peak of paid donors' blood transfusion, which might be contaminated with HCV because of the prior amphetamine abuse and needle sharing [81]. In many countries, new acquisition of HCV infection is decreasing due to growing concern about blood-transmitted infections, especially HIV, and this trend should be further encouraged considering the absence of effective vaccination against either HCV or HIV.

Screening for HCV infection

Patients infected with HCV usually remain asymptomatic until they develop decompensation of cirrhosis or advanced HCC, when antiviral treatments are hardly effective. The Ministry of Health, Welfare, and Labor in Japan started a national screening program in 2002 for HCV (and HBV) infection among people older than 40 years, in view of the high prevalence of HCV infection in this age group. By the end of 2006, 9 million people had been screened, among whom 110,000 patients were detected to have HCV infection and 110,000 patients with HBV infection [82]. The cost-effectiveness of such programs depends on the prevalence of viral infection among the target population.

Treatment of acute hepatitis C

Although HCV is not as infectious as HBV or HIV, chronicity is established in 70–80% of patients who have acute HCV infection. After exposure to HCV, such as needlestick injury, serum HCV should be monitored. The incidence of acute hepatitis C is reported to be 1.8% after injury with an HCV-contaminated needle. IFN therapy is to be considered to prevent chronicity once acute HCV infection is confirmed. [83, 84]

Treatment of chronic hepatitis C

Nishiguchi et al. [85] showed in an RCT that IFN therapy reduced the incidence of HCC in HCV-positive patients with compensated cirrhosis. The preventive effect was stronger in patients who showed sustained virologic response than in patients who failed to attain the response [86]. Several nonrandomized cohort studies showed similar effects on the reduction of HCC development [87–89]. One nonrandomized study detected no significant difference in HCC occurrence, but the low response rate and relatively small sample size may have been responsible for these results [90]. Several meta-analyses on randomized and nonrandomized studies on IFN therapy for patients with compensated cirrhosis concluded that the incidence of HCC was significantly reduced with therapy [91, 92].

The effect of IFN therapy on HCC incidence in noncirrhotic patients has been evaluated in nonrandomized studies. Although some studies failed to detect significant risk reduction in treated patients, all studies agree that the risk is reduced in patients who show sustained virologic response or persistent normalization of serum ALT levels [88, 93–95]. Since the incidence of HCC among noncirrhotic patients is not high, a large-sized sample and/or a long-term observation would be required to detect the effect of antiviral therapy on HCC prevention. The fact that IFN therapy improves liver histology in sustained virologic responders may also contribute to prevention of HCC [96]. Although documentation is poor, a combination with ribavirin is likely to produce a stronger effect on HCC prevention among overall treated patients [97]. In most studies, a smaller risk reduction was found in transient responders, i.e., those who showed a temporary response during IFN administration, whereas no effects were detected in nonresponders. Since treatment has a possible effect on HCC prevention even in transient responders, long-term maintenance IFN administration may be beneficial to patients with refractory chronic hepatitis C. Several nonrandomized studies reported reduction in HCC incidence with such treatments [98, 99]. However, a large-scale RCT performed in the United States revealed no reduction in HCC even with 3.5 years of peginterferon maintenance therapy [100]. The reasons for this difference are yet to be elucidated.

Viral-unrelated prevention of HCC

Recommendations
Prevention of HCC by elimination of aflatoxin contamination is advised (2a, B).
Prevention of HCC in patients with nonalcoholic steatohepatitis (NASH) is primarily through lifestyle modification with diet and exercise (2, B).

Aflatoxin

Aflatoxins are one of the most potent hepatocarcinogens and are easily acquired by human through exposure to mycotoxins. The incidence of HCC may be reduced by eliminating aflatoxin through proper food storage [78, 101]. The steady decrease in HCC incidence in affluent regions such as Singapore and Shanghai may be, in part, due to the decrease in aflatoxin contamination in the food as a result of economic development [102].

Chen et al. [54] elucidated in a community-based cohort study in Taiwan that a synergistic effect on HCC existed

between HBsAg carrier status and aflatoxin exposure. Another case–control study conducted in Sudan assessed the population-attributable risk of aflatoxin and HBV infection, jointly and separately, with respect to HCC. It demonstrated that reduction of aflatoxin contamination of foods and HBV vaccination may be useful public health strategies in HCC prevention [103].

Coffee

Coffee has a favorable effect on liver function and liver diseases, particularly in high-risk individuals, making it a substance of interest for the prevention of HCC [104–113].

Two meta-analyses on the relationship between coffee and HCC conducted by Bravi et al. [114] and Larsson et al. [115] provided substantial evidence that there is an inverse relation between coffee and HCC. The findings from these meta-analyses indicate a reduced risk of liver cancer, among both individuals with and without a history of liver disease. Although impressive reviews are available, it is still too early in making direct recommendations regarding coffee intake.

Vitamin K_2

Vitamin K_2 inhibits the growth of various neoplastic cells, including hepatoma cells, by causing cell-cycle arrest and apoptosis through different proposed mechanisms [116–122].

An RCT involving the use of vitamin K_2 in the prevention of HCC in women with HBV- or HCV-related cirrhosis proved that there could be a possible role for this as primary preventive agent [122]. The safety, relatively low cost, and ease of use make vitamin K_2 a suitable candidate for clinical trials that assess the value of combination of chemoprevention or chemotherapy in at-risk patients or in patients with a confirmed diagnosis of HCC [116, 122–125].

Although short-term effects seem appealing, additional multicenter randomized controlled studies are needed to look into long-term effects of vitamin K_2.

Tobacco and alcohol intake

It is still controversial whether cigarette smoking is a risk factor for HCC [48, 49]. Many authors support the fact that heavy alcohol intake is strongly associated with HCC [49–51]. Alcohol also increases the risk for HCC in patients with chronic hepatitis B and C [102]. Therefore, abstinence of heavy alcohol drinking is probably beneficial in reducing the risk of HCC.

NASH and HCC

Nonalcoholic steatohepatitis has been reported to affect 2–3% of the world's population, making it probably the most common liver disorder today [126]. Of these patients with NASH, 23% progress to liver cirrhosis in 10–15 years [127]. It has been observed that at the time of diagnosis, advanced fibrosis is already found in 30–40% of NASH patients, and 10–15% already have established cirrhosis. Since NASH may progress to cirrhosis (NASH being responsible for 70% of cryptogenic cirrhosis) [128], HCC development may be a part of the natural history of this disease [129]. A recent study by Chen et al. [58], which enrolled 23,820 residents in Taiwan with a 14-year follow-up, showed that extreme obesity (BMI $\geq$ 30 kg/m^2) was independently associated with a fourfold risk of HCC in anti-HCV-positive subjects and a twofold risk of HCC in those without HBV or HCV after controlling for other metabolic components. Diabetes was associated with HCC in HBsAg-positive, anti-HCV-positive, or both HBsAg- and anti-HCV-negative subjects, with the highest risk in those with HCV infection [RR (multivariate-adjusted relative risk) 3.52, 95% CI 1.29–9.24] and lowest in HBV carriers (RR 2.27, 95% CI 1.10–4.66). The study also found more than 100-fold increased risk of HCC in HBV or HCV carriers with both diabetes and obesity, indicating synergistic effects of metabolic factors and hepatitis [58].

Patients who have NASH-related cirrhosis carry a substantial risk for early development of HCC and a poor prognosis because of the limited therapeutic options due to relevant comorbidity. This raises the issue of careful screening and surveillance for HCC in NASH patients who have advanced liver disease. Control of risk factors such as type II diabetes, obesity, and dyslipidemia is recommended as the first and most important approach in managing people with NAFLD and NASH and preventing development of cirrhosis and HCC [130].

Lifestyle measures such as dietary modifications based on the metabolic profile (obesity, type II diabetes, hyperlipidemia, and hypertension) and increasing physical activity in the form of aerobic exercise should be encouraged in all patients with NAFLD. There is currently a level II evidence to support the beneficial role of dietary restriction (mainly aimed at improving insulin sensitivity) and exercise in the management of NAFLD [131].

Since NAFLD and NASH are closely associated with insulin resistance, pharmacologic treatment has been targeted on insulin-sensitizing drugs. Several studies on the use of insulin-sensitizing drugs have been done. Chavez-Tapia et al. [132] conducted a systematic review of nine studies on the use of either metformin or thiazolidinediones and indicated that these drugs improve insulin resistance and liver function.

Hemochromatosis and HCC

Hepatocellular carcinoma is long known to be associated with HH [63]. The risk for the development of HCC in patients with HH was estimated to be more than 200-fold increase in early publications [62, 133]. A subsequent Danish study also showed a 93-fold increase of HCC in HH [134]. However, the true incidence of HCC in HH may be achieved from population-based studies. Two such studies from the United States and Sweden showed a strong association of HCC and HH [64, 135]. In addition to HH, the hepatic iron overload owing to other causes, such as homozygous beta thalassemia [136] and the dietary form observed in South African blacks [137], is also associated with an increased risk of HCC. There is also evidence that marked iron overload in the setting of end-stage liver disease is also associated with HCC. However, the current data are inconclusive on the relation between mild or moderate iron overload associated with hepatitis C or alcoholic liver disease [138]. Because iron depletion by phlebotomy is safe and effective, it appears prudent to screen patients with chronic liver disease for iron overload and to institute iron depletion if iron overload is identified.

Surveillance and diagnosis

Surveillance

Recommendations
Surveillance for HCC in high-risk populations is recommended (2a, B).
Surveillance for HCC should be performed by ultrasonography (US) and α-fetoprotein (AFP) every 6 months (2a, B).

Rationale for surveillance

As described above, high-risk populations (e.g., cirrhosis with HBV or HCV infection) with HCC have been clearly identified by many epidemiological studies. However, the effectiveness of surveillance programs has still to be demonstrated through prospective RCTs, comparing the survival of participants with or without surveillance, though they may be susceptible to lead-time bias. To date, there is only one study that has proved the benefit of surveillance [139]. Zhang et al. [139] recruited 18,186 patients with chronic hepatitis due to HBV in China. The study revealed that surveillance with biannual AFP measurement and US reduced the mortality from HCC by 37% in spite of the fact that the compliance of scheduled tests was only 58.2%. It is desirable that this result should be validated in patients with other etiologies (e.g., chronic infection with HCV). However, it is highly unlikely that any such randomized study could be undertaken now because the surveillance of patients with cirrhosis is widely accepted and recruiting patients to a nonscreening arm of such a study would be almost impossible.

Who should be screened?

The efficacy of surveillance unambiguously depends on the incidence of HCC in the target population. However, because the risk of HCC in patients with chronic liver disease increases continuously with the number of risk factors, defining the population who should be screened is rather difficult. In addition, threshold for cost-effectiveness of surveillance program differs according to the economic situation of each country. Therefore, we recommend cirrhotic patients with HBV and HCV as candidates for surveillance at the present moment.

Recently, a study to better define the risk of chronic viral hepatitis by considering all important clinical and virologic features is ongoing. The results may be validated in the future [140].

What modality should be used?

Diagnostic tests universally available to date are imaging modalities including US, CT, and MRI, and a tumor marker such as AFP. AFP is the most widely studied screening test for HCC [141–143]. However, it is known that a significant proportion of small HCCs (e.g., ≤3 cm) do not secrete AFP to achieve a diagnostic level [142]. Furthermore, the level of AFP is elevated in patients with both HCC and chronic liver disease; thus, there is wide overlapping between the two groups [144, 145]. Most studies adopt a cutoff value of 20 ng/mL for AFP, with a sensitivity ranging from 49 to 71% and specificity from 49 to 86% in HCCs smaller than 5 cm [146–154]. Limitations in the sensitivity and specificity of AFP in surveillance of high-risk populations have led to the use of US as an additional method for the detection of HCC [142, 155–157].

Sensitivity of US is 78–90%, with 93% specificity [142, 148, 157]. In some countries such as Japan, concomitant measurement of des-γ-carboxyprothrombin (DCP) and lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) reportedly increases the detectability of small HCC [146, 147, 149–151, 153, 154]. The use of CT or MRI with contrast media can attain a higher diagnostic accuracy than US, but their use is costly.

Optimal interval for screening

The optimal interval of diagnostic tests in a surveillance program should be assessed from the view of cost-effectiveness because it is clear that more frequent tests can

detect HCC nodules of smaller size. Many studies have adopted an interval of 6 months between periodic diagnostic tests [155–157], although there are no randomized studies that have determined the optimal interval.

Thus, we propose periodic US and AFP measurements every 6 months as a minimum requirement. More frequent examinations, including new tumor markers such as DCP or AFP-L3 and CT/MRI, should be considered according to the medical circumstances of each country.

Tumor markers

Recommendations
α-Fetoprotein alone is not recommended for the diagnosis of HCC (1b, A).
Cutoff value of AFP should be set at 200 ng/mL for diagnosis (1b, A).
Simultaneous measurement of AFP and DCP provides higher sensitivity without decreasing specificity (1b, A).

Tumor makers are used in the diagnosis, prognosis, and evaluation of HCC. When a tumor marker is evaluated as a diagnostic test, its accuracy should be evaluated in terms of sensitivity, specificity, LR+, and LR+ [158]. Generally, the serum level of a tumor marker increases with the tumor size. Therefore, the range of tumor sizes should be considered in the evaluation of studies. A systematic review of studies published between 1982 and 2002 to evaluate the diagnostic accuracy of tumor markers for HCC is already available [159]. For the development of APASL consensus statement for HCC, we performed additional systematic review of studies published from 2003 to August 2008. Summary of recent studies that met the inclusion criteria is shown in Table 1 [160–169]. The results of the studies that evaluated AFP, DCP, and AFP-L3 were grossly compatible with the previous review.

α-Fetoprotein

α-Fetoprotein has served as a diagnostic test for HCC since the 1970s, when most patients with HCC were diagnosed at an advanced stage and with clinical symptoms [170]. A level of 500 ng/mL was considered diagnostic then. However, the usefulness of AFP as a diagnostic test in small HCCs is limited. According to this systematic review, the sensitivity, specificity, and LR+ of AFP in diagnosing HCC smaller than 5 cm in diameter ranged from 0.49 to 0.71, 0.49 to 0.86, and 1.28 to 4.03, respectively, with a cutoff value of 20 ng/mL and 0.04 to 0.31, 0.76 to 1.0, and 1.13 to 54.25, respectively, with a cutoff value of 200 ng/mL [159]. In a meta-analysis, AFP with a cutoff value of 200 ng/mL showed a better combined LR+ than with that of 20 ng/mL (5.85 vs. 2.45). The cutoff value of AFP should be set at 200 ng/mL instead of 20 ng/mL in the diagnosis of HCC.

Des-γ-carboxyprothrombin

Des-γ-carboxyprothrombin, also known as prothrombin induced by vitamin K absence-II, is an abnormal prothrombin protein that is increased in the serum of HCC patients. Since the report by Liebman et al. [171], DCP has been recognized as not only a highly specific marker for HCC but also a predictor of prognosis of HCC patients [172, 173]. According to the systematic review, the sensitivity, specificity, and LR+ of DCP in HCC smaller than 5 cm in diameter ranged from 0.14 to 0.54, 0.95 to 0.99, and 6.86 to 29.7, respectively, with a cutoff value of 40 mAU/mL and 0.07 to 0.56, 0.72 to 1.0, and 3.56 to 13.0, respectively, with a cutoff value of 100 mAU/mL [159]. In the meta-analysis, DCP with a cutoff value of 40 mAU/mL showed a better combined LR+ than with that of 100 mAU/mL (12.60 vs. 4.91).

Lens culinaris agglutinin-reactive fraction of AFP

AFP-L3 is a fucosylated variant of AFP that reacts with lens culinaris agglutinin A and can differentiate an increase in AFP due to HCC from that in patients with benign liver disease [174–176]. According to the systematic review, the sensitivity, specificity, and LR+ of AFP-L3 in HCC smaller than 5 cm in diameter ranged from 0.22 to 0.33, 0.93 to 0.94, and 4.63 to 30.8, respectively, with a cutoff value of 10% and 0.21 to 0.49, 0.94 to 1.0, and 8.06 to 45.1, respectively, with a cutoff value of 15% [159]. In the meta-analysis, AFP-L3 with a cutoff value of 15% earns better combined LR+ than with a cutoff value of 10% (13.1 vs. 4.89).

Glypican-3

GPC3 is a heparan sulfate proteoglycan anchored to the plasma membrane. It has been reported that GPC3 messenger RNA levels are increased in HCC [177, 178]. To date, a lot of studies reported the usefulness of GPC3 in the differential diagnosis of HCC. However, the vast majority of reports were based on the immunohistochemical studies. Capurro et al. [164] reported sensitivity of 0.53 and specificity of 0.95 with a cutoff value of 117 ng/mL on a study of serum samples from 53 healthy individuals and 71 patients with hepatitis or HCC. More evidence is needed to recommend GPC3 in daily practice.

Combination of tumor markers

Simultaneous measurement of tumor markers improves sensitivity without decreasing specificity when they have a

Table 1 Summary of studies on tumor markers for HCC published since 2003

Reference	Diagnostic test	Study design	Country	Patients with HCC				Control		
				n	Etiology	Characteristics of HCC	Modalities of diagnosis	*n*	Etiology	Characteristics of patients
Marrero et al. [160]	AFP, DCP	CC	USA	55	4% with HBV 46% with HCV 13% with ALT	NR	100% by pathology	152	7% with HBV 50% with HCV	32% with NL 34% with CH 35% with LC
Cui et al. [161]	AFP, DCP, GGTII	CC	China	120	81% with HBV 0% with HCV	26%, ≤3 cm	74% by pathology 26% by imaging	90	92% with HBV 1% with HCV	100% with LC
Wang et al. [162]	AFP, DCP	CC	China	61	46% with HBV 39% with HCV	38%, ≤2 cm 26%, 2–3 cm 36%, >3 cm	77% by pathology 23% by imaging	66	53% with HBV 42% with HCV	49% with CH 51% with LC
Sterling et al. [163]	AFP. AFP-L3	CC, CO	USA	74	100% with HCV	28%, <2 cm 68%, ≤5 cm	92% by imaging	298	100% with HCV	100% with LC
Capurro et al. [164]	AFP, GPC3	CC	Canada	34	NR	NR	NR	91	NR	58% with NL 20% with CH 22% with LC
Hippo et al. [165]	AFP, GPC3	CC	Japan	69	NR	NR	62% by pathology 38% by imaging	134	NR	28% with LC 72% with NL
Nguyen et al. [166]	AFP	CC	USA	163	100% with HCV	50%, ≤3.5 cm	53% by pathology 47% by imaging	149	100% with HCV	100% with LC
Soresi et al. [167]	AFP	CC	Italy	197	8% with HBV 75% with HCV	NR	NR	272	8% with HBV 77% with HCV	100% with LC
Arrieta et al. [168]	AFP	CC	Mexico	193	7% with HBV 30% with HCV	NR	100% by pathology	74	0% with HBV 45% with HCV	100% with LC
Paul et al. [169]	AFP	CC	India	101	NR	31%, ≤5 cm	NR	194	NR	100% with LC

AFP α-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *CC* case–control study, *CH* chronic hepatitis, *Co* cohort study, *DCP* des-γ-carboxy prothrombin, *GGTII* hepatoma-specific band of serum γ-glutamyl transferase, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *LC* liver cirrhosis, *NL* normal liver, *NR* not reported

weak association. Sensitivity, specificity, and LR+ of AFP and DCP in small HCCs were 0.48, 0.99, and 48 with a cutoff value of 200 ng/mL for AFP and 40 mAU/mL for DCP [179].

Ultrasonography

Recommendations
Ultrasonography is a screening test and not a diagnostic test for confirmation (2b, B).
Contrast-enhanced US (CEUS) is as sensitive as dynamic CT or dynamic MRI in the diagnosis of HCC (2b, B).

The evaluation of intranodular hemodynamics is important for the diagnosis of hepatic malignancies because the pathologic findings of hepatic malignancies are closely related to intranodular hemodynamics. B-mode US is useful for the screening of liver diseases but cannot demonstrate tumor vascularity. Color Doppler imaging reveals the arterial pulsating flows, such as a basket pattern flow and a "spot" pattern flow, for hepatic tumor differentiation [180, 181]. However, color Doppler US does not detect pulsatile flow in some HCCs. The reasons for this are as follows: first, color Doppler US cannot detect flows that are perpendicular to the sound field [182]. Second, the technique uses an estimate of the mean Doppler frequency shift at a particular position. On the contrary, power Doppler imaging measures the Doppler energy, which is based on the integrated power of the Doppler signal instead of its mean Doppler frequency shift. Some studies reported that power Doppler sonography was more sensitive for the depiction of blood vessels than color Doppler imaging [182, 183]. These techniques are noninvasive and inexpensive; however, they have some limitations including a low sensitivity of detecting the microflow in the nodules.

Efforts have been made to improve both sonography equipment and contrast agents to detect flow in tumors with more sensitivity [184, 185]. Sonography with an intra-arterial CO_2 microbubble contrast agent enables the detection of intratumoral hemodynamics. The differential diagnosis of hepatic tumors has become possible with contrast-enhanced, harmonic US based on tumor vascularity [186]. CEUS using Levovist bubbles involves the use of a nonlinear backscatter property of the resonant microbubbles produced by an intravenously administered contrast agent; it allows microflow imaging of nodules and eliminates clutter signals. However, Levovist bubbles easily collapse by ultrasound wave emission because of its fragile property. Therefore, Levovist-enhanced harmonic US images are basically obtained intermittently, and real-time images can be obtained within a short period of time at an early vascular phase and Kupffer imaging in the postvascular phase by a single sweep scan of the liver.

With the development of second-generation contrast media such as SonoVue or Sonazoid, which are made of a hard shell containing bubbles, contrast-enhanced, harmonic US has entered a new era. SonoVue and Sonazoid produce stable, nonlinear oscillations in the low-power acoustic field (i.e., low mechanical index) and supply great details of the second harmonic signals in real time. These contrast agents provide detailed perfusion features of the microvascular bed of the liver parenchyma and tumor during the vascular phase. Moreover, Kupffer imaging in the postvascular phase, which is stable for at least 3 h after injection and tolerable for multiple scanning, can be obtained in the low-power acoustic field because Sonazoid microbubbles are phagocytosed by Kupffer cells [187].

D'Onofrio et al. [188] reported that SonoVue-enhanced US detected hepatic malignancy as defects in the sinusoidal phase, with a sensitivity of 85%, specificity of 88%, positive predictive value of 92%, and negative predictive value of 77%. In our study, Sonazoid-enhanced harmonic US detected hepatic malignancy with a sensitivity of 95% (208/219), specificity of 93.3% (28/30), positive predictive value of 99% (208/210), and negative predictive value of 97.4% (38/39). These favorable results can be attributed to the characteristic features of Kupffer imaging.

Hatanaka et al. [189] reported that intranodular vascularity was detected in 99.4% of HCCs on contrast-enhanced, harmonic US. In the remaining 0.6% of HCCs, no blood signal was detected. In contrast, 98.9% of HCCs showed hyper- or isoperfusion on dynamic CT. Most of the HCCs showed HCC perfusion patterns on contrast-enhanced, harmonic US. The sensitivity and specificity of the HCC pattern were 96.6 and 94.4%, respectively. The positive and negative predictive values of this pattern were 97.7 and 91.9%, respectively.

SonoVue- or Sonazoid-enhanced harmonic US is a promising technique for the noninvasive characterization of hepatic tumors on the basis of the presence/absence of the characteristic features of each tumor type.

CT, MRI, and other imaging modalities

Recommendations
Dynamic CT or dynamic MRI is recommended as a first-line diagnostic tool for HCC when a screening test result is abnormal (1a, A).
Hallmark of HCC during CT scan or MRI is the presence of arterial enhancement, followed by washout of the tumor in the portal-venous and/or delayed phases (1b, A).

Detection and characterization of focal lesions in the liver are critical for screening patients with chronic liver disease. US is the most widely used modality for HCC screening and surveillance, largely due to its relatively low