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Ⅲ. 研究成果の刊行物・別刷

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

Kenichi Takayasu[1]
Shigeki Arii[2]
Iwao Ikai[3]
Masatoshi Kudo[4]
Yutaka Matsuyama[5]
Masamichi Kojiro[6]
Masatoshi Makuuchi[7]
for the Liver Cancer Study Group of Japan

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

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

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

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

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

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[1]Department of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Address correspondence to K. Takayasu.

[2]Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University, Graduate School of Medicine, Tokyo, Japan.

[3]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

[4]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan.

[5]Department of Biostatistics, School of Health Sciences and Nursing University of Tokyo, Tokyo, Japan.

[6]Department of Pathology, Kurume University School of Medicine, Kurume, Japan.

[7]Department of Surgery, Japanese Red Cross Medical Center, Tokyo, Japan.

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

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

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

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

Subjects and Methods

Patient Characteristics

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

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

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

Tumor Characteristics

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

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

Technique

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

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

Statistical Analysis

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

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

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

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

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

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

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

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

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

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

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

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

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

Results

Patient Characteristics in the Whole Sample

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

Crude Survival of TACE Patients and Patients Undergoing Therapy Without Embolization

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

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

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

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

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

Discussion

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

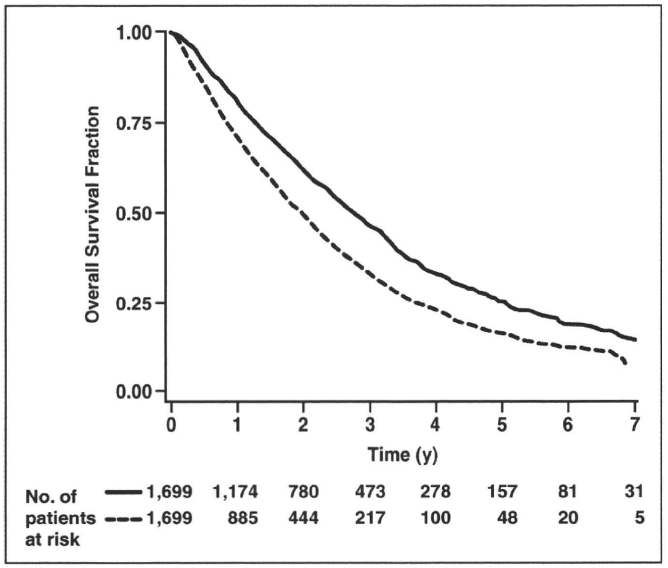

Fig. 1—Graph shows comparison of survival rates among patients with unresectable hepatocellular carcinoma treated with iodized oil transarterial chemoembolization (TACE) (*n* = 1,699 patients) (*solid line*) and those treated with iodized oil transarterial infusion therapy without embolization (*n* =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

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

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

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

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

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

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

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

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

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

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

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

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

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

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REVIEW

The 2008 Okuda lecture: Management of hepatocellular carcinoma: From surveillance to molecular targeted therapy

Masatoshi Kudo

Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka-Sayama, Osaka, Japan

Key words
contrast enhanced ultrasound, early hepatocellular carcinoma, Gd-EOB-DTPA, hepatocellular carcinoma, molecular targeted agent, sonazoid, staging system, surveillance, tumor marker.

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Correspondence
Professor Masatoshi Kudo, Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka-Sayama, Osaka 589-8511, Japan.
Email: m-kudo@med.kindai.ac.jp

Abstract

Hepatocellular carcinoma (HCC) is responsible for approximately 600 000–700 000 deaths worldwide. It is highly prevalent in the Asia-Pacific region and Africa, and is increasing in Western countries. Alpha fetoprotein (AFP) alone is insufficient for HCC screening. A combination with other tumor markers, such as PIVKA-II and AFP-L3, and periodical ultrasound surveillance is necessary. Sensitivity of AFP in depicting HCC is highest, followed by PIVKA-II and AFP-L3, but the order of the specificity is inverse, AFP-L3, PIVKA-II, and AFP. Sonazoid-enhanced ultrasound (US) is extremely useful to characterize hepatic tumors equal to or more than multidetector row computed tomography (MDCT). Sonazoid-enhanced US with defect re-perfusion imaging is a breakthrough technique in the treatment of HCC. Defect re-perfusion imaging will markedly change the therapeutic strategy for liver cancer. Gd-EOB-DTPA-magnetic resonance imaging is a newly developed imaging technique in the detection and diagnosis of HCC. It is the most sensitive tool in the differentiation of early HCC from dysplastic nodules. Regarding the treatment strategy, there has been no established systemic chemotherapy for advanced HCC, except for Sorafenib. Empirically, intrahepatic arterial infusion chemotherapy using implanted reservoir port is known to be effective in response rate and overall survival for advanced HCC with vascular invasion. Sorafenib in combination with transcatheter arterial chemoembolization or adjuvant use after ablation or resection will significantly prolong the life expectancy if ongoing clinical trials provide positive results. In conclusion, it is expected that readers will gain deeper insight into the latest progress and updated diagnosis and treatment of HCC described in this review.

Surveillance for early detection of HCC

Definition of the population at high-risk for HCC

Hepatocellular carcinoma (HCC) is responsible for approximately 600 000–700 000 deaths worldwide. It is highly prevalent in the Asia-Pacific region and Africa, and is increasing in Western countries.[1] Persistent infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the highest risk factors for hepatocarcinogenesis. The carcinogenesis risk for HBV-infected persons is about 200 times higher than for those non-infected, and the risk may be higher by approximately fivefold in patients with HCV-related cirrhosis compared with those with HBV-related cirrhosis. The characteristics of HCV-associated carcinogenesis are fibrosis stage 4 (F4), in which liver cirrhosis is complete in most cases, male gender and age 60 years or older. The yearly carcinogenesis rate of cirrhosis type C is 7–8% in Japan, which is higher than in Europe, Australia and North America (1–3% per year),[2] this difference might be attributed to the higher mean age of carriers.

Liver cirrhosis induced by causes other than HBV and HCV is also a risk. Thus, HCC occurs in some cases of liver cirrhosis associated with nonalcoholic steatohepatitis (NASH), alcoholic liver disease, primary biliary cirrhosis (PBC), hemochromatosis, alpha-1 antitrypsin deficiency and autoimmune hepatitis (AIH). For patients with any of these disorders, the course of the disease should be followed with close attention to hepatocarcinogenesis. In addition, alcohol increases the risk of chronic hepatitis B- and C-associated liver carcinogenesis, and obesity increases the risk of HCV-related hepatocellular carcinoma (HCC). In summary, patients with chronic hepatitis B and C and non-viral liver cirrhosis are defined as high-risk populations for HCC in both Evidence-Based Practice Guidelines,[3] the Consensus-Based Clinical Practice Manual[4] proposed by the Japan Society of Hepatology (JSH), and the Practice Guideline published by the American Association of Study of the Liver (AASLD).[5] Patients with liver cirrhosis from HBV or HCV are defined as a super high-risk population.[3,4]