2. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.
3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
4. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
5. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81.
6. Sala M, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology. 2004;40:1352–60.
7. Llovet JM, Bisceglie AD, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100: 698–711.
8. Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma. Are response evaluation criteria in solid tumors reliable? Cancer. 2009;115:616–23.
9. Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, et al. Comparison of tumor response by response evaluation criteria in solid tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer. 2012;118:147–56.
10. Landis JR, Koch GG. The measurement of observer agreement for caterogical data. Biometrics. 1977;33:159–74.
11. Watanabe H, Kunitoh H, Yamamoto S, Kawasaki S, Inoue A, Hotta K, et al. Effect of the introduction of minimum lesion size on interobserver reproducibility using RECIST guidelines in non-small cell lung cancer patients. Cancer Sci. 2006;97: 214–18.
12. Al-Aynati M, Chen V, Salama S, Shuhaibar H, Treleaven D, Vincic L. Interobserver and intraobserver variability using the Fuhrman grading system for renal cell carcinoma. Arch Pathol Lab Med. 2003;127:593–6.
13. Hagen PJ, Hartmann IJ, Hoekstra OS, Stokkel MP, Postmus PE, Prins MH. Comparison of observer variability and accuracy of different criteria for lung scan interpretation. J Nucl Med. 2003;44:739–44.
14. Travis WD, Gal AA, Colby TV, Klimstra DS, Falk R, Koss MN. Reproducibility of neuroendocrine lung tumor classification. Hum Pathol. 1998;29:272–9.

Ups J Med Sci Downloaded from informahealthcare.com by National Cancer Center Library on 05/14/13
For personal use only.

RIGHTSLINK

CLINICAL STUDY

Prospective Study of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: An Asian Cooperative Study between Japan and Korea

Masafumi Ikeda, MD, Yasuaki Arai, MD, Sang Joon Park, MD, Yoshito Takeuchi, MD, Hiroshi Anai, MD, Jae Kyu Kim, MD, Yoshitaka Inaba, MD, Takeshi Aramaki, MD, Se Hwan Kwon, MD, Seiichiro Yamamoto, PhD, Takuji Okusaka, MD, Japan Interventional Radiology in Oncology Study Group (JIVROSG), and Korea Interventional Radiology in Oncology Study Group (KIVROSG)

ABSTRACT

Purpose: To evaluate the safety and efficacy of transcatheter arterial chemoembolization used for the treatment of unresectable hepatocellular carcinoma (HCC) with an Asian cooperative prospective study between Japan and Korea.

Materials and Methods: Patients with unresectable HCC unsuitable for curative treatment or with no prior therapy for HCC were enrolled. The patients underwent transcatheter arterial chemoembolization with emulsion of Lipiodol and anthracycline agent, followed by embolization with gelatin sponge particles, which was repeated on an as-needed basis. The primary endpoint was 2-year survival rate, and the secondary endpoints were adverse events and response rate.

Results: The 2-year survival rate of 99 patients was 75.0% (95% confidence interval, 65.2%–82.8%). The median time-to-progression was 7.8 months, and the median overall survival period was 3.1 years. Of 99 patients, 42 (42%) achieved a complete response, and 31 (31%) had a partial response. The response rate was 73% using modified Response Evaluation Criteria in Solid Tumors. The grade 3–4 toxicities included increased alanine aminotransferase level in 36%, increased aspartate aminotransferase level in 35%, thrombocytopenia in 12%, and abdominal pain in 4% of patients. All other toxicities were generally transient.

Conclusions: Asian transcatheter arterial chemoembolization demonstrated sufficient safety and reasonable efficacy as a standard treatment for unresectable HCC. These results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

ABBREVIATIONS

AFP = alpha fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, FAS = full analysis set, HCC = hepatocellular carcinoma, PIVKA II = protein induced by vitamin K absence or antagonist-II, RECIST = Response Evaluation Criteria in Solid Tumors

Primary liver cancer accounted for > 38,000 and 15,000 deaths per year in Japan and Korea, respectively; it is the fourth most common cause of death after lung, stomach, and colorectal cancers in Japan, and it is the third most

From the Division of Hepatobiliary and Pancreatic Oncology (M.I.), National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, 277-8577, Japan; and Department of Diagnostic Radiology (Y.A., Y.T.) and Hepatobiliary and Pancreatic Oncology Division (T.O.), National Cancer Center Hospital, Tokyo, Japan; and Department of Radiology (S.J.P.), Sun General Hospital, Daejeon, Korea; and Department of Radiology (H.A.), Nara Medical University, Kashihara, Japan; and Department of Radiology (J.K.K.), Chonnam University Hospital, Korea; Department of Diagnostic and Interventional Radiology (Y.I.), Aichi Cancer Center Hospital, Nagoya, Japan; and Division of Diagnostic Radiology (T.A.), Shizuoka Cancer Center, Shizuoka, Japan; and Department of Radiology (S.H.K.), Kyung Hee University Medical Center, Korea; and Cancer Information Services and Surveillance Division (S.Y.), Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan. Received May 29, 2012; final revision received December 28, 2012; accepted January 7, 2013. **Address correspondence to** M.I.; E-mail: masikeda@east.ncc.go.jp

None of the authors have identified a conflict of interest.

© SIR, 2013

J Vasc Interv Radiol 2013; 24:490–500

http://dx.doi.org/10.1016/j.jvir.2013.01.003

common cause of death after lung and stomach cancers in Korea (1). Of all primary liver cancers, approximately 95% in Japan and 85% in Korea are hepatocellular carcinomas (HCCs), which are mostly attributable to chronic hepatitis or liver cirrhosis caused by persistent infection with hepatitis C or B viruses. Hepatitis B infection is more prevalent in Korea, whereas hepatitis C infection is more common in Japan (2). Despite these differences in etiology, the treatment strategy for HCC is the same in Japan and Korea. Curative therapies, such as hepatic resection or liver transplantation, are applicable in only a small proportion of patients because of excessive tumor invasion or poor hepatic function or both. Although local ablative therapy, such as radiofrequency ablation, has an effectiveness equivalent to that of hepatic resection for HCCs $\leq$ 3 cm in size and with three or fewer nodules, it is unsuitable for tumors > 3 cm or for multiple tumors. For this stage of HCC, transcatheter arterial chemoembolization is the main therapeutic option (3–5). Transcatheter arterial chemoembolization has been shown to prolong survival significantly in several randomized controlled trials compared with chemotherapy alone (6) or conservative treatment (7–13). Meta-analyses (14,15) have also demonstrated a clear survival benefit of transcatheter arterial chemoembolization for unresectable HCC (**Table 1**).

Transcatheter arterial chemoembolization with Lipiodol (Guerbet; Roissy CdG, France) and anthracycline agents followed by embolization with gelatin sponge particles has been widely used as a practical standard treatment in Asian countries for > 30 years (16). Transcatheter arterial chemoembolization was used in Asian countries long before the confirmation of its survival benefit in randomized controlled trials (6–13) because these techniques were originally developed in Japan (17–19) and spread among Asian countries. However, no prospective clinical study has been fully conducted to provide convincing data that can support this treatment. Additionally, there are many technique differences between Asian transcatheter arterial chemoembolization and transcatheter arterial chemoembolization performed in Western countries. The so-called conventional transcatheter arterial chemoembolization reported in Western studies differs from Asian transcatheter arterial chemoembolization in the details of the treatment. A prospective clinical study was conducted to evaluate Asian transcatheter arterial chemoembolization for unresectable HCC. The aim of this study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization with a single-arm, Japan-Korea cooperative prospective study.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients for study entry had unresectable HCC that was unsuitable for curative treatments. Patient inclusion criteria were as follows: histologically or clinically diagnosed HCC excluding mixed type; no previous treatment for HCC; not a candidate for hepatic resection, liver transplantation, or local ablative therapy; hypervascular lesion showing enhancement in the early phase on computed tomography (CT) or magnetic resonance (MR) imaging with bolus contrast injection; no tumor thrombosis in the first branch or main portal vein; Eastern Cooperative Oncology Group performance status of 0–2; Child-Pugh classification of A or B; adequate hematologic, hepatic, renal, and cardiac function (leukocytes $\geq$ 3,000/mm^3, platelets $\geq$ 50,000/mm^3, serum bilirubin $\leq$ 3.0 mg/dL); age $\geq$ 20 years old; and written informed consent.

The exclusion criteria were as follows: extrahepatic metastasis; hepatic vein invasion or biliary invasion; ruptured tumor; prior biliary enteric bypass or endoscopic transampullary stent placement or percutaneous biliary drainage; clinically significant refractory ascites or pleural effusion; severe arterioportal or arteriovenous shunts in the liver; allergy to contrast medium precluding angiography; severe and active comorbidity such as heart disease or renal disease; hepatic encephalopathy or severe mental disorder; active gastrointestinal bleeding; active concomitant malignancy; pregnancy, lactation, or childbearing potential in women; and men who are sexually active and not willing or able to use medically acceptable forms of contraception. The inclusion and exclusion criteria were almost same as those in the clinical trial conducted by Llovet et al (12).

The pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast-enhanced CT or MR imaging of the abdomen and x-ray or CT of the chest were performed before treatment for staging to assess the local extension of the tumor and to exclude the presence of distant metastasis.

Transcatheter Arterial Chemoembolization Procedure

Patients with unresectable HCC underwent transcatheter arterial chemoembolization using an emulsion of epirubicin or doxorubicin and Lipiodol followed by gelatin sponge injection. The dose of anticancer agents and Lipiodol used in transcatheter arterial chemoembolization was determined according to tumor size; only the maximum doses were defined in this study: 100 mg/body for epirubicin, 70 mg/body for doxorubicin, and 20 mL for Lipiodol. Epirubicin or doxorubicin dissolved in aqueous nonionic contrast medium was mixed with Lipiodol to form an emulsion using the pumping technique. The resulting emulsion had to be injected immediately. Transcatheter arterial chemoembolization was performed as follows: (i) tumor enhancement and the feeding artery were confirmed using abdominal angiography; (ii) a catheter was inserted into the feeding artery of the HCC, and the emulsion containing epirubicin or doxorubicin with Lipiodol was injected; (iii) embolization of the feeding artery was achieved using small pieces of gelatin sponge until the disappearance of tumor stain; (iv) the therapeutic effect

Table 1. Randomized Controlled Trials of Transcatheter Arterial Embolization with Conservative Therapy

Author, Year	Treatment	No. Patients	Response Rate (%)	1-y Survival (%)	2-y Survival (%)	*P* Value	Treatment Duration	Embolic Material	Anticancer Agent	Lipiodol
Lin et al, 1988 (6)	Transcatheter arterial embolization	21	62	42	25		Monthly	Gelatin sponge	None	Absent
	Transcatheter arterial embolization + 5-FU	21	48	20	20		Monthly		5-FU	Absent
	5-FU	21	9.5	13	13	< .005	Monthly		5-FU	
Pelletier et al, 1990 (7)	Transcatheter arterial chemoembolization	21	33	24	NA		2nd, 6th, 12th mo	Gelatin sponge	Doxorubicin	Absent
	Best supportive care	21	0	33	NA	NS				
GRETCH, 1995 (8)	Transcatheter arterial chemoembolization	50	16	62	38		Every 2 mo	Gelatin sponge	Cisplatin	Present
	Best supportive care	46	5	43	26	.13				
Pelletier et al, 1998 (9)	Transcatheter arterial chemoembolization + TMX	37	24	51	24		Every 3–4 mo	Gelatin sponge	Cisplatin	Present
	TMX	36	5.5	55	26	.77				
Bruix et al, 1998 (10)	Transcatheter arterial embolization	40	55	70	49		On demand	Gelatin sponge + coil	None	Absent
	Best supportive care	40	0	72	50	.72				
Lo et al, 2002 (11)	Transcatheter arterial chemoembolization	40	27	57	31		Every 2–3 mo	Gelatin sponge	Cisplatin	Present
	Best supportive care	39	2.6	31	11	.002				
Llovet et al, 2002 (12)	Transcatheter arterial chemoembolization	40	35	82	63		Every 2–6 mo	Gelatin sponge	Doxorubicin	Present
	Transcatheter arterial embolization	37	43	75	50		Every 2–6 mo	Gelatin sponge		
	Best supportive care	35	0	63	27	.009				
Doffoël et al, 2008 (13)	Transcatheter arterial chemoembolization	62	NA	51	25		Every 2–6 mo	Gelatin sponge	Epirubicin	Present
	TMX	61	NA	46	22	.68				

5-FU = 5-fluorouracil; NA = not available; TMX = tamoxifen.

was confirmed using contrast-enhanced CT or MR imaging (bolus injection) after 6 weeks ± 2.

The treatment was repeated if tumor progression was observed. The treatment could also be repeated even without tumor progression for disease control on an as-needed basis. If no residual tumor was found, transcatheter arterial chemoembolization was not performed periodically, and a follow-up contrast-enhanced CT or MR imaging examination was repeated every 3 months ± 2. When tumor recurrences were observed on a follow-up CT or MR imaging examination, the transcatheter arterial chemoembolization procedure was repeated. The protocol treatment was discontinued if any of the following criteria for the discontinuation of the protocol therapy occurred: obvious tumor progression at the site of treatment at an evaluation performed 6 weeks ± 2 after transcatheter arterial chemoembolization, tumor thrombosis in the first branch or main portal vein, intended use of another appropriate therapy for persistent or recurrent tumors, grade 4 nonhematologic toxicities other than aspartate aminotransferase (AST) or alanine aminotransferase (ALT), an accumulated dose of epirubicin > 750 mg/m^2 body surface area or an accumulated dose of doxorubicin > 500 mg/m^2 body surface area, or technical difficulties associated with the performance of transcatheter arterial chemoembolization. If the protocol therapy was discontinued, another anticancer treatment was allowed without restriction. Also, if transcatheter arterial chemoembolization was effective in reducing the tumor and the patient was eligible for other curative therapies, hepatic resection or local ablative therapy was allowed.

Response and Toxicity Assessment

Contrast-enhanced CT or MR imaging was performed at 6 weeks ± 2 after transcatheter arterial chemoembolization and every 3 months ± 2 thereafter. The tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) (19). Serum alpha fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA II) levels were measured at 6 weeks ± 2 after the first transcatheter arterial chemoembolization procedure. The AFP or PIVKA II response was assessed for patients who had a level before treatment of 100 ng/mL or ≥ 100 mAU/mL; a positive response was defined as a reduction by > 50% compared with the level before treatment. Regarding the adverse events that were observed, the incidence per grade based on the worst grade of the adverse events in an individual case was calculated. The severity of all adverse events was evaluated according to the National Cancer Institute Common Terminology Criteria for adverse events, version 3.0. Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up examination. Time-to-progression was defined as the time from the date of the initial treatment to the first documentation of progression. The period until the discontinuation of transcatheter arterial chemoembolization was defined as the time from the date of the initial treatment to the discontinuation of the protocol therapy. The overall survival time and time-to-progression were calculated using the Kaplan-Meier method.

Statistical Considerations

The aim of this clinical study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization and to confirm the reproducibility of the therapeutic effect compared with that observed in a randomized controlled trial conducted by Llovet et al (12). The primary endpoint of this trial was the 2-year survival rate, and the secondary endpoints were overall survival, the response rate, and the frequency of adverse events. The number of enrolled patients was determined using the confidence interval (CI) method based on the assumption that the 2-year survival rate in the transcatheter arterial chemoembolization group studied by Llovet et al (12) was 63%. Because the enrollment of 100 patients in this study would ensure a 10% two-sided CI, we planned to enroll 100 patients. This clinical study was a multicenter cooperative study conducted in Japan and Korea, and the annual registration of 100 patients was feasible. The total study period was set as 3 years, estimating that case accrual would occur during the first year and that the remaining 2 years would serve as the follow-up period to determine the 2-year survival rate. This population was defined as the full analysis set (FAS), including any patients who received at least one course of the study treatment and excluding any patients who withdrew their informed consent to participate in this study. This open-label, multiinstitutional, single-arm prospective study was approved by the review board of each institution and was conducted in accordance with the Declaration of Helsinki. This trial was registered in UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000975). Patient registration and data collection were managed by the clinical research data center of the clinical trial office at the National Cancer Center in Japan. The quality of data was ensured through careful review by the data center staff and the coordinating investigator of this study. All the data were frozen on January 31, 2011, and all the analyses were performed by a statistician (S.Y.).

RESULTS

Patient Characteristics

Between January 2008 and January 2009, 102 patients were enrolled in this trial at 19 institutions in Japan and 8 institutions in Korea (**Table 2**). Three patients were excluded from the analysis because they withdrew their informed consent, and all their data were extracted from the study. The characteristics of the remaining 99 FAS patients are listed in **Table 3**.

Table 2. Enrolled Institutions and Numbers of Patients

Institution	No. Enrolled Patients
National Cancer Center Hospital East	12
National Cancer Center Hospital	12
Nara Medical University	10
Chonnam University Hospital	7
Aichi Cancer Center Hospital	6
Shizuoka Cancer Center	6
Kyung Hee University Medical Center	6
Ishikawa Prefectural Central Hospital	4
Kobe University	4
The Catholic University of Korea Uijeongbu St Mary's Hospital	4
The Cancer Institute Hospital of JFCR	3
Shinshu University	3
Fukuoka University	3
Keijinkai Teine Hospital	2
Niigata Cancer Center	2
Okinawa Prefectural Nanbu Medical Center & Children's Medical Center	2
Catholic University St Paul's Hospital	2
Cheju National University Hospital	2
Korea University Anam Hospital	2
Samsung Medical Center	2
Seoul National University Hospital	2
Tochigi Cancer Center	1
Ryugasaki Saiseikai Hospital	1
The Jikei University School of Medicine	1
Aichi Medical University	1
Shitennoji Hospital	1
Hyogo College of Medicine	1

Table 3. Patient Characteristics (n = 99)

Characteristics	No. Patients (%)
Korea	24 (24%)
Japan	75 (76%)
Age (y)	
Median	70
Range	45–84
Sex	
Male	67 (68%)
Female	32 (32%)
ECOG performance status	
0	86 (87%)
1	12 (12%)
2	1 (1%)
Hepatitis B surface antigen positive	19 (19%)
Hepatitis C virus antibody positive	52 (53%)
Child-Pugh classification	
A	80 (81%)
B	19 (19%)
Ascites present	5 (5%)
Maximum tumor size (mm)	
Median	39
Range	11–110
No. tumors	
Single	34 (34%)
Multiple	65 (66%)
Tumor distribution	
Unilobar	64 (65%)
Bilobar	35 (35%)
AFP (ng/dL)	
Median	35.4
Range	1.8–102,700
Protein induced by vitamin K absence or antagonist-II (mAU/mL)	
Median	154
Range	0.02–66,400

AFP = alpha fetoprotein; ECOG = Eastern Cooperative Oncology Group.

Transcatheter Arterial Chemoembolization Procedure

A median of two transcatheter arterial chemoembolization procedures (range, one to nine procedures) were performed during the follow-up period. Transcatheter arterial chemoembolization using epirubicin was performed in 76 patients (77%), and transcatheter arterial chemoembolization using doxorubicin was performed in 25 patients (25%). Mainly epirubicin was used in Japan, whereas mainly doxorubicin was used in Korea. However, doxorubicin was administered together with mitomycin and cisplatin in two patients, which was judged as a serious deviation from the study's protocol. The median doses of epirubicin, doxorubicin, and Lipiodol were 45 mg/body (range, 10–70 mg/body), 40 mg/body (range, 10–60 mg/body), and 5 mL (range, 1.5–20 mL). The artery used for the administration of the anticancer agent in the initial transcatheter arterial chemoembolization was the subsegmental branch in 51 patients (37%), the segmental branch in 42 patients (30%), the left or right hepatic artery in 35 patients (25%), and other arteries such as the inferior phrenic artery in 10 patients (7%). There were 62 patients (63%) who discontinued the protocol treatment. The median period until transcatheter arterial chemoembolization discontinuation was 17.8 months. After the discontinuation of this protocol treatment, 59 patients (60%) received subsequent therapy including hepatic arterial infusion chemotherapy (14 patients), transcatheter arterial chemoembolization with other anticancer agents (13 patients), local ablation (13 patients), systemic chemotherapy (10 patients), radiotherapy (6 patients), and hepatic resection (3 patients).

Adverse Events

The adverse events associated with the first transcatheter arterial chemoembolization procedure observed in the 99 FAS patients are listed in **Table 4**. Grade 3 or higher anemia, neutropenia, and thrombocytopenia occurred in 1 (1%), 1 (1%) and 12 (12%) patients. In patients undergoing

Table 4. Adverse Events of First Transcatheter Arterial Chemoembolization (n = 99)

	No. Patients (%)			
	Grade 1*	Grade 2*	Grade 3*	Grade 4*
Hematologic toxicity				
Leukocytes	30 (30)	12 (12)	0 (0)	0 (0)
Neutrophils	11 (11)	14 (14)	1 (1)	0 (0)
Hemoglobin	53 (54)	14 (14)	1 (1)	0 (0)
Platelets	45 (45)	25 (25)	11 (11)	1 (1)
Nonhematologic toxicity				
Malaise	42 (42)	10 (10)	0 (0)	0 (0)
Anorexia	37 (37)	4 (4)	0 (0)	0 (0)
Nausea	22 (22)	4 (4)	0 (0)	0 (0)
Vomiting	10 (10)	1 (1)	0 (0)	0 (0)
Fever	55 (56)	9 (9)	0 (0)	0 (0)
Abdominal pain	24 (24)	12 (12)	4 (4)	0 (0)
Alopecia	1 (1)	0 (0)	–	–
Gastrointestinal hemorrhage	0 (0)	0 (0)	1 (1)	0 (0)
Liver abscess	0 (0)	0 (0)	1 (1)	0 (0)
Bilirubin	28 (28)	36 (36)	2 (2)	0 (0)
AST	28 (28)	32 (32)	30 (30)	5 (5)
ALT	26 (26)	31 (31)	31 (31)	5 (5)
Alkaline phosphatase	57 (58)	4 (4)	1 (1)	0 (0)
Hypoalbuminemia	49 (49)	35 (35)	0 (0)	–
Creatinine	12 (12)	3 (3)	0 (0)	0 (0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Grading according to Common Terminology Criteria for Adverse Events, version 3.0.

transcatheter arterial chemoembolization for unresectable HCC, the most common nonhematologic toxicities were hepatic dysfunction, as indicated by increased AST, ALT, and bilirubin levels. Grade 3 or higher AST, ALT, abdominal pain, and bilirubin nonhematologic toxicities were observed in 35 (35%), 36 (36%), 4 (4%), and 2 (2%) patients; these toxicities were transient so the patients recovered within 1 month. No treatment-related deaths occurred in this series. During this protocol treatment, serious adverse events were observed in two patients (2%). One patient developed a grade 5 spontaneous perforation of the small intestine because of paralytic ileus occurring 32 days after transcatheter arterial chemoembolization. This patient had a past history of multiple surgeries of the ileus, and the incident was judged as being unrelated to the transcatheter arterial chemoembolization treatment by an independent data monitoring committee. The other patient developed a grade 3 gastrointestinal hemorrhage on day 2 after the transcatheter arterial chemoembolization procedure. This hemorrhage was caused by Mallory-Weiss syndrome as a result of frequent vomiting after transcatheter arterial chemoembolization; the patient recovered without any specific treatment. No cumulative toxicities, including cardiac toxicity, were reported in this study.

Tumor Response

All 99 treated patients were included in the response evaluation, and the tumor response at 6 weeks ± 2 after the first transcatheter arterial chemoembolization procedure was evaluated using modified RECIST. A complete response was shown in 42 patients (42%), and 31 patients (31%) had a partial response, producing an overall response rate of 73% (95% CI, 64%–82%). Stable disease was present in 18 patients (18%), and 7 patients (7%) had progressive disease. Serum AFP and PIVKA II levels were reduced by > 50% in 76% and 90% of the patients who had a level before treatment of ≥ 100 ng/mL and ≥ 100 mAU/mL, respectively.

Overall Survival and Time-to-Progression

Of the 99 patients, 86 had developed disease progression at the time of the analysis. The median time-to-progression was 7.8 months. The pattern of disease progression was locoregional recurrence in 66 patients (67%), a new lesion in the liver in 53 patients (54%), vascular invasion in 8 patients (8%), and distant metastases in 8 patients (8%). At the time of the analysis, 33 patients had died, and the median survival time, 1-year survival rate, and 2-year survival rate for all 99 patients were 3.1 years, 89.9% (95% CI, 81.7%–94.3%), and 75.0% (95% CI, 65.2%–82.8%) (**Fig 1**). In addition, the median survival time, 1-year survival rate, and 2-year survival rate of 97 patients, calculated after excluding the two patients treated with doxorubicin together with mitomycin and cisplatin, were also almost the same (data not shown). The 2-year survival rates were 77.4% in Japan and 67.0% in Korea ($P = .57$) (**Fig 2**).

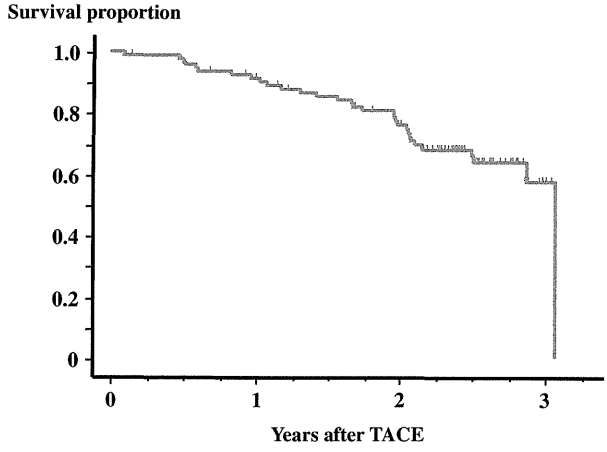

Figure 1. Overall survival and progression-free survival curves for 99 patients who underwent transcatheter arterial chemoembolization (TACE) for unresectable HCC. The tick marks indicate censored cases. (Available in color online at *www.jvir.org.*)

DISCUSSION

The survival benefit of transcatheter arterial chemoembolization for unresectable HCC has been confirmed by several randomized controlled trials (6,11,12) and meta-analyses (14,15). However, there is no consensus on the standard method of transcatheter arterial chemoembolization regarding the use of anticancer agents, embolic material, technical details, and the treatment schedule. The term "conventional transcatheter arterial chemoembolization" or "classic transcatheter arterial chemoembolization" has been widely used in the literature more recently. Common understanding is that conventional transcatheter arterial chemoembolization refers to Lipiodol chemoembolization, no matter what drug or embolic agent is used. However, there is no definition or consensus in terms of technical aspects of conventional transcatheter arterial chemoembolization. Conventional transcatheter arterial chemoembolization lacks consistency and includes a wide variety of anticancer drugs and dosages and techniques, which precludes the comparison of the previous studies of transcatheter arterial chemoembolization. For example, transcatheter arterial chemoembolization procedures with Lipiodol using a single drug or combination of two or three drugs and procedures with or without particulate embolic agents including gelatin sponge, polyvinyl alcohol, and spherical beads all have been referred to as "conventional transcatheter arterial chemoembolization." The schedule of conventional transcatheter arterial chemoembolization treatments has also been inconsistent among previous studies; transcatheter arterial chemoembolization was performed regularly in some studies and on an as-needed basis in others. Conventional transcatheter arterial chemoembolization cannot be justified as being the standard transcatheter arterial chemoembolization when conducting a randomized trial evaluating new treatments such as drug-eluting beads.

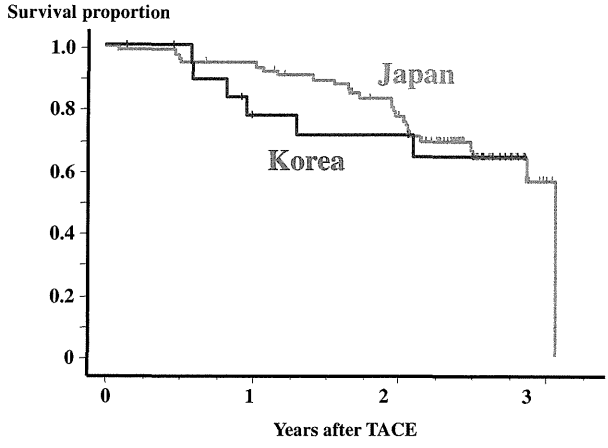

Figure 2. Comparison of overall survival curves between Japan (red line) and Korea (blue line). The tick marks indicate censored cases. TACE = transcatheter arterial chemoembolization. (Available in color online at *www.jvir.org.*)

Asian transcatheter arterial chemoembolization is characterized by using anthracycline agents with Lipiodol and gelatin sponge in an on-demand basis. It may be categorized as conventional transcatheter arterial chemoembolization; however, the technique is different from other conventional transcatheter arterial chemoembolization procedures. Elucidation of Asian transcatheter arterial chemoembolization by a prospective clinical study is warranted to develop better and new treatments for HCC. Because a randomized controlled trial comparing transcatheter arterial chemoembolization with a conservative therapy as a control is not feasible in countries such as Korea and Japan, where Asian transcatheter arterial chemoembolization has been performed as a practical standard therapy for a long time, we decided to conduct a single-arm prospective study to clarify the treatment efficacy and safety of Asian transcatheter arterial chemoembolization.

For comparison with the results of Llovet et al (12), which was the most notable study and had the most favorable antitumor effect among eight randomized controlled trials (**Table 1**) (6–13), the eligibility criteria except age and cardiac ejection fraction (**Table 5**) and study endpoints were set to be same. However, regarding transcatheter arterial chemoembolization procedures, we maintained the Asian transcatheter arterial chemoembolization in this study. With regard to the comparison of the patient characteristics between our study and the Llovet et al (12) study (**Table 5**), the median age before transcatheter arterial chemoembolization was slightly younger and the proportions of men and patients infected with hepatitis C virus were slightly higher in Llovet's study than in the present study. The hepatic reserves, as indicated by the Child-Pugh classification and the presence of ascites, were favorable in our study. The tumor-related factors were similar between our study and their study. The numbers of transcatheter arterial chemoembolization treatment sessions were also similar. Statistically, no significant differences in the patient characteristics were observed between our study and their study.

Table 5. Differences between Current Study and Llovet's Study

		Current Study (n = 99)		Llovet's Study (n = 40)		*P* Value
Eligibility criteria						
Age		Not limited		≤ 75 y		
Cardiac ejection fraction		Not limited		< 50%		
Treatment						
Anticancer agent		Doxorubicin or epirubicin		Doxorubicin		
Maximum dose of anticancer agents		Doxorubicin, 70 mg/body; epirubicin, 100 mg/body		75 mg/m^2		
Maximum dose of Lipiodol		20 mL		10 mL		
Periods of transcatheter arterial chemoembolization		On demand		Periodically		
Patient characteristics*						
Age (y)	Mean [95% CI]	69	[65–75]	63	[61–66]	
Sex	Male	67	(68)	32	(80)	
	Female	32	(32)	8	(20)	.21
ECOG performance status	0	86	(87)	35	(88)	
	1	12	(12)	4	(10)	
	2	1	(1)	1	(3)	.77
Hepatitis B surface antigen	Positive	19	(19)	4	(10)	.28
Hepatitis C virus antibody	Positive	52	(53)	33	(82)	.002
Child-Pugh classification	A	80	(81)	31	(78)	
	B	19	(19)	9	(23)	.83
Ascites	Present	5	(5)	6	(15)	.10
Maximum tumor size (mm)	Mean [95% CI]	42	[30–48]	49	[40–58]	
No. tumors	Single	34	(34)	13	(32)	
	Multiple	65	(66)	26	(65)	.99
Tumor distribution	Bilobar	35	(35)	19	(47)	.55
Antitumor effects						
Response evaluation		Modified RECIST		WHO criteria		
Response rate		73.7%		35%		< .0001
Overall survival						
1 y		89.9%		82		
2 y		75.0%		63		
Median (y)		3.1		2.1		

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.
* Unless otherwise indicated, values are number (%).

Patients with advanced HCC treated with transcatheter arterial chemoembolization tend to experience severe myelosuppression and hepatotoxicity because most of them have liver cirrhosis, which is usually associated with compromised hepatic function, leukocytopenia, and thrombocytopenia. However, in this study, the hematologic toxicities were very mild because small amounts of epirubicin (median, 45 mg/body) and doxorubicin (median, 40 mg/body) were used as combined anticancer agents. Hepatotoxicity, as indicated by increases in AST and ALT levels, was frequently observed (grade 3–4 increased AST, 35%; grade 3–4 increased ALT, 36%), but these toxicities were transient. There were no treatment-related deaths, and transcatheter arterial chemoembolization was generally tolerated in patients with advanced HCC.

In 2006, when this study was initially planned, we planned to evaluate the tumor response according to our original modified RECIST version 1.0. The concept of our modified RECIST, which evaluate tumor response based on the change in the viable part of the HCC, had been adapted into the study protocol. Unexpectedly, this concept was similar to that of modified RECIST advocated by Lencioni and Llovet in 2010 (20), which are now often used to evaluate tumor response in patients with advanced HCC. Therefore, we evaluated the response rate according to modified RECIST. The response rate in this study was very high (73%), possibly because approximately two-thirds of the transcatheter arterial chemoembolization procedures were performed subsegmentally (37%) or segmentally (30%). In Japan and Korea, transcatheter arterial chemoembolization might be performed more selectively and carefully (21,22).

The median survival time, 1-year survival rate, and 2-year survival rate for all 99 FAS patients were 3.1 years, 89.9%, and 75.0%, and no significant differences were observed between the Japanese and Korean patients. A favorable overall survival was obtained in our study, and the result was superior to the result reported by Llovet et al (12) (2-y survival, 63%). In addition, the 2-year survival rate for all subgroups in this study except for the Child-Pugh B subgroup and the subgroup with ascites seemed to be superior to Llovet's study (**Table 6**). Our results could

Table 6. Subgroup Analysis of Patients Treated with Transcatheter Arterial Chemoembolization

		n	2-y Survival (%)	*P* Value
Host-related variables				
Age (y)	≥ 70	49	72.7	
	< 70	50	76.9	.86
Sex	Male	67	77.6	
	Female	32	69.0	.36
Hepatitis B surface antigen	Positive	19	66.2	
	Negative	80	77.1	.87
Hepatitis C virus antibody	Positive	52	75.5	
	Negative	47	74.5	.14
Ascites	Present	5	40.0	
	Absent	94	77.1	.03
Performance status	0	86	77.8	
	1–2	13	52.7	.18
Child-Pugh classification	B	19	39.1	
	A	80	83.7	< .0001
Country	Korea	24	67.0	
	Japan	75	77.4	.57
Tumor-related variables				
No. tumors	Single	34	87.3	
	Multiple	65	68.7	.007
Maximum tumor size (cm)	> 3.0	64	66.1	
	≤ 3.0	35	90.6	.02
Tumor stage (UICC 6th edition)	III	57	66.7	
	I or II	42	89.6	.0008
AFP (ng/mL)	< 100	62	82.6	
	≥ 100	35	63.7	.14
PIVKA II (mAU/mL)	≥ 100	49	64.6	
	< 100	37	84.5	.12
Treatment-related variables				
Epirubicin		73	76.7	
Doxorubicin		23	65.4	.50

AFP = alpha fetoprotein; PIVKA II = protein induced by vitamin K absence or antagonist-II; UICC = Union Internationale Contre le Cancer (International Union Against Cancer).

be regarded as reference data for the usefulness of Asian transcatheter arterial chemoembolization for HCC, and the results of Asian transcatheter arterial chemoembolization in this study might be used as a reference arm for the development of new therapies for unresectable HCC in the future. Several reasons for the superior survival of our study compared with Llovet's study (12) may be pointed out. The first is the treatment interval between repeated sessions. In our study, treatment was repeated on demand, whereas in Llovet's study treatment was repeated regularly with a scheduled interval (see earlier). The second reason is the transcatheter arterial chemoembolization techniques. Experience with transcatheter arterial chemoembolization is much greater in Japan and Korea than it is in Western countries, and various microcatheter systems and CT angiography systems were used in our study. The third reason is the selection bias of the enrolled patients. No significant differences in patient characteristics were observed between our study and Llovet's study; however, the patients of our study might have had better backgrounds in hepatic function or tumor condition. It has been speculated that host genetic factors and environmental factors may affect the tumor behavior, which may account for the differences between our study and the Llovet et al (12) study.

This study has several limitations. It is a single-arm, non–randomized controlled study, and it is impossible to clarify the difference of results compared with other studies, although no statistically significant differences were observed in patient characteristics. Also, in this cooperative study of two countries, there might be some differences in the details of transcatheter arterial chemoembolization techniques and medical care to the patients. However, these limitations do not have a major influence on the interpretation of our results because this study was carried out as a prospective clinical study.

Drug-eluting beads have been introduced more recently as a new embolic material for transcatheter arterial chemoembolization (23,24). Combination therapy using transcatheter arterial chemoembolization and molecularly targeted agents, such as sorafenib, has also been reported (25,26). The survival benefit of transcatheter arterial chemoembolization for unresectable HCC has been confirmed by the results of several randomized controlled trials (6,11,12) and meta-analyses (14,15), and transcatheter arterial chemoembolization has been recognized as an effective palliative treatment option for advanced HCC. However, the optimal transcatheter arterial chemoembolization procedures, including combination with anticancer agents and embolic material; optimal timing of the transcatheter arterial chemoembolization procedures; proper patient selection for transcatheter arterial chemoembolization; and survival benefit of the combination of molecularly targeted agents with transcatheter arterial chemoembolization have not yet been fully clarified. To improve the survival of patients with advanced HCC treated with transcatheter arterial chemoembolization, these problems should be resolved by prospective trials.

In conclusion, Asian transcatheter arterial chemoembolization, which has been widely used for many years in Asian countries, showed a favorable efficacy for unresectable HCC in patients without curative treatment options, with reasonable survival data and tolerable adverse events. Our data suggest Asian transcatheter arterial chemoembolization can be regarded as one of the standard treatments in this field, and these study results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

ACKNOWLEDGMENT

This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour, and Welfare of Japan and the National Cancer Center Research and Development Fund.

We thank the members of the Clinical Research Data Center, Clinical Trial Office, for their support with the data management (Ms. Michiyo Tada and Mr. Yushi Nagai) and the members of the study committee for safety and efficacy monitoring (Dr. Nobushige Hayashi, Dr. Yasuhiro Matsumura, and Dr. Kei Muro).

REFERENCES

1. Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T. The Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clinl Oncol 2011; 41:139–147.
2. Ikai I, Arii S, Okazaki M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. The Liver Cancer Study Group of Japan. Hepatol Res 2007; 37:676–691.
3. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version. Dig Dis 2011; 29:339–364.
4. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42:1208–1236.
5. Shin SW. The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. Korean J Radiol 2009; 10: 425–434.
6. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. Gastroenterology 1988; 94:453–456.
7. Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990; 11:181–184.
8. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995; 332: 1294–1296.
9. Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. J Hepatol 1998; 29:129–134.
10. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized controlled trial in a single institution. Hepatology 1998; 27:1578–1583.
11. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35:1164–1171.
12. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359:1734–1739.

13. Doffoël M, Bonnetain F, Bouché O, et al. Multicentre randomised phase III trial comparing tamoxifen alone or with transarterial lipiodol chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Fédération Francophone de Cancérologie Digestive 9402). Eur J Cancer 2008; 44:528–538.
14. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224:47–54.
15. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37:429–442.
16. Kawai S, Tani M, Okamura J, et al. Prospective and randomized trial of lipiodol-transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a comparison of epirubicin and doxorubicin (second cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. Semin Oncol 1997; 24(2 suppl 6):S6–38–S6-45.
17. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 1983; 148:397–401.
18. Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 1989; 170:783–786.
19. Uchida H, Ohishi H, Matsuo N, et al. Transcatheter hepatic segmental arterial embolization using lipiodol mixed with an anticancer drug and Gelfoam particles for hepatocellular carcinoma. Cardiovasc Intervent Radiol 1990; 13:140–145.
20. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30:52–60.
21. Miyayama S, Matsui O, Yamashiro M, et al. Ultraselective transcatheter arterial chemoembolization with a 2-F tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. J Vasc Interv Radiol 2007; 18:365–376.
22. Ji SK, Cho YK, Ahn YS, et al. Multivariate analysis of the predictors of survival for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: focusing on superselective chemoembolization. Korean J Radiol 2008; 9:534–540.
23. Lencioni R, Malagari K, Vogl T, et al. A randomized phase II trial of a drug eluting bead in the treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization [abstract 4598]. J Clin Oncol. 26 2008(suppl):.
24. van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011; 34:368–376.
25. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011; 47:2117–2127.
26. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization with doxorubicin-eluting beads for intermediate-stage hepatocellular carcinoma: phase II, randomized, double-blind SPACE trial [abstract LBA154]. J Clin Oncol 2012; 30(suppl 4).

● 特別寄稿 ●

医師主導の多施設共同臨床試験におけるUMINインターネット症例登録センター（UMIN-INDICE）の活用: 日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）での評価

曽根 美雪[*1] 荒井 保明[*2] 木内 貴弘[*3] 石川ひろの[*3] 青木 則明[*3]
稲葉 吉隆[*4] 吉岡 哲也[*5] 新槇 剛[*6] 小林 健[*7] 松岡 利幸[*8]
穴井 洋[*9] 谷川 昇[*10] 大須賀慶悟[*11] 竹内 義人[*2] 奥坂 拓志[*12]
金澤 右[*13] 松井 修[*14] 遠藤 啓吾[*15]

〔*Jpn J Cancer Chemother* **39**(4): 619-623, *April*, 2012〕

Shared Web-Based Data Center for Multi-Institutional Clinical Trials: Evaluation of UMIN-INDICE (University Hospital Medical Information Network-Internet Data and Information Center for Medical Research) in Clinical Trials of JIVROSG (Japan Interventional Radiology in Oncology Study Group): Miyuki Sone[*1], Yasuaki Arai[*2], Takahiro Kiuchi[*3], Hirono Ishikawa[*3], Noriaki Aoki[*3], Yoshitaka Inaba[*4], Tetsuya Yoshioka[*5], Takeshi Aramaki[*6], Takeshi Kobayashi[*7], Toshiyuki Matsuoka[*8], Hiroshi Anai[*9], Noboru Tanigawa[*10], Keigo Osuga[*11], Yoshito Takeuchi[*2], Takushi Okusaka[*2], Susumu Kanazawa[13], Osamu Matsui[*14] and Keigo Endo[*15] (*[1]*Iwate Medical University*, *[2]*National Cancer Center*, *[3]*The University of Tokyo*, *[4]*Aichi Cancer Center*, *[5]*Narumi Hospital*, *[6]*Shizuoka Cancer Center*, *[7]*Ishikawa Prefectural Central Hospital*, *[8]*Osaka City University*, *[9]*Nara Medical University*, *[10]*Kansai Medical University*, *[11]*Osaka University*, *[12]*Okayama University*, *[13]*Kanazawa University*, *[14]*Gunma University*)

Summary

A patient registration system is mandatory for establishing the scientific credibility of the multi-center clinical trials. The Japan Interventional Radiology in Oncology Study Group (JIVROSG) was organized in 2002 to establish evidence supporting the procedures used in interventional radiology. The Internet Data and Information Center for Medical Research (INDICE), provided by the University Hospital Medical Information Network (UMIN), has been utilized for patient registration in the clinical trials of JIVROSG. In this study, the safety and efficacy of UMIN-INDICE were evaluated. From 2002 to 2010, 18 clinical trials, including one international trial, were conducted. A total of 736 patients were enrolled from 51 institutions. No significant trouble was encountered during this period. A questionnaire survey demonstrated that 90% of participating researchers could use this system without difficulties. UMIN-INDICE may contribute to promoting clinical trials as an infrastructure of multicenter studies. **Key words**: Clinical trials, Internet, Data center, Infrastructure (*Recevied May 31, 2011/Accepted Aug. 3, 2011*)

要旨 前向き研究として行われる臨床試験においては，研究の科学的信頼性を担保するために症例の事前登録が必須である。日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）は，画像ガイド下に経皮的治療を行うinterventional radiology（IVR）のがん治療におけるエビデンスを確立することを目的に2002年に発足した多施設共同臨床試験組織であり，開始当初より大学病院医療情報ネットワーク（University hospital Medical Information Net

[*1] 岩手医科大学・放射線科
[*2] 国立がん研究センター中央病院・放射線診断科
[*3] 東京大学UMINセンター
[*4] 愛知県がんセンター・中央病院放射線診断・IVR部
[*5] 鳴海病院・放射線科
[*6] 静岡県立がんセンター・放射線科
[*7] 石川県立中央病院・放射線科
[*8] 大阪市立大学・放射線科
[*9] 奈良県立医科大学・放射線科
[*10] 関西医科大学・放射線科
[*11] 大阪大学・放射線科
[*12] 国立がん研究センター中央病院・肝胆膵内科
[*13] 岡山大学・放射線科
[*14] 金沢大学・放射線科
[*15] 群馬大学・放射線科

連絡先: 〒020-8505 岩手県盛岡市内丸19-1 岩手医科大学・放射線科
曽根 美雪

work: UMIN）が提供する共同利用型のインターネット・データセンター（Internet Data and Information Center for Medical Research: INDICE）を用いて症例登録を行ってきた。本研究では，UMIN-INDICEの安全性と有用性をJIVROSGにおける運用実績に基づき検証した。2002～2010年の間に行われた27本の臨床試験において，85施設から736症例が登録され，研究遂行に支障を来す運用トラブルやセキュリティに関連するトラブルはみられなかった。また，研究者を対象に行ったアンケート調査では，90%という高い頻度で「UMIN-INDICEを用いた症例登録は容易ないしは比較的容易」との回答であった。UMIN-INDICEは多施設共同臨床試験における症例登録システムとして安全性が高く，かつ研究者にとって有用であり，臨床研究のインフラストラクチャーとしてエビデンス生成に寄与すると考えられた。

はじめに

臨床試験におけるインフラストラクチャーは，多施設共同臨床研究を遂行する上で最も重要な要件の一つである。しかし，研究者主導の場合，データセンターなどのインフラストラクチャー構築は容易ではなく，臨床研究推進の障壁の一つとなっている。

日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）は，画像ガイド下に経皮的治療を行うinterventional radiology（IVR）のがん治療におけるエビデンスを確立することを目的として，2002年に発足した[1]。JIVROSGでは活動開始当初より，研究遂行のためには昼夜を問わず症例登録が可能なシステムを用いることが必要と考え，大学病院医療情報ネットワーク（University Hospital Medical Information Network: UMIN）が提供するインターネット・データセンターINDICE（Internet Data and Information Center for Medical Research）を利用してきた。

インターネットを利用した症例登録システムやデータセンターの有用性，利便性は過去にも報告されているが，一つのプロジェクトのために独自に構築したものが多い[2-4]。一方，UMIN-INDICEは共同利用型のデータセンターであり，多数の研究に実績をもつ信頼性の高いシステムを安価に利用することが可能である[5]。本研究の目的は，複数の研究を随時施行する多施設共同研究組織において，共同利用型のインターネット・データセンターを利用することの安全性ならびに有用性を評価することである。

Ⅰ．対象・方法

1．JIVROSGの概要

JIVROSGは公的競争的研究費を経済的基盤として，研究者主導による臨床試験を行っている多施設共同研究組織である。2011年1月の時点で85施設が参加し，これまでに27試験を実施し，海外施設との共同試験も行った。主要構成メンバーはIVRを専門とする放射線科医であるが，これに若干名の内科，外科，整形外科，産婦人科医なども含まれている。

2．UMIN-INDICEの概要

UMIN-INDICEは研究者主導の臨床試験におけるインフラストラクチャーを提供している。症例登録と割り付け，データ収集，ホームページ・サービス，メーリングシステムからなり，2000年に運用が開始された。症例登録システムは，UMINの基本システムを基に研究プロトコールごとにカスタマイズする形で開発されるため，研究グループがサーバなどのハードやソフトウエアを購入する必要はない。システムはパスワードで保護されたウェブサイト上に構築され，サーバの保守作業の時以外は24時間365日，登録が可能である。IDはUMINの他のコンテンツと共通のものが使用され，パスワードは共通のものに加えて研究グループ固有のものが発行される[6]。ソフトウエアの開発にはおおよそ2～6か月を要し，費用は当該研究依頼者がUMINに支払う形となっている。

UMIN-INDICEのサーバの管理・保守は専門の技術者により無休で運営されており，物理的侵入対策としてセンター入室者の指紋による個人認証，カメラによる入退室監視を施行している。また，ネットワーク侵入対策として，ファイアウォールの二重設置，侵入検知システム，通信の暗号化を行い，さらにデータは毎日バックアップされ遠隔保存も行われている。

3．JIVROSGでの臨床試験運用の実際

研究に参加する担当医は，インターネットを介してJIVROSGの研究者のみがアクセスできる研究者限定ページ[6]にログインし，該当する試験の症例登録ページを選択する（図1）。必要項目を記入すると症例選択規準がシステムにより確認され，登録番号およびランダム化比較試験の割り付けが決定される（図2，3）。割り付け・登録が完了すると研究グループ担当者へ登録番号と施設のみを記載したE-mailが送付される。インターネットを介して行うのは症例登録のみであり，これ以降のデータ収集はcase report form（CRF）をJIVROSGのデータセンターにFAXで送信して行う。症例登録に関する質問やトラブルの相談がある場合には，JIVROSGのUMIN担当医師に連絡し，必要に応じてUMINにも連絡をとり対処する。

PierTea Press of Integrated Electronic Repository

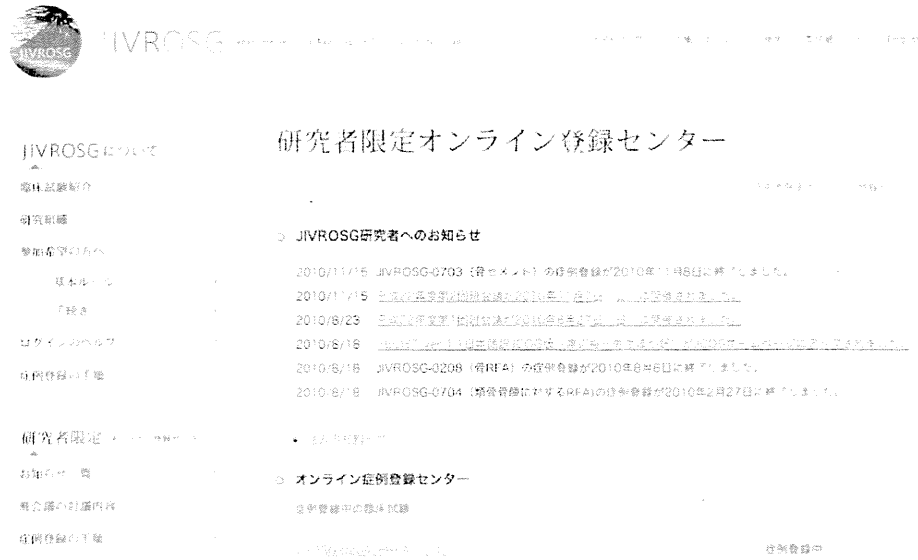

図 1　JIVROSGの研究者限定ページ（http://jivrosg.umin.jp/）

◇適格条件チェックリスト

1	総胆管を主座とする根治術不能悪性胆道閉塞を有す症例	● Yes ○ No
2	チューブによる内外瘻化が完了している症例	● Yes ○ No
3	P.S.（ECOG）：0，1，2	● Yes ○ No
4	血清ビリルビン値 5．0 mg/dl 以下	● Yes ○ No
5	主要臓器（骨髄、心、肝、肺、腎など）機能が保持されている症例 1) 白血球数 ＞＝ 3，000 2) 血小板数 ＞＝ 50，000 3) プロトロンビン時間 ＞＝ 50％ 4) 血清 Cr ＜＝ 2．0 mg/dl 5) Normal EKG（ただし、臨床的に問題とならない不整脈、虚血性変化は適格）	1) ● Yes ○ No 2) ● Yes ○ No 3) ● Yes ○ No 4) ● Yes ○ No 5) ● Yes ○ No
6	4週間以上の生存が見込める	● Yes ○ No
7	患者本人から文書による同意が得られている	● Yes ○ No

◇除外条件チェックリスト

1	胆管空腸吻合術後再発、肝細胞癌、十二指腸癌、癌性腹膜炎、粘液産生腫瘍症例ではない	● Yes ○ No
2	ファーター乳頭部より肛門側の腸管に通過障害がない	● Yes ○ No

図 2　UMIN-INDICEの症例登録画面

4．運用実績の検討

UMIN-INDICEを用いたJIVROSG臨床試験における登録の症例数と，登録に伴うトラブルの有無および種類について検討した。

5．システムの安全性と安定性の検討

症例登録システムのトラブルや個人情報漏洩の有無について検討した。

6．ユーザの利便性の検討

研究者に対して，システムの利便性および満足度についてのアンケート調査を行った。対象は，JIVROSG開始当初より参加し，症例登録経験をもつ研究者41名である。質問票を郵送し，回答をFAXにて回収した。質問票は，回答者の特徴，JIVROSGにおける症例登録の経験，利便性（5段階評価），他の研究への参加経験がある場合はそれとの比較（5段階評価）で構成した。

Ⅱ．結　果

1．運用実績

2003年2月～2010年7月までに27の臨床研究がJIVROSGにて施行され，このうち18試験でUMIN-INDICEを用いた症例登録が行われた。UMIN-INDICEを用いなかったのは，後ろ向き研究と別の症例登録シス

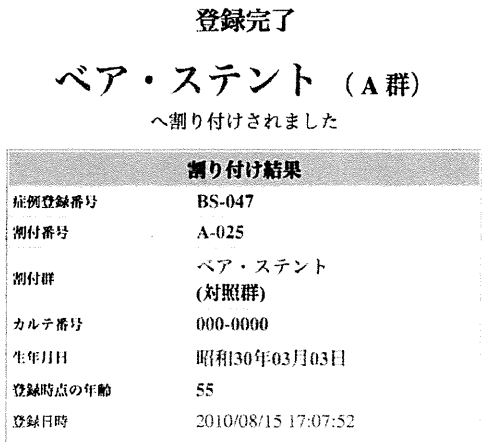

図 3 UMIN-INDICE の登録・割り付け終了画面（テスト登録用）

表 2 UMIN-INDICE における登録の難易度（n=30）

	人数（%）
登録回数	
1	3 (10)
2～10	21 (70)
11～20	3 (10)
20<	3 (10)
症例登録システムへのログオン	
容易	11 (36)
比較的容易	15 (50)
どちらでもない	2 (7)
比較的困難	2 (7)
困難	0 (0)
症例登録	
容易	13 (43)
比較的容易	14 (47)
どちらでもない	2 (7)
比較的困難	1 (3)
困難	0 (0)

テムが使用された前向き研究である。51 施設（うち海外 9 施設）から総数 736 症例の登録が行われた。

登録に伴うトラブルとして，研究者のパスワード紛失または未取得による事務局での代理登録が 5 回，第 I 相試験での登録一時停止の際の周知不備が 1 回みられた。これらのトラブルは電話または電子メールで 2 日以内に対処され，治療の遅延や症例登録の中止はみられなかった。

2．システムの安全性と安定性

UMIN-INDICE のシステムに起因する登録不能やデータ消失などのトラブルはみられなかった。ランダム化比較試験において，センターでのランダム化に関連するトラブルはみられなかった。また，個人情報漏洩が危惧されるトラブルはみられなかった。

表 1 アンケート回答者の背景（n=30）

特徴	人数（%）
性別	
男性	28 (93)
女性	2 (7)
年齢（歳）	
20～29	0 (0)
30～39	14 (47)
40～49	13 (43)
50～59	3 (10)
パソコン使用年数	
<1	0 (0)
−5	2 (7)
−10	5 (16)
10<	23 (77)
インターネット使用年数	
<1	0 (0)
−5	4 (13)
−10	14 (47)
10<	12 (40)

表 3 UMIN-INDICE の利便性についての満足度（n=30）

満足度	人数（%）
満足	15 (50)
やや満足	12 (40)
どちらでもない	3 (10)
やや不満足	0 (0)
不満足	0 (0)

3．ユーザの利便性に関するアンケート結果

該当する 41 名のうち，30 名（73%）から回答が得られた。93%が男性であり，30 歳台，40 歳台が 90%を占めた。パソコン使用歴は 10 年以上が 93%，インターネット使用歴は 10 年以上が 87%であった（表 1）。

登録サイトへのログオンについては，「容易」または「比較的容易」の回答が 86%，症例登録については，「容易」または「比較的容易」の回答が 90%であった（表 2）。UMIN-INDICE の利便性については，「満足」ないし「やや満足」が 90%であった（表 3）。他の共同研究に参加経験のある 17 名によると，他の研究での症例登録方法で最も多いのは FAX（82%）であった。17 名中 15 名（88%）が，「他の方法よりも UMIN-INDICE のほうがよい」と回答した。

Ⅲ．考　察

エビデンスを創るために前向き研究として行われる臨床試験において，症例の事前登録は研究の科学的信頼性を担保するために必須である[5,7]。複数の試験を行う多施設共同研究グループにおいては，グループ内に設置した

データセンターの業務の一つとして患者登録システムを運営することが多く，かつてはFAXや電話がその手段であった。近年，インターネットの普及に伴い，インターネットを用いた症例登録が増加している[2-4]。症例登録にインターネットを用いることの利点として，症例適格性のチェックと症例番号の発行が即時完了できること，24時間いつでも症例登録が行えることがあげられる。特に時間帯の制限がないことは，多忙な日常診療と並行して行われる臨床研究において大きな利点である。われわれの検討では，700例を超える症例すべてで症例登録が問題なく完遂されており，UMIN-INDICEの実行可能性ならびに有効性は極めて高いと考えられた。

研究者主導でインターネットを用いた研究基盤を構築するには，自前のサーバを立ち上げてデータセンターを構築する方法と，企業に依頼して構築する方法，公的データセンターを利用する方法がある。自前のシステム構築には，ソフトウエアの開発とシステム維持に手間やコストがかかり，研究資金や人的資源が限定される研究者主導のグループでは実現困難なことが多い。企業に依頼する場合は，研究グループの手間は節減されるが，ソフトウエアの開発に要する時間は大幅に減少するとは限らず，また，一般に開発および維持のコストは高額であり，研究資金が恒常的に確保されないと使用は難しい。国内には国営の公的データセンターは存在しないが，UMIN-INDICEはこれに近い位置付けであり，データセンター用の情報システムおよびその運用管理を種々の研究グループが共同利用する形態をとっている[5]。この結果，研究グループが自前でサーバを用意する必要はなく，運用コストは大幅に削減される。UMIN-INDICEは2000～2010年に159のプロジェクトで利用され，登録された症例の合計は107万例を超えており[8]，このような運用管理の集中化が結果として信頼性とセキュリティならびにユーザの利便性の向上につながっている[5]。われわれの経験においても，UMIN-INDICEの利便性と信頼性が再確認された。一方，UMIN-INDICEは，データセンター機能のすべてを提供しているわけではない。データセンターに必要な人材のうち情報処理専門家，システムエンジニア，プログラマー，オペレーターを擁しているが，研究計画の作成やデータの品質管理にかかわる生物統計学者やデータマネージャーは含まれていない。このため，生物統計学者およびデータマネージャーは，研究グループごとに依頼する必要がある。

UMIN-INDICEの利便性については，われわれの検討においては高いと考えられた。理由として，同じシステムを用いることにより操作法の習得が1回で済むことと，パスワードが共通で管理が容易であることがあげられる。したがって，複数の臨床試験を行うJIVROSGのような研究グループにおいては，特に有用性が高いと考えられる。ユーザの利便性を考えるに当たっては，インターネット環境が近年急速に整備されたことも重要な要素である。マイナーなトラブルとしてパスワードの紛失があったが，研究グループ内での連絡先および対処法を明確にしておくことで迅速に対応でき，登録不能のトラブルはみられなかった。

本研究の限界として，他の症例登録法との直接比較を行っていない点があげられる。しかし，JIVROSGでは他の多施設共同研究への参加経験がない研究者が多数を占めており，そのような初心者にとっても使用しやすいシステムであることが示された点は意味があると考えられる。

結論として，複数の臨床研究を行う多施設共同研究組織であるJIVROSGにおいて，共同利用型のUMIN-INDICEは症例登録システムとして有用かつ安全性が高く，臨床研究のインフラストラクチャーとしてエビデンス生成に寄与すると考えられた。

文　献

1) 荒井保明: がん治療における多施設共同研究—JIVROSG (Japan Interventional Radiology in Oncology Study Group)—. *IVR* 会誌 **20**(1): 4-7, 2005.
2) Lallas CD, Preminger GM, Pearle MS, *et al*: Internet based multi-institutional clinical research: a convenient and secure option. *J Urol* **171**(15): 1880-1885, 2004.
3) Winger M, Kincaid H, Lin P, *et al*: A web-based system for managing and co-ordinating multiple multisite studies. *Clinical Trials* **2**(1): 42-49, 2005.
4) Marshall WW and Haley RW: Use of a secure internet web site for collaborative medical research. *JAMA* **284**(14): 1843-1849, 2000.
5) 木内貴弘: 医療・医学サポートの最前線 (2) インターネットによる臨床・疫学研究の運用. 日産婦会誌 **56**(2): 246, 2004.
6) JIVROSG web site: http://jivrosg.umin.jp/
7) 福田治彦: 肺癌 診断・治療の最前線 治療の総論 研究者主導臨床試験のインフラストラクチャー. 癌の臨床 **49**(10): 1199-1210, 2003.
8) UMIN-INDICE web site: http://indice.umin.ac.jp/

CLINICAL STUDY

Safety and Efficacy of Primary Metallic Biliary Stent Placement with Tract Embolization in Patients with Massive Ascites: A Retrospective Analysis of 16 Patients

Keitaro Sofue, MD, Yasuaki Arai, MD, Yoshito Takeuchi, MD, Hiroyasu Fujiwara, MD, Hiroyuki Tokue, MD, and Kazuro Sugimura, MD, PhD

ABSTRACT

Purpose: To evaluate the safety and efficacy of primary metallic biliary stent placement with tract embolization in patients with massive ascites.

Materials and Methods: Sixteen patients with malignant biliary obstruction and massive ascites (age range, 44–79 y; median age, 59 y) were treated with primary percutaneous stent placement with tract embolization. These patients were unsuitable candidates for endoscopic intervention. Etiologies of biliary obstruction were gastric cancer with hilar nodal metastases (n = 9), pancreatic carcinoma (n = 5), cholangiocarcinoma (n = 1), and gallbladder carcinoma (n = 1). Eight patients had nonhilar lesions and the remaining eight had hilar lesions. Percutaneous accesses to the biliary system and stent placements were performed in a one-step procedure, and catheters were removed with tract embolization with metallic coils.

Results: Stent placement and tract embolization were successful in all patients, without external drainage catheters left in place. Significant reduction of serum bilirubin level was observed in 14 patients (87.5%). No bile peritonitis or intraperitoneal hemorrhage occurred. Major complications included postprocedural cholangitis (12.5%), bloody bowel discharge (6.2%), and right pleural effusion (25.0%). One patient who died 19 days after intervention was deemed to represent a procedure-related mortality. During the survival period (range, 19–175 d; median, 66 d), stent occlusion was noted in two patients at 6 and 159 days after the procedure. Primary stent patency was achieved in 14 patients (87.5%).

Conclusions: Primary biliary stent placement with tract embolization is technically safe and offers an effective palliative treatment option for patients with malignant biliary obstruction and massive ascites when endoscopic intervention is not possible.

ABBREVIATION

PTBD = percutaneous transhepatic biliary drainage

Most patients with malignant biliary obstruction have advanced-stage cancers with dismal prognoses (1). Percutaneous transhepatic biliary drainage (PTBD) and metallic stent placement are established methods to manage malignant biliary obstruction (2–4) when endoscopic intervention is not possible.

The disadvantage of PTBD is its association with hemorrhage, bile leakage, and catheter dislodgment, with reported incidences of less than 5% each (5–8). Especially in patients with massive ascites, PTBD is thought to be relatively contraindicated because of the high risk of intraabdominal bleeding and peritonitis caused by bile leakage, which is believed to be secondary to the presence of a tube passing through ascites (9). As a result, selection of the treatment approach can be difficult in patients with malignant obstructive jaundice and massive ascites who are unsuitable candidates for endoscopic intervention.

Some studies have demonstrated that transhepatic tract

From the Division of Diagnostic Radiology (K. Sofue, Y.A., Y.T., H.F., H.T.), National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; and Department of Radiology (K. Sofue, K. Sugimura), Kobe University Graduate School of Medicine, Kobe, Japan. Received September 25, 2011; final revision received January 15, 2012; accepted January 20, 2012. **Address correspondence to** K. Sofu; E-mail: ksofue@ncc.go.jp

None of the authors have identified a conflict of interest.

© SIR, 2012

J Vasc Interv Radiol 2012; 23:521–527

DOI: 10.1016/j.jvir.2012.01.073

Table 1. Disease and Treatment Details of Patients Undergoing One-Step Biliary Stent Placement with Transhepatic Tract Embolization

Pt. No.	Age (y)/ Sex	Primary Tumor	Biliary Obstruction	Degree of Biliary Dilation	Puncture Site/No.*	Stents	Paracentesis
1	57/ F	PC	Nonhilar	Moderate	Right/1	2	No
2	59/ M	PC	Nonhilar	Moderate	Right/1	1	Yes
3	72/ M	PC	Nonhilar	Severe	Right/1	1	Yes
4	74/ F	PC	Nonhilar	Mild	Left/1	2	No
5	57/ M	GC	Nonhilar	Moderate	Right/1	1	No
6	65/ M	GC	Nonhilar	Mild	Right/1	1	Yes
7	74/ F	GC	Nonhilar	Moderate	Right/1	1	Yes
8	50/ M	GBC	Nonhilar	Moderate	Right/1	1	No
9	60/ M	GC	Hilar (Bismuth I)	Severe	Left/1	2	No
10	66/ M	GC	Hilar (Bismuth I)	Moderate	Left/1	1	No
11	58/ M	GC	Hilar (Bismuth II)	Moderate	Left/1	4	No
12	52/ M	GC	Hilar (Bismuth III)	Moderate	Right/1	1	Yes
13	68/ F	GC	Hilar (Bismuth III)	Moderate	Right/2	3	No
14	44/ M	PC	Hilar (Bismuth III)	Moderate	Right/2	3	No
15	79/ M	CC	Hilar (Bismuth III)	Severe	Right/1	1	No
16	56/ M	GC	Hilar (Bismuth IV)	Moderate	Right/3	3	No

Note.— CC = cholangiocarcinoma, GBC = gallbladder carcinoma, GC = gastric cancer, PC = pancreatic carcinoma.
* Puncture number refers to the number of accesses into the biliary system.

embolization can prevent the complications associated with percutaneous intervention (10–15). Stent placement in a one-step procedure could immediately resolve biliary obstruction, shortening the duration of placement of the temporary drainage catheter (4,16–18). In addition, percutaneous biliary metallic stent placement with tract embolization performed in a single session might be a favorable method to manage biliary obstruction in patients with massive ascites who are not suitable candidates for endoscopic intervention or in whom endoscopic treatment has failed.

The purpose of the present study was to evaluate the safety and efficacy of primary metallic biliary stent placement with tract embolization in patients with massive ascites.

MATERIALS AND METHODS

Patient Population

This retrospective study was conducted in accordance with the principles of the amended Declaration of Helsinki, and with the approval of the institutional review board. Between July 2005 and June 2010, 16 patients with malignant biliary obstruction and massive ascites, in whom conventional endoscopic drainage failed or could not be performed because of altered anatomy after surgery, were treated with primary percutaneous expandable metallic stent placement. The patient population included 12 men and four women with a mean age of 62 years (median, 59 y; range, 44–79 y; **Table 1**).

Etiologies of malignant biliary obstruction were gastric cancer with nodal metastases (n = 9), pancreatic carcinoma (n = 5), cholangiocarcinoma (n = 1), and gallbladder carcinoma (n = 1). The diagnosis of biliary obstruction was confirmed by computed tomography (CT) and/or ultrasonography (US; **Fig 1a**). Eight patients had lesions involving the middle and distal common bile duct, and eight had proximal bile duct (ie, hilar) lesions. The latter were classified according to Bismuth classification as follows: type I, n = 2; type II, n = 1; type III, n = 4; and type IV, n = 1 (**Table 1**). All 16 patients had massive ascites caused by peritoneal dissemination and/or advanced disease, and five patients had liver metastases. Massive ascites was defined as a large amount of fluid in the paracolic regions and around the liver at the proposed puncture site, and resulted in a tense abdomen determined with imaging and physical examination (9,19). Cytologic examination of the ascites was performed in 12 of 16 patients, and a malignant cytologic result was revealed in nine patients.

In 11 of the 16 patients, endoscopic intervention was attempted, but resulted in failure because of gastroduodenal invasion by the primary disease (n = 8) or rigidity of the papilla of Vater (n = 3). In the remaining five patients, the endoscopic approach was not attempted because of previous surgery with Roux-en-Y conversion.

Procedures

Written informed consent was obtained from all patients before the procedures. All procedures were performed under local anesthesia with 1% lidocaine and conscious sedation with midazolam and pentazocine or fentanyl. Intravenous broad-spectrum antibiotic prophylaxis was routinely administered 6 hours before the procedure in all patients

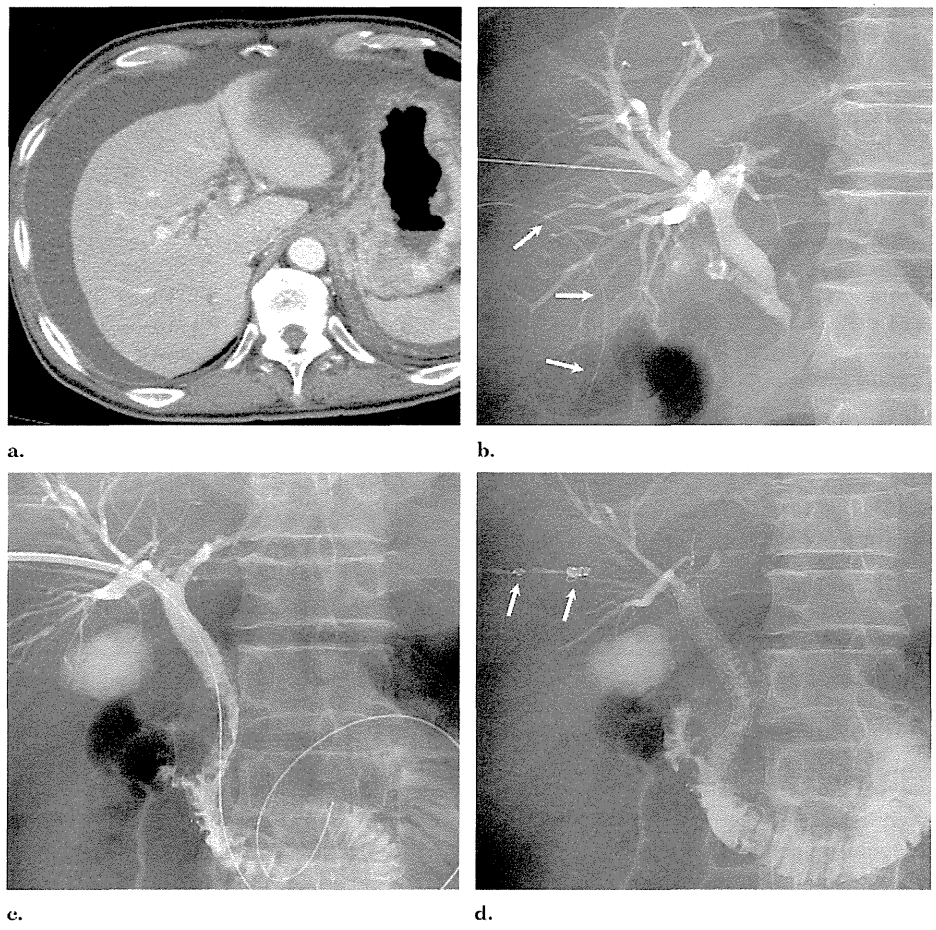

Figure 1. Gastric cancer with nodal metastasis in a 65-year-old man (patient 6; Table 1). **(a)** Contrast-enhanced CT before stent placement shows dilated intrahepatic biliary ducts and massive ascites. **(b)** Percutaneous transhepatic cholangiography reveals tight stricture at the distal common bile duct. Note that a 6-F tube was placed around the liver surface (arrows). **(c)** Cholangiography performed after stent placement shows good expansion of the stent and good flow of contrast material through the stent. **(d)** Embolization of the transhepatic tract was performed with metallic coils (arrows).

and continued for as long as 5 days after the procedure. Percutaneous puncture, insertion of the catheter into the intrahepatic biliary duct, and stent placement were performed in a single session without leaving an external drainage catheter. No patients had suspected cholangitis before the procedure, as we performed stent placement only for patients without combined infection. In five of the 16 patients, 6-F catheters were placed around the liver surface to monitor for intraperitoneal hemorrhage during the procedure before PTBD.

The appropriate intrahepatic bile duct was punctured with a 21-gauze needle (Top, Tokyo, Japan) under US guidance, and percutaneous transhepatic cholangiography was then performed to confirm obstruction of the bile duct (**Fig 1b**). After placement of a 6.5-F catheter (Seeking catheter; Hanako, Saitama, Japan) and a 0.035-inch angled hydrophilic guide wire (Radifocus Guide Wire M; Terumo, Tokyo, Japan) past the obstruction and into the duodenum, the overall length of the obstruction was confirmed with injection of contrast material. The guide wire was exchanged for a 0.035-inch guide wire (Amplatz Extra-Stiff Guide Wire; William Cook Europe, Bjaeverskov, Denmark), an introducer sheath (Create Medic, Yokohama, Japan) was inserted to increase the diameter of the tract, and the expandable metallic stent was then placed. Uncovered stents were placed through 7-F sheaths, and covered stents were placed through 10-F sheaths. Covered stents were mainly used in patients with aggressive pancreatic cancer based on operator preference. Seven patients who had common bile duct or Bismuth type I obstructions were each treated with a single stent. There were three patients in whom it was difficult to span the distance with a single stent (**Table 1**). In the six patients with Bismuth type II, III, and IV obstructions, attempts were made to minimize the number of punctures to prevent bile leakage or intraperitoneal hemorrhage as much as possible and to place the minimum number of stents required to drain at least 50% of the liver volume (3). The stents placed in the common bile duct extended 1 cm beyond the papilla of Vater in all patients. All placed stents were fully expanded with predilation (n =