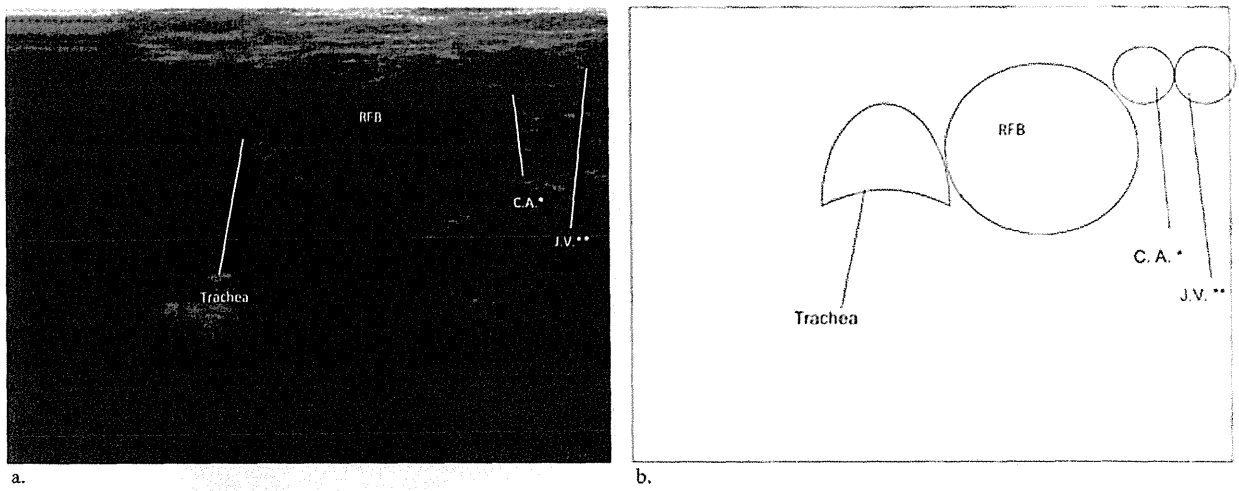


a. b.

Figure 2. US depiction **(a)** and schema **(b)** of RFB placed at cervical esophagus and inflated with diluted contrast medium. CA = carotid artery, JV = jugular vein.

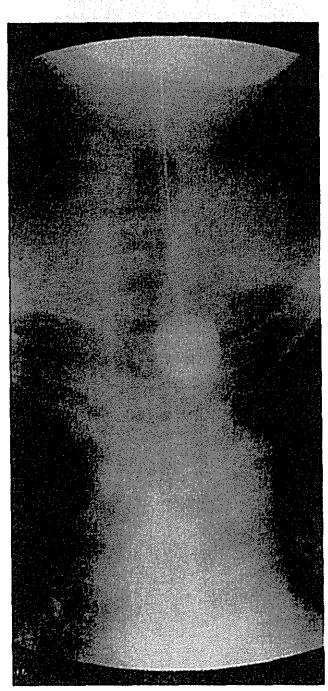


Figure 3. Radiograph of RFB placed at cervical esophagus.

Outcome Evaluation

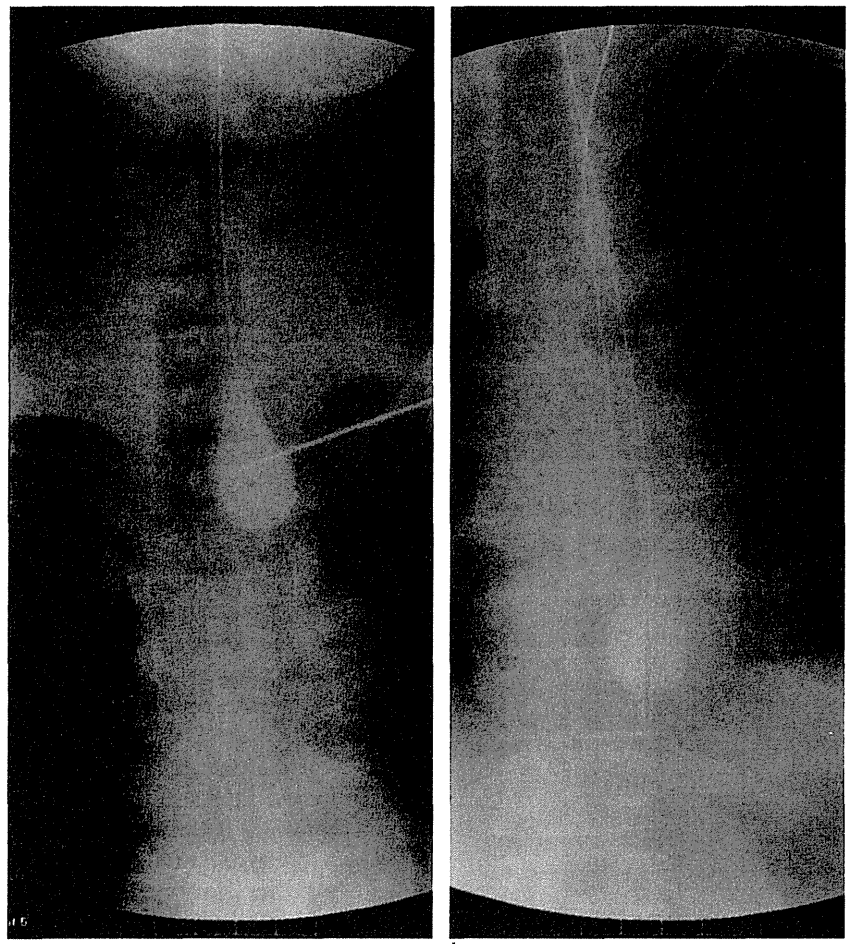
Because the median survival time for patients with terminal malignant bowel obstruction was reported to be 17 days (4), the evaluation observation period was set to 4 weeks. Subjective symptoms were monitored after 1, 2, 3, and 4 weeks and classified into the following five levels: (i) "much more comfortable than NGT"; (ii) "slightly more comfortable than NGT"; (iii) "same level of discomfort as NGT"; (iv) "slightly more uncomfortable than NGT"; and (v) "much more uncomfortable than NGT." When subjective symptoms remained at level 1 for two consecutive weeks or longer, the procedure was considered markedly effective, and when subjective symptoms remained at level 1 or 2 for two consecutive weeks or longer, the procedure was simply considered effective. The procedure was considered ineffective in all other cases. The efficacy rate was calculated as the ratio of markedly effective cases and effective cases to all those enrolled.

The safety of PTEG was evaluated by using the National Cancer Institute Common Toxicity Criteria, version 2.0. Because this study was not conducted with the aim of evaluating the functions of the indwelling tube, complications were not evaluated if the symptoms were improved by exchanging the indwelling tube.

Procedure time was calculated as the length of time from the start of nasal cavity and pharynx anesthesia to fixation of the tube to the skin. Procedure completion was defined as completed insertion of the tube from the cervical esophagus to the lower esophagus or more distal portion (anal side). The technical success rate was calculated as the ratio of cases in which the procedure was completed among all those enrolled.

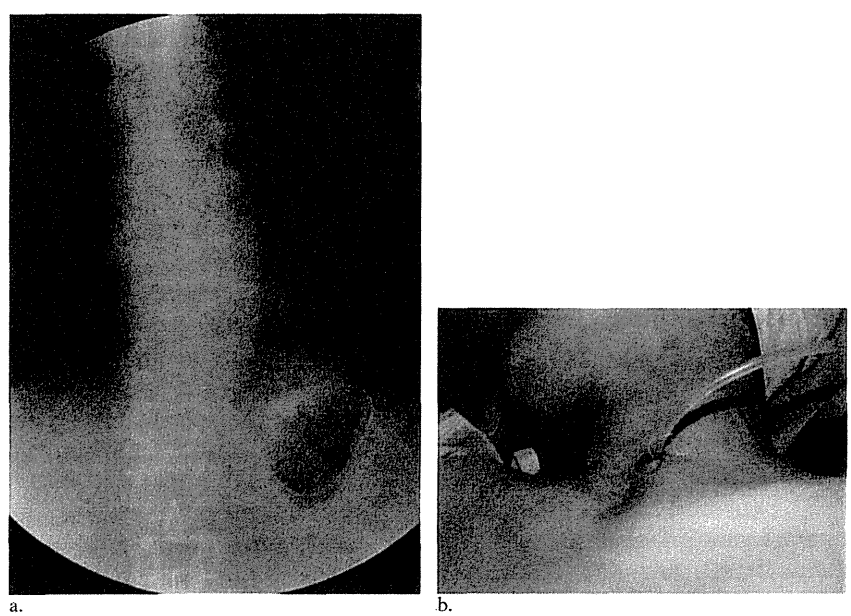
Statistical Analysis

To identify the number of cases required to evaluate serious adverse events and the efficacy rate, one-sample binomial *t* tests were performed (null hypothesis H0, $P = \pi 0$; alternative hypothesis H1, $P = \pi$). For adverse events with $\pi 0 = 0.10$ and $\pi = 0.30$ (where the predicted value for complications was 10%, and $\geq$ 30% was considered unacceptable), values of $\alpha = 0.05$ and $\beta = 0.20$ yielded a sample size of 30. For the efficacy rate with $\pi 0 = 0.50$ and $\pi = 0.80$, values of $\alpha = 0.05$ and $\beta = 0.20$ yielded a sample size of 19. As the required sample size for the present study, it was considered necessary to enroll 30 cases to evaluate serious adverse events, and this number was increased by 10% in anticipation of protocol deviations. Therefore, enrollment of 33 cases was planned.



a. b.

Figure 4. J-type guide wire is inserted into the balloon through the outer tube of the puncture needle **(a)** and guided to the lower esophagus along with the RFB catheter **(b)**.



a. b.

Figure 5. **(a, b)** The indwelling tube is inserted through the sheath and fixed to the skin surface. (Available in color online at *www.jvir.org.*)

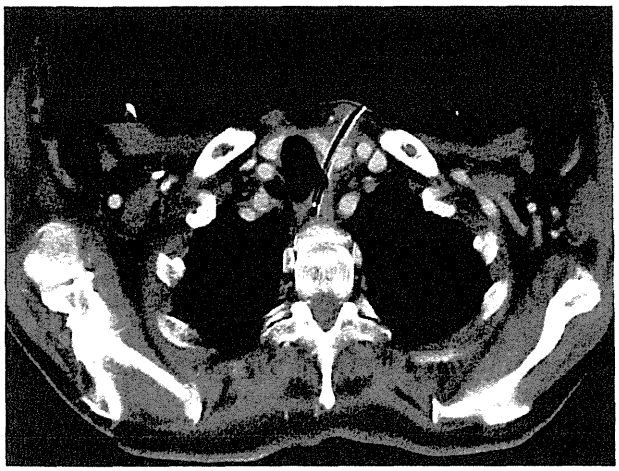


Figure 6. In the case of tracheoesophageal fistula, the tube is inserted into the esophagus through the trachea.

RESULTS

Patient Characteristics

From February 2003 to December 2005, 33 patients from five institutions (21 women, 12 men; median age, 61 y; range, 31–74 y; **Table**) were enrolled in the study. All cases fulfilled the inclusion criteria, and none met any exclusion criteria. The primary cancer sites consisted of the stomach in 18 cases, the colon and rectum in five cases, the pancreas in three cases, the ovaries in two cases, and others in five cases. Peritoneal dissemination was present in 26 cases. The median duration of NGT insertion until study registration was 13 days. The median survival time was 73 days (range, 6–340 d).

Treatment and Safety

The procedure was a success in all 33 cases. Median procedure time was 28.5 minutes (range, 6–60 min). The indwelling tube was a gastric tube in 30 cases (kit accessory, n = 4; 12-F gastric tube, n = 15; 14-F gastric tube, n = 10; 15-F gastric tube, n = 1) and an ileus tube in three cases. Nasal bleeding occurred in one case during the placement procedure and improved after conservative management. No other severe complications were observed during the procedure.

A tracheoesophageal fistula resulting in grade 2 aspiration pneumonia was observed in one case 29 days after the procedure. When changing the tube in this case, exchange of respiratory air and synchronizing air was observed from a fistula. Contrast enhancement of the fistula identified a tracheoesophageal fistula. Confirmatory computed tomography revealed that the indwelling tube passed through the trachea at one point (**Fig 6**). Low-grade fever was observed in this case before the procedure. Because the symptoms did not change during the period after completion of the PTEG procedure until the appearance of the tracheoesophageal fistula, and the patient was not feeding orally, the patient was treated conservatively with antibiotics and other treatment without removing the tube. No other serious hematologic or nonhematologic complications were observed.

Within 30 days of the PTEG procedure, death occurred in a total of seven cases; however, these deaths were confirmed by the safety and efficacy committee to have resulted from deterioration of the preexisting medical condition.

Table. Characteristics of the 33 Patients Included in the Study

Characteristic	Value
Sex	
Male	12
Female	21
Age (y)	
Median	61
Range	31–74
ECOG PS	
0	0
1	10
2	13
3	10
4	0
Primary cancer site	
Stomach	18
Colon	5
Pancreas	3
Ovary	2
Other	5
Carcinomatous peritonitis	
Yes	26
No	7
Previous tube placement	
Yes	100
No	0
Previous NGT placement time (d)	
Median	13
Range	2–18
Follow-up duration (d)	
Median	73
Range	6–340

ECOG = Eastern Cooperative Oncology Group, NGT = nasogastric tube, PS = performance status.

Efficacy

Evaluation of efficacy during the 4 weeks specified as the evaluation observation period identified 20 markedly effective cases, 10 effective cases, and three ineffective cases, for an efficacy rate of 91% (30 of 33 cases). Of the three ineffective cases, two cases could not be properly evaluated (ie, results collected for 2 wk) as a result of early death from aggravation of primary disease, and one patient could not be asked about subjective symptoms because of deterioration of general status. Each of these patients had given an evaluation of "more comfortable than NGT" in their first evaluation. None of the

33 patients gave an evaluation of "more uncomfortable than an NGT."

As of October 2011, 31 patients had died, all with their PTEG intact. Two patients were lost to follow-up; their catheters had not been removed, and they had not experienced known complications during their recorded follow-up.

DISCUSSION

The first method for placing a tube into the cervical esophagus was reported by Chen et al in 1983 (7), and Nakano et al (8) performed the first percutaneous cervical esophagus puncture and tube insertion in 1993. The method was later established as PTEG by Oishi et al (6) in 1994. This was developed to be one treatment option for the patient who needs enteral tube insertion or bowel decompression. Therefore, the main indication for PTEG is similar to that for percutaneous gastrostomy, but it is easy to create for patients with prior gastrectomy and/or malignant ascites (6,9,10) because the PTEG is then a "percutaneous esophagostomy." Since PTEG was developed, there has been no prospective evaluation performed to our knowledge. Therefore, the present study was conducted to evaluate PTEG prospectively (9).

In the present study, switching from NGT to PTEG improved subjective symptoms in 30 of 33 cases (91%). The remaining three patients who could not be evaluated also responded that PTEG was more comfortable than NGT during the period in which they could be asked about subjective symptoms, suggesting that PTEG was not necessarily ineffective in these cases. Of the 31 cases evaluated as effective, 20 were evaluated as markedly effective, demonstrating that PTEG contributes strongly to patient satisfaction (11).

Oishi et al (9) described the results of PTEG creation as 100% technical success without any major complications (minor complications, such as tube obstructions, stomal leakage, wound infection, unrecovered tube migration, and minor bleeding, occurred in 23.5% of their cases), and the time for PTEG creation was approximately 15 minutes (from RFB insertion to tube placement) (9). The present study generally used PTEG kits for the procedure, which resulted in the achievement of a 100% technical success rate. Despite the multicenter nature of the study and the short history of the procedure, no failures were encountered, and the median procedure duration was slightly less than 30 minutes, indicating the ease of the procedure. Moreover, PTEG can be used for a wide variety of cases. Because it is a gastric tube that accesses the bowels via the cervical esophagus, the procedure can also be performed for patients who have undergone gastrectomy or for patients with massive ascites or carcinomatous peritonitis, without worrying about tumor infiltration from the puncture hole or puncture route into the abdominal cavity (6,9,10,12,13). In the present study, 26 cases had peritoneal dissemination, and PTEG may be particularly well suited to such patients.

In terms of serious complications, one patient was observed to have aspiration pneumonia as a result of a tracheoesophageal fistula. No previous studies have reported tracheoesophageal fistula (6,9,10,12,13). In the PTEG procedure, the esophagus that is usually positioned behind the trachea is forced by RFB expansion to float upward to sit next to the trachea, enabling puncture only into the esophagus. In patients with a fragile trachea, it remains possible that the membranous part of the trachea may become transformed with RFB expansion as the esophagus floats upward. Alternatively, insufficient RFB expansion could result in mistaken puncture of surrounding structures.

One possibility for the case with tracheoesophageal fistula is that the membranous part of the trachea rose upward together with the esophagus so that the trachea became inserted into the puncture route, resulting in a transtracheal puncture that caused the fistula. Another possibility is that insufficient expansion resulted in inadequate displacement of the trachea, so that the puncture was made through the trachea. Transformation of the membranous part of the trachea from the RFB and the resulting erroneous puncture would not be easily visible using US alone. US can be used to make the puncture after confirming that the puncture site is a sufficient distance from the trachea to preclude erroneous puncturing of cervical veins or arteries. This could then be followed by x-ray fluoroscopy to confirm the path of the guide wire and dilator sheath or introducer sheath to avoid damage to the trachea. Alternatively, a linear probe or similar device could be used to make a vertical puncture to avoid damaging surrounding organs. The case in the present study that presented with a tracheoesophageal fistula was only treated conservatively with antibiotics and did not develop serious aspiration pneumonia. The tube should possibly have been removed as soon as the transtracheal puncture was detected.

Seven cases in the present study (21%) had an early death within 30 days; however, this was likely unavoidable, as all cases involved patients with terminal malignant tumors. The median survival time for patients with terminal malignant bowel obstruction has been reported to be 17 days (4). Moreover, Udomsawaengsup et al (12) reported that seven patients with terminal malignant bowel obstruction (41%) had an early death within 30 days (12). No other complications were observed as a result of the procedure in the present study, and no fistula infections or other serious adverse events that required PTEG removal were encountered. Even though one tracheoesophageal fistula was observed, the procedure still appears very safe to perform.

Some limitations of the present study include the single-arm, non-randomized nature of the trial and the small sample size. As the subjects were patients with NGTs, they

likely chose to participate in the study because they were feeling distress from the tube. Some degree of selection bias therefore appears likely. In addition, we did not use the approach of QOL evaluation that is widely used for this type of experiment. Finally, the small sample size may have hampered the identification of adverse events. Therefore, we have planned and are presently conducting a randomized phase III trial with a larger sample size that uses QOL evaluation as the primary endpoint.

In conclusion, PTEG appears useful for relieving pain and discomfort from NGT insertion for bowel decompression in patients with a terminal malignant tumor. PTEG should be considered an efficacious method for bowel decompression in patients who are ineligible for surgical procedures, percutaneous gastrostomy, or percutaneous enterostomy.

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CLINICAL STUDY

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

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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

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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**).

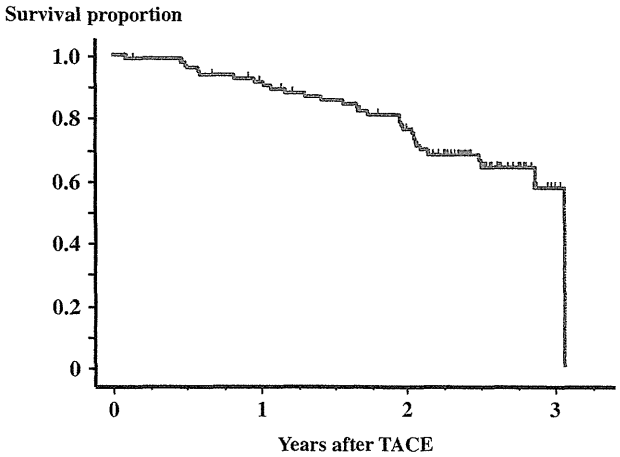

Figure 1. Overall survival and progression-free survival curves for 99 patients who underwent transcatheter arterial chemoembolization (TACE) for unresectable HCC. The tick marks indicate censored cases. (Available in color online at *www.jvir.org.*)

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.

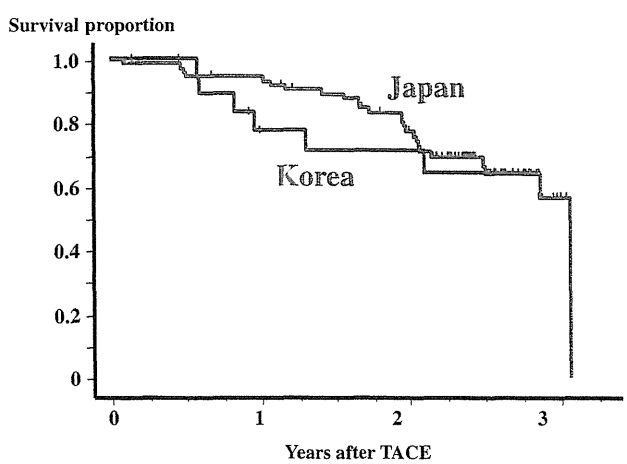

Figure 2. Comparison of overall survival curves between Japan (red line) and Korea (blue line). The tick marks indicate censored cases. TACE = transcatheter arterial chemoembolization. (Available in color online at *www.jvir.org.*)

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.

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CASE REPORT

Successful balloon-occluded retrograde transvenous obliteration for bleeding duodenal varices using cyanoacrylate

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Abstract

A 76-year-old woman with hepatitis C cirrhosis presented with tarry stools and hematemesis. An endoscopy demonstrated bleeding duodenal varices in the second portion of the duodenum. Contrast-enhanced computed tomography revealed markedly tortuous varices around the wall in the duodenum. Several afferent veins appeared to have developed, and the right ovarian vein draining into the inferior vena cava was detected as an efferent vein. Balloon-occluded retrograde transvenous obliteration (BRTO) of the varices using cyanoacrylate was successfully performed in combination with the temporary occlusion of the portal vein. Although no previous publications have used cyanoacrylate as an embolic agent for BRTO to control bleeding duodenal varices, this strategy can be considered as an alternative procedure to conventional BRTO using ethanolamine oleate when numerous afferent vessels that cannot be embolized are present.

Key words: Bleeding duodenal varices; Balloon-occluded retrograde transvenous obliteration; Cyanoacrylate; Combination therapy; Temporary portal vein occlusion

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INTRODUCTION

Bleeding duodenal varices is a rare complication in patients with portal hypertension, occurring in only 0.4% of these patients, and is often life-threatening because of the difficulty in diagnosis and treatment[1]. Treatment options include a surgical procedure, endoscopic treatment[2], and endovascular treatment, including transjugular intrahepatic portosystemic shunts (TIPS)[3,4] and balloon-occluded retrograde transvenous obliteration (BRTO)[5-10]. Although several studies have reported successful results using BRTO alone[5-8], some difficult cases with large varices or numerous collaterals requiring a combined approach have been reported[7,9], and no previous publications have used cyanoacrylate as an embolic agent for BRTO to control bleeding duodenal varices. We herein report a case with bleeding duodenal varices that were successfully embolized using cyanoacrylate and BRTO in combination with temporary occlusion of the portal vein.

CASE REPORT

A 76-year-old woman with liver cirrhosis secondary to hepatitis C presented with tarry stools and hematemesis. An urgent endoscopy demonstrated bleeding varices in the second portion of the duodenum (Figure 1A). She had no esophageal or gastric varices. Although banding

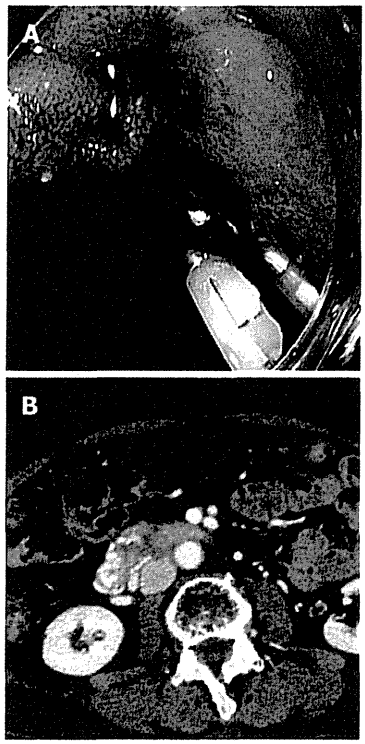

Figure 1 Endoscopy and computed tomography of the duodenum. A: Endoscopy demonstrates bleeding varices in the second portion of the duodenum; B: Contrast-enhanced computed tomography reveals markedly tortuous varices around the wall in the second and third portion of the duodenum.

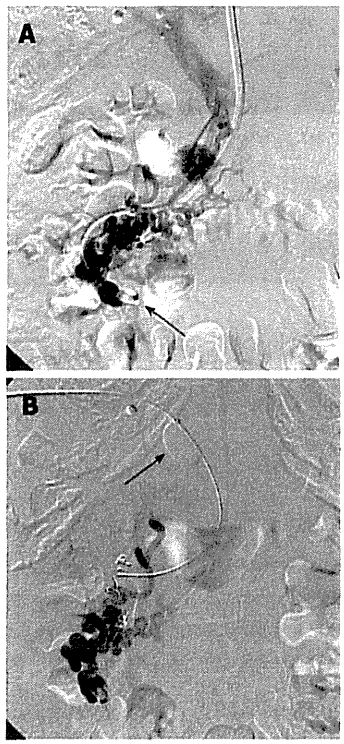

Figure 2 Balloon-occluded retrograde venography. A: Balloon-occluded retrograde venography (BRTV) shows the dilated efferent vein and the duodenal varices, but the contrast material quickly disappears through several afferent veins. Note that the balloon was inflated in the right ovarian vein (arrow); B: BRTV with occlusion of the main portal trunk (arrow) after embolization of one of the afferent veins reveals the complete opacification of the duodenal varices.

and clipping for the varices was attempted, the bleeding continued and frequent blood transfusions were required. Laboratory findings were as follows: red blood cell, 232 $\times$ $10^4/\mu L$; hemoglobin, 6.8 g/dL; hematocrit, 20.4%; platelets, 96 000/mL; total bilirubin, 1.36 mg/dL; serum albumin, 3.3 g/dL; and prothrombin time, 15.7 s (reference, 11.3 s). Neither ascites nor encephalopathy was observed. Child-Pugh's classification was graded as B. Contrast-enhanced computed tomography (CT) revealed markedly tortuous varices around the wall in the second and third portion of the duodenum (Figure 1B). Several afferent veins of the varices appeared to have developed, and the right ovarian vein draining into the inferior vena cava was detected as an efferent vein. We planned BRTO to embolize the duodenal varices after obtaining informed consent from the patient.

An 8-French guiding sheath introducer was inserted into the inferior vena cava *via* the right internal jugular vein. A 5.2-French, 9-mm cobra-shaped balloon catheter was inserted into the efferent vein through the right ovarian vein, and the balloon was inflated to occlude the efferent vein. Balloon-occluded retrograde venography (BRTV) showed that the dilated efferent vein and the duodenal varices were filled with contrast material, but the contrast material quickly disappeared through several afferent veins (Figure 2A). Because BRTO alone may have failed to achieve adequate sclerosant accumulation because of the leakage into the portal vein, antegrade transhepatic embolization of the afferent veins was attempted.

A 5-French sheath introducer was inserted through the left lateral portal branch, and one of the afferent veins was embolized using two microcoils (MicroNester coil; Cook, Inc, Bloomington, Indiana, United States). However, several remaining afferent veins could not be embolized, and the contrast material also disappeared through the afferent veins. We then placed a balloon catheter into the main portal trunk to control the hepatopetal flow of the afferent veins. BRTV with occlusion of the main portal trunk revealed the disappearance of the hepatopetal portal flow and complete opacification of the duodenal varices (Figure 2B). A microcatheter was coaxially advanced to the duodenal varices through the retrograde route, and a total of 4 mL of 20% cyanoacrylate with ethiodized oil was injected into the duodenal varices (Figure 3).

The following day, a contrast-enhanced CT examination confirmed the complete accumulation of the ethiodized oil replacement in the duodenal varices (Figure 4) and the patency of either portal vein or systemic circulation. Liver function was preserved after the procedure. Four days after the procedure, an endoscopy showed that hemostasis of the bleeding duodenal varices had been achieved. No evidence of bleeding of the duodenal varices was found on follow-up CT and endoscopy examinations performed four months after the procedure.

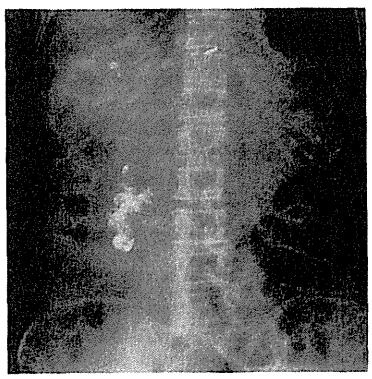

Figure 3 Radiograph after embolization of the duodenal varices demonstrates complete and adequate accumulation of the ethiodized oil in the varices.

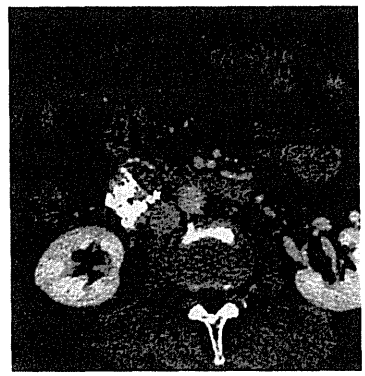

Figure 4 Contrast-enhanced computed tomography after embolization of the duodenal varices shows the complete accumulation of ethiodized oil in the varices.

DISCUSSION

BRTO is an established endovascular treatment for gastric varices[11] but has only been described for the treatment of bleeding duodenal varices in a few reports with limited numbers of clinical patients[5-10]. The advantages of BRTO over TIPS for duodenal varices are that it can completely embolize targeted varices and that it does not reduce portal flow, avoiding further exacerbation of hepatic function and encephalopathy without a significant mortality rate[4,8]. However unlike gastric varices, successful treatment with BRTO alone for duodenal varices is not always feasible and often require combined therapies with an endoscopic or anterograde transhepatic approach, as significant communications or complex hemodynamics between the efferent and afferent veins often complicate treatment and necessitate combined therapy[7,9].

In the present case, some of the afferent veins may have enabled collateral hepatopetal flow during balloon occlusion of the afferent vein, and pressure among the duodenal varices varied, resulting in insufficient filling with the contrast material. At first, coil embolization was attempted *via* a transhepatic portal venous approach, as reported by previous investigators[5,7-9], but not all the afferent veins could be embolized because of the difficulty in catheterizing the tortuous vessels. Second, we performed temporary balloon occlusion of the portal vein. This method was effective because a change in the hemodynamics of the duodenal varices occurred. Temporary occlusion of the main portal trunk may increase the pressure of hepatopetal flow, and the direction of flow in the afferent veins changes from hepatopetal to hepatofugal. This mechanism is similar to that of temporary balloon occlusion of the splenic artery during BRTO for gastric varices to control the portal pressure gradient[12].

In our case, we used cyanoacrylate, not ethanolamine oleate, as a sclerosant. Every investigator has used ethanolamine oleate as the most suitable sclerosant during BRTO for duodenal varices[5-10]. However, ethanolamine oleate was not suitable in our case, because it requires several hours to achieve full effort and may increase the risk of portal venous thrombosis under temporary portal venous balloon occlusion. On the other hand, cyanoacrylate rapidly solidifies with fast polymerization upon exposure to an ionic solution[13], and we believe that this was the best way of minimizing the duration of portal venous occlusion. The potential shortcomings of cyanoacrylate are adhesion to the balloon catheter system or inadvertent embolization upon balloon removal. This should be kept in mind as a note of caution whenever attempting to use cyanoacrylate. To prevent this complication, it would be advantageous to ensure that a microcatheter is advanced to the targeted duodenal varices and only duodenal varices are embolized, with minimal volume of cyanoacrylate.

Endoscopic injection sclerotherapy using cyanoacrylate has been performed as an effective measure[2], but it has the drawback of perforation, tissue injury, and unclear visualization because of massive hemorrhage. Moreover, endoscopic injection of cyanoacrylate also carries a risk of embolism of either portal vein or systemic circulation[14]. Endovascular injection of cyanoacrylate can prevent untargeted embolization such as portal vein or pulmonary artery, confirming the hemodynamics of the duodenal varices using contrast material.

Bleeding duodenal varices is a rare condition that is difficult to diagnose and is potentially life-threatening. BRTO using cyanoacrylate was successfully performed for control of bleeding duodenal varices in the present case. This is an alternative procedure to conventional BRTO using ethanolamine oleate when insufficient filling of the varices with sclerosant occurs and several afferent vessels cannot be adequately embolized.

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